SYNTHESES AND REACTIONS OF THE PIPERIDINE SPIRANES

A Thesis

by

Dennis Leon Stachiw, M.Sc. (Manitoba)

Submitted to the Faculty of Graduate Studies and Research of McGill University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Montreal, Canada,
August, 1957

ACKNOWLEDGMENTS

The author would like to express his sincere gratitude and appreciation to:

Dr. A. Taurins, for his helpful advice and guidance throughout this work;

Canadian Industries (1954) Limited for the fellowship held during the academic year 1956-1957;

the Chemistry Department of McGill University for a Demonstratorship held during the session 1955-1956.

TABLE OF CONTENTS

DISCUSSION (contd.) Page

EXPERIMENTAL (Contd.) Page

LIST OF TABLES

LIST OF FIGURES

GENERAL INTRODUCTION

The first objective of this work was to synthesize certain substituted cyclohexanespiropiperidines (3-azaspiro-(5.5)hendecanes). A survey of the literature indicates that this is a relatively neglected field despite the systematic work on piperidine derivatives which has been stimulated by their potentialities in pharmacology. The compounds synthesized included: 3-methyl-3-azaspiro(5.5)hendecane-1-hydroxymethyl (XIX) and -1,5-dihydroxymethyl (XVIII), 3-methyl-3-azaspiro(5.5)hendecane-1-carboxylic and -1,5-dicarboxylic acids (XXII, XXI) and 3-azaspiro(5.5)hendecane (V). The corresponding 3-azaspiro(5.5)hendecane-2,4-diones were used exclusively as starting materials; their preparation was not in all cases previously reported.

The second objective was to study the infrared absorption spectra of 3-azaspiro(5.5)hendecanes in an effort to correlate the prominent absorption maxima with structural elements. The study disclosed that in unstrained 3-azaspiro-(5.5)hendecane-2,4-diones the N-H stretching absorption occurs at 3200 and 3100 cm.$^{-1}$ and the carbonyl stretching absorption at 1720 and 1680 cm.$^{-1}$. The latter is shifted to higher

frequencies in strained rings. Strain was apparent in all the disubstituted diones with substituents (COOH, CN) vicinal to the quaternary carbon. 3-Azaspiro(5.5)hendecane-2-imino-4-oxo-compounds could be distinguished from 2,4-diones by their different absorption in both the N-H and C=O stretching region. The infrared spectra of cyclohexanespiropiperidine carboxylic acids indicated that these compounds possess zwitterion structure.

The infrared investigation required the preparation of certain other closely related compounds for comparison. They included the known 4,4-dimethylpiperidine-2,6-diones and two new spiranes, 3-oxa- and 3-thiaspiro(5.5)hendecanes. Attempts to synthesize the known spiro(5.5)hendecane by a new method failed in the final stage.

HISTORICAL INTRODUCTION

The spiranes are polycyclic compounds in which the rings are joined at one point only, the linking atom thus being common to both ring systems. If the rings are strainless the bonds of this "spiro atom" will assume undistorted tetrahedral configuration. Carbon is the most common spiro atom but numerous spiranes are known containing in place of carbon such atoms as nitrogen, phosphorus, and boron, or even metals such as beryllium, copper or zinc. All these atoms display tetravalency because of their ability to coordinate. The tetrahedral configuration of the spiro atom determines the mutually perpendicular orientation of the rings. Such orientation lowers the symmetry of the system which may be further reduced by appropriate substitution giving rise to non-superimposable and hence optically active structures despite the lack of an asymmetric carbon atom.

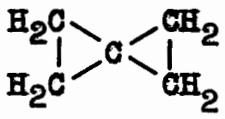
The most common spiranes contain one spiro linkage. Compounds having more than two such linkages are rare and no compounds containing more than four spiro atoms have been synthesized.

Until recently no spirocyclic compounds have been found to occur in nature.

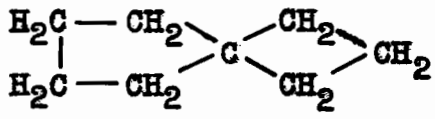
NOMENCLATURE

The term "spiro", at present generally accepted, was first proposed by Baeyer (1) in 1900 to designate compounds having a carbon atom common to two rings (in Latin, spira, meaning "Brezel", an article of bakery).

Originally the term "spiro" was placed between the names of the constituent rings. For example, I was named cyclopropanespirocyclopropane and II cyclopentanespirocyclobutane.



I



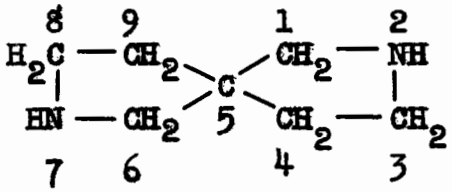
II

Such a system may be ambiguous especially in the more complex, substituted spiro compounds. According to current nomenclature, the simple spiro systems are named by placing the prefix spiro- before the name of the normal aliphatic hydrocarbon of the same number of carbon atoms. Immediately after the prefix is a bracket containing the number of atoms found in each ring. For example, I would be called spiro(2.2)-pentane, and II spiro(4.3)octane. The numbering starts from the ring member vicinal to the spiro atom.

If hetero atoms are present these are indicated by

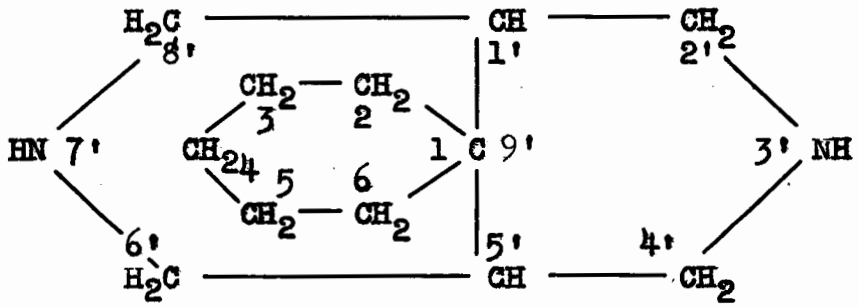
prefixing oxa-, oza-, thia-, etc. to the name. For example III is called 2,7-diazaspiro(4.4)nonane.

In complex spiro systems the names of constituent rings



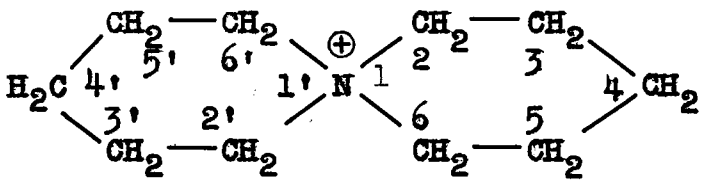
III

are retained along with their individual numbering system. The position of spiro ring fusion is indicated by non-braceted numbers. For example, IV is called spiro(cyclohexane-1,9'-(3,7)-diazabicyclo(3.3.1)nonane)



IV

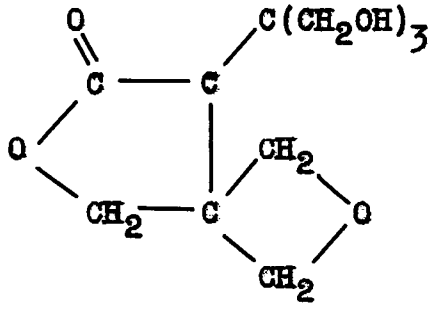
Similar nomenclature is preferred for compounds in which the spiro atom is nitrogen, as in V, which is called 1,1'-spirobipiperidinium rather than 6-azaspiro(5.5)hendecane.



V

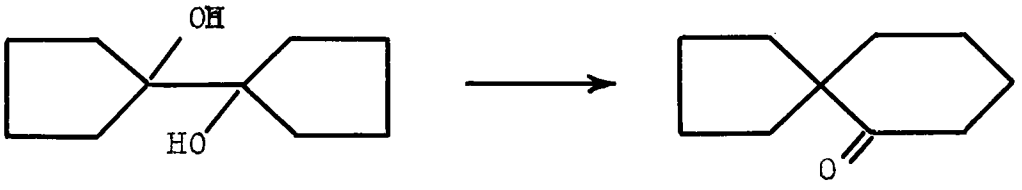
EARLY HISTORY

The first compound (VI) proved to contain spiro linkage was synthesized by Tollens and Rave in 1892 by the action of formaldehyde on levulinic acid (2).



VI

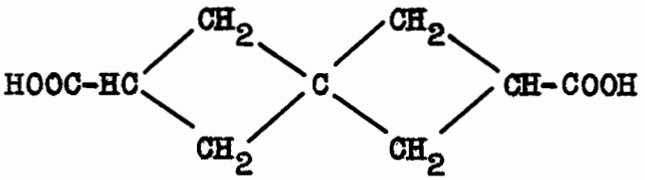
Meiser reported in 1899 the synthesis of spiro(5.4)-decane-5-one (VII) by rearrangement of dicyclopentenyl pinacol (3).



VII

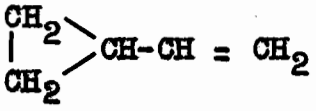
The compounds were first recognized as a distinct group by Baeyer (1) who suggested for them the name "spiro".

In 1907 Fecht synthesized spiro(3.3)heptane-2, 6-dicarboxylic acid (VIII); he is also credited with the first study of the stability of spiranes and their ease of cyclization (5). A conclusion inferred from this work was that

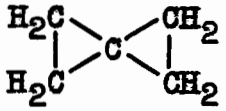


VIII

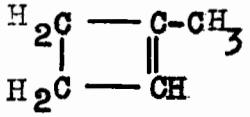
the stability of the constituent rings is not affected when the two form a spiro-linked system. His final work on so-called "vinyl methylene" (ibid.) at the time presumed to be vinylcyclopropane (IX) supported the spirocyclic structure (X). This structure remained undisputed until 1923 when Ingold (6) proved that the compound was actually methylcyclobutene (XI).



IX



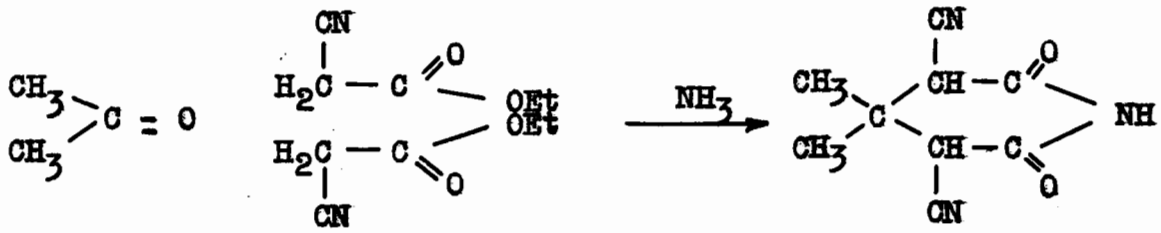
X



XI

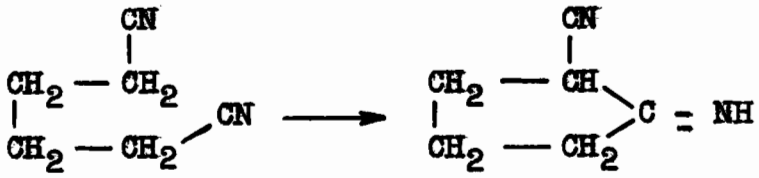
PIPERIDINE SPIRANES

In 1900 Guareschi (7) showed that derivatives of piperidine can be readily obtained in good yields by reacting ketones with ethyl cyanoacetate in the presence of an excess of ammonia. For example, acetone treated in this way produced 3, 5- dicyano-4, 4-dimethylpiperidine-2, 6-dione.

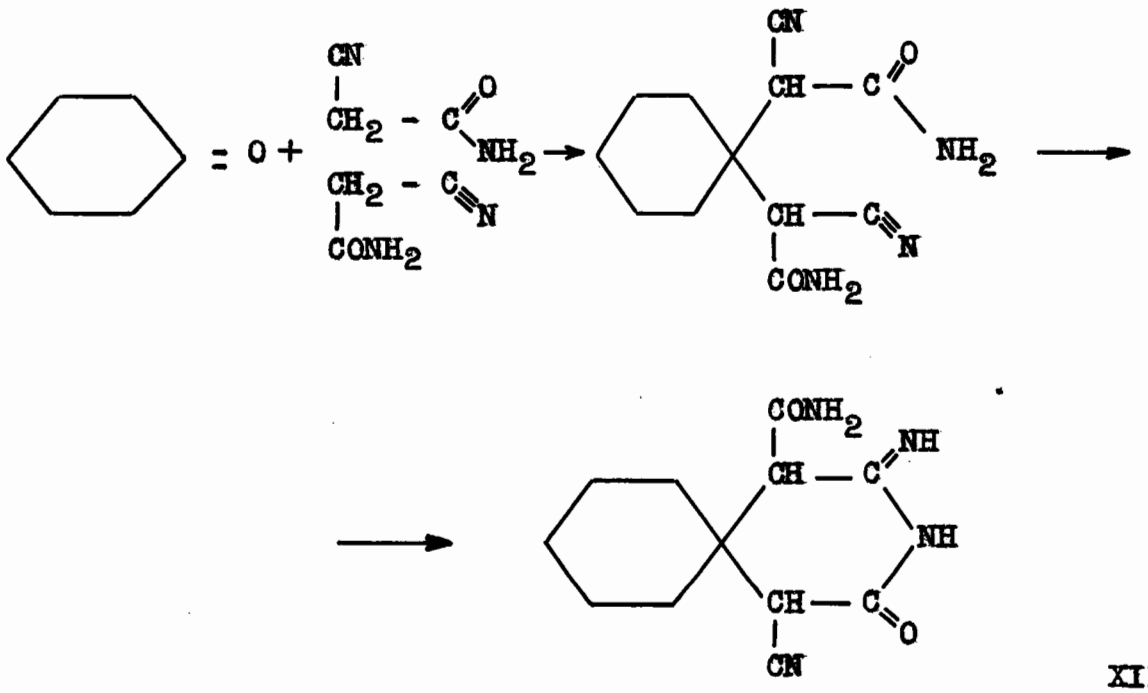


a) The Structure of the Condensation Product of Cyclohexanone with Cyanoacetamide

If cyclic ketones were used in such a condensation reaction, one would expect the formation of spiropiperidine derivatives, but the reaction was never attempted by Guareschi. It remained for Thorpe to demonstrate the applicability of the modified Guareschi condensation to the synthesis of piperidine spiranes. He showed in 1909 (8) that a chain compound carrying a cyano group on each end readily cyclizes to form an imino compound. For example, adiponitrile when boiled in alcoholic solution with a trace of sodium ethoxide formed 1-cyano-2-imino-cyclopentane (ibid.). Thorpe concluded



that by using cyanoacetamide instead of cyanoacetate it would be possible under suitable conditions to cyclize the condensation product in a similar manner. The reasoning proved

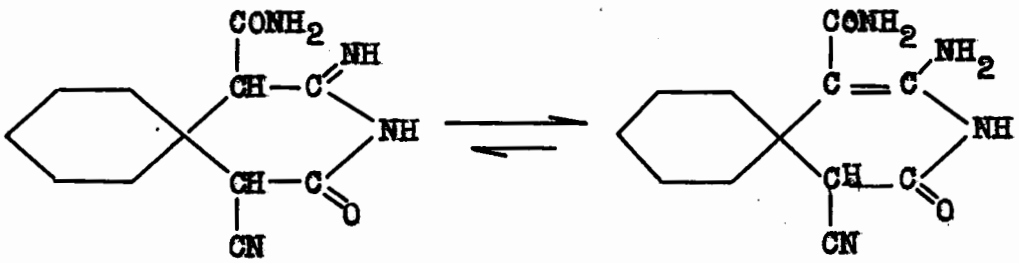


XII

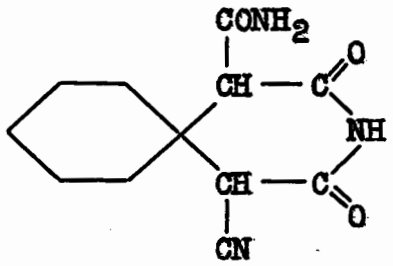
correct, as a condensation of cyanoacetamide with cyclohexanone in the presence of a little piperidine produced an excellent yield of 3-azaspiro(5.5)-hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (XII) a derivative of cyclohexane-

spiropiperidine (9). Henceforth, this compound will be referred to as "imino imide".

Thorpe presented the following extensive evidence to prove that imino imide was a tautomeric compound reacting in two forms, the amino tautomer predominating at normal temperatures.



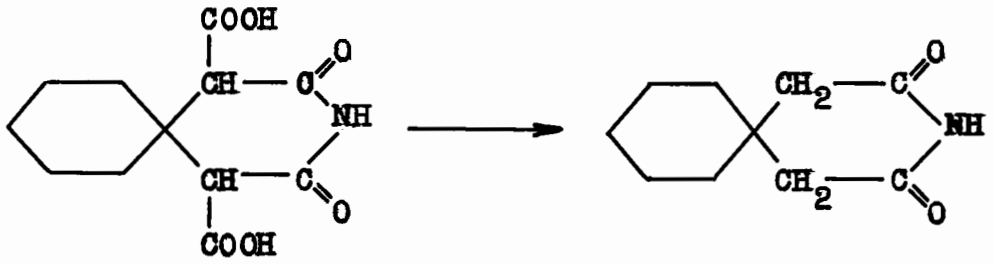
1. The substance is a mono-acidic base; its salt with chloroplatinic acid showed the expected analysis. It formed a clear solution with dilute hydrochloric acid, which if immediately treated with sodium acetate precipitated the imino imide (XII) practically unchanged, but if allowed to stand precipitated 3-azaspiro(5.5)hendecane-5-cyano-2, 4-dioxo-1 carboxamide (XIII) formed by hydrolysis of the amino form of the tautomeric compound (XII).



XIII

The imino imide was completely transformed into 3-azaspiro-(5.5)hendecane-5-cyano-2, 4-dioxo-1-carboxamide (XIII) when the solution of the former in dilute hydrochloric acid was boiled for a short time.

2. When the base (XII) was treated with an excess of sodium hydroxide, it formed a clear, yellow solution, the color of which disappeared on boiling. Evolution of ammonia accompanied the process. When the boiling was continued until all the ammonia had been eliminated, the solution, after acidification, yielded a dibasic acid (XIV) which was readily decarboxylated to produce 3-azaspiro(5.5)hendecane-2, 4-dione (XV).

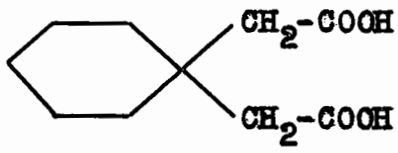


XIV XV

The yield of dione (XV) by this last process was not very satisfactory, as the action of alkali on the base also proceeded in another direction, with the formation of some cyclohexanone and malonic acid.

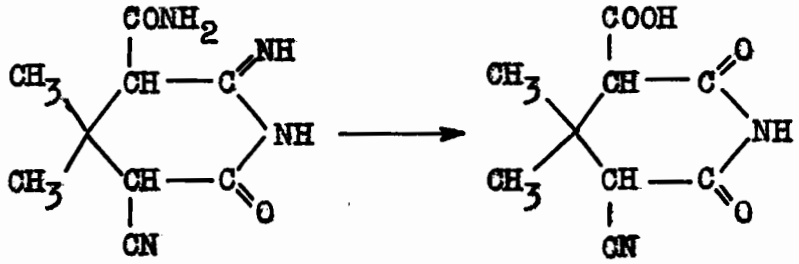
3. When imino imide (XII) was heated with 70% sulphuric acid for three hours, it was quantitatively converted

into cyclohexane-1, 1-diacetic acid (XVI).



XVI

4. If a similarly constituted condensation product of cyanoacetamide and acetone (XVII) was boiled for a long time with water, ammonia was evolved and if this was continued until all the ammonia was eliminated, the product was found to be cyanoacid (XVIII).

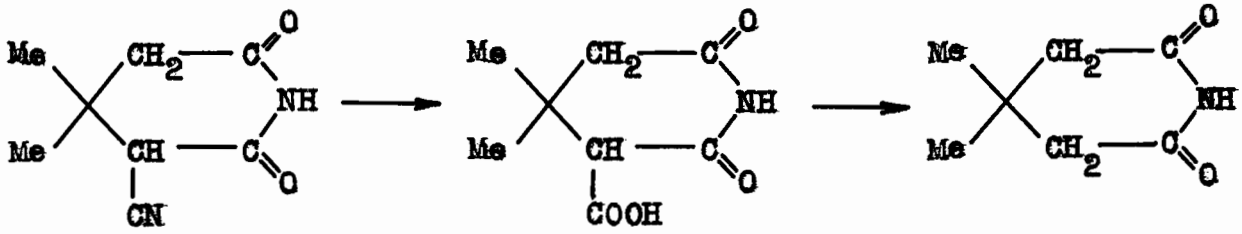


XVII XVIII

It was evident that an intermediate product, the ammonium salt of the acid, was formed first, but that it dissociated on boiling with water, yielding the free acid.

5. When the cyano acid (XVIII) was heated, carbon dioxide was eliminated, and the nitrile (XIX) was formed.

This substance was also produced upon prolonged boiling of a solution of 4, 4-dimethylpiperidine-5-cyano-2-imino-6-oxo-3-carboxamide (XVII) in dilute hydrochloric acid. Heating the cyanoacid with aqueous alkali hydroxides converted it to the salt of the carboxylic acid (XX). The latter can be decarboxylated by heating; the product was 4, 4-dimethyl-piperidine-2, 6-dione (XXI) (ibid.)



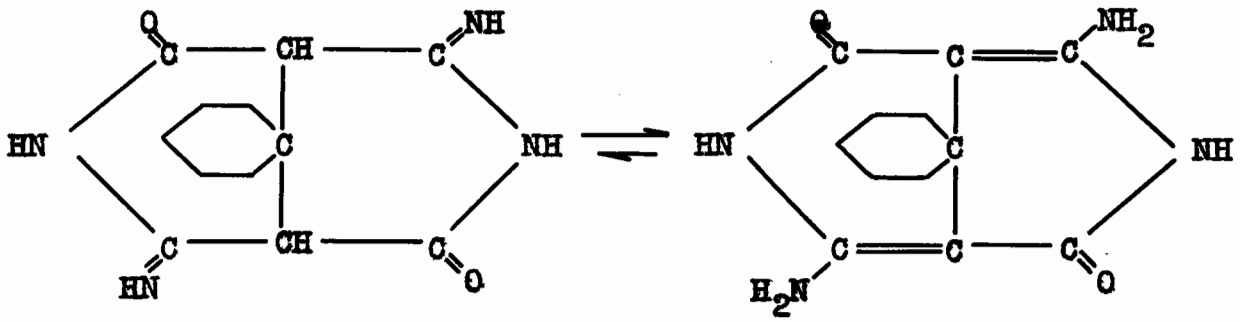
XIX XX XXI

This evidence enabled Thorpe to establish the structure of the condensation product of cyanoacetamide with cyclohexanone.

b) Reactions of the Imino Imide (XII)

Experiments with 3-azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (XII) revealed that under certain conditions it undergoes a further imino condensation with the formation of a second imino imide ring having three carbon atoms in common with the first (9). Thus when it was treated with sodium ethoxide in alcohol a sparingly soluble

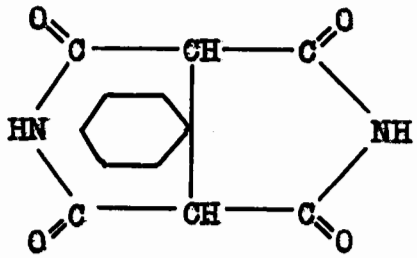
sodium salt was formed; the addition of acetic acid produced a crystalline substance the reactions of which showed it to be 2', 6'-diimino-4',8'-dioxo-spiro(cyclohexane-1, 9'-(3, 7)-diazabicyclo(3.3.1)nonane) or "diimino diimide" (XXII)



XXIIa XXIIb

The structure of this substance was deduced from the following experimental data.

1. It is a diacid, tautomeric compound reacting in the two forms (XXIIa, b) of which the "vinylamine" form predominates under ordinary conditions. This is shown by its behaviour with dilute hydrochloric acid in which it forms a clear solution when cold, but from which the original substance is precipitated practically unchanged on the addition of sodium acetate. When the solution in dilute hydrochloric acid is warmed, both imino groups are at once eliminated and the diimide (XXIII) is precipitated.



XXIII

2. When boiled with potassium hydroxide, one imido ring is broken, and if this treatment is continued until all the ammonia has been evolved, the dibasic acid (XIV) is formed. The fact that the second ring is so readily broken by alkali hydroxide, when it is well known that the imides of the glutaric series are very stable toward this reagent, shows that it is under a greater strain than the single ring.

3. When boiled with 70% sulphuric acid the diimino diimide is completely converted into cyclohexanel, 1-diacetic acid (XVI).

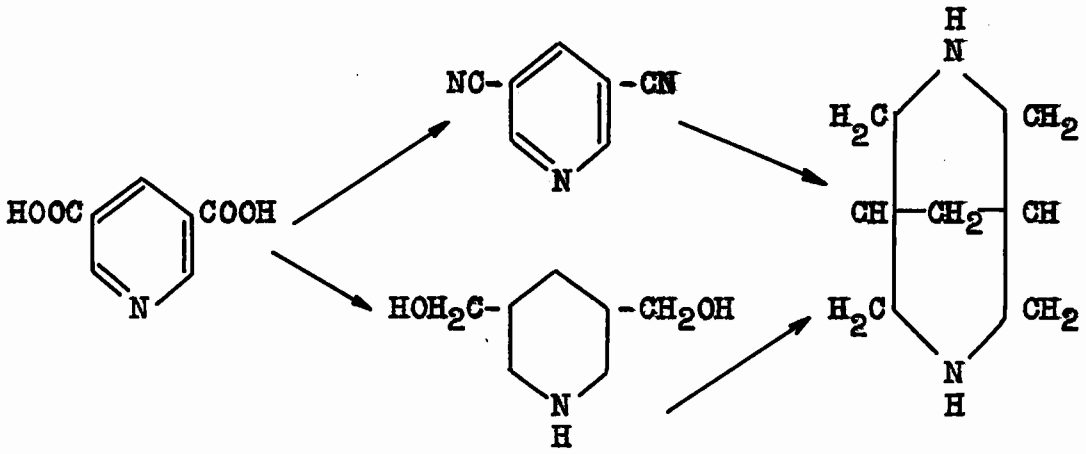
The double ring is also produced by other reagents than sodium ethoxide; for example, it is the first product formed by the action of aqueous alkali hydroxides on the imino imide. The latter compound dissolves in the reagent giving a yellow solution; the color rapidly disappeared on warming. If the solution is cooled as soon as the color has disappeared, and is then acidified with acetic acid, the pure diimino diimide (XXII) is precipitated.

c) Condensed Piperidine Rings

The diimino diimide (XXII) and the diimide (XXIII) may be regarded as derivatives of cyclohexanespirobispidine. The bispidine (XXIV) which has been synthesized only recently

(10, 11) represents a condensed ring system involving two piperidine rings and is correctly named 3, 7-diazabicyclo-(3.3.1)nonane. The starting compound for the synthesis was dinicotinic acid which in the first method of preparation was converted to 3, 5-dicyanopyridine by way of diacyl chloride and amide. The dinitrile yields bispidine upon hydrogenation with Raney nickel (10).

In the second method (11) the ester of the acid is first hydrogenated to produce the piperidine ring, then reduced to 3, 5-dihydroxymethylpiperidine. Treatment with hydrobromic acid followed by ammonia yields bispidine.

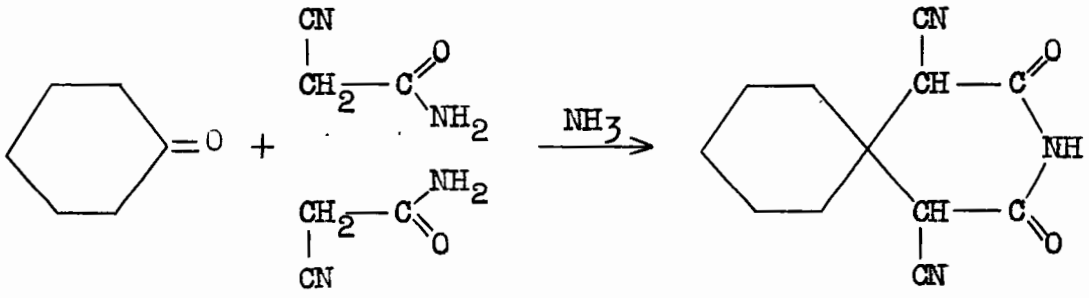


XXIV

d) Thorpe's Mechanism of Condensation of Ketones with Cyanoacetamide and Cyanoacetate

In the condensation of cyanoacetamide with cyclohexanone a small quantity of another product is formed besides

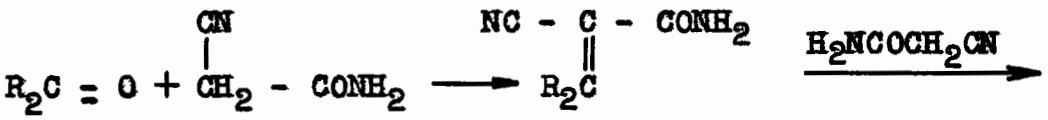
the imino imide (XII) (9). With piperidine as a condensing agent this substance separates from the mother liquor on standing, after the imino imide has been filtered off, and can be readily separated from the main product of the reaction by virtue of its insolubility in dilute hydrochloric acid. If condensation is effected by treatment with alkali hydroxide, the same substance separates on acidification of the alkaline filtrate with acetic acid. The yield of this material, which ordinarily does not exceed 5%, can be considerably increased by carrying out the condensation at higher temperatures. The compound was proved (12) to be 3-azaspiro(5.5)hendecane-1,5-dicyano-2,4-dione (XXV) and is found as the sole product of the condensation of ethyl cyanoacetate with cyclohexanone under Guareschi conditions.



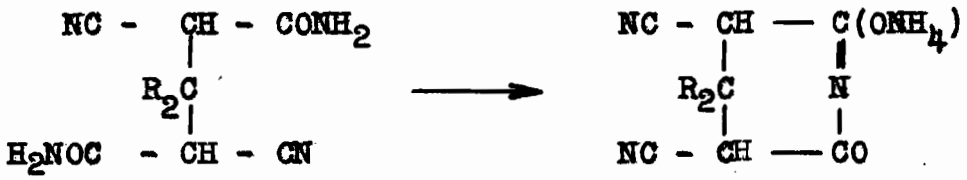
XXV

Kon and Thorpe (13) suggested a mechanism to explain the formation of the two condensation products. They assumed the formation of the unsaturated intermediate (XXVI) to be

the initial step. The mode of addition of a second molecule of cyanoacetamide to this unsaturated intermediate is different in the two reactions. For a catalytic reaction addition is "trans" since this, according to Thorpe, is a more stable configuration.



XXVI

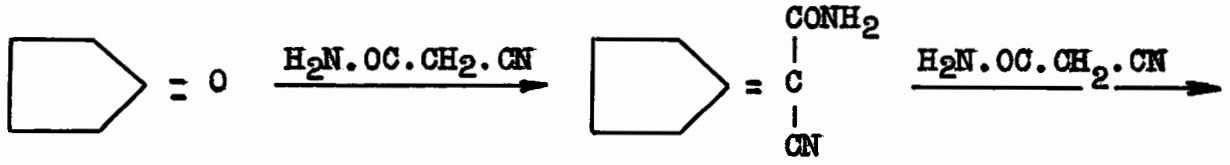


XXVII

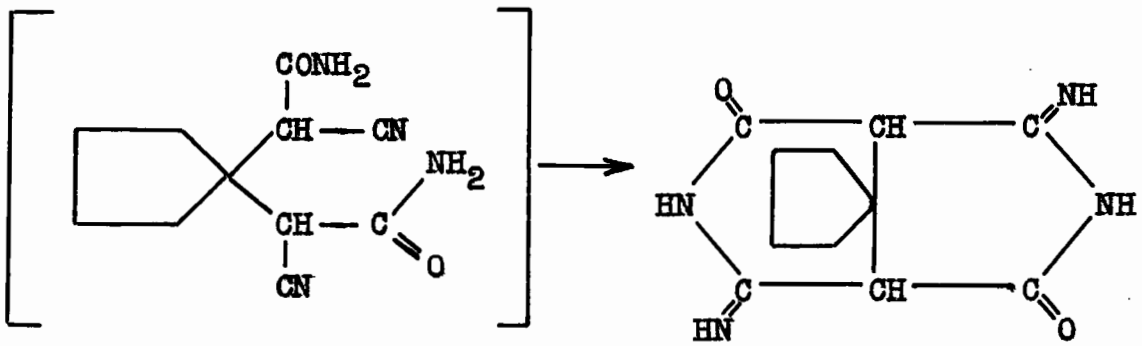
In the Guareschi reaction the presence of an excess of ammonia causes the "cis" derivative to be produced, because of the tendency of the compound to form the ammonium salt (XXVII). The latter is therefore an "enforced" reaction and can be made to yield condensation products in cases where a true catalytic process such as the cyanoacetamide reaction fails through the inability of the ketone to undergo condensation (ibid.). It is found, for example, that the cyanoacetamide reaction can be effected with all ketones having

two secondary carbon atoms next to the carbonyl group. If one of these is tertiary, as in 2-methylcyclohexanone, the cyanoacetamide condensation fails, but products can be obtained by the Guareschi method, although in diminished yield. If both carbon atoms are tertiary, both the cyanoacetamide and Guareschi reactions fail; this also occurs if one carbon atom is quaternary, as in camphor and pinacolone (ibid.).

The suggestion that the first step in condensation involves the formation of an unsaturated compound is supported by the reaction of cyclopentanone with cyanoacetamide. Here the main product is cyclopentylidene-cyanoacetamide (XXVIII), which is capable of condensing with another molecule of cyanoacetamide to form the "diimino compound" (XXIX). This provides strong evidence in favour of the two-step mechanism concluded by cyclization (ibid.).

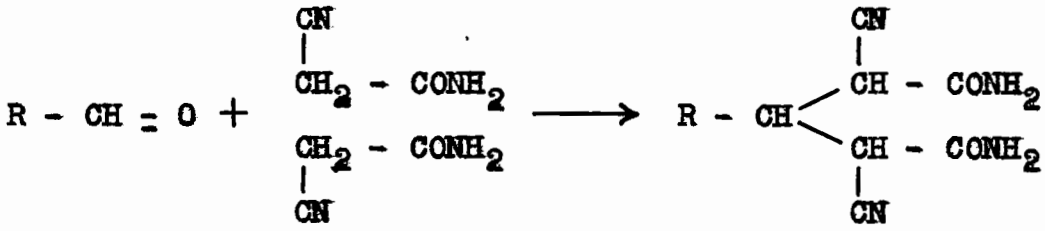


XXVIII



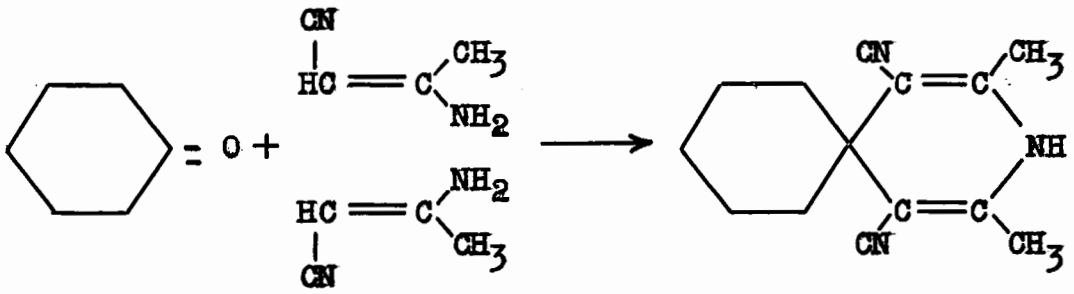
XXIX

The precipitation of the unsaturated compound is due entirely to its insolubility in the aqueous medium used, because if a sufficient quantity of alcohol is added, the reaction follows the normal course with the direct production of the diimino derivative (ibid.). That the cyclization step necessarily follows the condensation is apparent from the reaction of cyanoacetamide with aldehydes (14), which produces open chain structures.



The yields of these products are very high, but there is also a small quantity of a cyclic imino compound formed. The extremely low solubility of these products again appears to be the reason for their separation from the solution before cyclization could occur (ibid.).

Recently, derivatives of 3-azaspiro(5.5)hendecane-1, 4-diene have been prepared by condensation of cyclohexanone with 2-aminocrotononitrile, in alcoholic solution in

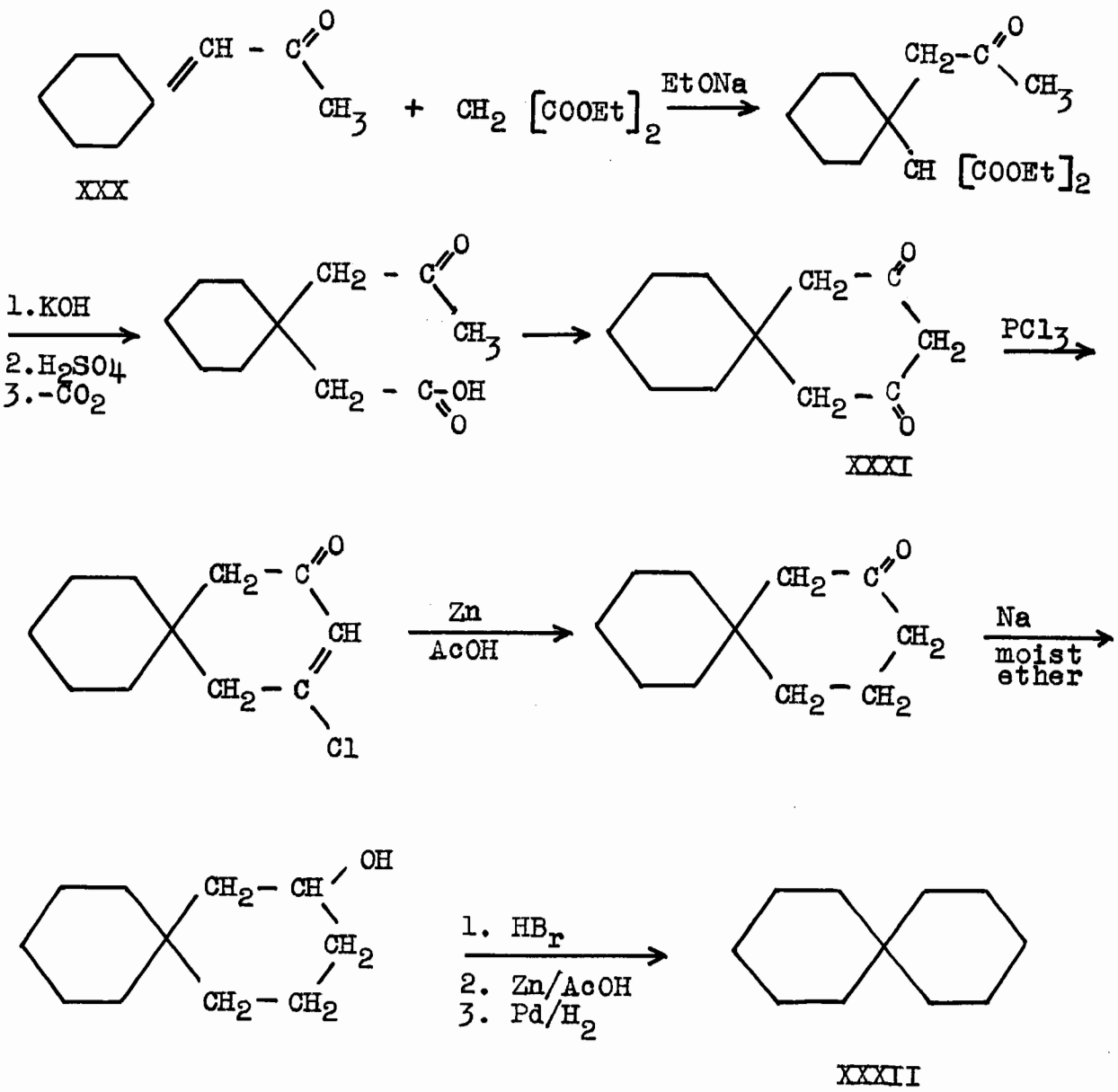


the presence of phosphorus pentoxide (15). 3-Methyl- and 4-methylcyclohexanones also produced condensation products, while, as in the cyanoacetamide condensation, the reaction failed with 2-methylcyclohexanone.

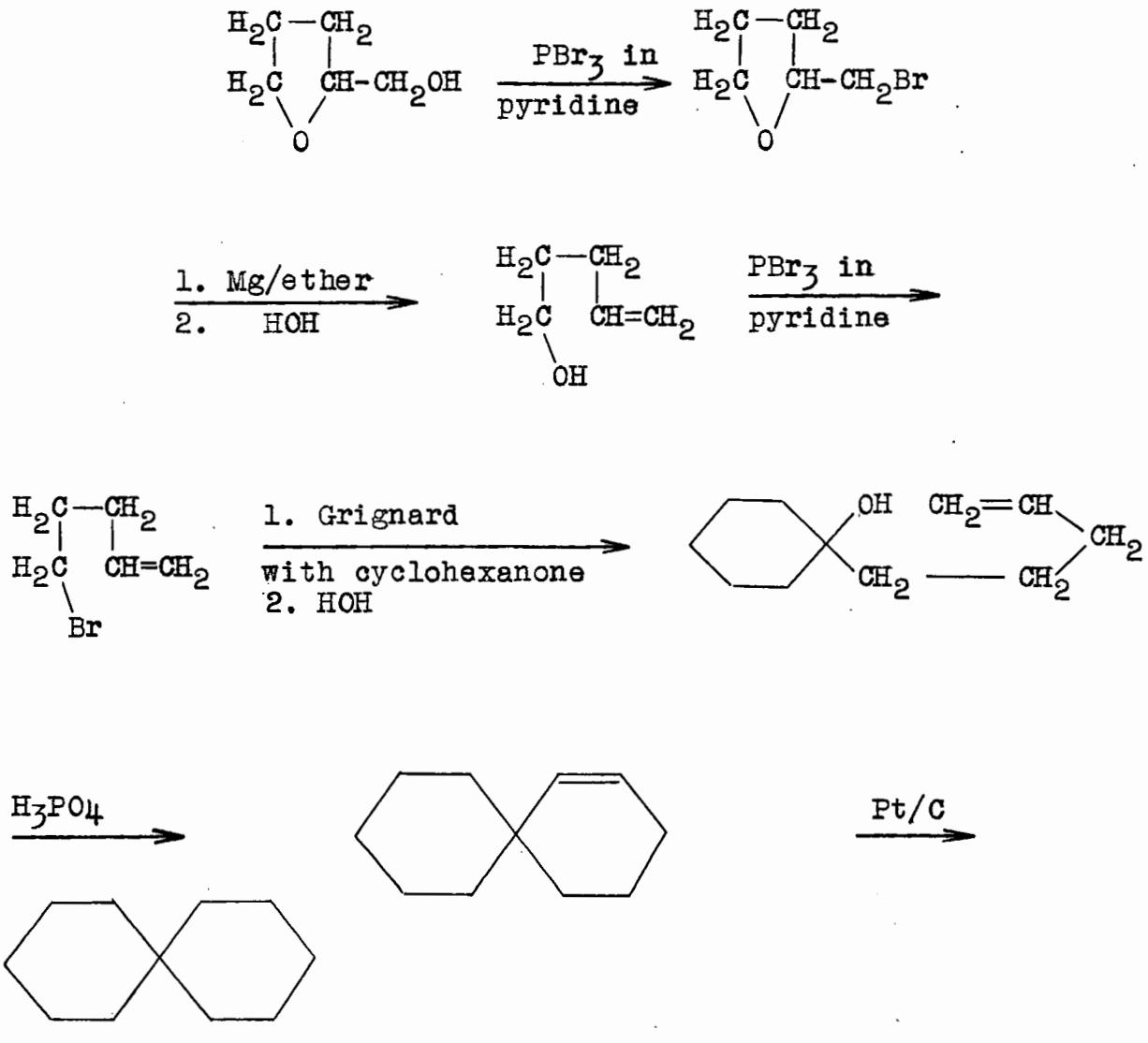
SPIRO(5.5)HENDECANE (XXXII)

The original synthesis by Norris and Thorpe (16, 17) was carried out in the course of a study of the effect of substitution in aliphatic chains on their tendency towards ring closure. Their method of preparation is of little practical value because of the number of steps involved and the low yields. The first step was the condensation of cyclohexanone with acetone to produce cyclohexylideneacetone (XXX) with a yield of 23% of the theoretical. This was next reacted with malonic ester in a Michael condensation; the product, after saponification, acidification and decarboxylation yielded spiro(5.5)-hendecane-2, 4-dione (XXXI). In a series of steps the latter was subsequently converted into a mixture of spiro(5.5)hendecane (XXXII) and spiro(5.5)-

hendecane; the mixture upon hydrogenation yielded pure spiro(5.5)hendecane (XXXII)



An elegant synthesis of spiro(5.5)hendecane has been developed recently by Zelinsky and Elagina (18) starting with tetrohydrofurfuryl alcohol.



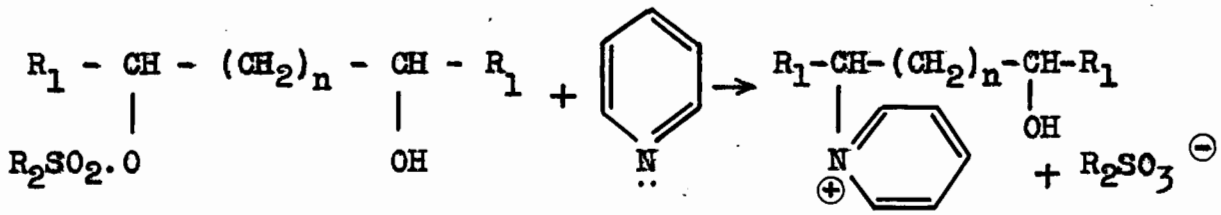
The overall yield was 9.6% of the theoretical.

THE FORMATION OF CYCLIC ETHERS FROM DIOLS

For the diols which do not readily form cyclic ethers the recent method of Reynolds and Kenyon (19) offers a distinct

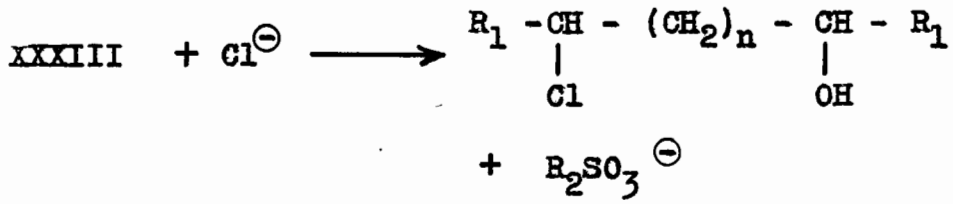
advantage. It consists of treatment of diols with acyl chlorides in the presence of pyridine bases. For example, with benzenesulphonyl chloride in pyridine, the first step involves esterification of the diol to form benzenesulphonate (XXXIII) followed by the formation of the desired product. Depending upon the conditions, at least three side reactions are possible:

1. Formation of the quaternary compound between the ester and tertiary amine

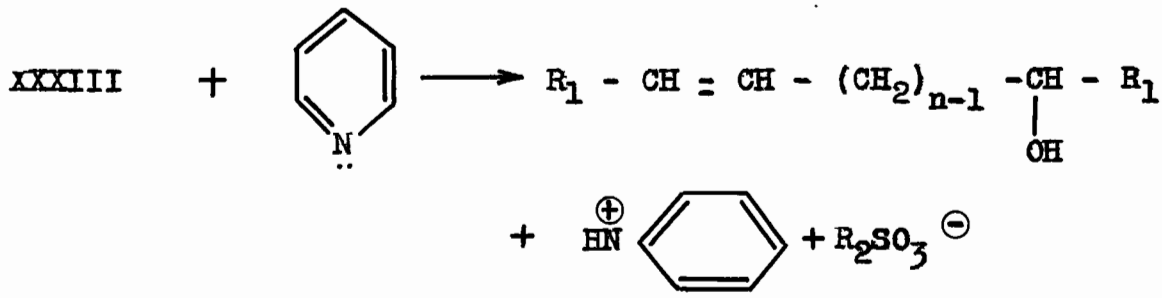


XXXIII

2. Replacement of the benzene-sulphonyloxy group by halogen from the amino hydrochloride to form an organic chloride



3. Splitting of the initially formed ester into an unsaturated compound and sulphonic acid

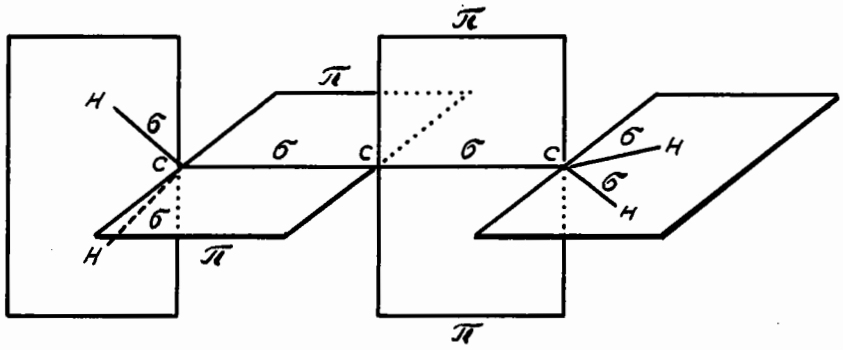


According to Reynolds and Kenyon (ibid.) reactions 2 and 3 play a negligible part in the synthesis of five- and six-membered ethers. Quaternization, however, interferes critically in the formation of tetrahydropyran. The yield of this compound with pyridine as a base was only 5%, the bulk of the material forming a quaternary salt as indicated in the first reaction. The yield was raised to 40% when 2, 6-lutidine was used instead of pyridine. 2, 6-Lutidine is known to possess a very low rate of quaternization. No mechanism for these reactions was given; its discussion follows on page 83.

CERTAIN ASPECTS OF THE STEREOCHEMISTRY OF THE SPIRANES

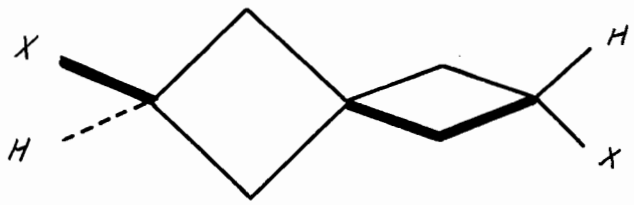
The mutually perpendicular orientation of the rings in spiro molecules is an essential factor in the stereochemistry of these compounds. In this respect a formal analogy can be drawn between spiranes and allenes. In allene, $CH_2 = C = CH_2$, for example, because of the trigonal (sp^2) hybridization of the terminal carbon atoms and the diagonal (sp) hybridization of the central carbon the two planes

containing the terminal carbons and the hydrogens attached to them are mutually perpendicular. Such a system has much



lower symmetry than the corresponding, hypothetical, planar system and becomes nonsuperimposable upon a single substitution at each end irrespective of the nature of the substituents. Hence 1, 3-disubstituted allenes always represent a d, l-mixture. However, in the case of 1, 1-substitution even the non-identity of the substituents is not sufficient to produce the asymmetry.

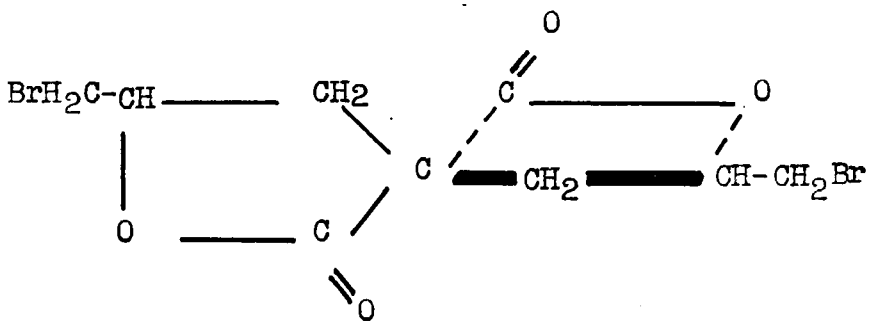
Similarly, in the case of spiro(3.3)heptane (XXXIV),



XXXIV

the symmetrical disubstitution (i.e. in positions 2,6) does not produce any asymmetric centers but the molecule cannot be superimposed on its mirror image and hence should exist in two optically active forms.

As early as 1902 Aschan (20), using spiro(3.3)heptane and spiro(5.5)hendecane, then unknown, pointed out that the presence of asymmetric carbon is not a necessary condition for optical activity. The experimental verification of this hypothesis with the same compounds was not demonstrated until 1928 when Backer and Schwink (21) resolved spiro(3.3)-heptane-2,6-dicarboxylic acid by means of brucine into optically active components. The specific rotation was found to be rather low. Lenchs and Gieseler (22), however, had noted as early as 1912 that the occurrence of three inactive stereoisomeric forms of 2,7-dioxaspiro(4.4)nonane-3,8-dibromomethyl-1,6-dione (XXXV) cannot be reconciled with the presence of only two asymmetric carbon atoms in the molecule. Because the two asymmetric carbon atoms are



XXXV

equivalent, the formula predicts only two forms, one meso and the other a d, l-mixture. If, however, the molecular asymmetry is taken into account, it is apparent that three racemic mixtures should exist (23).

PIPERIDINE DERIVATIVES AND ANALGESIC ACTIVITY

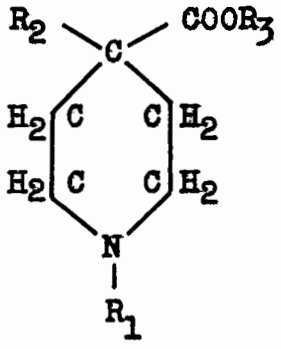
In 1939 Eisleb (24, 25) discovered a method for the preparation of 4-phenylpiperidine derivatives from phenylacetonitrile and Schaumann (26) tested them for analgesic action. The results of the testing left no doubts that a long search for a potent synthetic analgesic was at last successful. A further progress resulted from the recognition of the structural elements of morphine molecule associated with analgesic activity. This aspect will be discussed in more detail later, attention being given first to a survey of important piperidine analgesics.

Piperidine derivatives of greatest pharmacological interest belong to two closely related groups:

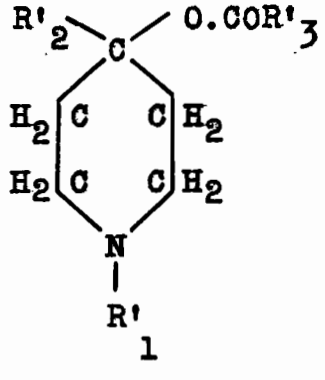
a) 1-alkyl-4-arylpiperidine-4-carboxylates and

b) 1-alkyl-4-arylpiperidine-4-acyloxy compounds.

a)



b)



The most important compound in the first group is ethyl 1-methyl-4-phenylpiperidine-4-carboxylate or meperidine. It combines the antispasmodic properties of atropine with the analgesic action of papaverine (24). Its neurospasmolytic action on muscle and a central analgesic action resembles morphine (26). The hydrochloride produces pronounced corneal anesthesia when applied directly to the eye (27).

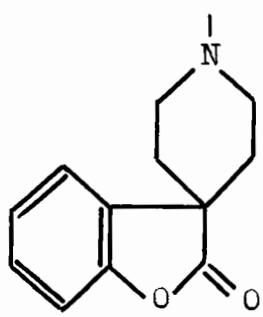
The effect of varying the substituent attached to the nitrogen atom was studied by Schaumann (26) and Thorp and Walton (28) in a series of N-substituted ethyl 4-phenylpiperidine-4-carboxylates. The methyl, ethyl and butyl derivatives exhibited analgesic activity, whereas phenyl, benzyl, cyclohexyl and carbethoxymethyl were not active. Variation of aryl substitution in a series ethyl 1-methyl-4-arylpiperidine-4-carboxylates showed m-hydroxyphenyl and o-tolyl to be more effective than phenyl, whereas p-amino-, p-hydroxy-, m-methoxy-, p-methoxyphenyl, and α-naphthyl were inactive (26, 29). Replacement of aryl by α-thiophene produced an active series although its most active members were inferior to meperidine (30).

In a group of 1-methyl-4-phenyl-4-acyloxypiperidines the optimal activity was found with the propionoxy group and was reported to be 10-30 times that of meperidine (31, 32). Activities of acetoxy and butyroxy compounds were 1/30

and one-half respectively of propionoxy derivatives (ibid.). Substitution of the phenyl residue by heterocyclic rings, alkyls or aralkyls generally produced compounds of low or no activity. Replacement by cyclohexyl residue ($R'_1 = CH_3$, $R'_3 = C_2H_5$) caused a decrease in activity to about one-third (33, 34). The compound, however, still retains a remarkable activity being about one-half that of morphine. A study of 4-arylpiperidyl ketones by Schaumann (25) showed that this series is comparable in analgesic action to the esters and actually contains compounds much more potent than any of the esters. For instance, ethyl 1-methyl-4-(3-hydroxyphenyl)piperidyl ketone had activity 10 times that of meperidine (35).

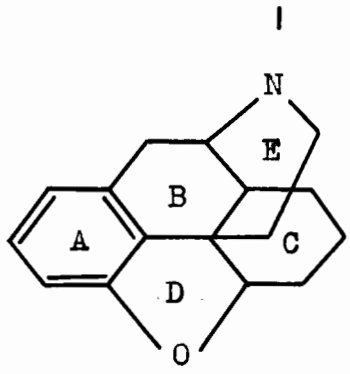
A number of active compounds was found in a series of 1-alkyl-3-arylpiperidine-3-carboxylates (29) none of them, however, having outstanding properties. Generally lower activity was exhibited by 1-alkyl-2-phenyl- and 1-alkyl-2-arylalkylpiperidines (32, 33). The analgesic activity 1/35 - 1/50 of morphine was reported with certain 1-alkyl-4-arylpiperidines (ibid.).

MacDonald (29) tested spirocyclic piperidine-benzofuran derivatives of the type shown below but found them to

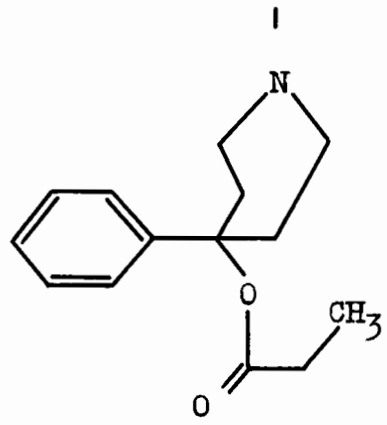


possess little or no analgesic activity.

Accumulated synthetic data indicate that substantial portion of morphine nucleus must be retained or simulated in order to obtain analgesic activity resembling that of morphine. Whereas the presence or simulation of rings A, E and C appears to be necessary, rings B and D do not seem



morphine nucleus



very active
1-methyl-4-phenyl-4-propionoxy-piperidine

to be essential. Although, for instance, in 4-phenyl-4-acyloxypiperidine series the carbonyl oxygen atom simulates the ether bridge in morphine it is not a necessary factor in the activity. The function of carbonyl group here is probably to assure the favourable spatial arrangement of the propionoxy chain which thus resembles more closely the ring C of morphine (36).

INFRARED ABSORPTION SPECTRA

1.) Ring Vibrations

No attempt has yet been made to correlate structural features specific to spiranes with infrared absorption. The feature distinguishing spiranes from other compounds is the presence of C - $\overset{|}{\underset{|}{C}}$ - bonds associated with the quaternary carbon atom. If absorption frequencies could be assigned to the stretching vibrations of such bonds it would be of great value in identifying spirocyclic compounds. However, as the energy of such vibrations is necessarily low, it would be difficult to distinguish them from -C-C- stretching vibrations particularly in the complex absorption pattern of the low frequency region. Moreover -C-C- stretching vibrations are usually not localized in individual bonds but involve the vibrations of the ring as a unit, and are thus very sensitive to changes in the immediate environment of the vibrating groups.

Appreciable frequency shifts may be caused by substitution (37). Even in simple cyclic systems such as cyclohexane unambiguous assignment has not yet been made. Morrison (38) analysed the published spectra of fifty cyclohexane derivatives and tentatively assigned the skeletal vibrations to two regions, 1055-1000 cm.$^{-1}$ and 1005 -952 cm.$^{-1}$. These assignments, however, do not apply to cyclohexanone

derivatives in which the introduction of the carbonyl group might be expected to alter any characteristic ring deformation frequencies (39).

Vetter and Tchamler (40) calculated the vibration frequencies of such six-membered saturated ring systems as cyclohexane, piperidine, pentamethylene oxide and pentamethylene sulphide. Theoretical vibration frequencies were computed by assuming the rings to have "chair" conformation and by treating methylene groups as point masses. Cyclohexane itself has a space group symmetry D_{3d}, whereas the presence of one hetero atom in the ring lowers the symmetry to C_s.

The assignment of frequencies to the four six-membered ring compounds according to Vetter and Tchamler is as follows:

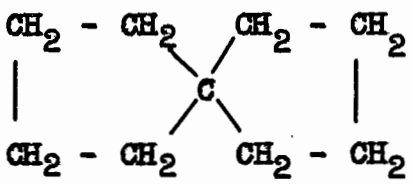
	Cyclohexane	Piperidine	Pentamethylene Oxide	Pentamethylene Sulphide
Skeletal Vibrations	862 s 901 s	858 s 937 mb 1050 m 1117 vs	813 m 874 s 1007 m 1041 s 1093 vs	659 s 1014 m
			Rocking (CH_2)	
	901 s 1015 m	782 m 791 m 855 s	756 w 835 w 855 m 971 m	826 s 933 w

Cyclohexane	Piperidine	Pentamethylene Oxide	Pentamethylene Sulphide
		Twisting (CH_2)	
1039 m	1193 m	1033 m 1153 m 1199 vs	1064 m 1129 w
		Wagging (CH_2)	
1259 s	1323 s 1384 w	1263 m 1277 m 1296 m 1352 w 1385 w	1219 m 1240 m 1264 s 1306 m 1302 w
		Bending (Scissoring) (CH_2)	
1450 vs	1448 s		

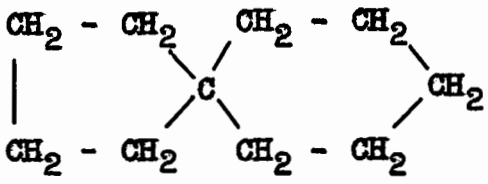
In condensed cyclohexane and cyclopentane systems, the mode of ring fusion makes a very considerable difference to the infrared spectrum. Even in spiranes, where the problem is simplified by the fact that the rings are joined at one point only and the nature of the spirane linkage ensures that the two rings lie in mutually perpendicular planes so that their interactions will be minimized, the interaction of skeletal vibrations introduces serious difficulties of interpretation.

Batuev (41), who studied Raman spectra of spiro(4.4)-nonane (XXXVI) and spiro(4.5)decane (XXXVII), has shown that in the former the skeletal vibration characteristic of the

cyclopentane ring is observed undisturbed at 890 cm.$^{-1}$.



XXXVI



XXXVII

The spectrum of spiro(4.5)decane (XXXVII) is more complex. Batuev selected six bands which he considered to be three sets of doublets: a) 783, 822, b) 796, 846, c) 878, 900. The averaged frequencies of each doublet, 802, 821 and 889 represent the chair cyclohexane, boat cyclohexane and cyclopentane ring vibrations respectively. Batuev's conclusion was that spiro(4.5)decane exists as a mixture of chair and boat conformation. In both forms the vibrations of the two rings couple through the quaternary carbon to split the original frequency into a doublet.

Batuev's treatment can be criticized for its unhesitant postulation of boat conformation, which is not at present generally accepted. However, though possibly incorrect, it illustrates clearly the spectral complexities resulting from ring coupling in spiranes.

The infrared spectrum of spiro(5.6)dodecane has been recorded by Laber (42) but no interpretation was offered.

The absorption maxima occurred at the following frequencies: 2930 (vs), 2860 (s), 1455 (vs), 1375 (s), 1300 (m), 1275 (m), 1245 (m), 1225 (w), 1190 (m), 1175 (m), 1150 (w), 1100 (w), 1080 (w), 1060 (m), 1040 (w), 990 (s), 970 (m), 945 (s), 935 (s), 885 (s), 865 (s), 850 (s), 840 (s), 815 (s), 770 (w), 765 (w, b), 700 (m).

2.) Secondary Amides and Lactams

The group O = C-NH- may be present in either open chain structures (secondary amides) or in cyclic compounds (lactams). There is a significant difference between the spectra of the two types of compounds which is principally due to the presence of the so-called amide II band in secondary amides. The nature of this rather controversial band is discussed on page 40. The individual vibrations of the group can be differentiated in the following way:

Vibration	Absorption Region
1. N - H stretching	3500 - 3050 cm.$^{-1}$
2. C = O stretching	1750 - 1650 cm.$^{-1}$
3. C - N stretching 4. N - H deformation	lack of agreement

While N - H and C = O stretching vibrations in secondary amides have been satisfactorily accounted for, no

unambiguous assignment of frequencies for N - H deformation and C - N stretching has yet been made despite extensive work in this field.

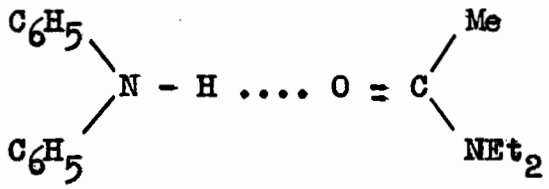
a) N - H Stretching Vibration

Primary and secondary amides exhibit absorption bands between 3500 and 3050 cm.$^{-1}$, resembling those for O - H stretching vibrations, in that they are shifted to lower wave numbers in the solid state where extensive hydrogen bonding may occur. Sutherland (43) assigned the following absorption ranges to two types of hydrogen bonding:

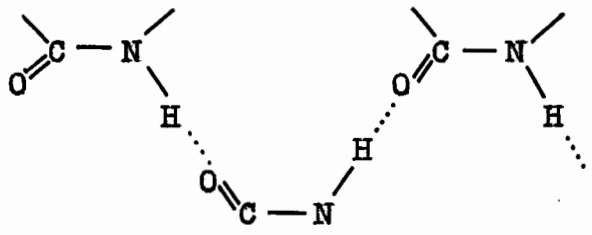
- N - H .... O = C -	3320 - 3240 cm.$^{-1}$
- N - H .... N -	3300 - 3150 cm.$^{-1}$
free N - H stretching	3500 - 3380 cm.$^{-1}$

The infrared spectra of N-monosubstituted amides in the solid state show two bands of 3330 - 3280 cm.$^{-1}$ and 3100 - 3060 cm.$^{-1}$ (44). Since the frequencies of the association bands of amides differ from those of amines, it is concluded that - N - H .... O = C - rather than - N - H .... N - linkages are chiefly involved. This conclusion is further supported by the observation of Richards and Thompson that mixed solutions of diphenylamine and acetodiethylamide in carbon tetrachloride show an absorption band at 3320 cm.$^{-1}$ similar to that of N-monosubstituted amides and distinct

from the 3430 cm.$^{-1}$ band shown by diphenylamine alone. This is attributed to the - N - H .... O = C linkage in the associated complex (45)

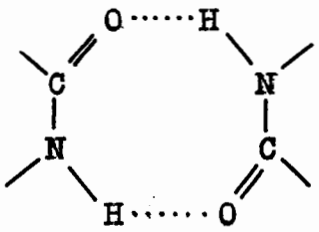


Attempts have been made to relate the three frequency ranges in the spectra of secondary amides to three hydrogen-bonded structures, as shown below.



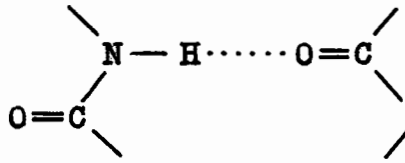
XXXVIII

Absorption region 3200 - 3160 cm.$^{-1}$
Cis linkages present in cyclic amides only



XXXIX

Absorption region 3100 - 3060 cm.$^{-1}$
Cis linkages present in both cyclic and noncyclic amides



Absorption region 3330 - 3280 cm.$^{-1}$
Trans linkages absent in cyclic amides

XL

Darman and Sutherland (46) and, independently, Tsuloi, Mizushima and collaborators (47) studied the cis linked complexes in cyclic amides, where trans association was excluded. In these compounds they failed to observe the 3330 - 3280 cm.$^{-1}$ band, but noted instead bands at 3200 - 3160 cm.$^{-1}$ and 3100 - 3060 cm.$^{-1}$. These experiments suggest that the 3300 - 3280 cm.$^{-1}$ band can be assigned to a trans linked aggregate (XL) and the 3200 - 3160 cm.$^{-1}$ band to a cis linked structure (XXXVIII) but provide no explanation for the band at 3100 - 3060 cm.$^{-1}$.

Edwards and Singh (48) reported absorption at 3220 and 3090 cm.$^{-1}$ for 2-piperidone, indicating cis linkages of the type (XXXVIII) and (XXXIX) but additional work is necessary before a more satisfactory assignment can be established for all three bands.

b) Amide I and Amide II Bands

Both primary and acyclic N-monosubstituted amides show two strong bands between 1710 and 1470 cm.$^{-1}$, commonly known as amide I and amide II bands. The amide I band arises

from what is essentially a C = O stretching vibration, but although the amide II band shows some behaviour suggestive of a N - H deformation its assignment is still a matter of controversy, especially in non-cyclic N-monosubstituted amides. The "amide I band" of N-monosubstituted amides in the solid state appears in the range 1710 - 1630 cm.$^{-1}$, while the "amide II band" is observed between 1580 and 1475 cm.$^{-1}$, and is usually weaker than the former (49). Richards and Thompson (45) reported an absorption band at 1540 - 1520 cm.$^{-1}$ in a variety of N-alkyl and N-benzyl mono-substituted amides in dioxane solution, which shifted to 1560 cm.$^{-1}$ in the solid state. The amide I band in lactams shows the normal behaviour of a C = O stretching vibration, but there is no absorption above 1500 cm.$^{-1}$ which could be identified as the amide II band. For example, Edwards and Singh (48) observed the C = O stretching absorption for 2-piperidone at 1760 cm.$^{-1}$. In the saturated five-membered rings the C = O stretching frequency is slightly raised as a consequence of ring strain.

While the assignment of the amide II band of primary amides to a N - H deformation vibration is consistent with the most of the known facts, none of the attempts to assign the amide II band of N-monosubstituted amides can be considered satisfactory. Some of the evidence supporting the view that the absorption is due to N— H deformation is as

follows:

1. The band is absent in N, N- disubstituted amides (45).

2. The extent and direction of the frequency shifts which occur with changes of state agree with those expected for N - H deformation (ibid.).

3. Polarization studies indicate an out-of-plane N - H vibration (50).

4. Deuteration weakens the amide II band and gives rise to a new absorption near 1130 cm.$^{-1}$ where the N - D deformation band might be expected (51).

The objections to this interpretation may be summarized:

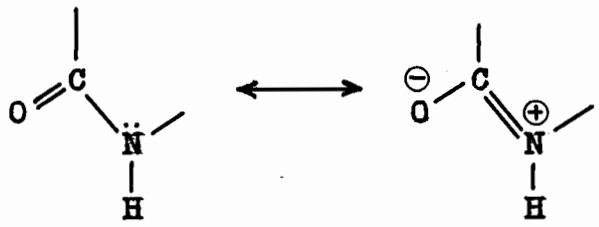
1. No explanation is offered for the absence of the amide II band from cyclic lactams (52, 53).

2. The absorption due to N - H deformation in secondary amines is extremely weak (53).

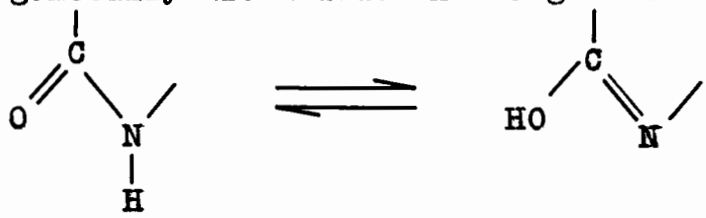
3. The amide II band is absent from Raman spectra (52).

4. The results of deuteration are ambiguous; the new absorption in the 1130 cm.$^{-1}$ region in deuterated compounds is too weak to account wholly for the reduction in the intensity of the amide II band (ibid.).

The most generally favoured alternative explanation is that the band arises from a C - N stretching vibration in which the C - N bond shows considerable double bond character due to resonance with the carbonyl group (54, 55).



The main objection to this is the absence of the amide II band in the tertiary amides. The idea that the amide I and II bands are due to the co-existence of two distinct compounds, such as would be required in a keto-enol equilibrium has now been generally discarded. Although the amide II band



could thus be attributed to a C = N stretching vibration, X-ray diffraction studies rule out such a possibility (56).

Miyazawa et al. (57) have recently proposed what may be the most satisfactory explanation of the origin of amide II band in secondary amides. They consider the three absorption regions in secondary amides (amide I: 1710 - 1630 cm.$^{-1}$; amide II: 1580 - 1475 cm.$^{-1}$; amide III: 1300 - 1200 cm.$^{-1}$) to be due not to a vibration of a specific bond but

to coupled vibrations of several vibrating units. The principal vibrations involved in the coupling are ν (C=O) (carbonyl stretching), ν (C-N) (carbon-nitrogen stretching), and δ (N-H) (nitrogen-hydrogen deformation). The amide I, II and III bands are related to these vibrations but not in a simple manner. The contribution of ν (C=O) is greatest to the amide I band, whereas that of δ (N-H) is very small since the amide I band hardly changes in frequency on deuteration. However, there will be a considerable contribution of ν (C-N) to this band if it is assumed that the C-N bond acquires partial double bond character, since its frequency is not much different from that of ν (C=O). For the simplest unsubstituted amide, Miyazawa was able to calculate the contribution of ν (C-N) to that of ν (C=O) in the amide I and amide III bands and designated these coupled vibrations ν_a and ν_s respectively. The amide I band of the monosubstituted amide is also considered to be a ν_a band since the frequency and its shift on deuteration are almost the same as those of the ν_a band in formamide. The determination of the vibration type corresponding to amide II and III bands in monosubstituted amides is more involved. Mathematical treatment, however, is still possible in the case of diformylhydrazine, spectroscopically the simplest monosubstituted amide. Calculations indicate that the II and III bands may be considered as arising from the

coupling of ν s and δ(N - N) frequencies. However, monosubstituted amides will generally have additional contributions of ν (C - R) and ν (N - R') to the amide II and III bands, and hence the mathematical treatment is no longer feasible.

Miyazawa's interpretation readily accounts for the absence of the amide II band in disubstituted amides and in the cis form of monosubstituted amides, as well as other controversial facts.

3. Spectra of Imides

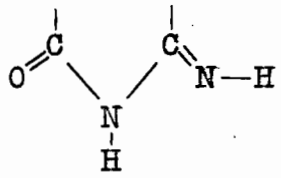
The group -CO - NH - CO - does not commonly occur in open chain compounds, but is found in many cyclic substances such as hydantoin or succinimide. The N - H stretching vibration of such compounds does not appear to be associated with a specific frequency and the available data are too limited to permit any generalizations. For example, succinimide shows two bands at 3145 and 3049 cm.$^{-1}$, hydantoin and alloxan each show one band at 3125 cm.$^{-1}$ and 3280 cm.$^{-1}$, respectively, whereas 5-methyl hydantoin gives two bands at 3333 and 3125 cm.$^{-1}$ (53).

The carbonyl absorption of these compounds appears as two widely separated bands in the regions 1790 - 1720 cm.$^{-1}$ and 1710 - 1670 cm.$^{-1}$ (ibid.). The first of these is

assigned to the 4- position carbonyl group, as it persists in compounds in which the C=O in the 2-position is replaced by C=S. The second could arise from C=N vibration but is assigned to the 2-position carbonyl, as it persists in compounds in which NH group is replaced by N-CH_3 (ibid.). The change from NH to N-CH_3 compounds does not cause any appreciable carbonyl shifts, and as the solid and solution spectra are closely parallel, it is concluded that there is little hydrogen bonding in the solid state (58).

4. Imino-imides

No compounds containing the group



have been investigated by infrared spectroscopy. The individual C=N stretching vibrations lie between 1680 and 1630 $cm.^{-1}$. They are appreciably stronger than C=C stretching vibrations but weaker than C=O bands. In aliphatic imines the C=N band is usually found near 1670 $cm.^{-1}$ and is displaced to a lower frequency in conjugated and aromatic systems (59).

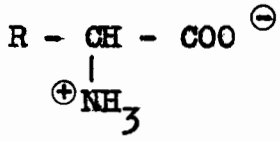
The =N-H stretching frequency of imines is in the range 3400 - 3300 $cm.^{-1}$, according to Colthup (60), in essentially the same region as the N-H vibration in trans-bonded

amide linkages (3330 - 3280 cm.$^{-1}$).

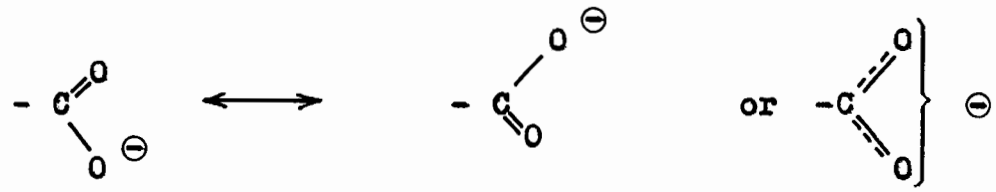
5. Spectra of Amino Acids

The infrared spectra of amino acids present strong evidence in favour of the zwitterion structure of these compounds.

Monocarboxylic monoamino acids show no absorption due either to N - H or C = O stretching vibrations, because no such structural units are present in the zwitterion form of amino acid molecule.



The bands actually observed are due to $\overset{+}{N}$ - H and ionized carbonyl stretching vibrations, the latter arising from the resonance of the carboxylate anion.



The absorption of the ionized group is shifted to a lower frequency than that of the corresponding neutral units.

In amino dicarboxylic acids, absorption bands are observed for the stretching vibrations of both the ionized

and unionized carboxylic groups (61).

Hydrochlorides of amino acids should give rise to the same absorption in the $\overset{\oplus}{N}$ - H stretching region although this has only been established in a few cases. There is, however, complete agreement that the ionized carbonyl absorption is replaced by that of the unionized group. Most studies of $\overset{\oplus}{N}$ - H absorption in amino acids have been done with the primary amino group; such absorption was reported to occur in 3130 - 3030 cm.$^{-1}$ region (62, 63, 64). Compounds incapable of assuming $\overset{\oplus}{N}H_3$ structures such as N - mono- or disubstituted amino acids, which contain $\overset{\oplus}{N}H_2$ or $\overset{\oplus}{N}H$ groups, might be expected to absorb at different frequencies, but no data are available.

Neutral amino acids and their salts all show absorption at 1600 - 1560 cm.$^{-1}$ which has been attributed to the ionic carboxyl group (64). The absorption vanishes on the formation of the quaternary hydrochloride in which the ionization of the carboxyl group is suppressed (53, 65). This behaviour is observed in all types of amino acids, whether the amino group has the $\overset{\oplus}{N}H_2$ or the $\overset{\oplus}{N}H_3$ structure.

For most amino acids, the carbonyl absorption occurs normally in the 1730 - 1710 cm.$^{-1}$ range (53, 65) except for α -amino acids, which absorb at an abnormally high frequency (1750 - 1740 cm.$^{-1}$). From the limited data available,

it appears that normal carbonyl absorption is also shown by the hydrochlorides of acids carrying secondary amino group. There are no data available for tertiary amino acids. However, it is interesting to note that infrared spectra of tertiary amine hydrochlorides show features indicating the presence of strong N-H .... X^- bonds. The spectrum of triethylamine hydrochloride shows no absorption in the usual N-H stretching frequency region (66) but there is a very strong band centered at 2540 $cm.^{-1}$ which must be the N-H frequency. The band is a well-defined doublet with maxima at 2500 and 2610 $cm.^{-1}$, the latter being the more intense; there are also two weaker satellites at 2630 $cm.^{-1}$ and 2740 $cm.^{-1}$. The large displacement of the band from its normal spectral location is attributed to the formation of a strong N-H ...Cl^- bond (ibid.).

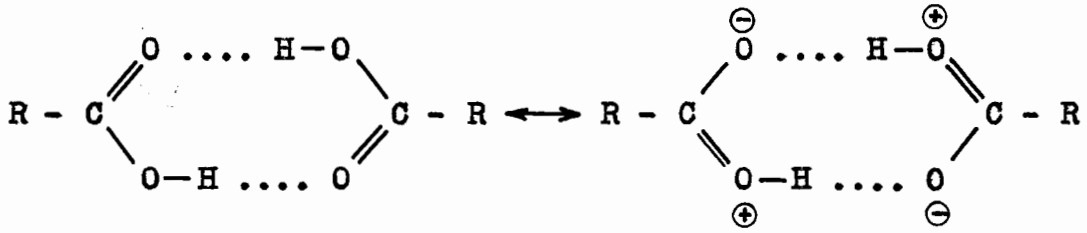
6. Infrared Spectra of β-diketones

The infrared spectra of such β-diketones as acetylacetone or dibenzoylmethane are consistent with the normally formulated enolic structure

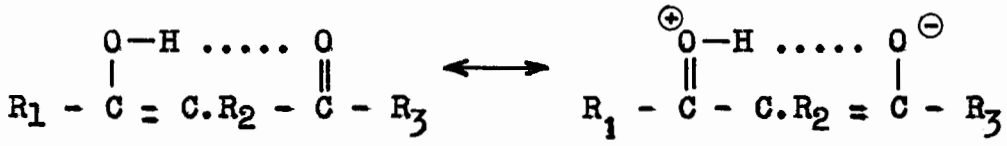
$$R_1\text{-}C(OH)=C.R_2\text{-}CO\text{-}R_3$$

However, the absorption pattern shows some unusual features which require further elaboration. The band near 3330 $cm.^{-1}$

where the simple hydrogen-bonded OH absorption occurs is absent, and a weak extremely broad band appears near 2700 cm.$^{-1}$. The absorption is similar in this respect to the very broad OH band of fatty acid dimers. The latter band is also shifted considerably beyond the normal hydrogen-bonded OH position to about 2940 cm.$^{-1}$. The greater strength of the hydrogen bonds in fatty acid dimers has been attributed to the presence of an ionic structure in resonance with the usual covalent one.



The ionic contribution is increased in the dimer because of the stabilization arising from the favourable position of the electropositive proton with respect to the negative carbonyl oxygen. The greater shift of the OH band in fatty acid dimers as compared, for example, with hydrogen-bonded alcohols, thus arises from the additional weakening of the O - H bond in the ionic structure (67). It is clear that a similar explanation can be applied to the enolized β-diketones, where again ionic resonance forms may contribute largely to the structure.

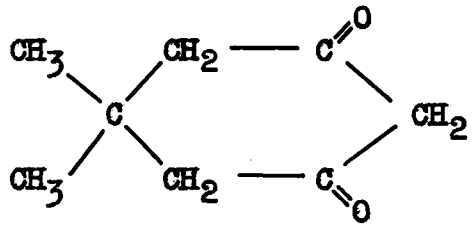


Thus the 2700 cm.$^{-1}$ band might be identified with the O - H vibration, greatly shifted and broadened as was observed with the fatty acid dimer (ibid.).

Enolized β-diketones also exhibit unusual behaviour in the carbonyl absorption region. They show a moderate band at 1709 cm.$^{-1}$ which is attributable to the keto- form. No band is observed in the usual conjugated ketone region (1695 - 1672 cm.$^{-1}$), but a very strong band appears around 1639 - 1538 cm.$^{-1}$. Since C = C bands are usually not very intense, these bands must be assigned to C = O. Both the extreme shift from the usual ketone C = O position and the abnormally high intensity may be reasonably explained again in terms of the resonance structures shown above. The enhanced participation of the ionic structure leads to a greater decrease in double bond character of the C = O bond than would occur with simple conjugation, resulting in a shift to a longer wave-length, while the increased charge on the carbonyl oxygen could account for the high intensity. If this interpretation is correct the failure to observe a C = C band must be attributed either to masking by the very strong C = O band or to a shift out of the double bond region caused by the loss of double bond character (ibid.).

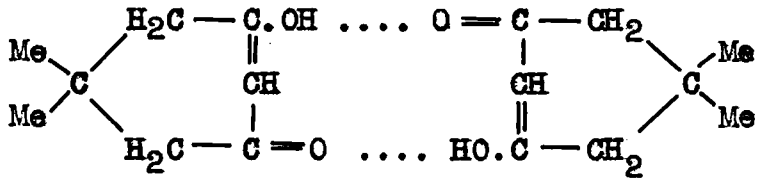
Rasmussen et al. (ibid.) investigated the infrared absorption of 5, 5-dimethyl-1, 3-cyclohexane dione (XLI).

This compound shows a strong band at 1702 cm.$^{-1}$ which indicates that a large proportion of the molecules exist in the



XLI

keto-form. The bands at 2632 cm.$^{-1}$ and 1605 cm.$^{-1}$, however, indicate a conjugated chelate type of enolization. Since the ring makes it sterically impossible for the OH of the enol form to approach closely enough to the carbonyl oxygen of the same molecule to interact with it, the necessary stabilization of the ionic structure must be accomplished through formation of a dimer such as



DISCUSSION

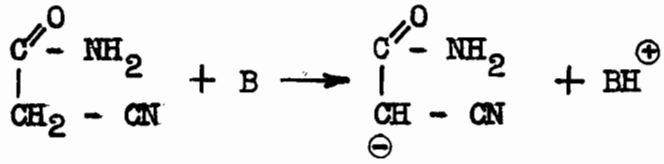
SYNTHESIS AND MECHANISM OF FORMATION OF 3-AZASPIRO(5.5)HENDECANE-5-CYANO-2-IMINO-4-OXO-1-CARBOXAMIDE (I)

With a few exceptions, 3-azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I) was used as the starting material for the preparation of all the compounds with which this investigation was concerned. For convenience the compound will be referred to as "imino imide". It was prepared by the condensation of cyclohexanone with cyanoacetamide in the presence of piperidine, as described by Thorpe (9), but although meticulous care was taken to reproduce the experimental details, it was not possible to attain the same yield. The average yield of the product was about 30%, whereas Thorpe reported a 90% yield. In agreement with Thorpe it was found that 3-azaspiro(5.5)hendecane-1, 5-dicyano-2, 4-dione (II, "dinitrile") was always a byproduct of the reaction.

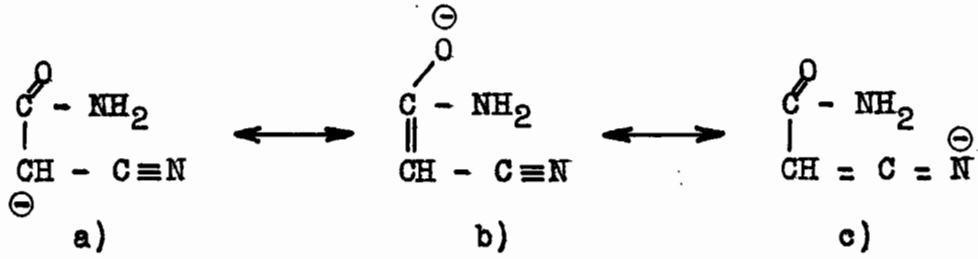
All attempts to increase the yield of imino imide (I) by varying the reaction conditions failed. Thus carefully purified cyanoacetamide and cyclohexanone gave about the same yields as the commercial grades. Concentrations of the reactants in aqueous solution were also varied to no avail. Condensations performed at higher temperatures,

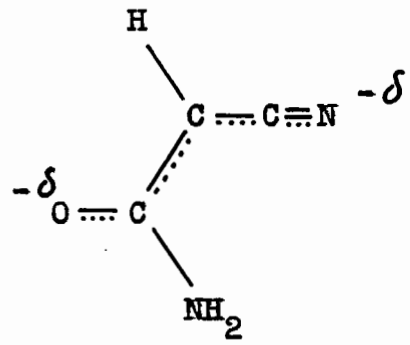
up to 40°, gave an increased rate of reaction and yield of "dinitrile" (II) but the recovery of imino imide was invariably less. The purity of the latter was also reduced by the increased formation of resinous material. On the other hand, below room temperature both the rate and yield of the product were depressed.

As a preliminary step in the mechanism of this condensation, it is assumed that the base abstracts a proton from the cyanoacetamide. Such a transfer should occur readily because of the strong activation of methylene group by adjacent carbonyl and nitrile groups.



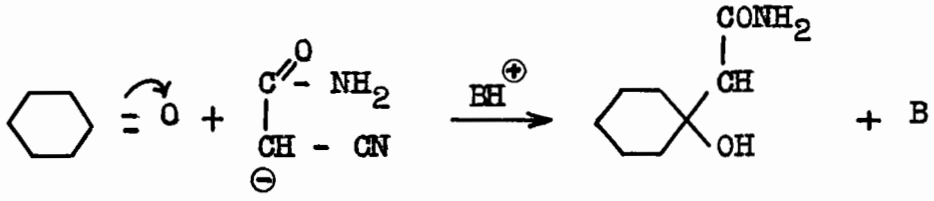
The resulting carbanion will be essentially planar because of the high degree of double bond character acquired by the bonds linking the methylene carbon, or in other terms, because of the large contribution of the resonance structures b and c to the resonance hybrid. The latter may best be described in terms of the mesomeric anion structure, d.



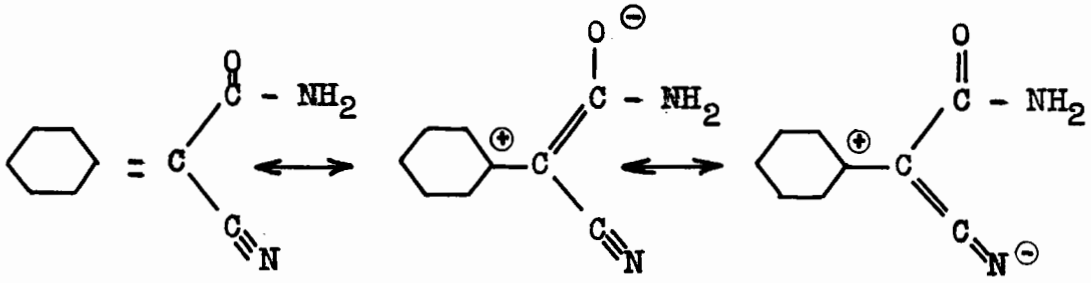


d)

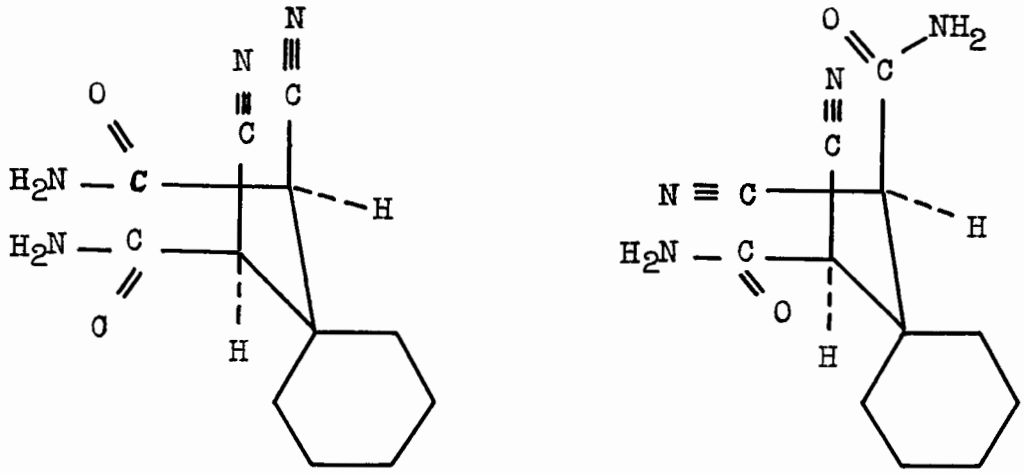
The attack of the carbanion on the molecule of cyclohexanone then proceeds by a mechanism similar to the Perkin or Knoevenagel reactions. The anion attaches itself to the positively charged carbonyl carbon, while the negatively charged oxygen attracts a proton.



In the next step a molecule of water is eliminated and the unsaturated compound is formed. Due to resonance, the substituted ring carbon will acquire a positive charge.



It thus becomes a target for attack by another molecule of cyanoacetamide (in the form of carbanion) with a mechanism essentially that of the Michael reaction. Because the carbanion is planar, either side of the plane is equally exposed to attack and hence from the ensuing reaction one would expect two products in equal quantities. Inspection of the corresponding molecular models does not reveal any steric preference for either of the two isomers

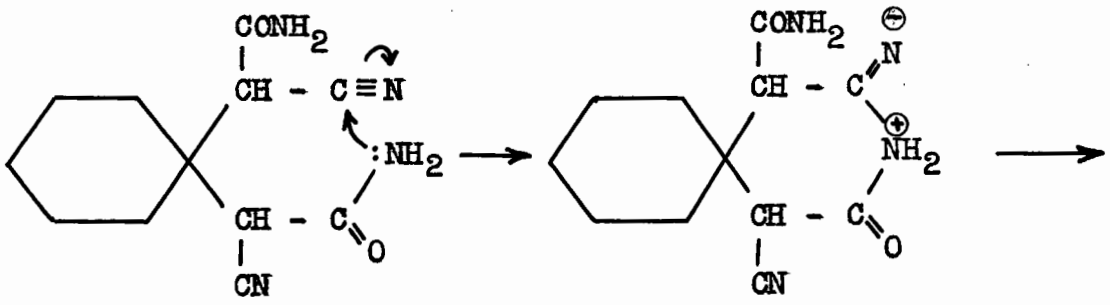


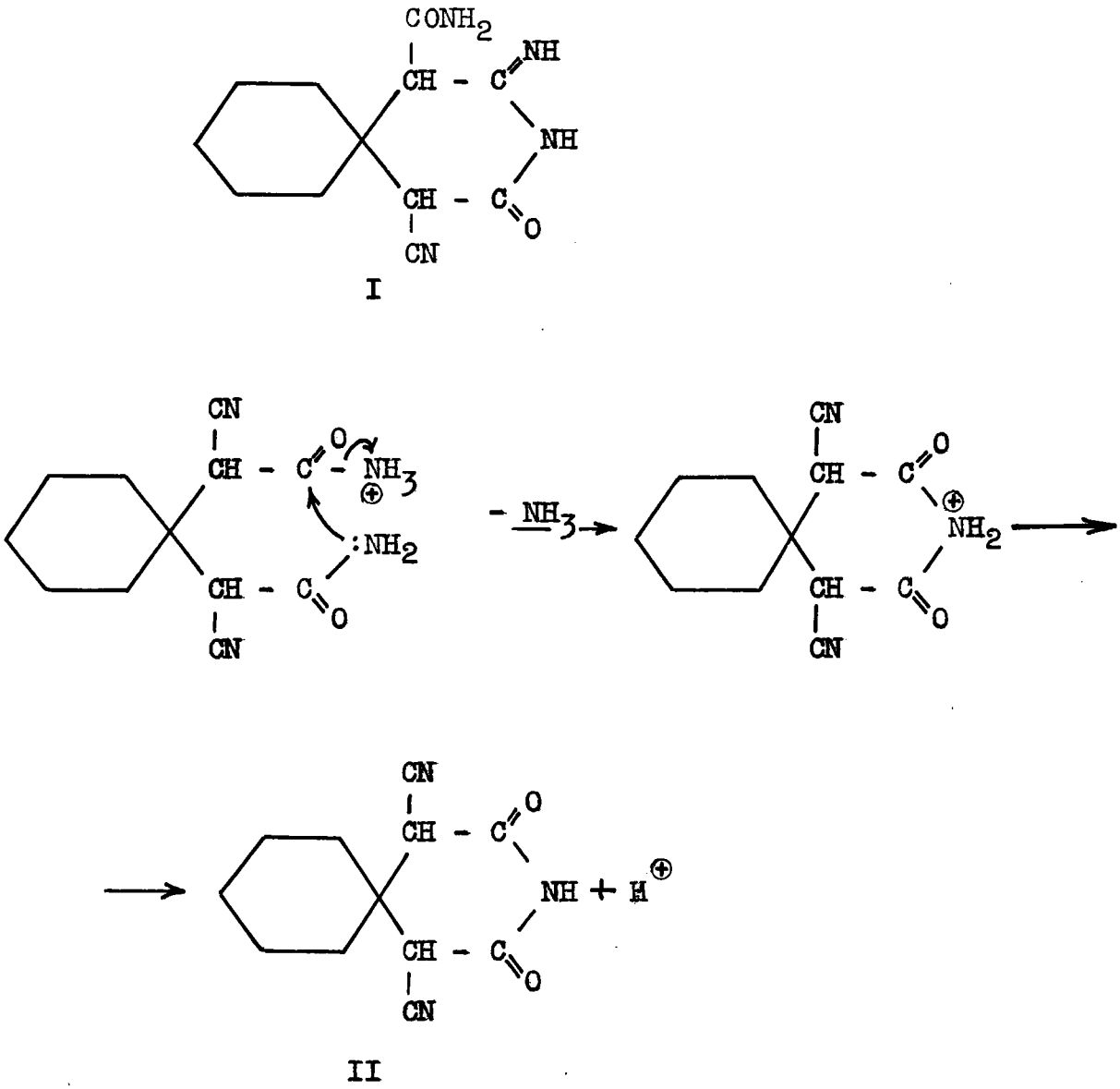
In the actual reaction, the yield of the dinitrile (II) was very much less than that of the imino imide (I) suggesting that they are formed by different mechanisms. This is supported by the observation that dinitrile (II) is the only product formed under Guareschi conditions of condensation, i.e., with a large excess of ammonia and at elevated temperature (12). Further evidence in favour of different mechanisms is the fact that the Guareschi reaction has lower steric requirements than the catalytic

reaction which occurs only when both carbons adjoining the ketonic carbonyl are at least secondary. If one of them is tertiary the catalytic reaction fails, although the product (dinitrile II) can still be obtained under Guareschi conditions.

Alkyl substitution of the carbonyl group has no effect on either the rate or yield of the condensation reaction. Acetone, acetaldehyde and cyclohexanone each forms the product with approximately the same yield and with equal facility. Theoretically, one would expect acetone to condense less readily than the other two ketones because of the decreased positive charge on the carbonyl carbon due to hyperconjugation.

The final step of the reaction involves the interaction of the terminal groups and leads to cyclization. The process may be regarded as a nucleophilic bimolecular substitution (SN_2)



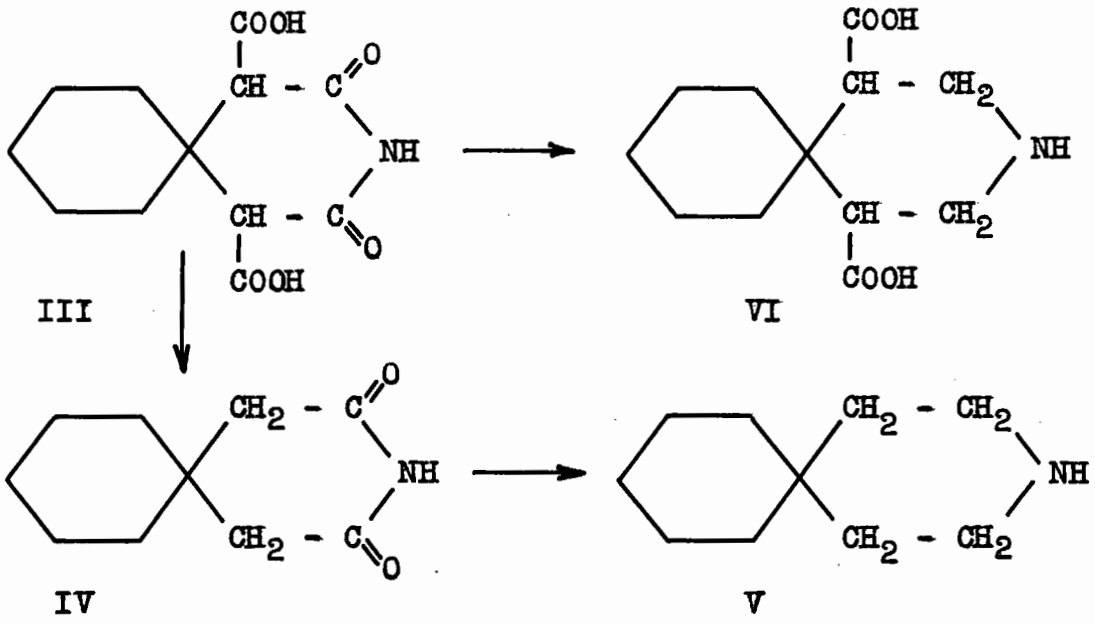


I

II

PREPARATION OF 3-AZASPIRO(5.5)HENDECANE-2, 4-DIOXO-1,5-DICARBOXYLIC ACID (III)

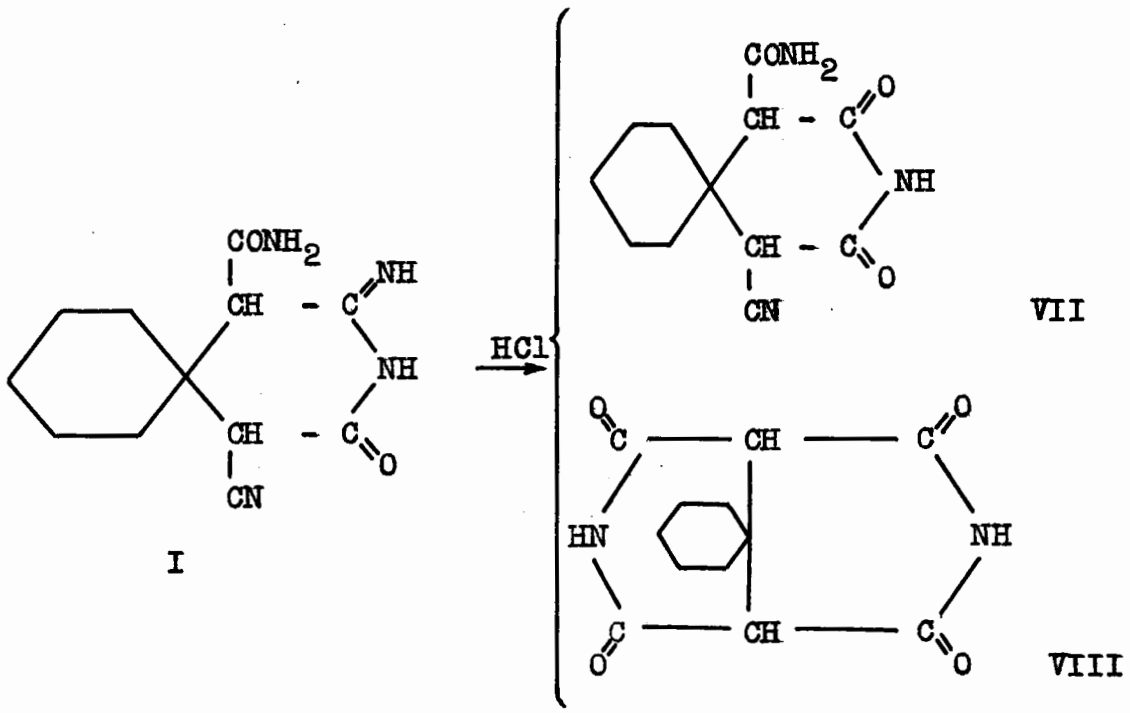
Preparation of this acid was of prime importance because of its expected, ready conversion to either 3-azaspiro(5.5)hendecane-1, 5-dicarboxylic acid (VI) or 3-azaspiro(5.5)hendecane (V).



Initial attempts to synthesize the acid involved the alkaline hydrolysis of 3-azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I, "imino imide") following the method of Thorpe (9). The yield was found to be very low and the product highly contaminated with resinous material. An improvement was sought by varying the concentration of potassium hydroxide between 5 and 40%. The time of hydrolysis was also varied but despite prolonged efforts no improvement was achieved. The only by-product identified was 3-azaspiro(5.5)hendecane-2, 4-dione (IV), apparently formed by decarboxylation of the acid.

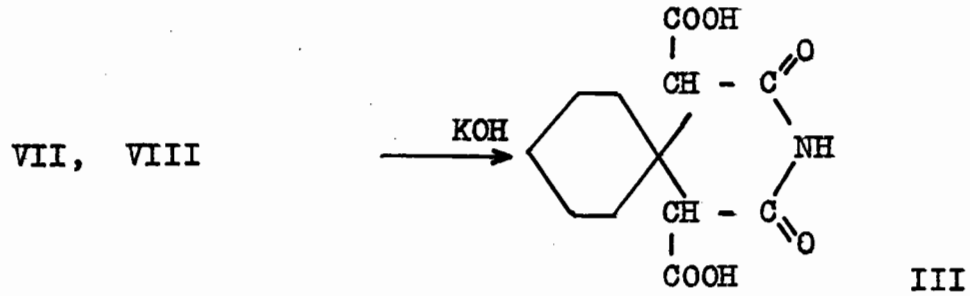
A satisfactory synthesis of the acid (III) was finally developed, starting with a different material. It was found that a mild acid hydrolysis of imino imide (I) yielded a

mixture of 3-azaspiro(5.5)hendecane-5-cyano-2, 4-dioxo-1-carboxamide (VII, "imido amide") and 2', 4', 6', 8'-tetroxo-spiro(cyclohexane-1, 9'-(2,7)-diazabicyclo(3.3.1)nonane) or "diimide" (VIII). This is in disagreement with Thorpe (9), who under similar conditions reported the formation of



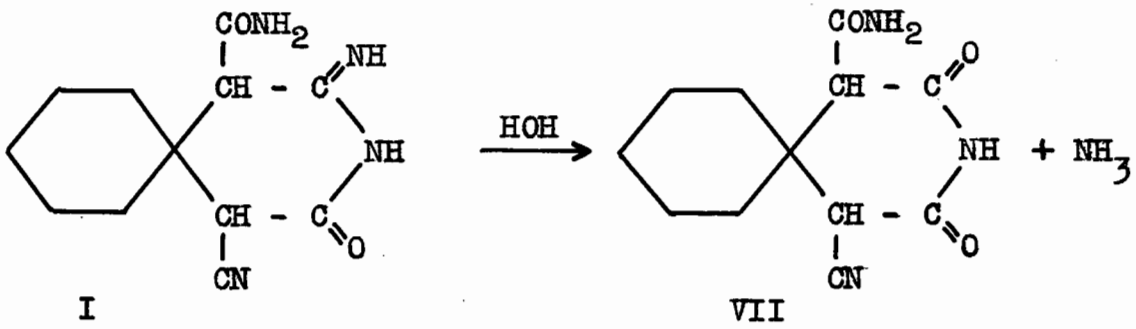
"imido amide", (VII) only. Formation of the diimide, (VIII) could not be avoided, as it was subsequently found that imino imide (I) cyclizes with remarkable ease under a variety of conditions. Since both imido amide and diimide yield 3-azaspiro(5.5)hendecane-2, 4-dioxo-1, 5-dicarboxylic acid (III) on alkaline hydrolysis the reaction was carried out without separating the two materials. The yield of the acid thus obtained was invariably good averaging 50% based on

imino imide (I).



III

It would appear that the low yield of the acid (III) from the alkaline hydrolysis of imino imide (I) was due to the instability of the imino imide ring; it was attacked before the imino group could be hydrolyzed, to produce the glutarimide ring. The stability of the latter ring towards

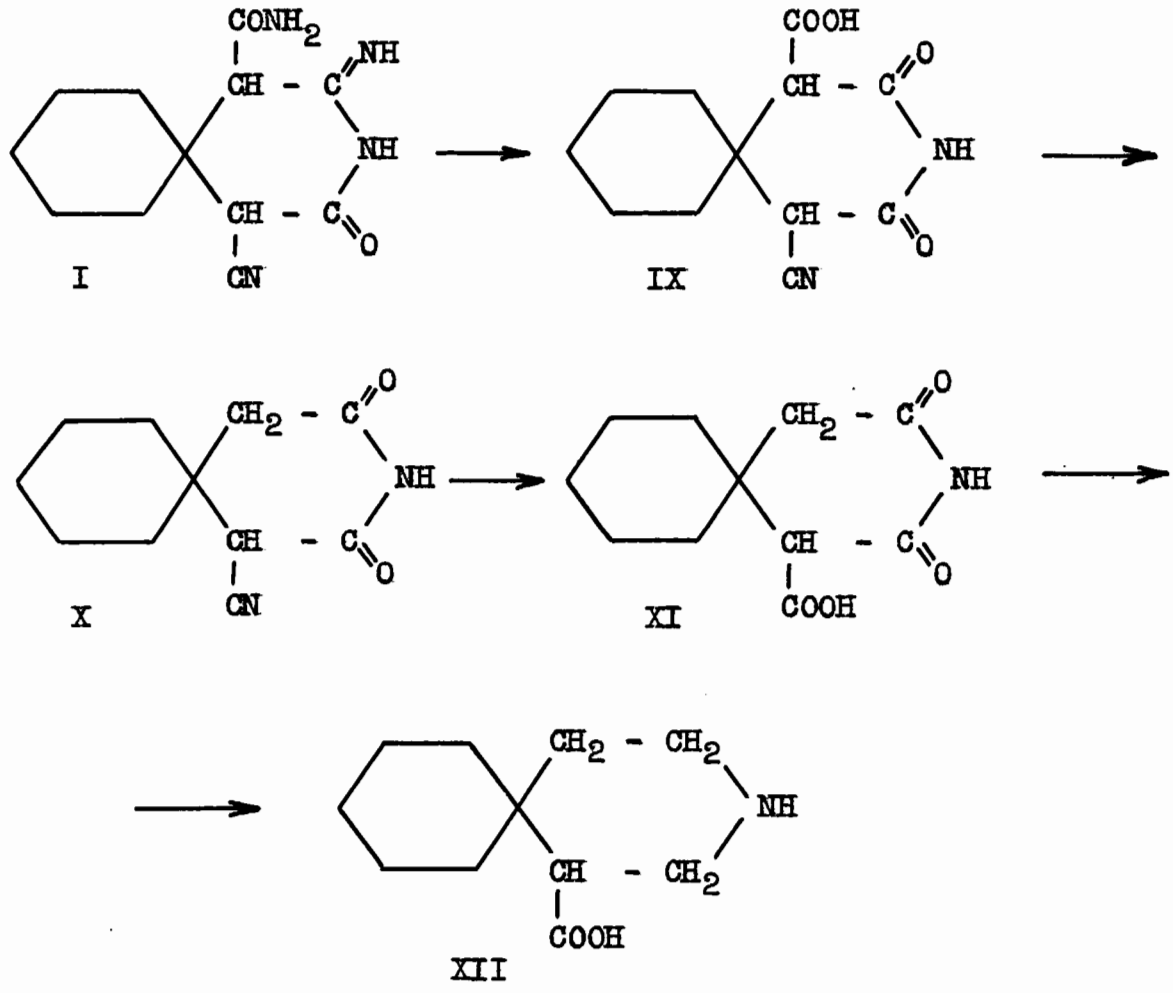


I VII

alkali hydroxides, even on prolonged boiling in aqueous solution, is probably responsible for the good yield of acid (III) in the new method.

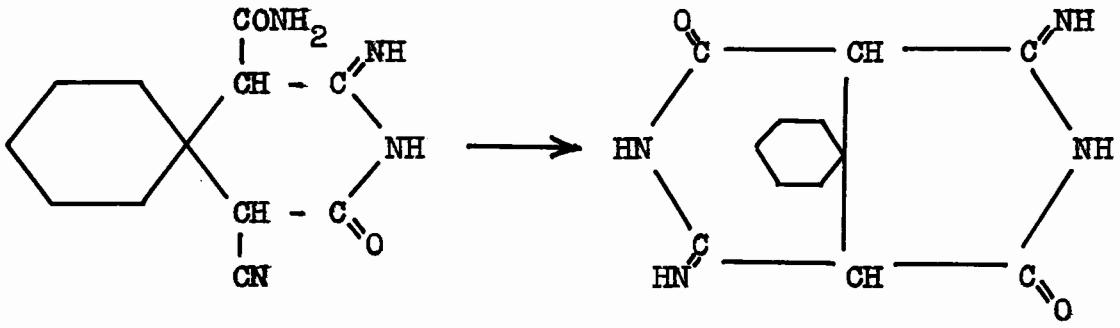
THE HYDROLYSIS OF "IMINO IMIDE" (I) IN NEUTRAL SOLUTION

In the present work a new type of hydrolysis of 3-azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I, "imino imide") was investigated as a method for the preparation of the monosubstituted 3-azaspiro(5.5)hendecane-2, 4-dione. This compound was subsequently used in the synthesis of 3-azaspiro(5.5)hendecane-1-carboxylic acid (XII).



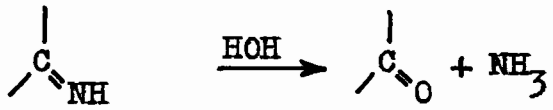
As mentioned previously (page 12), Thorpe (9) obtained 4,4-dimethylpiperidine-5-cyano-2,6-dione by either mild acid or neutral aqueous hydrolysis of 4,4-dimethylpiperidine-5-cyano-2-imino-6-oxo-3-carboxamide. Similar methods were employed in the present investigation, with entirely different results. The acid hydrolysis had to be abandoned because it yielded largely diimide (VIII). Other minor products identified included 3-azaspiro(5.5)hendecane-2,4-dione (IV), cyclohexane-1,1-diacetic acid and 3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV).

On the other hand, "neutral" hydrolysis of imino imide (I) was hampered by the much lower solubility of the compound compared to that of the 4,4-dimethylpiperidine-5-cyano-2-imino-6-oxo-3-carboxamide used by Thorpe. Neutral hydrolysis was finally carried out in a very large volume of water; the product, which separated from the solution after several hours of boiling, was found to be 2',6'-diimino-4',8'-dioxo-spiro(cyclohexane-1,9'-(2,7)-diazabicyclo(3.3.1)nonane), or "diimino diimide", (XIII) obtained in 60-70% yield. Thus the first step in the hydrolysis of imino imide (I) was cyclization, whereas in the similarly constituted "dimethyl derivative" the amide and imino groups were converted to carboxyl and carbonyl respectively, forming 4,4-dimethylpiperidine-5-cyano-2,6-dioxo-3-carboxylic acid.



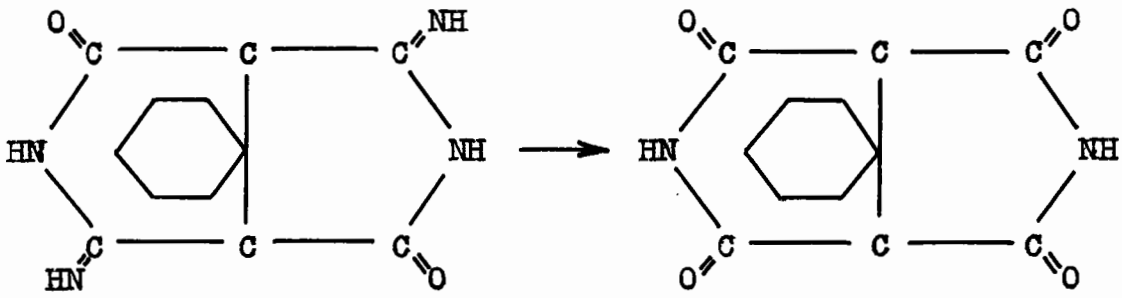
I XIII

Since the imino group is known to hydrolyze readily to the carbonyl group, it seemed doubtful that both imino groups were unaffected by prolonged boiling in water.



Ample evidence was therefore sought to confirm the structure. The melting point (298° - 300°d) coincided with the value given by Thorpe (303°d). The starting material (imino imide, I) also melts in the same region (305°d), but it differs from the diimino diimide (XIII) in its higher solubility and the presence of cyano group absorption band in its infrared spectrum. The substance was readily soluble in dilute hydrochloric acid, suggesting the presence of an imino group, known to possess mildly basic character. A crystalline solid which separated from the acid solution on prolonged standing

proved to be the diimide (VIII), apparently formed by the hydrolysis of the imino groups.



XIII VIII

The diimide (VIII) was formed immediately, when the solution of diimino diimide (XIII) in dilute hydrochloric acid was heated to the boiling point. The absence of the imide group, $O = \overset{|}{C} - NH - \overset{|}{C} = O$, in the molecule of diimino imide was indicated by infrared spectrum. The characteristic NH stretching absorption of imides at 3200 and 3100 $cm.^{-1}$, and the carbonyl absorption at 1725 $cm.^{-1}$, were absent. The two bands observed at 1675 and 1640 $cm.^{-1}$ correspond to C = O and C = N stretching vibrations. A strong, broad band at 1525 $cm.^{-1}$ not found in the spectra of glutarimides appears to be characteristic of the $HN = \overset{|}{C} - NH$ group, although its nature is not clearly understood.

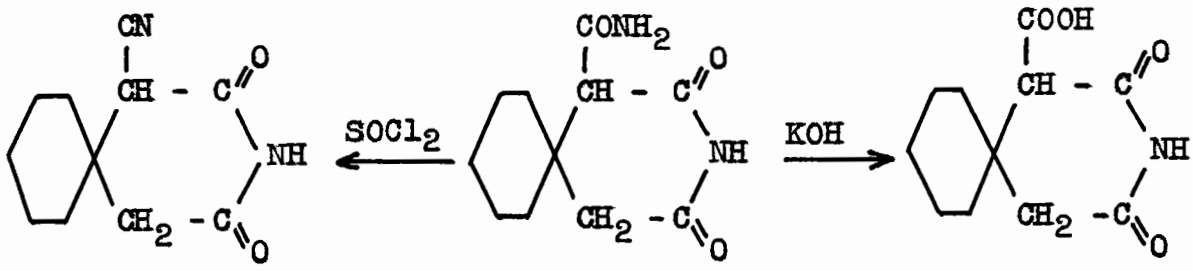
The final proof of the structure of the diimino imide (XIII) was secured by its independent preparation using the

method of Thorpe (9). The infrared spectra of the two compounds proved to be identical.

Knowledge of the structure of diimino diimide (XIII) facilitated the selection of conditions favouring the continuation of the hydrolysis. The aqueous solution of imino imide (I) was kept highly dilute to prevent the precipitation of the sparingly soluble diimino diimide (XIII). It was expected that prolonged boiling would hydrolyze the imino groups to form the diimide (VIII).

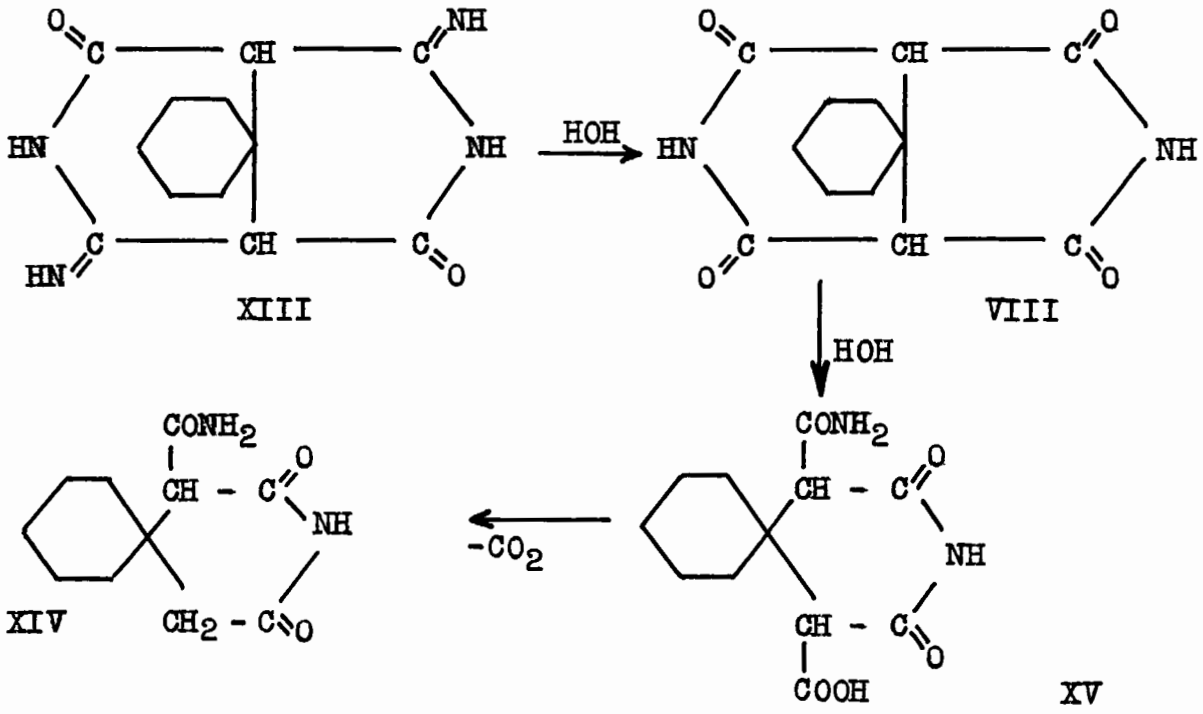
It was mentioned previously (page 15) that the condensed diglutarimide system is less stable than a monocyclic imide. Thus, the alkaline hydrolysis of diimide (VIII) opens one glutarimide ring, producing a dicarboxylic acid (VI, page 15). Similar ring opening was expected in the present hydrolysis, and after boiling for 24 hours a product which proved to be 3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV) was isolated. Its structure was confirmed by converting it to the corresponding acid (XI) by alkaline hydrolysis; the acid formed was not identical with the known 3-azaspiro(5.5)hendecane-2, 4-dioxo-1, 5-dicarboxylic acid (VI) but both formed the same product, 3-azaspiro(5.5)-hendecane-2, 4-dione (IV) on decarboxylation. Treatment of the carboxamide (XIV) with thionyl chloride yielded the

nitrile (X), the identity of which was confirmed by its infrared absorption which showed bands characteristic of the glutarimide ring and the cyano group.



X XIV XI

The final stage of the hydrolysis apparently proceeds through the formation of an intermediate (XV) which readily loses a carboxy group to form 3-azaspiro(5.5)hendecane-2, 4-dioxo-1-carboxamide (XIV). The failure to isolate this intermediate confirms its instability; this behaviour is similar



XIV XV

to that of related 3-azaspiro(5.5)hendecane-2,4-dioxo-mono- and dicarboxylic acids which decarboxylate with great facility.

The ultimate proof that the aqueous hydrolysis of 3-azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I, imino imide) involves the formation of diimino diimide (XIII) and diimide (VIII) as intermediates was furnished by starting with either of these compounds and conducting the hydrolysis under the conditions originally chosen for the imino imide (I). A yield of about 60% of 3-azaspiro(5.5)-hendecane-2,4-dioxo-1-carboxamide (XIV) was found in both cases.

Since the amide (XIV) is also converted by prolonged hydrolysis to 3-azaspiro(5.5)hendecane-2,4-dione (IV) the optimal yields are secured with the minimum hydrolysis time.

The failure of the acid hydrolysis of imino imide (I) to produce 3-azaspiro(5.5)hendecane-1-carboxamide (XIV) can now be explained. Unlike the action of water, the effect of boiling dilute mineral acid is to produce a rapid cyclization with hydrolysis of the imino groups, causing precipitation of the insoluble diimide (VIII) in bulk. Small quantities of 3-azaspiro(5.5)hendecane-2-4-dioxo-1-carboxamide (XIV), 3-azaspiro(5.5)hendecane-2,4-dione (IV), and cyclohexane-1,1-diacetic acid (page 62) are formed only from the hydro-

lysis of minute amounts of diimide (VIII) present in the solution.

In the aqueous hydrolysis of imino imide, cyclization, hydrolysis of imino groups, and ring reopening are all slow processes; if the rates of cyclization and formation of diimide (VIII) are slower than the rate of ring reopening, the reaction will proceed to completion without precipitation of the slightly soluble intermediates.

THE SYNTHESIS OF 3-AZASPIRO(5.5)HENDECANE-2, 4-DIOXO-1-CARBOXYLIC ACID (XI)

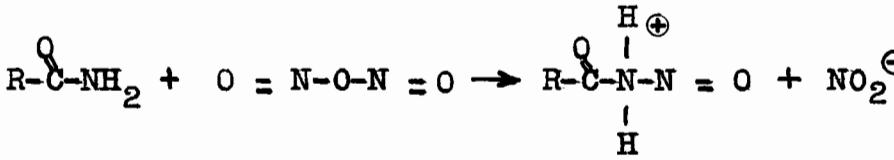
The synthesis was first tried with 3-azaspiro(5.5)-hendecane-2, 4-dioxo-1, 5-dicarboxylic acid (III) as a starting material. It was converted to the monosodium salt, with the expectation that decarboxylation would yield the sodium salt of the corresponding monocarboxylic acid (XI). Experiments showed, however, that the salt loses both carboxyl groups, even under very mild treatment such as heating the dry substance at 90°.

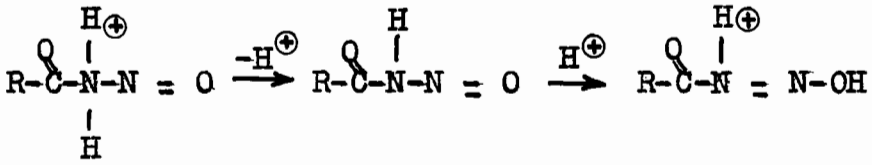
A simple synthesis of the monocarboxylic acid (XI) seemed possible following the successful preparation of 3-azaspiro(5.5)hendecane-2, 4-dioxo-1-carboxamide (XIV). For reasons unknown, however, direct alkaline hydrolysis of

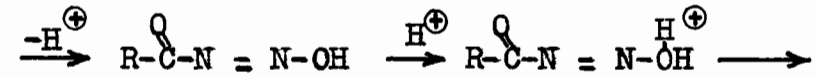
this compound yielded a mixture of products from which only minute amounts of 3-azaspiro(5.5)hendecane-2, 4-dioxo-1-carboxylic acid (XI) could be isolated. Initially, aqueous alkali hydroxides were used, and the concentration and hydrolysis time were varied over a considerable range. Other modifications of the experimental conditions included the replacement of water by methanol or ethanol in an attempt to moderate the reaction. The product obtained upon acidification of the solution was invariably an extremely viscous oil. Upon digesting with acetone a small quantity of solid acid could be isolated but its purification proved difficult as it readily decarboxylated in the solution at slightly elevated temperatures. When dissolved in aqueous alkali hydroxide and precipitated with mineral acid the compound reverted to an oil.

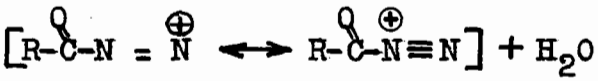
A satisfactory yield of 3-azaspiro(5.5)hendecane-2, 4-dioxo-1-carboxylic acid (XI) was first obtained by the action of sodium nitrite on a solution of 3-azaspiro(5.5)-hendecane-2, 4-dioxo-1-carboxamide (XIV) in concentrated sulphuric acid at 0°. The mechanism of the reaction is clearly one of aqueous deamination (68, 69) and may be presumed to proceed by the following steps:

$$2HNO_2 \rightleftharpoons 2H_2O + N_2O_3$$

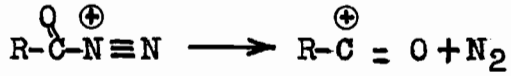




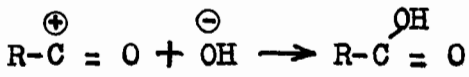




Since in aliphatic compounds the diazonium cation is not stabilized by resonance it decomposes immediately into nitrogen and carbonium cation



The carbonium cation forms the carboxylic acid by reaction with an hydroxyl anion



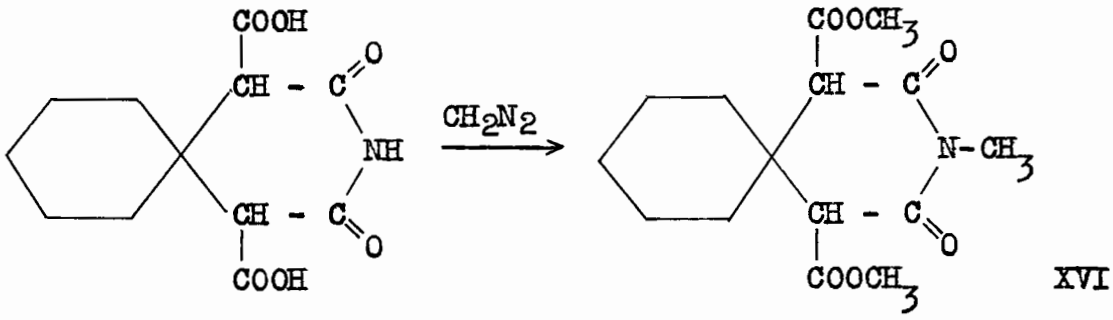
The success of the reaction was primarily due to the low temperature employed which minimized degradation or undesirable side reactions.

THE ESTERIFICATION OF 3-AZASPIRO(5.5)HENDECANE-2, 4-DIOXO-CARBOXYLIC ACIDS

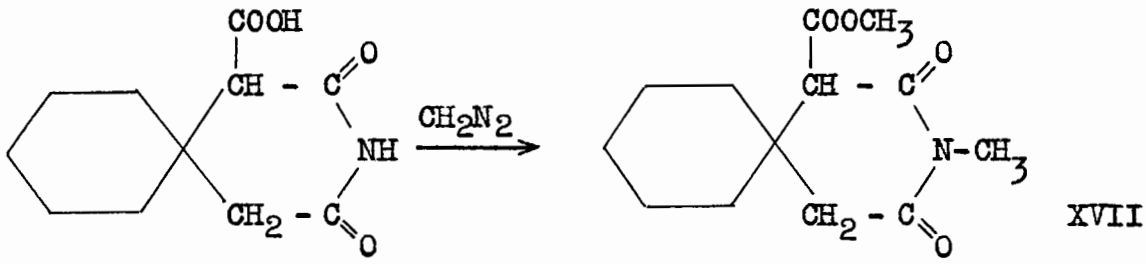
Conversion of 3-azaspiro(5.5)hendecane-2, 4-dioxo-carboxylic acids into the corresponding 3-azaspiro(5.5)-hendecane acids involved the reduction of imide carbonyl groups. Initial attempts of reduction with lithium aluminum hydride were unsuccessful, for several reasons. First, there was some evidence that the starting materials decomposed during the refluxing in ether solution; this was not entirely unexpected as the acids are known to be unstable. Second, both acids (III, XI) were rather sparingly soluble in ether; the Soxhlet extraction which had to be used required unusually long periods of refluxing. Finally, the reduction of free acids was generally not recommended in the literature (70) because of the formation of insoluble intermediates.

The problem was finally solved by converting the acids to esters which were both stable and readily soluble in organic solvents. The usual esterification methods proved ineffective. Treatment of an ethanolic solution of the acid with dry hydrogen chloride gave no reaction, while refluxing in the presence of concentrated sulphuric acid resulted in the complete decarboxylation of the acid. Esterification of

the acids was finally accomplished by treatment with diazomethane in ether solution, despite their insolubility in the solvent. Analysis of the product and its infrared spectrum indicated that a methyl group was also added to the imide nitrogen.



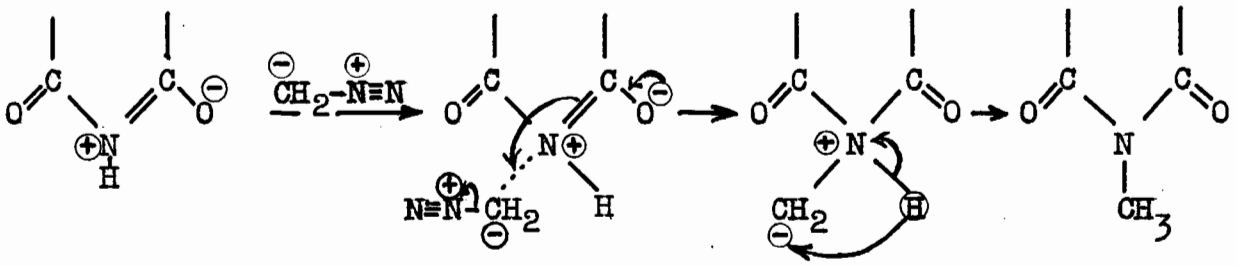
XVI



XVII

This behaviour parallels that of phthalimide and succinimide when methylated with diazomethane (70, 71). The mechanism of the methylation can be explained by assuming an increased importance of the resonance structures of glutarimide in which nitrogen carries a positive charge. This is a reasonable assumption in the presence of nucleophilic reagents. Attack by diazomethane would then proceed

through the formation of an ionic quaternary complex which could revert to covalency by an appropriate electron shift and the migration of a proton.

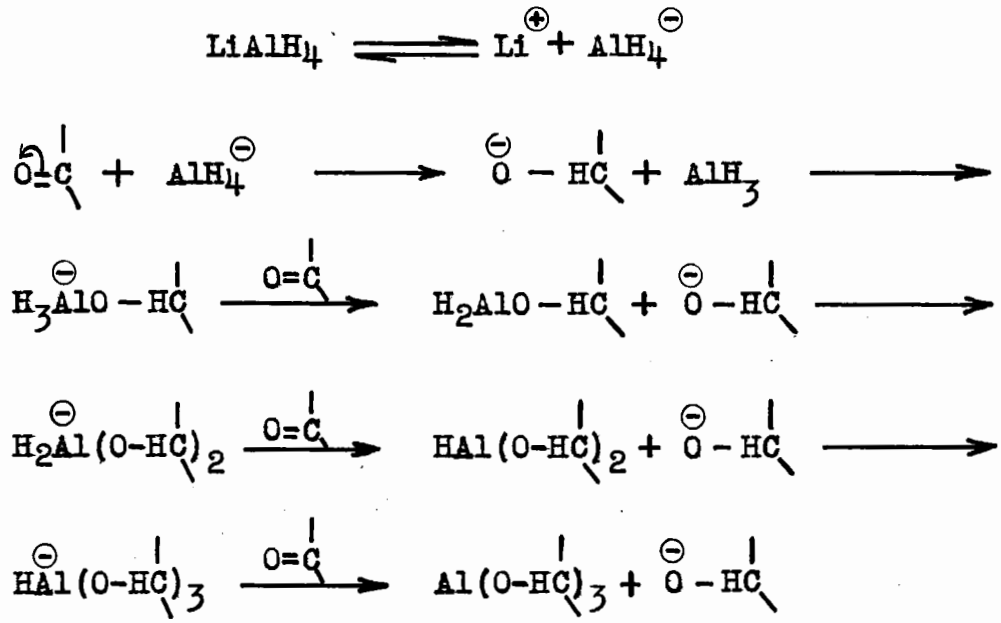


REDUCTION OF 3-AZASPIRO(5.5)HENDECANE-2,4-DIONES WITH LITHIUM ALUMINUM HYDRIDE

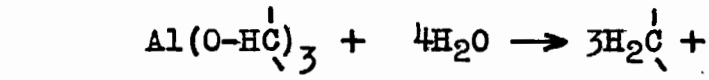
Lithium aluminum hydride was used without exception in all reductions involving the imide group. The reagent proved to be very convenient and gave consistently good yields. This result was somewhat surprising as imides are usually considered very difficult to reduce (72). In no case could any side products be detected. For sparingly soluble imides tetrahydrofuran proved to be a more satisfactory solvent than ether. The only difficulty was encountered in the isolation of the products. The aluminum hydroxide formed by the hydrolysis of the hydride was found to occlude appreciable quantities of the product. Initially it was hoped that a good recovery of the product could be attained by dissolving the aluminum hydroxide in concentrated

aqueous sodium hydroxide and extracting the solution with organic solvent. This treatment, however, produced a mixture containing large quantities of undissolved solid and hence the intended extraction with organic solvent could not be performed. An alternative method consisting of repeated digestion of aluminum hydroxide with ether and filtering was rather involved and failed to extract the product completely. The procedure finally adopted, which gave excellent recovery, was the extraction of the solids in a Soxhlet apparatus.

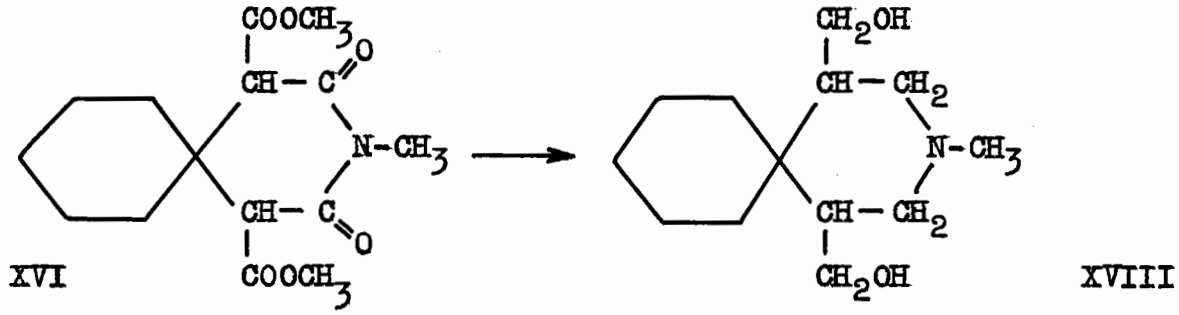
The mechanism of lithium aluminum hydride reduction can be regarded as a nucleophilic bimolecular substitution (73). The attacking nucleophilic agent is the aluminum hydride anion. In the case of imides the reduction probably involves the following sequence of displacement reactions.



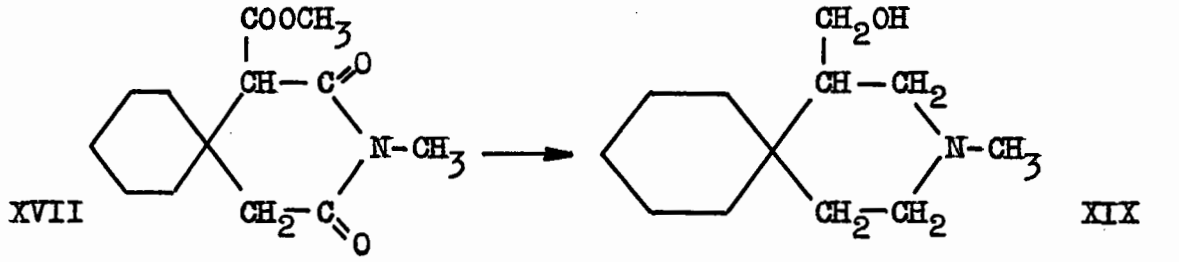
The final product is formed by hydrolysis.



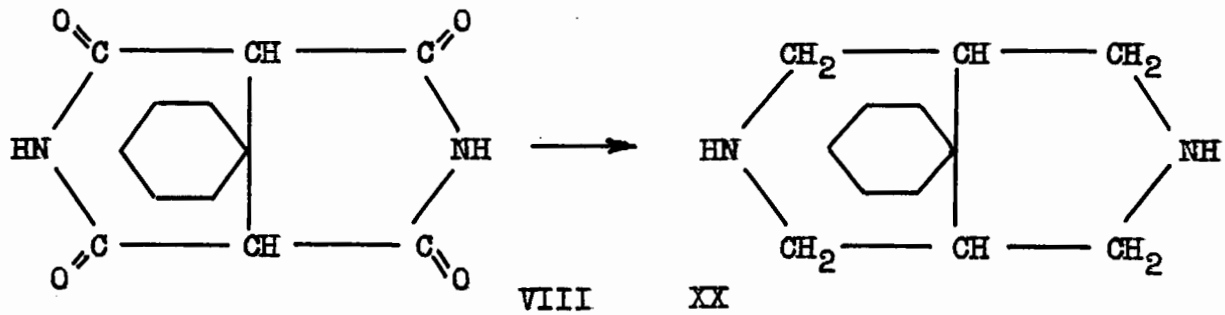
The following reductions were effected by lithium aluminum hydride:



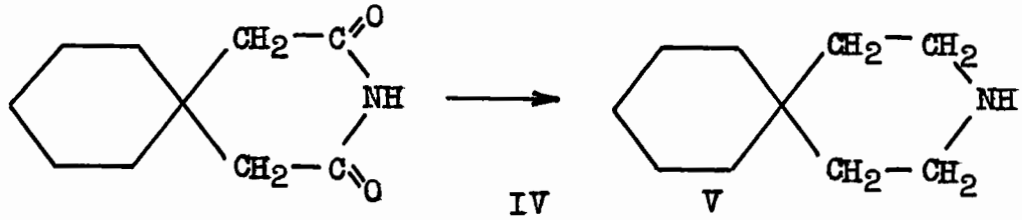
XVI XVIII



XVII XIX



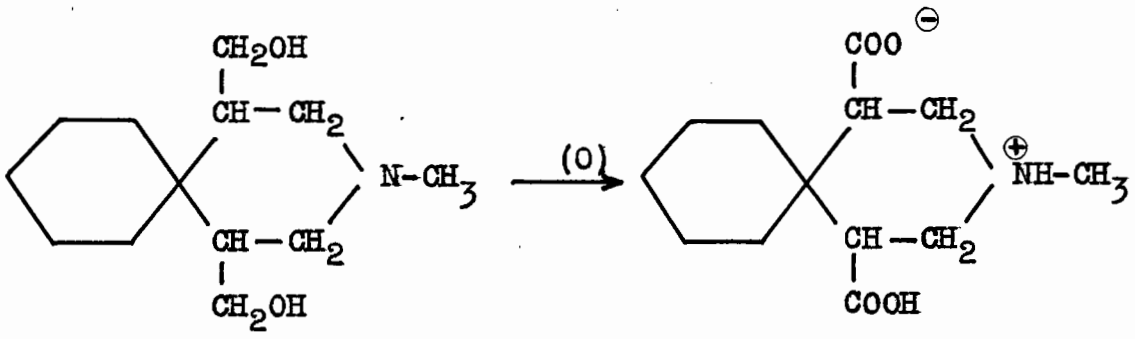
VIII XX



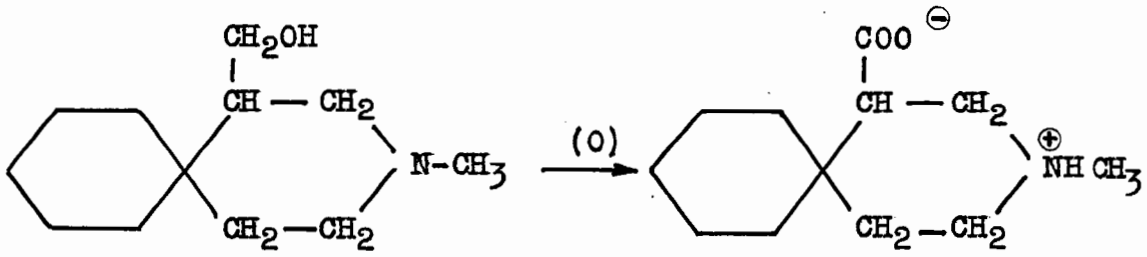
IV V

3-AZASPIRO(5.5)HENDECANE-CARBOXYLIC ACIDS

Reduction of the esters of 3-azaspiro(5.5)hendecane-2,4-dioxo-carboxylic acids (XVI, XVII) resulted in the formation of 3-azaspiro(5.5)hendecane-hydroxy-methyls (XVIII, XIX). To obtain the corresponding acids (XXI, XXII) it was necessary to reoxidize the hydroxymethyl groups. Although a variety of reagents will oxidize primary alcohols to the



XVIII XXI



XIX XXII

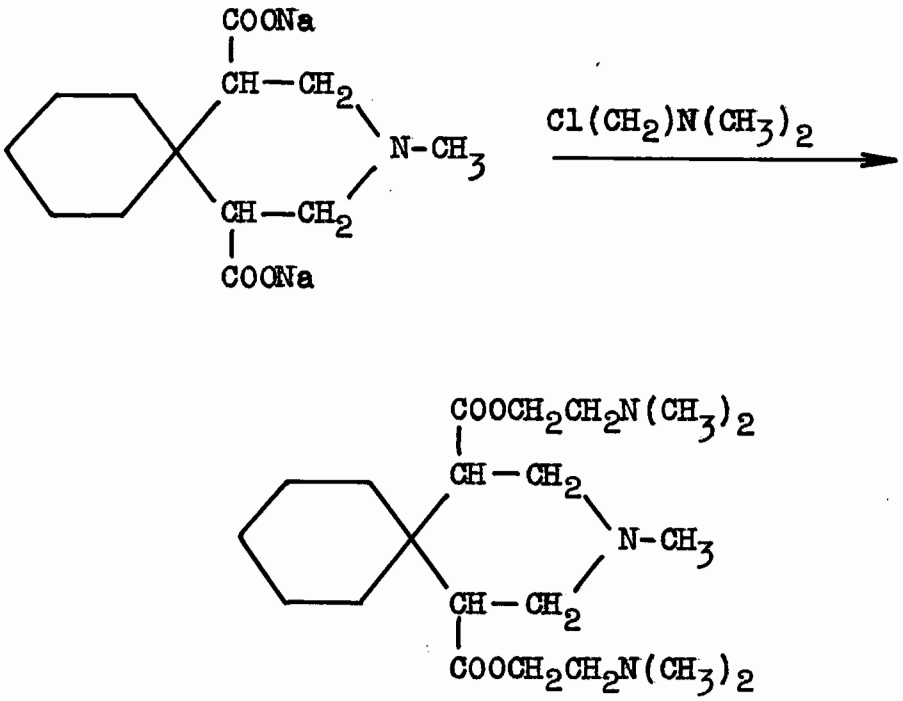
corresponding carboxylic acids most of them could not be used because they attack the piperidine ring. For example, ring opening occurs readily with neutral or alkaline

permanganate yielding a variety of products (74, 75). The action of bromine at elevated temperatures leads to partial bromination and aromatization (76). With hydrogen peroxide piperidine-N-oxide is formed (77); prolonged action produces δ-aminovaleraldehyde (78).

The oxidizing agent finally chosen was chromic oxide in dilute sulphuric acid solution. Although it is said to be inert to the piperidine ring (79), it apparently did cause some degradation of 3-methyl-3-azaspiro(5.5)hendecane-1,5-dihydroxymethyl (XVIII), since the yield of the dicarboxylic acid never exceeded 50%.

The relation between the structure of certain piperidine derivatives and their physiological activity has been already discussed (page 28). It was pointed out that in a series of 1-alkyl-4-arylpiperidine-4-carboxylates the high activity of certain members is maintained when the aryl is substituted by a cyclohexyl group. 3-Methyl-3-azaspiro(5.5)-hendecane-carboxylic acids bear some structural resemblance to this series and it seemed possible that they might possess some activity. 2-Dimethylaminoethyl 3-methyl-3-azaspiro(5.5)-hendecane-1,5-dicarboxylate (XXIII) was prepared but preliminary testing of the hydrochloride indicated no activity.

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (XXI) was not converted to the corresponding anhydride

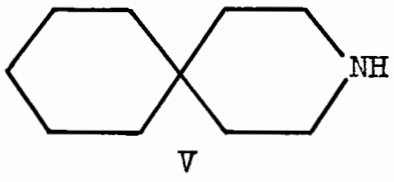


XXIII

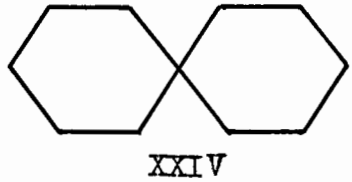
by prolonged treatment with acetic anhydride. A crystalline material isolated from the reaction mixture showed infrared absorption in the region 1825 - 1775 cm.$^{-1}$ associated with the carbonyl stretching vibration of anhydrides. The product appeared to be an amine salt of acetic acid. The failure to form anhydride indicates that the acid has trans-configuration and hence should be capable of resolution into optical isomers. Attempts to resolve it via strychnine salt, however, were not successful. It is possible that this failure was due to a very low specific rotation of the optical isomers. Attempts to resolve 3-methyl-3-azaspiro(5.5)hendecane-1 carboxylic acid (XXII) were also unsuccessful. In the first attempts d-tartaric acid was used but was soon abandoned in favour of d-camphorsulphonic acid.

AN ATTEMPTED SYNTHESIS OF SPIRO(5.5)HENDECANE (XXIV)

In the investigation of the characteristic infrared absorption of spiranes it seemed desirable to compare the spectra of compounds as simple as possible to avoid complexities arising from substitution. The synthesis of one such simple spirane, 3-azaspiro(5.5)hendecane has already been described (page 75). The synthesis of several other simple related spiranes was undertaken. These were 3-oxa- and 3-thiaspiro(5.5)hendecanes (XXV, XXVI) and spiro (5.5)-hendecane (XXIV). The latter, the simplest of the series, is of particular interest.

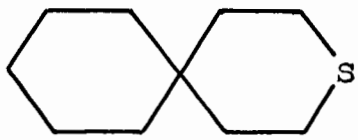


V



XXIV

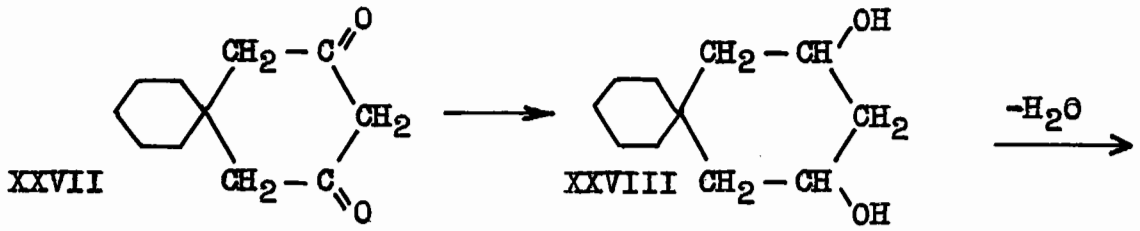
XXV



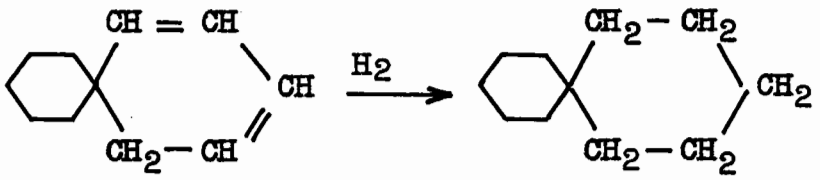
XXVI

The first attempts to synthesize spiro(5.5)hendecane (XXIV) started with the preparation of spiro(5.5)hendecane-2,4-dione (XXVII) by the method of Norris and Thorpe (page 21). The conversion of dione (XXVII) to spiro(5.5)hendecane as described by the two authors involved a number of inefficient reactions and tedious purification. If the dione

could be reduced to the corresponding saturated diol (XXVIII) the synthesis of spiro(5.5)hendecane would be greatly simplified as shown below.

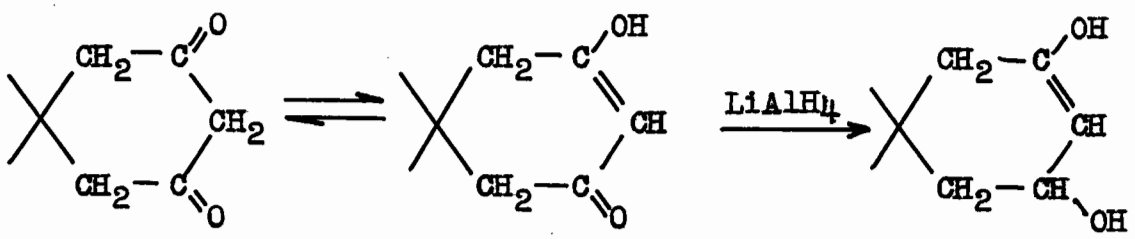


XXVII XXVIII



XXIV

The dione was reduced with lithium aluminum hydride; the infrared spectrum of the product indicated that it was an unsaturated diol (XXIX). The reaction apparently proceeded in the following manner:

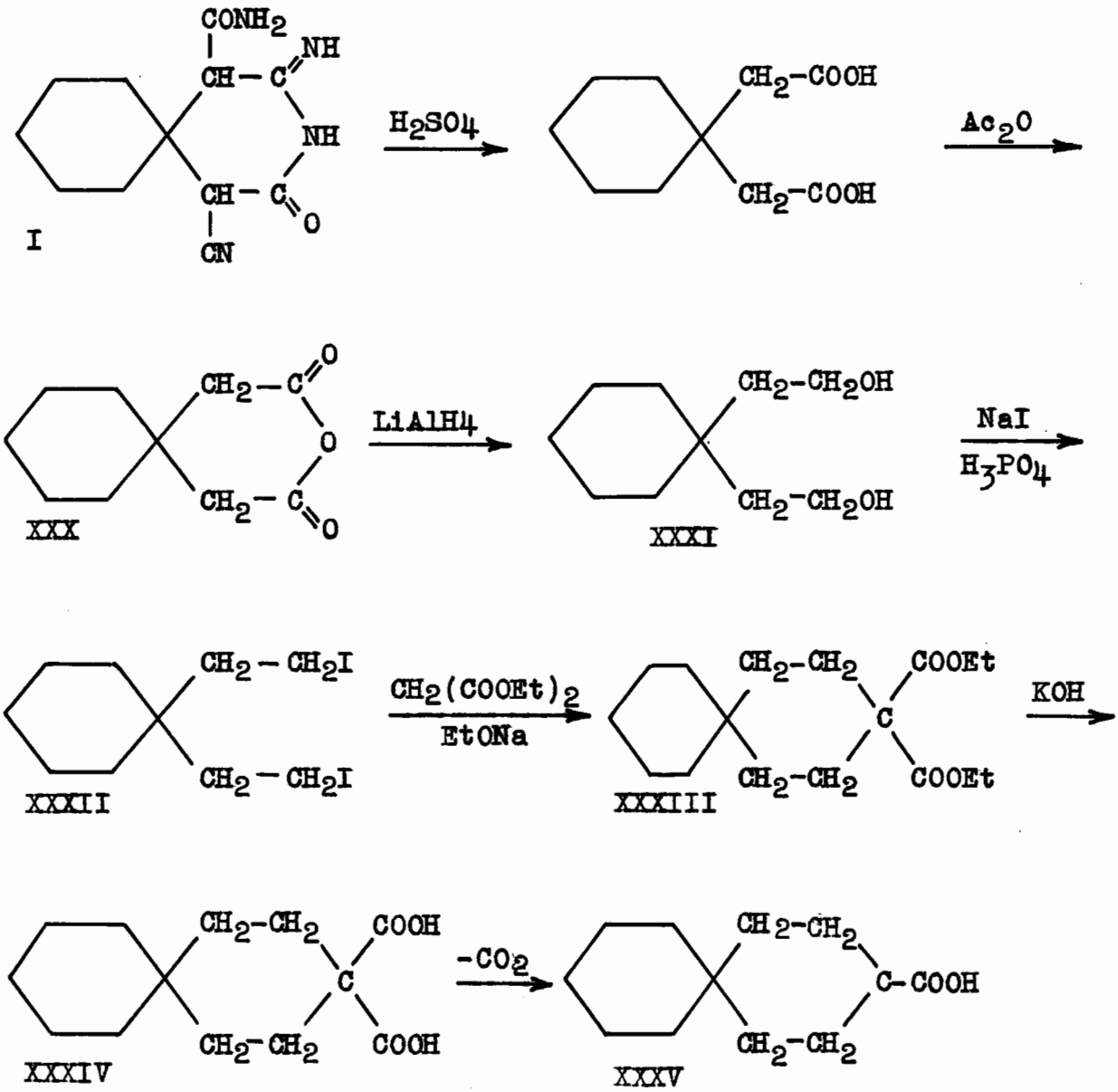


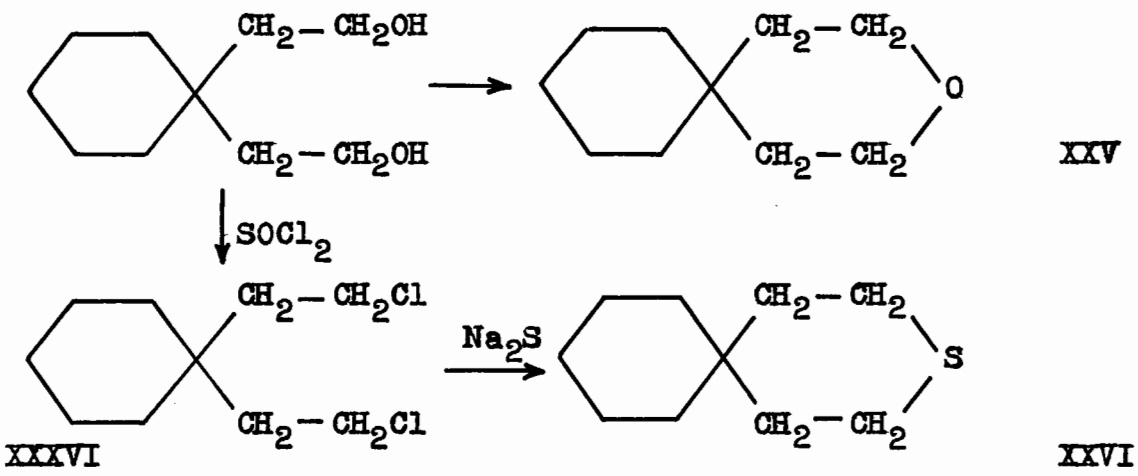
XXIX

Since no convenient method to convert the unsaturated diol into spiro(5.5)hendecane was available, the synthesis

via the dione (XXVII) was abondoned.

A more promising method was subsequently developed. Although a relatively large number of steps was involved it had the advantage of being adaptable to the synthesis of related spiranes such as 3-oxa- and 3-thiaspiro(5.5)hendecanes. The reaction scheme is illustrated below.





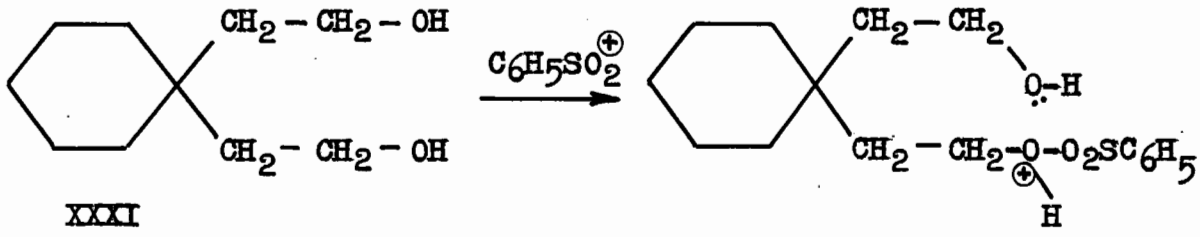
XXXVI XXV XXVI

All the reactions proceeded with good yields and purification of the products presented no difficulties. In the malonic ester condensation cyclohexane-1,1-di(2-ethyl chloride) (XXXVII) was used originally but the yield was low. The recovery of the condensation product using the corresponding diiodide (XXXII) averaged 60%. Direct conversion of spiro(5.5)hendecane-3-carboxylic acid (XXXV) to spiro-(5.5)hendecane (XXIV) was unsuccessful, as the compound proved rather resistant to decarboxylation. After several hours of boiling in quinaldine in the presence of copper powder as a catalyst the compound was recovered unchanged. The Hunsdiecker reaction (80) was also tried, without success. The cause of the failure could not be determined due to the limitations of time.

THE MECHANISM OF THE FORMATION OF 3-OXASPIRO(5.5)HENDECANE (XXV)

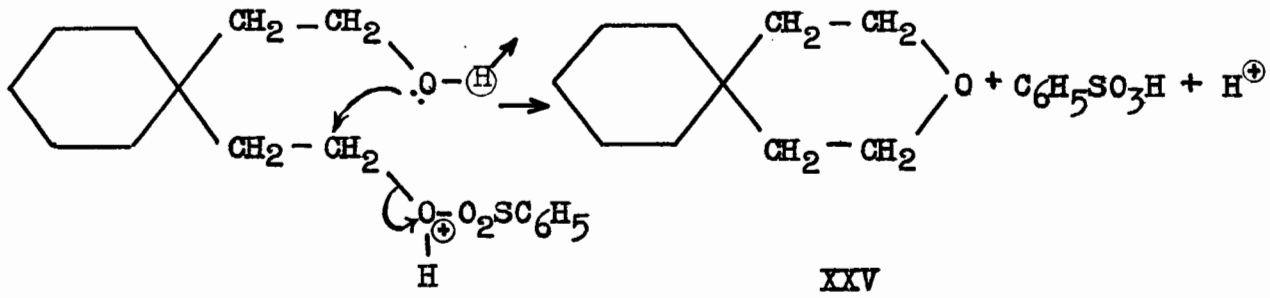
In the cyclization of cyclohexane-1,1-di(2-ethanol) (XXXI) by treatment with benzenesulphonyl chloride the initial step is probably the attack of the benzenesulphonium cation on the hydroxyl oxygen, forming an oxonium compound.

$$C_6H_5SO_2Cl \rightleftharpoons C_6H_5SO_2^{\oplus} + Cl^{\ominus}$$



XXXI

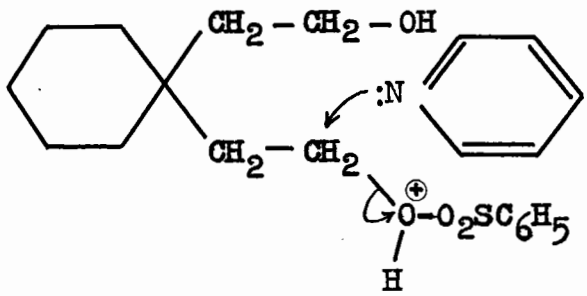
In a subsequent step the unshared pair of electrons of the second hydroxyl oxygen interacts with the carbon atom on the side remote from the carbon oxygen bond.



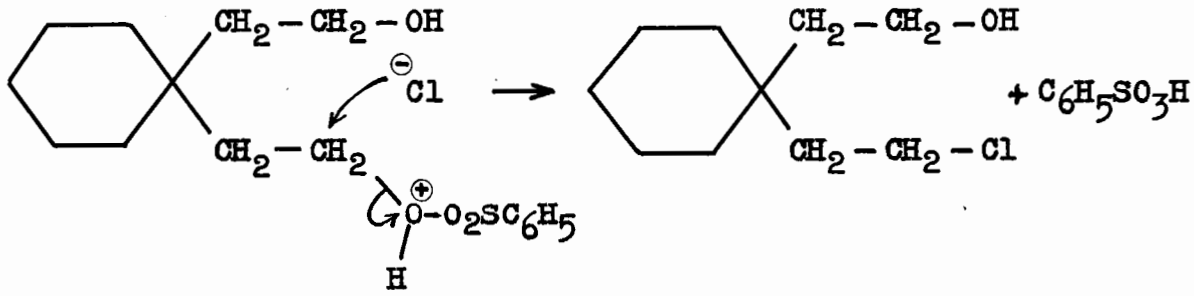
XXV

Simultaneously there is the loosening of C-O$^{\oplus}$ bond, leading to its rupture, with the formation of the new C-O bond in a single

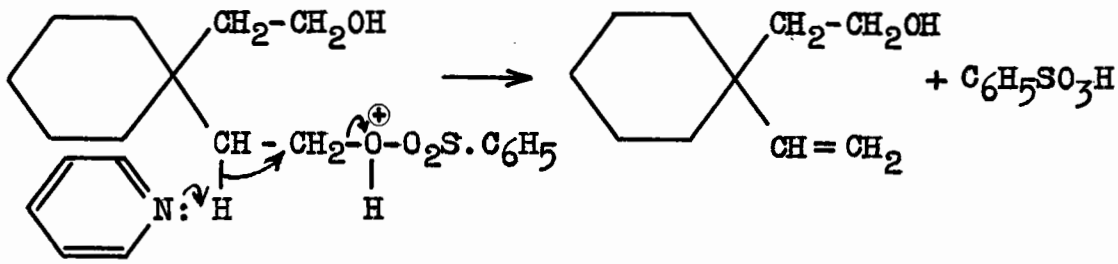
concerted process. This may be regarded as nucleophilic aliphatic substitution proceeding by an S_N2 mechanism. The origin of side products such as a quaternary complex or an organic halide mentioned by Reynolds and Kenyon (page 24) now becomes clear. They are formed by the reactions of other nucleophilic agents such as pyridine or chloride ion which compete for the electrophilic center



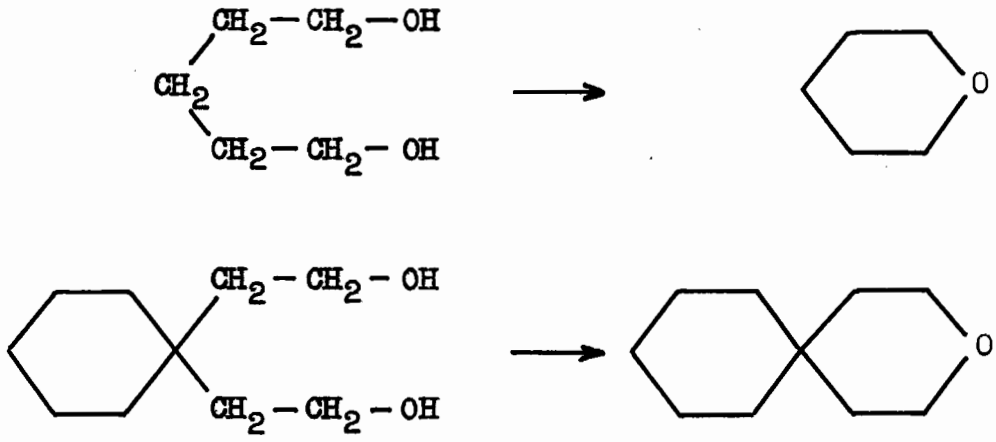
→ quaternary complex



On the other hand, an unsaturated product (ibid.) may be formed by an olefinic elimination reaction with an E2 mechanism.

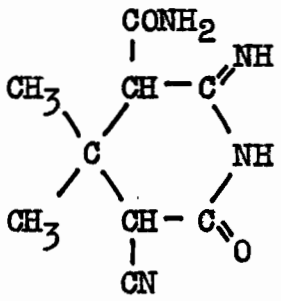


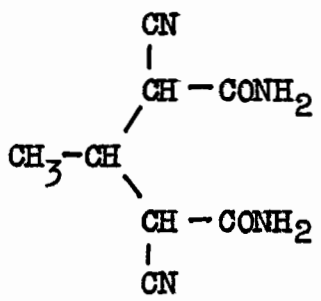
The yield of 3-oxaspiro(5.5)hendecane in the present synthesis was much higher (75%) than that of the structurally similar tetrahydropyran reported by Reynolds and Kenyon (page 25). There is little doubt that the yield of the former could be considerably improved since the reaction was only tried once. The greater ease of ring closure must be attributed to chain substitution



It was shown by Ingold (81) that gem-dimethyl substitution of chains is particularly effective in facilitating ring closure. Another example of this, the condensation products of acetone (XXVII) and acetaldehyde (XXVIII) with cyanoacetamide has already been discussed (page 20).

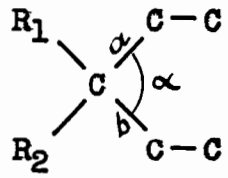
XXXVII





XXXVIII

Ingold showed that if the bond angle, α, external to two groups R_1 and R_2 was a function of the size of those groups it was possible to account for the behaviour observed in certain ring closure reactions.

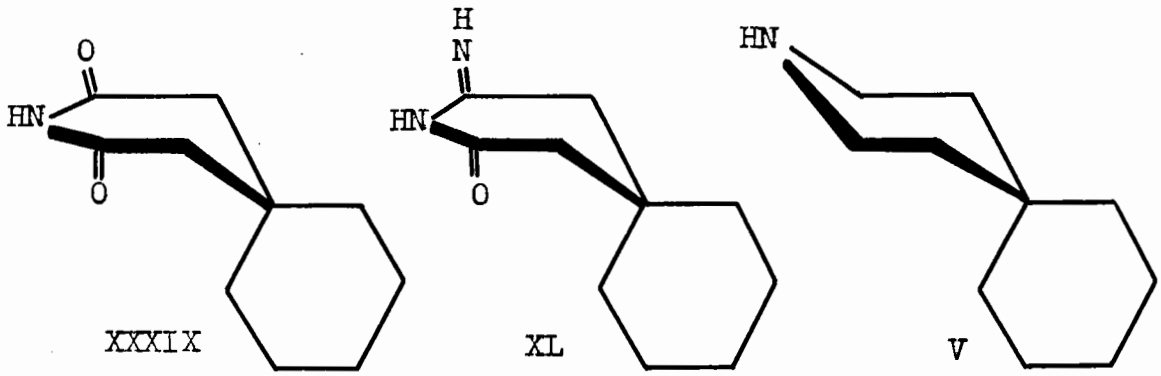


Ring closure also appears to be influenced by a steric factor. If the rotation about bonds a and b is restricted by the R groups, the statistical probability of ring closure is increased by the enforced orientation of the chain ends (82).

CERTAIN ASPECTS OF THE STEREOCHEMISTRY OF 3-AZASPIRO(5.5) HENDECANES

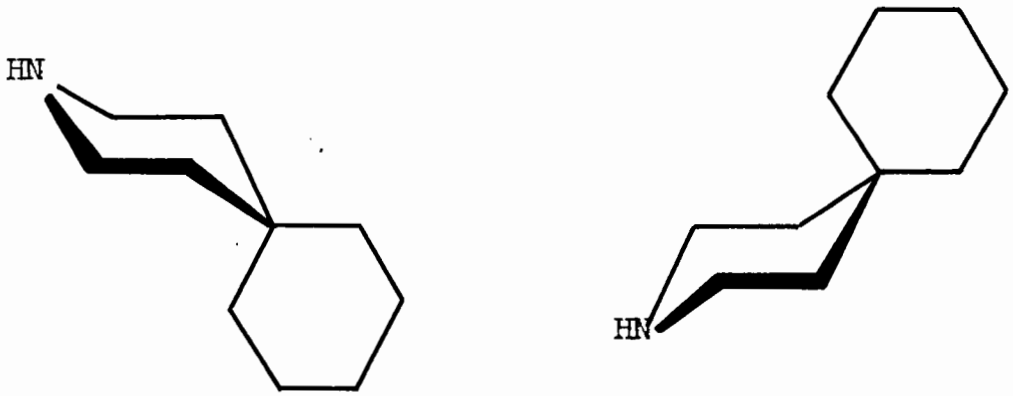
The two constituent rings of 3-azaspiro(5.5)hendecanes are mutually perpendicular. According to modern ideas, the cyclohexane ring exists in a chair form. The same form is also assumed by piperidine, pentamethylene oxide and pentamethylene sulphide in 3-aza-, 3-oxa- and 3-thiaspiro(5.5)-hendecanes. On the other hand, the glutarimide and glutarimino imide rings present in 3-azaspiro(5.5)hendecane-2,4-diones (XXXIX) and -2-imino-4-oxo- compounds (XL) are

essentially planar due to the trigonal (sp^2) hybridization of the bonds adjoining C=O or C=N groups.



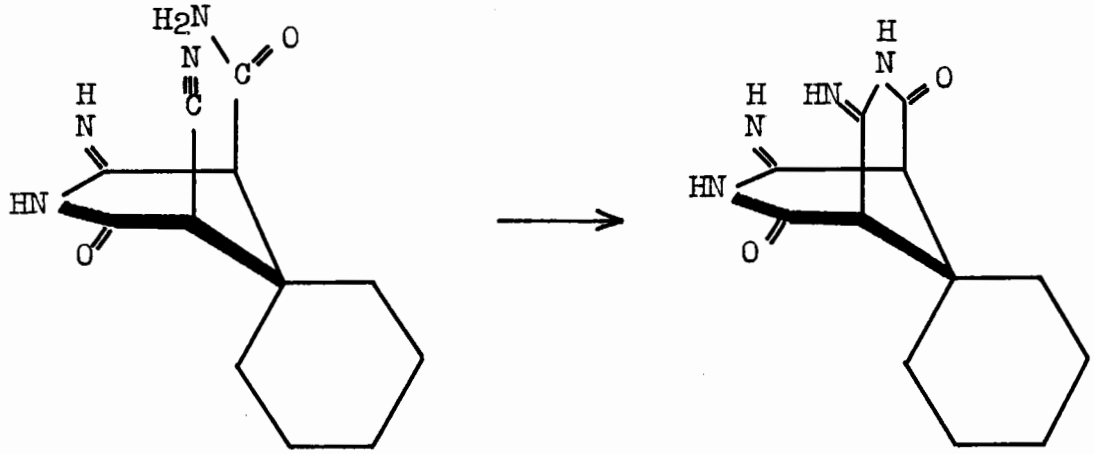
XXXIX XL V

Because the two rings are joined at one point only, there is complete freedom of ring conversion, i.e. changing from one chair conformation to the opposite one. But, as the molecular models show, such conversion will produce only two non-superimposable structures irrespective of the presence of a heteroatom in position 3.

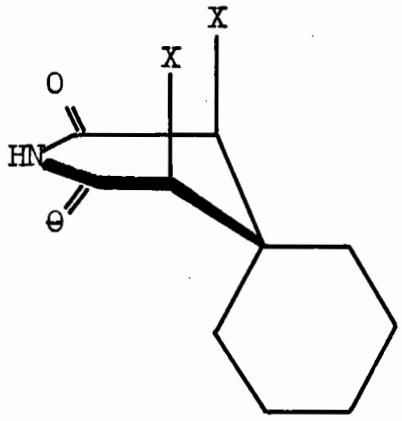


Because the activation energy of ring conversion is very low (2 - 3 kcal./mole) it is impossible to separate the two conformations. On the other hand, there is some evidence

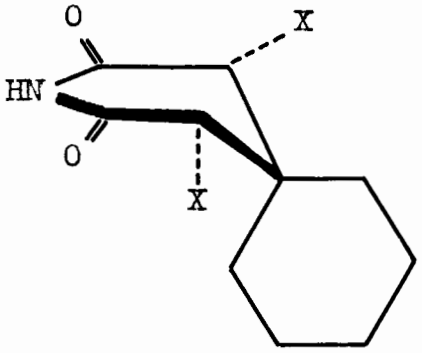
suggesting that 1,5-disubstitution in 3-azaspiro(5.5)hendecane-2,4-diones tends to stabilize diaxial rather than diequatorial conformation. 1,5-Disubstituted 3-azaspiro-(5.5)hendecane-2,4-diones obtained by either the Thorpe or Guareschi reaction have cis configuration, which is indicated by the great ease of 1,5-ring closure.



The cis isomer can exist in two conformations, diaxial and diequatorial.



cis, diaxial



cis, diequatorial

Inspection of the molecular models shows that both conformations are sterically hindered, although the steric compression in the diaxial conformation appears to be considerably greater than the hindrance caused by the single group approaching the cyclohexane ring in the diequatorial conformation. However, another factor may affect the stability of the diequatorial conformation (cis). The carbonyl groups in positions 2 and 4 have their dipole moments in the same plane and pointing approximately in the same direction as, for example, the 1,5-diequatorial cyano groups. The strength of this interaction is largely a matter of speculation, but there is some evidence suggesting that it may be significant. The reduction of 3-azaspiro(5.5)-hendecane-2,4-dioxo-1,5-dicarboxylic acid yields the corresponding 3-azaspiro(5.5)hendecane acid which, unlike the former, does not form an anhydride and hence must have trans-configuration;since none of the reactions involved could reasonably produce inversion, it may be inferred that the inversion at one asymmetric center was a direct consequence of the reduction of the imide carbonyl groups. The latter are probably enforcing cis configuration in 1,5-disubstituted 3-azaspiro(5.5)hendecane-2,4-diones, presumably due to polar effects which oppose the diequatorial conformation. More conclusive evidence for the diaxial

conformation of cis-1,5-disubstituted 3-azaspiro(5.5)hendecane-2,4-diones is provided by infrared spectra (page 99).

The trans configuration (axial, equatorial) is apparently the more stable one in 3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid, since spontaneous inversion to form the trans isomer occurs upon the reduction of the corresponding 2,4-dioxo-acid (cis). Although in unsubstituted 3,5-piperidinedicarboxylic acids cis (diequatorial) is the more stable configuration, it would be hindered in the corresponding 4,4-dialkyl derivatives which are sterically equivalent to 3-azaspiro(5.5)hendecane-1,5-dicarboxylic acids. However, it is interesting to note that trans-cyclohexane-1,3-dicarboxylic acid was found to be more stable than the cis isomer (diequatorial) although this represents a conformational anomaly (83).

INFRARED SPECTRA

a) The Spectra of Glutarimides

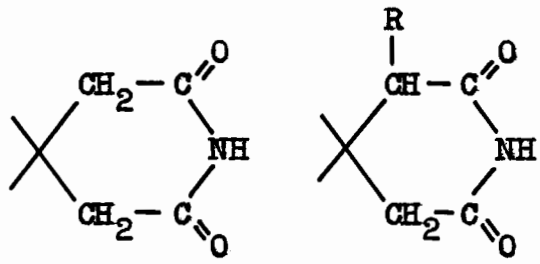
In the course of present investigation, the infrared spectra of 13 compounds containing the glutarimide ring, including that of unsubstituted glutarimide, have been recorded. The compounds and the relevant absorption bands are listed in Table I. For the purpose of discussing the

TABLE I

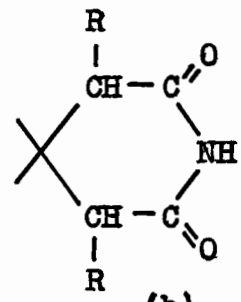
N-H and C=O Stretching Frequencies of Glutarimides

"Unsubstituted and monosubstituted" glutarimides				
Piperidine-2,6-dione (glutarimide)	3220 vb	3120	1700 vb	1665 vb
4,4-Dimethylpiperidine-2,6-dione	3200 b	3090	1720	1685
3-Azaspiro(5.5)hendecane-2,4-dione (IV)	3190 vb	3090	1720	1685
3-Azaspiro(5.5)hendecane-1-cyano-2,4-dione (X)	3180 vb	3080	1720	1685 vb
3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV)	3200 vb	3110	1720	1675
3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylic acid (XI)	3180 b	3080 b	1725 vb	1680 vb
Methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylate (XVII)	-	-	1730	1670
"Disubstituted" glutarimides				
4,4-Dimethylpiperidine-3,5-dicyano-2,6-dione	3220	3120	1740	1715
2, 4, 6, 8-Tetroxo-9,9-dimethyl-3,7-diazabicyclo(3.3.1)-nonane (XLI)	3210 vb	3100	1720 vb	1700 vb
3-Azaspiro(5.5)hendecane-1,5-dicyano-2,4-dione (II)	3205	3110	1725 vb	-
3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid (III)	3200 vb	3100	1705 vb	-
3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid anhydride (XLII)	3200 b	3100	1737	1705
2',4',6',8'-Tetroxo-spiro(cyclohexane-1,9'-(2,7)-diazabicyclo(3.3.1)nonane) ("diimide") VIII)	3220 b	3100	1750	1710
Succinimide (53)	3140	3050	1770	1690

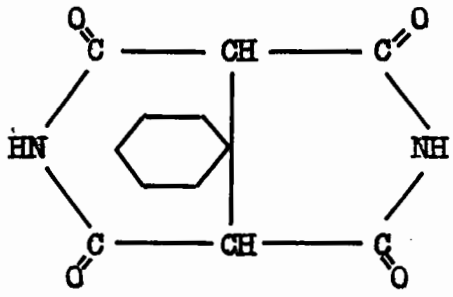
infrared spectra, they have been divided into two groups: a) "unsubstituted and monosubstituted" and b) "disubstituted" glutarimides (R represented the following groups: CN, $CONH_2$, COOH, $COOCH_3$). The bicyclic compounds (VIII, XLI, XLII) are, of course, considered as "disubstituted" glutarimides.



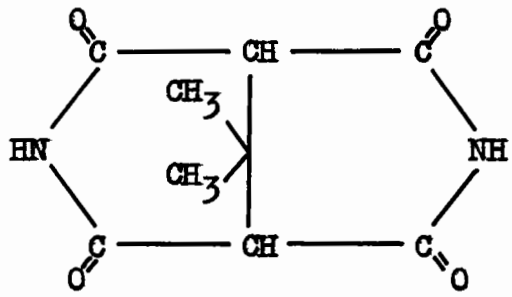
(a)



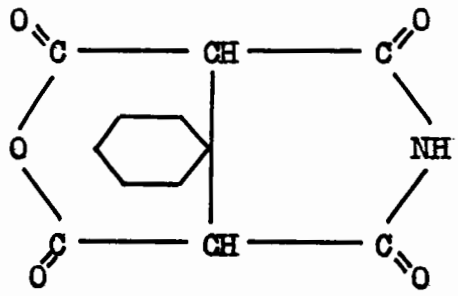
(b)



VIII



XLI



XLII

The spectra established clearly that N-H stretching vibrations occur in two frequency regions, 3200 and 3100 $cm.^{-1}$. The two

Fig. 1

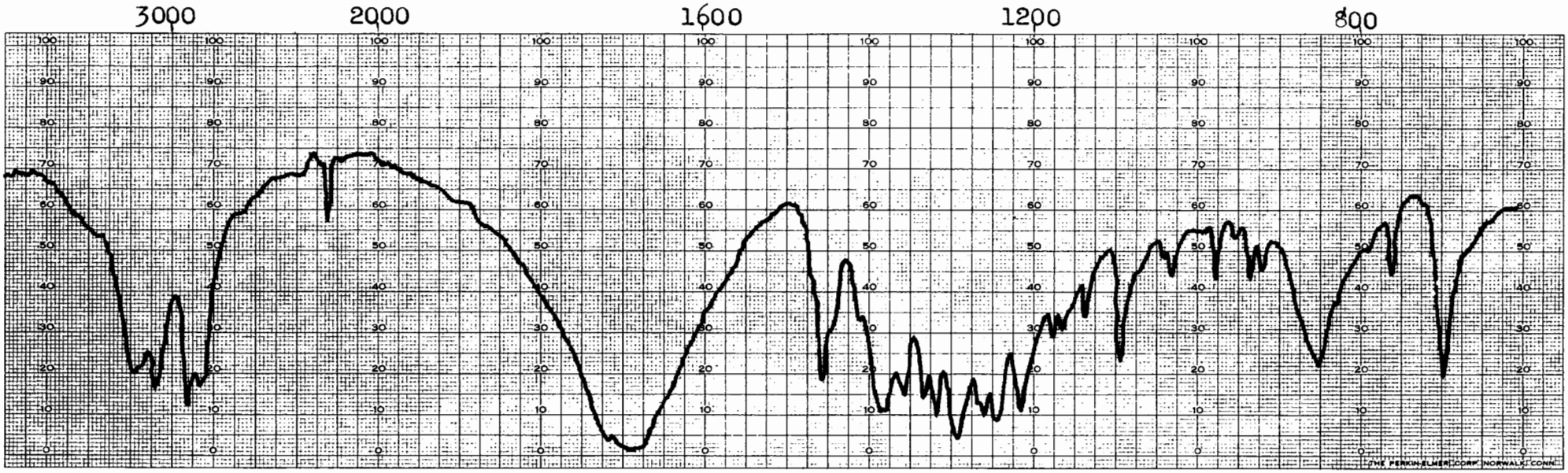
Infrared Absorption Spectra of:

3-Azaspiro(5.5)hendecane-1-cyano-2,4-dione (X)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV)

Wave Numbers in $cm.^{-1}$

X



XIV

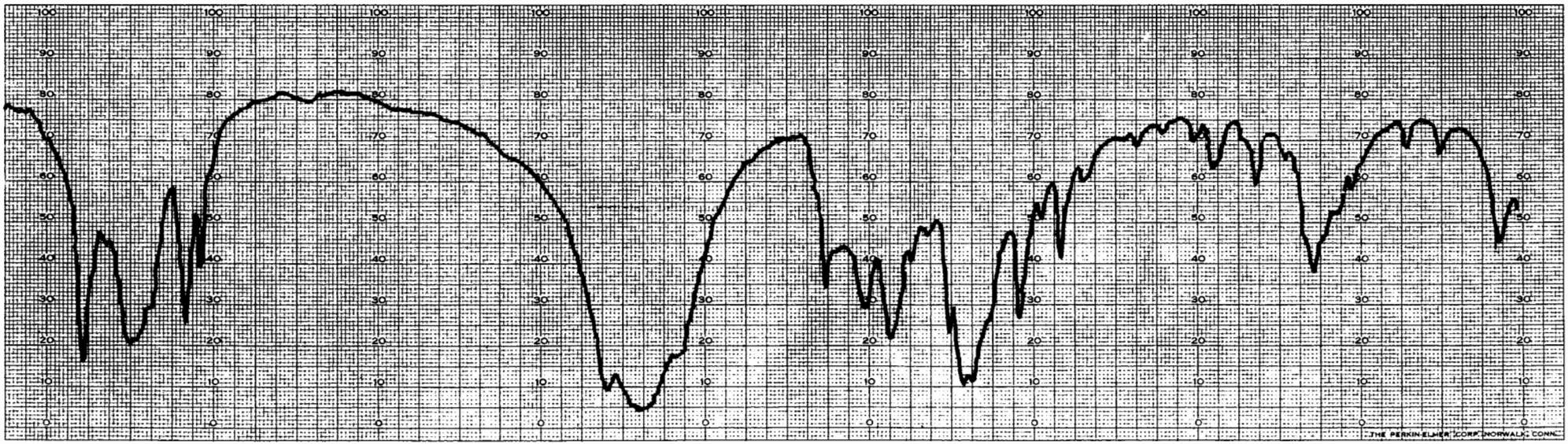


Fig. 2

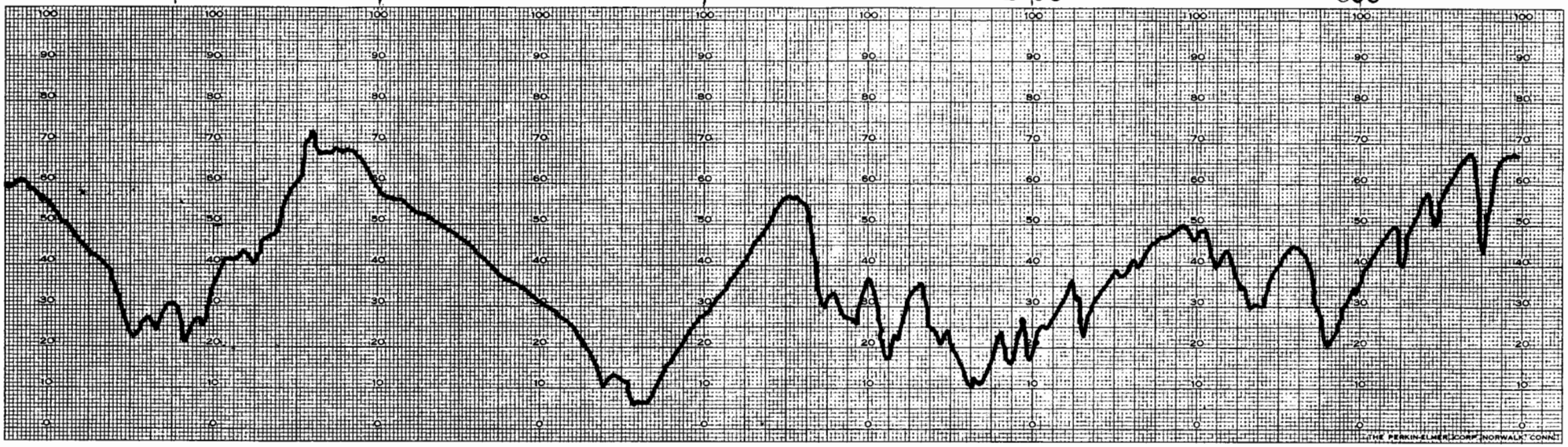
Infrared Absorption Spectra of:

3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylic acid (XI)

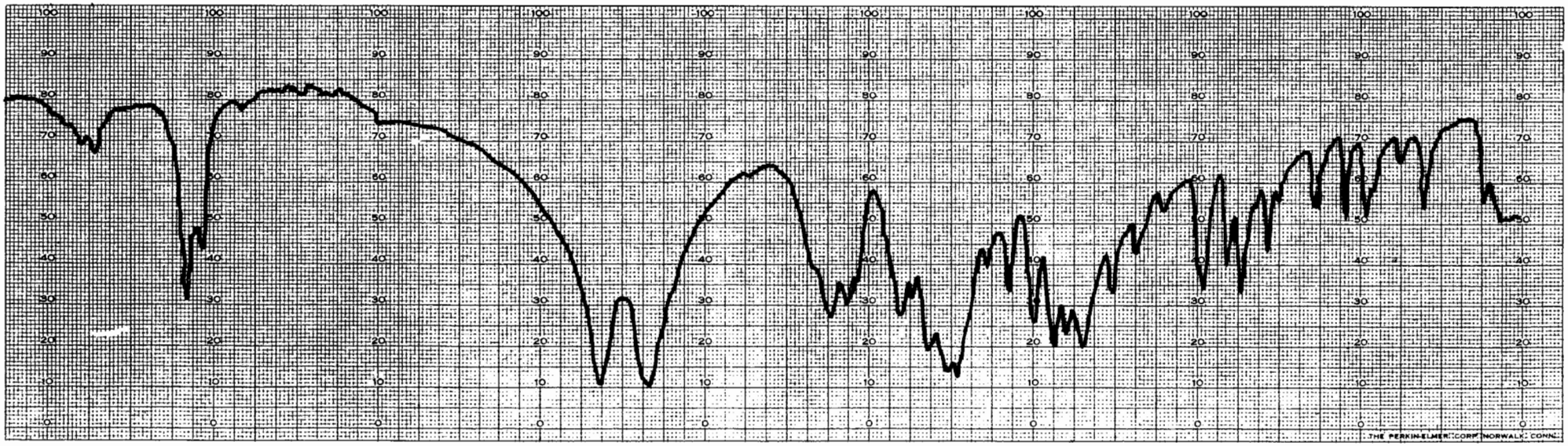
Methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylate (XVII)

Wave Numbers in $cm.^{-1}$

XI



XVII



bands provide an excellent means of identifying glutarimide rings. They are clearly separated from the N-H stretching bands of primary amides as shown in the spectrum of 3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV, Fig. 1). Similarly the stretching band of acyclic secondary amides at 3400 - 3300 cm.$^{-1}$ can be readily distinguished. The proof that the bands at 3200 and 3100 cm.$^{-1}$ represent N-H stretching vibrations was provided by the spectrum of methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylate (XVII, Fig. 2). Due to the introduction of a methyl group, the nitrogen in this compound is tertiary, and the N-H absorption should be eliminated. No absorption was observed in the region 3300 - 3000 cm.$^{-1}$. The two weak bands at 3440 and 3370 cm.$^{-1}$ are C=O overtones.

The C=O stretching vibrations of "unsubstituted and monosubstituted" glutarimides (group a) leads to absorption in two regions, 1680 and 1720 cm.$^{-1}$, with the exception of glutarimide which shows bands at 1700 and 1665 cm.$^{-1}$. The somewhat lower position of these bands in the latter compound may be associated with the absence of 4,4-disubstitution, a common feature in all the remaining glutarimides. The C=O stretching vibration of "disubstituted" glutarimides (group b) was found to occur in a higher frequency region. The lower absorption band was at about 1710 cm.$^{-1}$. The exact position of the second band could not be determined

Fig. 3

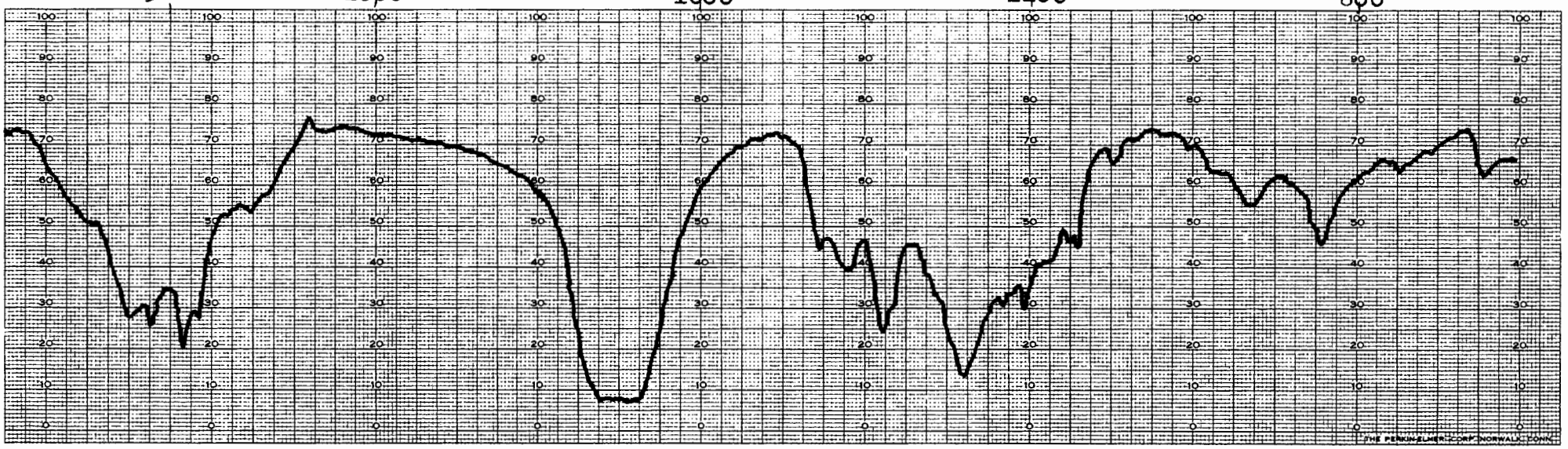
Infrared Absorption Spectra of:

3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid (III)

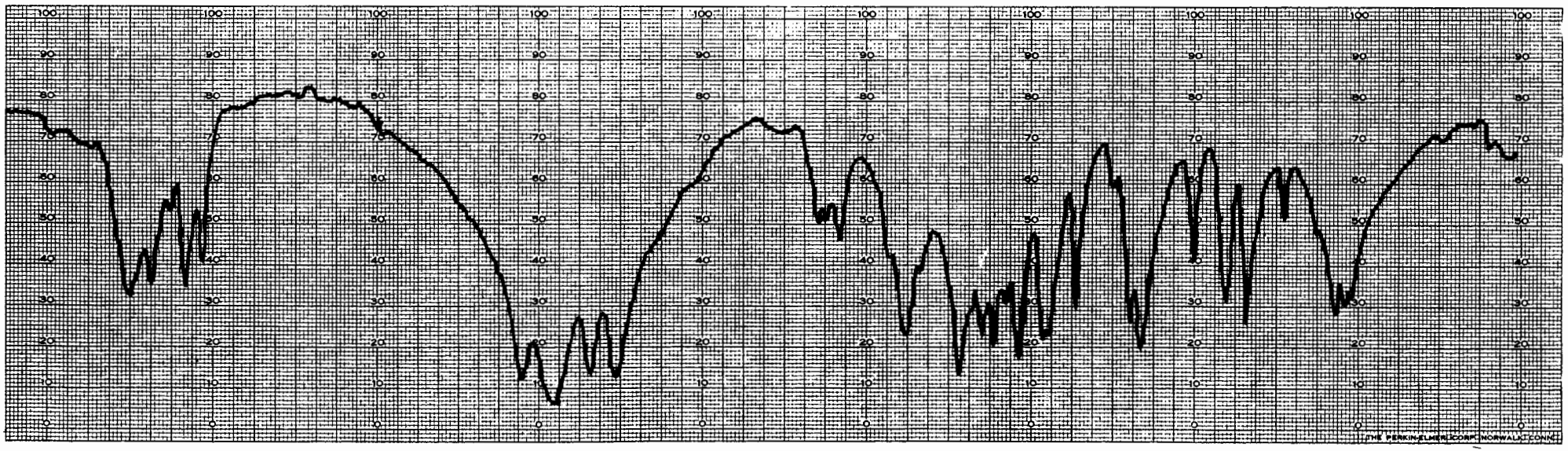
3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid anhydride (XLII)

Wave Numbers in $cm.^{-1}$

III



XLII



with any accuracy because of a strong overlapping of the two bands, but whenever the separation was more satisfactory the shift to a higher frequency of about 25 cm.$^{-1}$ was apparent. In 3-azaspiro(5.5)hendecane-2,4-dioxo-carboxylic acids the presence of carboxyl carbonyl groups cannot be detected in the spectrum because their absorption coincides with that of imide carbonyl. On the other hand, the carbonyl stretching vibrations of anhydrides (84) are quite distinct (bands at 1820 and 1785 cm.$^{-1}$), as in the spectrum of 3-azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid anhydride (XLII, Fig. 3). The spectrum of methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylate (XVII, Fig. 2) shows that methyllation of the imide nitrogen has no effect on carbonyl absorption.

The higher frequency of the C=O stretching vibration in "disubstituted" glutarimides is probably due to one of two causes. If the substituents were diequatorial, the shift could be due to electrostatic interaction similar to that in equatorial α-haloketones (85). If, however, the substituents were diaxial, the resulting high steric compression would almost certainly introduce strain into the glutarimide ring which would be manifested in a shift of the carbonyl bands to higher frequency. In the discussion of stereochemistry (page 89), some evidence opposing the diequatorial conformation of "disubstituted" glutarimides

Fig. 4

Infrared Absorption Spectra of:

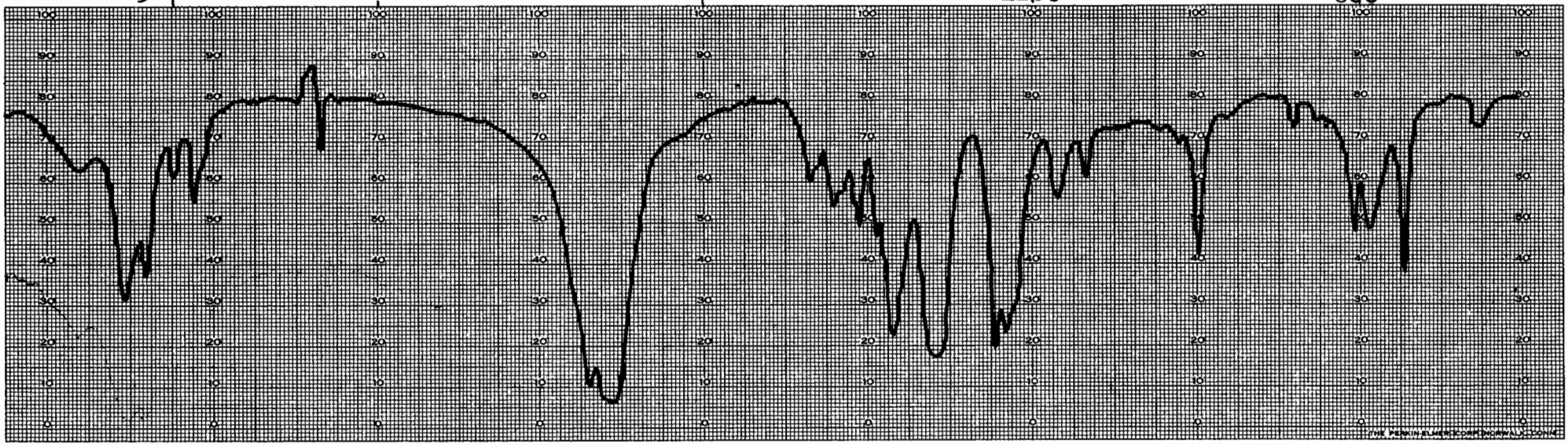
4,4-Dimethylpiperidine-3,5-dicyano-2,6-dione (XLV)

3-Azaspiro(5.5)hendecane-1,5-dicyano-2,4-dione (II)

XLV

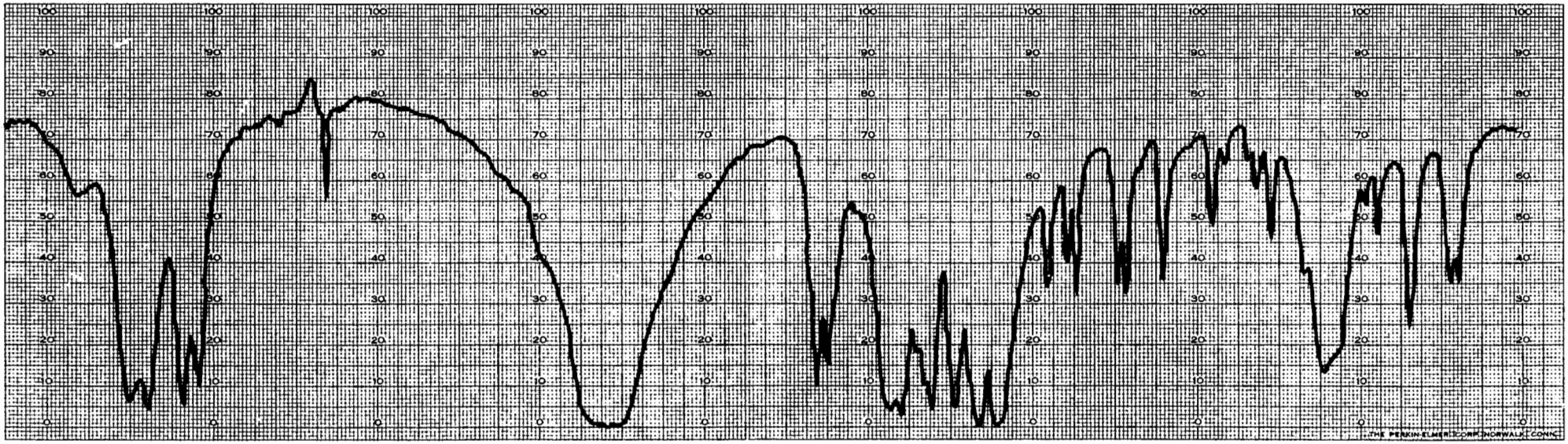
Wave Numbers in cm.$^{-1}$

3000 2000 1600 1200 800



% Absorption

II



was presented. Infrared spectra provide a more convincing argument in favour of the diaxial conformation of cis-"di-substituted" glutarimides. It seems probable that the frequency shifts caused by steric and electrostatic effects would be of a different order of magnitude. This implies that the frequency shift in bicyclic glutarimides (VIII, XLI, XLII), in which the diaxial conformation of the substituents is ensured by their incorporation in the ring, would be different from that in the "disubstituted" glutarimides if the latter were in the diequatorial conformation. That this is not the case is clearly demonstrated by the spectra of 4,4-dimethylpiperidine-3,5-dicyano-2,6-dione (Fig. 4) and 3-azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid anhydride (Fig. 3), which show almost identical frequency shifts.

The absorption of succinimide in the carbonyl region is reported (53) to occur at a higher frequency than that of glutarimide. The shift is attributed to the strain in the five-membered ring. Similar shifts have been observed in the carbonyl stretching frequencies of cyclopentanone (86) and butyrolactam (48, 53) compared with those of cyclohexanone and valerolactam respectively. Like lactams (48), all glutarimides show no absorption in the amide II region (1580 - 1475 cm.$^{-1}$) of their infrared spectra. The stability

Fig. 5

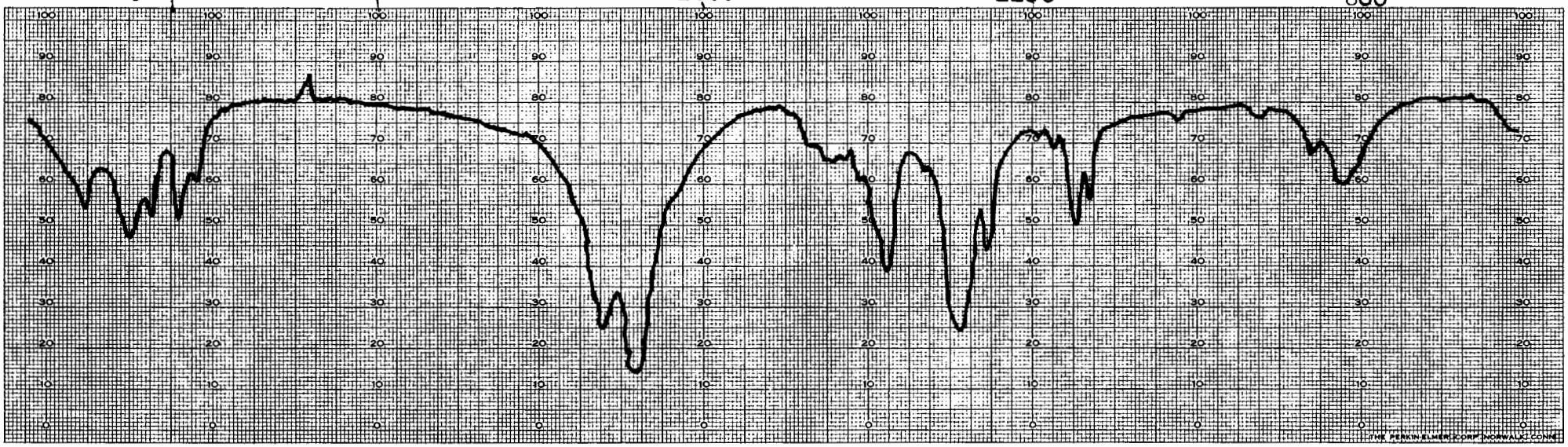
Infrared Absorption Spectra of:

4,4-Dimethylpiperidine-2,6-dione (XLIV)

3-Azaspiro(5.5)hendecane-2,4-dione (IV)

Wave Numbers in cm.$^{-1}$

XLIV



% Absorption

IV

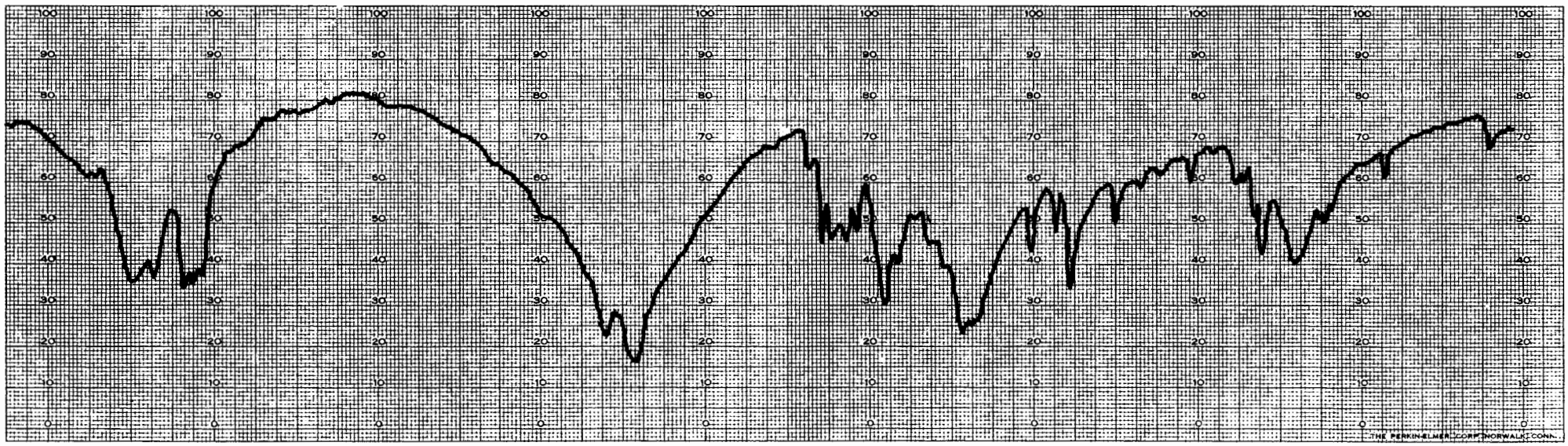


Fig. 6

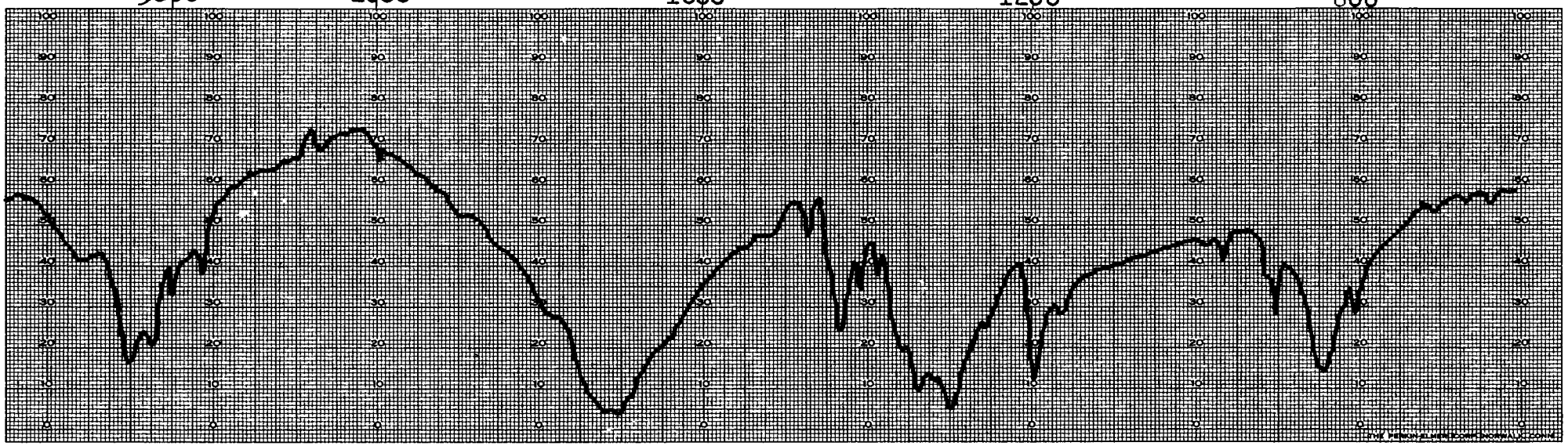
Infrared Absorption Spectra of:

2,4,6,8-Tetroxo-9,9-dimethyl-3,7-diazabicyclo-(3.3.1)nonane (XLI)

2',4',6',8'-Tetroxo-spiro(cyclohexane-1,9'-(3,7)-diazabicyclo(3.3.1)nonane (VIII)

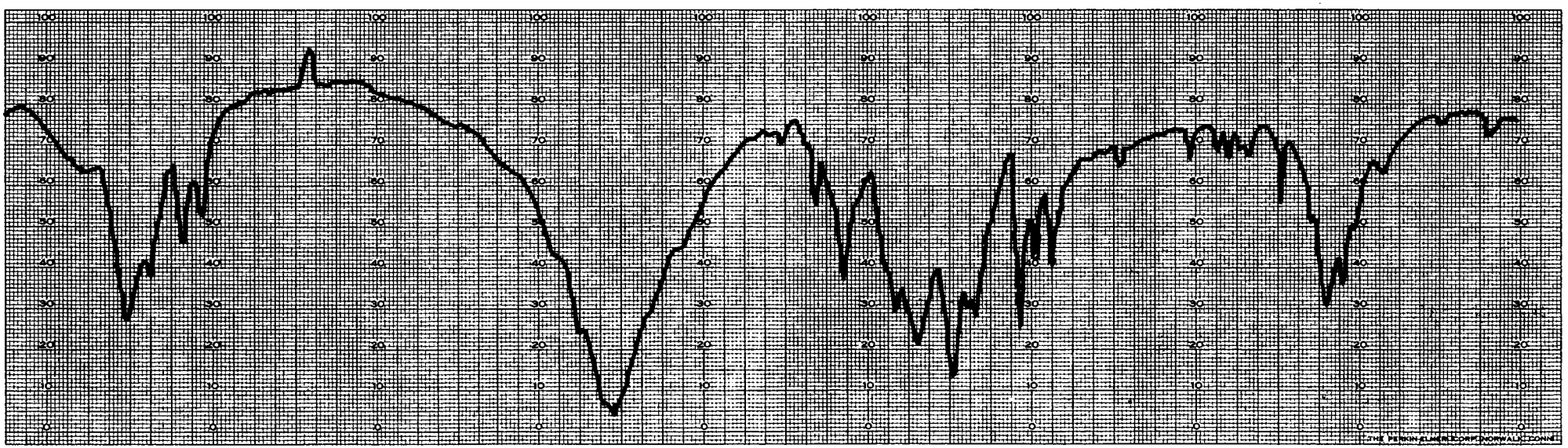
Wave Numbers in $cm.^{-1}$

XLI

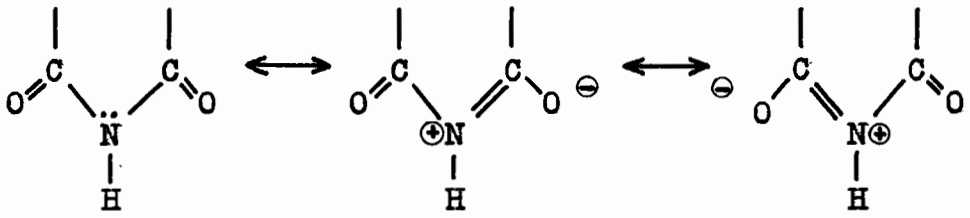


% Absorption

VIII



of imides is sometimes attributed to the large contribution of ionic structures to the resonance hybrid.



While such structures may be important in the transition states of imide reactions, there is no indication of resonance under ordinary conditions. The infrared spectra of imides clearly support the classical covalent structure. The effect of resonance would be to decrease the double bond character of carbonyl groups and to increase that of single C-N bonds, so that the system O=C-N-C=O would be partially conjugated. This effect would be manifested by a considerable downwards shift of the carbonyl stretching frequency, which was not observed.

b) Glutarimino Imides

These are compounds which contain the following structure.

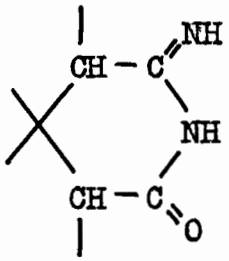


Fig. 7

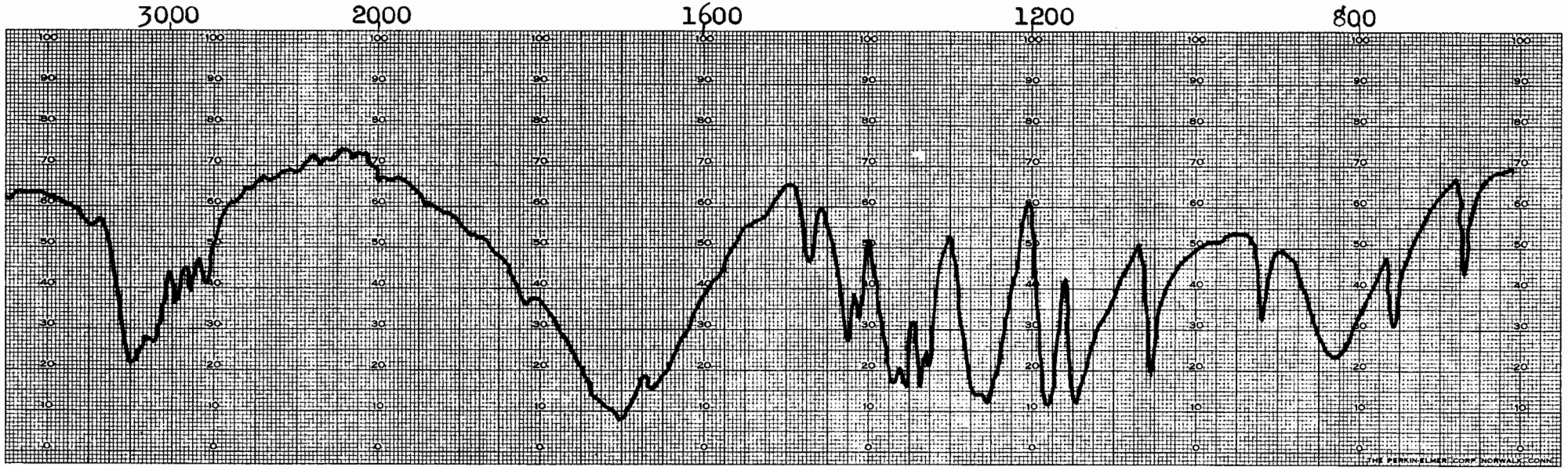
Infrared Absorption Spectra of:

Piperidine-2,6-dione (XLVI)

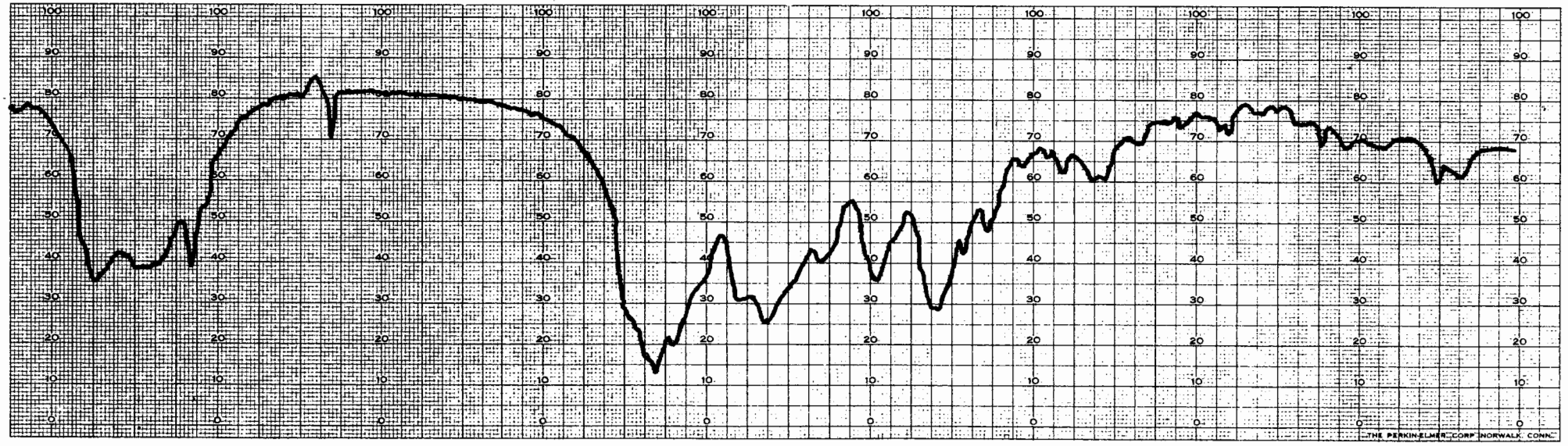
3-Azaspiro(5.5)hendecane-5-cyano-
2-imino-4-oxo-1-carboxamide (I)

Wave Numbers in cm.$^{-1}$

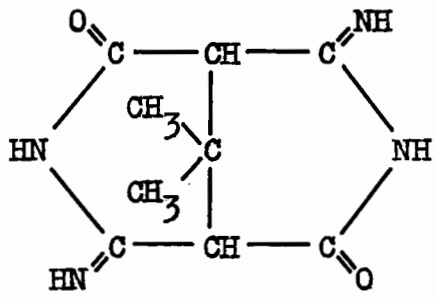
XLVI



I



They may be regarded as derivatives of glutarimides in which one carbonyl is replaced by a C=NH group. The spectra of three compounds of this type have been recorded. These were 3-azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I, Fig. 7), 2',6'-diimino-4',8'-dioxo-spiro-(cyclohexane-1,9'-(2,7)-diazabicyclo(3.3.1)nonane) or "diimino diimide" (XIII, Fig. 8) and 2,6-diimino-9,9-dimethyl-3,7-diazabicyclo(3.3.1)nonane-4,8-dione (XLIII, Fig. 8)



XLIII

The infrared absorption of these compounds shows little similarity to that of glutarimides. The bands at 3200 and 3100 cm.$^{-1}$, characteristic of N-H stretching in glutarimides, are replaced by a single broad band at 3300 cm.$^{-1}$. In 3-azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I), this band is obscured by the overlapping of the primary amide N-H stretching absorption. It should be noted that due to the presence of two NH groups differing in environment (one nitrogen is cyclic, the other exocyclic) two bands rather than a single one would be expected. The presence of the single band also contradicts Thorpe's view that such

Fig. 8

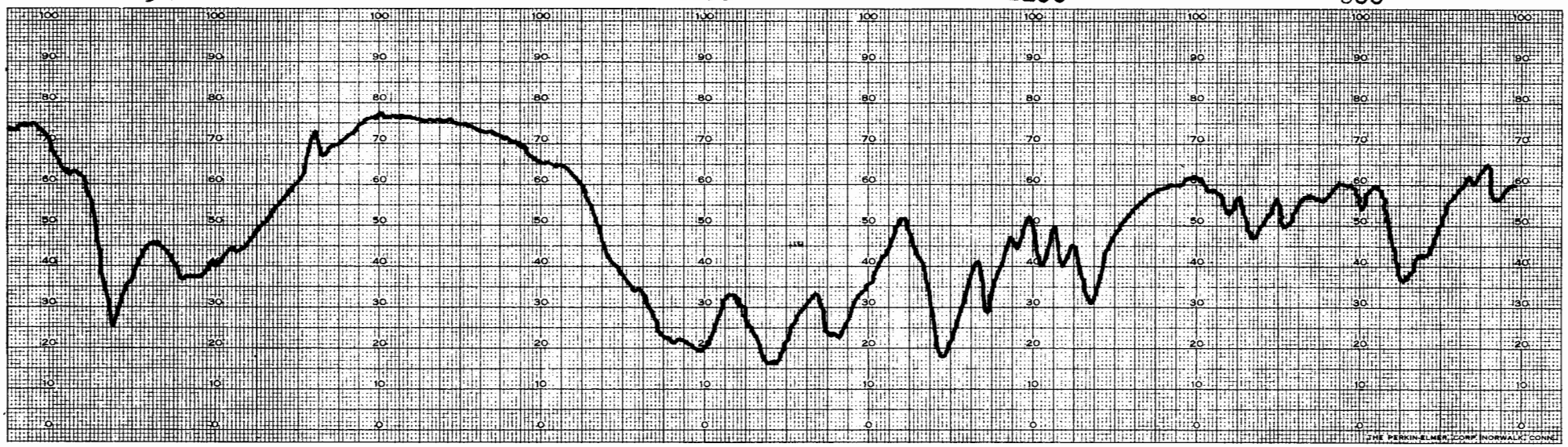
Infrared Absorption Spectra of:

2,6-Diimino-9,9-dimethyl-3,7-diazabicyclo(3.3.1)-nonane-4,8-dione (XLIII)

2',6'-Diimino-4',8'-dioxo-spiro(cyclohexane-1,9'-(3,7)diazabicyclo(3.3.1)nonane) (XIII)

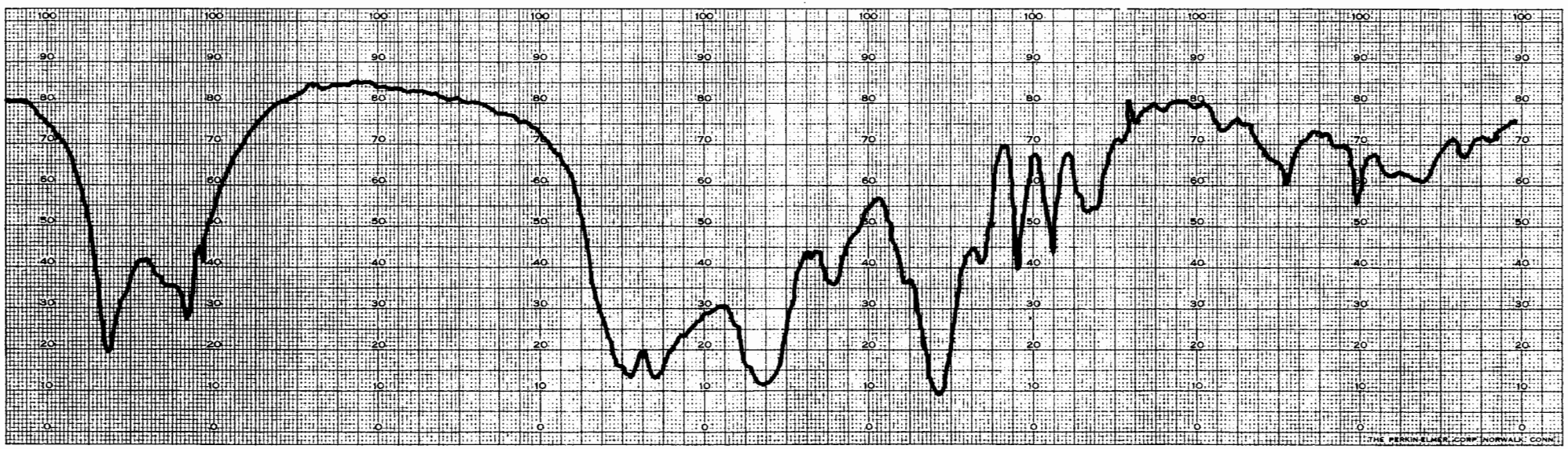
Wave Numbers in $cm.^{-1}$

XLIII



% Absorption

XIII



compounds exist in a tautomeric equilibrium with the "vinyl amine" structure in which the latter predominates (page 14). If this were true, additional bands should be observed in the region 3400 - 3300 cm.$^{-1}$ due to the asymmetrical and symmetrical modes of vibration of the NH_2 group.

The two bands at 1690 and 1660 cm.$^{-1}$ may be assigned to C=O and C=N stretching vibrations respectively. Comparison with the same region in the glutarimide spectra reveals that the higher frequency band assigned to one of the two carbonyl groups (1720 cm.$^{-1}$) in the latter has been replaced in the imino imide spectra by the C=N stretching absorption at 1660 cm.$^{-1}$. A strong, broad band at 1525 cm.$^{-1}$ is very significant, as it is entirely absent from the spectra of all the glutarimides investigated. The only strong band reported in this region is associated with the amide II absorption due to the O=C-NH group, which is observed in acyclic secondary amides in the range 1580 - 1475 cm.$^{-1}$. The O=C-NH and HN=C-NH groups are somewhat similar, and it is possible that the latter could also give rise to an amide II band. Confirmation of this belief is found in the recently reported spectrum (87) of the condensation product of trichloroacetonitrile with primary amines, which proved to have the following structure (R is an alkyl group)

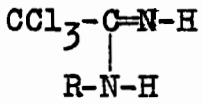


Fig. 9

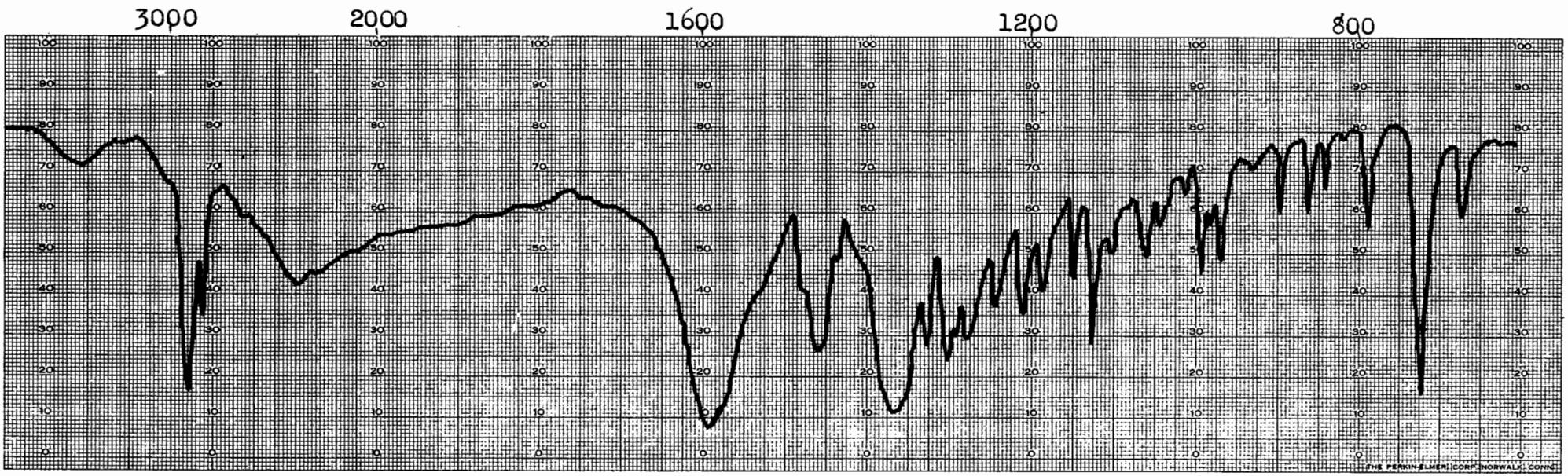
Infrared Absorption Spectra of:

3-Methyl-3-azaspiro(5.5)hendecane-1-carboxylic acid (XXIIa)

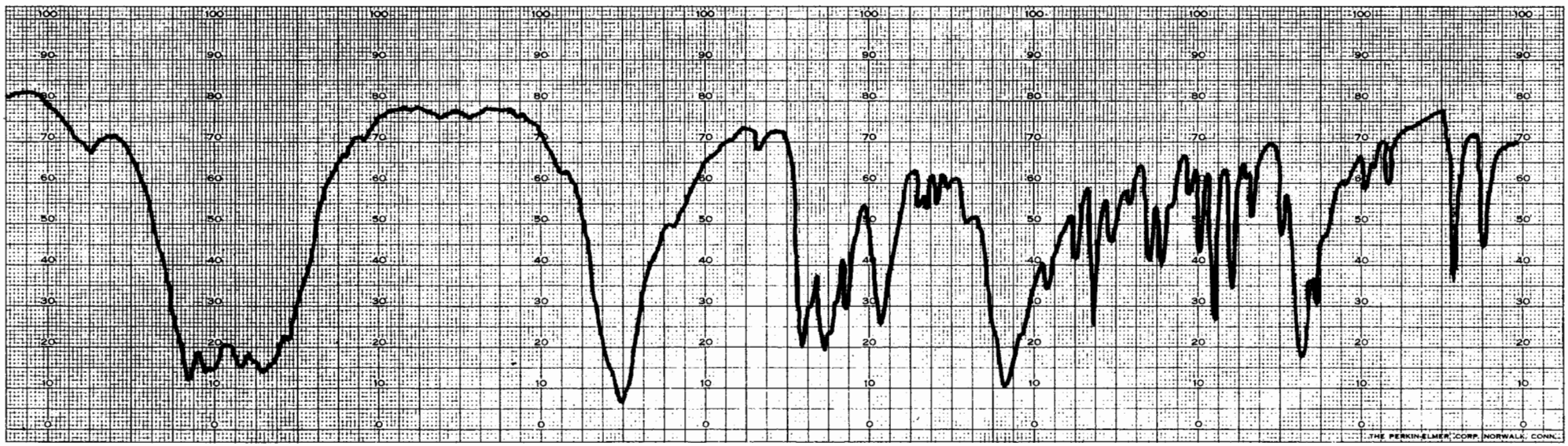
3-Methyl-3-azaspiro(5.5)hendecane-1-carboxylic acid hydrochloride (XXIIb)

Wave Numbers in $cm.^{-1}$

XXIIa



XXIIb



These compounds showed, in addition to the absorption at 1660 - 1630 cm.$^{-1}$ due to the C=N stretching vibration, a very strong, broad band at 1520 cm.$^{-1}$ which could be the amide II band of the HN=C-NH group.

c) 3-Methyl-3-azaspiro(5.5)hendecane-carboxylic Acids and their Hydrochlorides

The infrared spectra of 3-methyl-3-azaspiro(5.5)-hendecane-carboxylic acids are in complete accord with the zwitterion structure proposed for amino acids. The mono-carboxylic acid (XXII, Fig. 9,a) shows no absorption in the region (2800 cm.$^{-1}$) characteristic of ordinary carboxylic acids which is due to a strongly bonded hydroxyl group (88). A broad band with a maximum at 2400 cm.$^{-1}$ is probably due to the $\overset{+}{N}$-H stretching vibration, by analogy to the spectra of tertiary amine hydrochlorides (66). The unusually low frequency of this absorption may be attributed to a particularly strong association, with a consequent loosening of $\overset{\oplus}{N}$-H bond, (ibid.) of the following type:

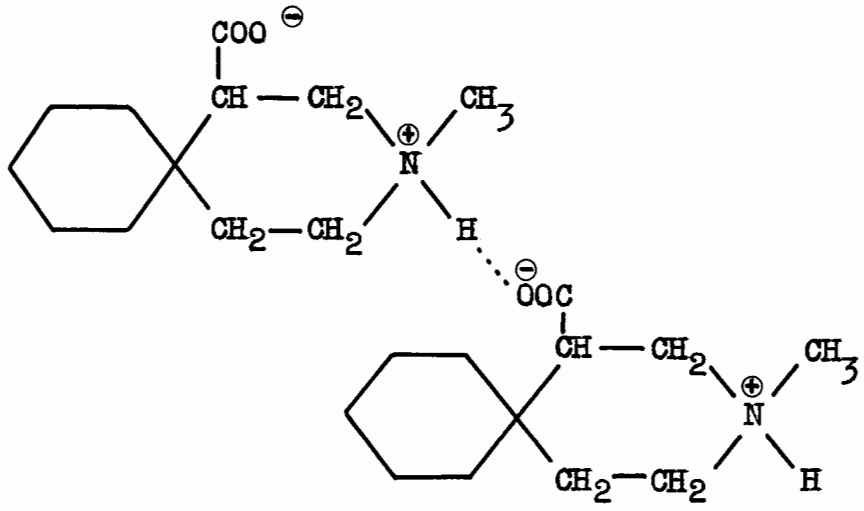


Fig. 10

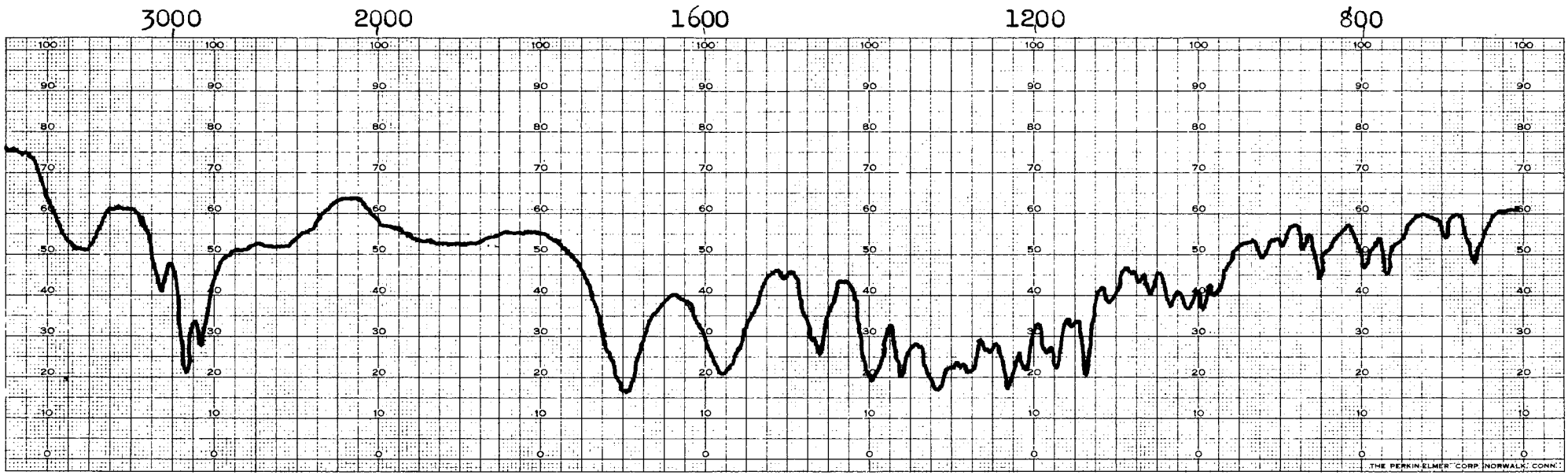
Infrared Absorption Spectra of:

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (XXIa)

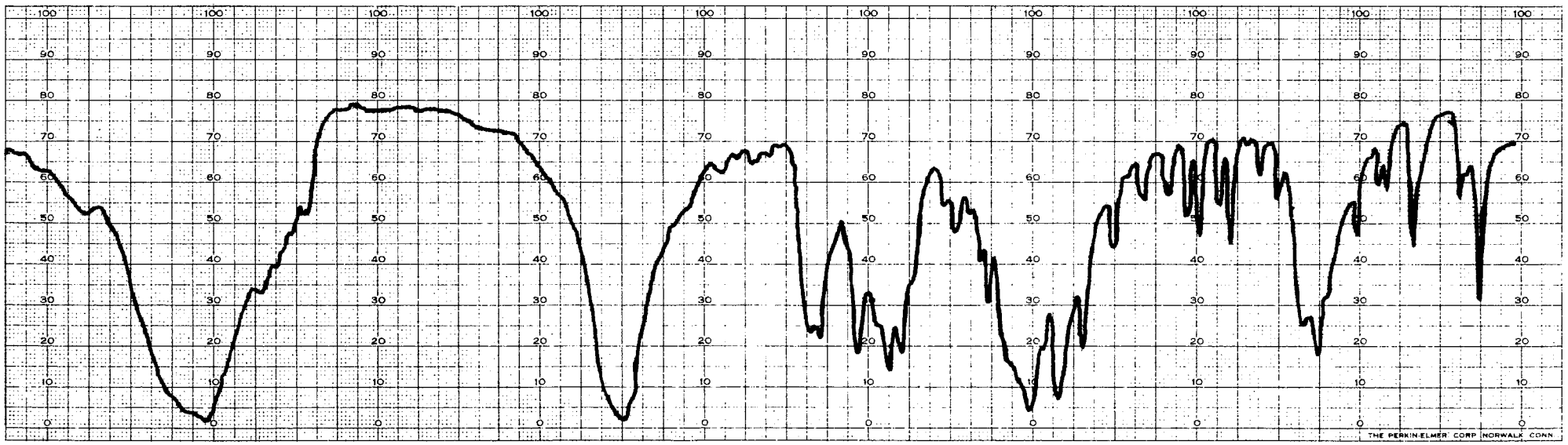
3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid hydrochloride (XXIb)

XXIa

Wave Numbers in cm.$^{-1}$

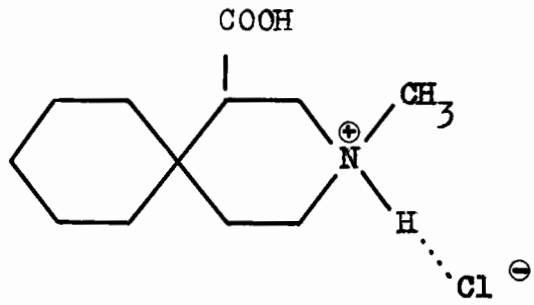


XXIb



No absorption near the normal carbonyl stretching frequency (1700 cm.$^{-1}$) of carboxylic groups was observed. A broad, strong band at 1590 cm.$^{-1}$ may be assigned to the mesomeric carboxylate anion (page 46).

The hydrochloride of 3-methyl-3-azaspiro(5.5)hendecane-1-carboxylic (Fig. 9b) acid exhibits a very strong, broad band between 2800 and 2300 cm.$^{-1}$ with a series of absorption maxima. This absorption is due to the strongly bonded carboxylic hydroxyl partly superimposed on the $\overset{\oplus}{N}$-H stretching absorption. The latter constitutes the lower part of the band; its large shift from the normal frequency is probably due to strong bonding with the chloride anion



The carbonyl absorption is represented by a single strong band at 1700 cm.$^{-1}$ as in ordinary carboxylic acids.

The spectrum of 3-methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (XXI, Fig. 10) has a broad band at 2800 - 2400 cm.$^{-1}$ which may be assigned to the combination of associated O-H and $\overset{+}{N}$-H stretching vibrations. The former

Fig. 11

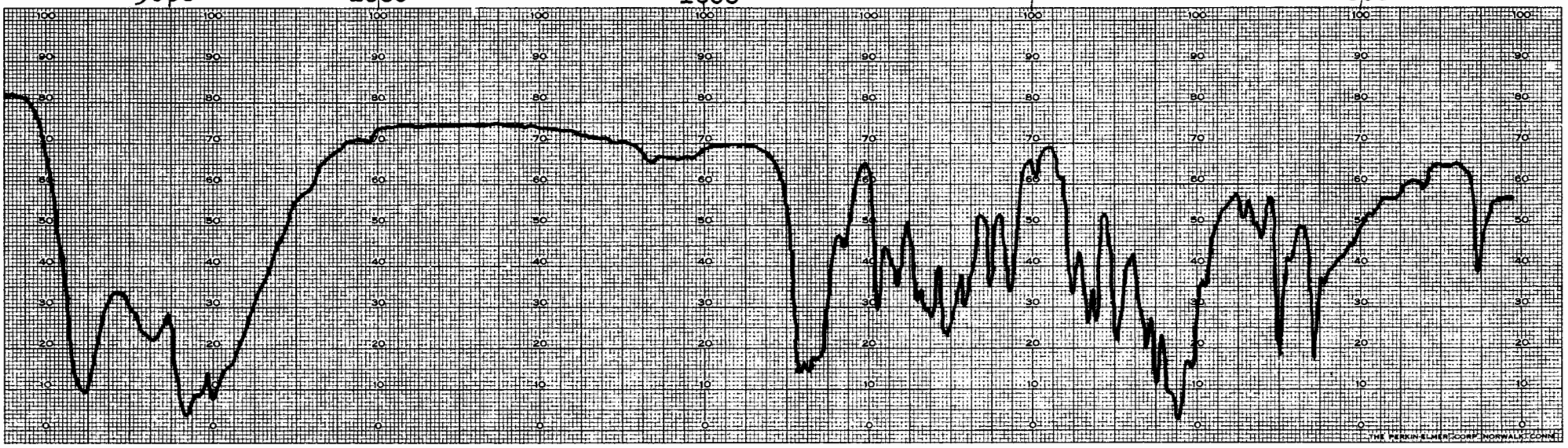
Infrared Absorption Spectra of:

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dihydroxy-methyl (XVIII)

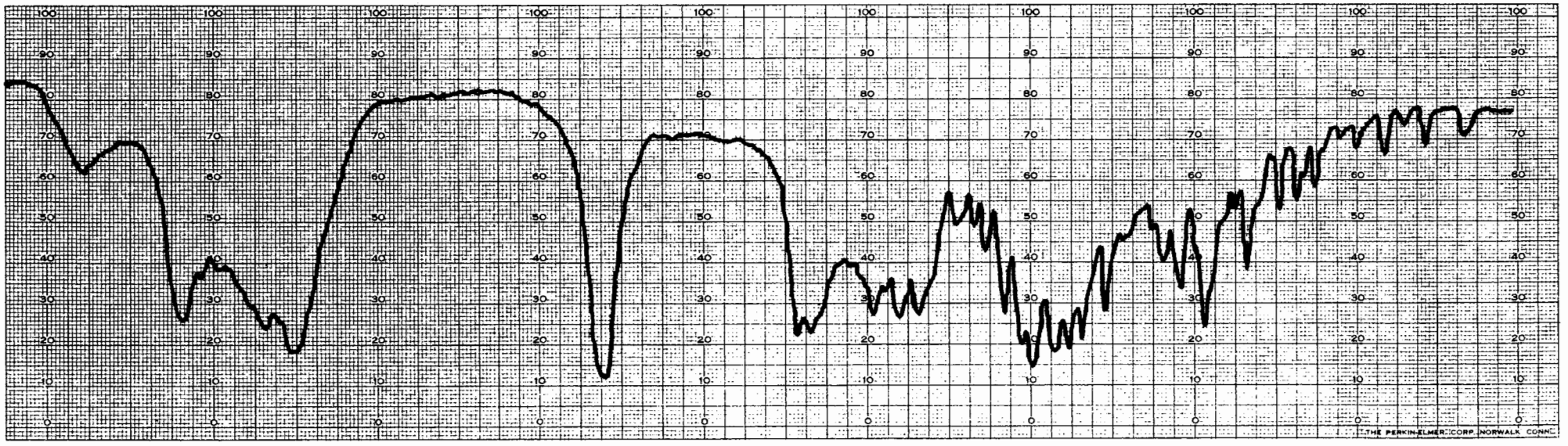
2-Dimethylaminoethyl 3-methyl-3-azaspiro(5.5)-hendecane-1,5-dicarboxylate hydrochloride (XXIII)

Wave Numbers in cm.$^{-1}$

XVIII



XXIII



is responsible for the absorption in the 2800 - 2600 cm.$^{-1}$ region, and the latter for that in the lower portion of the band. The two strong, broad bands at 1700 and 1580 cm.$^{-1}$ correspond to neutral and ionic carbonyl stretching vibrations respectively. The origin of the 3060 cm.$^{-1}$ band is unknown.

In the spectrum of the hydrochloride of 3-methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (Fig. 10b) a strong, broad band at 2800 - 2500 cm.$^{-1}$ arises from the stretching vibrations of the strongly associated O-H and N-H bonds. Both carbonyl groups absorb at the identical frequency of 1700 cm.$^{-1}$, coincident with the carbonyl absorption of ordinary acids.

The spectrum of 2-dimethylaminoethyl 3-methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylate hydrochloride (XXIII, Fig. 11) is similar to that of the corresponding hydrochloride of the free acid (XXI). The carbonyl absorption, however, occurs at 1725 cm.$^{-1}$ instead of 1700 cm.$^{-1}$ due to the effect of esterification on the carbonyl stretching vibration (89).

d) Spectra of Spiro(5.5)hendecanes

An examination of the spectra of the three closely related spiranes, 3-azaspiro(5.5)hendecane (V, Fig. 12),

Fig. 12

Infrared Absorption Spectra of:

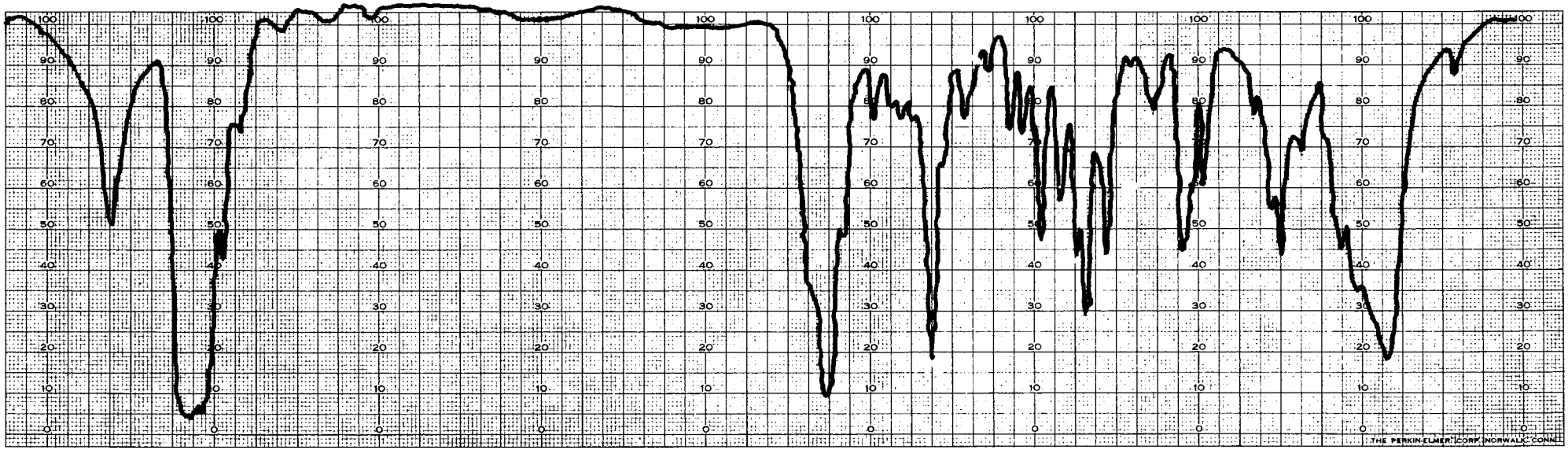
3-Azaspiro(5.5)hendecane (V)

3-Oxaspiro(5.5)hendecane (XXV)

Wave Numbers in cm.$^{-1}$

3000 2000 1600 1200 800

V



% Absorption

XXV

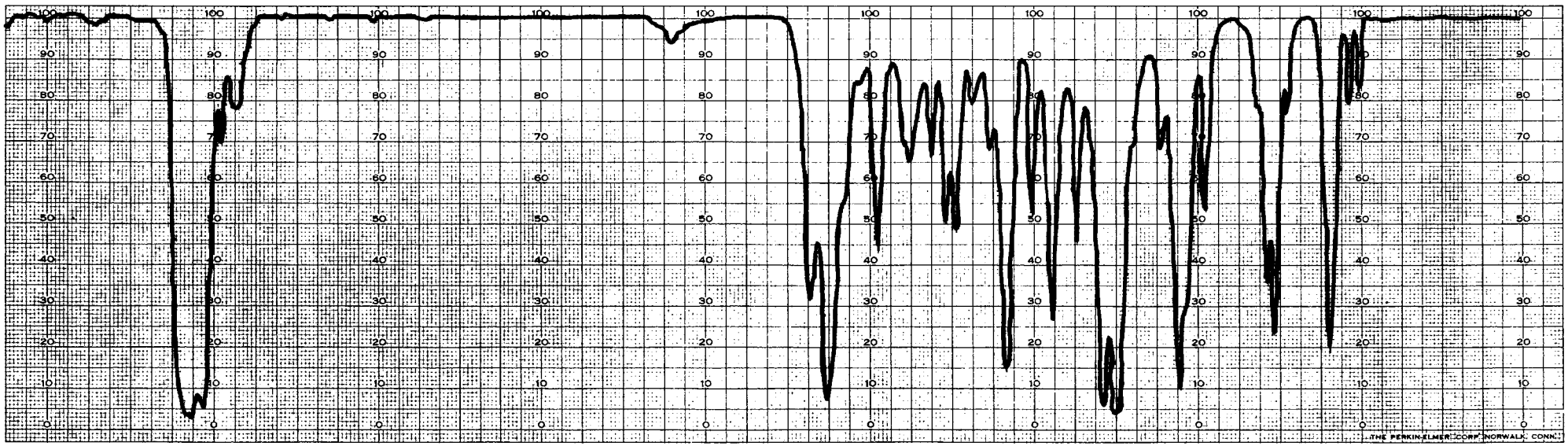


Fig. 13

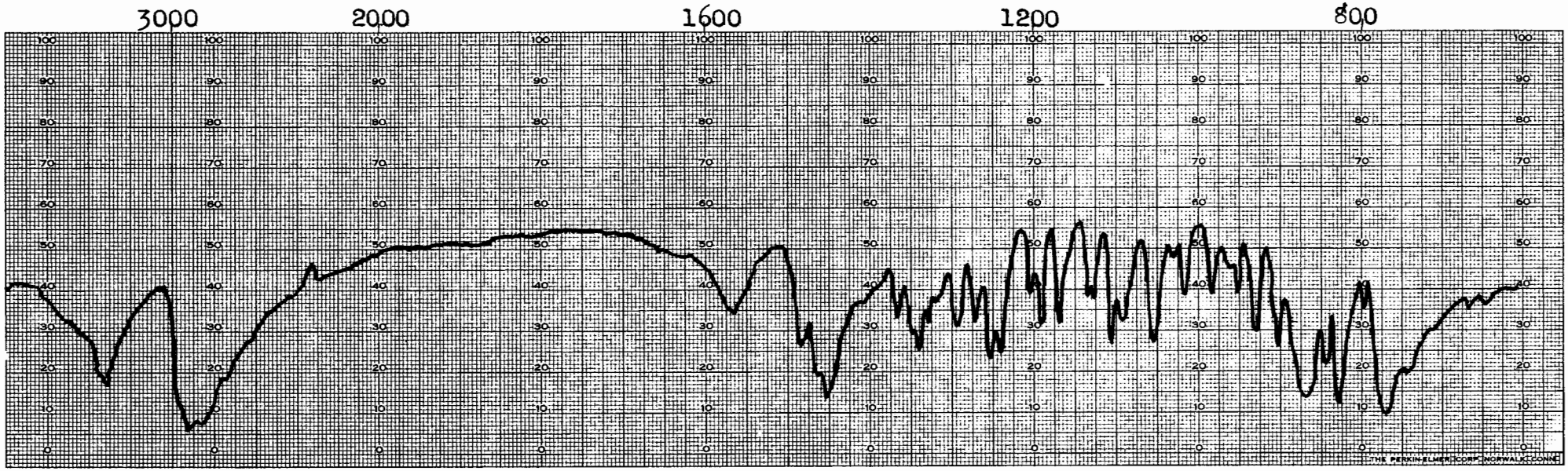
Infrared Absorption Spectra of:

Spiro(cyclohexane-1,9'-(3,7)diaza-bicyclo(3.3.1)nonane) (XX)

3-Thiaspiro(5.5)hendecane (XXVI)

Wave Numbers in cm.$^{-1}$

XX



XXVI

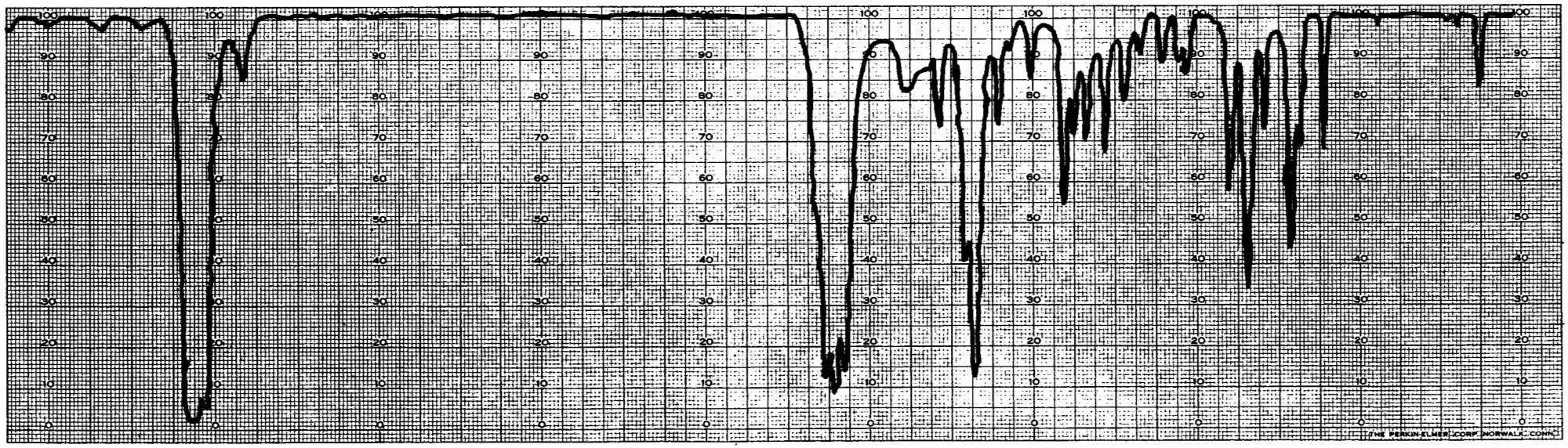


TABLE II

Stretching and Deformation Frequencies in Spiro(5.5)hendecanes

	3-Azaspiro(5.5)-hendecane	3-Oxaspiro(5.5)-hendecane	3-Thiaspiro-(5.5)-hendecane
Rocking (CH_2)	775 vs (b) 805 s (b)	838 s 990 m	-
Twisting (CH_2)	1190 m	1022 s 1145 m 1202 m	-
Wagging (CH_2)	1325 vs	1295 m 1390	1270 s
Bending (CH_2)	1450 vs	1452 vs 1472 s	1432 vs 1443 vs 1453 vs
Stretching CH	2860 vs 2940 vs	2850 vs 2940 vs	2845 vs 2910 vs
Stretching NH	3300 m	-	-
Stretching C-O-C	-	1100 vs	-
Stretching C-S-C	-	-	652 m (90)

3-oxaspiro(5.5)hendecane (XXV, Fig. 12) and 3-thiaspiro-(5.5)hendecane (XXVI, Fig. 13) revealed a complex pattern of absorption. There was no common feature in the three spectra which could be identified with the C-C- stretching frequency, typical of spiranes. The only bands identified were those arising from the stretching and deformation vibrational modes of CH bonds which were determined by comparison with the known spectra (40) of such cyclic compounds as piperidine, tetrahydropyran, pentamethylene sulphide and cyclohexane. These absorption maxima are listed in Table II.

e) Spectrum of Spiro(5.5)hendecane-2,4-dione (XXVII)

The infrared spectrum of spiro(5.5)hendecane-2,4-dione (XXVII, Fig. 14) was determined both in the solid phase and in chloroform solution. The latter was essentially similar to the spectrum of 5,5-dimethylcyclohexane-1,3-dione reported by Rasmussen et al (page 50). The strongly perturbed O-H stretching absorption reported to occur at 2663 $cm.^{-1}$ was found at 2675 $cm.^{-1}$. The carbonyl absorption of the non-enolized ketone was represented by bands at 1730 and 1707 $cm.^{-1}$ compared to 1724 and 1702 $cm.^{-1}$ found by Rasmussen (ibid.). A strong, broad band at 1611 $cm.^{-1}$ is due to the carbonyl stretching vibration of the associated, ionic

Fig. 14

Infrared Absorption Spectra of:

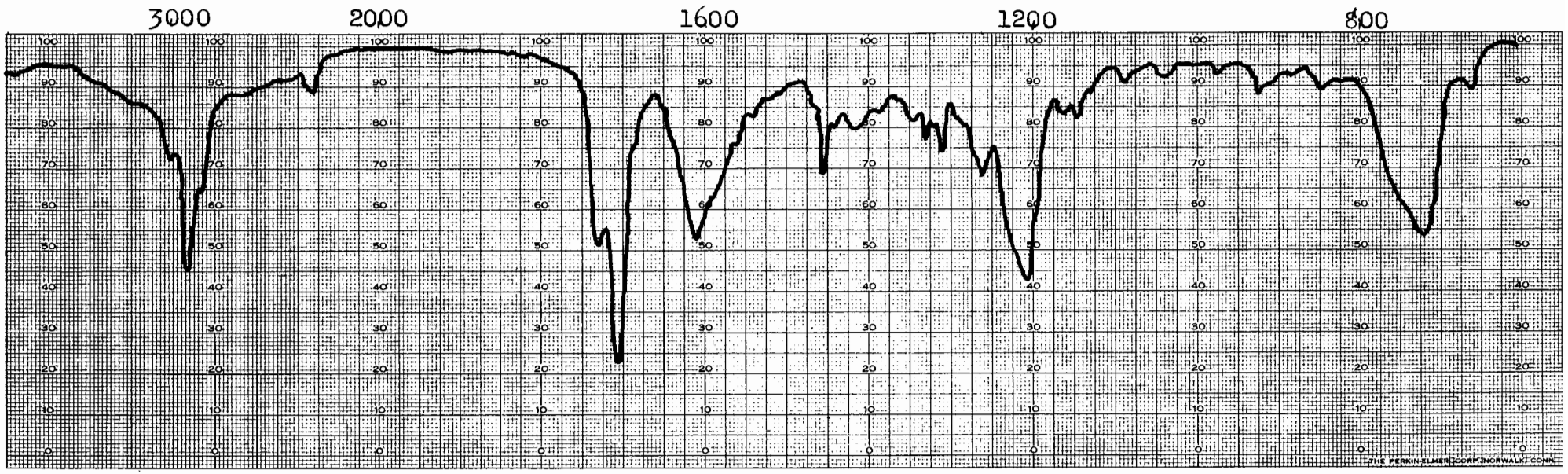
Spiro(5.5)hendecane-2,4-dione (XXVII)

a) Chloroform solution

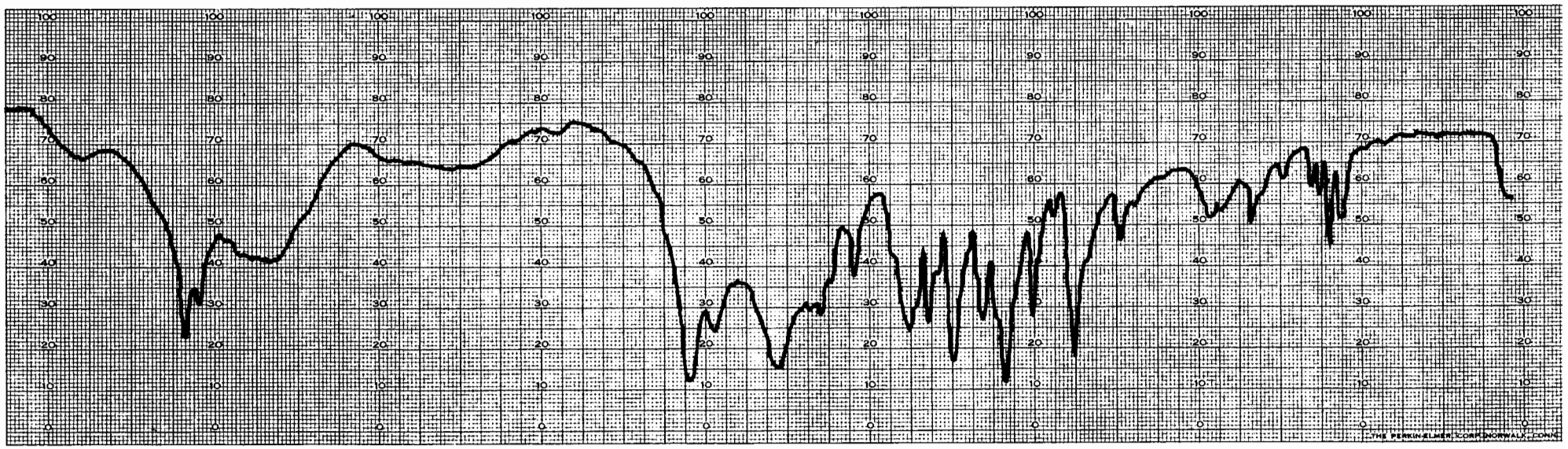
b) Solid

XXVIIa

Wave Numbers in $cm.^{-1}$



XXVIIb



structure; in the spectrum of 5,5-dimethylcyclohexane-1,3-dione it was reported at 1605 cm.$^{-1}$ (ibid.).

The spectrum of the solid differs considerably from that of the chloroform solution. The O-H band is more intense, considerably broadened and shifted to a lower frequency (2800-2400 cm.$^{-1}$). Absorption due to ketonic carbonyl is entirely absent. The band at 1611 cm.$^{-1}$ persists but additional bands, at 1585 and 1510 cm.$^{-1}$, absent from the solution spectrum, and of uncertain origin, are observed. The absence of keto group absorption suggests that the dione exist entirely as an enolic dimer stabilized by resonance (page 51). The presence of the new bands may indicate several degrees of association in the solid state, each with a different resonance structure. The result would be the presence of carbonyl groups having different degrees of double bond character and hence absorbing in different regions.

The formal structure of spiro(5.5)hendecane appears to be related to 3-azaspiro(5.5)hendecane-2,4-dione. The spectral evidence shows that the similarity is only superficial. While glutarimides are adequately described in terms of conventional structural formulas, β-diketones exist largely in the form of associated, enolic complexes to which there is a large contribution by ionic resonance forms.

Fig. 15

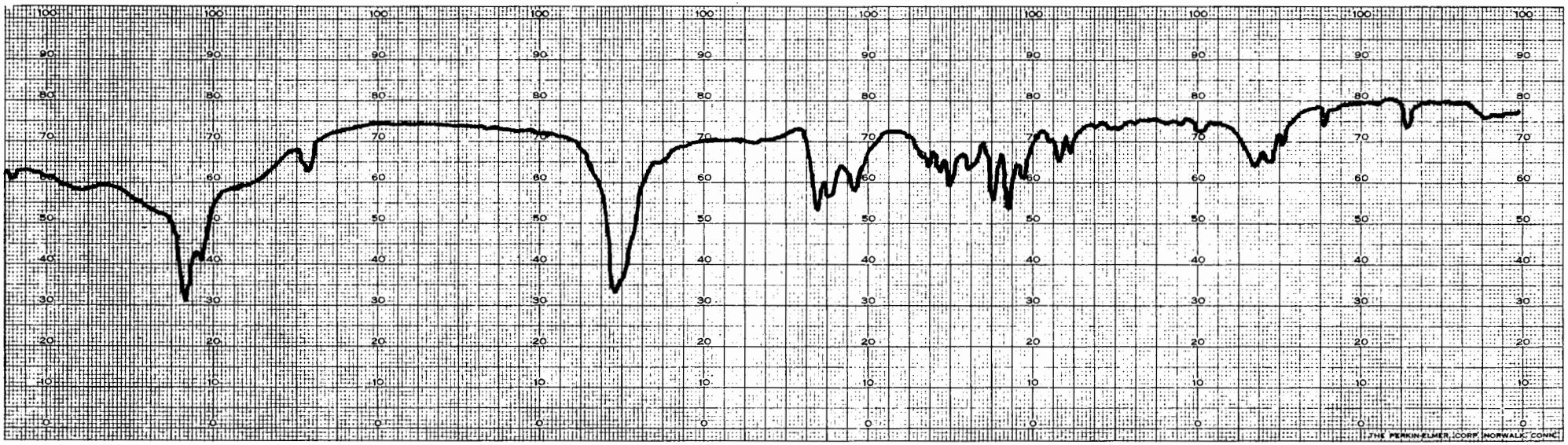
Infrared Absorption Spectra of:

Spiro(5.5)hendecane-3-carboxylic acid (XXXV)

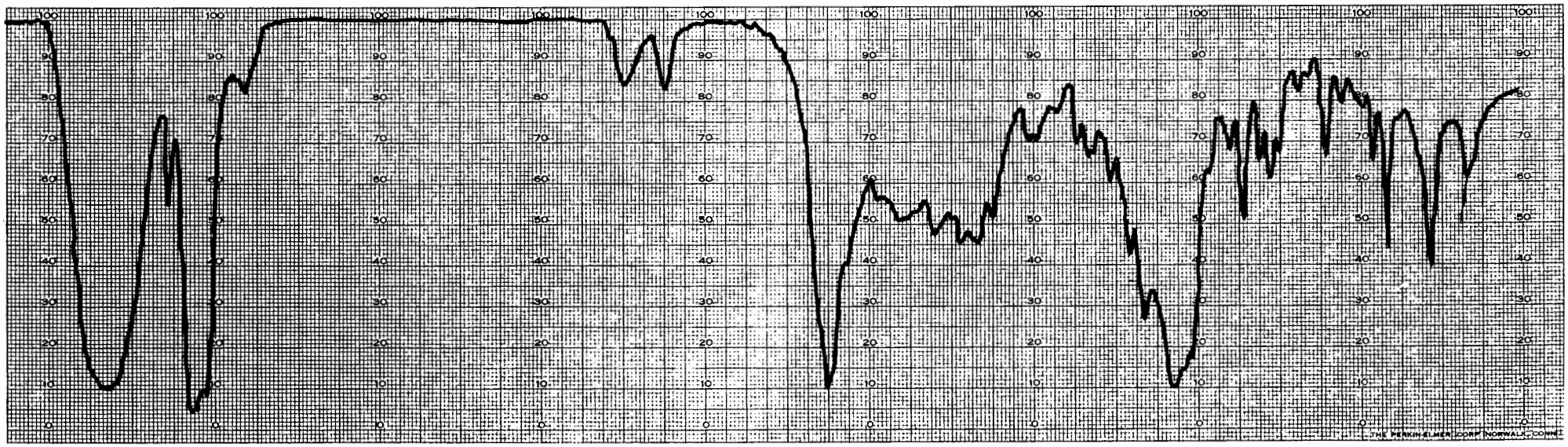
The product of the reduction of spiro(5.5)-hendecane-2,4-dione (XXIX)

Wave Numbers in $cm.^{-1}$

XXXV



XXIX



EXPERIMENTAL

All carbon, hydrogen and nitrogen analyses were carried out in the laboratory of W. Manser in Zurich, Switzerland. Chlorine in amine hydrochlorides and equivalent weights of acids were determined by the author.

All melting points reported in this work have been corrected using the set of melting point standards prepared by Baeyer Company, Leverkusen, Germany.

Infrared Absorption Spectra

The infrared absorption spectra were recorded on a Perkin-Elmer model 21 double beam spectrophotometer equipped with a sodium chloride prism. The settings of the instrument during the scanning of spectra were as follows: response 1:1, gain 5.5, speed 5-6, resolution 927 and suppression 0. The scale was 100 cm.$^{-1}$/cm. in the absorption range 3800 - 2000 cm.$^{-1}$ and 100 cm.$^{-1}$/4 cm. in the range of 2000 - 600 cm.$^{-1}$. Potassium bromide technique was exclusively used with solid compounds. The former was of infrared quality and was obtained from the Harshaw Chemical Co., Cleveland, Ohio. Preparation of potassium bromide discs was carried out under

standardized conditions. The quantity used in a single disc was about 400 mg. The weight of the sample amounted to 1 - 2 mg. The mixing was done in a stoppered ampule containing four small steel balls, which was shaken in a Perkin-Elmer vibrator for three minutes. Potassium bromide was compressed into a disc by applying a pressure of 20,000 lbs./sq. in. for two minutes.

In tabulating the absorption maxima the following symbols were used to designate the intensity and appearance of bands: vw (very weak, w (weak), m (medium), s (strong), vs (very strong), vb (very broad), b (broad), sh (shoulder).

Preparation of 3-Azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I, imino imide)

The compound was prepared by the method of Thorpe (9). Cyclohexanone (25.5 ml;0.246 mole) was added to the solution of cyanoacetamide (40 gm.; 0.475 mole) in water (250 ml.) and the solution treated with a small quantity of piperidine. After 24 hours the condensation product (37 gm.) was filtered, dried and used without purification for the next step. The pure material was obtained by dissolving the crude imino imide in cold, dilute hydrochloric acid and immediately precipitating with sodium acetate solution. The filtrate from

the original condensation product yielded a small quantity of a solid on long standing. When recrystallized from ethanol it melted at 206°. According to Thorpe (9) this compound is 3-azaspiro(5.5)hendecane-1,5-dicyano-2,4-dione (II).

3-Azaspiro(5.5)hendecane-5-cyano-2,4-dioxo-1-carboxamide (VII)

The imino imide (I, 37 gm.; 0.149 mole) was dissolved in dilute hydrochloric acid and the solution boiled for a short time. There was an immediate precipitation of a white, crystalline material which after the solution cooled to room temperature was filtered, washed with water and dried. The product thus obtained (25 gm.) was a mixture of approximately equal quantities of (VII) and diimide (VIII). Pure (VII) was obtained by extracting the mixture with hot ethanol in which (VIII) is insoluble. By recrystallization from dilute ethanol pure (VII) was obtained melting at 265°. Thorpe (9) reported a melting point of 260°.

3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic Acid (III)

The mixture of compounds (25 gm.) obtained by acid hydrolysis of imino imide (I) was dissolved in 15% aqueous solution of potassium hydroxide (250 ml.) and the solution

boiled for four hours. Hot water was added occasionally to maintain the volume of the solution constant. After the evolution of ammonia had ceased, the boiling was continued for a short time and the solution cooled on ice. It was then made strongly acidic by the gradual addition of 20% hydrochloric acid with vigorous agitation, and was left in the refrigerator overnight. Next day the precipitated acid was filtered and washed on filter with ice-cold water. The product was purified by repeated dissolving in aqueous sodium bicarbonate and reprecipitating with dilute hydrochloric acid. After a thorough drying in vacuum the acid (18 gm.) melted at 117° with decarboxylation. The same melting point was reported by Thorpe (ibid.).

3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic Acid Anhydride (XLII)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid (1 gm.) was treated with acetic anhydride (5 ml.) in a small, stoppered flask. After 24 hours of standing at room temperature with occasional agitation the acid dissolved. The solution was allowed to stand for two more days, following which the acetic anhydride was removed under vacuum at room temperature. Higher temperatures were avoided throughout

the operation because of the instability of the acid. The solid residue was digested with hot benzene and the insoluble residue filtered off. It proved to be the unreacted acid (0.27 gm.). The benzene solution yielded on cooling white needles (0.63 gm.) which after two recrystallizations from the same solvent melted at 213 - 214° to a colorless liquid. The compound was insoluble in sodium bicarbonate but dissolved readily in the cold, dilute sodium hydroxide. The solution after a few hours of standing was acidified with dilute hydrochloric acid. A white, crystalline compound which separated was found to be readily soluble in sodium bicarbonate with a vigorous gasing. It melted at 117° with decarboxylation and hence proved to be 3-azaspiro(5.5)-hendecane-2,4-dioxo-1,5-dicarboxylic acid (III). This proves that the original product was the corresponding acid anhydride. The infrared spectrum showed two strong bands at 1820 and 1785 cm.$^{-1}$ due to the anhydride carbonyl (91) and two other bands at 1735 and 1705 cm.$^{-1}$ associated with the imide carbonyl stretching vibration. In addition bands at 3200 and 3100 cm.$^{-1}$ associated with the N-H stretching vibration of glutarimides were also observed.

3-Azaspiro(5.5)hendecane-2,4-dione (IV)

This compound was prepared by the method of Thorpe (9).

Pure dicarboxylic acid (III, 12 gm.; 0.0455 mole) was heated in large test tube on an oil bath at 130 - 140° until evolution of carbon dioxide had slowed. The temperature was then raised to 180° and kept in this region for one hour. The tube was then cooled, the solid digested with hot benzene, boiled with charcoal and filtered hot. On cooling the filtrate yielded white needles (7.0 gm.) which after recrystallization from benzene melted at 168°, in agreement with the literature (ibid.).

3-Azaspiro(5.5)hendecane (V)

Lithium aluminum hydride (4 gm.; 0.105 mole) was dissolved in anhydrous, pure tetrahydrofuran (200 ml.) by refluxing for four hours with stirring. Pure, dry 3-azaspiro(5.5)hendecane-2,4-dione (IV, 6 gm.; 0.0331 mole) was placed in the extraction thimble of a Soxhlet apparatus which was then fitted to the flask. The solution was refluxed until all the dione was extracted which required 48 hours. The refluxing was continued for another 24 hours, the solution then cooled on ice and excess hydride decomposed by the careful addition of water with efficient stirring. The solid material was then filtered off and extracted four times with 100 ml. portions of ether. Tetrahydrofuran from the original filtrate was removed by distillation, the

residual oil combined with the condensed ethereal extract and dried over solid potassium hydroxide. Ether was then removed and the oil distilled under reduced pressure. The distillate (3.5 gm.) was collected at 114 - 116°/24 mm.; it was a colorless, mobile liquid having a strong, unpleasant smell resembling piperidine. On standing in the air it was slowly converted to a white solid, melting at 70 - 80° which is probably a hydrated carbonate formed by the reaction of the base with atmospheric carbon dioxide and moisture. The base was readily soluble in alcohol, ether and benzene but insoluble in water. Hydrochloric acid reacted vigorously with the compound; the product after three recrystallizations from chloroform melted at 240 - 241°. Calculated for $C_{10}H_{20}NCl$: Cl, 18, 61. Found: Cl, 18.71. Reaction with p-nitrobenzoyl chloride yielded a solid derivative which after recrystallization from dilute ethanol formed pale yellow scales melting at 118°. Calculated for $C_{17}H_{22}N_2O_3$:C, 67.50; H, 7.34; N, 9.26. Found: C, 67.25; H, 6.91; N, 9.47.

Esterification of 3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic Acid (III)

To the ethereal solution of diazomethane obtained by decompesition of N-methylnitrosothiourea (80 gm.; 0.667 mole) with 50% aqueous potassium hydroxide (92) the acid (33.5 gm.;

0.125 mole) was added in small portions with occasional agitation. After 12 hours all the acid dissolved and there was no evolution of gas. The solution was left to stand for 24 hours following which most of the ether was removed by distillation, the remainder being eliminated under reduced pressure. Vacuum distillation of the residue yielded a heavy, extremely viscous, colorless oil (31 gm.) boiling at 195 - 201°/2 mm. Since diazomethane has been reported (70) to methylate smoothly the imide nitrogen, the product is methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylate (XVI). A small quantity of the ester was kept in a vacuum desiccator for several weeks, after which time it partly crystallized but attempts failed to recrystallize it.

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dihydroxymethyl (XVIII)

Lithium aluminum hydride (16 gm.; 0.422 mole) was dissolved in absolute ether (250 ml.) by refluxing with stirring for three hours. A two-necked flask equipped with a condenser and separatory funnel containing the solution of ester (XVI) (30.5 gm.; 0.098 mole) in absolute ether (100 ml.) was used for the reaction. Agitation was effected by means of a magnetic stirrer. The solution of ester was added at such a

rate that a mild refluxing was maintained. After all the solution had been added, the mixture was refluxed for 12 hours and then cooled on ice. The excess hydride was decomposed by the careful addition of water, ether solution filtered and the solid material extracted with ether in a Soxhlet apparatus. The extract was combined with the original ether filtrate, the combined solutions reduced to a small volume and dried over solid potassium hydroxide. The ether was next removed, first by ordinary distillation, later under vacuum. The oily residue was kept under vacuum until it solidified. The yield of a crude material was 17 gm. A small quantity recrystallized three times from chloroform-petroleum ether mixture yielded white, granular crystals, melting at 147 - 148°. Calculated for $C_{13}H_{25}NO_2$:C, 68.89; H, 11.01; N, 6.16. Found: C, 68.48; H, 10.91; N, 6.15. The compound is readily soluble in ethanol and chloroform, sparingly soluble in ether and ethyl acetate and insoluble in petroleum ether, benzene and water. A hydrochloride was formed by dissolving the substance in dry ether and passing hydrogen chloride gas through the solution. It melted at 245 - 247° after recrystallization from ethanol-ethyl acetate. Calculated for $C_{13}H_{26}NO_2Cl$: N, 5.31; Cl, 13.50. Found: N, 5.20; Cl, 13.48.

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic Acid (XXI)

A solution of 3-methyl-3-azaspiro(5.5)hendecane-1,5-dihydroxylmethyl (XVIII, 17 gm.; 0.075 mole) in 25% sulphuric acid (70 ml.) was added slowly to the solution of chromic oxide (35 gm.; 0.35 mole) in water (70 ml.) with stirring. There was a strong evolution of heat. When all the solution had been added, it was heated on the steam bath for three hours. The reaction mixture was then cooled and the excess of chromic oxide reduced by passing sulphur dioxide for three hours. The removal of chromium and sulphate ions was accomplished by introducing an excess of boiling solution of barium hydroxide (150 gm. in 500 ml. of water). The solution was heated on the steam bath and the excess barium hydroxide removed as barium carbonate by adding dry ice with an efficient stirring. The precipitated solids were filtered off and extracted five times with large quantities of hot water, the slurry being filtered each time. The combined filtrates (about two liters) were treated carefully with dilute sulphuric acid until the addition caused no further precipitation of barium sulphate. This occurred at pH 2.7. The precipitated barium sulphate was filtered, the filtrate evaporated on a steam bath to a small volume, boiled with charcoal and filtered hot. A large crop of crystals was obtained on cooling. The filtrate was evaporated further and it yielded an additional quantity of crystals.

The combined yield was 5.2 gm. A small quantity of the substance was recrystallized three times from water. It melted at 293 - 294° with decomposition. The compound is strongly hygroscopic. When thoroughly dried it gained 7% weight in 15 minutes, which is equivalent to one mole of water. There was some indication that drying at 100° in a vacuum did not remove all the water from the compound. It was apparently due to this reason that analyses did not give a good agreement. Calculated for $C_{13}H_{21}NO_4$: C, 61.22; H, 8.23; N, 5.49. Found: C, 59.24; H, 8.47; N, 5.17. Calculated for $C_{13}H_{21}NO_4 \cdot \frac{1}{2}H_2O$: C, 59.21; H, 8.34; N, 5.31.

Since dicarboxylic monoamino acids behave as monocarboxylic acids when titrated with alkali hydroxides in presence of phenolphthalein (93, 94) it was possible to determine equivalent weight. Calculated: 255.3. Found: 257. The acid was insoluble in all common organic solvents, including ethanol. When treated with 20% hydrochloric acid and evaporated to dryness it formed a hydrochloride which after recrystallization from aqueous acetone melted at 273-275° with decomposition. Calculated for $C_{13}H_{22}NO_4Cl$: Cl, 12.18. Found: Cl, 11.84. The acid failed to yield an ester when its solution in absolute ethanol was treated with dry hydrogen chloride. The product isolated after the removal of ethanol was hydrochloride of the free acid. Esterification with diazomethane was also unsuccessful. Most of the acid

remained undissolved after standing for four days in the ethereal solution of diazomethane. Evaporation of ether solution yielded a very small quantity of oil having strong amine smell. It was dissolved in dry ether and treated with dry hydrogen chloride. A white solid precipitated immediately but after some time it reconverted to oil. The insoluble solid from the diazomethane solution melted considerably lower (180 - 190°) than the starting material. It probably represented a mixture of monoester and the unreacted acid. The infrared spectrum is in complete agreement with the main structural features and in addition it supports the zwitterion structure of the compound.

Synthesis of Spiro(cyclohexane-1,9'-(3,7)-diazabicyclo (3.3.1)nonane (XX)

The starting material for this preparation was 2', 4', 6', 8'-tetroxo-spiro(cyclohexane-1,9'-(3.7)-diazabicyclo-(3.3.1)nonane) or "diimide" (VIII). It was prepared by the method described by Thorpe (9).

The "diimide" (4.3 gm.; 0.172 mole) was reduced by lithium aluminum hydride (5 gm.; 0.132 mole) using tetrahydrofuran as a solvent (250 ml.). Soxhlet extraction apparatus was employed; the solution was stirred mechanically. It took

five days of refluxing to extract all the diimide. Further treatment was very similar to the one employed in the preparation of 3-azaspiro(5.5)hendecane (V). After the removal of solvent, an oil having strong amine smell was obtained. On long standing in a vacuum desiccator it partly crystallized in the form of large prisms, but attempts to isolate them failed, the material reconverting to oil on being exposed to air. Because of this, the substance was converted to hydrochloride and purified by recrystallization from ethanol. It melted at 277 - 279° with decomposition. Calculated for $C_{12}H_{24}N_2Cl_2$: C, 53.83; H, 9.03; N, 10.47; Cl, 26.52. Found: C, 53.76; H, 8.90; N, 9.92; Cl, 26.58. The hydrochloride (0.52 gm.) was treated with 25% solution of aqueous potassium hydroxide, the liberated oil extracted with ether and ether extract dried over solid potassium hydroxide. The ether solution was then decanted and ether removed in a vacuum desiccator. A white, crystalline material was left; it melted sharply at 73°. The infrared absorption spectrum showed a broad band of high intensity at 3340 cm.$^{-1}$ corresponding to a bonded NH stretching vibration and no absorption in the carbonyl region.

Attempted Selective Acid Hydrolysis of the Imino Imide (I)

The purpose of this reaction was to hydrolyze the carboxamide group of the imino imide (I) to carboxyl without

affecting the nitrile group. It was expected that in this way the monosubstituted 3-azaspiro(5.5)hendecane-2,4-dione would be obtained by removing the unstable carboxylic group. The method employed was based on the procedure of Thorpe (9) for the hydrolysis of 4,4-dimethylpiperidine-5-cyano-2-imino-6-oxo-3-carboxamide (XXXVII).

1st. Attempt

The imino imide (10 gm.; 0.0403 mole) was dissolved in 10% hydrochloric acid (750 ml.) and the solution refluxed with stirring for 30 hours. A large quantity of a solid material separated from the solution in the initial stage of the hydrolysis. The material (5.1 gm.) was filtered off; it melted at 400° and hence proved to be the "diimide" (VIII). The filtrate was evaporated to 100 ml. and cooled. The deposited crystalline product was filtered and treated with sodium bicarbonate solution. The extract yielded on acidification an acid (0.43 gm.) which after recrystallization from dilute ethanol melted at 180°. Calculated for cyclohexane-1,1-diacetic acid, $C_{10}H_{16}O_4$, equivalent weight: 100. Found: 101. The melting point reported by Thorpe (9) was 181°. The bicarbonate insoluble material (0.27 gm.) was found to be diimide (VIII). The filtrate was taken to dryness, washed with a large quantity of water to remove ammonium chloride and treated with sodium bicarbonate solution. There was no reaction and

acidification of the filtered solution yielded no precipitate. The solid was next extracted with boiling benzene and the extract filtered, evaporated to a small volume, and cooled. A crystalline material was obtained. It melted at 167° after recrystallization from benzene and showed no depression with 3-azaspiro(5.5)hendecane-2,4-dione (IV). The yield was 0.65 gm. The benzene insoluble material (0.60 gm.) melted at 212 - 230°. It was insoluble in all common organic solvents with the exception of hot glacial acetic acid.

2nd. Attempt

The imino imide (I, 10 gm.; 0.0402 mole) was dissolved in 10% hydrochloric acid (750 ml.) and the solution refluxed with stirring for 12 hours. The yield of the insoluble diimide (VIII) was 5.9 gm. The filtrate was processed as in the previous attempt. The following compounds were isolated:

cyclohexane-1,1-diacetic acid	0.1 gm.
3-azaspiro(5.5)hendecane-2,4-dione (IV)	0.3 gm.
substance melting at 207 - 225°	1.4 gm.

The last product resembled closely the material melting at 212 - 230° isolated in a previous attempt. It was readily soluble in cold, dilute potassium hydroxide; a viscous oil

which precipitated upon acidification could not be crystallized despite numerous attempts. An attempt was made to hydrolyze the compound with 15% potassium hydroxide. The solution in potassium hydroxide was boiled for two hours; there was a continuous evolution of ammonia. After it was cooled and acidified with 20% hydrochloric acid, an oil precipitated which again could not be crystallized. Since the bulk of imino imide reacted to produce the diimide and the prospects of obtaining a satisfactory yield of a monosubstituted spiro(5.5)hendecane-2,4-dione appeared remote, further attempts of acid hydrolysis of imino imide were discontinued.

Aqueous Hydrolysis of the Imino Imide

1st. Attempt

The imino imide (10 gm.; 0.0403 mole) was dissolved in water (1500 ml.) by heating to boiling with agitation. After a period of five hours, a solid material began to separate in the form of fine needles. The solution was then cooled down to room temperature and the crystals filtered off. The substance (5.2 gm.) melted at 275° and was insoluble in all common organic solvents. It also did not dissolve in dilute sodium hydroxide but readily dissolved in dilute

hydrochloric acid. The solution yielded on long standing at room temperature a solid proved to be diimide (VIII). The original filtrate yielded on evaporation a small quantity of crystalline material (1.2 gm.) melting at 213 - 225°. It was insoluble in common organic solvents but dissolved easily in cold, dilute sodium hydroxide. The compound was not soluble in hydrochloric acid even on boiling. The substance was purified by recrystallization from a large volume of boiling water; it separated from this solvent in large, thick needles melting at 228 - 235°. Six crystallizations from boiling water brought the melting point to 252 - 253°. The compound proved to be identical with materials melting at 212 - 230° and 207 - 225° obtained in a previous acid hydrolysis of imino imide after they had been similarly purified.

2nd. Attempt

The imino imide (10 gm.) was dissolved in boiling water (3 liters) and the boiling continued until no more ammonia was evolved; the process required four days. No separation of solid material was observed. The solution was next evaporated to 500 ml., boiled with charcoal and filtered hot. The filtrate yielded on cooling a crystalline

substance which was filtered, washed with water and dried. It melted at 225 - 233°. The substance (3.1 gm.) was extracted with hot benzene; on evaporation to a small volume the extracts yielded a compound (0.9 gm.) melting at 155 - 160°, which after purification proved to be the dione (IV). The benzene extracted substance melted at 238 - 242° and after a few recrystallizations from boiling water, it melted at 252° showing no depression with the similar product of the previous hydrolysis. The original filtrate was evaporated to about 100 ml. and yielded on cooling an additional quantity of the product. The yield of the benzene extracted material was 1.5 gm. The infrared spectrum of the compound melting at 252° showed strong absorption bands at 3430, 3200 and 3100 cm.$^{-1}$ indicating N-H stretching vibration of the primary amide and the glutarimide ring. Calculated for 3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV), $C_{11}H_{16}N_2O_3$: C, 58.98; H, 7.19; N, 12.50. Found: C, 59.35; H, 7.02; N, 12.36. The best conditions for the preparation of this compound were found when the duration of hydrolysis was limited to 24 hours. For optimum conditions the yield of the product was 5.25 gm. from 10 gm. of crude imino imide. The yield of dione (IV) was 0.5 gm. Certain quantity of the product was present in the residue obtained by the evaporation to dryness of the final

filtrate but it was strongly contaminated with dark, amorphous products which were difficult to separate.

Hydrolysis of the Diimino Diimide (XIII) and the Diimide (VIII) by Water

Pure diimino diimide (1.1 gm.; 0.0045 mole) was introduced into one liter of boiling water. After six hours of boiling with stirring, it dissolved completely. The solution was then evaporated to 150 ml. and cooled. The separated crystals were filtered, washed with water and dried. They melted at 246 - 249°, and when recrystallized from water showed no depression with the previous product of aqueous hydrolysis, melting at 252°. An additional quantity of the product was obtained on evaporation of the filtrate, bringing the total yield to 0.83 gm.

The results of aqueous hydrolysis of the diimide (VIII) carried out under similar conditions were almost identical.

Synthesis of 3-Azaspiro(5.5)hendecane-1-cyano-2,4-dione (X)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV, 0.2 gm.) was treated with thionyl chloride. The initially vigorous reaction soon subsided; the mixture was then refluxed on the steam bath for 30 minutes and cooled on ice.

Water was next added very carefully to decompose unreacted thionyl chloride. The solution was then filtered, washed with water and the dark solid recrystallized from a large volume of hot water. The product melted at 192 - 194°. The infrared spectrum showed characteristic N-H stretching bands of glutarimides at 3200 and 3100 cm.$^{-1}$ and a sharp band at 2245 cm.$^{-1}$ associated with the absorption of the nitrile group. The carbonyl stretching absorption was also observed in the region characteristic of glutarimides (1730 - 1670 cm.$^{-1}$)

Attempted Partial Decarboxylation of 3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic Acid (III)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid (III, 0.5 gm.) was dissolved in 0.1 N potassium hydroxide (16.2 ml.; titre, 0.8687). The amount of hydroxide was calculated so as to neutralize exactly half of the quantity of acid. The solution was evaporated to dryness under the reduced pressure at room temperature. The dry residue was next heated on the oil bath at 100° for 20 minutes. The material thus treated was insoluble in water. After washing with water and recrystallization from benzene, it melted at 165° and proved to be 3-azaspiro(5.5)hendecane-2,4-dione. Similar experiments showed that partial decarboxylation of

the acid by route of monosodium salt was not feasible as a simultaneous elimination of both carboxylic groups occurred even on mild heating.

Alkaline Hydrolysis of 3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV)

The amide (XIV, 3 gm.) was dissolved in 15% potassium hydroxide (12 ml.) and boiled for two hours in an open beaker. Water was added occasionally to maintain the original volume. The solution was cooled on ice and acidified with 20% hydrochloric acid. There was an immediate separation of a viscous oil. The aqueous solution was decanted. The oil reacted vigorously with sodium bicarbonate. It was dissolved in acetone and the solution left to evaporate slowly. The crystalline solid which separated on standing was filtered and washed on filter with a little acetone. The material (0.33 gm.) melted at 132° with a vigorous evolution of gas. Several attempts to recrystallize it, using either ethanol-benzene or acetone-carbon tetrachloride mixtures failed because the compound decarboxylated even at temperatures below the boiling point of these solvents. Attempts to purify the crude acid by dissolving in sodium bicarbonate solution and reprecipitating with dilute hydrochloric acid also failed since on acidification of the solution the acid precipitated as an oil. The bicarbonate insoluble material represented on the average

15% of the starting material and consisted of approximately equal quantities of the starting material and dione (IV).

Preparation of 3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylic acid (XI)

The method employed has been described by Thorpe (9). 3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV, 4 gm.; 0.0178 mole) was dissolved in concentrated sulphuric acid (11 ml.) and the solution cooled below 0°. 20% Sodium nitrite solution (20 ml.) was added drop by drop with a vigorous agitation. After 30% of sodium nitrite had been added, a solid material began to separate. The solution after the addition was left for a few hours at room temperature. It was then cooled to 0° and diluted to twice the original volume by adding ice. The solid was filtered and washed on filter with cold water. The material (2.5 gm.) was dried under vacuum; it melted at 134° with foaming and subsequent resolidification. The new solid melted at 161°. A small quantity of acid was decarboxylated and the product recrystallized from benzene. It melted at 167° and showed no depression with 3-azaspiro(5.5)hendecane-2,4-dione (IV).

The product was found to be completely soluble in aqueous sodium bicarbonate. When reprecipitated with dilute

hydrochloric acid, filtered and dried it melted at 135°. The melting point could not be raised by repeating the process. The infrared spectrum showed two bands at 3200 and 3100 cm.$^{-1}$, characteristic of glutarimides and no absorption above this region. A very broad band near 2600 cm.$^{-1}$, similar to that found in carboxylic acids (strongly bonded O-H stretching vibration) was also present. Calculated equivalent weight for $C_{11}H_{15}NO_4$ (XI): 225. Found: 225.

Cyclohexane-1,1-diacetic Acid Anhydride (XXX)

The preparation was based on the method of Thorpe (9). Crude imino imide (I, 33 gm.; 0.133 mole) was dissolved in concentrated sulphuric acid (85 ml.), some water (13 ml.) added and the solution heated on a sand bath until a vigorous evolution of carbon dioxide took place. The solution was then kept at this temperature (130 - 140°) until no more gas evolved which required seven hours. It was then cooled, diluted with equal volume of water and gradually heated to the boiling point. After a few hours of boiling the solution was cooled again and a large volume of water added. The precipitated crude cyclohexane-1,1-diacetic acid was filtered and washed with ice cold water. It was next dissolved in

sodium bicarbonate solution, boiled with charcoal, filtered and acidified with dilute sulphuric acid. Finally it was recrystallized from dilute ethanol. The material (24 gm.) melted at 179 - 180°. Literature melting point (9) was 181°. The acid (24 gm.; 0.12 mole) was refluxed for four hours with acetic anhydride (70 ml.; 0.63 mole). Acetic anhydride was then distilled off and the product distilled under reduced pressure, collecting at 143 - 152°/2 mm. The yield was 20.5 gm. A small quantity after two recrystallizations melted at 73°. The same melting point was reported by Thorpe (ibid.).

Cyclohexane-1,1-di(2-ethanol) (XXXI)

Cyclohexane-1,1-diacetic acid anhydride (XXX, 19.5 gm.; 0.107 mole) was placed in the extraction thimble of Soxhlet apparatus which was fitted into a flask containing the solution of lithium aluminum hydride (10 gm.; 0.266 mole) in absolute ether (250 ml.). After the solution had been refluxed for 12 hours all the anhydride dissolved. The solution was refluxed for another 6 hours following which the excess hydride was decomposed with water. The solution was filtered and the solid material extracted with ether, using Soxhlet extractor. Ether was then removed and the residual oil distilled under vacuum. It was collected at 152 - 157°/2 mm.

The infrared spectrum showed no bands in the carbonyl absorption region and a broad, high intensity band at 3400 cm.$^{-1}$ corresponding to bonded O-H stretching vibration. Prominent absorption was also observed in the region 1065 - 1000 cm.$^{-1}$ associated with O-H deformation vibrations.

The oily material crystallized when kept in the refrigerator for a few hours. The solid (17.5 gm.) melted at 45 - 49°. After two recrystallizations from carbon tetrachloride the compound melted at 55°. It was insoluble in water and ligroin sparingly soluble in benzene, ether and carbon tetrachloride, and readily soluble in ethyl and methyl alcohol. Calculated for $C_{10}H_{20}O_2$: C, 69.70; H, 11.70. Found: C, 69.35; H, 11.83.

3-Oxaspiro(5.5)hendecane (XXV)

Cyclization of cyclohexane-1,1-di(2-ethanol) was first attempted following the method of Newman and Whitehouse (95). Dry hydrogen chloride was passed into the solution of diol in benzene at room temperature. Some evolution of heat was observed at the beginning. After three hours the solution was shaken with water and sodium bicarbonate solution and finally dried over the anhydrous sodium sulphate. Benzene was removed by distillation and the residual oil

distilled under reduced pressure. A small quantity of a mobile, colorless liquid was collected at 90 - 120°/28 mm. It had a pleasant smell resembling that of essential oils. The bulk of liquid distilled at 150 - 160°/2 mm.; it represented the unreacted material.

A successful synthesis of 3-oxaspiro(5.5)hendecane was accomplished using the method of Reynolds and Kenyon (19). The diol (16.7 gm.; 0.097 mole) was dissolved in 2,6-lutidine (45 ml.; 0.445 mole) which had been previously purified by fractionation and dried by refluxing over barium oxide with the subsequent distillation. The solution was placed in a 100 ml. three-necked flask equipped with a stirrer, condenser and the separatory funnel containing benzenesulphonyl chloride (12 ml.; 0.0492 mole). The stirring was started, the solution heated to boiling and benzenesulphonyl chloride added dropwise to the solution. After the addition refluxing was continued for another hour and the solution cooled to room temperature. Sufficient water was added to dissolve the solids and the solution extracted three times with 150 ml. portions of ether. The combined ether extracts were shaken with dilute sulphuric acid (200 ml.) in the separatory funnel, the acid layer removed and the extraction with acid repeated twice. After the removal of lutidine the ether solution was shaken three

times with water and then condensed to about 50 ml. It was then dried over the anhydrous potassium carbonate. The ether was removed by distillation and the residual oil fractionated under reduced pressure. Most of the liquid (11 gm.) distilled at 102 - 103°/23 mm. The infrared spectrum showed no absorption due to either hydroxyl or carbonyl groups. A very intense band at 1100 cm.$^{-1}$ was very likely due to antisymmetric C-O-C stretching vibration (96, 97), characteristic of strainless cyclic ethers. Calculated for $C_{10}H_{18}O$: C, 77.81; H, 11.77. Found: C, 77.2; H, 11.91.

Spiro(5.5)hendecane-2,4-dione (XXVII)

The starting material for this preparation, cyclohexylideneacetone was synthesized by the method of Wallach (98). To the solution of pure, dry cyclohexanone (49.25 gm.; 0.5 mole) in dry acetone (29 gm.; 0.5 mole) a 5% solution of sodium ethoxide in absolute ethanol (245 ml.) was added over a period of two hours with stirring. The mixture was cooled on ice. After the addition fresh ice was packed and the solution left to stand overnight. A large quantity of water was then added to the solution, the separated oil extracted with ether and ether removed from the combined extracts by distillation. The residue was steam distilled and the distillate extracted a few times with ether. The

ether solution was reduced to a small volume and dried over the anhydrous sodium sulphate. Ether was then removed and the residual liquid fractionated under the reduced pressure. A fraction distilling at 90 - 105°/24 mm. (11 gm.) was collected.

Preparation of dione from cyclohexylideneacetone followed the procedure of Norris and Thorpe (16). Cyclohexylideneacetone (11 gm.; 0.086 mole) and dry, freshly distilled ethyl malonate (13 ml.; 0.0768 mole) were refluxed for two hours in a 5% solution of sodium ethoxide in absolute ethanol (30 ml.). The hot reaction mixture was then poured into the boiling solution of barium oxide (68.5 gm.) in water (615 ml.). The solution was refluxed for twenty hours. It was then cooled, the unsaponified malonic ester extracted with ether, the solution acidified with concentrated hydrochloric acid and boiled for 15 minutes; the separated oil was extracted with chloroform. The combined chloroform extracts were evaporated to a small volume, dried over the anhydrous sodium sulphate and the solvent removed by distillation. The residual oil solidified on cooling. It was purified by four recrystallizations from benzene. The compound (2.1 gm.) formed white needles melting at 169°. The melting point reported by Norris and Thorpe (ibid.) was 170.5°

Reduction of Spiro(5.5)hendecane-2,4-dione (XXVII)

The dione (1.3 gm.) was introduced directly into the ethereal solution of lithium aluminum hydride (1.5 gm. in 100 ml. of dry ether) in small portions. A moderate reaction accompanied the addition. Originally extraction with ether using Soxhlet assembly was attempted but the compound turned out to be completely insoluble in ether. After the addition refluxing with stirring was continued for 24 hours. The solution was processed in a usual way, the solids filtered off and extracted with ether using Soxhlet apparatus. The combined ethereal solutions were evaporated to a small volume, dried over the anhydrous sodium sulphate and the ether distilled off. The quantity of the residual oil was not sufficient to permit fractionation. The infrared spectrum showed a very strong, broad band in the O-H stretching region (3350 $cm.^{-1}$) its intensity indicating more than one hydroxyl group. The presence of a very broad and strong band in the region 1100 - 1000 $cm.^{-1}$ (O-H deformation vibrations) confirmed this opinion. A sharp, medium intensity band at 3020 $cm.^{-1}$ together with weak, broad bands at 1700 and 1650 $cm.^{-1}$ indicated the unsaturation. The product was next refluxed for three hours in benzene over phosphorus pentoxide in order to eliminate

hydroxyl groups by dehydration. Benzene was subsequently removed leaving a small quantity of a semisolid, brown material. Its infrared spectrum showed a complete absence of OH absorption but there was also no indication of unsaturation. The spectrum resembled closely that of a saturated hydrocarbon, suggesting the polymerization of the dehydrated product.

Methyl 3-Methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylate (XVII)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylic acid (XI, 6 gm.; 0.0266 mole) was treated with the ethereal solution of diazomethane produced by the decomposition of N-methylnitrosothiourea (12 gm.; 0.1 mole) with 50% potassium hydroxide. After six hours all the acid dissolved. The solution was left to stand overnight and the ether subsequently removed by distillation. The oily residue solidified on long standing in vacuum. The crude material (6.75 gm.) was recrystallized three times from methanol. It melted at 82°. The infrared spectrum showed the absence of N-H stretching bands proving the methylation of the imide nitrogen. The presence of glutarimide ring was apparent from the two strong bands at 1728 and 1670 $cm.^{-1}$ and their overtones at

3440 and 3370 cm.$^{-1}$. The ester carbonyl stretching absorption was apparently superimposed on the imide carbonyl stretching frequency at 1728 cm.$^{-1}$. Calculated for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.54; H, 7.60; N, 5.55.

3-Methyl-3-azaspiro(5.5)hendecane-1-hydroxylmethyl (XIX)

Lithium aluminum hydride (3 gm.; 0.079 mole) was dissolved in ether (150 ml.) by refluxing for three hours. Methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylate (XVII, 4.3 gm.; 0.017 mole) was placed in the extraction thimble of the Soxhlet apparatus and the solution refluxed until all the ester had been transferred into the reaction flask. The refluxing and stirring continued for six hours following which the solution was cooled on ice, the excess hydride decomposed in a usual way and the solids filtered. They were next extracted with ether using Soxhlet apparatus and the ether extract combined with the original filtrate. The ether solution was reduced to a small volume by distillation and treated with equal volume of petroleum ether. After several hours the product crystallized. The filtrate of these crystals was evaporated to dryness yielding an additional quantity of the solid material. The total yield of the crude product was 3.0 gm. A small quantity was recrystallized twice from ether-petroleum ether mixture. It melted

at 92°. The compound was readily soluble in ether, chloroform, benzene, alcohol and mineral acids but insoluble in water and ligroin. Calculated for $C_{12}H_{23}ON$: C, 73.05; H, 11.75; N, 7.14. Found: C, 72.53; H, 11.45; N, 7.06.

3-Methyl-3-azaspiro(5.5)hendecane-1-carboxylic Acid (XXII)

The modified procedure of Karrer and Widmer (99) used for exhaustive oxidation of piperidine was employed. Crude 3-methyl-3-azaspiro(5.5)hendecane-1-hydroxymethyl (XIX, 1 gm.) was dissolved in 25% sulphuric acid (6 ml.) and the solution added drop by drop to a solution of chromic oxide (2 gm.) in water (5 ml.) with stirring. A considerable evolution of heat was observed. After the addition the solution was heated on the steam bath for two hours with stirring. Certain amount of tarry material formed at this stage. The solution was cooled and sulphur dioxide passed for three hours to reduce the excess of chromic oxide. It was next boiled to expel the sulphur dioxide and subsequently treated with a solution of barium hydroxide (15 gm.) in boiling water (15 ml.). The slurry was heated for some time on the steam bath and the excess of barium hydroxide removed by adding dry ice with good agitation. The precipitation was completed at pH 5.5 of the solution. The mixture was filtered

hot and the solids treated three times with 200 ml. portions of boiling water, the resulting slurry being filtered each time after an efficient stirring. The combined filtrates were heated to boiling and treated very carefully with dilute sulphuric acid exactly to the point when the addition did not cause any further precipitation of barium sulphate. The precipitate was filtered and the solution evaporated to dryness on the steam bath. The solid residue was dissolved in a small quantity of hot water, boiled with charcoal, filtered and the filtrate condensed to a small volume. A crystalline material in a form of shiny scales separated on cooling. It melted at 301°; the recrystallization failed to raise the melting point above this value. The filtrate after evaporation to a small volume and cooling, yielded an additional portion of crystals. The combined yield was 0.68 gm. Part of the acid was converted to hydrochloride. The salt was purified by two recrystallizations from ethanol-ethyl acetate. It melted at 267 - 269°. Found: Cl, 14.12%. Calculated for $C_{12}H_{22}NO_2Cl$: Cl, 14.32%. The infrared spectrum showed a broad band at 2800 - 2400 $cm.^{-1}$ representing the strongly perturbed O-H and $\overset{+}{N}$-H stretching vibrations and a strong band at 1700 $cm.^{-1}$ due to carbonyl stretching vibration. The spectrum of the free amino acid showed a broad band at 2400 $cm.^{-1}$ due to $\overset{+}{N}$-H stretching vibration and a

strong band at 1592 cm.$^{-1}$ assigned to carbonyl stretching absorption of the carboxylate anion. Calculated for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 67.93; H, 10.07.

Cyclohexane-1,1-di(2-ethyl chloride) (XXXVI)

The preparation was based on the procedure of Ahmed and Strong (100) for the conversion of 1,9-nonane diol to 1,9-dichlorononane. Cyclohexane-1,1-di(2-ethanol) (XXXI, 14.5 gm.; 0.0843 mole) was treated with pyridine (4 ml.) in a three-necked flask equipped with stirrer, condenser and a separatory funnel containing thionyl chloride (38.6 gm.; 0.324 mole). The mixture could not be cooled on ice as required because the diol solidified at this temperature preventing the stirring. The addition of thionyl chloride therefore was carried out at room temperature. No evolution of heat was observed. After the addition the solution was left to stand for 24 hours. It was next refluxed for three hours, cooled on ice and treated carefully with cold water while an efficient stirring was maintained. The solution was then extracted with ether, the ether extract shaken successively with 50% sulphuric acid, water and aqueous solution of sodium bicarbonate and then dried over the anhydrous sodium sulphate. Vacuum fractionation of the oil left

after the removal of ether yielded a mobile liquid (1.5 gm.) distilling at 60 - 70°/3 mm. It had a pleasant smell resembling camphor. The boiling point and the absence of chlorine indicated that it was 3-oxaspiro(5.5)hendecane. The bulk of the material distilled at 115 - 119°/2 mm. The distillate (12.2 gm.) was a medium heavy liquid containing chlorine. It was refractionated collecting the product at 115 - 116°/2 mm.

3-Thiaspiro(5.5)hendecane (XXVI)

A method of Whitehead and collaborators (101) for the preparation of cyclic sulphides was employed. Cyclohexane-1,1-di(2-ethyl chloride) (XXXVI, 11 gm.; 0.0525 mole) was added drop by drop to the boiling solution of sodium sulphide nonahydrate (19 gm.; 0.079 mole) in dilute ethanol (20 ml. of ethanol in 16 ml. of water). After addition, the refluxing was continued for five hours and subsequently left to stand overnight. The following day most of the solvent was removed under vacuum, the residue treated with water and steam distilled. The distillate was extracted with ether. The residual oil left after the removal of ether was dissolved in little ethanol and the solution added drop by drop to a boiling solution of mercuric chloride (77 gm.; 0.283 mole) in ethanol (220 ml.) with an efficient stirring.

After the addition the solution was refluxed for one hour and allowed to cool to room temperature. It was then filtered and the crystalline addition product recrystallized three times from ethanol. The last crystallization failed to raise the melting point (166°). The compound (19.5 gm.) was next treated with 15% hydrochloric acid and the solution steam distilled. The distillate was extracted with ether, ether solution shaken with dilute sodium bicarbonate solution and dried over the anhydrous sodium sulphate. Vacuum distillation of the oil left after the removal of ether yielded a mobile, colorless liquid (7.1 gm.) boiling at 100 - 106°/5 mm. The material was fractionated twice; the main fraction collected at 100 - 102°/5 mm. The product contained sulphur; it had a penetrating, characteristic smell. The infrared spectrum did not show any absorption in the O-H and carbonyl stretching region. The band due to C-S-C stretching vibration was found at 654 cm.$^{-1}$ in agreement with the literature (102). Calculated for $C_{10}H_{18}S$: C, 70.52; H, 10.64. Found: C, 69.79; H, 10.57.

Preparation of Glutarimide

The compound was prepared by the method of Sircar (103). Glutaric acid was treated with concentrated ammonia and the solution evaporated to dryness under vacuum. The

dry diammonium salt was heated to 200° in a sublimator. The imide deposited on the walls of the condenser was purified by resublimation. The melting point (154°) showed agreement with the literature (ibid.)

Synthesis of 4,4-dimethylpiperidine-5-cyano-2-imino-6-oxo-3-carboxamide (XXXVII)

The compound was synthesized by condensing acetone with cyanoacetamide in presence of little piperidine. The preparation was entirely analogous to that of the imino imide (I) described on page 121. The yield was 32%. As in the condensation of cyclohexanone with cyanoacetamide a small quantity of "dinitrile" (4,4-dimethylpiperidine-3,5-dicyano--2,6-dione) was also produced.

2,4,6,8-Tetroxo-9,9-dimethyl-3,7-diazabicyclo(3.3.1) nonane (XLI)

The preparation followed a method of Thorpe (9). 4,4-Dimethylpiperidine-5-cyano-2-imino-6-oxo-3-carboxamide (XXXVII) was dissolved in cold, dilute potassium hydroxide and the solution warmed until the yellow color was discharged. It was then rapidly cooled to 0° and treated with a large quantity of glacial acetic acid. The precipitated compound was purified by dissolving in dilute hydrochloric acid and

reprecipitating with sodium acetate. The solution in hydrochloric acid yielded on boiling the product purified by sublimation. It volatilizes at elevated temperatures without melting.

4,4-Dimethylpiperidine-2,6-dione

The preparation was based on a modified procedure of Thorpe (9). 4,4-Dimethylpiperidine-5-cyano-2-imino-6-oxo-1-carboxamide was dissolved in 10% potassium hydroxide and the solution boiled for several hours. Hot water was added occasionally to compensate for the evaporation. The solution was cooled, acidified with 20% hydrochloric acid and evaporated to dryness on the steam bath. The solid residue was heated in a sublimator to about 200°. The sublimate was collected and resublimed. The melting point (146°) coincided with the value reported by Thorpe (ibid.).

Synthesis of 2-Dimethylaminoethyl 3-Methyl-3-azaspiro(5.5)-hendecane-1,5-dicarboxylate Hydrochloride (XXIII)

A method of Tilford et al. (104, 105) was employed. 3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (0.255 gm.; 0.001 mole) was added to a solution of sodium (0.115 gm.; 0.005 mole) in absolute 2-propanol (8 ml.) The

solution was refluxed for a short time and 2-chlorodimethylaminoethyl hydrochloride (0.725 gm.; 0.005 mole) was added. The reaction mixture was refluxed for 24 hours. After the evaporation to dryness under vacuum at room temperature the residue was treated with a solution of sodium bicarbonate, taken to dryness again and the residue redissolved in water. The aqueous solution was extracted with two 25 ml. portions of ether and the combined ether extracts dried over the anhydrous sodium sulphate. Dry hydrogen chloride was next passed through the solution, the precipitated solid washed on filter with ether and dried in vacuum at 100°. It melted at 229° with decomposition. The infrared spectrum showed a strong, broad band with peaks at 2550 and 2420 $cm.^{-1}$ due to strongly perturbed N-H vibration and a single, strong band at 1720 $cm.^{-1}$ corresponding to the ester carbonyl stretching frequency. Calculated for $C_{21}H_{42}O_4N_3Cl_3$: C, 49.76; H, 8.34; N, 8.29; Cl, 20.98. Found: C, 49.65; H, 8.37; N, 8.07; Cl, 21.13.

Attempted Resolution of 3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic Acid (XXI)

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (.255 gm.; 0.001 mole) was dissolved in fifty ml. of boiling ethanol and treated with the solution of

strychnine (.334 gm.; 0.001 mole) in chloroform (5 ml.). The solution was evaporated to a smaller volume, some ethyl acetate added and it was then left to stand for 24 hours at room temperature. The separated crystals were filtered and recrystallized twice from ethanol-ethyl acetate mixture. The compound was subsequently treated with a dilute solution of sodium hydroxide and the solution extracted a few times with a large volume of chloroform to remove the free strychnine. The alkaline solution containing the salt of the amino acid was treated with dilute sulphuric acid to pH 9, filtered, condensed to a very small volume and inspected in the polarimeter. No optical activity could be detected.

Attempted Resolution of 3-Methyl-3-azaspiro(5.5)hendecane-1,5-dihydroxymethyl (XVIII)

The solution of 3-methyl-3-azaspiro(5.5)hendecane-1,5-dihydroxymethyl (.227 gm.; 0.001 mole) in ethanol (10 ml.) was treated with the solution of d-camphorsulphonic acid (.23 gm.; 0.001 mole) in ethyl acetate (10 ml.). The solution was evaporated to a small volume, some ethyl acetate added, the volume reduced again by evaporation and the solution allowed to cool. The crystals separating after a long period of standing were filtered and recrystallized four times

from ethanol-ethyl acetate mixture. They were next treated with little dilute sodium hydroxide and the mixture extracted with ether. The ether solution was filtered, condensed to a small volume and inspected in the polarimeter. The compound proved to be inactive.

Attempted Resolution of 3-Methyl-3-azaspiro(5.5)hendecane-1-carboxylic Acid (XXII)

The procedure was identical with the one employed in the resolution of 3-methyl-3-azaspiro(5.5)hendecane-1-hydroxymethyl (XIX) by means of d-camphorsulphonic acid. The product showed no optical activity.

Preparation of Cyclohexane-1,1-di(2-ethyl iodide) (XXXII)

Preparation followed a method described by Wood, Stone and Shechter (106, 107). Cyclohexane-1,1-di(2-ethanol) (XXXI, 26 gm.; 0.15 mole) was treated with 95% phosphoric acid (90 gm.) and powdered, dry sodium iodide (100 gm.; 0.67 mole). 95% Phosphoric acid was prepared by adding a calculated quantity of phosphorus pentoxide to the commercial (85%) phosphoric acid. Care had to be exercised because of a strong evolution of heat accompanying the process. The reaction mixture was heated on the oil bath for eight hours at 120° with frequent manual agitation. It was then cooled, treated with a large

quantity of water and filtered. The solid material was washed on filter with water and then dissolved in ether; the ether solution was shaken with 10% solution of sodium thiosulphate, dried and ether removed under vacuum. The material was purified by recrystallization from methanol. It melted at 59°. The yield of the pure material was 53.6 gm.

Synthesis of Spiro(5.5)hendecane-3,3-dicarboxylic Acid (XXXIV)

Cyclization with malonic ester was based on the procedure described by Birch et al. (108). Sodium (6.83 gm.; .296 mole) was added to the absolute ethanol (100 ml.) contained in a 250 ml. three-necked flask equipped with a reflux condenser, magnetic stirrer and a separatory funnel containing the solution of cyclohexane-1,1-di(2-ethyl iodide) (29.14 gm.; 0.0743 mole) in 50 ml. of absolute ethanol. After all the sodium dissolved the solution was allowed to cool to 60° and was then treated with ethyl malonate (23.8 gm.; 0.1485 mole). While a good stirring was maintained the alcoholic solution of diiodide was added in a slow, steady stream; the addition was completed in three minutes. The solution was next refluxed for eight hours and left to stand overnight. It was then diluted with 700 ml. of water and extracted four times with 200 ml. portions of ether. The combined ether extracts were washed successively with water, 5% hydrochloric

acid, sodium bicarbonate and water. The solution was finally condensed to about 50 ml. volume, dried over the anhydrous sodium sulphate and ether removed by distillation. The residue was distilled under vacuum and a heavy, colorless oil (14 gm.) collected at 133 - 137°/2 mm. The product was refluxed in the solution of ethanolic potassium hydroxide (10 gm. in 20 ml. of 50% ethanol) for four hours. The solution was evaporated to a very small volume under vacuum at room temperature and the residue treated with water. A clear, yellow solution was produced. It was extracted twice with ether to remove the unsaponified ester. The solution was next acidified with 20% hydrochloric acid while efficient stirring and cooling was maintained. A very fine, white solid was precipitated; it was filtered, washed on filter with cold water and finally recrystallized from dilute ethanol. The yield was 8.75 gm. It melted at 191° with decarboxylation. Calculated equivalent weight for $C_{13}H_{20}O_4$: 120. Found: 121.

Synthesis of Spiro(5.5)hendecane-3-carboxylic Acid (XXXV)

Spiro(5.5)hendecane-3,3-dicarboxylic acid (8.7 gm.) was heated in a large test tube on the oil bath at 200 - 210° until the evolution of carbon dioxide had ceased. The material solidified on cooling. It was dissolved in n-hexane, boiled

with charcoal, filtered and condensed to a small volume. The solution yielded white scales (6.4 gm.) on long standing in the refrigerator; after recrystallization from dilute ethanol they melted at 79°. The infrared spectrum showed a weak broad band at 2600 - 2700 cm.$^{-1}$ characteristic of O-H stretching vibration of acids and a single strong band in the carbonyl stretching region at 1710 cm.$^{-1}$. Found equivalent weight: 197. Calculated for spiro(5.5)hendecane-3-carboxylic acid: 196. Calculated for $C_{12}H_{20}O_2$: C, 73.3; H, 10.25. Found: C, 73.22; H, 10.14.

Attempted Synthesis of Spiro(5.5)hendecane (XXIV)

The first attempt involved a direct decarboxylation of spiro(5.5)hendecane-3-carboxylic acid (XXXV). The acid (1 gm.) was boiled for 10 hours in quinaldine (20 ml.; boiling point 247°) in presence of 0.2 gm. of copper powder as a catalyst. After a few hours a fresh catalyst was added. No evolution of gas could be observed. After the solution cooled to room temperature it was treated with a large excess of 20% sulphuric acid, cooled, filtered and extracted with ether. The extracts were washed with water and shaken with 10% sodium hydroxide in a separatory funnel. The alkaline extract yielded on acidification a solid (0.65 gm.) which after recrystallization from dilute ethanol melted at 78° and proved to be the starting material. The original ether

solution was shaken with dilute sulphuric acid and water and finally dried over the anhydrous potassium carbonate. Evaporation of ether left no residue.

In a second attempt the Hunsdiecker reaction (80) was employed. The silver salt of the acid was first prepared following the method of Allen and Wilson (109).

The acid (5.95 gm.; 0.0303 mole) was exactly neutralized with potassium hydroxide solution in the presence of phenolphthalein; the solution was made to 75 ml. and was subsequently treated with 10% solution of silver nitrate until the addition failed to produce any further precipitation. Vigorous stirring was maintained during the addition. The precipitated silver salt of the acid was filtered, washed with methanol and dried in vacuum. The yield was 8.55 gm. It was next placed in a 100 ml. three-necked flask and connected to the vacuum pump keeping the two necks stoppered. The flask was heated on the oil bath to 100° for 48 hours. The heating was then discontinued, 50 ml. of dry carbon tetrachloride added, the stirring started and the mixture refluxed while the solution of bromine in dry carbon tetrachloride was being added slowly until the permanent brown coloration resulted. The mixture was filtered, the solid material washed on filter with little carbon tetrachloride and the combined filtrates shaken with a dilute solution of sodium bisulphite in a separatory funnel. The solution

was next dried over the anhydrous sodium sulphate, the solvent removed and the residue distilled under vacuum. A yellow oil was collected at 140 - 160/3 mm.; it soon solidified. The compound (4.45 gm.) gave a positive halogen test. The high boiling point made it doubtful that the product was the expected 3-bromo-spiro(5.5)hendecane.

In an attempted reduction of the bromide to the corresponding hydrocarbon, the procedure of Hirschbaum and Daus (110) was employed. The bromide (4.45 gm.) was dissolved in 50 ml. of absolute 1-propanol and finely sliced sodium (3 gm.) added to the solution which was stirred mechanically. After all the sodium had dissolved the solution was refluxed for one hour and cooled. A large quantity of water was then added and the solution extracted twice with light petroleum ether. The combined extracts were evaporated to about 30 ml., dried over anhydrous sodium sulphate and the ether removed by distillation. Some 1-propanol was also extracted; the residue was fractionated, but after all the propanol had been removed the residual oil could not be distilled because of a very high boiling point. It was obvious that the material was not the expected spiro(5.5)hendecane which boils at $210^{\circ}/730$ mm. (17).

Because of the shortage of time it was not possible to account for the failure of the reaction.

TABLE III

Infrared Absorption Maxima

of

4,4-Dimethylpiperidine-2,6-dione (XLIV)

3-Azaspiro(5.5)hendecane-2,4-dione (IV)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV)

3-Azaspiro(5.5)hendecane-1-cyano-2,4-dione (X)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylic Acid (XI).

XLIV		IV		XIV		X		XI	
3420	m	3200	s b	3430	vs	3180	vs	3195	s
3200	s b	3080	s	3200	vs vb	3080	vs	3080	s
3090	m	2940	s	3100	vs sh	2925	vs	2910	s b
2870	w	2900	s	2935	vs	2860	vs	2600	m b
1725	vs	2860	s	2860	s	2250	m	1722	vs
1782	vs	1715	vs	1720	vs	1695	vs b	1680	vs b
1470	w	1678	vs	1677	vs b	1457	vs	1452	m
1450	w	1470	w	1455	s	1411	s	1415	m
1427	w	1453	m	1405	vs b	1385	vs	1375	s
1412	w	1440	m	1375	vs b	1357	vs	1365	s
1390	s	1425	m	1348	m	1335	vs	1310	s
1377	s	1410	m	1335	m	1318	vs	1275	vs
1332	w	1377	m	1330	m	1295	vs	1265	vs b
1287	vs	1360	m	1300	vs	1260	vs	1227	vs
1255	s	1337	w	1285	vs vb	1245	vs	1205	vs
1195	vw	1322	m sh	1257	vs sh	1215	vs	1175	m
1175	w	1284	vs	1190	w	1177	m	1145	w
1147	s	1270	vs	1167	m	1165	m	1137	m
1130	m	1198	m	1137	w b	1137	m	1090	w
1025	vw	1169	m	1090	vw	1095	s	1070	w
923	vw	1150	s	1075	vw b	1045	w	1002	w
862	w	1095	w	1043	vw	1032	w	977	m
822	m	1065	w	1005	vw	977	w	930	m b
610	vw	1040	w	980	w b	955	vw	840	s
		1005	w	930	w	935	w	805	m
		975	w	895	vw	920	w	750	m
		950	vw	860	s	852	s	707	w
		940	vw	830	w sh	790	vw	648	m
		927	w	817	w	763	w		
		915	m	800	vw	697	s		
		875	m	745	vw				
		847	w	702	vw				
		840	w	630	m b				
		832	w						
		765	w						
		632	w						

TABLE IV

Infrared Absorption Maxima

of

Methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylate (XVII)

4,4-Dimethylpiperidine-3,5-dicyano-2,6-dione (XLV)

3-Azaspiro(5.5)hendecane-1,5-dicyano-2,4-dione (II)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic Acid (III)

3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic Acid Anhydride (XLII)

XVII		XLV			II			III			XLII	
3440	vw	3450	w	b	3460	w	b	3200	s		3200	s
3375	vw	3220	s		3205	vs	b	3100	s		3100	s
2930	s	3120	s		3110	vs		2940	s		3000	w
2850	m	2990	w		2940	vs		2860	s		2930	s
1728	vs	2890	m		2865	vs		2600	m	b	2850	s
1673	vs	2280	w		2260	w		1700	vs	b	1820	vs
1495	s	1735	vs		1720	vs	vb	1455	m		1782	vs
1478	s	1717	vs		1464	vs		1417	m	b	1735	vs
1413	s	1465	w		1450	vs		1377	s		1705	vs
1360	s	1435	m	b	1410	w	sh	1280	vs		1460	w
1348	s	1412	m		1372	vs	vb	1230	s		1450	w
1328	vs	1405	s		1360	vs	vb	1207	s		1430	m
1305	vs	1383	s		1340	vs	sh	1150	m		1375	m
1293	vs	1362	vs	b	1330	vs	sh	1140	m		1353	s
1255	m	1313	vs	b	1323	vs		1097	vw		1335	m
1230	m	1240	vs	b	1295	vs		1007	vw		1287	vs
1200	s	1225	vs		1265	vs	b	930	w	b	1260	s
1175	s	1165	m	b	1242	vs	vb	845	m		1245	s
1160	s	1130	w		1182	m		747	vw		1230	m
1140	vs	1040	vw	b	1158	m		707	vw		1215	vs
1105	m	1018	w		1147	s		644	w		1185	s
1075	w	993	s		1096	s					1177	s
1040	vw	877	vw		1087	s					1140	s
993	s	847	vw	b	1070	vw					1100	vw
965	m	802	s	b	1040	s					1080	s
945	s	785	s		982	w					1065	vs
915	m	740	s		965	vw					1000	m
860	w	650	vw	b	937	vw					960	s
853	w				928	w					935	s
820	w				910	w					890	w
792	w				870	m					850	w
750	vw				845	vs	vb				827	s
720	w				793	w					815	s
643	w				777	w					695	vw
625	m				740	s					640	vw
					689	s						
					679	s						

TABLE V

2,4,6,8-Tetroxo-9,9-dimethyl-3,7-diazabicyclo(3.3.1)-nonane (XLI)

2',4',6',8'-Tetroxo-spiro(cyclohexane-1,9'-(3,7)diaza-bicyclo(3.3.1)nonane) (VIII)

2,6-Diimino-9,9-dimethyl-3,7-diazabicyclo(3.3.1)nonane-4,8-dione (XLIII)

2',6'-Diimino-4',8'-dioxo-spiro(cyclohexane-1,9'-(3,7)-diazabicyclo(3.3.1)nonane) (XIII)

3-Azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I)

XLI			VIII			XLIII			XIII			I		
3210	vs		3220	vs		3300	vs		3300	vs		3400	s	b
3100	vs		3100	s		3200	s	sh	3000	m	sh	3150	s	b
3000	m		2940	m		2960	s	b	2930	s		2930	s	
2850	m		2840	m		2870	s	b	2850	m		2850	m	sh
1720	vs		1750	s		2700	m	b	1690	vs		2250	w	
1705	vs		1710	vs		1685	vs	b	1660	vs		1670	vs	
1473	m		1505	w		1635	vs	b	1525	vs	b	1640	vs	
			1462	m										
1435	s		1430	s		1605	vs	b	1468	m		1555	s	b
1409	m		1366	m		1520	vs	b	1448	s		1525	s	
1387	m		1337	s		1450	s	sh	1350	s	sh	1460	m	b
1357	s		1295	vs		1437	s	b	1312	vs		1395	s	
1337	vs		1215	vs		1310	vs		1262	m		1320	s	b
1317	vs		1195	m		1255	s		1220	s		1285	m	
1298	vs		1116	m		1220	w		1175	m		1255	m	
1196	vs		1093	w		1190	m		1130	m		1212	w	
1164	m	vb	1006	w		1163	m		1090	w		1182	vw	
990	w	vb	975	w		1130	s		1075	vw		1165	w	
968	w		960	w		960	w		1040	vw		1125	w	
912	m	sh	945	vw		930	w		965	w		1110	w	
903	s		935	vw		895	w		890	w		1075	vw	
845	s	b	897	m		845	vw		805	m		1020	vw	
805	s		860	m		800	vw		765	w	b	960	vw	
698	w		840	s		745	m		725	w	b	850	w	
670	w		820	s		660	vw		620	w		815	w	
640	w		805	m		630	w					705	w	
			772	w								675	w	b
			708	w	b									
			642	w										

TABLE VI

Infrared Absorption Maxima

of

Glutarimide (XLVI)

Spiro(5.5)hendecane-2,4-dione (XXVII)

Product of the Reduction of Spiro(5.5)hendecane-2,4-dione (XXIX)

Spiro(5.5)hendecane-3-carboxylic Acid (XXXV)

XLVI		XXVII			XXIX		XXXV
		Solution #		Solid			
3400	w b	3020	w	3420 vs	3330	vs b	2935 vs
3200	s	2930	s	2940 s	3020	m	2850 s
3100	s	2860	m	2870 m b	2920	vs	1707 vs
2990	m	1730	m	2740 m b	2840	vs	1462 m
2915	m	1707	vs	2670 m	2650	vw	1445 m
2840	m	1610	m b	2620 m	1700	w	1325 w
1817	m b	1560	w	1620 vs	1650	w	1312 w
1702	vs b	1455	m	1587 s	1450	vw	1300 m
1663	vs b	1440	vw	1512 vs b	1362	m b	1277 w
1470	w	1417	vw b	1475 s	1320	m	1248 m
1425	s	1345	vw	1460 s	1290	m	1230 m
1410	m	1330	w	1440 m	1270	m	1212 w
1370	vs	1311	w	1420 m	1250	m	1180 vw
1355	vs	1263	m	1353 s	1205	w	1168 w
1387	vs	1207	s	1343 s	1195	w	1155 w
1350	s	1162	vw	1330 s	1170	w	995 vw
1255	vs	1145	vw	1317 m	1148	w	930 w
1180	vs	1090	vw	1300 vs	1130	m	913 w
1145	vs	975	vw	1282 m	1107	m	895 w
1055	s	925	w	1260 s	1085	m	743 vw
920	m	842	w	1247 s	1065	s	
830	s b	720	m b	1235 vs	1030	vs	
757	m	665	w	1200 s	1007	vs	
670	w			1175 w	985	w	
				1150 vs	960	w	
				1095 m	945	m	
				1077 w	925	w	
				1045 vw	912	m	
				987 w	900	w	
				970 w	880	vw	
				945 vw	865	vw	
				935 m	845	m	
				897 w	825	vw	
				863 w	800	vw	
				853 w	785	m	
				840 m	768	m	
				825 w	713	s	
				615 w	670	m	

3% Chloroform solution, 0.1 mm. cell.

TABLE VII

Infrared Absorption Maxima

of

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dihydroxymethyl (XVIII)

2-Dimethylaminoethyl 3-methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylate hydrochloride (XXIII)

3-Azaspiro(5.5)hendecane (V)

3-Oxaspiro(5.5)hendecane (XXV)

3-Thiaspiro(5.5)hendecane (XXVI)

XVIII		XXIII		V	XXV	XXVI
3420	vs	3430	w	3290 m	2930 vs	2910 vs
3080	s	2945	s	2920 vs	2845 vs	2845 vs
2930	vs	2860	m	2860 vs	2765 w	2665 vw
2860	vs	2545	vs b	2760 s	2700 w	1455 vs
2800	vs b	2410	vs b	2680 w	1640 vw	1445 vs
1670	vw	1725	vs	1448 vs	1473 s	1430 vs
1635	vw	1482	vs	1427 m	1452 vs	1355 vw
1485	vs	1468	vs	1390 w	1390 m	1315 w
1475	vs	1390	s	1370 w	1350 w	1283 m
1465	vs	1377	s	1357 w	1325 w	1270 vs
1430	m	1315	s	1343 w	1307 m	1242 w
1390	s	1287	w	1320 vs	1295 m	1205 w
1375	m	1270	w	1307 m	1275 vw	1162 m
1365	s	1235	m	1280 w	1255 w	1150 w
1340	s	1212	s	1250 vw	1234 vs	1135 w
1330	s	1210	vs	1225 w	1202 m	1113 w
1325	s	1198	vs	1208 w	1177 s	1088 w
1305	s	1170	vs	1185 m	1147 m	1068 vw
1283	s	1155	vs	1163 m	1115 vs	1040 w
1277	m	1137	s	1143 s	1100 vs	1022 vw
1250	m	1107	s	1132 vs	1045 w	1012 w
1227	s	1085	w	1106 s	1020 vs	960 m
1195	vw	1050	w	1078 vw	990 m	937 s
1167	vw	1032	m	1050 w	915 m	917 w
1150	s	1015	m	1020 s	908 s	835 m
1132	s	987	s	1002 m	892 w	825 m
1123	s	950	w	988 m	840 vs	845 m
1095	s	935	m	927 w	817 w	650 w
1062	vs	895	m	907 m	805 w	
1050	vs	875	m	895 s		
1035	vs	865	w	869 w		
		852	w			
1023	vs	820	vw	841 w		
1006	vs	801	vw	820 s		
990	m	765	w	803 s		
943	w	735	w	762 vs		
928	w	715	w	680 vw		
920	m	665	w			
900	vs					
885	m					
857	vs					
845	m					
826	m					
823	m					
812	m					
784	w					
757	w					
723	w					
690	vw					
655	m					

TABLE VIII

Infrared Absorption Maxima

of

3-Methyl-3-azaspiro(5.5)hendecane-1-carboxylic Acid (XXIIa)

3-Methyl-3-azaspiro(5.5)hendecane-1-carboxylic Acid Hydrochloride (XXIIb)

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic Acid (XXIa)

3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic Acid Hydrochloride (XXIb)

Spiro(cyclohexane-1,9'-(3,7)-diazabicyclo(3.3.1)-nonane) (XX)

XXII

a			b	
3430	w	b	3390	w
2920	vs		2930	vs
2845	m		2840	vs
2400	m	b	2810	vs
1592	vs	b	2680	vs
1460	s		2460	vs
1435	w		2440	vs
1367	vs	b	1700	vs
1325	s		1535	vw
1303	s		1482	vs
1290	s		1455	vs
1280	s		1425	s
1245	m		1385	vs
1212	m		1340	w
1186	m		1330	w
1150	m		1317	w
1127	s		1305	vw
1102	m		1280	w
1057	m		1235	vs
1045	w		1185	m
1013	vw		1150	m
995	m		1127	s
982	w		1105	m
970	m		1080	w
935	vw		1060	m
897	w		1045	m
873	w		1010	w
842	w		995	m
820	vw		980	s
788	m		957	m
723	vs		940	vw
673	m		933	w
			897	m
			875	vs
			855	s
			820	w
			795	w
			785	vw
			767	w
			685	m
			647	m

XXI

a			b	
3440	w	b	3420	w
3050	w		2830	vs b
2935	vs		2570	s
2860	vs		2350	m
1695	vs	b	1700	vs
1580	vs	b	1470	s
1500	w		1460	s
1470	s		1412	vs
1460	vs		1375	vs
1395	vs		1360	vs
1360	vs		1307	vw
1300	s		1295	w
1290	s		1265	w
1277	s		1255	m
1260	m		1205	vs
1252	m		1170	vs
1230	vs		1140	vs
1210	s		1100	m
1185	m		1065	w
1172	s		1035	w
1153	m		1010	w
1130	vs		995	m
1107	m		970	w
1070	m		957	m
1057	m		923	vw
1032	m		900	w
1012	m		870	s
993	m		853	vs
980	m		805	m
920	m		775	w
893	w		765	w
870	w		732	m
852	m		675	w
795	m		650	s
770	m			
695	w			
660	m			

XX

3330	vs	
2930	vs	
2860	vs	b
1565	w	b
1485	s	b
1465	vs	
1455	vs	
1367	m	
1350	s	
1340	s	
1330	m	
1320	m	
1314	m	
1295	m	
1272	m	
1255	s	
1240	s	
1205	m	
1191	m	
1170	m	
1135	m	
1127	m	
1105	s	
1092	s	
1055	s	
1030	w	
1017	m	
983	m	
962	w	
930	s	
903	s	
867	vs	b
845	s	
828	vs	
798	m	
770	vs	b
742	vs	b
665	m	b
645	m	b

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

1. The following substituted 3-azaspiro(5.5)hendecanes have been synthesized starting from the corresponding diones: 3-methyl-3-azaspiro(5.5)hendecane-1-hydroxymethyl (XIX) 3-methyl-3-azaspiro(5.5)hendecane-1,5-dihydroxymethyl (XVIII) 3-methyl-3-azaspiro(5.5)hendecane-1-carboxylic acid (XXII) 3-methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (XXI). Examples of unsubstituted cyclohexanespiropiperidine rings were provided by the synthesis of 3-azaspiro(5.5)hendecane (V) and spiro(cyclohexane-1,9'-(3,7)-diazabicyclo(3.3.1)-nonane) or cyclohexanespirodipiperidine (XX).

2. The synthesis of 3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylic acid (XI), the starting material for the preparation of 3-methyl-3-azaspiro(5.5)hendecane-1-carboxylic acid (XXII), was accomplished by aqueous hydrolysis of 3-azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I) followed by deamination of the resulting amide (XIV). A study of this hydrolysis disclosed that it involved cyclization in the preliminary stage, producing the "diimino diimide" (XIII). On prolonged boiling in water the ring reopened, yielding after decarboxylation 3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxamide (XIV). The hydrolysis confirmed the labile character of diglutarimide rings in contrast to the high stability of monoglutarimides.

3. 3-Methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (XXI) was obtained by the reduction of a diester of the corresponding dioxo-acid (III). The original synthesis of the latter by Thorpe was modified to produce consistently good yields.

4. The conversion of 3-azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid (III) to the corresponding 3-azaspiro-(5.5)hendecane acid (XXI) involved a change from the original cis to trans configuration. Since the reactions involved should not by themselves lead to inversion, this suggests that trans is the more stable configuration of 3-methyl-3-azaspiro(5.5)hendecane-1,5-dicarboxylic acid (XXI).

5. The 2-dimethylaminoethyl ester of 3-methyl-3-azaspiro(5.5)-hendecane-1,5-dicarboxylic acid hydrochloride (XXIII) was synthesized, but preliminary testing indicated no local anesthetic activity.

6. The infrared spectra support the diaxial conformation of cis 1,5-disubstituted 3-azaspiro(5.5)hendecane-2,4-diones.

7. Lithium aluminum hydride was used in the reduction of 3-azaspiro(5.5)hendecane-2,4-diones to produce the corresponding 3-azaspiro(5.5)hendecanes. It was found an excellent reducing agent for these compounds.

8. The infrared spectra of 3-methyl-3-azaspiro(5.5)hendecane carboxylic acids could be readily correlated with the zwitterion structure of these compounds. The spectra of their hydrochlorides showed absorption typical of the ordinary acids, together with strongly bonded N-H stretching absorption characteristic of tertiary amine hydrochlorides.

9. The infrared spectra of 3-azaspiro(5.5)hendecane-2,4-diones showed NH stretching absorption occurring at 3200 and 3100 ± 20 cm.$^{-1}$. The two imide carbonyl groups absorbed at 1720 and 1680 cm.$^{-1}$ respectively. The carbonyl absorption was shifted to higher frequency by 1,5-disubstitution, indicating that such substitution introduces strain into the glutarimide ring. This evidence was substantiated by comparison with the spectra of certain 4,4-dimethylpiperidine-2,6-diones and glutarimide.

10. The spectra of 3-azaspiro(5.5)hendecanes containing the O=C-NH-C=NH group showed absorption entirely different from those containing the O=C-NH-C=O group (glutarimides) both in the N-H and C=O stretching regions. A new band at 1520 cm.$^{-1}$ in the former compounds was probably "amide II absorption" of the HN-C=NH group.

11. Despite a formal resemblance to 3-azaspiro(5.5)hendecane-2,4-dione (IV), spiro(5.5)hendecane-2,4-dione (XXVII) showed

an essentially different pattern of infrared absorption. The spectrum of the former can be correlated with the formal structure of the compound, whereas the absorption of the latter indicates a strongly associated enolic structure with an appreciable contribution by ionic resonance forms.

12. A method for the preparation of 3-oxa- and 3-thiaspiro(5.5)-hendecanes (XXV, XXVI) has been developed and their spectra compared with that of a closely related 3-azaspiro(5.5)-hendecane (V).

13. Spiro(5.5)hendecane-3-carboxylic acid (XXXV) has been prepared; the method suggests a new route for the preparation of the known spiro(5.5)hendecane (XXIV).

14. Besides the compounds already mentioned, V, XI, XIV, XVIII, XIX, XX, XXI, XXII, XXIII, XXV, XXVI and XXXV, the following new compounds have been prepared and characterized; the asterisk indicates a measurement of the infrared spectrum.

3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid anhydride (XLII)*
Methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1-carboxylate (XVII)*
Methyl 3-methyl-3-azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylate (XVI)
3-Azaspiro(5.5)hendecane-1-cyano-2,4-dione (X)*
Cyclohexane-1,1-di(2-ethanol) (XXXI)*
Cyclohexane-1,1-di(2-ethyl chloride) (XXXVI)
Cyclohexane-1,1-di(2-ethyl iodide) (XXXII)
Ethyl spiro(5.5)hendecane-3,3-dicarboxylate (XXXIII)
Spiro(5.5)hendecane-3,3-dicarboxylic acid (XXXIV)

15. The infrared spectra of the following known compounds have been recorded for the first time.

3-Azaspiro(5.5)hendecane-2,4-dione (IV)
3-Azaspiro(5.5)hendecane-1,5-dicyano-2,4-dione (II)
3-Azaspiro(5.5)hendecane-2,4-dioxo-1,5-dicarboxylic acid (III)
2',4',6',8'-Tetroxo-spiro(cyclohexane-1,9'-(3,7)-diazabicyclo(3.3.1)nonane) (VIII)
Glutarimide (XLVI)
4,4-Dimethylpiperidine-2,6-dione (XLIV)
2,4,6,8-Tetroxo-9,9-dimethyl-3,7-diazabicyclo(3.3.1)nonane (XLI)
2,6-Diimino-9,9-dimethyl-3,7-diazabicyclo(3.3.1)nonane-4,8-dione (XLIII)
2',6'-Diimino-4',8'-dioxo-spiro(cyclohexane-1,9'-(3,7)-diazabicyclo(3.3.1)nonane (XIII)
4,4-Dimethylpiperidine-3,5-dicyano-2,6-dione (XLV)
3-Azaspiro(5.5)hendecane-5-cyano-2-imino-4-oxo-1-carboxamide (I)
Spiro(5.5)hendecane-2,4-dione (XXVII)

BIBLIOGRAPHY

1. Baeyer, A., Ber. 33, 3771 (1900).
2. Rave, P. and Tollens, B., Ann. 276, 74 (1893).
3. Meiser, W., Ber. 32, 2055 (1899).
4. Fecht, H., Ber. 40, 3883 (1907).
5. Gustavson, E., J. prakt. Chem. 54, 101 (1896).
6. Ingold, C. K., J. Chem. Soc. 123, 1706 (1923).
7. Guareschi, I., Chem. Zentr. 5 (I), 577 (1901).
8. Thole, F. B. and Thorpe, J. F., Trans. Chem. Soc. 95, 1901 (1909).
9. Thole, F. B. and Thorpe, J. F., Trans. Chem. Soc. 99, 442 (1911).
10. Bohlmann, F., Otlawa, N. and Keller, R., Ann. 587, 162 (1954).
11. Galinovsky, F. and Langer, H., Monatsh. 86, 449 (1955).
12. Thorpe, J. F. and Wood, A. S., Trans. Chem. Soc. 103, 1586 (1913).
13. Kon, G. A. R. and Thorpe, J. F., Trans. Chem. Soc. 115, 686 (1919).
14. Day, J. N. E. and Thorpe, J. F., Trans. Chem. Soc. 117, 1465 (1920).
15. Messajah, T., M. Sc. Thesis, McGill University, Montreal, 1956.
16. Norris, W. S. G. P. and Thorpe, J. F., Trans. Chem. Soc. 119, 1204 (1921).
17. Norris, W. S. G. P., J. Chem. Soc. 1926, 245.
18. Zelinsky, N. D. and Elagina, N. V., Dokl. Akad. Nauk U.S.S.R. 87, 755 (1952).
C.A. 48, 542 (1954).

19. Reynolds, D. D. and Kenyon, W. O., J. Am. Chem. Soc. 72, 1953 (1950).

20. Aschan, O., Ber. 35, 3389 (1902).

21. Backer, H. J. and Schwink, H. B. J., Rec. trav. chim. Pays Bas. 50, 921 (1931).

22. Leuchs, H. and Gieseler, E., Ber. 45, 2114 (1912).

23. Freudenberg, K., Stereochemie, Vol. II, 804. Franz Deuticke, Leipzig and Wien, 1932.

24. Eisleb, O. and Schaumann, O., Deut. Med. Wochschr., 65, 967; C.A., 33, 9442 (1939).

25. Eisleb, O., Ber. 74, 1433 (1941).

26. Schaumann, O., Arch. Exptl. Pharmakol. 196, 109 (1940). C.A., 35, 2976 (1941).

27. Way, E. L., Science 101, 566 (1945).

28. Thorp, R. H. and Walton, E., J. Chem. Soc., 1948, 559.

29. MacDonald, A. D., Woolfe, G., Bergel, F., Morrison, A. L and Rinderknecht, H., Brit. J. Pharmacol. 1, 4 (1946). C.A., 40, 6660 (1946).

30. Blicke, F. F., U.S. pat. 2,425,721; 2,425,722; 2,425,723; C.A., 42, 614-615 (1948).

31. Jenson, K. A., Lindquist, F., Rekling, E. and Wolffbrandt, C. G., Dansk. Tids. Farm. 17, 173 (1943); C. A., 39, 2506 (1945).

32. Lee, J., Ziering, A., Berger, L. and Heinemann; Jubilee Vol. Emil Barell p. 264. Hoffmann-LaRoche, Basel, 1946. Ref. 36, p. 455.

33. Berger, L., Ziering, A. and Lee, J., J. Org. Chem., 12, 904 (1947).

34. Randall and Lehmann, J. Pharmcol. Exptl. Therap. 93, 314 (1948). Ref. 36, p. 457.

35. Eisleb, O., Med. u. Chem., 4, 213 (1942). Ref. 36, Vol. II, p. 227.

36. Lee J. Analgesics, B. Partial Structures Related to Morphine. In "Medicinal Chemistry". Vol. I, p. 438. C. M. Suter, Editor-in-Chief. John Wiley and Sons Inc., N. Y., 1951.

37. Bellamy, L. J., "The Infrared Spectra of Complex Molecules", p. 24. The Methuen Co., London, 1956.

38. Morrison, L. W., J. Chem. Soc. 1951, 1614.

39. Lecompte, M. J., Compt. rend. 221, 50 (1945).

40. Voetter, H. and Tchamler, H. Monatsh. 84, 134 (1953).

41. Batuev, M. I., Izvest. Akad. Nauk U.S.S.R. Otdel Khim. Nauk, 1, 3 (1947).
C.A. 42, 4463 (1948).

42. Laber, G., Ann. 588, 79 (1954).

43. Sutherland, G. B. B. M., Disc. Farad. Soc., 9, 274 (1950).

44. Jones, R. N. and Sandorfy, C. The Application of infrared and Raman spectroscopy to the elucidation of molecular structure. In "Technique of organic chemistry" IX. Edited by A. Weissberger. Interscience Publishers, Inc. New York, 1956, p. 523.

45. Richards, R. E., Thompson, H. W., J. Chem. Soc. 1947, 1248.

46. Darman, S. E. and Sutherland, G. B. B. M. Nature 164, 440 (1949).

47. Mizushima, S., Simanuti, T., Nagakura, S., Kuratani, K., Tsuloi, M., Baba, H. and Fujioka, O., J. Am. Chem. Soc. 72, 3490 (1950).

48. Edwards, O. E. and Singh, T., Can. J. Chem. 32, 683 (1954).

49. Ref. 34, p. 526.

50. Elliot, A., Ambrose, E. J. and Temple, R. B., J. Chem. Phys. 16, 877 (1948).

51. Ref. 37, p. 102.

52. Lenormant, H., Disc. Farad. Soc. 9, 319 (1950).

53. Randall, H. M., Fowler, R. G., Fuson, N. and Dangl, J. R. Infrared Determination of Organic Structures. Van Nostrand, New York, 1949.

54. Lenormant, H., Bull. soc. chim. 5, 459 (1950).

55. Lenormant, H., Ann. chim. 5, 459 (1950).

56. Ref. 44, p. 528.

57. Miyazawa, T., Shimanouchi, T. and Mizushima, S., J. Chem. Phys. 24, 408 (1956).

58. Ref. 37, p. 195.

59. Goulden, J. D. S., J. Chem. Soc. 1953, 997.

60. Colthup, N. B., J. Opt. Soc. Amer. 40, 397 (1950).

61. Ref. 37, p. 200.

62. Freymann, R. L. and Freymann, E. D., Proc. Ind. Acad. Sci. 8, 301 (1938).

63. Thompson, H. W., Nicholson, R. M. and Short, L. W. Discuss. Farad. Soc. 9, 222 (1950).

64. Fuson, N., Josien, M. L. and Powell, R. L., J. Am. Chem. Soc. 74, 1 (1952).

65. Lenormant, H., J. Chem. Phys. 43, 327 (1946).

66. Lord, R. C. and Merrifield, R. E., J. Chem. Phys. 21, 166 (1953).

67. Rasmussen, R. S., Tunnicliff, D. D. and Brattain, R. R., J. Am. Chem. Soc. 71, 1068 (1949).

68. Ingold, C. K., "Structure and Mechanism in Organic Chemistry", p. 397. Cornell University Press, Ithaca, N. Y., 1953.

69. Hine, J., "Physical Organic Chemistry", p. 364. McGraw Hill Co., N. Y., 1956.

70. Labruto, G., Gaz. chim. ital. 63, 266 (1933).

71. Smith, L. I., Chem. Rev. 23, 202 (1938).

72. Brown, W. G., Organic Reactions, VI, 469 (1951). John Wiley & Sons Inc., N. Y.

73. Trevoy, L. W. and Brown, W. G., J. Am. Chem. Soc. 71, 1675 (1949).

74. Koenigs, B., Ber. 14, 1856 (1881).

75. Ginzberg, A., Ber. 36, 2705 (1903).

76. Schotten, C., Ber. 15, 427 (1882).

77. Haase, F. and Wolffenstein, R., Ber. 37, 3228 (1904).

78. Werwick, W. and Wolffenstein, R., Ber. 31, 1553 (1898).

79. Koenigs, W., Ber. 12, 2341 (1879).

80. Hunsdiecker, H. and Hunsdiecker, C., Ber. 75, 291 (1942).

81. Ingold, C. K., Trans. Chem. Soc. 119, 305 (1921).

82. Hammond, G. S., "Steric Effects on equilibrated Systems" in "Steric Effects in Organic Chemistry" p. 468. Edited by Newman, M. S. John Wiley & Sons, Inc., N. Y. 1956.

83. Skita, A. and Roessler, R., Ber. 72, 461 (1939).

84. Wasserman, H. H. and Zimmerman, H. E., J. Am. Chem. Soc., 72, 5787 (1950).

85. Jones, R. N., Ramsay, D. A., Herling, F. and Dobriner, K., J. Am. Chem. Soc. 74, 2828 (1952).

86. Lecomte, J., J. phys. radium. 6, 127,257 (1945). Ref. 44, p. 485.

87. Grivas, J., M. Sc. Thesis, McGill University, Montreal, 1957.

88. Flett, M. S. C., J. Chem. Soc. 1951, 962.

89. Grove, J. F. and Willis, H. A., J. Chem. Soc. 1951, 877.

90. Sheppard, N., Trans. Farad. Soc. 46, 429 (1950).

91. Ref. 37, p. 110.

92. Vogel, A. E., "A Textbook of Practical Organic Chemistry", p. 844. Longmans, Green and Co., Toronto, 1948.

93. Skraup, Z. H., Monatsh. 17, 378 (1896).

94. Winkelblech, K., Z. Phys. Chem. 36, 566 (1901).

95. Newman, M. S. and Whitehouse, H. S., J. Am. Chem. Soc. 71, 3664 (1949).

96. Ref. 37, p. 104.

97. Barrow, G. M. and Searles, S., J. Am. Chem. Soc. 75, 1175 (1953).

98. Wallach, O., Ann. 394, 362 (1912).

99. Karrer, P. and Widmer, A., Helv. Chim. Acta 9, 886 (1926).

100. Ahmad, K., Bumpus, F. M. and Strong, F. M., J. Am. Chem. Soc. 70, 3392 (1951).

101. Whitehead, E. W., Dean, R. A. and Fidler, F. A., J. Am. Chem. Soc. 73, 3692 (1951).

102. Ref. 37, p. 292.

103. Sircar, S. S. G., J. Chem. Soc., 1927, 1252.

104. Tilford, C. H., Van Campen, M. G. and Shelton, R. S., J. Am. Chem. Soc. 69, 2902 (1947).

105. Tilford, C. H., Doerle, L. A., Van Campen, M. G. and Shelton, R. S., J. Am. Chem. Soc. 71, 1705 (1949).

106. Wood, G. W., J. Chem. Soc., 1953, 3327.

107. Stone, H. and Shechter, H., J. Org. Chem. 15, 491 (1950).

108. Birch, S. F., Dean, R. A. and Whitehouse, E. V., J. Org. Chem. 19, 1449 (1954).

109. Allen, C. H. F. and Wilson, C. V., "Organic Syntheses", Vol. 26, p. 52. John Wiley and Sons, N. Y., 1946.

110. Hirschmann, H., Hirschmann, F. B. and Daus, M. A., J. Biolog. Chem. 178, 751 (1949).