The Condensation of β-Aminocrotononitrile With Cyclohexanones.

by

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Table of Contents

General Introduction

Historical Introduction

Discussion

Table of Contents

Page

Experimental

General Introduction

The initial object of this work was to synthesize a series of 2,6-dimethyl-3,5-dicyano-1,4-dihydro pyridine spiranes, (LV), by condensing β-aminocrotononitrile with cyclohexanone and various alkyl-substituted cyclohexanones, in alcoholic hydrogen chloride, as reported by von Meyer (17). Hydrolysis of the cyano groups to carboxyl groups, followed by esterification, would result in the formation of 3,5-dicarbethoxyl derivatives of (LV). It was felt that these derivatives might exhibit pharmacologic activity as local anaesthetics. Demerol is an example of a piperidine derivative which is used as an analgesic.

When it was impossible to duplicate the condensation reported by von Meyer, a search for a new way of bringing about the desired condensation was undertaken. It was further decided to study the effect on the reaction, of methyl groups in various positions on the cyclohexane ring, with a view to learning something as to how the condensation occurred.

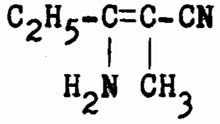
Finally, the resistance of the cyano groups to all attempts at hydrolyzing them, necessitated that a new approach to the synthesis of the desired 3,5-dicarbethoxylated derivatives of LV-LX be sought. For this purpose, it was decided to attempt the condensation of 2 moles of ethyl β-aminocrotonate, with 1 mole of cyclohexanone or alkyl-substituted cyclohexanone, using polyphosphoric acid as the condensing agent.

Historical Introduction

β-Aminocrotononitrile

In 1848, Frankland and Kolbe (24) reported that metallic potassium reacted with propionitrile, in the absence of a solvent, gave sodium cyanide, ethane and an organic base, which they named 'cyanoethine'. E. von Meyer elucidated the structure of 'cyanoethine' in 1889. It was shown to be 4-amino-2,6-diethyl-pyrimidine.

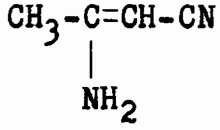
von Meyer (9,10) investigated the action of metallic sodium on propionitrile, in benzene solution, and obtained a product, which he named 'dipropionitrile'. It was α-methyl-β-aminovaleronitrile (I) or 2-methyl-3-aminovaleronitrile.



$$C_2H_5-\underset{H_2N}{\underset{|}{C}}=\underset{CH_3}{\underset{|}{C}}-CN$$

(I)

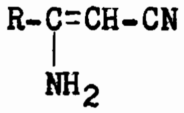
R. Holtzwart (7,8) obtained a dimer of acetonitrile, which he named 'diacetonitrile', by treating acetonitrile with metallic sodium, in ether and in benzene solution. It was later named β-aminocrotononitrile (II) or 3-aminocrotononitrile



$$CH_3-\underset{NH_2}{\underset{|}{C}}=CH-CN$$

(II)

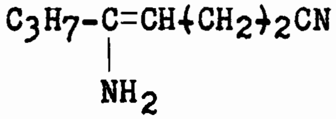
E. von Meyer (11,12,17) and Holtzwart (8), extended their investigations of the reactions of nitriles with metallic sodium, to aromatic nitriles, and to mixtures of aromatic nitriles with acetonitrile, in solution. In all cases, dimers of the general formula (III) were obtained.



$$R\text{-}\underset{\mathrm{NH_2}}{\underset{|}{C}}\text{=CH-CN}$$

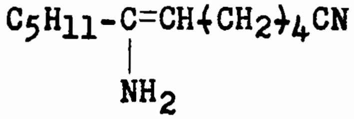
(III)

The reaction of butyronitrile and of capromitrile with metallic sodium, gave 5-amino-oct-4-enyl nitrile, (IV) and 7-amino-dodec-6-enyl nitrile, (V) respectively.



$$C_3H_7\text{-}\underset{\mathrm{NH_2}}{\underset{|}{C}}\text{=CH}(CH_2)_2CN$$

(IV)



$$C_5H_{11}\text{-}\underset{\mathrm{NH_2}}{\underset{|}{C}}\text{=CH}(CH_2)_4CN$$

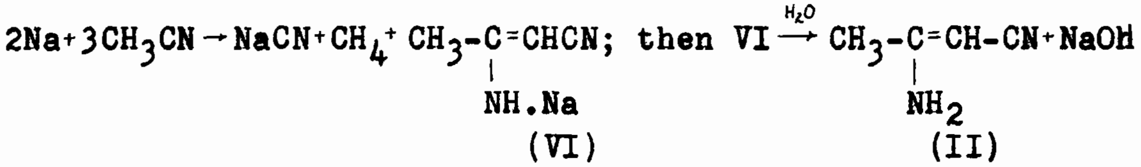
(V)

In these condensations, the γ-hydrogen, rather than the α-hydrogen of the second molecule of nitrile, takes part in the condensation.

Reynolds, Humphlett, Swaner and Hauser (19), found that other basic reagents such as sodium hydride, sodium azide and diisopropylmagnesium bromide, could be used, in place of metallic sodium, as the condensing agent. The products formed may be represented by III. Valeronitrile and phenylacetonitrile, condensed with sodium to form similar dimers (19).

Claisen (6) reported the preparation of β-aminocrotononitrile, in small yield, by heating 5-methyl isoxazole in a solution of ammonia, in absolute methanol.

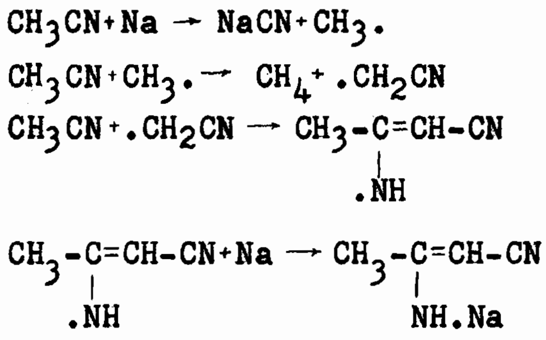
It is now thought that β-aminocrotononitrile is formed accordingly:



$$2Na+3CH_3CN \rightarrow NaCN+CH_4+CH_3-\underset{\underset{NH.Na}{|}}{C}=CHCN; \text{ then VI} \xrightarrow{H_2O} CH_3-\underset{\underset{NH_2}{|}}{C}=CH-CN+NaOH$$

(VI) (II)

Holtzwart proposed a mechanism for the formation of II, involving sodium acetonitrile as an intermediate, which he claimed reacted further with another mole of acetonitrile forming VI. The proof he advanced for the existence of sodium acetonitrile was, however, rather inconclusive (25). Conn and Taurins (30) have proposed a mechanism involving the formation of free radicals.



$$CH_3CN+Na \rightarrow NaCN+CH_3.$$
$$CH_3CN+CH_3. \rightarrow CH_4+.CH_2CN$$
$$CH_3CN+.CH_2CN \rightarrow CH_3-\underset{\underset{.NH}{|}}{C}=CH-CN$$
$$CH_3-\underset{\underset{.NH}{|}}{C}=CH-CN+Na \rightarrow CH_3-\underset{\underset{NH.Na}{|}}{C}=CH-CN$$

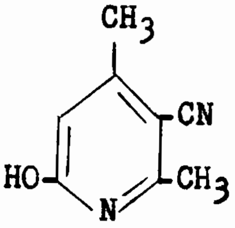
The two main types of reactions of β-aminocrotononitrile are:

(i) Cyclization to form substituted pyridine or dihydropyridine compounds.

(ii) Substitution of the α-hydrogen, or of the hydrogen of the amino group, to form branched-chain compounds (1,3,4,5,12,13,14,15,17,20).

Reactions such as those in category (ii) will not be discussed in connection with this work, since the initial object the syntheses was to form spiro compounds.

Holtzwart (8) observed that β-aminocrotononitrile reacted, when heated in water, to form a water-insoluble compound, $C_8H_8N_2O$, which melted at 293°. Moir (18) elucidated the structure of $C_8H_8N_2O$, and showed it to be 2,4-dimethyl-3-cyano-6-hydroxy-pyridine (VII).



(VII)

von Meyer (12) and his students had shown that Holtzwart's compound, $C_8H_8N_2$, was unaffected by acetyl chloride, hydro-oxylamine and nitrous acid. Moir showed that it was also stable to:

(i) Prolonged boiling with a 10 per cent aqueous or alcoholic solution of sodium hydroxide.

(ii) Prolonged boiling with methyl iodide and sodium hydroxide.

(iii) Heating at 80° with fuming sulphuric acid or at 120° with 70 per cent sulphuric acid.

(iv) Prolonged boiling with acetic anhydride .

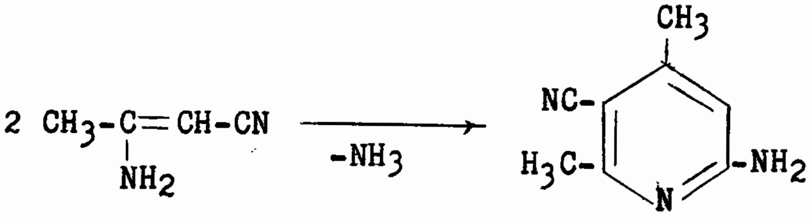
When $C_8\ H_8N_2O$ was heated for six hours in a sealed tube, in concentrated hydrobromic acid (d 1.47) at 170°, a large yield of 2,4-dimethyl-6-hydroxy-pyridine, C_7H_9ON, a substance first described by Hantzsch (22), was obtained. Presumably, the

C_7H_9ON was derived from the original $C_8H_8N_2O$, by replacing the cyano group by a hydrogen atom. Ammonia and carbon dioxide were by-products. Zinc dust distillation of $C_8H_8N_2O$ produced a small amount of liquid with a distinct pyridine-like odour. As further proof, the $C_8H_8N_2O$ was chlorinated, with phosphorous pentachloride, to the 6-chloropyridine compound, which yielded 3-cyano-2,4-dimethylpyridine, when hydrogenated. This evidence fixed the structure of $C_8H_8N_2O$ as being the one shown in VII.

Holtzwart (23) obtained a base, $C_8H_9N_3$, by the interaction of acetyl chloride and β-aminocrotononitrile. The same compound, $C_8H_9N_3$, was obtained by reacting β-aminocrotononitrile with a variety of reagents, such as ethyl chlorocarbonate, ethylene dibromide, benzoyl chloride, benzyl cyanide, cyanoacetic acid, anthranilic acid and alcoholic hydrogen chloride. Each of these reagents is capable of inducing the condensation of two molecules of β-aminocrotononitrile, by the removal of a molecule of ammonia, thus,

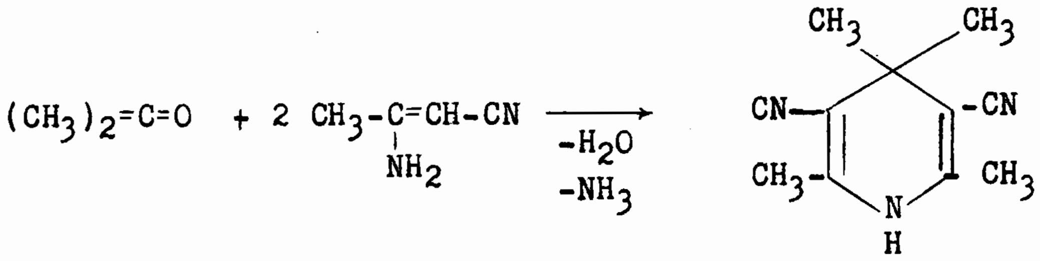
$$2C_4H_6N_2 \longrightarrow C_8H_9N_3 + NH_3$$

Nitrous acid reacted with the compound, liberating nitrogen, and precipitating VII. This established the structure of $C_8H_9N_3$, as 3-cyano-6-amino-2,4-dimethylpyridine (VIII)



(VIII)

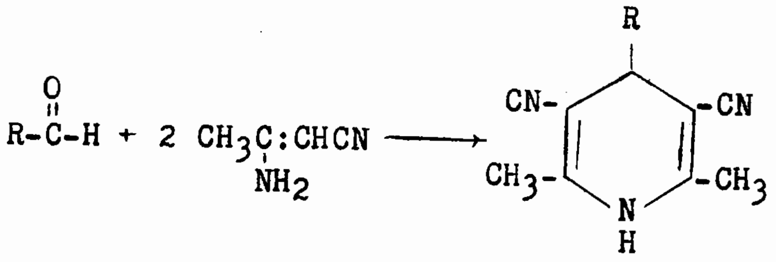
Compounds containing the carbonyl group react readily with β-aminocrotononitrile, to form substituted pyridines and dihydropyridines. The reaction of saturated ketones is of particular interest in this connection. von Meyer reported the preparation of 3,5-dicyano-1,4-dihydropyridines in yields of 34 to 80 per cent, by this reaction. Two molecules of β-aminocrotononitrile, condense with one molecule of the ketone, in alcoholic hydrogen chloride at 5° , to form the dicyano-dihydropyridine compound. The reaction with acetone was depicted as being,



(IX)

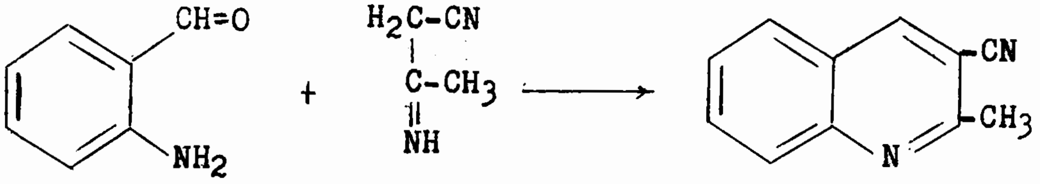
It was found to be impossible to hydrolyze the cyano groups, in analogs of IX, to the corresponding carboxylic acids. Chromic acid oxidation of IX, in glacial acetic acid, was reported to have produced 3,5-dicyano-4-methylpyridine, in good yield (17).

Aldehydes, in glacial acetic acid solution, reacted with β-aminocrotononitrile, in a manner similar to ketones (15), according to the general equation:



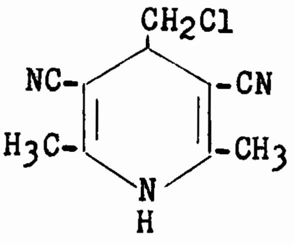
; R=H-, CH_3-, C_6H_5-

Substituted benzaldehydes, with the exception of o-aminobenzaldehyde, reacted to give dihydropyridine compounds, with the corresponding substituent phenyl group, in the 4-position. β-Aminocrotononitrile reacted with o-aminobenzaldehyde to form 2-methyl-3-cyanoquinoline (X), instead of the expected 4-(o-aminophenyl) pyridine compound.



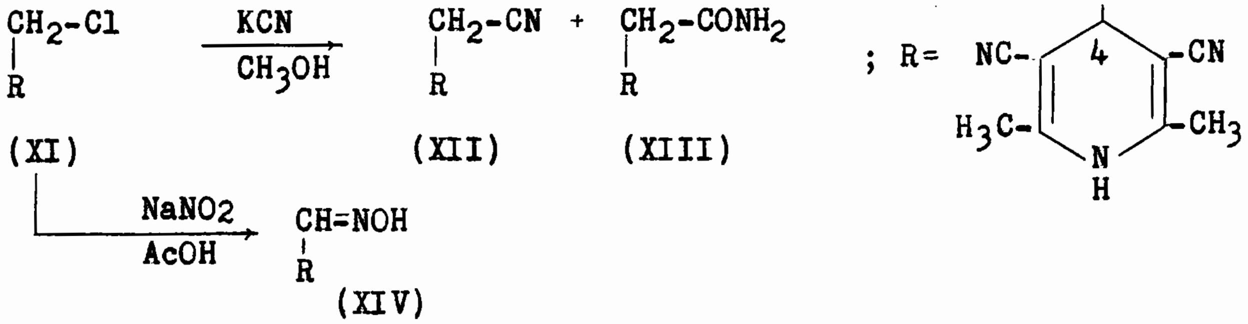
(X)

Benary and Lowenthal (2), investigated the condensation of β-aminoerotononitrile with bis(2-chloroethyl) ether, $(ClC_2H_4)_2O$, and isolated 4-chloromethyl -3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine (XI).



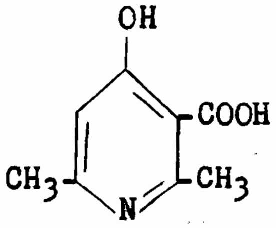
(XI)

Treatment of a methanol solution of XI with potassium cyanide gave the corresponding 4-cyanomethyl and 4-carbamoylmethyl derivatives, (XII) and (XIII) respectively, while a solution of XI in glacial acetic acid gave the oxime (XIV), when treated with sodium nitrite.



(XI) (XII) (XIII) (XIV)

Von Meyer (13,15) isolated 4-hydroxy -2,6-dimethylpyridine-3-dicarboxylic acid (XV) from the reaction between β-aminocrotononitrile and ethyl acetoacetate, in the presence of a small quantity of pyridine.



(XV)

The reaction of succinic acid, and of other α-hydroxy acids with β-aminocrotononitrile (16) gave 2,4-dimethyl -3-cyano-6-hydroxypyridine.

In general, the 1,4-dihydropyridines were readily dehydrogenated by treatment, in alcohol, with nitrous acid.

Cyclohexanone and Methylcyclohexanones

One of the earliest reported preparations of cyclohexanone, was from the dry distillation of calcium pimelate (31). A variation of this preparation, consisted of heating pimelic acid, $HOOC(CH_2)_5COOH$, with acetic anhydride (32).

Grignard (33) synthesized cyclohexanone by reacting pentamethylene magnesium bromide and carbone dioxide.

Markownikoff (34) reports a preparation from a mixture of nitrocyclohexane, acetic acid and zinc.

Sabatier and Senderens (35) prepared cyclohexanone from cyclohexanol, by dehydrogenating it over a finely divided, hot, copper catalyst. Holleman et al (35) recommended the passage of a slight current of air through the reaction tube, at the same time that the cyclohexanol vapours were passed through. This was to prevent reduction of the cyclohexanol by the liberated hydrogen. The air oxidized the hydrogen.

The oxidation of cyclohexanol with chromic acid (36), gave satisfactory yields of cyclohexanone. Separation of the cyclohexanone from cyclohexanol, could be achieved through the sodium bisulfite addition compound.

Hotz (37) prepared cyclohexanone by reacting cyclohexanol, in the presence of water and calcium carbonate, with bromine or chlorine vapours.

Two methods (38) involving electroysis are also reported.

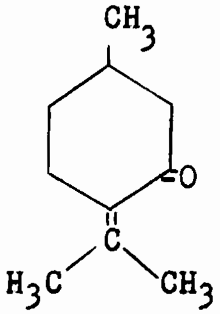
Another preparation was from cyclohexanone 2-carboxylic acid-(1). Carbon dioxide was liberated from the acid at room temperature (39). Alternatively, the ethyl ester of cyclohexanone -2-carboxylic acid, when boiled with dilute sulphuric acid gave cyclohexanone.

Looft (40) isolated cyclohexanone from the products obtained by the dry distillation of wood.

Recently, it has been obtained largely by catalytic dehydrogenation of cyclohexanol or by its oxidation, or from cyclohexane by oxidation (41).

2-Methylcyclohexanone may be obtained by analogous syntheses, using the appropriate methyl derivatives.

Wallach (42) synthesized 3-methylcyclohexanone from pulegone (XVI), 4(8)-p-menthene-3-one,



(XVI)

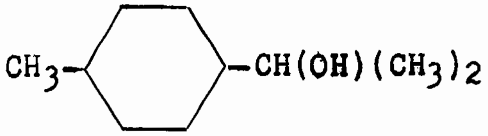
either in the presence of dry formic acid, or of water. When XVI is heated in the presence of water, elevated pressure is required.

4-Methylcyclohexanone has been prepared by distilling γ-methylpimelic acid, in the presence of calcium oxide (43). It has also been synthesized by dehydrogenation of 4-methyl-cyclohexanol over copper (44). Perkin (45) prepared the ketone by treating 4-methyl -cyclohexanol carboxylic acid with concentrated sulphuric acid at -10°. The yield was seldom better than 30 per cent owing to the concomitant formation of tetrahydro-p-toluic acid.

3,3,5-Trimethylcyclohexanone may be prepared either by the chromic acid oxidation of dihydroisophorol 946) or by the reduction of isophorone with hydrogen, on a palladium catalyst (47).

In 1934, Tiffeneau and Tchoubar (47) prepared alkyl cyclohexanones, by the action of Grignard reagents, on α-chlorocyclohexanones. The reaction proceeds by the indirect replacement of the halogen, by an alkyl group. They (T. and T.) also prepared cyclohexanone (48) by dehydrating cis-1,2-cyclohexanediol with alumina. Traces of cyclopentylformaldehyde formed as a by-product.

Huckel and Nerdel (49) in 1937 prepared 4-methyl cyclohexanone from dihydro-α-terpineol (XVII), by chromic acid oxidation.



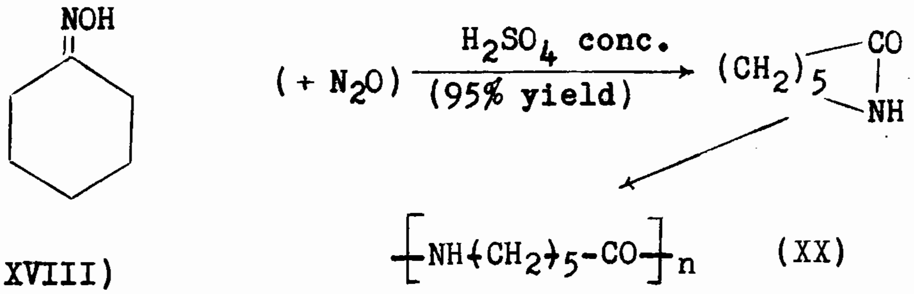
(XVII)

Recently, Ohta and Sato (50), prepared cyclohexanone by the catalytic dehydrogenation of cyclohexanol. The catalyst had the following composition:

Al	40-50%
Cu	50-60
Zn	0-5

Extensive studies on cyclohexanone and methylcyclohexanones, reveal their extreme chemical versatility. A selection from among their principal reactions will be given.

Cyclohexanone and methylcyclohexanones form the usual carbonyl group derivatives e.g. oximes, semicarbazones, phenylhydrazones and bisulfite addition compounds. These derivatives have, in many instances, been reacted further to form valuable products (51,59,60).



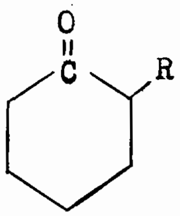
(XVIII)

(XIX)

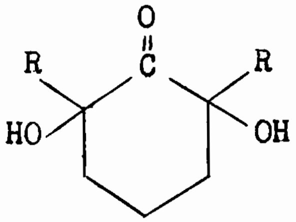
(XX)

Cyclohexanone oxime,(XVIII), may be converted by a Beckmann rearrangement, to ε-caprolactam, (XIX). This lactam is a starting material for Nylon-type superpolyamides (XX).

An interesting basis for the comparison of cyclohexanone and methylcyclohexanones, is the reactions with aromatic aldehydes. Generally, unsubstituted cyclohexanone was found to be more reactive than methylcyclohexanones. Benzaldehyde reacts with an excess of cyclohexanone in a very dilute aqueous alcoholic solution (52), to form 2-α-hydroxybenzyl-cyclohexanone (XXI) and 2,6-bis[α-hydroxybenzyl]-cyclohexanone XXII).



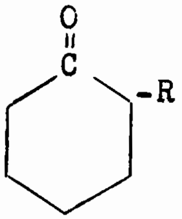
(XXI)



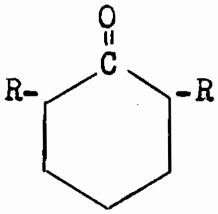
(XXII)

; R= $C_6H_5CH(OH)-$

The same reactants gave, in the presence of sodium ethoxide (53,54), 2-benzylidene-cyclohexanone (XXIII) and 2,6-dibenzylidene-cyclohexanone (XXIV).



(XXIII)



(XXIV)

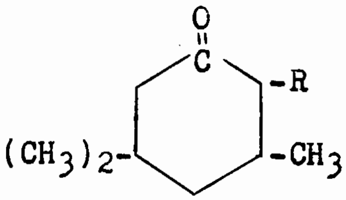
; R= $C_6H_5CH=$

Wallach (52) reported that 2-methylcyclohexanone, when reacted with benzaldehyde gave a yellow oil, whose composition he did not elucidate, and further that the condensation does not occur in alkaline medium.

3-Methylcyclohexanone reacted with benzaldehyde in alcoholic solution (55), to give 2-benzylidene-5-methyl-cyclohexanone.

4-Methylcyclohexanone gave the same reactions with aldehydes as the unsubstituted cyclohexanone.

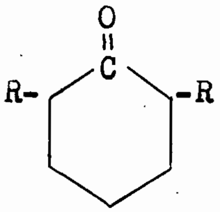
Merling and Welde (56) reported the formation of a monobenzal compound (XXV), by the reaction of 3,3,5-trimethylcyclohexanone with benzaldehyde, in the presence of sodium ethoxide and ether.



; R= $C_6H_5CH=$

(XXV)

Cyclohexanone reacted with o-nitrobenzaldehyde in the presence of 98-100 per cent formic acid (52) forming 2,6-bis [o-nitrobenzylidene]-cyclohexanone (XXVI). The reaction would not take place in alkali, however.

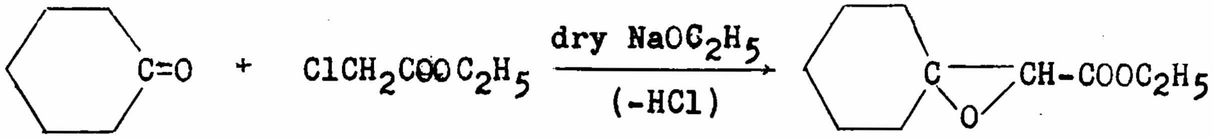


(XXVI)

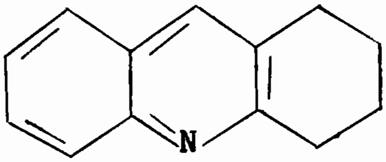
; R= $NO_2C_6H_4CH=$

When o-nitrobenzaldehyde was reacted with 3-methylcyclohexanone in the presence of formic acid (52), the product formed was 3-methyl-2,6-bis [o-nitrobenzylidene]-cyclohexanone.

Cyclohexanone reacted to give the Darzens condensation (57), which is the formation of glycidic esters by the condensation of aldehydes or ketones with esters of α-haloacids.

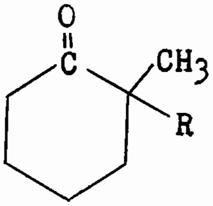


Borsche (58) reported the preparation of 1,2,3,4-tetrahydroacridine (XXVII) by reacting cyclohexanone with o-aminobenzaldehyde at 30°



(XXVII)

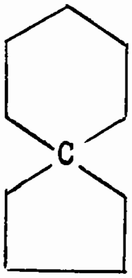
The synthesis of β-ketoamines from the condensation of cyclohexanone, 2-methylcycohexanone, 3-methylcyclohexanone and 4-methylcyclohexanone with benzoic acid in the presence of aniline and alcohol has been reported (61): 2-methyl-2-[phenyl (phenylamino) methyl] cyclohexanone, (XXVIII); 3-methyl-2(or6)-[phenyl(phenylamino) methyl] cyclohexanone and 4-methyl-2-[phenyl(phenylamino) methyl] cyclohexanone are the respective products when 2-,3- and 4-methylcyclohexanones are reacted as described.

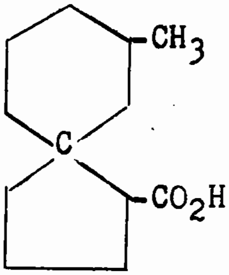


; R= $-CH(C_6H_5)NH.C_6H_5$

(XXVIII)

A new route to the synthesis of spiro compounds, such as cyclohexane-spiro-cyclopentane (XXIX) and 3-methylcyclohexane-spiro-cyclopentan-2-one-5-carboxylic acid (XXX), from the cyanohydrin of the corresponding ketone, has been reported by Chatterjee (62,63).



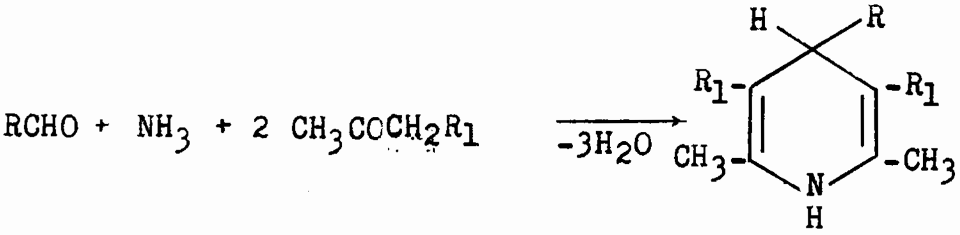


(XXIX) (XXX)

Dihydropyridines

The chemistry of the dihydropyridines may be considered to be essentially that of the piperidines, since the difference between a pyridine compound and dihydro- or tetrahydropyridine derivatives is often a matter of definition.

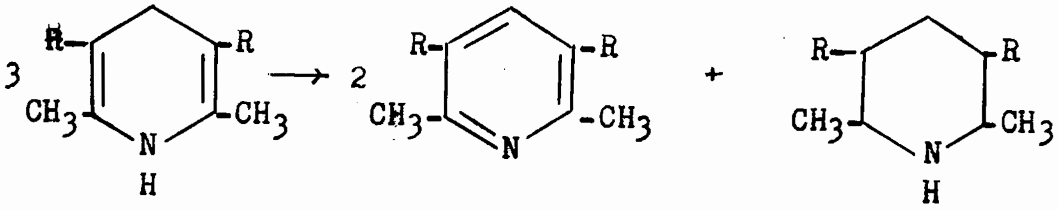
One of the earliest syntheses of dihydro-pyridines, was that of Hantzsch (64), who obtained R-substituted 3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydro-pyridines (XXXI), using a mixture of an aldehyde, acetoacetic ester, and ammonia.



R_1 = -COOEt ; R= H etc.

(XXXI)

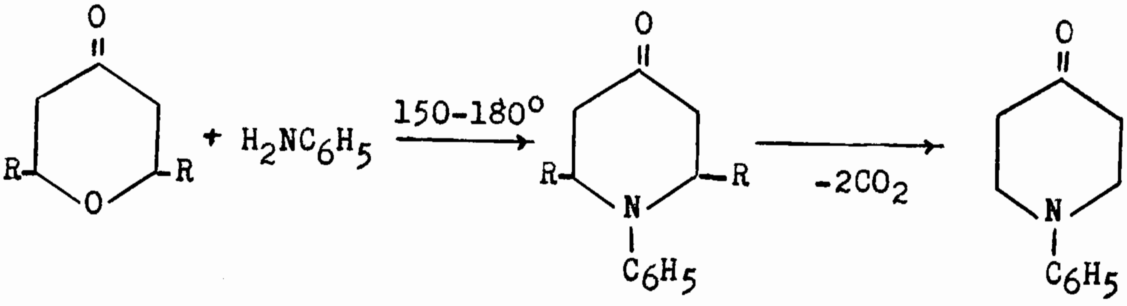
Oxidation of(XXXI) to the pyridine derivative, is sometimes accomplished through a disproportionation reaction (65), in which one molecule of the dihydropyridine is reduced.



R= -COOEt

Von Meyer (17) reported the synthesis, in good yield, from the reaction of 'dinitriles' with ketones of a number of 4,4-dialkyl-1,4-dihydropyridines.

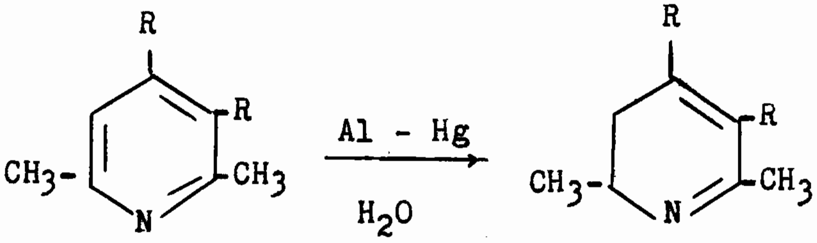
Primary amines, when reacted on pyrones, such as chelidonic acid (66), form dihydropyridines, e.g. N-phenyl-4-pyridone (XXXII)



R= -COOH

(XXXII)

The direct reduction of carboxylic acids or esters to dihydropyridines (67,68,69), has been achieved, using amalgamated aluminum, sodium hydrosulfite or sodium amalgam.

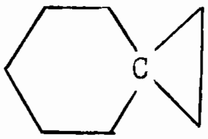


; R= -COOEt (67)

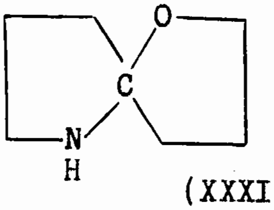
Spiranes

Compounds having a carbon atom common to two rings are known as spirocyclic compounds, or spiranes, since their figure-of-eight formulae suggest the 'Brezel', a common German article of bakery (in latin, spira).

Two systems of nomenclature for spiranes are currently in use. For example, the compound C_8H_{14}, (XXXIII), may be named spiro[2.5] octane or cyclohexane-spirocyclopropane. Compound, (XXXIV), is named as 1-ox-6-azaspiro[4.4] nonane

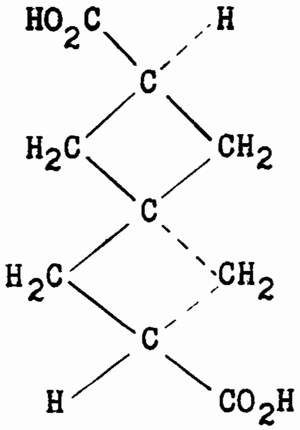


(XXXIII)

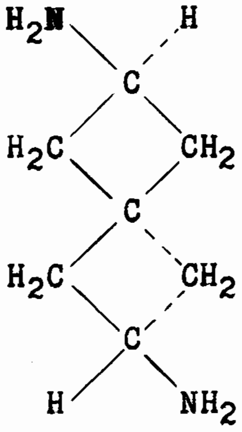


(XXXIV)

Aschan (70) pointed out that properly substituted spiranes are asymmetric molecules, and hence should be capable of resolution. Backer and Schurink (71) studied the resolution of spirocycloheptanedicarboxylic acid (XXXV), but could only obtain products of low activity ($[M]_D$ + 1.9°) Pope and Jansen (72) showed, however, that the corresponding amine, diaminospirocycloheptane (XXXVI), could readily be resolved into enantiomorphic forms, which had considerable optical activity. The hydrochloride had $[M]_{4358}$ + 30°

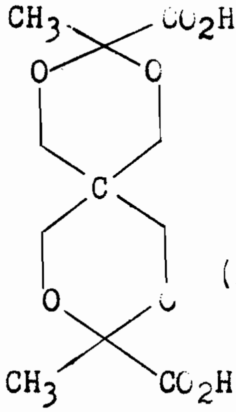


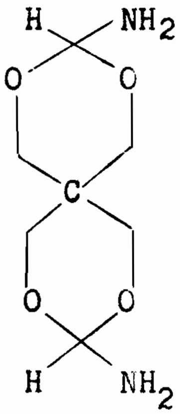
(XXXV)



(XXXVI)

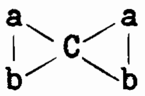
Boeseken (73) prepared spirocyclic compounds by condensing pentaerythritol, $C(CH_2OH)_4$, with pyruvic acid (XXXVII) and with aminoacetaldehyde (XXXVIII)


(XXXVII)

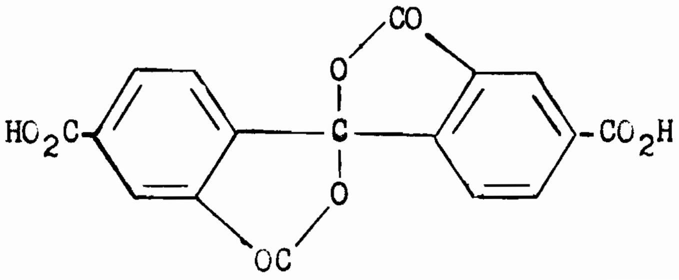

XXXVIII)

Although(XXXVII) and (XXXVIII) were resolvable, the products showed only small optical activity.

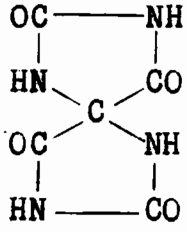
There is another type of centroasymmetrical spirocyclic compounds, consisting of two identical unsymmetrical rings, having a carbon atom in common, as represented by the formula.



The first compound of this type to be obtained in antimeric optically active forms, was the ketodilactone of benzophenone-2,4,2',4'-tetra carboxylic acid (XXXIX). It was resolved by means of phenylethylamine (74).


(XXXIX)

The simplest spirocyclic compound which has been resolved, is spiro-5,5-dihydantoin(XL),



(XL)

whose optically active forms have been fully investigated by Pope and Whitworth (75). Spiranes of this class, have been obtained in optically active modifications, by Leuchs (76) and by Radulescu (77).

Chelates of metals, of the spirane type, such as the beryllium derivative of acetylacetone, and copper derivatives of benzoylpyruvic acid, are known, and have been resolved (78), but will not be considered here.

Discussion

Introduction

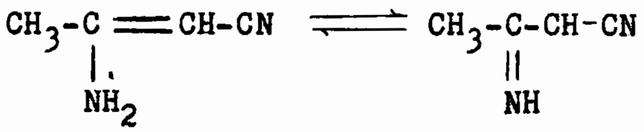
It was found that cyclohexanone and various methylcyclohexanones condensed with β-aminocrotononitrile (II) in the presence of phosphorus pentoxide, to give compounds which appeared to be substituted dihydropyridine spiranes. The ensuing discussion deals with the preparation of (II) and its condensation with the above mentioned ketones.

The reaction of metallic sodium (2g.atoms) on acetonitrile (3 moles), in benzene solution, resulted in the formation of a gaseous product, methane, and a crystalline solid, which was a mixture of the sodium salt of β-aminocrotononitrile and sodium cyanide. β-Aminocrotononitrile was obtained by decomposing an ether slurry of the mixture of sodium salts with water, at 40°.

von Meyer (12) obtained (II) in the form of two crystalline modifications: high melting (79-83°) and low melting (52-53). He postulated the ketimine-enamine tautomerism of (II), but did not offer any proof of this idea.

Conn and Taurins (30) in a recent investigation, have shown that:

(i) The existence of ketimine (XLIV)-enamine (XLIII) tautomerism in (II) must be excluded, since the observed ultraviolet absorption indicated that both modifications have identical electronic configurations when dissolved in polar solvents.



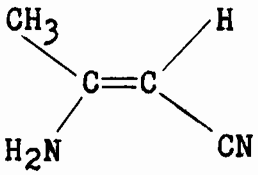
$$CH_3-\underset{NH_2}{\underset{|}{C}}=CH-CN \rightleftharpoons CH_3-\underset{NH}{\underset{||}{C}}-CH-CN$$

(XLIII) (XLIV)

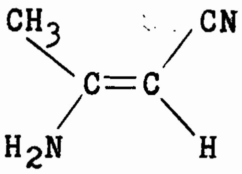
Further evidence in favour of excluding the existence of tautomerism was given by a calculation of the heats of solution of the two modifications at the melting point. The two modifications give values which were identical within the limits of experimental error. They assumed that the heats of melting of the two modifications would be of the same order of magnitude, and almost identical to each other, since it is known that in an ideal solution, the heat of solution of a solid is identical with its heat of melting at the same temperature. The heats of melting of enamine and ketimine tautomers would not be identical, thereby ruling out such tautomers as possible structures for the two modifications of (II).

(ii) The existence of polymorphism in the two modifications of (II) must also be excluded since both modifications have definite melting points and give nearly identical values of the heat of fusion.

(iii) Since the two possibilities to explain the existence of the two modifications of (II) were excluded, cis-trans isomerism was proposed. They assigned the cis configuration (XLI) to the low-melting modification and the trans configuration (XLII) to the high-melting modification.

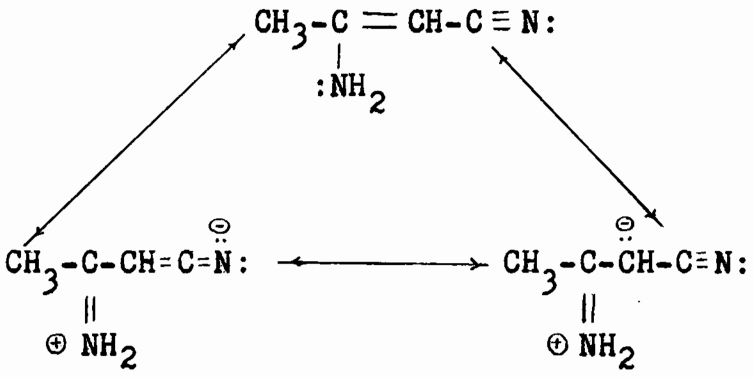


(XLI)



(XLII)

(iv) Ionic structures (XLV) of (II) may be considered as contributing, in varying degrees to the resonance hybrid of the molecule in polar solvents.



(XLIV)

These statements were made on the basis of the observed ultraviolet spectra.

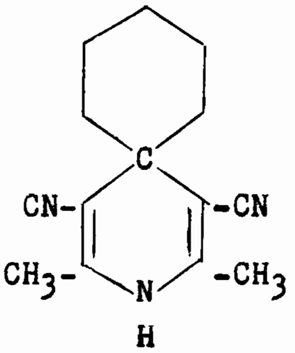
Since it had been shown that the cis and trans isomers were identical in their reactions, and that the cis (or low melting) modification was the more stable, it was decided to prepare this modification only, for use in this work. Several small departures from the procedure used by Conn (25) should perhaps be mentioned. It was found that a heating mantle amply and efficiently provided the modest heat required to maintain the mixture at reflux. An oil bath, such as was used by Conn, might conceivably reduce the danger of fire, in the event of breakage of the flask.

The reflux time of 24-30 hours mentioned by Conn, was reduced to 8 hours, which appeared to be sufficient. In fact, it was observed that excessive refluxing produced an inferior product. The clean-cut isolation of the cis isomer appeared to be dependent on the temperature of the water used to decompose the mixture of sodium salts. Conn used water at 30°. It would seem that water at 40°, induced a more homogeneous separation. The vigorously exothermic decomposition reaction caused the volatilization of most of the ether (b.p. 34.6°), even when water at 30°was used. Slightly warmer water (40°) should not, therefore, markedly increase the amount of ether lost, since the water was added, in small amounts, to the slurry which was many times the volume of the water being added.

Different solvents, concentrations and temperatures were tried before deciding that recrystallization of crude β-aminocrotononitrile was accomplished most satisfactorily from benzene. For this purpose, β-aminocrotononitrile was dissolved in benzene (1:1 by weight) and the resulting solution was heated to 80°, filtered, then allowed to cool slowly to room temperature. Mixtures of the cis and trans isomers were obtained at lower temperatures and greater dilution. Refrigeration of dilute solutions invariably resulted in either freezing of the solution or a sparse amount of poor grade crystals. Heating to 80° apparently converted any of the high melting (or trans) modification, formed during the decomposition of the sodium salt mixture, to the desired stable cis isomer.

Attempted Condensation of Cyclohexanone with β-Aminocrotononitrile (in Alcoholic Hydrogen Chloride)

von Meyer (17) has described a series of condensations between 'dinitriles' and ketones, in which two moles of the 'dinitrile' condensed with one mole of the ketone to form dihydropyridine derivatives such as (XLVI),



(XLVI)

(formed by the condensation of two moles of β-aminocrotononitrile with one mole of cyclohexanone). A summary of von Meyer's description and recommendations is as follows:

(i) It was better to work with small quantities of the reagents e.g. 0.02 g-mole and 0.01 g.-mole respectively.

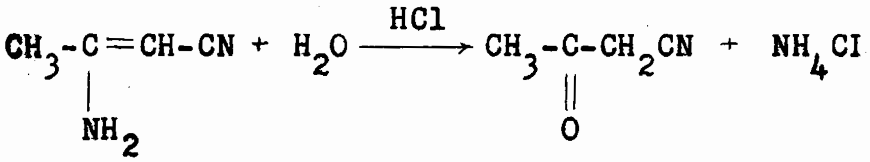
(ii) The 'dinitrile', dissolved in a slight excess of the ketone, was added to 15 ml. of absolute alcohol and cooled to 5°. With 'benzacetodinitrile' i.e. 3-aminocinnamonitrile, a 30% excess of the ketone was used, the amounts of reagents being as specified in (i).

(iii) To the solution in (ii) was added "a little more than" 0.01g.-mole of alcoholic hydrogen chloride.

(iv) After "a few days" standing, a white precipitate was reportedly isolated. All compounds resulting from the interaction of various dinitriles and ketones crystallized well. They were all practically water-insoluble, and difficultly soluble in cold alcohol, ether and benzene.

When the synthesis described by von Meyer was attempted, the product which he claimed formed "after a few days standing", was not observed after a three weeks stand at room temperature. No ready explanation has been found for the failure of this reaction to occur as described, although several possibilities suggest themselves. It would appear that some crucial step in the procedure was either unknown to von Meyer, who did not actually perform the work described, or was considered unimportant by him and hence not reported. Then there is the matter of what is meant by "slightly more than" sufficient hydrogen chloride to neutralize the ammonia liberated in the condensation. An excess of 10% and 44% hydrogen chloride was tried by the author, without success. Perhaps the failure of the attempted reaction was due to the absence of an excess of the Ketone (cf. von Meyer's recommendations #ii). This does not appear to be very probable however, since small weighing errors, for example, would readily afford a sizeable excess of one or other reactant.

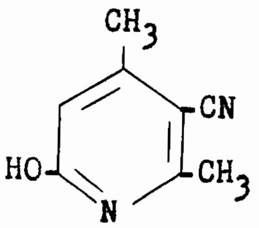
Careful examination of the reaction mixture revealed that ammonium chloride was the only solid product formed. The presence of ammonium chloride could be explained, apart from any reaction between liberated ammonia from the condensation of two amino groups, by the reaction described by Holtzwart (79), in which β-aminocrotononitrile (II) was hydrolyzed in 25% hydrochloric acid, to cyanoacetone (XLVII) and ammonia.



$$CH_3-\underset{NH_2}{\underset{|}{C}}=CH-CN + H_2O \xrightarrow{HCl} CH_3-\underset{O}{\underset{\|}{C}}-CH_2CN + NH_4Cl$$

(II) (XLVII)

Because the volume of alcoholic hydrogen chloride (300ml.) was large relative to that of the reactants (~5ml.) it was thought probable that the desired product would separate upon concentrating the solution. Successive reduction of the volume of the solution, to one half, one-quarter, and finally evaporation to dryness, under reduced pressure, resulted in the production of ammonium chloride, in amounts far in excess of that which would form by the condensation of an amino group in each of two moles of β -aminocrotononitrile. The lability of β-aminocrotononitrile has already been described by Holtzwart (8) and by Moir (18), who found that in hot water, it underwent self-condensation to form VII.



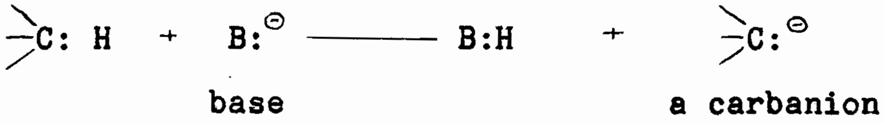
(VII)

It must therefore be concluded that, under the conditions described, β -aminocrotononitrile did not condense with cyclohexanone, but rather that it suffered de-amination.

Attempted Condensation of β-Aminocrotononitrile with Cyclohexanone in Alcoholic Sodium Bicarbonate.

The failure of β-aminocrotononitrile to condense with cyclohexanone in alcoholic hydrogen chloride, prompted this attempt in a slightly alkaline medium.

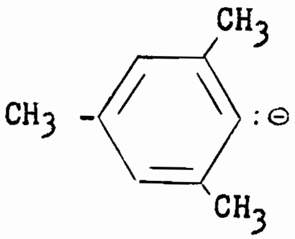
Basic materials have, in varying degrees, the ability to abstract a proton from acidic substances. The proton deficient substance is a carbanion e.g.



The carbanion formed must possess great stability due to resonance structures. A study of the relative ability of bases to act as proton abstractors, has shown that the most powerful bases for this purpose are the triphenylmethide (XLVIII) and the mesityl (XLIX) anions.

$(C_6H_5)_3C:\ominus$

(XLVIII)

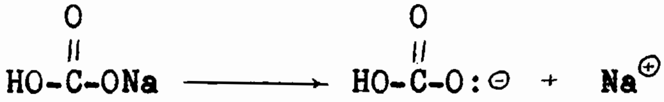


(XLIX)

The following sequence has been observed among the aliphatic series.

$$(CH_3)_3CO:\ominus > (CH_3)_2CHO:\ominus > C_2H_5O:\ominus > CH_3O:\ominus$$

Sodium bicarbonate ionizes to form the sodium cation and the bicarbonate anion, which corresponds



$$HO\text{-}\overset{\overset{O}{\|}}{C}\text{-}ONa \longrightarrow HO\text{-}\overset{\overset{O}{\|}}{C}\text{-}O:\ominus + Na^{\oplus}$$

to $B:^{\ominus}$ in the scheme given. It was hoped that the bicarbonate anion would prove sufficiently powerful as a proton extractor. The failure of the desired condensation to take place, showed that sodium bicarbonate was not suitable for this purpose.

Attempted Condensation of β-Aminocrotononitrile-Hydrogen Chloride Complex with Cyclohexanone.

β-Aminocrotononitrile reportedly reacted with hydrochloric acid in dry benzene (80) to form a compound containing 27.5% Cl, after a long stand in a dessicator over calcium oxide and sulphuric acid. The powder was described as being white and amorphous. $C_4H_6N_2.HCl$ contains 29.9% Cl.

A product believed to be the same as the one reported above, was prepared by passing dry hydrogen chloride gas into a benzene solution of β-aminocrotononitrile, which was immersed in an ice-salt bath. Dry hydrogen chloride gas should have the advantage, over hydrochloric acid, of avoiding the danger of causing hydrolytic degradation of β-aminocrotononitrile (79). The product was a very pale buff colour and seemingly amorphous. It was insoluble in water, alcohol and benzene. Because of its water-insolubility, its amorphousness, and the general indefiniteness of its composition, the compound was designated as a hydrogen chloride complex of β-aminocrotononitrile.

The reason for forming this complex was to have hydrogen chloride 'in situ', and thereby bring about the desired condensation. This would presuppose, however, that the hydrogen chloride in the complex was readily removable by polar solvents. It was found, in support of this supposition, that a dispersion of the complex in water, gave a precipitate of silver chloride, when treated with aqueous silver nitrate.

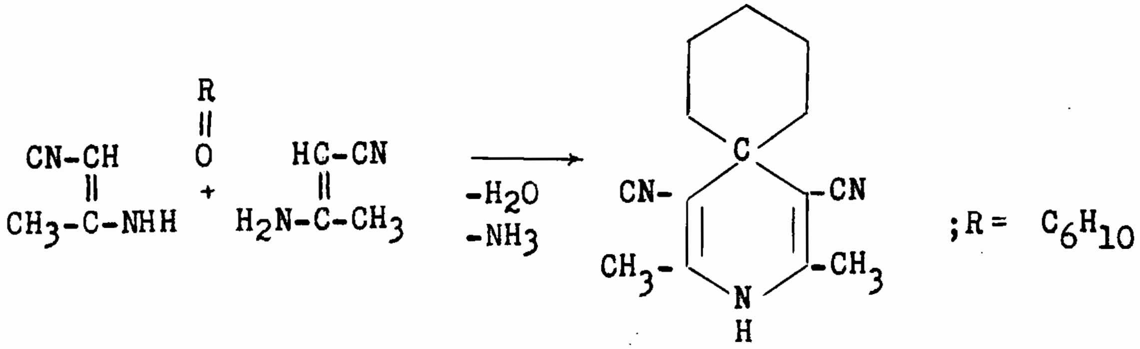
Absolute ethanol was chosen as the reaction medium because it was a reasonably polar solvent in which both β -aminocrotononitrile and cyclohexanone were readily soluble. Furthermore, the ionization of the hydrogen chloride of the complex should have been enhanced in the polar medium.

The condensation did not occur however, probably because hydrogen chloride was not a sufficiently strong condensing agent under these conditions.

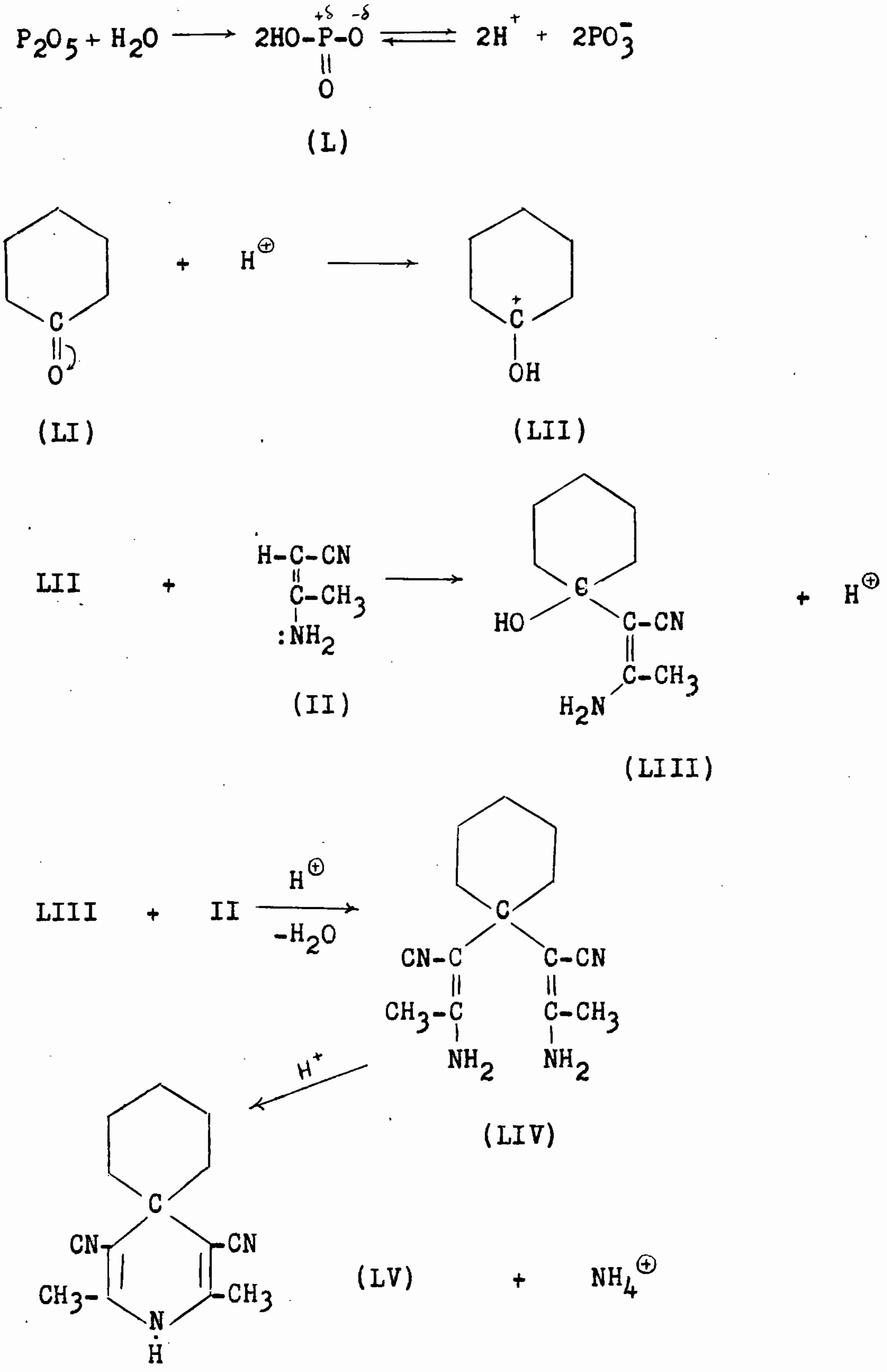
Condensation of Cyclohexanone and Methylcyclohexanones with β -Aminocrotononitrile (Phosphorus Pentoxide as condensing agent).

Since the condensation involved the elimination of a mole of water and of ammonia, it seemed probable that phosphorus pentoxide would be suitable as the condensing agent, because of its acidity and vigorous dehydrating ability.

A general mechanism to explain the successful condensation of β -aminocrotononitrile with cyclohexanone; 3-and 4-methylcyclohexanone; 3,3,5-trimethylcyclohexanone, and the failure of the reaction with 2-methyclcyclohexanone will now be proposed and discussed. The mechanism of classical Organic Chemistry, involving a simultaneous termolecular collision,



Proposed Mechanism:

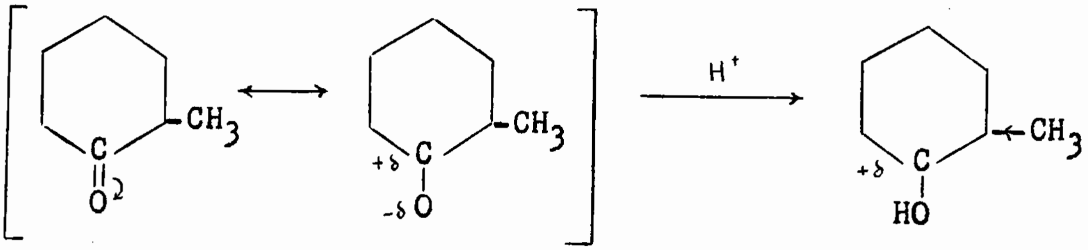


$$P_2O_5 + H_2O \longrightarrow 2HO\text{-}\overset{+\delta}{P}(=O)\text{-}\overset{-\delta}{O} \rightleftharpoons 2H^+ + 2PO_3^-$$

is unsatisfactory because of the rarity of such collisions (81). An ionic mechanism, involving the formation of a carbonium ion, is therefore proposed.

In the proposed scheme, phosphorus pentoxide reacts with a trace amount of water, which would be present in 99.5% + alcohol, to form metaphosphoric acid (L). The structure given for (L) is in keeping with the tendency of phosphorus to exhibit quadricovalency (82). A proton attacks the oxygen of the carbonyl group in cyclohexanone, forming a carbonium ion (LII). The positive carbon atom of the carbonium ion then joins with the α-carbon atom of β-aminocrotononitrile, and in so doing eliminates its proton, forming (LIII). Another carbonium ion is formed by the protonation of the hydroxyl group in (LIII), followed by the elimination of water. β-Aminocrotononitrile adds to this carbonium ion, as in the previous instance, forming LIV. The elimination of ammonia from (LIV), as the ammonium cation results in the formation of the dihydropyridine spirane (LV).

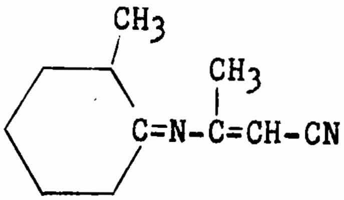
It is evident that in the proposed mechanism, the all-important step is the addition of the α-carbon atom of β-aminocrotononitrile to the positively charged carbon atom of the carbonium ion. The effect of the methyl group on this addition was studied. A methyl group in the 2-position should, by the inductive effect (+Is), cause considerable delocalization of the π electrons of the carbonyl group towards oxygen. The resulting partial dipolarity of



(LVI)

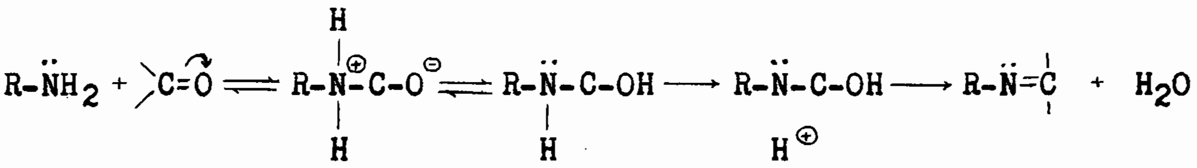
2-methylcyclohexanone is destroyed by the formation of a carbonium ion (LVI). In this instance, however, the positivity of the 1-carbon atom should be effectively diminished by the inductive effect $(+I_s)$ of the methyl group. The addition of β-aminocrotononitrile to this carbon atom should therefore be impeded, if not altogether prevented. A methyl group in the 3- or 4- position should not have any appreciable effect on the positivity of the 1-carbon atom, and therefore on the condensation. Three methyl groups, two carbon atoms away from the 1-carbon atom, might conceivably have some retarding influence on the condensation reaction.

Some support for the foregoing ideas was obtained by experiment. It was found that the desired condensation did not occur with 2-methylcyclohexanone. A product of undetermined structure was isolated, but it was not the spiro compound. One suggestion as to the possible nature of the product is given (LVII).



(LVII)

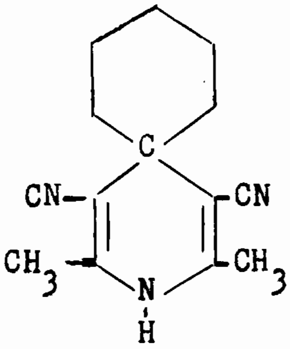
Such a structure could have resulted from the condensation of an amino and carbonyl group. Acid-catalyzed reactions of this type are well known.

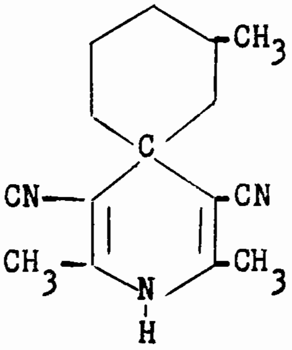


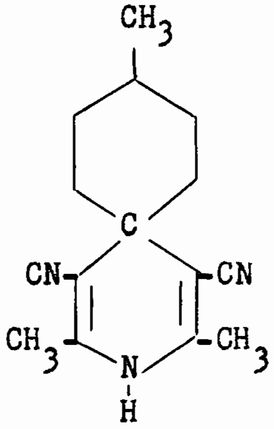
$$R\text{-}\ddot{N}H_2 + \rangle C{=}\ddot{O} \rightleftharpoons R\text{-}\overset{H}{\underset{H}{\overset{\oplus}{N}}}\text{-}C\text{-}O^{\ominus} \rightleftharpoons R\text{-}\underset{H}{\ddot{N}}\text{-}C\text{-}OH \longrightarrow R\text{-}\ddot{N}\text{-}C\text{-}OH \; H^{\oplus} \longrightarrow R\text{-}\ddot{N}{=}C\langle \; + \; H_2O$$

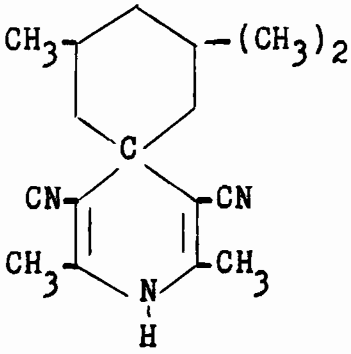
Failure of the desired condensation reaction with 2-methylcyclohexanone, cannot be satisfactorily explained by steric hindrance, since the lack of coplanarity in the cyclohexanone molecule, would nullify any such argument. The condensation did occur, however, with cyclohexanone, 3- and 4- methylcyclohexanone and 3,3,5-trimethylcyclohexanone, the yield of the condensation product (LV) etc. being respectively 48.5%, 43.6%, 66.4% and 3.4%. In the case of 3,3,5-trimethylcyclohexanone, the comparatively low yield (3,4%) might be explained as being due to an appreciable $+I_s$ effect of three methyl groups, two carbon atoms away from the positively charged 1- carbon atom. It must be emphasized however, that the yields given are intended as possibly being indicative of a trend, and should not be interpreted as being absolute values on which to predicate generalizations.

The structures assigned the products,


(LV)


(LVIII)


(LIX)

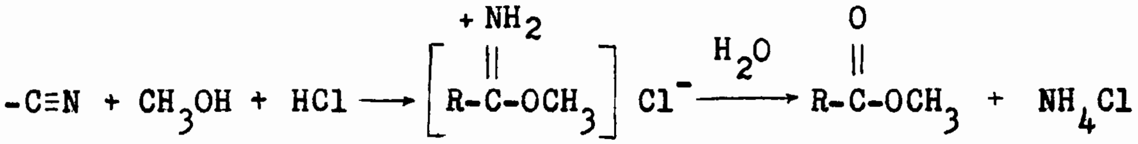

(LX)

have been arrived at mainly by inductive reasoning. It will be recalled that cyclization of β-aminocrotononitrile is a very common reaction (2,8,12,13,15,16,17,18,23). The interaction of cyclohexanone and β-aminocrotononitrile should therefore result in the formation of a bicyclic compound, accompanied by the elimination of ammonia. The presence of ammonia, as the ammonium ion, was detected in the reaction mixture, by the usual qualitative procedure. Its presence cannot be explained by assuming a condensation such as the one which produces compounds of the type as shown (LVII). The stability of the dihydropyridine constituent of (LV) etc. compares with that of a somewhat analogous compound, (VII), which had been investigated by von Meyer (12) and by Moir (18). No chemical elucidation of the structure of (LV) to (LX) was achieved, since no way of modifying these products could be found. They did not form derivatives with either p-toluenesulphonyl chloride or picric acid, and resisted all attempts at hydrolyzing their cyano groups. A fuller discussion of this latter point will be given subsequently.

The products, LV-LX, were found to be insoluble in water, concentrated sulphuric and hydrochloric acids, and 20% sodium hydroxide solution. They were readily soluble in pyridine, ethanol, acetone and ethyl acetate.

Attempted Hydrolysis of Cyano Groups in (LV).

The next step in the synthesis originally planned, would be the hydrolysis of the cyano groups in LV-LX to carboxyl groups, followed by esterification. Every attempt made to hydrolyze the cyano groups ended in failure. Three of the unsuccessful procedures are perhaps worthy of special mention. First, it was found that the starting material, (LV), was destroyed when heated, in 75% sulphuric acid, for 30 min. at 150-160°, then for an additional 30 min. at 178° . Second it was observed that heating over a micro burner flame, in concentrated orthophosphoric acid, for 7 hrs. caused resinification of the starting material. Finally, an attempted direct esterification of the starting material by methylalcoholic hydrogen chloride

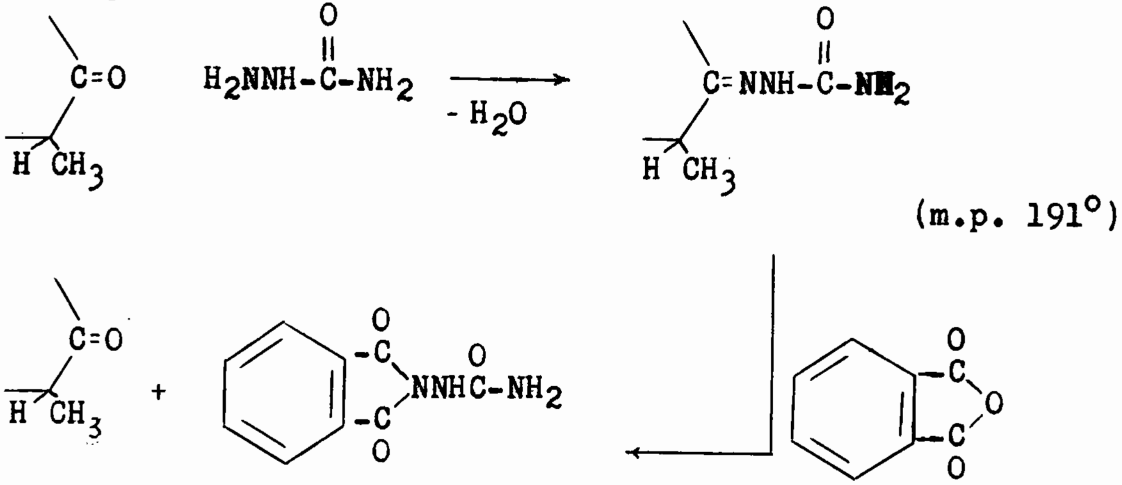


$$-C\equiv N + CH_3OH + HCl \longrightarrow \left[R-\overset{+NH_2}{\overset{\|}{C}}-OCH_3 \right] Cl^- \xrightarrow{H_2O} R-\overset{O}{\overset{\|}{C}}-OCH_3 + NH_4Cl$$

was unsuccessful; the only product isolated proved to be starting material.

Preparation of 2-Methylcyclohexanone

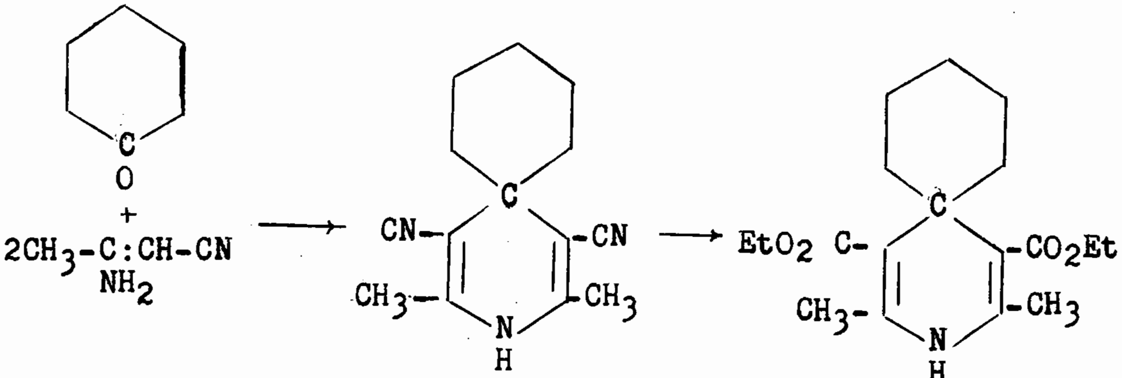
The reduction of chromic acid, and concomitant oxidation of 2-methylcyclohexanol to 2-methylcyclohexanone, was readily observed by the formation of green chromic ions (Cr^{+++}). Steam distillation of the reaction mixture gave an 86% yield of the crude ketone, whereas extraction with ether gave a yield of 83%. The crude ketone readily formed the sodium bisulfite addition compound, but considerable difficulties were subsequently encountered with this compound. First, the bisulfite addition compound appeared to be quite hygroscopic, and dissolved partially while being dried on the filter. Decomposition of the bisulfite addition compound with a 10% sodium hydroxide solution (86) was rather unsuccessful, giving a yield of the ketone of about 20%. After distillation, a yield of 18.5% of pure ketone was obtained. The semicarbazone (m.p. 191°) which formed readily, resisted all efforts to decompose it by steam distillation in the presence of phthalic anhydride. This was intended as an improved means of purification



Summarizing, the author recommends that the ketone be prepared by chromic acid oxidation of the alcohol, followed by extraction of the reaction mixture with ether and purification through the bisulfite addition compound, which is decomposed with sodium carbonate solution (87), followed by distillation.

<u>A Proposed Synthesis</u>.

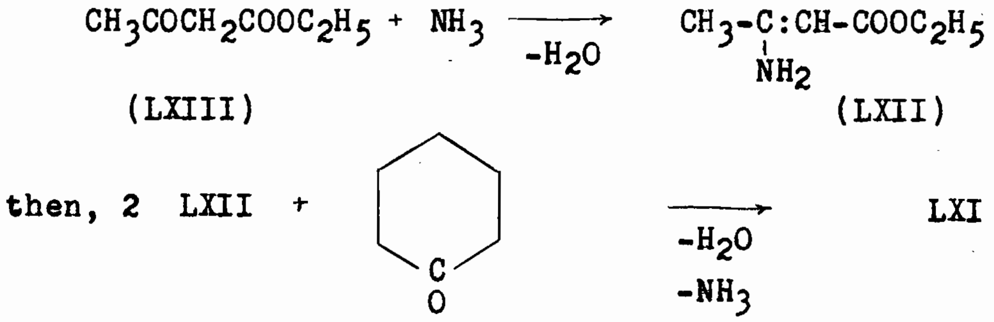
Originally it was throught that the synthesis would proceed as follows:



(LV) (LXI)

Analogs of (LXI) have been synthesized by the Hantzsch Pyridine Synthesis (88), which consists of condensing ammonia, an aldehyde and acetoacetic ester.

As mentioned previously, (LV) resisted attempts to hydrolyze and subsequently esterify, its cyano groups. Some new route of synthesis of (LXI) must therefore be found. A suggested synthesis consists of condensing ethyl β-aminocrotonate (LXII) with cyclohexanone. (LXII) may be prepared by reacting ammonia with ethyl acetoacetate, (LXIII), (28).



$$CH_3COCH_2COOC_2H_5 + NH_3 \xrightarrow[-H_2O]{} CH_3-\underset{NH_2}{C}:CH-COOC_2H_5$$

(LXIII) (LXII)

The principal problem would be to find a condensing agent to remove the α-hydrogen atom of LXII, which should undoubtedly have been rendered labile through its activation by the carbethoxy group. Polyphosphoric acid was tried by the author as the condensing agent. It was found, on the basis of the one attempt made, to be apparently unsuitable for this reaction, although it has reportedly been effective as a cyclizing agent in many instances (29). Lack of time prevented repetition of the attempted synthesis. It is felt, however, that use of a mild condensing agent such as sodium ethoxide will result in the desired condensation.

Experimental

Preparation of β-Aminocrotononitrile.

A 2-l. round-bottom flask, with a ground-glass joint, was fitted with a reflux condenser protected with a calcium chloride drying tube. The flask was immersed in an ice salt cooling bath. A solution of redistilled acetonitrile (246g.;6 moles) in 800 ml. of benzene, dried over sodium wire, was placed in the flask. Metallic sodium (92g.;4 moles), cut in small pieces, was added through the condenser at a rate such as to cause the solution to reflux gently. An immediate reaction was noted; gas bubbles, presumably methane, and a white flake-like solid, consisting of a mixture of sodium cyanide and the sodium salt of β-aminocrotononitrile, formed. The reaction mixture was refluxed, by means of an electric heating mantle for 8 hours. A pale-yellow solid separated as a large-granuled precipitate. This solid material was collected by filtration with suction, and washed in the funnel, with a little acetonitrile and finally, dry benzene. An ether slurry of the residue was prepared, in a 600 ml. beaker. Water, at about 40°, was gradually added until decomposition of the β-sodioaminocrotononitrile to β-aminocrotononitrile, was complete. The resulting pale-amber two layer liquid was transferred to a separatory funnel, and the separated aqueous layer was extracted with three portions of ether, these extracts being added to the original ethereal layer. Crude β-aminocrotononitrile remained after the ether had been removed by distillation at reduced pressure. The crude β-aminocrotononitrile, dried over calcium chloride, was recrystallized several times from benzene to give a virtually white powder, melting at 51-53°. For this purpose, a solution of crude β-aminocrotononitrile in benzene (1:1 by weight) was heated to 80°, filtered through a heated funnel into an Erlenmeyer flask, which was then stoppered and allowed to cool slowly to room temperature. After removing the fine colourless needles by filtration with suction, the filtrate was evaporated to dryness on a steam bath, at reduced pressure. The recovered crude was recrystallized from benzene as described. By working up the filtrates, the total yield of pure product was found to be 118 g. (70% of the theoretical).

Attempted Condensation of β-Aminocrotononitrile with Cyclohexanone in Alcoholic Hydrogen Chloride.

The synthesis attempted was that reported by von Meyer (17).

Freshly prepared absolute ethanol (300 ml.), distilled successively from calcium oxide and magnesium, was placed in a 1-l. Florence flask, which was immediately stoppered and weighed. Dry hydrogen chloride gas, generated by allowing concentrated hydrochloric acid (100 ml.) to drop slowly into concentrated sulphuric acid (150 ml.) and passing the evolved gas through concentrated sulphuric acid, was passed into the alcohol, immersed in an ice-salt bath at 5°, until saturation was achieved. The flask and contents, when weighed, was found to contain 1.05g. (0.0288 mole) of hydrogen chloride gas. After re-immersing the flask in the cooling bath, 1.96 g. (0.02 mole) of freshly redistilled cyclohexanone (b.p. 156°) and 3.28 g.(0.04 mole) of β-aminocrotononitrile (m.p. 51°) were added, and the flask was immediately re-stoppered. After one hour, the flask was removed from the bath and allowed to stand at room temperature. The flask stood for three weeks, at room temperature, during which time it was periodically examined for signs of the reported crystalline product (17).

Trace amounts of a fine white, seemingly crystalline product were noted almost immediately. This was later shown to be ammonium chloride. All efforts to isolate the desired condensation product failed, ammonium chloride being the only crystalline product obtained.

Attempted Condensation of β-Aminocrotononitrile with Cyclohexanone in Alcoholic Sodium Bicarbonate.

In each of six test tubes was placed a mixture of 0.1225g (0.00125 mole) cyclohexanone and 0.205g. (0.0025 mole) β-aminocrotononitrile. Saturated aqueous sodium bicarbonate solution, water and alcohol was added to each test tube in the amounts indicated. The tubes were heated on a steam bath for about one minute, then stoppered and allowed to cool to room temperature.

A white crystalline precipitate formed, prior to heating, in tubes #1 and #2. Careful examination of the precipitate showed it to be sodium bicarbonate.

Oily globules formed, after the heating, in tubes #3,#4,#5 and #6. Although the identity of the oil was not definitely established, it was thought to be separated reaction mixture.

Test Tube No.	Ml.Sat'd Aq. $NaHCO_3$ Sol'n.	Alcohol Sol'n.		Approx. % Sat'n of $NaHCO_3$ Sol'n.	
		Ml. H_2O	Ml. C_2H_5OH	Aqueous	Alcoholic
1	1.0	0.0	5.0	100.	16.7
2	0.9	0.6	4.5	60.	15.
3	0.2	4.8	1.0	4.	3.3
4	0.1	5.4	0.5	1.8	1.7
5	0.9	4.1	1.0	18.	15.
6	1.0	4.5	0.5	18.2	16.7

It was not found possible to isolate a product, other than as previously indicated, from any of the reaction mixtures.

Attempted Condensation of β-Aminocrotononitrile, Hydrogen Chloride-β-Aminocrotononitrile Complex and Cyclohexanone.

Dry hydrogen chloride gas was caused to flow into a solution of 4.1 g. (0.05 mole) of β-aminocrotononitrile, m.p. 51°, in 200 ml. of benzene (dried over sodium wire). A pale-yellow solid separated from the solution. The precipitate (3.1g) was removed by filtration with suction, and dried on the filter. The product did not melt up to 210°. It was thought that the product was a complex of β-aminocrotononitrile with hydrogen chloride, instead of β-aminocrotononitrile hydrochloride, since it was water-insoluble and seemingly amorphous. The complex was used without further purification in the subsequent procedures.

A small quantity of the complex was shaken with water in a test tube. Aqueous silver nitrate was added to the supernatant liquid, whereupon a precipitate of silver chloride formed. This confirmed the presence of chlorine, and consequently of hydrogen chloride, in the molecule.

A mixture of 1.64g (0.02 mole) of β-aminocrotononitrile and 1.96g. (0.02 mole) of cyclohexanone was dissolved in 25 ml. of absolute alcohol. While the solution was being stirred vigorously, 2.37g. of the β-aminocrotononitrile-hydrogen chloride complex was gradually added. The mixture was stoppered and set aside at room temperature for several days. Examination of the mixture indicated that the desired condensation had not taken place, since all of the hydrochloride complex was recovered.

Condensation of β-Aminocrotononitrile with Cyclohexanone (Phosphorus Pentoxide as condensing agent).

A solution of cyclohexanone[1] (1.96g; 0.02 mole) and β-aminocrotononitrile (3.28g; 0.04 mole) in 12.5 ml. of absolute alcohol, was prepared in a 250 ml. cork-stoppered Erlenmeyer flask. The flask was then immersed in an ice-salt cooling bath, and cooled to about 5°. Phosphorus pentoxide (1.42g; 0.01 mole) was added in small portions to the cooled solution, which was agitated manually. A vigorous reaction was observed as each portion of the condensing agent was added. The solution showed a marked increase in viscosity after an overnight stand, at room temperature. About 200 ml. of cold water was added to the reaction mixture, which was stirred manually. The resulting speckled-brown solid was removed by filtration with suction, washed with water, saturated sodium bicarbonate solution, again with water, and finally dried on the filter.

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[1] dried over anhydrous sodium sulfate and redistilled; b.p. 155°

Recrystallization of the crude product was achieved by dissolving it in a minimum of hot ethanol and adding water, with shaking, until the first permanent opaqueness was observed. The pure product, believed to be cyclohexyl-spiro-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine (LXIII), $C_{14}H_{17}N_3$, separated readily as white, flake-like crystals, on standing at room temperature. After two recrystallizations, the product melted sharply at 135-6°. The yield was 2.2 g. (48.5% of the theoretical).

Anal. calc. for $C_{14}H_{17}N_3$: N, 18.48%

Found: N, 18.74%

Condensation of β-Aminocrotononitrile with 3-Methylcyclohexanone (Phosphorus Pentoxide as condensing agent).

The condensation and crystallization were carried out exactly as with cyclohexanone.

Reactants:	12.5 ml. absolute alcohol
	2.22 g. (0.02 mole) 3-methylcyclohexanone[1]
	3.28 g. (0.04 mole) β-aminocrotononitrile
	1.42 g. (0.01 mole) phosphorus pentoxide

The product, 3-methylcyclohexyl-spiro-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine, (LVIII), $C_{15}H_{19}N_3$, was a white, lustrous, crystalline material, melting at 167-9°, dec.

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[1] dried over sodium sulfate and redistilled; b.p. 166-8°.

after two recrystallizations. Yield was 2.1 g. (43.6% of theoretical).

Anal. calc. for $C_{15}H_{19}N_3$; C,74.64; H,7.93; N,17.43%
Found: C,75.10; H,7.59; N,17.73%

Condensation of β-Aminocrotononitrile with 4-Methylcyclohexanone (Phosphorus Pentoxide as condensing agent)

The condensation and crystallization were carried out exactly as with cyclohexanone.

Reactants: 12.5 ml. absolute alcohol
2.22 g. (0.02 mole) 4-methylcyclohexanone[1]
3.28 g. (0.04 mole) β-aminocrotononitrile
1.42 g. (0.01 mole) phosphorus pentoxide

The product, 4-methylcyclohexyl-spiro-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine, (LIX), $C_{15}H_{19}N_3$, was a white, flake-like, crystalline material, melting at 169-170°, after two recrystallizations. Yield was 3.2 g. (66.4% of theoretical).

Anal. calc. for $C_{15}H_{19}N_3$: C,74.64; H,7.93; N,17.43%
Found: C,74.80; H,7.65; N,17.69%

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[1] dried over sodium sulfate and redistilled; b.p. 169-171°

Condensation of β-Aminocrotononitrile with 3,3,5-Trimethyl-cyclohexanone (Phosphorus Pentoxide as condensing agent).

A. Preparation of 3,3,5-Trimethylcyclohexanone:

The ketone was prepared by chromic acid oxidation of practical grade 3,3,5-trimethylcyclohexanol, obtained from Brickman Ltd., Montreal.

A 1-l. three-neck round bottom pyrex flask. was fitted with a mechanical stirrer, thermometer and cylindrical separatory funnel (500 ml. capacity). In this flask was placed a mixture of,

142.g. (1.0 mole) 3,3,5-trimethylcyclohexanol
59.6 g. (0.2 mole) sodium dichromate, dihydrate
250. ml. of water

The mixture was heated to 80°, being stirred vigorously during the heating. A solution of,

59.6 g. (0.2 mole) sodium dichromate, dihydrate
154. g. (1.57 moles) conc. sulfuric acid
250. ml. of water

contained in the separatory funnel, was added at a rate such as to keep the temperature of the mixture at about 80°. Stirring was continued during this addition. The crude ketone was obtained by steam distilling the reaction mixture. A total of 130.5 g. (91.8% of the theoretical) of the ketone was procured by the combined operations of steam distillation, and extraction of the aqueous phase with ether, followed by volatilization of the ether.

The crude product was converted to the sodium bisulfite addition compound, which was dried on the filter with suction. Treatment of the dried product with a 10% solution of sodium hydroxide, resulted in the liberation of the ketone. Final purification of the ketone was achieved by distilling this latter product, and collecting the fraction 190.5-191.5° (reported b.p.$_{760}$ 188.5-189.5°) The yield of 3,3,5-trimethylcyclohexanone was 86.6g. (62% of the theoretical).

B. Condensation with β-Aminocrotononitrile

The condensation was carried out exactly as with cyclohexanone.

Reactants: 25 ml. absolute ethanol
5.6 g. (0.04 mole) 3,3,5-trimethylcyclohexanone
6.56 g. (0.08 mole) β-aminocrotononitrile
2.84 g. (0.02 mole) phosphorus pentoxide

Precipitation of the crude product was achieved by adding water to the reaction mixture, with manual stirring. The dried crude was dissolved in a minimum of hot ethyl acetate. To the solution thus formed, was added petroleum ether (b.p. 100-120°), the volume of which was approximately half that of the ethyl acetate. Upon cooling to room temperature, a wispy, seemingly white powder separated from the yellow solution. The powder (0.15g.) was found to be a pale buff colour, upon being dried. An attempted melting point on this by-product, revealed that while charring began at 190°, true melting was still absent at 260°. The filtrate from the original recrystallization attempt, was evaporated to dryness at reduced pressure, and the residue was dissolved in hot alcohol. The addition of water, until the first opaqueness appeared, followed by allowing the solution to cool to room temperature, resulted in the formation of a white, crystalline product, which melted at 205-6°, after two recrystallizations from dilute ethanol. The yield of the product. 3,3,5-trimethylcyclohexyl-spiro-3,5-dicyano-

2,6-dimethyl-1,4-dihydropyridine, (LX), $C_{17}H_{23}N_3$, was 0.4 g. (3.4% of the theoretical).

Anal. calc. for $C_{17}H_{23}N_3$: C, 75.80; H,8.60; N,15.60%
Found: C,76.10 ; H,8.40; N, 15.92%

Attempted Condensation of β-Aminocrotononitrile with 2-Methylcyclohexanone (Phosphorus Pentoxide as condensing agent.

A. Preparation of 2-Methylcyclohexanone:

The ketone was prepared by chromic acid oxidation of practical grade 2-methylcyclohexanol, obtained from Brickman Ltd., Montreal, in a procedure identical to that followed in the preparation of 3,3,5-trimethylcyclohexanone from the corresponding alcohol.

Reagents: 114 g. (1.0 mole) 2-methylcyclohexanol
59.6 g. (0.2 mole) sodium dichromate, dihydrate
250. ml. of water

59.6 g. (0.2 mole) sodium dichromate, dihydrate
154. g. (1.57 moles) conc. sulphuric acid
250. ml. of water

Crude 2-methylcyclohexanone, 93.2 g. (86.3% of theoretical) was purified, with considerable difficultly, through the sodium bisulfite compound. The pure ketone, 20. g. (18.5% of theoretical) gave a semicarbazone melting at 191° (reported value (85); 191°), and distilled at 161-163° (reported value ; 163°)

B. Attempted Condensation with β-Aminocrotononitrile

The attempted condensation was carried out exactly as with cyclohexanone.

Reactants: 15 ml. absolute ethanol
2.22 g. (0.02 mole) 2-methylcyclohexanone
3.28 g. (0.04 mole) β-aminocrotononitrile
1.42 g. (0.01 mole) phosphorus pentoxide

The crude 1.9 g. isolated in the usual manner, gave when recrystallized from dilute ethanol, 0.5 g. of a pale-yellow product, which melted in the vicinity of 300° with considerable decomposition. A structure (see "Discussion") has been suggested for this product. It was not thought to be the desired spiro compound, because of its melting point and appearance. The remaining 1.4 g. of the crude was reclaimed, as a pale buff-coloured powder, from the filtrate by evaporation.

Attempted Hydrolysis of Cyano Groups in (LXIII)

Many attempts to bring about the desired hydrolysis were made, but each met with failure. For conciseness, a tabulation of the salient experimental details is given in the accompanying table. In each case, the starting material was place in a 50 or 100 ml. extraction flask, under a reflux condenser provided with a calcium chloride drying tube.

ATTEMPTED HYDROLYSIS OF CYANO GROUPS IN SPIRO COMPOUND, LXIII

Solvent	Wt. of LXIII Used	"Catalyst"	Temp. °C	Reflux Time	Observation Starting Material		New Product Formed
					Recovered	Destroyed	
H_2SO_4;25ml. *	5g.	75%H_2SO_4	150-60 178	30 min. 30 min.	-	+	-
H_2SO_4;25ml. *	1g.	2N H_2SO_4	110	4 hrs.	+	-	-
C_2H_5OH;5ml.	1g.	conc.HCl;25ml.	micro burner steam bath	30 min. 1 hr.	+	-	-
abs.CH_3OH;50ml	1.135g	dry HCl(g) to saturation	steam bath	12 hr.	+	-	-
EtAc;5ml **	1.g	92%HAc;25ml. ***	micro burner	5 hr.	+	—	-
EtAc;5ml. **	1.g.	conc.H_3PO_4;25ml	micro burner	7 hr.	-	+	-
2NNaOH;25m. *	1g.	2NNaOH	110	3 hr.	+	-	-
alc. NaOH	2.3g.	10% alc.NaOH; 25ml.	micro burner	4 hr.	+	-	-
alc. KOH	2.3g.	7%alc.KOH; 25ml.	steam bath	6.5hr.	+	-	-

* Starting Material Insoluble In "Solvent" Indicated

** Ethyl Acetate, $CH_3COOC_2H_5$

*** Acetic Acid, CH_3COOH

Summary and Contributions to Knowledge

1. β-Aminocrotononitrile was prepared according to the method of Holtzwart. Optimum conditions for the decomposition of β-sodioaminocrotononitrile and the recrystallization of crude β-aminocrotononitrile have been suggested.

2. 2-Methylcyclohexanone and 3,3,5-trimethylcyclohexanone have been prepared by chromic acid oxidation of the corresponding alcohol.

3. The condensation of β-aminocrotononitrile with cyclohexanone, in alcoholic hydrogen chloride, reported by von Meyer, could not be duplicated.

4. Condensation of β-aminocrotononitrile with cyclohexanone, 3- and 4-methylcyclohexanone and 3,3,5-trimethylcyclohexanone to form substituted dihydropyridine spiranes was achieved using phosphorus pentoxide as the condensing agent, and absolute ethanol as the solvent. The condensation did not go with 2-methylcyclohexanone.

5. The effect of variously situated methyl groups was studied, the observed reactivity being explained by the inductive effect $(+I_s)$.

6. A mechanism for the formation of the spiro compounds synthesized in this work has been proposed. An explanation of the failure of the condensation reaction with 2-methylcyclohexanone is offered.

7. It was not possible to hydrolyze the cyano groups of the spiro compounds synthesized.

8. A new route of synthesis of the desired dicarbethoxylated spiro compounds, e.g. (LXI), has been proposed. Polyphosphoric acid was tried and found to be unsuitable as the condensing agent in the proposed synthesis.

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