STUDIES ON THE PREPARATION AND REACTIONS OF DIACYLAMIDES AND CYCLIC IMIDES

A Thesis

by

Robert I. Scott, B.Sc.

(University of British Columbia)

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, 1955

ACKNOWLEDGMENT

The author wishes to express his sincere gratitude to Professor A. Taurins, for his guidance, interest and invaluable advice during the course of this investigation.

Grateful acknowledgments are also made to the following sources of financial assistance: (1) National Research Council for a Studentship with a summer extention (1952-54); (2) to the Board of Governors of McGill University for two demonstratorships (1952-53), (1954-55).

TABLE OF CONTENTS

GENERAL INTRODUCTION

The present investigation was undertaken with two objectives in view, firstly, to study the possibility of transforming diacylamides into N-halogen derivatives by the interaction with alkaline potassium hypobromite reagent, and secondly, to investigate the transformation of the cyclic imides into β-amino acids in the Hofmann rearrangement reaction. Since the latter reaction may involve the formation of N-halogen compounds as intermediates, it seemed desirable to prepare several of the unknown N-halogen derivatives of the cyclic imides.

Investigations in recent years have shown the importance of several N-halogen derivatives of acid amides and cyclic imides, such as N-bromoacetamide and N-bromosuccinimide, as brominating agents, especially in connection with the Wohl-Ziegler reaction. Since the number of these N-halogen derivatives available for these reactions is limited, it seemed desirable to study the preparation and use of some new related compounds. The characteristic feature of compounds showing the ability to form N-halo compounds is the acidity of the hydrogen in the N-H group, which is activated by the presence of the carbonyl group.

The N-bromocompounds are generally prepared by two methods: (a) by the addition of bromine to an alkaline solution of the amide or imide, and (b) by the reaction of bromine on the silver salt of the N-H compound in an anhydrous medium.

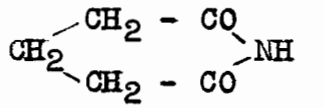
HISTORICAL INTRODUCTION

CHEMISTRY OF DIACYLAMIDES AND CYCLIC IMIDES

Diacylamides and cyclic imides contain the characteristic group, $-C^{=O}-NH-C^{=O}-$, consisting of a nitrogen atom linked to two carbonyl groups. They are in essence the nitrogen analogs of acid anhydrides in the sense that the lacton oxygen atom of anhydrides is substituted by an imino group.

Since diacylamides are actually secondary amides, the same nomenclature is used as for the corresponding primary amides. When the two acyl radicals are the same, the prefix "di" is added to the monoacylamide. Thus if in acetamide, a hydrogen atom of the amino group is substituted by a second acetyl radical, the compound is denoted as diacetamide. When the two acyl groups are different, the amide is named as the derivative of the amide of the largest acyl group present, eg. $C_6H_5CONHCOCH_3$ is called N-acetylbenzamide and not N-benzoylacetamide.

Imides are compounds of a bivalent acid radical and an $>NH$ or substituted $>NH$ group. They are therefore derivatives of ring systems. In the I.U.P.A.C. system of nomenclature the ending "imide" is added to the name of the hydrocarbon. However, for the low molecular weight imides, they are usually referred to by their common name.

As an illustration  is called pentanimide under the I.U.P.A.C. system (1) although the common name of glutarimide is also accepted.

The condensation of an acid amide with its corresponding acid chloride is one of the most general methods of formation of diacylamides (2, 3).

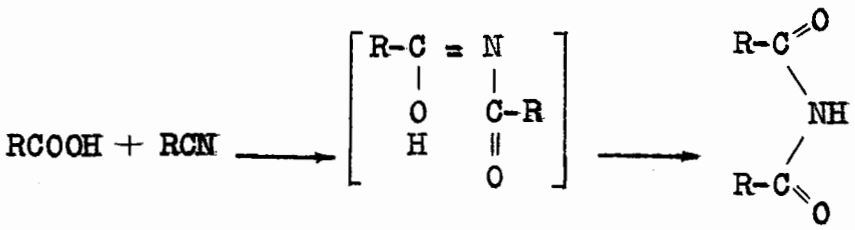
$$RCONH_2 + RCOCl \longrightarrow (RCO)_2NH + HCl$$

The reaction is carried out in the presence of an organic base such as pyridine. The amide is usually dissolved in a large excess of the base. On the addition of the acid chloride there is evolution of much heat and hence the reaction vessel must be cooled in an ice bath. This method affords excellent yields of the diacylamides.

Diacylamides are also prepared by the condensation of the acid with the nitrile at a temperature of 200° (3, 4, 5, 6).

$$RCOOH + RCN \longrightarrow (RCO)_2NH$$

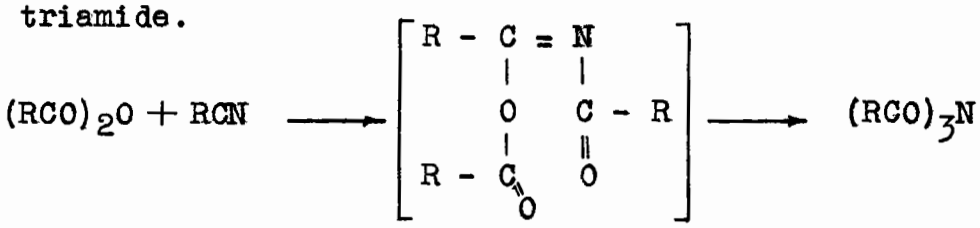
The mechanism involves addition followed by rearrangement. The addition of the acid as RCO^+ and OH^- to the nitrile is believed to occur as follows:



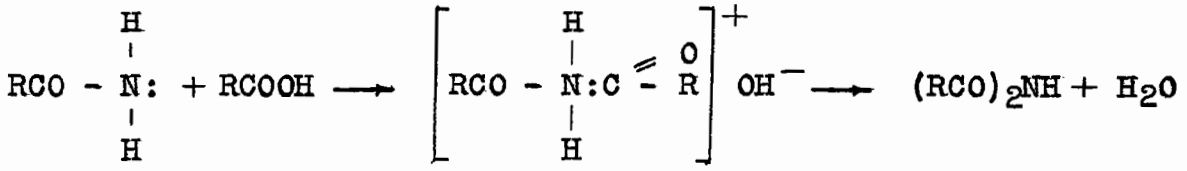
Evidence for the intermediate was afforded by the fact that anhydrides add to nitriles to give triamides.

$$(RCO)_2O + RCN \longrightarrow (RCO)_3N$$

In such a case, acyl must add to the nitrogen atom and the O-aryl to the carbon atom followed by rearrangement to give the triamide.



In many cases in the preparation of diacylamides above, the nitrile was replaced by the corresponding amide. Under similar conditions of reaction with acids, diacylamides were formed in good yields. The mechanism involved was thought to be the formation of an ammonium intermediate which when heated loses a proton to give a secondary amide and water thus:



Recently Polya and Tardrew (7) found an excellent method for preparing diacylamides, in particular diacetamide. The hydrochloride salt of the amide is refluxed for a short time with a slight excess of acetic anhydride. Excellent yields are obtained and the product is not contaminated by triamides.

Other methods of formation of diacylamides are the following: Reaction of acid chlorides with nitriles in the presence of $AlCl_3$ (8).

$$C_6H_5COCl + C_6H_5CN \xrightarrow{AlCl_3} \left[C_6H_5C^{+}=N-C^{=O}-C_6H_5\right]AlCl_4^{-}$$

$$\xrightarrow{HOH} HCl + AlCl_3 + C_6H_5-C^{OH}=N-C^{=O}-C_6H_5 \rightleftharpoons$$

$$C_6H_5C^{=O}-NHC^{=O}-C_6H_5$$

i ii iii

The initial step in the reaction was postulated as the formation of an intermediate complex (i) which subsequently decomposed with water to regenerate the catalyst $AlCl_3$ and to give the enol form of the amide (ii). It of course tautomerized to the more stable form (iii).

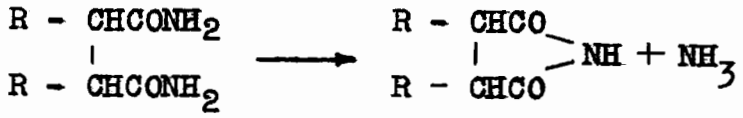
Cyclic imides are usually prepared by treating the dibasic acid with concentrated aqueous ammonia and subsequently heating the diammonium salt formed to 200°.

$$\begin{matrix} R-CH-COOH \\ | \\ R-CH-COOH \end{matrix} + 2NH_4OH \longrightarrow \begin{matrix} R-CH-CONH_4 \\ | \\ R-CH-CONH_4 \end{matrix} \longrightarrow$$

$$\begin{matrix} R-CH-CO \\ | \\ R-CH-CO \end{matrix}\!\!>NH + NH_3 + 2H_2O$$

The corresponding anhydride may also be used satisfactorily in place of the acid.

In many cases diamides were used as they lose a molecule of ammonia very easily on warming to give imides.



However, sometimes the conditions are too drastic and the acid decomposes, for example in the preparation of α, β -dihydroxysuccinimide from the dihydroxysuccinic acid (9). Such imides can often be prepared by treating the dimethyl ester with anhydrous ammonia and allowing the reaction mixture to stand several days at room temperature. The residue which deposits is then warmed under reduced pressure for several hours and ammonia is evolved. The imide which remains is recrystallized from an appropriate solvent. The yields from this method are generally very poor.

Diacylamides are white crystalline solids. The lower members are soluble in water while the higher molecular weight compounds are more or less insoluble. The low molecular weight diacylamides when impure have a very disagreeable odor resembling the excrement of mice. Cyclic imides are generally solids which are quite insoluble in water.

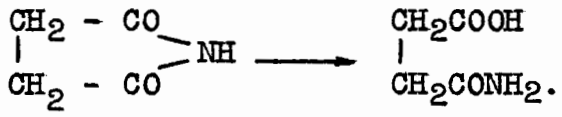
Diacylamides when heated to 200° or distilled, decompose to give a mixture of the corresponding primary

amide, acid, and nitrile.

$$(RCO)_2NH \longrightarrow RCN + RCOOH + RCONH_2.$$

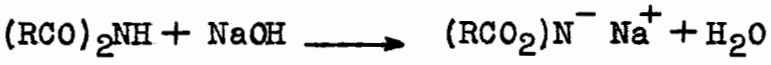
Secondary amides hydrolyze very readily under the influence of alkali, giving at first the acid RCOOH and the amide $RCONH_2$. The latter may hydrolyze further to the acid. With mixed secondary amides the reaction could follow two courses giving either the acid RCOOH and the amide $R'CONH_2$ or the acid R'COOH and the amide $RCONH_2$. In the aliphatic series usually a mixture of all four is obtained. The same mixture of products is obtained in alkaline hydrolysis of aromatic diacylamides, although the rate of reaction is much slower. Titherley and Stubbs (10) observed that acyl-aroyl secondary amides were always decomposed with alkali almost exclusively into the aliphatic acid and aromatic amide. They postulated that this was due to the fact that the aromatic acyl group is so much larger than the aliphatic group that hydrolysis across the latter is more rapid. Thus, in the alkaline hydrolysis of N-acetylbenzamide preferential hydrolysis should occur at the acetyl-nitrogen bond. Actually, only acetic acid and benzamide were obtained.

Cyclic imides are hydrolyzed very little in aqueous solution, however, with alkali they form the acid amide derivative of the corresponding acid.

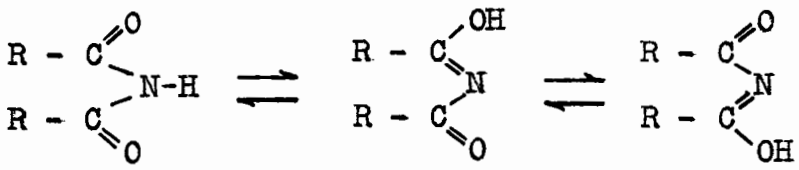


If the reaction is prolonged the amide group is hydrolyzed further to the acid.

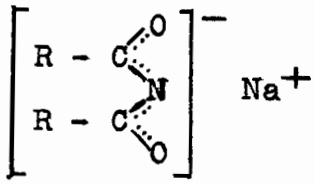
If one of the hydrogen atoms of ammonia is replaced by an acyl group then primary amides are produced which are weaker bases than water. The carbonyl group exerts an electron-attracting effect which decreases the ability of the nitrogen atom to share its unshared electron pair. With diacylamides and cyclic imides the attraction for electrons is so great that the remaining hydrogen atom may be removed as a proton in strong aqueous alkaline solutions. The imides are therefore weak acids.



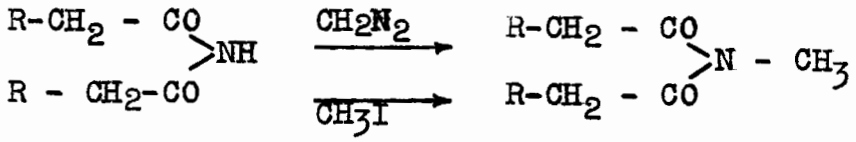
Consequently due to the presence of the active hydrogen, diacylamides and cyclic imides both react with metals to form salts. Like primary amides, they both may undergo tautomerism as follows:



The metallic derivatives are usually depicted in the form:



The sodium derivatives react with alkali iodides to give N- alkyl derivatives (11). Similarly treatment with diazomethane affords N-methyl substitution products.



FORMATION OF N-HALOGEN DERIVATIVES OF AMIDES AND IMIDES.

In 1882, Hofmann (12) prepared N-bromoamides by reacting equimolar quantities of bromine and amide in a concentrated alkaline solution. According to Hofmann, bromine reacted with acetamide by direct substitution, forming the hydrate of N-bromoacetamide $CH_3CONHBr \cdot H_2O$. On warming to 50° it lost its water of hydration giving pure N-bromoacetamide which melted at 106°.

Seliwenow (13, 14) considered all N-brominated amides as derivatives of hypobromite and represented their decomposition by water as giving equimolar quantities of hypobromite and amide. Francois (15) found that Seliwenow's reaction was reversible and that hypobromite reacts quantitatively with acetamide forming a compound which he formulated

as the salt $CH_3CONH_2.HBrO$. This compound, of course, was identical with that obtained by Hofmann.

Boismenu (16) prepared a series of N-halogen derivatives of acetamide and of several other monoamides (Table I). He established that the monochloroamides are colorless, crystalline compounds which were fairly stable when stored in a cool dry place. The dichloroamides (17) on the other hand were extremely unstable, corrosive yellow liquids which decomposed on standing to form the corresponding monochloroamides. The bromo and iodo derivatives followed a similar pattern. N-Bromoformamide (18) was prepared by the reaction of nascent hypobromite with formamide. White unstable crystals deposited which melted at 87-88°. Unlike N-bromoacetamide the compound separated without any water of hydration. The N-iodoamides were secured by shaking the amide in an ethereal solution with small portions of iodine and silver oxide, until all the iodine had been consumed. N-Iodoformamide was found to be extremely unstable, decomposing even in vacuum or under an atmosphere of carbon dioxide. They all gave with methyl acetate a grey precipitate which on treatment with dry ammonia detonated. N-Chloroacetamide when reacted with silver oxide was converted into acetonitrile.

TABLE I (Melting Point)

	N-Cl	N-Br	N-I	$N{=}Cl_2$
Formamide	-	87-8°	95°	Liquid
Acetamide	110°	106	143	"
Propionamide	34	80	128	"
Isobutyramide	-	92	-	"
Benzamide	16	133	-	"

Eckert and his collaborators (19) treated numerous aliphatic diamides with alkaline hypobromite and obtained the corresponding diisocyanates which were to be used for cross linking of cellulose. During the course of the investigation they isolated the N, N'-dibromo and N, N'-dichloro intermediates formed by the initial reaction of hypobromite or chlorite with the diamides. The dibromo derivatives were quite stable. The tetrahalo amides were also synthesized in the same manner; however, they were very unstable and the yields extremely poor.

The formation of N-halodiacylamides has never been reported in the literature except for the preparation of N-chlorodibenzamide (20). It was produced by passing a stream of anhydrous chlorine gas through a chloroform suspension of silver dibenzamide (21). The chlorodibenzamide deposited as white needles which melted at 86°.

Although the preparation of N-halodiacylamides has been almost non-existant numerous cyclic N-haloimides have been produced, the most important being N-bromosuccinimide and N-bromophthalimide. Nevertheless very few methods for the formation of N-bromosuccinimide have been reported. Seliwenow (14) originally prepared the N-bromo compound by treating succinimide with N-bromoacetimide. The overall yield was 72 percent.

In 1893, Lengfeld and Stieglitz (22) obtained the same product by treating succinimide with bromine in an aqueous sodium bicarbonate solution. N-Bromosuccinimide precipitated out and was filtered off. Ziegler (23) modified the procedure by brominating in an ice-cold potassium hydroxide solution of the imide. The yield obtained was about 75-81 percent. This procedure has been used in nearly all cases for producing cyclic N-bromoimides.

Lamchen (24) pointed out that half the bromine was converted into bromide and was useless for the process, also that at least one equivalent of sodium hydroxide was consumed. He devised a process in which hypobromite was produced without the use of liquid bromine and with only a small quantity of sodium hydroxide. An ice-cold solution of imide and alkali was electrolyzed between platinum electrodes with just sufficient sodium hydroxide to keep the solution colorless. Of every two bromide ions discharged

at the anode, one again entered the solution as a bromide ion after reaction with hydroxyl ion. Thus, for every bromine ion discharged, one molecule of N-bromosuccinimide was formed. Simultaneously one hydroxyl ion was produced and one molecule of hydrogen liberated. N-Bromosuccinimide due to its low solubility in water, separated out at the anode. Consequently, every bromide ion was utilized and the hydroxyl ions required were produced in the process. However, the yield was only 66 percent.

Tafel (25) prepared N-bromopyrrolidone by treating an ice-cold 20 percent alkaline solution of α-pyrrolidone with bromine and allowing the solution to stand several days in the dark. Yellow crystals of N-bromo-α-pyrrolidone separated out which melted at 95°. When the concentration of alkali was increased from 20 percent to 40 percent, N-bromo-α-pyrrolidone separated out directly upon the addition of bromine (26).

N-Iodoimides are usually prepared by treating the silver salt of the imide with iodine in an anhydrous medium. If the solvent is not anhydrous the yield is seriously diminished. As an illustration, Bunge (27) prepared N-iodosuccinimide by iodination of the silver salt of succinimide in ordinary ethyl acetate solution. He reported a yellow solid melting at 110-135° with decomposition. Djerassi and Lemke (28) modified the procedure by carrying out the reaction in

anhydrous acetone. In contrast to Bunge's report, N-iodosuccinimide was found to be a stable, colorless solid melting at 200°.

The N-chloro derivatives were obtained by passing a stream of chlorine gas through a cold alkaline solution of the imide. The chloro compound which separated out was quickly filtered off and then recrystallized from an appropriate solvent.

N-Haloamides have been classified as "positive halogen" compounds. They are characterized experimentally by their ability to liberate iodine from hydroiodic acid and are so called because they can be represented as reacting by heterolytic bond fission to give halogen cations, and imide anions.

iv. $(C_4H_4O_2)NBr + HI \longrightarrow (C_4H_4O_2)NH + I_2 + HBr.$

v. $(C_4H_4O_2)NBr \longrightarrow (C_4H_4O_2)N:^{-} - Br^{+}$

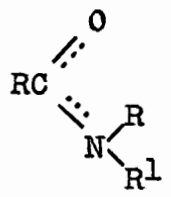
$Br^{+} + 2I^{-} \longrightarrow Br^{-} + I_2$

Organic molecules containing strong electron-attracting groups promote reactions of type (iv). These groups greatly diminish the normal tendency for a covalent halogen compound to split on activation to yield a stable anion. Nevertheless, it does not mean that bond fission like type (v) is the only possible alternative. Theoretical calculations by Waters (29) showed that in several typical "positive

halogen" compounds, the inductive and mesomeric effects of the organic substituents hardly more than neutralized the polarization of the carbon-nitrogen and nitrogen-halogen bonds. Therefore homolytic bond fission (vi) may require far less activation energy than any heterolytic dissociation thus producing a neutral organic radical and an uncharged halogen atom.

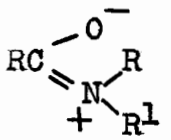
$$(C_4H_4O_2)NBr \longrightarrow (C_4H_4O_2)N^{\bullet} + Br^{\bullet} \quad \ldots\ldots\ldots \text{ vi}$$

Recently Lenormant (30) studied the infra-red spectra of amides in the region of 6 μ. He found that interesting results were obtained in connection with acetamide and its N-substituted derivatives. Acetamide was found to have characteristic infra-red absorption bands at 6.00 μ, 7.10 μ, and 11 μ. However, if one of the hydrogens or the nitrogen was substituted by a sodium ion, then only one band was obtained at 6.40 μ. Similarly N-bromoacetamide gave a single band at 6.00 μ. He stated that the apparent anomalies of the infra-red spectra of acetamide in the region of 5-8 μ could be explained by the influence of the nitrogen atom on the neighbouring carbonyl group. The presence of this atom determines the very strong tendency towards mesomerism. He represented the molecules by the following formula:



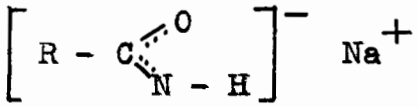
vii

The participation of the excited form (viii), calculated starting from the carbonyl frequencies are in accord with the value obtained from the dipole moment. It amounts to about 15 percent.



viii

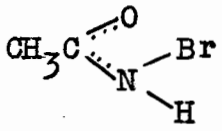
The metallic derivatives of amides, in particular the sodium derivative, have an ionic structure with resonance almost completely between the oxygen and nitrogen atoms. Consequently, Lenorment introduced another form (ix) to account for this ionic structure.



ix

N-Bromoacetamide gave only a single band at 6.00 μ. The spectrum of this substance slightly resembled that of the

structure represented in figure (vii) where both hydrogens on the nitrogen atom have been replaced by alkyl groups. Since its interpretation does not necessitate any reference to the positive ionization of the nitrogen radical, the structure was assumed to be purely covalent.

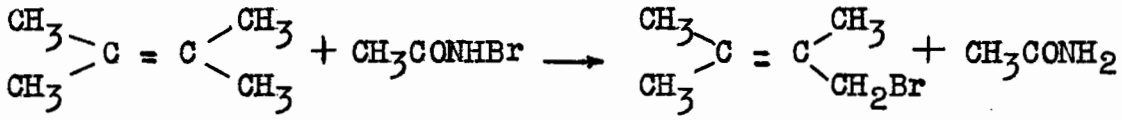


X

The reason for this structure resides probably in the relatively strong electro-negativity of bromine which opposes the formation of a Br^+ ion.

N-HALOGEN DERIVATIVES AS REAGENTS IN ORGANIC CHEMISTRY

In 1919, Wohl (31, 32) reported that on treatment of an olefin with N-bromoacetamide or N-bromophthalimide, hydrogen in the olefin was substituted by bromine in the allyl position. For example, 2, 3-dimethyl-2 - butene gave with N-bromoacetamide the 1-bromo derivative.



In 1942, Ziegler (23) reported that N-bromosuccinimide was a more efficient reagent than N-bromoacetamide used by Wohl

for allylic bromination. The chief reason was that bromination could be carried out as a rule at a much lower temperature and that N-bromosuccinimide was very stable and readily available. N-Chlorosuccinimide, N-bromoglutarimide and N-bromohexahydrophthalimide were found wholly unsatisfactory and could not be used in this type of reaction. Many compounds such as N-bromonaphthalimide (33) were eliminated either because of their relatively large molecular weight or that they were not available in any great quantity. Djerassi has presented a thorough review (34) concerning the Wohl-Ziegler reaction.

The usual procedure adopted in carrying out the reaction is that developed by Ziegler and his collaborators (23). The olefin is dissolved in an inert anhydrous solvent such as carbon tetrachloride or ether. The N-bromoimide is added and the reaction mixture refluxed. The completion of the reaction can be ascertained by testing for the absence of bromine with starch-iodide solution. The insoluble imide is filtered off and the bromo-substitution product isolated from the filtrate. In many instances it has been found advantageous to add catalysts, the most frequently used being benzoylperoxide and phenyldiazonium chloride. In the bromination of unsaturated steroids (35) photocatalysis has often been employed.

The mechanism of the reaction is of great interest, for it has been deduced that bromination can occur either by a free radical or ionic mechanism. Waters (36) pointed out that if the reaction is of the free radical type, then halogenation in the α-methylenic position is to be expected. Both Farmer (37) and Hey (38) favoured this type of reaction especially when photocatalysis and peroxide catalysts were involved. N-Bromosuccinimide was depicted by Bloomfield (39) as undergoing a thermal homolytic dissociation to produce a bromine atom and the imide radical (xi).

$$(C_4H_4O_2)NBr \longrightarrow (C_4H_4O_2)N^{\bullet} + Br^{\bullet}$$

xi

The imide radical (xi) can subsequently acquire a hydrogen atom from the α-methylenic carbon of the olefin.

$$(C_4H_4O_2)N^{\bullet} + -CH_2-CH = CH- \longrightarrow (C_4H_4O_2)NH + -\dot{C}H-CH = CH-$$

The olefin radical can therefore either react with another molecule of imide to promote chain propagation (xii) or combine with a free bromine atom to form a molecule of bromo-substituted olefin (xiii).

xii $\quad -\dot{C}H-CH = CH- + (C_4H_4O_2)NBr \longrightarrow -CHBr-CH = CH- + (C_4H_4O_2)N^{\bullet}$

xiii $\quad -\dot{C}H-CH = CH- + Br^{\bullet} \longrightarrow -CHBr-CH = CH-$

An attempt to demonstrate the homolytic dissociation of positive halogen compounds was reported by Robertson and Waters (40), who measured the catalytic effect of such substances on the auto-oxidation of tetralin. N-Bromosuccinimide was found to be a very efficient catalyst in contrast to N-bromophthalimide and N-bromoacetamide. As a result, reactions involving (a) preferential bromination of a carbon atom adjacent to the double bond and which are catalyzed by peroxides, (b) substitution reactions with various olefins, and (c) the reaction with α-carbon atoms of ketones (41) can all be interpreted as involving bromine atoms and free radical intermediates.

On the other hand, N-bromoamides and -imides react with aromatic hydrocarbons in the presence of anhydrous aluminum chloride to give ring bromination as opposed to side chain substitution with peroxide catalysts (42). Further, N-bromoacetamide has been reported (43) to be a source of bromine for acid catalyzed olefin addition reactions in which a hydroxylic solvent is also involved. Such reactions are interpreted as ionic with bromine behaving as if it were a positive ion.

Thus, N-bromoimides seem to be capable of supplying either bromine atoms or positive bromine. It must be remembered that the conjectural thoughts on the mechanism of the Wohl-Ziegler reaction are based on isolated examples only.

However, due to the strong electron-attracting power of the bromine atom it would seem that reactions involving N-haloimides would favour a homolytic fission of the nitrogen-halogen bond rather than one in which formation of positive bromine ion is favoured.

N-Iodosuccinimide showed no free radical activity when refluxed for six hours with toluene in the presence of benzoyl peroxide and strong light. Previously it was discovered (42) that under these conditions, N-bromosuccinimide reacted very readily. Similarly when the iodo derivative was treated with a 2-heptene-2-ol acetate with or without a solvent up to 82 percent of pure iodoheptanone was obtained.

$$C_4H_9CH = C\begin{matrix}OAC\\CH_3\end{matrix} \longrightarrow C_4H_9CHIC(=O)CH_3$$

In addition, 90 percent of N-acetylsuccinimide was isolated. The formation of the latter product suggested to the authors (44) that the reaction proceeded by an ionic mechanism. Consequently they postulated that the reaction took place through an intermediate iodonium complex.

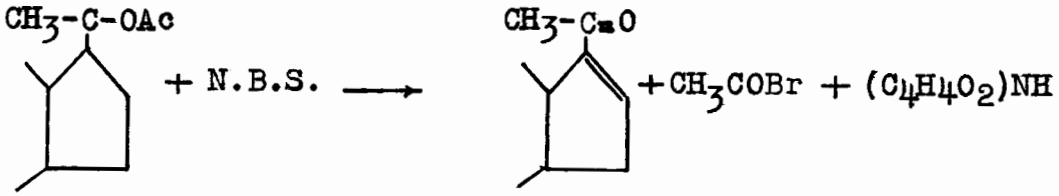
$$C_4H_9CH = C\begin{matrix}OAC\\CH_3\end{matrix} \longrightarrow C_4H_9CH\begin{matrix}-\\I\end{matrix}\begin{matrix}OAC\\+\end{matrix}C - CH_3 + (C_4H_4O_2)N:^- \longrightarrow$$

xiv

$$\longrightarrow C_4H_9CHIC(=O)CH_3 + (C_4H_4O_2)NCOCH_3$$

The only reaction of N-bromosuccinimide with an

enol-acetate was the reaction with 3α, 12α, 20-triacetoxy-pregnene (45). A 50 percent yield of 3α, 12α-diacetoxy-20-keto- $\Delta^{16(17)}$-pregnene was produced.



The homolytic fission which occurs in N-bromosuccinimide to generate a bromine atom has been attributed to the electronegative effect of the imide ring. Henne and Zimmer (46) concluded that if this was correct, then perfluorination of the imide should increase the acidic character of the active hydrogen in succinimide and the positive character of bromine in perfluorinated N-bromosuccinimide. This was found to be correct and similar observations were made with other perfluorinated imides such as glutarimide. The positive character of bromine in perfluorinated N-bromosuccinimide was shown by the fact that iodine could be liberated quantitatively from an aqueous solution of iodide, and bromine from an aqueous solution of bromide. In addition, at room temperature, toluene was brominated entirely in the ring with perfluorinated N-bromosuccinimide while N-bromosuccinimide reacted very little or not at all at room temperature. N-Bromoglutarimide was ineffective as a brominating agent.

Compounds which have become of some importance in

connection with the Wohl-Ziegler reaction are the 1, 3-dichloro- and 1, 3-dibromohydantoins and their 5-aklyl substituted derivatives. Orazi (47) found that if 1, 3-dibromo-5, 5-dimethylhydantoin was substituted for N-bromosuccinimide in the dehydrogenation of tetrahydronaphthalene, it gave an 84-87 percent yield of naphthalene. Similarly it was determined (48) that the structure of 1, 3-dichloro-5, 5-dimethylhydantoin was that of an N-halogenated amide and exhibits activity in chlorinating toluene to that of N-chlorosuccinimide and N-chlorophthalimide.

Kruse and his collaborators (49) reported that the N-halo-succinimides were used in the differentiation of alcohols and amines, and in the detection of amino alcohols. In general the tests were carried out in a carbon tetrachloride solution on a water bath at 80°. Primary alcohols with N-bromosuccinimide gave a permanent orange color, whereas the color disappeared with secondary alcohols with the formation of an orange precipitate. No observable color change occurred with most tertiary alcohols.

N-Iodosuccinimide gave with primary amines a permanent brown colored solution, whereas the color faded rapidly with secondary amines. Tertiary amines also gave a brown color but could be distinguished from primary amines as the former gave an orange precipitate with N-bromosuccinimide while the primary amines did not react.

Amino alcohols were also detected with N-bromosuccinimide. A positive test for the compounds was the presence of a brown ring floating on the top of the solution after heating. On cooling, succinimide appeared at the top of the solution.

HOFMANN REACTION OF AMIDES AND IMIDES

Perhaps the most interesting as well as important reaction of amides is that known as the Hofmann reaction. In this reaction an amide is converted to an amine of one less carbon atom by treatment with alkaline potassium hypobromite (12).

$$RCONH_2 + Br_2 + 4KOH \longrightarrow RNH_2 + CO_3^{=} + 2Br^{-} + 2H_2O$$

Hofmann (50, 51) initially recognized the significance and general applicability of the reaction, and since he and his co-workers have been the initial contributors to the detailed studies of this reaction, it has become commonly known as the Hofmann reaction.

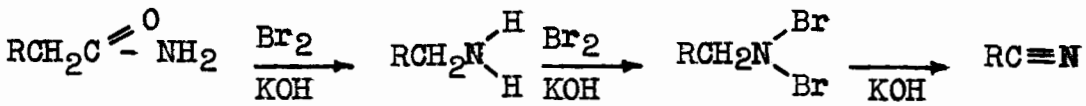
Generally the procedure usually adopted in carrying out the Hofmann reaction is essentially that developed by Hoogewerff and Van Dorp (52, 53, 54). The amide is dissolved in an ice cold alkaline solution of potassium hypobromite and the solution is subsequently warmed to 70-75° to effect

rearrangement. After a period of 15 minutes to one hour, depending on the type of amide, the reaction mixture is steam distilled into a slight excess of dilute hydrochloric acid. When the distillate is evaporated to dryness, the hydrochloride of the desired amine remains which is freed from impurities by washing with ether or chloroform. In the case where the amine is not volatile with steam, it may be removed from the reaction mixture by extraction with ether. It is precipitated as the hydrochloride from the dry ethereal solution with gaseous hydrogen chloride and then treated as above.

In order to obtain the best yields, the amount of bromine used is quite critical. A large excess must be avoided since the yield of amine may be reduced by side reactions. A slight excess amounting to 10-20 percent, however, is necessary since even with freshly prepared hypobromite solutions only 80-90 percent of the expected activity is realized.

The Hofmann reaction of amides is one of the most practical methods for the synthesis of amines of lower molecular weight. The hypobromite reaction works best on amides that contain less than seven carbon atoms. Acetamide, propionamide, butyramide, valeramide, the amide of caproic acid, and heptanamide all reacted to give yields of 80 percent or better of the primary amines (50, 51).

However, it was found that as the molecular weight of the amide was increased beyond seven carbon atoms, the yield of amine was seriously decreased. Thus, heptylamine was secured in only 30 percent yield, octyl and nonylamines only in traces. This was due particularly to two secondary reactions, in one of which the bromine and alkali reacted with the amines formed and produced nitriles as follows:



Hoogewerff (55) succeeded in preventing the formation of nitriles in many cases by steam distilling the amine as soon as it was formed. In the other secondary reaction by which the yield of amine was diminished, acylalkylureas were formed.

With increasing molecular weight of the amide, the formation of alkylacylurea was favoured and in the higher series, they were the chief product of the reaction of bromine and aqueous alkali with monoamides. As an illustration, Turpin (56) prepared heptadecylamine by converting stearamide by means of aqueous potassium hypobromite into Stearylheptylurea and subsequently distilling the urea with lime. However, since half the urea molecule was consumed in preparing the amine, the yield obtained was necessarily low.

Lengfeld and Stieglitz (22) attempted to prepare hydroxylamines by reacting sodium methoxide with N-bromo-acetamide according to the following equation:

$$CH_3CONHBr + NaOCH_3 \longrightarrow CH_3CONHOCH_3 + NaBr.$$

Instead a molecular rearrangement, analogous to that observed by Hofmann (50) occurred in the course of the reaction, and a urethane was produced in place of the isomeric hydroxylamine (57, 58).

$$CH_3CONHBr + NaOCH_3 \longrightarrow CH_3NHCOOCH_3 + NaBr$$

Jefferys (59) extended this reaction to higher molecular weight amides. She tried to prepare the N-halogen derivatives of long chain amides but was unsuccessful. Consequently she attempted to effect rearrangement of the amides in an alcoholic solution without the isolation of the intermediate haloamides. Urethanes were obtained in quantitative yields. The corresponding amines were obtained on distillation of the urethanes with lime. It was stressed that to prevent the formation of ureas, it was necessary that the rearrangement must take place as soon as possible. When the reaction proceeded slowly, one molecule of the bromamide after undergoing rearrangement united at once with a second molecule of amide to form urea according to:

$$RCONHBr + RCONH_2 + NaOCH_3 \longrightarrow RCONHCONHR + NaBr + CH_3OH.$$

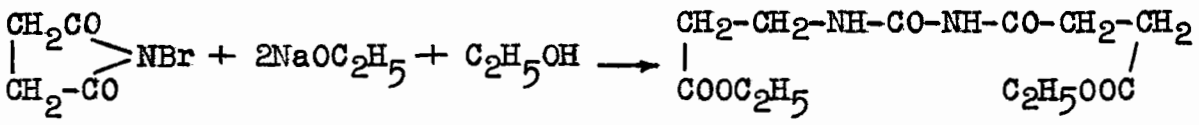
As an illustration, lauramide on treatment with aqueous alkaline hypobromite solution gave largely N-undecyl-N^1-laurylurea (60). But treatment of the amide in methanol with sodium methoxide and bromine gave a 90 percent yield of methylundecylcarbamate, which was converted almost quantitatively to the undecylamine.

$$2C_{11}H_{23}O_2NH_2 + NaOBr + H_2O \longrightarrow C_{11}H_{23}CONHCONHC_{11}H_{23}$$

$$C_{11}H_{23}CONH_2 + NaOCH_3 + Br_2 \longrightarrow C_{11}H_{23}NHCOOCH_3 \longrightarrow$$

$$C_{11}H_{23}NH_2$$

This was also confirmed by Swartz (61) and Folin (62) who reacted sodium methylate with N-bromosuccinimide at 45° for ten minutes. They both obtained the same derivative of urea (xv) in 3 percent yield.



xv

When the addition of bromine was rapid, then the urethane was produced in over 90 percent yield. In general, low molecular weight amides and imides give poor yields of alkylacylureas, whereas the situation is reversed with the larger molecular weight compounds under conditions where the addition of bromine is such that the formation of ureas would be favoured.

A complete review of the Hofmann reaction up to the year 1946 has been given by Wallis and Lane (147).

It was concluded that isocyanates derived from the higher aliphatic amides react more rapidly with the N-haloamides than with water and alkali. Consequently, when the amides are subjected to the Hofmann reaction in an aqueous medium, only small amounts of the expected amines are formed. Although amines arise from the hydrolysis of alkylacylureas, they are largely oxidized to nitriles by the excess of hypobromite present.

$$RNHCONHCOR + H_2O \longrightarrow RNH_2 + RCONH_2 + CO_2$$

$$RCH_2NH_2 + 2OX^- \longrightarrow RCN + 2X^- + 2H_2O$$

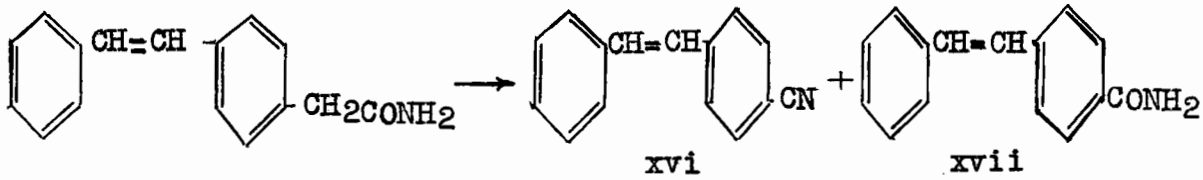
All amides of this type may be converted in good yields to urethanes by reaction in methanol.

Phenylpropionamide formed initially the N-chloro-compound which reacted with alkali to give phenylpropylamine. The latter was converted immediately into benzyl cyanide (63).

$$C_6H_5CH_2CH_2CONH_2 \longrightarrow C_6H_5CH_2CH_2CONHCl \longrightarrow C_6H_5CH_2CH_2NH_2$$

$$\longrightarrow C_6H_5CH_2CN.$$

The reaction of hypobromite with α-(4-styrylphenyl)-acetamide should have given the amine but yielded instead an unexpected result (64). The products were 4-cyanostilbene (xvi) and stilbene-4-carboxyamide (xvii). The latter was the principal product, while no trace of the amine was found.

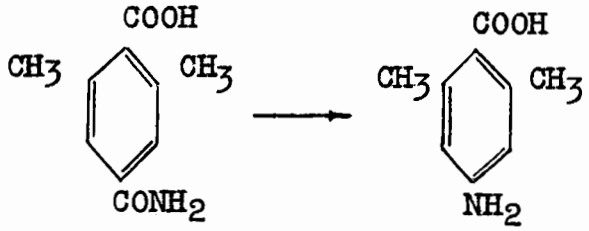


xvi xvii

The formation of nitriles by the oxidation of the amines formed initially in the Hofmann reaction has already been mentioned above and also occurs with acetylenic derivatives (65). But the formation of the next lower homolog was quite novel.

No special difficulties were encountered with arylaliphatic amides unless the aromatic ring contained hydroxyl or a similar function. In such cases low yields resulted from side reactions involving halogenation of the ring.

Alicyclic amidic acids were converted easily to amino acids. For example, 3, 5-dimethyl-4-carboxybenzamide on treatment with hypobromite was converted in an unreported yield to 2, 6-dimethyl-4-aminobenzoic acid (66).



Higher acid-amides, like the higher monoamides are best treated with sodium methoxide and bromine in methanol solution rather than with aqueous alkaline hypobromite. ω-Carbomethoxyaminopelargonic acid was obtained from sebacamidic acid in 75 percent yield (67). It was subsequently converted in quantitative yield to ω-aminopelargonic acid.

In the case of diamides, different products were obtained depending on the number of carbon atoms between the

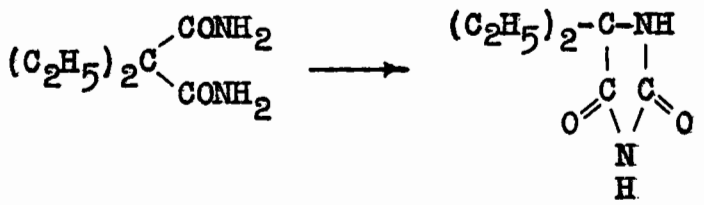
two amidic groups. Diamides of adipic acid (68, 69) and its higher homologs were rearranged to diamines without difficulty in hypohalite solution.

$$NH_2CO(CH_2)_nCONH_2 \longrightarrow NH_2(CH_2)_nNH_2 \qquad n \geq 4$$

Ssolonia (70) converted suber-and decamide into hexa-and octamethylenediamines respectively. Similarly azelaic acid and sebacamide (71) were rearranged into 1, 7-diaminoheptane and 1, 8-diaminooctane.

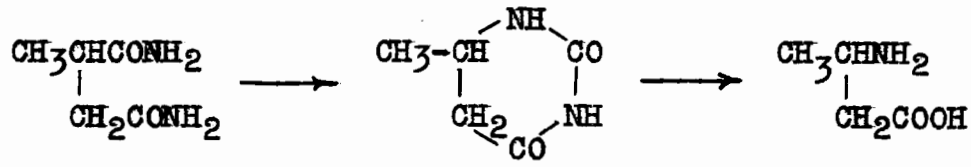
Von Baum discovered that D(+)-β-methyladipamide (72) could undergo a Hofmann rearrangement without loss of optical activity. A 70 percent yield of D(+)-β-methyl-1, 4-diaminobutane was secured.

Succinamide was converted not to ethylenediamine but to dihydrouracil, which was evidently formed by the reaction leading to alkylacylureas (73). If an excess of alkali was employed at a higher temperature, then β-alanine was produced. Under similar reaction conditions maleinamide was transformed into uracil (74) and diethylmalonamide to 5, 5-diethylhydantoin.



Methylsuccinamide with hypobromite solution yielded 4-methyldihydrouracil which on treatment with concentrated

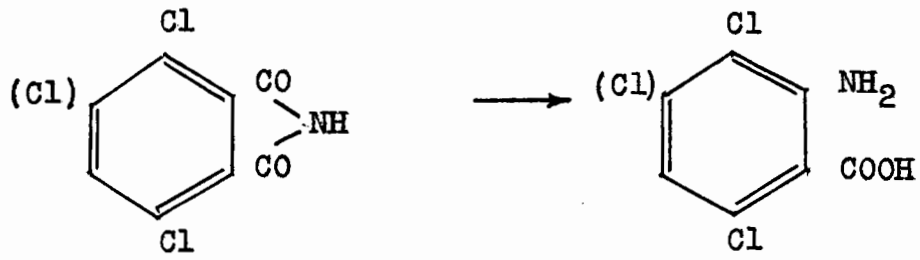
hydrochloric acid afforded β-amino butyric acid (75).



Benzamide, naphthalamide and their homologs were converted smoothly by aqueous alkaline hypobromite to the corresponding amines. If free or methylated phenolic hydroxyl groups were present in the aromatic amides, however, halogenation of the ring occurred with serious lowering of the yield. This effect was minimized by the use of hypochlorite and a large excess of alkali. The rearrangement was then rapid enough to compete favourably with the side reaction of halogenation.

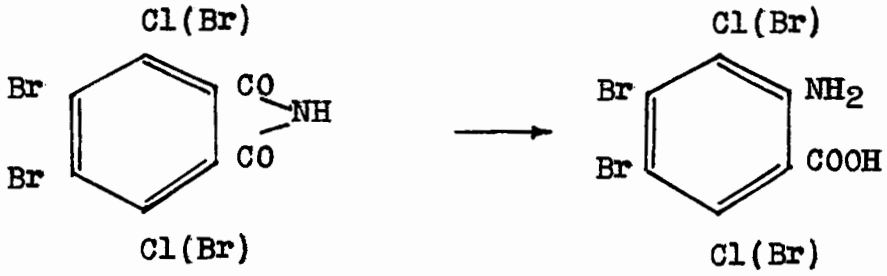
Extensive application of the reaction has been made in the production of anthranilic acids from phthalimide and its substituted homologs (75).

One of the earliest investigators who explored the Hofmann reaction of substituted phthalimides was Graebe (76, 77). He reacted hypobromite with 3, 6-dichloro- and 3, 4, 6-trichlorophthalimide and obtained the corresponding 3, 6-dichloro- and 3, 4, 6-trichloroanthranilic acids.

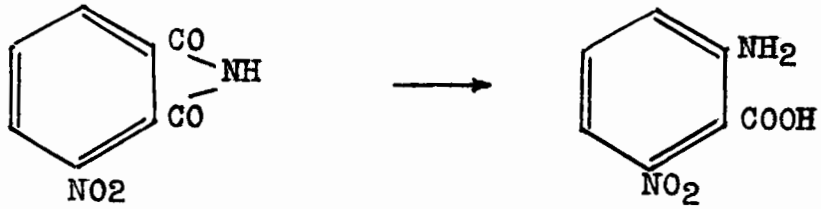


Similarly tetrachlorophthalimide was converted, smoothly, to tetrachloroanthranilic acid in 75 percent yield (78, 79).

In 1909, Lesser and his collaborators (80) applied the reaction to the 4, 5-dibromo, tetrabromo, and 4, 5-dibromo-, 3, 6-dichloro derivatives of phthalimide. All rearranged quite easily and substantial yields of each amino acid was obtained.

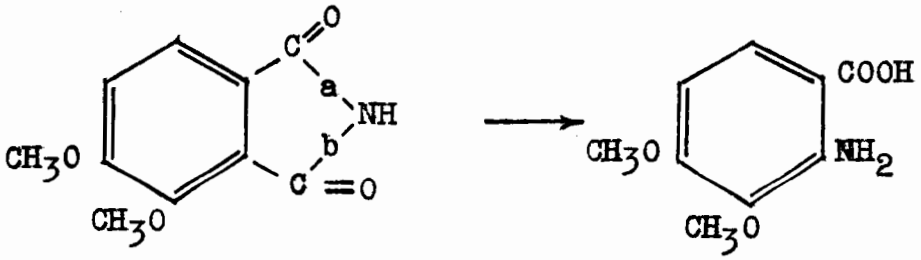


In connection with the Hofmann rearrangement of unsymmetrically substituted phthalimides, theoretically, certain isomeric anthranilic acids can be produced. Thus, in the Hofmann reaction of 3-nitro-phthalimide, the nitro group by withdrawing electrons at position '2' would cause preferential hydrolysis at that point and therefore rearrangement would occur at position '1'. It was found that over 80 percent of 6-nitroanthranilic acid was produced.



In general it was found that one isomer usually predominated

or formed exclusively. In most cases it was possible to predict the formation of one product over the other knowing the electronic effects of the substituents. Previously it was noted that in the Hofmann rearrangement of benzamides, hydrolysis was greatly enhanced by substituents that withdrew electrons from the $-C(=O)-N-$ linkage into the ring (81). As an example, a methoxyl group in the ortho position to the $C(=O)-N$ linkage in benzamide was found to be far less effective in promoting hydrolysis than the same substituent in the para position. Therefore, applying this argument to the Hofmann reaction of 3, 4-dimethoxyphthalimide, hydrolysis of the imide linkage would be expected to occur at the "a" position (xviii). Only 3, 4-dimethoxyanthranilic acid was obtained (82).

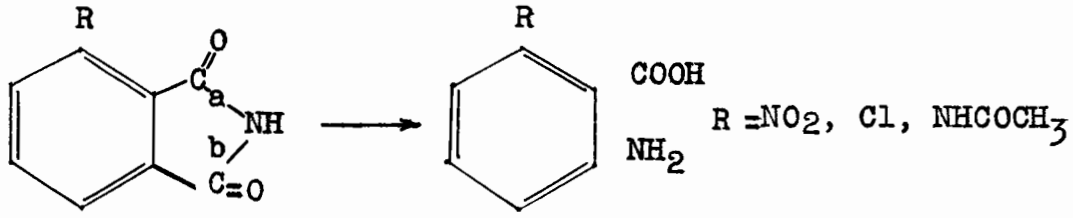


xviii

Similarly, 4-nitroanthranilic acid was the only product produced in the reaction of aqueous hypohalite with 4-nitrophthalimide (83, 84).

Moore (85) determined whether the application of the Hofmann reaction to substituted derivatives of phthalimide

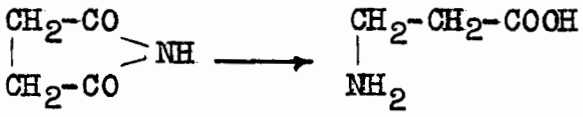
would serve for the preparation in quantity of certain substituted anthranilic acids. Further, he investigated the effect of the nature and position of the substituting group on the preparation of the two isomers produced. 4-Chlorophthalimide yielded 63 percent of 4-chloroanthranilic acid and 28 percent of the 5-chloro isomer which was in the form of an anhydride. With 4-sulfophthalimide only a trace of the 4-isomer was isolated and none of the 5-sulfoamino acid. 3-Acetylaminophthalimide was rearranged in 40 percent yield to 6-aminoanthranilic acid. Therefore, considering substituents at position "3", a nitro group which exerts a -I, -M effect and an acetylamino group which yields a -I, +M effect, both hydrolysis the imide ring at position a.



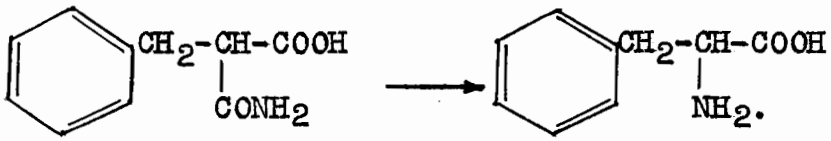
At position "4" we have the same situation. A nitro group and chlorine group both cause preferential hydrolysis at the same position "6".

Thus, in every case the derivative in which the amino group takes up a meta position with respect to the substituting group, was produced in the larger quantity, irrespective of the nature of the group and its position.

Successful application of the reaction has also been observed with succinimide (86) which rearranged in 45 percent yield to β-alanine.

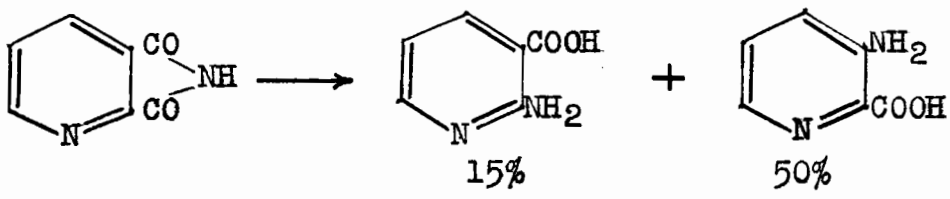


Gaudry (87) sought to prepare α-amino acids by this method. He applied the Hofmann reaction to 2-carboxy-3-phenylpropionamide and obtained d, l-β-phenylalanine in fairly good yield.



On further application of the reaction to the monoamide of anisylmalonic acid, he was unable to isolate any tyrosine. The main drawback to the overall reaction was the difficulty in obtaining the starting material in good yield.

The amide and imide derivatives of pyridine have been subjected to a Hofmann rearrangement. Kirpal (88) converted 3,4-dicarboxamide to 3-amino-4-pyridinecarboxylic acid. The imide of quinolinic acid underwent a Hofmann rearrangement to give two products, 2-amino-3-pyridinecarboxylic acid and 3-amino-2-pyridinecarboxylic acid.



Similarly 2-carboxynicotinamide (89) and 4-carboxynicotinamide (90) were rearranged to 3-amino-2-pyridinecarboxylic acid and 3-amino-4-pyridinecarboxylic acid respectively.

Further, 3-carboxypyridine-2-carboxamide (91) and 3-carboxypyridine-4-carboxamide (92) produced 2- and 4-aminonicotinic acid respectively.

The mechanism of the Hofmann rearrangement is known to proceed in steps, since several stages have been identified by the isolation in certain cases of N-bromoamides and alkylisocyanates whose formation is indicated below:

a. $CH_3CONH_2 + Br_2 + KOH \longrightarrow CH_3CONHBr + KBr + H_2O$

b. $CH_3CONHBr + KOH \longrightarrow [CH_3\text{-}CO\text{-}\ddot{N}:] + KBr + H_2O$

xix

c. $[CH_3\text{-}CO\text{-}\ddot{N}:] \longrightarrow CH_3\text{-}N = C = O$

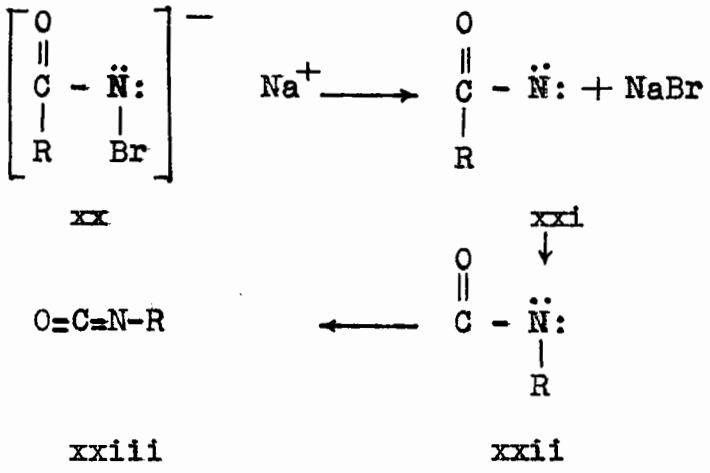
d. $CH_3\text{-}N = C = O + 2KOH \longrightarrow CH_3NH_2 + K_2CO_3$

The formation of the isocyanate intermediate indicated

that the reaction involved a rearrangement quite similar to the Curtius (93) and Lossen (94) rearrangements. Although the starting materials are quite different for the three rearrangements, the formation of an isocyanate (R-N = C = O) intermediate is common to all three.

The true mechanism of the Hofmann reaction has as yet not been actually proven since no quantitative studies have ever been carried out on the rearrangement process. The most satisfactory mechanism which has been proposed up to now is that of Whitmore (95) for reactions involving a 1, 2-shift.

For convenience, the 1, 2-shift is usually described as proceeding in three distinct steps although in the actual rearrangement they may all occur simultaneously.

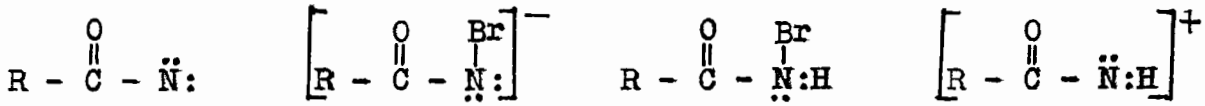


xx xxi xxiii xxii

The first step involves the formation of an unstable intermediate (xxi) in which the nitrogen atom has only six electrons (open sextet) in its valence shell. The second step

involves the rearrangement itself. Since the nitrogen atom in the intermediate contains only six electrons, considerable instability of the molecule exists. This is partially alleviated by the migration of the group R and its pair of electrons forming a second intermediate (xxii). It has been stressed vigorously by Whitmore that the electrons move initially from the nitrogen to the carbon atom and they drag the atom R with them. In the final step, the strain which remains in the intermediate (xxii) is relieved and a stable product (xxiii) is produced.

The formation of the postulated intermediate (xxi)



xxi xx xxiv xxv

should take place more readily from the anion (xx) than from the neutral N-haloamide (xxiv) since in the first reaction only one bond must be broken while in the latter two would have to be broken.

In addition, it is much more difficult to form the alternative intermediate (xxv) from the neutral haloamide (xxiv) than that of the intermediate (xxi) from the anion (xx).

Since in the Hofmann rearrangement, an alkyl radical migrates from the carbon to the nitrogen atom, the rearrange-

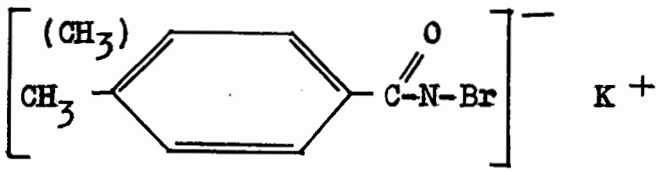
ment corresponds to that which takes place in the Beckmann reaction (96). When an intramolecular rearrangement takes place, a substituent in the phenyl radical occupies the same position before and after the rearrangement (97).

Slossen (98) determined whether the Hofmann and Beckmann rearrangements could still proceed when the hydrogen atom necessary for the splitting off of hydrogen bromide had been replaced by an alkyl group. Also, if the hydrogen atom in question was attached to the nitrogen atom and not to the oxygen of one of the carbonyls. He discovered that if acetylamylamine was treated with hypochlorous acid, N-chloroacetylamylamine was formed. The same compound was obtained when amylchloroamine was acetylated by means of acetic anhydride (99) thus proving that the halogen was attached to the nitrogen atom and not to the oxygen of one of the carbonyls.

During the course of the Hofmann reaction it is possible to isolate the alkali salts of certain bromobenzamides. According to Stieglitz (58) the formation of the isocyanate involves at first the removal of the hydrogen as a proton followed by the release of bromide ion and rearrangement of the molecule. Therefore, the rate determining step must be the release of the halide ion from the haloimide anion. The rearrangement, if it is a separate step, occurs very quickly as the molecule is stabilized. As a result, the ease of rearrangement of a bromoamide with alkali would be dependent

upon the rate of removal of bromide ion. Hauser (100) made a quantitative study of the rates of decomposition of the sodium salts of a series of meta and para substituted N-bromo benzamides. The reaction was found to be accelerated by the introduction of electron releasing substituents into the meta or para positions of the migrating phenyl group, and retarded by the introduction there of electron attracting groups.

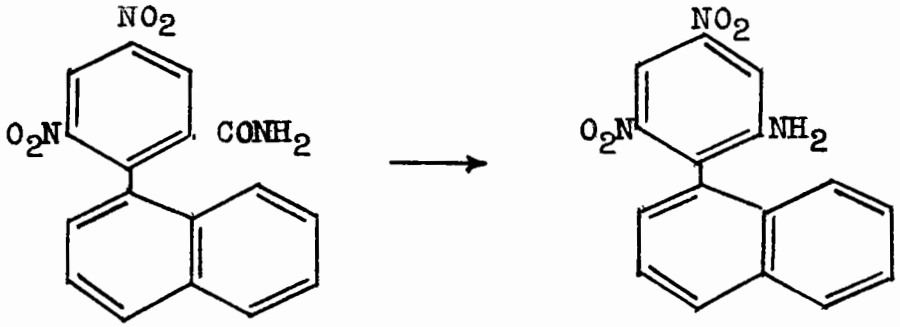
Thus, methyl and methoxyl groups which decrease the acidic strength of the corresponding benzoic acid facilitate rearrangement, while



substituents such as nitro and cyano groups which increase the acidity of the corresponding benzoic and impedes the rearrangement.

In 1931, Wallis (101) observed the retention of optical activity when the appropriate derivatives of benzylpropionic acid were converted by Hofmann rearrangement into α-benzylethylamines. The optical rotations observed made it certain that the reaction proceeded with the retention of configuration. Further, he submitted an optically active compound of the diphenyl type (102) to the Hofmann reaction, again obtaining an apparently optically pure amine.

Dissociation of the diphenyl radical from the amido group



at any stage of the reaction would have permitted free rotation and resulted in a racemic product. It must be emphasized, however, that in neither of the last two cases was a direct evaluation of the optical purity of the resultant amine made by comparison of its rotatory power with that of the active amine prepared by resolution of the d, l-compound.

Kenyon and his collaborators (103, 104) from a study of the rearrangement of (+) - hydratropamide observed that the retention of configuration or optical activity was the preservation of asymmetry in the molecule. (+) - Hydratropamide $C_6H_5CH(CH_3)CONH_2$ was prepared and submitted to the Hofmann reaction. It was selected for the following reasons:

a) The product ∝-phenylethylamine had been resolved by numerous workers (105).

b) The radical $C_6H_5\dot{C}HCH_3$ would be expected to yield a stronger tendency to release an electron than the radicals $CH_3CH_2\dot{C}HC_6H_5$ and $C_6H_7\dot{C}HC_6H_3(NO_2)_2$. Hence, if rearrangement occurred by dissociation of the amide molecule

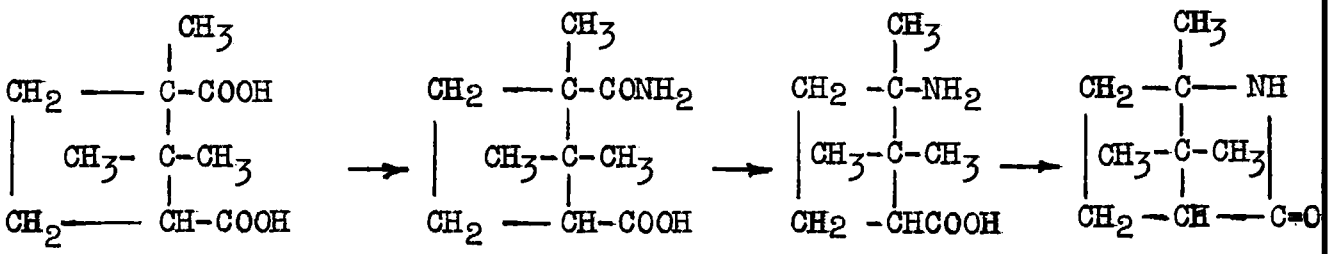
followed by racemization, it would be more evident in the rearrangement of hydratropamide than in the cases which had been reported previously. The retention of configuration suggests that the migrating group does not become separated from the molecule.

c) Since the rotatory power of both hydratropic acid and α-phenylethylamine are fairly large, any racemization which occurred during the reaction could be estimated with a great deal of accuracy. (+)-Hydratropamide was rearranged with 95 percent retention of optical activity into (-) -phenylethylamine. Although the yield was found not to be as high as for corresponding nucleophilic rearrangements, the small amount of racemization which occurred could be traced to the use of aqueous alkali, a strong racemizing agent.

For many years, it was assumed that the asymmetric carbon atom retained its configuration while undergoing the Hofmann rearrangement (103, 106, 107). However, the type of compounds used did not allow any unqualified statement concerning the stereochemistry of the migration. Most authors stated that no inversion needed to be involved in the Hofmann rearrangement. Archer (108) pointed out that there existed in the literature for some time, experimental evidence to prove that no inversion of configuration occurs in the Hofmann

reaction. The evidence was established by Noyes and his co-workers (109, 110, 111, 112, 113, 114).

Camphoric acid (xxvi) was converted to β-camphoramidic acid (xxvii) (cis). Treatment with hypobromite gave aminodihydrocampholytic acid (xxviii), which, when heated for ten minutes with a solution of sodium acetate in acetic anhydride gave the lactam (xxix). The latter upon hydrolysis



xxvi (cis) xxvii (cis) xxviii (cis) xxix

gave the amino acid (xxviii) in optically pure form, showing that no inversion took place during lactamization. The amino and carboxyl groups in (xxviii) must be "cis" to each other. Since the starting acid (xxvi) was of the "cis" series and since the only reaction wherein inversion might have occurred was the Hofmann rearrangement, it was concluded that no inversion took place when the amide (xxvii) was converted to the amine (xxviii). If on the other hand, inversion had occurred during the conversion of (xxvii) to (xxix), the latter would have been of the trans series.

The same reactions were carried out with the three isomers of β-aminocamphoramidic acid (115, 116, 117). Substantially the same result was obtained in each case, namely,

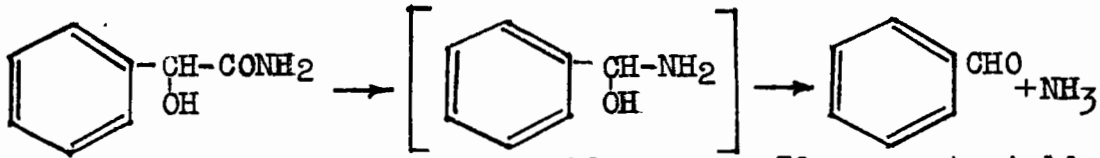
that no inversion took place during the Hofmann rearrangement.

In general, alkaline hypobromite solution is usually used in the Hofmann rearrangement reaction. The main reason being that bromine can be easily weighed or measured volumetrically. However, in many instances it has been found advantageous to use sodium hypochlorite. This reagent usually permits a lower reaction temperature and hence, especially with compounds containing aromatic hydroxyl groups, results in distinctly higher yields of the amine (118). In the following table is a list comparing the yields obtained with hypobromite and hypochlorite in the arrangement of some phthalimides to the corresponding anthranilic acids.

TABLE II

	HOCl	HOBr
Phthalimide	95%	75%
Dichloro "	90	73
Tri " "	90	76
Tetra " "	98	95

When aqueous sodium hypochlorite reacts with amides of α-hydroxy acids, aldehydes are obtained. Weerman (119) converted mandelamide into benzaldehyde.

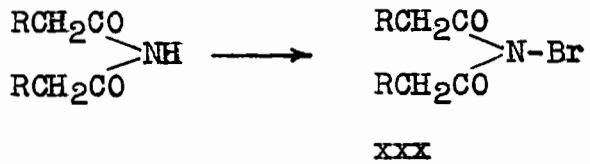


Similarly, α-gluconamide gave a 50 percent yield of d-arabinose and l-arabinosamide produced l-erythrose in 30 percent yield when subjected to a Hofmann rearrangement.

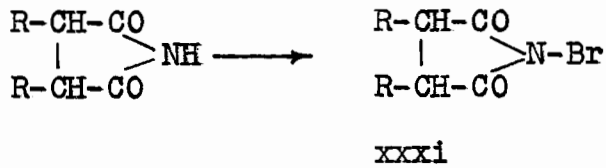
DISCUSSION

In recent years, investigators have shown the importance of several N-halogen derivatives of acid amides and cyclic imides as halogenating agents, particularly in connection with the Wohl-Ziegler reaction. Since the number of N-halogen derivatives available for these reactions was limited, it seemed desirable to study the preparation and use of some new related compounds. The characteristic feature of all compounds which form N-halo compounds is the acidity of the hydrogen in the N-H group, which is activated by the presence of the carbonyl group.

The present investigation was undertaken with the possibility of transforming diacylamides into N-halogen derivatives (xxx) and the preparation of several unknown N-halogen derivatives (xxxi) of cyclic imides.



xxx



xxxi

The N-bromo compounds are generally prepared by two general methods: (a) by the addition of bromine to an alkaline

solution of the amide or imide, and (b) by the reaction of bromine on the silver salt of the N-H compound in an anhydrous medium.

The procedure generally used for preparing N-bromo-amides by means of alkaline hypobromite was that developed by Oliveto and Gerold (120) for brominating acetamide. The hypobromite solution was prepared initially by dissolving one equivalent of bromine in two equivalents of an ice-cold 50 percent solution of potassium hydroxide.

$$Br_2 + 2KOH \longrightarrow KOBr + KBr + H_2O$$

One equivalent of the amide was then added to the cold hypobromite solution. The N-bromo derivative formed was simply filtered off or if it was soluble in the aqueous medium, it was isolated by extraction with chloroform or ether.

$$\begin{matrix} RCO \\ \diagdown \\ \quad NH \\ \diagup \\ RCO \end{matrix} + KOBr \longrightarrow \begin{matrix} RCO \\ \diagdown \\ \quad NBr \\ \diagup \\ RCO \end{matrix} + KOH$$

If the N-bromo compound formed is quite susceptible to hydrolysis, an alternative procedure is used in which bromine is added to the silver salt of the N-H compound in an anhydrous medium.

The silver bromide which precipitates is filtered off and the N-bromo derivative is separated from it.

$$>N\text{-}Ag + Br_2 \longrightarrow >N\text{-}Br + AgBr$$

REACTION OF POTASSIUM HYPOBROMITE WITH DIACETAMIDE

One of the difficulties encountered prior to this investigation was in securing pure starting material which was not contaminated by acetamide. The best procedure for preparing the secondary amide was the reaction of acetic anhydride with bisacetamide hydrochloride (121).

$$(CH_3CO)_2O + (CH_3CONH_2)_2\ HCl \longrightarrow 2(CH_3CO)_2NH + HCl + 2H_2O$$

The reaction mixture was fractionally distilled and diacetamide was collected at 106°/6 mm. However, since acetamide distilled over at the same temperature, it was always present in the distillate due to some decomposition of the hydrochloride salt. Therefore, the product was always contaminated by some of the primary amide. It was found that fractional crystallization from ligroin as reported by Polya (122) provided a good method for separating diacetamide from acetamide.

Initially, the same procedure for preparing N-bromoacetamide (120) was tried for the bromination of diacetamide. Diacetamide was added to an ice-cold solution of potassium hypobromite at 0°. Since no precipitate was formed the aqueous solution was extracted with chloroform. The extraction with chloroform produced a strong odor of isonitrile (i.e. CH_3-NC) indicating that hydrolysis had taken place. The presence of isonitrile was not due to the reaction of hypobromite with diacetamide but it presented evidence for the formation of methylamine. Amines when treated with chloroform in the

presence of alkali are converted into the corresponding isonitriles.

$$CH_3NH_2 + CHCl_3 + 3KOH \longrightarrow CH_3NC + 3KCl + 3H_2O$$

The formation of methylamine indicated that acetamide on treatment with potassium hypobromite had undergone a Hofmann rearrangement.

$$CH_3CONH_2 + Br_2 + 4KOH \longrightarrow CH_3NH_2 + 2KBr + K_2CO_3 + 2H_2O$$

The yield of amine, however, was necessarily quite small. On distillation of the chloroform solution no product was obtained.

The hydrolysis of diacetamide was confirmed by the fact that on evaporation of the aqueous solution a sizeable quantity of acetamide was obtained. Thus, it was concluded that diacetamide when treated with hypobromite solution was hydrolyzed to acetamide and acetic acid.

Theoretically, the reaction of hypobromite can take place by two mechanisms. Either the hydrolysis of the diacylamide precedes the bromination (a) or else the bromination occurs initially followed by hydrolysis (b).

a) $(CH_3CO)_2NH + KOH \longrightarrow CH_3COOK + CH_3CONH_2 \xrightarrow{KOBr} CH_3CONHBr + KOH$

b) $(CH_3CO)_2NH + KOBr \longrightarrow (CH_3CO)_2NBr \xrightarrow{KOH} CH_3COOK + CH_3CONHBr$

If the reaction proceeded by mechanism "b" then the main product formed should have been N-bromoacetamide which was not the case.

Also the second mechanism cannot account for the formation of methylamine since all the alkali is consumed in neutralizing the acetic acid formed on hydrolysis. Therefore it was concluded that the reaction proceeded by mechanism (a). If the reaction proceeded by the former mechanism, then on the formation of the potassium salt of acetic acid, one equivalent of alkali was consumed in neutralizing the acid. Remembering that the original ratio of alkali to imide was 2:1, then upon the addition of bromine only half of the halogen should react. In the preparation of hypobromite, two equivalents of alkali are required for every one of bromine. Thus, an excess of bromine should be present in the reaction mixture and this was observed to be true.

Treatment of diacetamide with two equivalents of hypobromite gave an excellent yield of N-bromoacetamide.

When the reaction was repeated in the presence of a large excess of alkali, all the acetamide formed by the hydrolysis was converted by means of a Hofmann rearrangement to methylamine in 67 percent yield.

$$(CH_3CO)_2NH + KOH \longrightarrow CH_3COOK + CH_3CONH_2$$

$$CH_3CONH_2 + KOBr + 2KOH \longrightarrow CH_3NH_2 + K_2CO_3 + KBr + H_2O$$

REACTION OF POTASSIUM HYPOBROMITE WITH DIBENZAMIDE

In the reaction of hypobromite solution with dibenzamide the same procedure was used as in the preparation of N-bromoacetamide. On subsequent extraction of the reaction mixture with chloroform a strong odor of isonitrile (C_6H_5NC) was detected, however, on evaporation of the chloroform layer under reduced pressure no residue remained. On extraction of the aqueous reaction mixture with ether only benzoic acid was obtained. Both cases indicated that hydrolysis of the diacylamide had taken place. Thus, treatment of dibenzamide with hypobromite solution produced benzoic acid and benzamide.

$$(C_6H_5CO)_2NH \longrightarrow C_6H_5COOH + C_6H_5CONH_2$$

It was observed that if the aqueous solution was allowed to remain overnight at 0^o, it colorized very slowly to a dark brown color and a reddish-black precipitate deposited. The latter on crystallization from water with addition of norite proved to be benzoic acid.

A portion of the colored aqueous filtrate was treated with $Ca(OCl)_2$ and a violet color was produced indicating the presence of aniline. As a result, it was evident from the reaction of $Ca(OCl)_2$ and the detection of isonitrile previously that some of the dibenzamide, formed on hydrolysis, had undergone a Hofmann rearrangement and was converted to

aniline.

The procedure was repeated, however, the reaction mixture was extracted immediately with ether. The ether layer (A) was washed with alkali, and the latter was recombined with the original aqueous solution (B). Acidification of (B) gave benzoic acid in 65 percent of the theoretical yield. The ethereal solution (A) was then washed with 5 percent hydrochloric acid to remove any aniline present. Neutralization of the acidic extract liberated free aniline in a yield of 6 percent. Distillation of the ether solution (A) left a white residue which was identified as benzamide. Counting the aniline present as being formed due to the rearrangement of benzamide, the total yield of amide obtained was 72.5 percent.

When the reaction was carried out as above in the presence of a large excess of alkali all the benzamide was converted to aniline.

Thus, it was concluded that N-bromodibenzamide cannot be prepared in this manner since dibenzamide was hydrolyzed into benzoic acid and benzamide. The latter rearranged quite easily to aniline. This was substantiated by the fact that N-bromobenzamide was prepared according to the procedure of Hoogewerff and Van Dorp (123). It was found to decompose quite readily in aqueous solution and in the presence of light and air. Rearrangement of N-bromobenzamide was effected quite readily and without difficulty at the

temperature of boiling ether in the presence of an excess of alkali.

Analogous to the hydrolysis and bromination of diacetamide, potassium hypobromite can react with dibenzamide in one of two ways. Either the hydrolysis of the diacylamide precedes the bromination (a), or the bromination occurs initially followed by hydrolysis (b).

(a) $(C_6H_5CO)_2NH \longrightarrow C_6H_5COOH + C_6H_5CONH_2 \longrightarrow C_6H_5CONHBr$

(b) $(C_6H_5CO)_2NH \longrightarrow (C_6H_5CO)NBr \longrightarrow C_6H_5COOH + C_6H_5CONHBr$

xxxii xxxiii

If the reaction proceeded by the former mechanism as was the case with diacetamide then the reaction mixture should contain an excess of bromine. However, this was not the case. Consequently mechanism (b) seemed more likely with the formation of the unstable haloamide (xxxii) which subsequently hydrolyzed to the N-haloamide (xxxiii) and the corresponding acid. The second mechanism was also supported by the fact that on the extraction of the hypobromite solution with ether, free benzoic acid was obtained which would not be the case if the reaction proceeded by mechanism (a). It was concluded that dibenzamide was quite stable in alkaline solution at 0°. This was verified by the work of Barth (21) who first prepared the sodium salt of the diacylamide by shaking a suspension of dibenzamide in a solution of sodium

hydroxide and filtering off the excess amide. If the aqueous solution was carefully evaporated to dryness under reduced pressure, sodium dibenzamide could be isolated. Therefore it was concluded that the hydrolysis of dibenzamide proceeded slowly in alkaline solution and at 0° at which temperature the halogenation was attempted, the speed of hydrolysis would be even slower.

The ease of inversion of N-bromobenzamide was shown to some extent by Brummer (124) who attempted to prepare dibenzylhydrazine by the reaction of N-bromobenzamide with sodium benzamide.

$$C_6H_5CONHBr + NaHNCOC_6H_5 \longrightarrow C_6H_5CONHNHCOC_6H_5$$

Instead of the expected hydrazine, however, he obtained a substituted urea.

Consequently, the formation of N-bromodibenzamide cannot be realized by means of potassium hypobromite which was so successful when applied to primary amides and a few cyclic imides.

As a result, an alternative route was tried in which the bromination was undertaken in an anhydrous medium. Previously Stieglitz and Earle (20) had prepared N-chlorodibenzamide by passing a stream of dry chlorine gas through an anhydrous suspension of silver dibenzamide. The N-chloro compound isolated was found to be easily hydrolzed by water and also decomposed quite readily in the presence of light and air.

The silver derivative was prepared by two methods. Initially, the method of Barth (21), mentioned above, was used in which the sodium salt of the diacylamide was treated with 5 percent $AgNO_3$ and the silver salt was deposited. A more satisfactory method for preparing the sodium derivative was by refluxing a suspension of sodium metal and dibenzamide in a dry ethereal solution. This method gave much better yields, however, the reaction was much slower.

Upon the addition of an equimolar quantity of bromine under anhydrous conditions, silver bromide deposited immediately and was filtered off. The filtrate, usually chloroform or ethyl acetate solution turned from light yellow color to a deep red indicating that decomposition or liberation of bromine had taken place. Attempts to precipitate out the derivative with solvents such as n-hexane proved fruitless. The solution was evaporated to dryness under reduced pressure in a nitrogen atmosphere. Red crystals remained, which were highly impure and could not be recrystallized. Only dibenzamide and decomposition products could be obtained.

Therefore, whereas the N-chloro derivative was quite stable, N-bromodibenzamide was extremely unstable. This is somewhat analogous to the results obtained by Slossen (125) who sought to prepare N-bromoalkylaroylamides. He found that the N-chloro compounds were fairly stable but that the corresponding N-bromo derivatives decomposed immediately upon formation.

PREPARATION OF ALKYL- AND ARYLSUBSTITUTED SUCCINIC ACIDS AND IMIDES

The alkyl- and arylsuccinic acids with exception of methylsuccinic acid were prepared by modified procedures that were developed initially by Lapworth and McRae (126). Methylsuccinic acid was prepared by treatment of ethyl crotonate with potassium cyanide to give the β-cyanoester which was subsequently hydrolyzed with barium hydroxide to the dibasic acid (127). Acidification of the reaction mixture

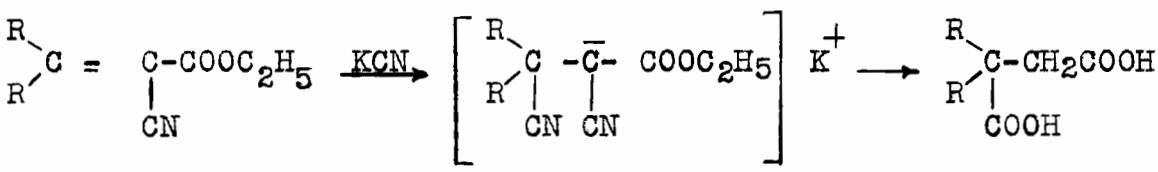
$$CH_3CH{=}CHCOOC_2H_5 \xrightarrow{KCN} \left[CH_3CH(CN)-\bar{C}HCOOC_2H_5\right] K^+ \longrightarrow CH_3-CH(CH_2COOH)COOH$$

with concentrated nitric acid gave the free methylsuccinic acid which was extracted with large quantities of ether and benzene. Although the procedure gave relatively large yields (70%) of methylsuccinic acid, it required considerable time for completion. This was due particularly to the fact that on the addition of barium hydroxide, the reaction mixture was concentrated under reduced pressure to a thick paste. The distillation was accompanied by frothing and as a result was carried out very slowly in order to prevent bumping. The addition of reagents to increase the surface tension of the solution did little to alleviate this condition. Subsequently, the synthesis was repeated as before except that on the addition of barium hydroxide the distillation of the

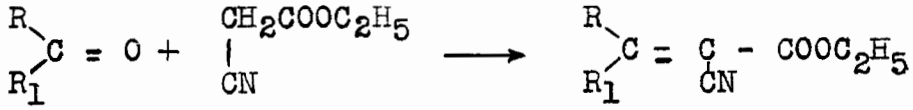
alkaline solution was carried out on a water bath at atmospheric pressure. It was found that the distillation was accompanied by very little decomposition and therefore the vacuum distillation was abandoned. The residue contained a mixture of inorganic salts and methylsuccinic acid in the form of its barium salt. The authors (127) acidified the residue with excess concentrated nitric acid and once more evaporated the solution to dryness under reduced pressure. It was found that this distillation could also be carried out at atmospheric pressure with very little decomposition.

It was difficult also to secure complete separation of the free dibasic acid from the inorganic material by numerous extractions with ether and benzene respectively. As a result, it was found more convenient and advantageous to undertake the extraction in a Soxhlet extractor. The quantity of solvent used was greatly reduced and a more thorough extraction was obtained. This was confirmed by the increase in yield to over 80 percent. These slight modifications in the procedure cut the reaction time almost in half.

2,2-Dimethylsuccinic and phenylsuccinic acids were prepared by the reaction of the appropiate alkylidenecyanoacetate with alcoholic potassium cyanide to give the intermediate (128) dicyano derivative. Subsequent hydrolysis of the intermediate with concentrated hydrochloric acid converted the dicyano ester to the corresponding dibasic acid.



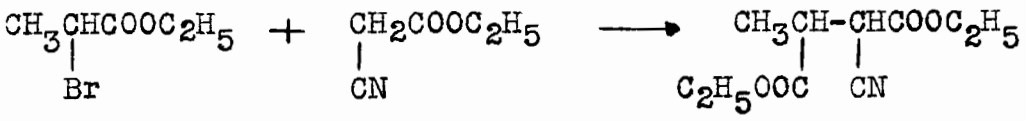
The alkylidenecyanoacetates themselves were easily secured by the condensation of ethyl cyanoacetate with the suitable aldehyde or ketone in the presence of a piperidine catalyst. It was essentially a Knoevengal reaction.



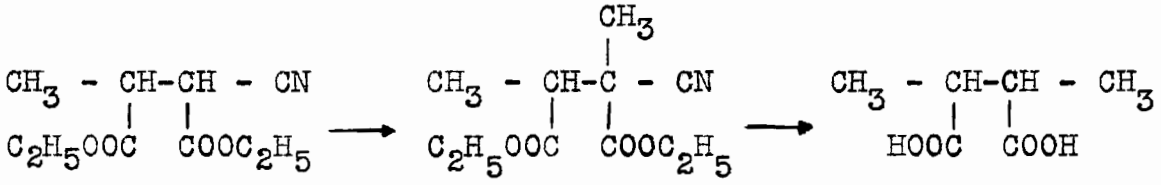
The preparation of phenylsuccinic acid was accomplished directly as reported by the authors (129), however, the procedure for 2,2-dimethylsuccinimide gave yields of only 50 percent (128). The low yield was attributed to the incomplete extraction of the acid from the reaction mixture. Whereas phenylsuccinic acid is insoluble in acidic solution and precipitates on cooling, dimethylsuccinic acid on the other hand is quite soluble. Normally, it was isolated by saturating the aqueous solution with ammonium sulfate and extraction with ether. It was found preferable to evaporate the acidic solution to dryness and extract the dibasic acid from the inorganic material in a Soxhlet extractor. This method afforded a more complete separation and gave better yields.

2,3-Dimethylsuccinic acid was prepared by the procedure as outlined by Boëschen and Van der Want (130).

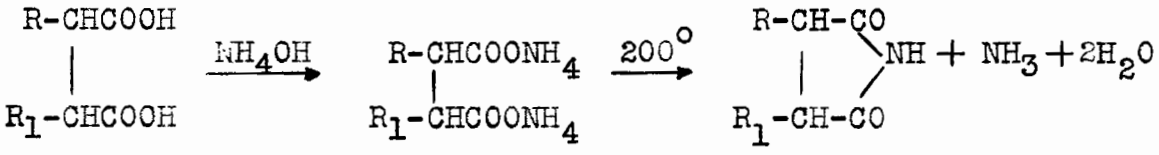
Ethyl bromopropionate was condensed with ethyl cyanoacetate in the presence of an alcoholic solution of sodium methoxide.



Treatment of the cyano ester with methyl iodide gave diethyl 2-cyano-2,3-dimethylsuccinate which was hydrolyzed to the dibasic acid.



The imides were prepared by treatment of the corresponding acids with concentrated aqueous ammonia and subsequent heating of the diammonium salts to 200° as follows:

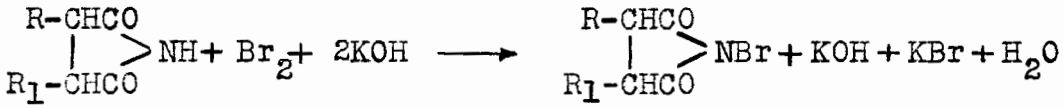


It was found that the general method for obtaining pure imides by distillation of succinimides at atmospheric pressure was accompanied by decomposition and as a result the yields were low. Much better results were obtained by sublimation of the imides under a pressure of 1 mm. The sublimation temperature was maintained 2° higher than the melting point of the imide being sublimed. In the preparation of 2,3-dimethylsuccinic acid, both meso-2,3-dimethylsuccinic acid and DL-2,3-dimethylsuccinic acid

were obtained. Both isomers, when treated with ammonia as above, gave the same imide which melted at 109-110°. It was designated as being the DL isomer, since on hydrolysis it was converted solely to DL-2,3-dimethylsuccinic acid (148).

N-HALOGEN DERIVATIVES OF ALKYL- AND ARYLSUCCINIMIDES

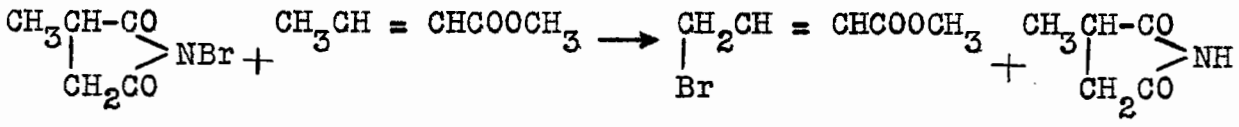
Contrary to the fact that the N-bromo derivatives of diacylamides could not be isolated as stable products, the N-halogen derivatives of C-alkylsuccinimides were obtained quite readily.



The N-bromo derivatives of methylsuccinimide, 2,2-dimethylsuccinimide, and DL-2,3-dimethylsuccinimide were all prepared by the same method as that used for N-bromosuccinimide. The imides were dissolved in a cold concentrated solution of alkali and an equivalent amount of bromine was added quickly with rapid stirring. The N-bromoimides precipitated, were filtered off immediately, and washed thoroughly with cold water to remove any inorganic salts. They were all recrystallized rapidly from water. The procedure found to be most effective was dissolving the impure

bromo derivative in an equivalent amount of preheated water and filtering rapidly through a fluted filter paper into a receiver which was surrounded by an ice-bath. The loss of material was very small when the recrystallization was carried out by this method. When dry and kept at 0°, the bromo compounds were stable for several weeks.

N-Bromomethylsuccinimide when treated with methylcrotonate gave a good yield of methyl γ-bromocrotonate.



The reactivity of N-bromomethylsuccinimide in this Wohl-Ziegler type reaction was comparable to that of N-bromosuccinimide.

The N-chloro derivatives of the imides were produced by passing a stream of chlorine gas through an ice-cold alkaline solution of the imide. It was necessary, however, to add an equivalent amount of ice to the reaction mixture as the chlorination was accompanied by a great evolution of heat. In general it was preferable to keep the external ice bath at -10° rather than at 0°. N-Chloromethylsuccinimide, N-chloro-2,2-dimethylsuccinimide, and N-chloro-DL-2,3-dimethylsuccinimide were all white crystalline solids.

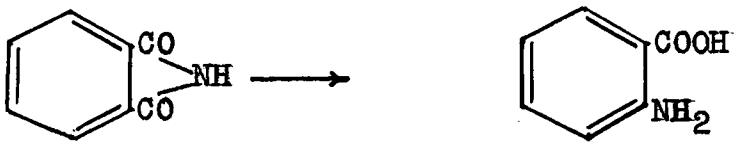
N-Iodo-2-methylsuccinimide, N-iodo-2,2-dimethylsuccinimide, and DL-2,3-dimethylsuccinimide were prepared by treatment of the silver salts of the respective imides with

iodine in an anhydrous solvent such as ethyl acetate or chloroform. Great care must be taken that the iodine and imide are in equimolar quantities since when a slight excess of iodine was present, great difficulty was encountered in the purification of the iodo derivatives. When pure the iodo compounds are all white crystalline solids.

N-Chlorophenylsuccinimide was prepared quite readily by the same procedure as was used above. However, the bromo derivative could not be isolated. Bromination with hypobromite produced an orange compound which melted at about 115-120°, however, it could not be crystallized. Recrystallization attempts always produced a small yield of phenylsuccinimide and decomposition products.

HOFMANN REARRANGEMENT OF CYCLIC IMIDES INTO β-AMINO ACIDS

In regard to the Hofmann rearrangement of cyclic imides into β-amino acids, extensive application of the reaction has been made in the production of anthranilic acids from phthalimide and its substituted homologs (75). Thus, phthalimide since it contains a five membered imide ring will rearrange to produce a β-amino acid.

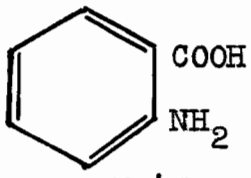


Similarly succinimide and its derivatives should also rearrange into β-amino acids. However, only the parent compound, suc-

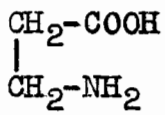
cinimide, had been subjected to a Hofmann rearrangement (86).

Consequently, an investigation was undertaken in which substituted succinimides were subjected to a Hofmann rearrangement with the following points in mind:

(1) Although both phthalimide and succinimide give β-amino acids, there is a fundamental difference in the type of β-amino acid formed. Thus, the former compound gives an amino acid in which the amino and acid groups are obtained as 1, 2-substituents on a benzene ring (xxxiv) whereas with succinimide, β-alanine (xxxv) is produced.



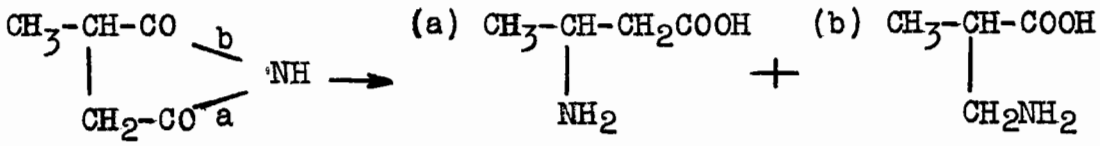
xxxiv



xxxv

As a result, with substituted succinimides, substituted β-alanines would be expected as products.

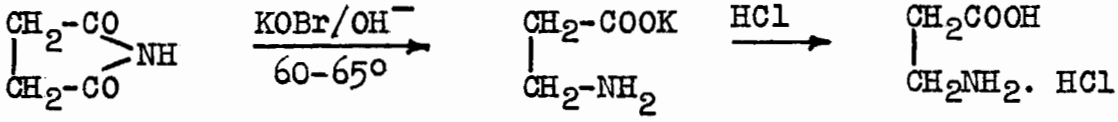
(2) It is important to remember that in the Hofmann rearrangement of unsymmetrically substituted succinimides, certain isomeric β-alanines can be theoretically produced. Thus, in the rearrangement of methylsuccinimide two products are theoretically possible, 3-aminobutyric acid (xxxvii) and 3-aminoisobutyric acid (xxxviii), depending on whether the ring opens at position "a" or "b" respectively.



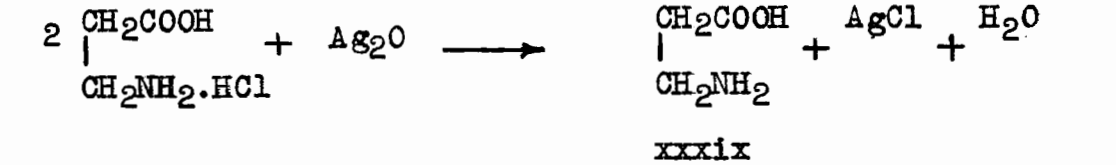
xxxvi xxxvii xxxviii

However, with unsymmetrically substituted phthalimides, it was found (85) that one isomer usually predominated or formed exclusively. In most cases it was possible to predict the formation of one product over the other knowing the electronic effects of the substituents. But, this is not the case with succinimide since it presents a non-conjugated system and the formation of one isomer predominating over the other cannot be freely predicted.

Initially, in the attempted rearrangement of alkyl substituted succinimides, the same procedure was followed as was used for succinimide (86). Succinimide was dissolved in an ice-cold solution of potassium hypobromite. The reaction mixture was warmed to 60-65° for several hours to effect rearrangement, then acidified with concentrated hydrochloric acid to Congo red. Evaporation of the solution to dryness



and extraction of the residue with absolute alcohol separated the amino acid from the inorganic salts. Since the amino acid was in the form of its hydrochloride salt, treatment with silver oxide produced free β-alanine (xxxix) which was isolated



xxxix

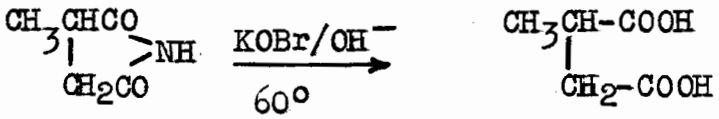
by concentrating down the aqueous solution to a small volume. The overall yield was approximately 45-50 percent of theory.

However, it must be remembered that with mono alkylsubstituted succinimides two isomeric amino acids are theoretically possible. For this reason, methylsuccinimide was chosen initially for study, since both possible products, 3-aminobutyric acid (xxxvii) and 3-aminoisobutyric acid (xxxviii), had already been reported by Babliano (131) and Fischer (132) respectively. Although the literature concerning the two substances is rather limited, from a knowledge of their properties a method of separation could be formulated if both were produced by the Hofmann rearrangement of methylsuccinimide.

An ice-cold alkaline solution of methylsuccinimide and potassium hypobromite was warmed to 60-65° for several hours, then cooled, and acidified to Congo red. Extraction of the dry residue with absolute alcohol produced a yellow oil (D) which was very soluble in water and alcohol, but insoluble in most organic solvents. Since the extraction with absolute alcohol may have caused partial esterification of the expected amino acids the oil (D) was refluxed with a small quantity of water for two hours. On cooling, the aqueous solution was extracted with ether. On distillation of the ether a yellow oil (E) remained. Analysis of (E) indicated that it was an acid. It was esterified with ethanol and distilled under reduced pressure as a colorless liquid (F) boiling at 105°/16 mm. The ester did not contain any nitrogen

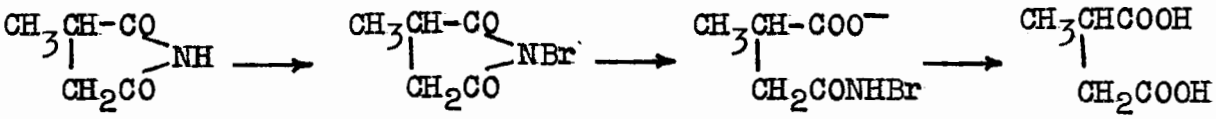
and analysis for carbon and hydrogen indicated that (F) was diethyl methylsuccinate. Its structure was confirmed by hydrolysis with dilute hydrochloric acid to methylsuccinic acid (XL) which must have been the prime constituent of the yellow oil (D).

As a result the main product obtained by the reaction of potassium hypobromite with methylsuccinimide at 60-65° was methylsuccinic acid.



XL

Therefore it was evident that under the above reaction conditions no Hofmann rearrangement took place, but instead the imide was hydrolyzed to the dibasic acid. From the knowledge that methylsuccinimide forms an N-bromo derivative it can be assumed with certainty that the initial step in the reaction was the formation of the N-bromo compound (XLI). The hydrolysis probably took place in two steps



XLI XLII

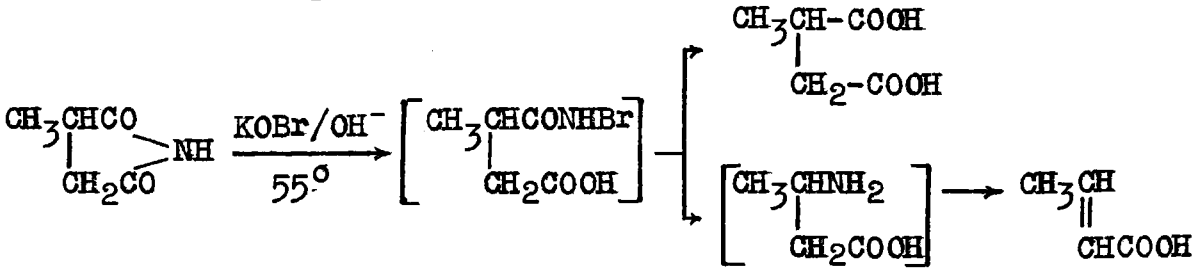
forming initially the intermediate N-bromo-3-methylsuccinamic acid (XLII) which subsequently hydrolyzed further to methylsuccinic acid. In the latter steps, at 60-65° the rate of

hydrolysis was probably much greater than the rate of rearrangement. Finally, it was concluded that the temperature at which Clarke and Behr (86) carried out the rearrangement of succinimide was too high for the methyl derivative. Therefore the temperature of the reaction was lowered to 55° and the reaction repeated.

Essentially, the same procedure was followed as above. The alcoholic extract on evaporation to dryness gave a yellow oil (G) which was then treated with silver oxide. Subsequent evaporation of the aqueous solution produced a dark oily yellow residue (H). The oil (H) was fractionally distilled under reduced pressure and the fraction which passed over at 55-60°/2 mm. was collected. On cooling it crystallized as white plates melting at 72°. It decolorized both 2 percent permanganate solution and a solution of bromine in carbon tetrachloride. A molecular weight determination tentatively identified the compound as crotonic acid. This inference was confirmed by a mixed melting point with reagent crotonic acid.

The residue from the distillation was esterified and distilled. A colorless liquid was obtained which was identified as diethyl methylsuccinate. The formation of the dibasic acid indicated that the reaction temperature was still too high. This was confirmed by the presence of crotonic acid

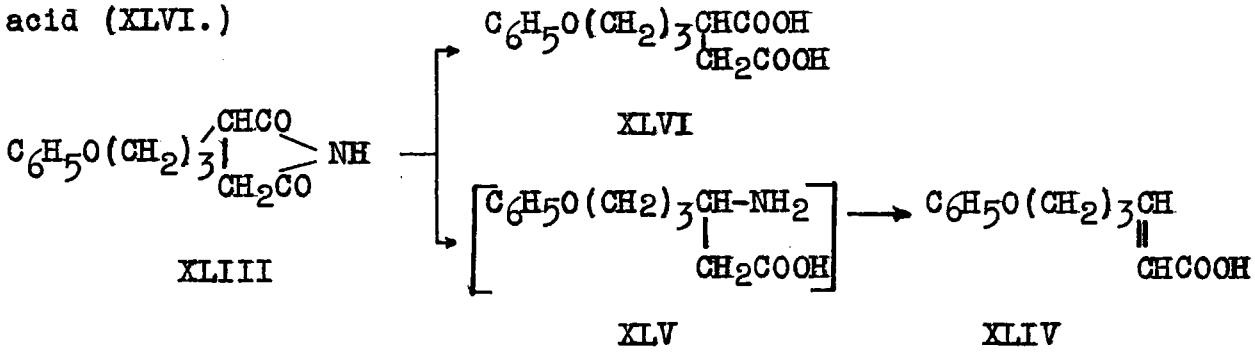
as one of the products. The formation of the latter also furnished concrete evidence that some rearrangement of methylsuccinimide had taken place.



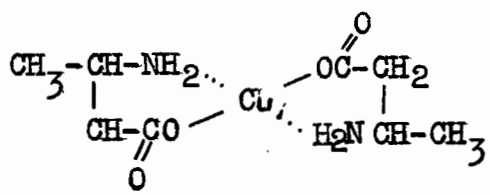
A well known characteristic of β-amino acids is that on heating in an alkaline solution they lose quite easily the elements of ammonia which is reminiscent of the behaviour of β-hydroxyacids.

$$HOCH_2CH_2COOH \xrightarrow{OH^-} CH_2 = CHCOOH.$$

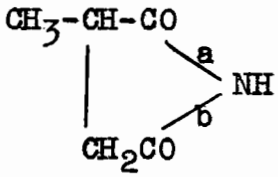
This was similar to the results obtained by King and his coworkers (132) who undertook a Hofmann reaction with γ-phenoxypropylsuccinimide (XLIII). The imide was subjected to a rearrangement at a temperature of 60°. They obtained a small quantity of 6-phenoxyhydrosorbic acid (XLIV), but were unable to isolate any of the intermediate amino acid (XLV). The main product from the reaction was γ-phenoxypropylsuccinic acid (XLVI.)



The temperature of the rearrangement was lowered another 5° and the procedure was repeated once more. The residue, obtained on evaporation of the alcoholic extract, was redissolved in absolute ethanol and dry hydrogen chloride gas was passed through the solution. It was hoped that by esterification the standard procedure of treating the amino acid (if formed) with silver oxide could be avoided. As a result, extraction of the ester from an alkaline solution, would provide the amino acid in the form of its ethyl ester. The alcoholic solution was poured into water, extracted with ether, and fractionally distilled under reduced pressure. A fraction was collected at 125-130°/38 mm. which was identified as ethyl crotonate by its subsequent hydrolysis to crotonic acid. The yellow viscous residue (I) from the distillation was neutralized with 33 percent sodium hydroxide and extracted with ether. Distillation of the ethereal solution yielded a colorless liquid which came over at 64-65°/15 mm. It was identified as ethyl 3-aminobutyrate. Hydrolysis with dilute hydrochloric acid produced a yellow oily residue (J) which could not be purified. However, it did form a copper complex with copper carbonate indicating the presence of 3-aminobutyric acid.



The conclusion which was drawn from the last reaction was that the formation of ethyl 3-aminobutyrate clearly indicated that hydrolysis of the imide ring had occurred at position "b" (XLVII).



XLVII

The failure to isolate any ethyl methacrylate or ethyl 3-aminoisobutyric acid showed that the ring was opened in only one position with hypobromite and that only one amino acid was formed in the rearrangement. Thus, a similarity could be drawn with the work of Moore (86) who found that in the Hofmann rearrangement of substituted phthalimides to the corresponding anthranilic acids, one isomer always predominated, or formed exclusively.

Finally, the rearrangement was attempted at a temperature of approximately 40-45°. From the alcoholic extract a sizeable quantity of a yellow oil (K) was obtained which did not contain any methylsuccinic or crotonic acid but did possess a considerable quantity of 3-aminobutyric acid by its formation of a copper complex with copper carbonate.

Nevertheless, it was found that the amount of impure amino acid obtained was rather small and that a sizeable quantity of the product always remained with the inorganic residue.

Previously Fischer (134) had noticed that ethyl 3-aminobutyrate hydrochloride was insoluble to a great extent in absolute ethanol. Since it can be safely assumed that the same amino acid was formed in our experiments, it is conceivable that some esterification took place during the extraction with absolute alcohol and that the insoluble ethyl 3-aminobutyrate hydrochloride was formed. As a result, the reactions were repeated using hydrobromic acid instead to neutralize the alkaline solution. It was thought that the use of hydrobromic acid would have a two-fold advantage. Initially, the hydrobromide salt of the ester may be more soluble in alcohol than the hydrochloride and secondly, the formation of a mixture of salts would be avoided. It was also decided at this stage to neutralize the amino acid only to the vicinity of its isoelectric point thereby reducing the amount of hydrobromide salt formed. Although the isoelectric points of β-amino acids have not been reported, it was assumed that they should correspond closely to those of the corresponding α-amino acids. Consequently, the solution was carefully titrated with 1N hydrobromic acid and the course of the neutralization plotted. A point of inflection was observed at a pH 5.8. When the reaction was repeated using the modifications in the procedure mentioned above, it was observed that on extraction with absolute alcohol, no nitrogeneous material was detected in the inorganic residue.

The impure amino acid (K) could not be crystallized nor distilled directly. With copper carbonate a copper salt

formed which decomposed at 215-217°. Treatment of the amino acid with picric acid gave a picrate which melted at 230-232°.

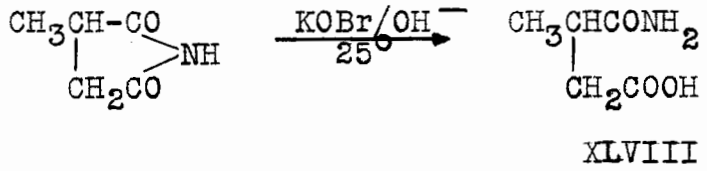
Purification of (K) was attempted by preparing the acyl derivative which in turn could be subsequently hydrolyzed back to the amino acid. Formylation was tried initially since, in general, formyl derivatives are more easily hydrolyzed. However, on formylation using the method of Stieger (135) only an oil was obtained which started to crystallize only after standing several months at 0°.

Treatment of the amino acid with benzoyl chloride gave the N-benzoyl derivative in excellent yield. Since the reaction of benzoyl chloride with the amino acid was very slow, the usual methods for preparing N-benzoyl derivatives could not be used. It was found that method used by Stieger (136) for benzoylating α-amino acids worked equally well with 3-aminobutyric acid. The m.p. of 154-155° and carbon, hydrogen, and nitrogen analysis were in agreement with that reported in the literature (137) for N-benzoyl-3-aminobutyric acid.

Prolonged boiling with sodium hydroxide and diazotation of the amino acid to give crotonic acid and 3-hydroxybutyric acid confirmed its structure as being that of 3-aminobutyric acid. The absence of methacrylic acid and 3-hydroxyisobutyric acid in the latter two reactions indicated that no 3-aminoisobutyric acid was produced in the Hofmann rearrangement of methylsuccinimide.

When the attempted rearrangement was carried out at room temperature (25°), the only product obtained was

3-methylsuccinic acid (XLVIII).

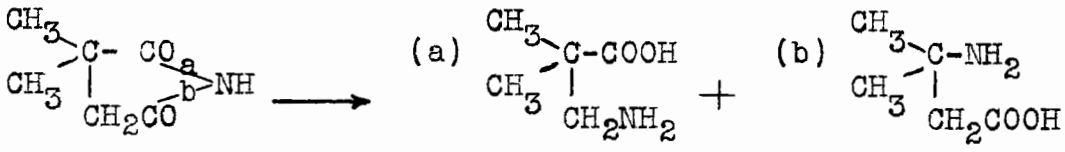


XLVIII

Thus, the temperature was not high enough to produce rearrangement. At 25°, the rate of hydrolysis was greater than the rate of rearrangement.

REACTION OF POTASSIUM HYPOBROMITE WITH 2,2-DIMETHYLSUCCINIMIDE

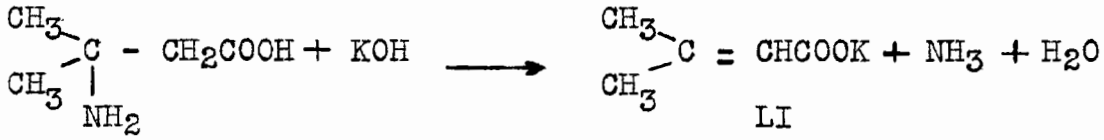
In the Hofmann rearrangement of 2,2-dimethylsuccinimide two products can be expected, 3-amino-2,2-dimethylpropionic acid (XLIX) or 3-amino-3-methylbutyric acid (L) depending on whether the imide ring opened at position "a" or "b" respectively.



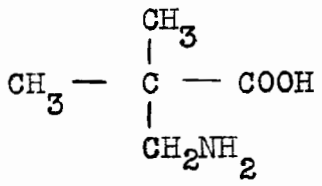
XLIX L

It was decided to follow the method used for methylsuccinimide above rather than that outlined by Clarke and Behr for succinimide (86). Consequently the reaction mixture of potassium hypobromite and 2,2-dimethylsuccinimide was warmed to 40-45° for three hours and acidified to pH 6 with 1N hydrobromic acid. Evaporation of the aqueous solution to dryness

and extraction with absolute methanol gave a yellow, viscous oil. It contained a substantial quantity of amino acid which was indicated by its formation of a copper complex salt with copper carbonate. The pure amino acid was obtained by three crystallizations from a 50 percent solution of methanol and ether. It deposited in small white needles which melted at 216-216.5°. It gave with benzoyl chloride an N-benzoyl derivative which was recrystallized from water. The N-benzoyl derivative melted at 140-141°. The agreement of melting points with that reported in the literature (138) indicated that the amino acid formed by the Hofmann rearrangement of 2,2-dimethylsuccinimide was 3-amino-3-methylbutyric acid (XLIX). This was confirmed by hydrolysis of the amino acid with dilute alkali to 3-methylcrotonic acid (LI).



The absence of the second isomer, 3-amino-2,2-dimethylpropionic acid (LII) was established by the same reaction. The yellow oil obtained from the alcoholic extraction above was treated with sodium hydroxide and refluxed for several hours. 3-Amino-3-methylbutyric acid (XLIX) should hydrolyze to the olefinic acid (LI), whereas 3-amino-2,2-dimethylpropionic acid (L) since it possesses no alpha hydrogen atom and cannot lose a molecule of ammonia, remains unchanged.



LII

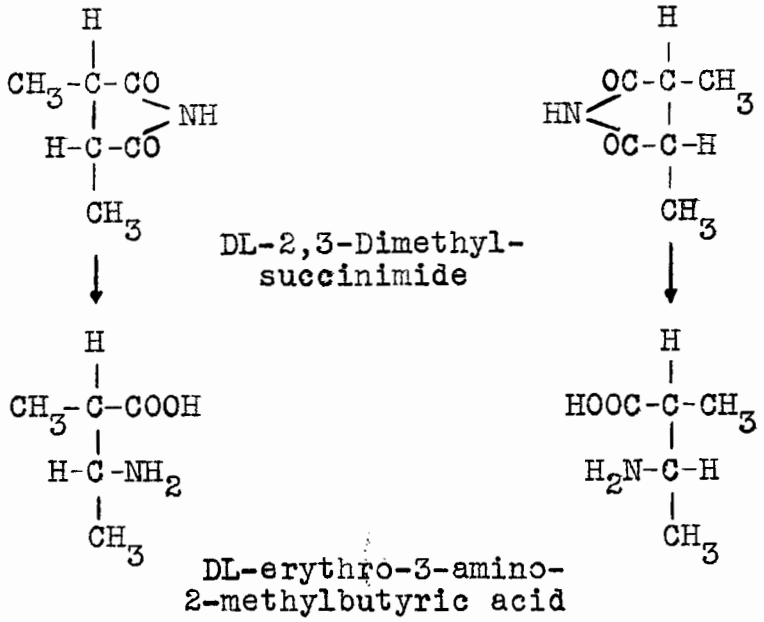
Prolonged boiling with alkali produced an olefinic acid which melted at 69-69.5°. It was identical to 3-methylcrotonic acid (LI). The residue did not contain any trace of 3-amino-2,2-dimethylpropionic acid.

Thus, 2,2-dimethylsuccinimide undergoes a Hofmann rearrangement when treated with alkaline hypobromite solution at 40° to give only one product, 3-amino-3-methylbutyric acid. This result was completely analogous to that obtained by the Hofmann rearrangement of methylsuccinimide.

When the reaction of hypobromite was repeated above at 50°, the main products obtained were 3-methylcrotonic acid and a smaller quantity of 3-amino-3-methylbutyric acid. Above 60°, only 2,2-dimethylsuccinic acid was produced.

REACTION OF POTASSIUM HYPOBROMITE WITH DL-2,3-DIMETHYL-SUCCINIMIDE

DL-2,3,-Dimethylsuccinimide upon treatment with alkaline potassium hypobromite should undergo a Hofmann rearrangement to yield 3-amino-2-methylbutyric acid. Since the amino acid has DL- configuration, the expected product will be the pair of enantiomorphs of DL-erythro-3-amino-2-methylbutyric acid.

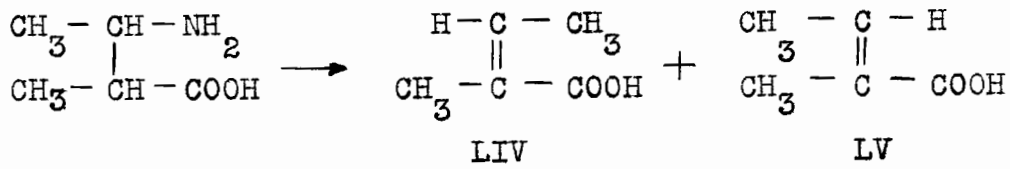


The same procedure was used as in the previous two cases, in which the alkaline hypobromite solution of the imide was warmed to 40-45°. Evaporation of the alcoholic extract afforded white crystals of the amino acid which gradually separated out as the solution was concentrated. The white residue was recrystallized several times from a 50 percent mixture of methanol and ether to a constant melting point of 231-232°. Analysis of the substance and formation of a copper complex confirmed the structure as being that of DL-erythro-3-amino-2-methylbutyric acid.

Treatment of the amino acid with benzoyl chloride gave N-benzoyl-3-amino-2-methylbutyric acid which was recrystallized three times from water. It was completely insoluble in ether and as a result was separated very easily from any benzoic acid formed during the course of the benzoylation.

Prolonged boiling with alkali converted 3-amino-2-

butyric and to tiglic acid (LIV) and some angelic acid (LV).



LIV LV

When the reaction with alkaline hypobromite and 2,3-dimethylsuccinimide was carried out at temperatures above 55° only 2,3-dimethylsuccinic acid was obtained.

REACTION OF POTASSIUM HYPOBROMITE WITH SUCCINIMIDE

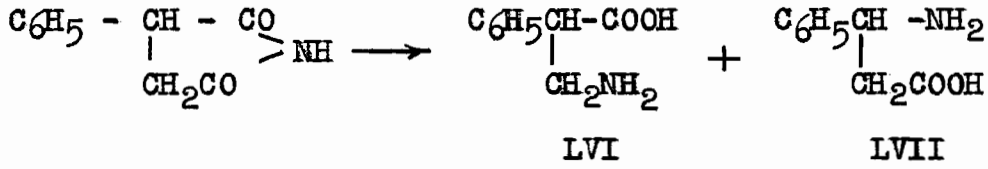
The reaction of potassium hypobromite with succinimide giving β-alanine was first reported by Hoogewerff and Van Dorp (13). The procedure of Clark and Behr (86) mentioned above is in essence a modification of that original preparation. However, in both procedures the yield of β-alanine amounted to only about 45-50 percent of theory. This poor yield was attributed to the following factors: (1) the rearrangement at 55-60° was always accompanied by some decomposition of the amino acid and (2) treatment of the alcoholic extract with silver oxide followed by hydrogen sulfide always produced a loss of the product. Since in the preparation used for the rearrangement of methylsuccinimide a lower temperature was used and the last step completely avoided, the same procedure was applied to succinimide.

The hypobromite solution of the imide was warmed to 40-45°, acidified to pH 6, and then evaporated to dryness.

Extraction with alcohol gave a yellow oil which on benzoylation was converted to N-benzoyl-3-amino propionic acid. The yellow oil itself was impure amino acid. The total yield based on starting material was never less than 58 percent. The reaction was advantageous apart from the slightly increased yield in that it required only half the usual time for completion.

REACTION OF POTASSIUM HYPOBROMITE WITH PHENYLSUCCINIMIDE

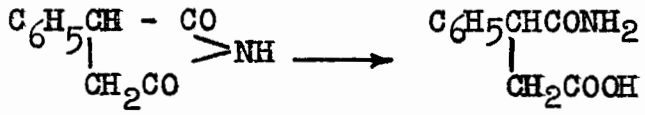
Theoretically, the reaction of potassium hypobromite with phenylsuccinimide in a Hofmann type reaction can yield two products: 3-amino-2-phenylpropionic acid (LVI), and 3-amino-3-phenylpropionic acid (LVII).



LVI LVII

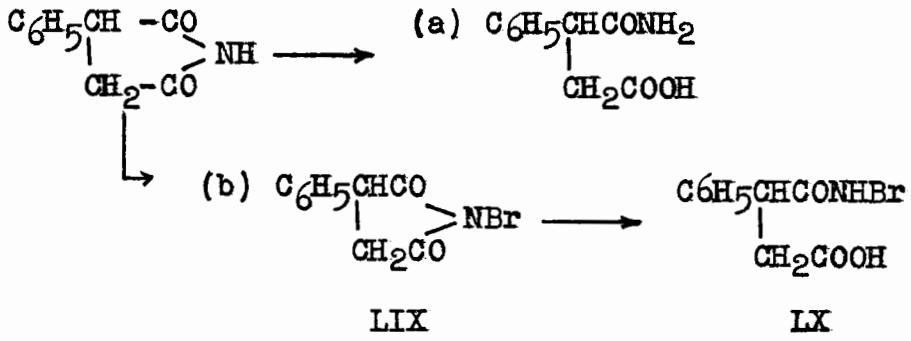
Phenylsuccinimide was selected for two reasons, firstly, because it is the first member of the series of arylsubstituted succinimides, and secondly both amino acids (LVI) and (LVII) have been reported in the literature. Posner (140) had synthesized both 2-phenyl- and 3-phenyl-2-amino-propionic acid by the reaction of an alcoholic solution of hydroxylamine with atropic and cinnamic acid respectively. Thus, knowing the properties of the two amino acids, in case both are formed by the Hofmann rearrangement of phenylsuccinimide, a method of separation of the two isomers could be formulated.

Initially, the same procedure was followed as was used for the rearrangement of methylsuccinimide. On evaporation of the alcoholic extract, a white residue deposited which upon recrystallization from water was identified as 3-phenylsuccinamic acid (LVIII).



LVIII

The formation of 3-phenylsuccinamic acid can be postulated as occurring in one of two ways: (a) The imide simply hydrolyzed to the amide without any reaction involving hypobromite, or (b) the hypobromite reacted with the imide



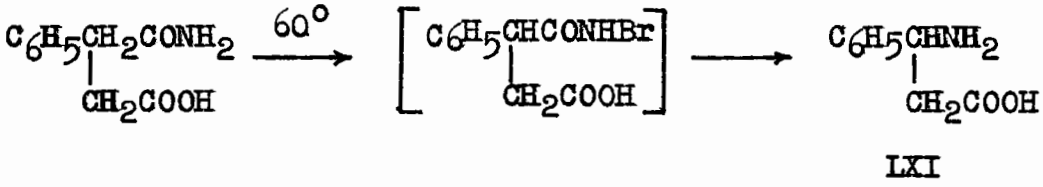
LIX LX

forming the N-bromo derivative (LIX), followed by ring opening to yield the intermediate N-bromo-3-phenylsuccinamic acid (LX). At a temperature of 40° the intermediate simply hydrolyzed to 3-phenylsuccinamic acid.

The first mechanism was eliminated on the basis that on treatment of phenylsuccinimide with dilute potassium hydroxide at 0° very little hydrolysis took place. But when the

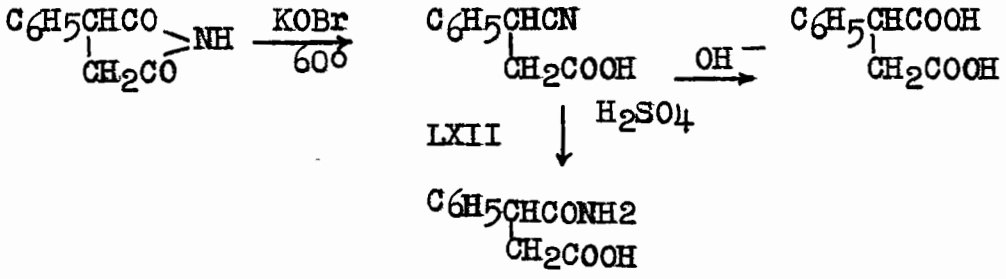
imide was added to a solution of potassium hypobromite at the same temperature none of the starting material was recovered. However, the formation of the N-bromo derivative (LIX) could not be verified since attempts to prepare and isolate N-bromophenylsuccinimide could not be accomplished. The formation of 3-phenylsuccinamic acid from the intermediate (LX) was probably due to the fact that the temperature of 40-45° was not high enough to effect rearrangement.

Treatment of 3-phenylsuccinamic acid with potassium hypobromite at 60° for a period of four hours gave a good yield of 3-amino-3-phenylpropionic acid (LXI).



LXI

The reaction of potassium hypobromite with phenylsuccinimide was repeated at a temperature of 60-65°. The aqueous solution on evaporation to dryness and extraction with methanol afforded a yellow oil which when treated with 50 percent ethanol deposited long white needles of 3-cyano-3-phenylpropionic acid (LXII). Its structure was verified by hydrolysis with (a) concentrated H_2SO_4 to 3-phenylsuccinamic acid and (b) with dilute alkali to phenylsuccinic acid.

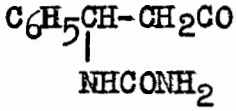


LXII

Evaporation of the alcoholic filtrate produced a yellow oil which upon crystallization from concentrated hydrochloric acid gave phenylsuccinic acid which was the main product of the reaction. Thus, at a temperature of 60° treatment of phenylsuccinimide with alkaline potassium hypobromite gave mainly phenylsuccinic acid and a smaller quantity of 3-cyano-3-phenylpropionic acid.

If the reaction was carried out at temperatures greater than 65°, the imide was converted completely to the dibasic acid.

As a result, it was concluded that phenylsuccinimide would not undergo a Hofmann rearrangement in a one step process as was the case with alkylsubstituted succinimides. It was necessary to isolate the intermediate 3-phenylsuccinamic acid which was subsequently rearranged to the corresponding 3-amino-3-phenylpropionic acid. The failure to obtain the amino acid directly was similar to the results obtained by McRae and his collaborators (141, 142, 143, 144) who did an extensive investigation on the reaction of potassium hypobromite with phenyl- and sym-diphenylsuccinamides. The object of their research was to secure the uracil intermediates which were produced with methylsuccinamide and succinamide (75). They observed that phenylsuccinamide was not converted to the uracil but gave instead 3-ureido-3-phenylpropionic acid (LXIII).



LXIII

Symmetrical diphenylsuccinamide gave an unusual reaction in which it was converted in 90 percent yield to diphenylacetic acid. Symmetrical diphenylsuccinimide simply hydrolyzed to diphenylsuccinamic acid.

EXPERIMENTAL

ANALYSIS

All solid materials to be analyzed were recrystallized two to three times from an appropriate solvent and dried under reduced pressure over phosphorous pentoxide for a period of twenty-four hours.

Carbon, hydrogen and nitrogen analyses were performed on a micro scale as single determinations by the Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Halogen and copper were determined by the iodometric method as outlined by Kolthoff and Sandell (145). The derivative was dissolved in 1N acid solution in the presence of an excess of potassium iodide. The iodine liberated was titrated with standard sodium thiosulfate solution using a starch indicator.

The purity of the amino acids and their derivatives were determined by neutralization with standard sodium hydroxide.

All melting points reported are uncorrected.

PREPARATION OF DIACETAMIDE

Two hundred grams of acetamide was dissolved in 1000 ml. of a 50 percent mixture of ether and ethanol. Dry

hydrogen chloride gas was passed through the solution which soon solidified to a crystal mass. The residue was filtered and washed several times with anhydrous ether. The hydrochloride was filtered and washed several times with anhydrous ether. It was recrystallized from ethanol, depositing as white needles which melted at 132-135°.

Seventy grams of the acetamide hydrochloride was refluxed with 90.8 gm. of freshly distilled acetic anhydride for 30 minutes. Fractions up to 125° were removed and the residue was distilled under reduced pressure. The fraction distilling at 104-106°/6 mm. was collected and dissolved in ether. Dry hydrogen chloride gas was passed through the solution to remove any acetamide as the hydrochloride. The ethereal solution was shaken thoroughly with 10 gm. of barium carbonate followed by 10 gm. of potassium carbonate. On removal of the ether, diacetamide was fractionally crystallized from ligroin. The product was heated with 12 parts of petroleum ether, decanted, and allowed to cool slowly. Diacetamide deposited as white needles melting at 80-80.5°.

REACTION OF POTASSIUM HYPOBROMITE WITH DIACETAMIDE

(molar ratio 1:1)

In a 100 ml. flask, 5.00 gm. (0.05 mole) of diacetamide was added to an ice-cold solution of 50 percent potassium hydroxide (10.92 gm.). Eight grams (0.05 mole) of bromine was

added at such a rate that the temperature of the hypobromite solution remained at 0°. The solution was stirred for two minutes, 4 gm. of salt was added, and the reaction mixture was extracted with 30 ml. of chloroform. The chloroform layer was decanted off and the extraction repeated twice with 20 ml. portions. The chloroform extracts were combined and dried over anhydrous sodium sulphate. The solution evolved a very strong odor resembling that of isonitrile. On evaporation of the chloroform, however, no residue remained.

The aqueous solution was evaporated to dryness under reduced pressure and the residue was extracted with alcohol. Evaporation of the alcohol under reduced pressure left a white residue which upon several recrystallizations from a 50 percent mixture of ether and alcohol melted at 81-81.5°. The product was identified as acetamide. A mixed melting with reagent acetamide gave no appreciable decrease in melting point (80.5-81°).

REACTION OF POTASSIUM HYPOBROMITE WITH DIACETAMIDE

(molar ratio 2:1)

The same reaction conditions were used as mentioned above with the exception that the quantity of hypobromite used was doubled. Upon the addition of diacetamide, the solution was stirred for an additional five minutes and then extracted with 30 ml. of chloroform. The chloroform layer was dried

and filtered by gravity through a fluted filter paper. An equal amount of n-hexane was added and the solution was cooled to 0° for 12 hours. Crystals of N-bromoacetamide deposited which melted at 104-105°. Yield 3.49 gm. (52 %).

Anal. Calcd. for C_2H_4ONBr: Br, 57.91 %.

Found: Br, 57.78 %.

REACTION OF ALKALINE HYPOBROMITE WITH DIACETAMIDE

A 100 ml. three-necked flask was fitted with a reflux condenser, a nitrogen inlet tube, and a separatory funnel. The condenser was connected to a trap containing 1N hydrochloric acid. In the flask, 21.84 gm. of 50 percent potassium hydroxide solution was placed and cooled to 0°. Nitrogen was bubbled through the alkaline solution at a very slow rate and 2.64 ml. of bromine was added dropwise followed by 5.122 gm. of diacetamide. The reaction mixture was stirred for an additional five minutes. The temperature of the solution was raised slowly to 65-70° and maintained for two hours. The acid solution in the trap was then carefully evaporated to dryness on a steam bath and the residue was thoroughly dried in a vacuum dessicator. The product was recrystallized twice from alcohol depositing as leaflets melting at 225-226°. Yield 1.09 gm. Neutralization of the product with standard sodium hydroxide confirmed its identification as methylamine hydrochloride.

Anal. Calcd. for CH_6NCl: M.W., 67.52

Found: M.W., 67.51.

PREPARATION OF DIBENZAMIDE

In a 1-liter flask, 121 gm. (1.0 mole) of benzamide was dissolved in 605 gm. of pure pyridine and cooled to 0°. Benzoyl chloride (140.5 gm.) was added to the pyridine solution at such a rate that the temperature of the reaction mixture did not rise above 5°. The resulting deep red solution which gradually deposited crystals of pyridine hydrochloride was left in an ice-bath for eight hours. The solution was shaken with 3 to 4 times its volume of water in order to remove most of the pyridine. An oil separated which was extracted with 150 ml. of ether. The ethereal extract was washed several times with 50 ml. portions of 2N H_2SO_4 to remove the final traces of pyridine. White needles of dibenzamide separated out and were filtered off. The excess ether was distilled and an oily residue remained which soon crystallized yielding more dibenzamide. The original aqueous solution on standing deposited also a further crop of dibenzamide. The total quantity recovered was nearly equivalent to the theoretical yield. The pure dibenzamide melted at 148°.

SILVER SALT OF DIBENZAMIDE

Twenty-five grams (0.11 mole) of dibenzamide was

added to an ice-cold 50 ml. solution containing 4.0 gm. (0.1 mole) of sodium hydroxide. The mixture was shaken until most of the dibenzamide had dissolved, then the excess was filtered off. On treatment with a slight excess of 5 percent silver nitrate, a grey-white precipitate of silver dibenzamide deposited which was collected at the suction pump. It was thoroughly dried overnight at 100°.

REACTION OF BROMINE WITH SILVER DIBENZAMIDE

Sixteen grams (0.048 mole) of the silver salt was suspended in 150 ml. of anhydrous chloroform and cooled to 0°. To the cold solution, 7.7 gm. (0.048 mole) of bromine was added dropwise. An immediate precipitate of silver bromide was obtained and filtered off. The chloroform solution was pale yellow in color but rapidly turned dark red. On distillation of the excess chloroform under reduced pressure in a nitrogen atmosphere red crystals remained which immediately decomposed with the evolution of bromine.

REACTION OF POTASSIUM HYPOBROMITE WITH DIBENZAMIDE AT 0°

Five grams (0.022 mole) of dibenzamide was dissolved in an ice-cold solution of 13 gm. of 10 percent potassium hydroxide. To the alkaline solution, 3.5 gm. (0.022 mole) of bromine was added dropwise over a period of ten

minutes. The reaction mixture was stirred for an additional two minutes until the solution became clear. The aqueous solution was extracted with three 25 ml. portions of ether and then was kept at 0° overnight.

The ether layer was dried and the excess ether distilled off. The residue, on recrystallization from water, deposited white needles of benzoic acid melting at 120-121°.

The aqueous layer turned dark brown in color and the dark precipitate which settled out was filtered off. It was identified after purification as more benzoic acid. The aqueous filtrate gave a violet color with $Ca(OCl)_2$ indicating aniline or an aniline derivative. Subsequent extraction with ether gave benzamide (m. p. 129°) and only a few milligrams of aniline.

REACTION OF POTASSIUM HYPOBROMITE WITH DIBENZAMIDE AT 40°

In a 100 ml. flask was placed 22.5 gm. (0.1 mole) of dibenzamide and 56 gm. of 10 percent potassium hydroxide. The solution was cooled to 0° and 16 gm. (0.1 mole) of bromine was added dropwise with rapid stirring. The reaction mixture became yellow in color and was extracted continuously with ether for one hour. The ethereal layer turned dark red as the extraction proceeded. The layers were separated and the ether layer (A) was washed with two 15 ml. portions of 5 percent sodium hydroxide which were subsequently combined

with the original aqueous solution (B).

Acidification of the aqueous solution (B) with 5 percent HCl deposited benzoic acid which was filtered off and recrystallized from water. Yield 7.89 gm.

The ethereal solution (A) above was washed with three 15 ml. portions of 5 percent HCl. The acidic washings were combined, neutralized with alkali, and extracted with ether (C). The ethereal solution (C) was distilled and aniline was collected at 182-184°. Yield 0.54 gm. (6%).

Distillation of the ether solution (A) left a white residue which was identified as benzamide. It was recrystallized from a mixture of petroleum ether and benzene depositing as white needles melting at 129-130°. Yield 8.04 gm. (66.5%).

The reaction above was repeated once more in the presence of a five fold excess of 10 percent potassium hydroxide and the time of the ether extraction was increased to three hours. The ether layer was separated off and the aqueous solution was warmed to 70° for 20 minutes. It was extracted with 50 ml. of ether and the ethereal solutions were combined and dried over magnesium sulphate. The excess ether was distilled off and the residue was distilled at atmospheric pressure. The aniline fraction was collected at 184-185°. Yield 7.62 gm. (82%).

The aqueous layer was acidified with 5 percent HCl and benzoic acid deposited in a yield of 11.1 gm. (91%).

METHYLSUCCINIC ACID

To 114 gms. (1.0 mole) of ethyl crotonate in 460 ml. of 95 percent ethanol was added a solution of 54 gm. (1.06 mole) of 95 percent sodium cyanide in 128 ml. of water. The solution was refluxed under stirring for five hours. A suspension of 150 gm. of barium hydroxide octahydrate in 286 ml. of hot water was added and the reaction mixture concentrated under reduced pressure to a volume of 400 ml. The mixture was again refluxed for five hours on a steam bath, then poured into a large porcelain evaporating dish and evaporated on a steam bath to a thick paste. The residue was cooled, dissolved in 171 ml. of nitric acid, (s.g. 1.4) and the resulting solution, under constant agitation, was evaporated to dryness. The residue was ground up fine and extracted in a Soxhlet extractor with 500 ml. of ether for several hours. Benzene (100 ml.) was added to the ethereal solution, and the excess ether distilled off. On cooling, methylsuccinic acid crystallized out of the benzene solution. The acid was filtered by suction, washed with 100 ml. of chloroform, and dried in air. The yield of methylsuccinic acid was 112 gm. and it melted at 110-111°.

METHYLSUCCINIMIDE

A mixture of 20 gm. of methylsuccinic acid and 20 gm. of concentrated aqueous ammonia solution was heated on an oil bath to 100°, until all the excess ammonia solution had been evaporated. The residue was heated to 210° until all fumes of ammonia had ceased to be evolved. The reaction mixture was cooled and extracted with 25 ml. of absolute alcohol. The alcoholic solution was filtered and the excess alcohol distilled off. The solid residue was sublimed at 70-75°/3 mm. White needles of pure methylsuccinimide was obtained, melting at 66°. Yield 15.5 gm.

2,2-DIMETHYLSUCCINIC ACID

Fifty grams (63 ml.) of pure dry acetone, 50 gm. (47 ml.) of ethyl cyanoacetate, and 0.5 gm. of piperidine were placed in a 500 ml. flask provided with a reflux condenser. The reaction mixture was allowed to stand 60 hours at room temperature and then was heated on a steam bath for 2 hours. The solution became dark brown in color. The cold reaction mixture was treated with 100 ml. of ether and washed with 100 ml. of 2N hydrochloric acid, followed by two 50 ml. portions of water. The ethereal solution was dried over anhydrous magnesium sulfate. It was distilled under reduced pressure and the ethyl isopropylidenecyanoacetate

collected at 114-116/14 mm. in a 55 gm. yield.

Forty grams of the ester was dissolved in 100 ml. of alcohol and intimately mixed with 40 ml. of water containing 19.2 gm. of potassium cyanide. The reaction mixture was allowed to stand 48 hours at the end of which time the excess alcohol was distilled off. Concentrated hydrochloric acid (600 ml.) was added to the residue and the whole mixture was refluxed until all the residue had dissolved (12 hours). The acidic solution was evaporated to dryness. The residue was ground up fine and placed in a Soxhlet extractor. It was extracted with ether for several hours. Subsequent distillation of the ether solution left a white reidue of 2,2-dimethylsuccinic acid which was recrystallized from concentrated hydrochloric acid. On cooling 17.3 gm. of the dibasic acid deposited as white needles which melted at 141-142°.

2,2-DIMETHYLSUCCINIMIDE

Twenty-five grams of 2,2-dimethylsuccinic acid was dissolved in 150 ml. of concentrated aqueous ammonia and the resulting solution was evaporated to dryness. The white residue was heated to 210° until all the ammonia had been driven off. The black residue was extracted with 10 ml. of absolute methanol and filtered. The methanol was evaporated off on a steam bath. The residue which sublimed

at 106-107° was collected and recrystallized from water. The imide crystallized in white needles which melted at 106°. Yield 21.1 gm. (84.4%).

2,3-DIMETHYLSUCCINIC ACID

To a solution of sodium ethoxide prepared from 27.6 gm. of sodium and 337 gm. of absolute alcohol was added 137 gm. of ethyl cyanoacetate. Ethyl α-bromopropionate (202 gm.) was added dropwise to the mixture with vigorous stirring. The reaction mixture was heated for one hour on a steam bath during which time sodium bromide precipitated out of the alcoholic solution. After cooling, it was diluted with 800 ml. of water and the oil which separated was extracted with ether. The ethereal solution was washed with sodium hydroxide and dried over magnesium sulphate. The diethyl α-cyano-β-methylsuccinate was distilled under reduced pressure and collected at 160°/22 mm. Yield 224 gm.

128.5 gm. of the product was dissolved in 180 gm. of absolute methanol. To the alcoholic solution, 5.75 gm. of sodium was added dropwise with strong external cooling. The resulting solution was heated on a water bath for one hour, cooled, diluted with 300 ml. of water, and the excess alcohol distilled off under reduced pressure. The aqueous solution was extracted with three 100 ml. portions of ether

and the ether extract was subsequently washed with 5 percent thiosulfate and 5 percent sodium bicarbonate solutions respectively. It was dried over magnesium sulfate. The excess ether was distilled off and the residue, diethyl 2-cyano-2,3-dimethylsuccinate, distilled at 172°/40 mm. Yield 121 gm.

The substituted succinate was placed in a two liter flask and refluxed with 1280 gm. of concentrated hydrochloric acid for 12 hours. A little decolorizing charcoal was added and the hot solution was filtered at the vacuum pump. On cooling white needles of DL-2,3-dimethylsuccinic acid deposited. The acid was filtered off and recrystallized twice from water, m.p. 208.5-209°. The acid filtrate was evaporated to dryness on a steam bath and the residue recrystallized from concentrated hydrochloric acid. White needles of meso-2,3-dimethylsuccinic acid crystallized out which melted after two further recrystallizations from benzene at 127-127.5°.

DL-2,3-DIMETHYLSUCCINIMIDE

Thirty grams of the high melting dibasic acid was dissolved in 75 ml. of concentrated aqueous ammonia and the excess water and ammonia distilled off. The residual ammonium salt was heated to 210° until all fuming ceased. On cooling, the residue was extracted with 20 ml. of methanol containing a little decolorizing charcoal. The alcohol

solution was filtered and the excess methanol distilled off on a steam bath. The residue was sublimed and the imide was collected at 110-115°/1 mm. The sublimate melted at 85-87°. On recrystallization from water, 23.3 gm. of 2,3-dimethylsuccinimide was obtained which melted at 109-110°.

The low melting meso-2,3-dimethylsuccinic acid was treated with ammonia as above under the same reaction conditions. The imide which was formed was identical to the product obtained from DL-2,3-dimethylsuccinic acid.

PHENYLSUCCINIC ACID

To a solution of 113 gm. (1 mole) of ethyl cyanoacetate in 275 ml. of 60 percent ethanol was added 106 gm. (1 mole) of benzaldehyde followed by 3 ml. of piperidine. During the addition the temperature of the solution slowly rose to 60°. When the reaction mixture had cooled to room temperature (25°), it was diluted with 100 ml. of water, and 56 gm. of potassium cyanide was added portionwise over a period of twenty minutes. Stirring was continued until a clear deep red solution was obtained. After dilution with 800 ml. of water, the mixture was acidified to Congo red with concentrated hydrochloric acid. The acidic solution was stirred until all the oil which had separated on acidification had solidified. The aqueous solution was decanted

and the residue taken up in 1600 ml. of concentrated hydrochloric acid. The acidic solution was refluxed for 12 hours, filtered hot, and allowed to cool slowly. White needles (163.7 gm.) of phenylsuccinic acid melting at 167° deposited and was filtered at the suction pump.

PHENYLSUCCINIMIDE

A mixture of 100 gm. of phenylsuccinic acid and 150 gm. of concentrated aqueous ammonia solution was heated on an oil bath to 100°, until all the excess ammonia solution had been evaporated. The residue was heated to 215° until all fumes of ammonia had ceased. On cooling, the residue was extracted with 25 ml. of absolute ethanol. The excess ethanol was distilled off on a steam bath and the solid reidue recrystallized from 1500 ml. of water containing 20 ml. of acetic acid. White needles of phenylsuccinimide deposited melting at 90.5-91°. Yield 44.5 gm.

N-CHLORO-2-METHYLSUCCINIMIDE

Methylsuccinimide (2.0 gm.) was added to an ice-cold solution of 1.56 gm. of sodium hydroxide in 10 ml. of distilled water; 15 gm. of crushed ice was added and 1.38 gm. of chlorine gas was passed through the solution at such a rate that the temperature of the reaction mixture did not

rise above 5°. The precipitate which formed was filtered off and washed with 5 ml. of cold water. It was dried thoroughly in a vacuum dessicator over P_2O_5. The dry N-chlorosuccinimide was recrystallized twice from a mixture of chloroform and n-hexane, depositing as fine white needles melting at 106-107°. Yield 1.7 gm.

Anal. Calcd. for $C_5H_6O_2NCl$: Cl, 24.02%.

Found: Cl, 23.89%.

N-BROMO-2-METHYLSUCCINIMIDE

A solution of 3.9 gm. sodium hydroxide in 16 ml. of water was placed in a 100 ml. flask and cooled to 0°. Five grams of methylsuccinimide was carefully added followed by 1.75 gm. of bromine. The solution was stirred rapidly during the addition and continued for two minutes more. The reaction mixture was filtered immediately and the precipitate of N-bromo-2- methylsuccinimide was washed with 15 ml. of cold water to remove any inorganic material. It was recrystallized twice from 4 ml. of water, depositing as white needles which melted sharply at 145.5°. Yield 6.51 gm.

Anal. Calcd. for $C_5H_6O_2NBr$: Br, 41.66%.

Found: Br, 41.52%.

SILVER SALT OF 2-METHYLSUCCINIMIDE

2-Methylsuccinimide (5 gm.) was dissolved in 250 ml. of boiling water. To the hot solution, 6.25 gm. of freshly prepared silver oxide was added and the reaction mixture was filtered at the suction pump. The filtrate was cooled to 0° and white crystals of silver 2-methylsuccinimide deposited. Yield 9.3 gm.

N-IODO-2-METHYLSUCCINIMIDE

In a 50 ml. flask, surrounded by an ice-bath and fitted with a mechanical stirrer, 3.4 gm. (0.132 mole) of iodine was dissolved in 25 ml. of anhydrous ethyl acetate. To the cold solution, 3 gm. (0.136 mole) of silver 2-methylsuccinimide was added portionwise and the stirring was continued at 0° for 30 minutes. The solution turned pale yellow and the silver iodide which deposited was filtered off. The excess ethyl acetate was distilled off and the yellow residue containing N-iodo-2-methylsuccinimide was recrystallized three times from benzene as fine white needles melting at 134-135°. Yield 2.8 gm.

Anal. Calcd. for $C_5H_6O_2NI$: I, 53.10%.

Found: I, 52.96%.

Solubility

Soluble in dioxane, chloroform, carbon tetrachloride and acetone.

Insoluble in hexane, cyclohexane, and benzene.
Decomposes in water, alcohol, and hot ethyl acetate.

REACTION OF N-BROMO-2-METHYLSUCCINIMIDE WITH METHYL CROTONATE

In a 50 ml. round-bottom flask, fitted with a reflux condenser, was placed 1.97 gm. (0.01 mole) of N-bromo-2-methylsuccinimide in 10 ml. of pure anhydrous carbon tetrachloride. To the mixture, 1.15 gm. (0.01 mole) of methyl crotonate was added and the solution was refluxed for six hours on a steam bath. As the reaction proceeded, methylsuccinimide precipitated out of the solution. The reaction mixture was cooled and filtered. The excess carbon tetrachloride was distilled off and the residual ester was distilled. Methyl γ-bromocrotonate was collected at 86-87°/15 mm. Yield 1.6 gm.

N-CHLORO-2,2-DIMETHYLSUCCINIMIDE

In a 100 ml. flask, 12.6 gm. (0.1 mole) of 2,2-dimethylsuccinimide was dissolved in a solution containing 11.2 gm. (0.20 mole) of potassium hydroxide dissolved in 30 ml. of water. The alkaline solution was cooled to 0° and 7.1 gm. of chlorine gas was passed through the reaction mixture. A white frothy precipitate formed which was filtered immediately at the suction pump and washed with 12 ml. of cold

water. The residue was recrystallized twice from 5 ml. of hot water. On immediate strong cooling, white needles of N-chloro-2,2-dimethylsuccinimide deposited which melted when pure at 109-110°. Yield 2.62 gm.

Anal. Calcd. for $C_6H_8O_2NCl$: Cl, 21.94%.

Found: Cl, 21.87%.

N-BROMO-2,2-DIMETHYLSUCCINIMIDE

In a 25 ml. flask containing 8 ml. of water was placed 1.8 gm (0.032 mole) of potassium hydroxide followed by 2 gm. (0.016 mole) of 2,2-dimethylsuccinimide. The alkaline solution was cooled to 0°, 2.56 gm. (0.016 mole) of bromine was quickly added, and the resulting mixture was stirred for an additional two minutes. The solution, which had become a pale yellow slush, was filtered and the residue washed with two 10 ml. portions of cold water. The residue was dissolved in a 50 ml. solution of boiling water which was then immediately filtered and cooled in an ice-bath. White needles of N-bromo-2,2-dimethylsuccinimide separated out melting at 164-164.5°. Yield 2.45 gm.

Anal. Calcd. for $C_6H_8O_2NBr$: Br, 38.83%.

Found: Br, 38.65%.

SILVER SALT OF 2,2-DIMETHYLSUCCINIMIDE

An excess of freshly prepared silver oxide (6.5 gm.) was added to a solution of 50 ml. of boiling water containing 5 gm. of 2,2-dimethylsuccinimide. The solution was filtered hot at the suction pump and kept at 0° for forty-eight hours. Crystals of the silver salt deposited and were filtered off. The salt was thoroughly dried over P_2O_5 in a vacuum dessicator. Yield 9.1 gm.

N-IODO-2,2-DIMETHYLSUCCINIMIDE

In a 50 ml. flask surrounded by an ice-bath and fitted with a mechanical stirrer was placed 1.76 gm. (0.007 mole) of iodine and 15 ml. of anhydrous ethyl acetate. To the iodine solution, 1.17 gm. (0.007 mole) of the silver salt of 2,2-dimethylsuccinimide was added carefully so that the temperature remained constant and the entire mixture was stirred for an additional 60 minutes. The solution was filtered by gravity through a fluted filter paper and the residue was washed with 5 ml. of ethyl acetate. The acetate solutions were combined and evaporated to dryness under reduced pressure. A white residue remained which was recrystallized from benzene. The N-iodo-2,2-dimethylsuccinimide melted when pure at 163-165° and was soluble in nearly all organic solvents.

Anal. Calcd. for $C_6H_8O_2NI$: I, 50.17%.
Found: I, 50.04%.

N-CHLORO-DL-2,3-DIMETHYLSUCCINIMIDE

In a 50 ml. flask, 6.3 gm. (0.05 mole) of DL-2,3-dimethylsuccinimide was added to a solution containing 5.6 gm. (0.10 mole) of potassium hydroxide dissolved in 15 ml. of distilled water. The solution was cooled to 0°, 15 gm. of crushed ice was added and 3.6 gm. of chlorine gas was passed through the reaction mixture. The precipitate which formed was filtered off and washed with 5 ml. of cold water. It was dried in a vacuum dessicator then recrystallized twice from 5 ml. of hot water. On immediate strong cooling, 2.4 gm. of N-chloro-DL-2,3-dimethylsuccinimide deposited which melted at 124-125°.

Anal. Calcd. for $C_6H_8O_2NCl$: Cl, 21.94%.
Found: Cl, 21.81%.

N-BROMO-DL-2,3-DIMETHYLSUCCINIMIDE

Bromine (2.52 gm.) was added quickly to an ice-cold aqueous solution containing 1.78 (0.03 mole) of potassium hydroxide and 2.0 gm. (0.015 mole) of 2,3-dimethylsuccinimide. The solution was stirred for several minutes. An orange precipitate deposited which was filtered off and washed with

25 ml. of cold water. The N-bromo derivative was recrystallized twice from water as very pale yellow needles melting at 160-161.5°. Yield 1.96 gm.

Anal. Calcd. for $C_6H_8O_2NBr$: Br, 38.83%.

Found: Br, 38.71%.

SILVER SALT OF DL-2,3-DIMETHYLSUCCINIMIDE

Five grams of 2,3-dimethylsuccinimide was dissolved in 100 ml. of boiling water. An excess of silver oxide (6.5 gm.) was added and the solution was filtered. The filtrate was cooled to 0° for twenty-four hours and white crystals of silver 2,3-dimethylsuccinimide deposited. Yield 8.0 gm.

N-IODO-DL-2,3-DIMETHYLSUCCINIMIDE

Two grams of iodine was dissolved in 15 ml. of anhydrous ethyl acetate and the solution was placed in a 50 ml. flask which was surrounded by an ice-bath and fitted with a mechanical stirrer. To the cold solution, 1.30 gm. of the silver salt of 2,3-dimethylsuccinimide was added carefully so that the temperature remained constant. The reaction mixture was stirred for sixty minutes and filtered. The residue was washed with 10 ml. of ethyl acetate. The ethyl acetate solutions were combined and evaporated to

dryness under reduced pressure. The iodo derivative was recrystallized twice from benzene depositing as white needles which melted at 181-182°. Yield 2.01 gm.

Anal. Calcd. for $C_6H_8O_2NI$: I, 50.17%.

Found: I, 50.07%.

N-CHLORO-2-PHENYLSUCCINIMIDE

In a 100 ml. flask was placed 2.1 gm. (0.038 mole) of potassium hydroxide in 10 ml. of water, 15 gm. of crushed ice, and 3.4 gm. (0.019 mole) of phenylsuccinimide. The flask was surrounded by an ice-bath so as to maintain the temperature of the solution at 0°. A stream of chlorine gas was passed through the solution and the precipitate which deposited was filtered at the suction pump. The residue was washed with 25 ml. of cold water and dried in a vacuum desiccator over P_2O_5. It was recrystallized twice from a 50 percent mixture of chloroform and n-hexane. N-Chloro-2-phenylsuccinimide deposited as white needles melting at 105-106°. Yield 2.6 gm.

Anal. Calcd. for $C_{10}H_8O_2NCl$: Cl, 16.92%.

Found: Cl, 16.72%.

Soluble in chloroform and benzene. Insoluble in n-hexane.

N-BROMO-2-PHENYLSUCCINIMIDE

To 14 ml. of a 10 percent solution of potassium hydroxide containing 4 gm. of 2-phenylsuccinimide, 3.6 gm. of bromine was added with vigorous stirring. The agitation was continued for five minutes more and the solution was filtered at the suction pump. The aqueous solution was extracted with chloroform and the latter layer was dried over $MgSO_4$. The excess chloroform was distilled off under reduced pressure and a yellow semi-crystalline substance remained which melted at 115-120°. All attempts to crystallize it failed. It liberated iodine from an acidic solution of potassium iodide. On standing in air, the bromo derivative rapidly decomposed.

Soluble in alcohol, benzene, chloroform, acetone and dioxane. Insoluble in water and petroleum ether.

REACTION OF POTASSIUM HYPOBROMITE WITH METHYLSUCCINIMIDE AT 60-65°

In a one-liter three-necked flask fitted with a mechanical stirrer was placed 15.1 gm. of potassium hydroxide and 225 ml. of water. The solution was cooled to 0° and 2.56 ml. of bromine was added dropwise with rapid stirring. To the cold hypobromite solution, 5.7 gm. of pure methylsuccini-

mide was introduced portionwise at such a rate that the temperature of the solution did not rise above 5°. The mixture was stirred until all the imide had dissolved and then was slowly warmed to 60-65° for two hours. The solution was cooled to room temperature and acidified to Congo red with concentrated hydrochloric acid (s.g.1.18). The acidic solution was evaporated to dryness under reduced pressure. The residue was extracted with 83 ml. of warm 95 percent ethanol, filtered, and the undissolved inorganic salts washed with 17 ml. of cold 95 percent ethanol. The alcoholic filtrates were combined and evaporated to dryness under reduced pressure. The residue once more was extracted with 15 ml. of warm absolute ethanol, filtered, and the ethanol solution evaporated to dryness under reduced pressure. A yellow oil (D) remained. It was dissolved in 16 ml. of water and refluxed for two hours. On cooling another yellow oil (E) separated which was extracted from the aqueous solution with ether. The ethereal solution was dried over $MgSO_4$ and the excess ether distilled off. The residual oil was esterified with 20 ml. of absolute ethanol in the presence of 0.5 gm. of concentrated H_2SO_4 (98%). The solution was heated on a water bath for two hours, then poured into 40 ml. of water. The ester was extracted with three 10 ml. portions of ether and dried over $MgSO_4$. The excess ether was distilled off and the residue distilled under reduced pressure. The fraction (F)

distilling at 105°/16 mm. was collected and identified as diethyl methysuccinate. Yield 3.7 gm.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.42; H, 8.57%.

Found: C, 57.63; H, 8.48%.

Diethyl methysuccinate was hydrolyzed with dilute hydrochloric acid and methylsuccinic acid was obtained, m.p. 110-111°.

The aqueous solution from the ether extraction above was diluted to 80 ml. and a suspension of freshly prepared silver oxide was added. It was stirred well and allowed to stand overnight. The silver salt was filtered and washed with water. Hydrogen sulphide was bubbled through the aqueous filtrate until all the silver sulphide had precipitated. It was filtered off and the aqueous layer concentrated down on a steam bath to a volume of 16 ml. Charcoal was added and the mixture filtered. Evaporation of the aqueous solution produced a yellow viscous oil which could not be distilled nor crystallized. Yield 212 mg.

REACTION OF POTASSIUM HYPOBROMITE WITH METHYLSUCCINIMIDE AT 55-60°

The same quantities of bromine, imide and base were used as in the previous experiment. The solution was warmed to 55-60° for two hours. It was then cooled to room

temperature and acidified to Congo red with concentrated hydrochloric acid. The aqueous solution was evaporated to dryness under reduced pressure. The residue was extracted with 80 ml. of warm 95 percent ethanol, filtered, and the alcoholic solution was evaporated to dryness under reduced pressure. A yellow oil (G) remained which was dissolved in 15 ml. of water and refluxed for one hour. The solution was diluted to 83 ml., an excess of freshly prepared silver oxide was added and the reaction mixture was allowed to stand overnight. The precipitated silver chloride was filtered off and washed with 25 ml. of water. The aqueous solution was saturated with hydrogen sulphide and filtered. The filtrate was concentrated down under reduced pressure. A dark yellow oil (H) remained which was fractionally distilled under reduced pressure. The fraction boiling at 55-60°/2mm. was collected. It decolorized permanganate and solidified on cooling. It melted at 72° on recrystallization from ligroin and was identified as crotonic acid. Yield 2.1 gm.

The residue from the distillation was dissolved in 20 ml. of absolute ethanol and dry hydrogen chloride gas was passed through the solution. The reaction mixture was poured into 50 ml. of water and extracted with ether. The ether layer was dried and distilled under reduced pressure. Diethyl methylsuccinate distilled over at 105°/16 mm. Yield 1.3 gm.

REACTION OF POTASSIUM HYPOBROMITE WITH METHYLSUCCINIMIDE AT 50-55°

The same quantities of starting materials were used as in the previous experiments. The solution, however, was only warmed to 50-55° for two hours and on cooling was acidified to p.H. 3 with concentrated hydrochloric acid. The solution was evaporated to dryness under reduced pressure. The residue was extracted with 80 ml. of ethanol and evaporated to dryness. The residue from the alcoholic extraction was dissolved in 50 ml. of absolute ethanol and dry hydrogen chloride gas passed through the solution. The excess alcohol was distilled off and a colorless liquid distilled over at 125-130°/38 mm. which was characterized as ethyl crotonate.

A yellow viscous oil (I) remained which was dissolved in 5 ml. of water, cooled to 0°, and neutralized to p.H. 5.8 with 33 percent sodium hydroxide. The solution was extracted with three 10 ml. portions of ether. The ether extracts were combined and dried over $MgSO_4$. The ether was distilled off and the residue distilled under reduced pressure. A colorless liquid (0.81 gm.) was collected at 64-65°/15 mm. which was identified as ethyl β-aminobutyrate.

The ester was hydrolyzed with dilute hydrochloric acid and a yellow oil (J) was isolated which could not be crystallized nor distilled. It did, however, form a copper complex with $CuCO_3$ indicating the presence of β-aminobutyric acid.

REACTION OF POTASSIUM HYPOBROMITE WITH METHYLSUCCINIMIDE AT 40-45° (HOFMANN REARRANGEMENT)

In a 200 ml. three-necked flask, fitted with a mechanical stirrer, was placed 3.33 gm. (0.072 mole) of potassium hydroxide in 90 ml. of water. The solution was cooled to 0° and 1.98 gm. (0.018 mole) of bromine was added dropwise. Two grams of methylsuccinimide was added portionwise and the reaction was stirred until all the imide had gone into solution. The mixture was warmed to 40° for two hours until a negative test was given for the presence of hypobromite. The solution was cooled and titrated with 1N hydrobromic acid to pH 5.82. The solution was evaporated to dryness under reduced pressure and the dry residue was extracted with 25 ml. of warm methanol. The alcoholic solution was filtered, the residue washed with 5 ml. of cold methanol, and the methanolic solution was evaporated to dryness under reduced pressure. A yellow oil (K) remained mixed with a little potassium bromide. The oil was taken up in 15 ml. of methanol, filtered, and the residue washed with 5 ml. of cold methanol. On evaporation of the methanol, 1.52 gm. of impure 3-aminobutyric acid remained as a yellow viscous oil (K).

COPPER SALT OF 3-AMINOBUTYRIC ACID

A few mg. of the yellow oil (K) was dissolved in 3 ml. of water and a slight excess of freshly prepared copper carbonate was added. The solution was thoroughly shaken, heated for two minutes on a steam bath, cooled, and filtered. The blue filtrate was evaporated to dryness under reduced pressure. A blue residue remained which was crystallized from 85 percent ethanol. On rapid heating, it decomposed at 215-217°.

Anal. Calcd. for $C_8H_{16}O_4N_2 \cdot 2H_2O$: C, 31.62; H, 6.63; N, 9.22; Cu, 19.08%.

Found: C, 32.01; H, 6.24; N, 9.12; Cu, 19.02%.

N-BENZOYL-3-AMINOBUTYRIC ACID

A solution of 48.5 ml. of 1N sodium hydroxide was placed in a 250 ml. three-necked flask fitted with a mechanical stirrer and two separatory funnels. The alkaline solution was cooled to 0° and 5 gm. of 3-aminobutyric acid was added portionwise over a period of five minutes. In one separatory funnel was placed 5.6 ml. of pure benzoyl chloride and in the second funnel 24.25 ml. of 2N NaOH. The stirrer was run at such a speed that the solution splashed violently on the sides of the flask. The sodium hydroxide was added to the reaction mixture at a rate four times as fast as the benzoyl

chloride over a period of at least two hours. The solution was stirred for an additional fifteen minutes, then acidified with 5N hydrochloric acid (9.7 ml.) to Congo red. The temperature of the reaction mixture was kept at 0° during the addition of the acid. The benzoyl derivative deposited as a yellow oil and was separated off. The aqueous layer was extracted with three 15 ml. portions of ether. The oil and ether extracts were combined and dried over $MgSO_4$. The ether was distilled off and the residue crystallized twice from 30 ml. of water. N-Benzoyl-3-aminobutyric acid deposited in fine white needles which melted at 154-155°. Yield 8.52 gm.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 63.76; H, 6.37; N, 6.71%.

Found: C, 64.02; H, 6.05; N, 6.68%

Neutral. Equiv.: Calc. 207; found 207.

ATTEMPTED RESOLUTION OF N-BENZOYL-3-AMINOBUTYRIC ACID WITH:

a) d-Methylbenzylamine

In 2 ml. of water, 0.9921 gm. (0.0048 mole) of the benzoyl derivative and 0.6050 gm. (0.0048 mole) of d-methylbenzylamine were added and warmed to 90°. The clear solution was allowed to cool slowly to room temperature, however, no crystallization occurred. The solution was concentrated down 0.25 ml. at a time but at each volume no crystallization took place. A white crystalline residue remained on evaporation to dryness which melted at 139-140°.

Further fractional crystallizations were attempted using as solvent: ethanol, methanol, acetone, dioxane, and ethyl acetate. In every case the same result as for water was obtained.

b) d-Brucine

In 5 ml. of water, 2.5023 gm. (0.0054 mole) of d-brucine and 1.1971 gm. (0.0054 mole) of the benzoyl derivative were dissolved by gentle warming on a steam bath. The solution was cooled to room temperature, however, no crystallization occurred. The solvent was reduced 0.25 ml. at a time without any crystallization. On complete evaporation of the water, a yellow oil remained. Attempts were made to fractionally crystallize it from ethanol, methanol, dioxane, acetone, and ethyl acetate, but negative results were secured in every case.

c) d-Cinchonine

The same procedure was used as above. d-Cinchonine (1.4720 gm.) and 1.0293 gm. of benzoyl derivative were dissolved in 5 ml. of boiling water. The solution was cooled slowly to room temperature, but once again no crystallization took place. Once more the solution was concentrated as above. At a volume of 1.25 ml. a solid solution of the substance was obtained. Attempts were made to fractionate the two

isomers from the following solvents: acetone, dioxane, ethyl acetate, ethanol, and methanol. However, in all cases it was not possible to fractionally crystallize them. The dry mixture of salts melted at 62-64°.

REACTION OF POTASSIUM HYPOBROMITE WITH METHYLSUCCINIMIDE at 25°

The same quantities of starting materials were used as in the preceding experiments. Upon the addition of hypobromite at 0°, the solution was warmed slowly to room temperature and maintained between 23-25° for four hours. The reaction mixture was acidified to Congo red with 1N hydrobromic acid and evaporated to dryness under reduced pressure. The residue was extracted with 25 ml. of methanol, filtered, and the excess methanol was distilled off under reduced pressure. The alcoholic reidue was recrystallized from 25 ml. of distilled water. 3-Methylsuccinamic acid (4.15 gm.) deposited in long white needles melting at 119.5-120°.

Neutral. Equiv. Calcd. for $C_5H_9O_3N$: 131.1

Found: 131.0

HOFMANN REARRANGEMENT OF 2,2-DIMETHYLSUCCINIMIDE

In a 500 ml. flask was placed 10 gm. of potassium hydroxide in 210 ml. of water. The solution was cooled to 0° in an ice bath and 3.7 gm. (0.023 mole) of bromine was added

slowly with vigorous stirring. 2,2-Dimethylsuccinimide (2.9) was added portionwise at such a rate that the temperature of the solution did not rise above 5°. The resulting solution was stirred for an additional fifteen minutes, then slowly warmed to 40°. The temperature was maintained at 40-45° for three hours. On cooling to room temperature, the reaction mixture was acidified to pH 6 with 1N hydrobromic acid. The solution was evaporated to dryness under reduced pressure. The residue was extracted with two 30 ml. portions of hot methanol, filtered, and washed with two 5 ml. portions of cold methanol. The methanolic solution was evaporated to dryness under reduced pressure. The oily residue was dissolved in 10 ml. cold methanol and a large excess of ether was added. Crystals of 3-amino-3- methylbutyric acid separated out and were collected at the suction pump. The amino acid was recrystallized twice from a mixture of methanol and ether (1:2) depositing as white needles melting at 216-216.5°. Yield 2.11 gm. (78%).

Anal. Calcd. for $C_5H_{11}O_2N$: C, 51.26; H, 9.47; N, 11.96%.
Found: C, 51.20; H, 9.51; N, 11.94%.
Neutral. Equiv: Calcd. 117; found 117.

COPPER SALT OF 3-AMINO-3-METHYLBUTYRIC ACID

One gram of the amino acid was dissolved in 5 ml. of water and treated with an excess of copper carbonate. The blue solution was filtered and evaporated to dryness under

reduced pressure over P_2O_5 in a vacuum dessicator. A blue residue remained which was dissolved in a little methanol and the methanol was allowed to evaporate slowly in a vacuum dessicator. The copper salt of 3-amino-3-methylbutyric acid remained as blue crystals which decomposed on heating above 215°.

Anal. Calcd. for $C_{10}H_{20}O_2N_2Cu.\ 2H_2O$: C, 40.60; H, 6.81; N, 9.47; Cu, 21.48%.

Found: C, 40.47; H, 6.88; N, 9.48; Cu, 21.23%.

N-BENZOYL-3-AMINO-3-METHYLBUTYRIC ACID

In a 250 ml. three-necked flask fitted with a mechanical stirrer and two separatory funnels was placed 13 ml. (0.013 mole) of 1N sodium hydroxide. The alkaline solution was cooled to 0° and 5 gm. of 3-amino-3-methylbutyric acid was carefully added so that the temperature of the solution remained at 0°. In one separatory funnel was placed 1.48 ml. of pure benzoyl chloride and in the second funnel 6.5 ml. of 2N sodium hydroxide. The alkali and benzoyl chloride were added with vigorous stirring over a period of two hours. The sodium hydroxide was run in at a rate four times as fast as that of the benzoyl chloride. The solution was stirred for an additional fifteen minutes, then acidified with 5N hydrochloric acid to Congo red. The benzoyl derivative

deposited as a gummy semi-solid and was filtered off. The crude N-benzoyl-3-amino-3-methylbutyric acid was dried under reduced pressure in a vacuum dessicator, then recrystallized twice from water. It deposited as white needles melting 140-141°.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.13; H, 6.83; N, 6.33%.
Found: C, 65.00; H, 6.88; N, 6.37%.
Neutral. Equiv.: Calcd. 221.2; found 221.0

HOFMANN REARRANGEMENT OF DL-2,3-DIMETHYLSUCCINIMIDE

Three grams (0.023 mole) of DL-2,3-dimethylsuccinimide was added to a cold solution of 9.8 gm. potassium hydroxide in 200 ml. of distilled water. 1.28 gm. (0.023 mole) of bromine was added with vigorous stirring and the agitation was continued for fifteen minutes. The solution was warmed to 40° for three hours, cooled, and acidified with 1N HBr to pH 6. The reaction mixture was evaporated to dryness under reduced pressure. The residue was extracted with 20 ml. of warm absolute methanol and filtered. The undissolved portion of the residue was washed with two 5 ml. quantities of cold absolute methanol. The filtrates were combined and evaporated to dryness under reduced pressure. A yellow oily semi-solid product remained. It was taken up in 5 ml. of methanol and on the addition of 5 ml. of ether, crystals of 3-amino-2-methylbutyric acid deposited. It gave a melting point of 231-232° after three recrystallizations

from a mixture of methanol and ether. Yield 2.23 gm.

Anal. Calcd. for $C_5H_{11}O_2N$: C, 51.25; H, 9.47; N, 11.96%.
Found: C, 51.20; H, 9.51; N, 11.94%.
Neutral. Equiv.: Calc. 117.1; found, 117.0.

COPPER SALT OF 3-AMINO-2-METHYLBUTYRIC ACID

An excess of copper carbonate was added to an aqueous solution containing 200 mg. of the amino acid. The reaction mixture was heated on a steam bath for several minutes and the blue solution formed was filtered. The filtrate was evaporated to dryness under reduced pressure in a vacuum dessicator. The blue residue was dissolved in a little methanol and allowed to evaporate slowly to dryness in a vacuum dessicator over P_2O_5. Blue crystals of the copper salt remained.

Anal. Calcd. for $C_{10}H_{20}O_2N_2Cu \cdot 2H_2O$: C, 40.60; H, 6.81; N, 9.47; Cu, 21.48%.
Found: C, 40.17; H, 6.98; N, 9.45; Cu, 21.31%.

N-BENZOYL-3-AMINO-2-METHYLBUTYRIC ACID

In a 100 ml. three-necked flask fitted with a mechanical stirrer and two separatory funnels was placed 8 ml. of 1N sodium hydroxide. The alkaline solution was cooled to 0° and 1 gm. (0.008 mole) of 3-amino-2-methylbutyric acid was carefully added. In one of the separatory funnels was placed

4 ml. of 2N sodium hydroxide and in the other 0.9 ml. (0.008 mole) of benzoyl chloride. The solution was agitated by a high speed stirrer and the sodium hydroxide was added at a rate four times as fast as the benzoyl chloride over a period of two hours. The solution was stirred for an additional fifteen minutes and acidified to Congo red with 5N hydrochloric acid. The temperature of the solution was kept at 0° during the acidification. The benzoyl derivative which deposited was filtered off and washed with a little ether to remove any benzoic acid which may contaminate the derivative. N-Benzoyl-3-amino-2-methylbutyric acid was recrystallized twice from 10 ml. of water depositing in fine white needles which melted at 160-161°. Yield 5.3 gm.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.13; H, 6.83; N, 6.33%.
Found: C, 65.01, H, 6.65; N, 6.29%.
Neutral. Equiv.: Calcd. 221.2; found 220.8.

HOFMANN REARRANGEMENT OF SUCCINIMIDE AT 40°

Twenty grams of succinimide was dissolved in an ice-cold solution containing 5.6 gm. KOH in 600 ml. of water. To the alkaline solution 10.3 ml. of bromine was added and the reaction mixture was stirred for an additional fifteen minutes. The solution was warmed to 40° for one hour and forty-five minutes and then acidified to pH 6 with 1N hydrobromic acid. The acidic solution was evaporated to dryness. The residue was extracted with 50 ml. hot methanol, filtered,

and then washed with two 10 ml. portions of cold methanol. The alcoholic solutions were combined and evaporated to dryness under reduced pressure. A yellow oil remained (15.2 gm.) which formed a copper salt.

Twelve grams of the oil was dissolved in 110 ml. of 1N NaOH and the solution was cooled to 0°. To the alkaline solution 12.76 gm. of benzoyl chloride and 55 ml. of 2N NaOH were added over a period of two hours. The solution was stirred for an additional fifteen minutes then acidified to Congo red with concentrated hydrochloric acid. The N-benzoyl-3-aminopropionic acid was filtered off and recrystallized from water. It deposited as white needles which melted at 119.5-120°. Yield 25.2 gm. (58%).

REACTION OF POTASSIUM HYPOBROMITE WITH PHENYLSUCCINIMIDE AT 40°

Four grams (0.025 mole) of bromine was added dropwise to an ice cold solution of 11.6 gm. of potassium hydroxide in 105 ml. of water. Phenylsuccinimide (4.0 gm.) was added portionwise over a period of fifteen minutes and the mixture was then warmed to 40-45° for four hours. The solution was cooled to room temperature and acidified to pH 6.0 with 1N hydrobromic acid. The aqueous solution was evaporated to dryness under reduced pressure and the residue extracted with 25 ml. of hot methanol. After filtration, the methanolic

filtrate was evaporated to dryness under reduced pressure. The white residue was recrystallized twice from water and was obtained as fine white needles melting at 158-158.5°. Yield 4.3 gm. It did not form a copper salt with copper carbonate. It did give a picrate which when recrystallized from alcohol melted above 300°. Analysis and reference to the literature (146) characterized the white residue as 3-phenylsuccinamic acid.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 62.16; H, 5.81; N, 7.21%.
Found: C, 62.24; H, 5.54; N, 7.12%.
Neutral. Equiv.: Calcd. 193.2; found 193.1.

HOFMANN REARRANGEMENT OF 3-PHENYLSUCCINAMIC ACID

To a solution of 1.3 gm. (0.022 mole) of potassium hydroxide in 50 ml. of water at 0° was added 0.46 gm. (0.003 mole) of bromine followed by 0.56 gm. (0.003 mole) of phenylsuccinamic acid. When all the acid-amide had dissolved, the solution was warmed slowly to 60° for four hours. The colorless reaction mixture was neutralized, when cool, with 1N hydrobromic acid to pH 6 and then evaporated to dryness under reduced pressure. The residue was extracted with 10 ml. of cold water and filtered. Crystallization of the undissolved residue from 1.5 ml. of water gave 0.306 gm. of 3-amino-3-phenylpropionic acid which melted on rapid heating at 230-231°.

Anal. Calcd. for $C_9H_{11}O_2N$: Neutral. Equiv., 165.2; found: 164.9. Treatment of the amino acid with Ag_2O gave a silver salt which melted at 239°.

Reaction of 3-amino-3-phenylpropionic acid with copper carbonate gave a copper complex salt.

Anal. Calcd. for $C_{18}H_{20}O_4N_2Cu$: Cu, 16.21%. Found: Cu, 16.09%.

REACTION OF POTASSIUM HYPOBROMITE WITH PHENYLSUCCINIMIDE AT 60-65°

A 10 percent solution (90 gm.) of potassium hydroxide was placed in a 250 ml. flask and cooled to 0°. To the cold alkaline solution, 4.8 gm. (0.03 mole) of bromine was added dropwise with rapid stirring, followed by 6 gm. (0.03 mole) of phenylsuccinimide. The solution was stirred at 0° for an additional twenty minutes then slowly warmed to 60-65° for four hours. The reaction mixture was cooled to room temperature and acidified to pH 6 with 1N hydrobromic acid. The solution was evaporated to dryness under reduced pressure and the residue extracted with 25 ml. of hot methanol. Evaporation of the methanolic solution produced a yellow oil which was subsequently redissolved in 50 percent ethanol and a little norite was added. The alcoholic solution was warmed for several minutes and filtered. Upon remaining several days at 0°, white needles of 3-cyano-3-phenylpropionic acid deposited which melted after two recrystallizations from

5 percent alcohol at 149-150°.

Evaporation of the original alcoholic filtrate gave a residue which was identified as phenylsuccinic acid, m.p. 167°.

One gram of 3-cyano-3-phenylpropionic acid was dissolved in 5 ml. (c) H_2SO_4 (98%) and allowed to stand several days at room temperature. The solution was poured into 15 gm. of crushed ice and extracted with three 10 ml. portions of ether. The excess ether was distilled off and the residue recrystallized from water. White needles of 3-phenylsuccinamic acid deposited melting at 158°.

Treatment with dilute alkali converted 3-cyano-3-phenylpropionic acid to phenylsuccinic acid, m.p. 167°.

SUMMARY AND CONTRIBUTION TO KNOWLEDGE

1. In aqueous solution, diacetamide hydrolyzed very easily even at 0° to acetamide and acetic acid. In a solution of potassium hypobromite the rate of hydrolysis of diacetamide was found to be more rapid than bromination, consequently, no N-bromo intermediate was formed. On treatment of dibenzamide with potassium hypobromite, the N-bromo derivative was formed which hydrolyzed immediately to benzoic acid and benzamide. The difference in the reactivity of diacetamide and dibenzamide with potassium hypobromite was attributed to the relative unstability of the former in aqueous solution. The reaction of bromine with silver dibenzamide under anhydrous conditions produced only decomposition products. Therefore, it was concluded that the N-bromo derivative of dibenzamide is relatively unstable and cannot be isolated as a stable product.

2. The procedures for preparing methylsuccinic acid and 2, 2-dimethylsuccinic acid were modified to obtain higher yields of the dibasic acids. The corresponding imides of alkyl substituted succinic acids were obtained in almost quantitative yields. In the purification of the imides, it was found advantageous to sublime them, rather than follow the normal procedure of distillation

under atmospheric conditions.

3. The N-chloro and N-bromo derivatives of alkyl substituted succinimides were prepared by treatment of the imides at 0° with aqueous potassium hypochlorite and potassium hypobromite, respectively. The halogen derivatives which precipitated were filtered off and recrystallized from the appropriate solvents.

The iodo derivatives were obtained by the reaction of iodine with the silver salts of the imides in an anhydrous solvent such as carbon tetrachloride or ethyl acetate.

The following N-halogen succinimides were prepared for the first time.

N-Chloromethylsuccinimide, m.p. 106-107°
N-Bromomethylsuccinimide, m.p. 145.5°
N-Iodomethylsuccinimide, m.p. 134-135°

N-Chloro-2,2-dimethylsuccinimide, m.p. 109-110°
N-Bromo-2,2-dimethylsuccinimide, m.p. 164-164.5°
N-Iodo-2,2-dimethylsuccinimide, m.p. 163-165°

N-Chloro-DL-2,3-dimethylsuccinimide, m.p. 124-125°
N-Bromo-DL-2,3-dimethylsuccinimide, m.p. 160-161.5°
N-Iodo-DL-2,3-dimethylsuccinimide, m.p. 181-182

N-Chloro-2-phenylsuccinimide, m.p. 105-106°

4. A general method has been found for the Hofmann rearrangement of methyl substituted succinimides into the corresponding β-amino acids. The characteristics of the method involve the addition of the imide to an ice-cold alkaline solution of potassium hypobromite. The solution is then warmed to 40-45° for several hours in order to

effect rearrangement and acidified to pH 6 with 1N hydrobromic acid. The aqueous solution is evaporated to dryness under reduced pressure and the amino acid is extracted from the residue with absolute methanol.

Methylsuccinimide, 2,2-dimethylsuccinimide, and DL-2,3-dimethylsuccinimide were rearranged to 3-aminobutyric acid, 3-amino-3-methylbutyric acid, and 3-amino-2-methylbutyric acid, respectively. It was observed that, although in the rearrangement of methylsuccinimide and 2,2-dimethylsuccinimide two products were theoretically indicated, only a single product was obtained. Hydrolysis of the imide ring always occurred preferentially at the C-N bond farthest from the substituted carbon atom.

5. DL-erythro-3-amino-2-methylbutyric acid, its benzoyl derivative and copper salt were all prepared for the first time.

6. Phenylsuccinimide would not undergo a Hofmann rearrangement to give the expected β-amino acid in a single step. Failure to obtain the N-bromo and N-iodo derivatives was attributed to the relatively large size of the phenyl group in comparison to the imide ring leading probably to steric hindrance.

However, the rearrangement was accomplished by initially hydrolyzing the imide to 3-phenylsuccinamic acid which in turn was smoothly converted to 3-amino-3-phenylpropionic acid.

BIBLIOGRAPHY

1. Patterson, A. M., Capell, L. T., and Magill, M. A., Chem. Abstracts 41, 5875 (1945).
2. Titherley, A. W., J. Chem. Soc. 79, 411 (1901).
3. Tarbouriech, A., Compt. rend. 137, 128 (1904).
4. Gautier, A., Compt. rend. 67, 1256 (1869).
5. Colby, C. E., and Dodge, F. D., Am. Chem. J. 13, 1 (1891).
6. Norstedt, C. and Wahlforss, H. A., Ber. 25, 637 (1892).
7. Polya, J. B. and Tardrew, P. L., J. Chem. Soc. 1081 (1948).
8. Krafft, F., Ber. 23, 2389 (1890).
9. Badoche, M. M., Compt. Rend. 216, 62-4 (1943).
10. Titherley, A. W. and Stubbs, L., J. Chem. Soc. 105, 299 (1914).
11. Hentschel, W., Ber. 23, 2395 (1890).
12. Hofmann, A. W., Ber. 14, 2725 (1881).
13. Seliwanow, T., Ber. 25, 3617 (1892).
14. Seliwanow, T., Ber. 26, 423 (1893).
15. Francois, M., Compt. rend. 148, 173 (1909).
16. Boismenu, E., Compt. rend. 153, 1482 (1912).
17. Boismenu, E., Compt. rend. 153, 878 (1912).
18. Boismenu, E., Compt. rend. 153, 948 (1912).
19. Eckert, P., Herr, E. and Wilczkawiak, V., Reyon Synthetica, Zellwolle 29, 2 (1951). Chem. Abstracts 45, 7527 (1951).
20. Stieglitz, J. and Earle, P., Am. Chem. J. 30, 420 (1908).
21. Barth, L. and Senhofer, C., Ber. 9, 977 (1876).

22. Longfeld, F. and Stieglitz, J., Am. Chem. J. 15, 215, 504 (1892).

23. Ziegler, K., Spath, A., Schaaf, E., Schumann, W., and Winkelmann, E., Ann. 551, 80 (1942).

24. Lamchen, M., J. Chem. Soc. 747 (1950).

25. Tafel, J. and Stern, M., Ber. 33, 2224 (1900).

26. Tafel, J. and Wassmuth, O., Ber. 40, 2831 (1907).

27. Bunge, N., Ann. 7, 117 (1870). (Supplement).

28. Djerassi, C., and Lenk, C. T., J. Am. Chem. Soc. 75, 2493 (1953).

29. Waters, W. A., J. Chem. Soc. 1551 (1933).

30. Lenorment, H., Bull. Soc. chim. France, 33-46 (1948).

31. Wohl, A., Ber. 52, 51 (1919).

32. Wohl, A., and Jaschinowski, K., Ber. 54, 476 (1921).

33. Francesconi, L. and Recchi, V., Gazz. Chim. Ital. 32, I, 45 (1902).

34. Djerassi, C., Chem. Rev. 43, 271 (1948).

35. Meystre, C. and Wettstein, A., Helv. Chim. Acta. 30, 1256 (1947).

36. Waters, W. A., Nature 154, 772 (1944).

37. Farmer, E. H., Trans. Faraday Soc. 38, 340 (1942).

38. Hey, D. H., Nature 156, 36 (1945).

39. Bloomfield, G. F., J. Chem. Soc. 114 (1944).

40. Robertson, A. and Waters, W. A., J. Chem. Soc. 492 (1947).

41. Djerassi, C. and Scholz, C. R., Experimentia 3, 107 (1947).

42. Schmid, H., Helv. Chim. Acta. 29, 1144 (1946).

43. Winstein, S. and Lucas, H. J., J. Am. Chem. Soc. 61, 1576 (1939).

44. Djerassi, C., and Lenk, C. T., J. Am. Chem. Soc. 75, 3494, (1953).

45. Djerassi, C. and Scholz, C. R., J. Org. Chem. 14, 660 (1949).

46. Henne, A. L. and Zimmer, W. F., J. Am. Chem. Soc. 73, 1103 (1951).

47. Orazi, O. O., Novelli, A., and Satellas, J. F., Andes Assoc. quim Argentina 38, No. 137, 12 (1950). Chem. Abstracts 44, 7778 (1950).

48. Bogaert-Verhoogan, D., and Martin, R. H., Bull. soc. chim. belges. 58, 567 (1949).

49. Kruse, P. F., Grist, K. L. and McCoy, T. A., Anal. Chem. 26, 1319 (1954).

50. Hofmann, A. W., Ber. 15, 407 (1882).

51. Hofmann, A. W., Ber. 15, 762 (1882).

52. Hoogewerff, M. S. and Van Dorp, W. A., Rec. Trav. chim. 10, 5 (1891).

53. Hoogewerff, M. S. and Van Dorp, W. A., Rec. Trav. chim. 10, 145 (1891).

54. Hoogewerff, M. S. and Van Dorp, W. A., Rec. Trav. chim. 15, 107 (1896).

55. Hoogewerff, M. S. and Van Dorp, W. A., Rec. Trav. chim. 6, 387 (1887).

56. Turpin, G. S., Ber. 21, 2486 (1888).

57. Lengfeld, F. and Stieglitz, J., Am. Chem. J. 16, 370 (1894).

58. Stieglitz, J., Am. Chem. J. 18, 752 (1896).

59. Jeffreys, E., Am. Chem. J. 22, 14 (1900).

60. Eherstadt, dissertation, Freiburg i. B., 1886. "Organic Reactions" Vol. III, p. 271. J. Wiley and Sons, 1946.

61. Swartz, S. E., Am. Chem. J. 19, 297 (1898).

62. Folin, O., Am. Chem. J. 19, 321 (1898).

63. Rinkes, I. J., Rec. Trav. chim. 39, 704 (1920).

64. Kon, G. A. R., J. Chem. Soc. 224 (1948).

65. Rinkes, I. J., Rec. Trav. chim. 39, 200 (1920).

66. Noyes, W. A., Am. Chem. J. 20, 812 (1899).

67. Flaschentrager, B., and Gebhardt, F., Z.Physiol. Chim. 192, 50 (1930).

68. Bayer and Co., Ger. pat. 216808 (1910). Chem. Zentra. I, 311 (1910).

69. Von Braun, J., and Lemke, G., Ber. 55, 3526 (1922).

70. Solonina, V., Bull. Soc. Chim [3], 16, 1878 (1896).

71. Van Breukeleveen, M. M., Rec. Trav. chim. 13, 34 (1894).

72. Von Braun, J., and Jostes, F., Ber. 59, 1091 (1926).

73. Weidel, H. and Roithner, E., Monatsh. 17, 183 (1896).

74. Rinkes, I. J., Rec. Trav. chim. 46, 268 (1927).

75. Mohr, E., Kohler, F., and Ulrich, H., J. prakt. Chem [2], 79, 281 (1909).

76. Graebe, C. and Rostowzew, S., Ber. 34, 2107 (1901).

77. Graebe, C. and Rostowzew, S., Ber. 35, 2747 (1902).

78. Villiger, V., and Blangey, L., Ber. 42, 3550 (1909).

79. Graebe, C. and Gouvevitz, S., Ber. 33, 2023 (1900).

80. Lesser, R. and Weiss, R., Ber. 46, 2641 (1913).

81. Hammett, L. P., "Physical Organic Chemistry", p. 188. McGraw Hill Book Co. N. Y., 1940.

82. Kuhn, C., Ber. 28, 809 (1895).

83. Seidel, H. and Bittner, J. C., Monatsh. 23, 418 (1902).

84. Kahn, R., Ber. 35, 471 (1902).

85. Moore, T. S., Marrack, M. T. and Proud, A. K., J. Chem. Soc. 119, 1786 (1921).

86. Clarke, H. T. and Behr, L. D., "Organic Syntheses". Coll. Vol. II, p. 19. J. Wiley and Sons, N. Y., 1943.

87. Gaudry, R., Can. Jour. of Chem. 23B, 234 (1945).

88. Kirpal, A., Monatsh. 23, 239 (1902).

89. Kirpal, A., Monatsh. 29, 728 (1908).

90. Gabriel, S. and Colman, J., Ber. 35, 2831, 3847 (1902).

91. Philips, A., Ber. 27, 840 (1894).

92. Philips, A., Ann. 288, 259 (1895).

93. Curtius, T., Ber. 23, 3023 (1890).

94. Lossen, W., Ann. 161, 347 (1872).

95. Whitmore, F. C., J. Am. Chem. Soc. 54, 3274 (1932).

96. Beckmann, E. and Correns, E., Ber. 55, 848 (1922).

97. Montagne, P. J., Ber. 51, 1479 (1918).

98. Slossen, E. E., Am. Chem. J. 29, 290 (1903).

99. Berg, A., Bull. soc. chim. [3] 3, 685 (1890).

100. Hauser, C. R. and Renfrow, W. B., J. Am. Chem. Soc. 59, 121 (1937).

101. Wallis, E. S., and Nagel, S. C., J. Am. Chem. Soc. 53, 2787 (1931.

102. Wallis, E. S. and Moyer, W. W., J. Chem. Soc. 55, 2598 (1933).

103. Archs, C. L. and Kenyon, J., J. Chem. Soc. 916 (1939).

104. Kenyon, J. and Young, D. P., J. Chem. Soc. 263 (1941).

105. Ingersoll, A. W., Babcock, S. A., and Burns, F. B., J. Am. Chem. Soc. 55, 411 (1933).

106. Von Braun, J. and Friehmelt, E., Ber. 66, 684 (1933).

107. Berstein, H. I. and Whitmore F. C., J. Am. Chem. Soc. 61, 1324 (1939).

108. Archer, S., J. Am. Chem. Soc. 62, 1872 (1940).

109. Noyes, W. A., Am. Chem. J. 16, 500 (1894).

110. Noyes, W. A. and Potter, R. S., J. Am. Chem. Soc. 34, 1067 (1912).

111. Noyes, W. A. and Nickell, L. F., J. Am. Chem. Soc. 36, 118 (1914).

112. Noyes, W. A., Am. Chem. J. 16, 506 (1894).

113. Noyes, W. A. and Knight, L., J. Am. Chem. Soc. 30, 1672 (1910).

114. Noyes, W. A. and Nickell, L. F., J. Am. Chem. Soc. 36, 124 (1914).

115. Noyes, W. A. and Skinner, G. S., J. Am. Chem. Soc. 39, 2699 (1917).

116. Weir, J., J. Chem. Soc. 99, 1273 (1911).

117. F. Bayer and Co., Chem. Zentra. I, 1263, 1834 (1911).

118. Villiger, V., Ber. 42, 3547 (1909).

119. Weerman, R. A., Rec. Trav. Chim. 37, 16 (1918).

120. Oliveto, E. P. and Gerold, C., "Organic Syntheses" Vol. 31, p. 17. J. Wiley and Sons, N. Y., 1951.

121. Polya, J. B., and Tardrew, P. L., J. Chem. Soc. 1081 (1948).

122. Polya, J. B. and Dunn, P., Rec. Trav. Chim. 69, 1297 (1950).

123. Hoogewerff, M. S. and Van Dorp, W. A., Rec. Trav. Chim. 8, 188 (1889).

124. Brunner, K., Ber. 47, 2676 (1914).

125. Slossen, E. E., Am. Chem. J. 29, 305 (1903).

126. Lapworth, A. and McRae, J. A., J. Chem. Soc. 121, 1699 (1922).

127. Brown, G., Smith L. and Webers, V., "Organic Synthesis" Vol. 26, p. 54. J. Wiley and Sons, N. Y., 1946.

128. Millar, C. A. and Long, L. M., J. Am. Chem. Soc. 73, 4895 (1951).

129. Vogel, A. E., "A Textbook of Practical Organic Chemistry", p. 479. Longmans, Green and Co. Toronto, 1948.

130. Boeseken, M. M., Schweizer, A. and Van der Want, G. F., Rec. Trav. Chim. 31, 93 (1912).

131. Babliano, L., Ber. 13, 312 (1880).

132. Fischer, E., Ber. 33, 2388 (1900).

133. King, F. E., Clifton, J. W. and Openshaw, H. T., J. Chem. Soc. 422 (1942).

134. Fischer, E. and Roeder, G., Ber. 34, 3751 (1901).

135. Stieger, R., J. Biol. Chem. 86, 695 (1930).

136. Stieger, R., J. Org. Chem. 9, 397 (1944).

137. Fischer, E., Ber. 35, 2663 (1902).

138. Heintz, W., Ann. 198, 46 (1879).

139. Hoogewerff, M. S. and Van Dorp, W. A., Rec. Trav. Chim. 10, 4 (1891).

140. Posner, T., Ber. 36, 4309 (1904).

141. McRae, J. A. and Vining, W. H., Can. Jour. of Research 6, 409 (1932).

142. McRae, J. A., Conn, R. and Platt, K. J., Can. Jour. of Research 15B, 46 (1937).

143. McRae, J. A., and Townshend, A. S., Can. Jour. of Research 11, 628 (1934).

144. McRae, J. A., Weston, A. W. and Hubbs, C. F., Can. Jour. of Research 15B, 434 (1937).

145. Kolthoff, I. M. and Sandell, E. B., "Textbook of Quantitative Inorganic Analysis", Third Edition, McMillan Company, page 600.

146. Anshutz, R., Ann. 354, 149 (1907).

147. Wallis, E. S., and Lane, J. F., "Organic Reactions", Vol. 111, P. 267. John Wiley and Sons, New York, 1946.

148. Bischoff, C. A., and Voit, E., Ber. 22, 650 (1899).