

THE APPLICATION OF THE
SCHMIDT REACTION TO THE PREPARATION OF
CERTAIN ω -AMINO ACIDS AND DIAMINES

by

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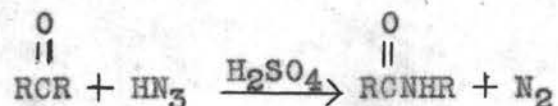
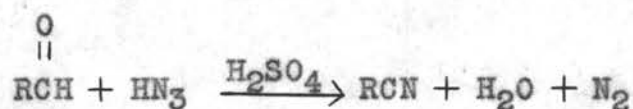
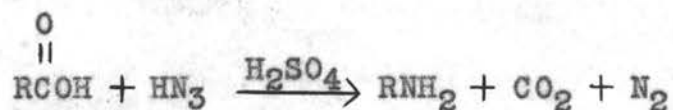
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THE APPLICATION OF THE SCHMIDT REACTION TO THE PREPARATION OF CERTAIN ω -AMINO ACIDS AND DIAMINES

INTRODUCTION

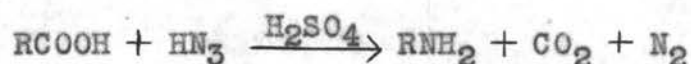
The reaction between hydrazoic acid and carbonyl compounds in the presence of strong mineral acids is known as the Schmidt reaction.



It was discovered by Karl Friedrich Schmidt in 1923 in a study of the decomposition of hydrazoic acid by sulfuric acid (26,p.511). He observed that the reaction products differed according to the temperature at which the reaction was maintained. At room temperature, for example, hydrazine sulfate was the main product, while at 60° to 70° centigrade aniline sulfate was formed in high yields. Acting on the hypothesis that during the decomposition of hydrazoic acid a free imino radical (NH) was formed which was capable of adding to a reactive group, Schmidt added benzophenone to the reaction mixture. A very fast reaction occurred and a quantitative yield of benzanilide was obtained (24,p.423). When he added hydrazoic acid to other

aldehydes and ketones he obtained nitriles and amides (26, p.511). Later he discovered that amines resulted from carboxylic acids, acid anhydrides, or acid halides when subjected to similar treatment (24,p.423).

The most extensive application of the Schmidt reaction has been in the preparation of amines from acids. The reaction, a convenient and efficient method for amine preparation, proceeds according to the following equation.



With straight-chain aliphatic acids the yield of amine generally ranges from 50% to 96% (3,p.842 and 18,p.177), the yield appearing to increase with the length of the carbon chain; this generalization, however, does not hold for acids of more complicated structure. The work of von Braun and Whitmeyer (33,pp.1742-1743) indicated that in the naphthenic acid series, where the lower members contain one and the higher members two cyclopentane rings, the yields seem to drop with the increase of molecular complexity.

The dibasic acids which have been investigated yield diamines in generally increasing yields as the distance between carboxyl groups increases. Thus, succinic acid gives ethylenediamine (8%) (17,p.537), adipic acid yields tetramethylenediamine (83%) (17,p.537) and dodecamethylenedicarboxylic acid (32,pp.2867-2868) gives

dodecamethylenediamine (90%), while malonic acid with hydrazoic acid, on the other hand, yields glycine (29%) (2,p.1568). Acids containing three carboxyl groups, two of which are attached to the same carbon atom have been reported to yield diamino acids. The diamino acid, itself, was inert to further treatment with hydrazoic acid (22, pp.1080-1081). The reaction was found to proceed quite smoothly even with carboxyl groups attached to tertiary carbon atoms (1,p.311).

One of the serious limitations of the process arises from the stability of the reactants to sulfuric acid, thus α -halo acids are dehydrohalogenated under the reaction conditions (31,pp.218-220 and 10,p.1458). Furthermore, not all amino acids are effected by hydrazoic acid. The amino group alpha to a carboxyl group in aliphatic amino acids has an inhibiting effect upon the reactivity of the carboxyl group (17,p.536). The protection given by the amino group decreases or disappears as the two groups are further separated. This has made it possible to synthesize diamino acids from α -amino-dicarboxylic acids (2,pp.1564-1568) and from tricarboxylic acids with two carboxyl groups attached to the same carbon (22, pp.1080-1081).

The position and type of ring substitution in aromatic acids have a marked effect on the reaction rates and

yields of amines. Briggs and Lyttleton investigated the Schmidt reaction with meta-substituted benzoic acids and found that the reaction rates were in reverse order of the acidities while the yields were independent of the acidity (7,p.42). The mono substituted methoxybenzoic acids all gave aminoanisoles in good yield (77% to 80%), but 3,4,5-trimethoxybenzoic acid yielded 3,4,5-trimethoxyaniline in only 35% yield showing the adverse effect of multiple substitution (7,p.422 and 17,p.537). With the toluic acids, however, the yields varied considerably with the position of the methyl group, thus o-,m-,p-toluidines were obtained in yields of 46%, 24%, and 70%, respectively (6,p.63). The position of substitution of the nitro group on benzoic acid also effects the yields. o-,m-,p-Nitro benzoic acids yield the corresponding nitro anilines in yields of 68%, 41%, and 63%, respectively (7,p.422 and 17,p.537).

The three phthalic acids have been converted to the corresponding aminobenzoic acids with mere traces of the diaminobenzenes (7,p.422 and 17,p.537). Anthranilic acid and its derivatives such as the acetyl, benzoyl, or p-toluyll are inert to hydrazoic acid, resembling α -amino acids in this respect (17,p.536).

Furthermore, pyridine and quinoline acids resemble α -amino acids in their behavior, thus pyridine-2-carboxylic acid, pyridine-2,3-dicarboxylic acid, 2,6-dimethylpyri-

dine-3,5-dicarboxylic acid, quinoline-6-carboxylic acid, and quinoline-8-carboxylic acid are inert to hydrazoic acid. On the other hand, 1-phenyl piperidine-4-carboxylic acid was reported to have given 4-amino-1-phenylpiperidine upon treatment by the Schmidt reaction (45%) (8,p.1650). This is the only reacting nitrogen heterocyclic acid thus far recorded.

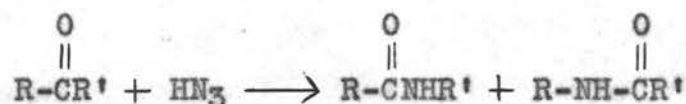
The only other heterocyclic acid compounds which have been subjected to the Schmidt reaction are the 4-tetrahydropyranyl substituted aliphatic acids. These reactions were described by Prelog and his co-workers in their studies of the alkaloids. 4-Tetrahydropyrancarboxylic acid was converted to 4-tetrahydropyranylamine in 44% yield by treatment with hydrazoic acid. The yields were somewhat higher (50% to 70%) when the pyran ring was further removed from the carboxyl group, thus 4-tetrahydropyranacetic acid yielded the corresponding amine in 52% yield (19,pp.37-46; 20,pp.231-242 and 21,pp.247-256).

From the few reactions with esters, acid chlorides, and anhydrides it appears that the reaction products from acid derivatives and hydrazoic acid are identical with those obtained directly by use of the corresponding acid except that the yields are lower (1,p.314).

Aldehydes and ketones are more reactive than acids toward hydrazoic acid. It is even possible to control the

reaction of a keto acid or ester in such a manner that only the keto group enters the reaction. Benzaldehyde and some of its substituted derivatives are reported to give two reaction products; benzonitrile and formanilide. The yield of the nitrile is dependent on the amount of sulfuric acid since it was decreased from 70% to 13% by varying the amount of sulfuric acid; at the same time the yield of formanilide changed from 5% to 50% (15,p.1168). Acetaldehyde is the only aliphatic aldehyde which has been reacted with hydrazoic acid and it was reported to yield only acetonitrile (25,p.3248).

Ketones react to give the corresponding acid amides according to the following equation.



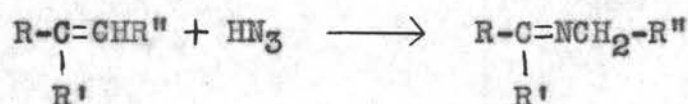
The symmetrical ketones yield one amide while two amides result from the unsymmetrical ketones. Smith and co-workers made a study of the Schmidt reaction on a series of para-substituted benzophenones, a series of phenyl alkyl ketones, and two unsaturated aralkyl ketones. They found that the ratios of the two isomeric amides formed in each case were nearly independent of para-substituents, but were greatly affected by changes in the steric environment of the carbonyl group (29,p.3722). Hydrazoic acid reacts with cyclic ketones in the same way as with open-chain ketones,

producing cyclic amides by ring enlargement (1,p.317).

Quinones react with hydrazoic acid in the absence of strong mineral acids and are therefore not considered as Schmidt reactions. The products are azides, amines or amides depending upon the quinone used.

Hydrazoic acid may also enter side reactions with groups other than carbonyl to form tetrazoles. Groups which react are nitriles, hydrocyanic acid, cyanamide, cyanogen, isocyanides, hydroxamic chlorides, imide chlorides, dichloroketones, and imido esters (1,pp.318-324).

Other reactions of hydrazoic acid are with unsaturated compounds and epoxides. Hydrazoic acid will react with unsaturated compounds at higher temperatures, forming Schiff's bases according to the following scheme (1,p.325).



Vander Werf obtained azido alcohols by subjecting epoxides to the Schmidt reaction (34,p.1234).

Although considerable use has been made of the Schmidt reaction, there are still a number of unanswered questions concerning its scope and limitations. Two of these are the influence of distance on the inhibiting effect of the amino group in amino substituted aliphatic

acids and the possibility of producing ω -amino acids from dibasic carboxylic acids.

For these reasons, coupled with the need for a source of ω -amino acids as intermediates in the synthesis of certain substituted nitrogen heterocyclics, this study was undertaken.

It was apparent that upon subjecting a dicarboxylic acid to the Schmidt reaction some ω -amino acid might be produced as well as the diamine. By using only sufficient hydrazoic acid to react with one carboxylic group it is possible that ω -amino acid might be produced as the principle product. Thus the reaction of several dicarboxylic acids was studied using equal molar quantities of hydrazoic acid and the organic acid, rather than a 2:1 ratio as had been previously reported (17,p.537 and 32,pp.2867-2868).

Since an ω -amino acid would be neutral while the diamine would be basic and any unreacted dicarboxylic acid would be acidic it is evident that the use of ion exchange columns would facilitate the separation of products and reactants.

Freudenberg, Walch, and Molter (9,p.87) suggested that an anion exchanger of the weakly basic type in the free-base form could be used for the adsorption of dicarboxylic amino acids from a mixture of amino acids. Later

investigations had shown that a quantitative uptake of the dicarboxylic amino acids could be achieved with only a slight retention of the neutral amino acids (30, pp. 21-26 and 23, p. 215).

On the basis of this information the solutions were passed through an IR4B column (weakly basic type resin) to remove the sulfuric acid and any unreacted organic acids. The eluate containing the diamine and ω -amino acid was then passed through an IRA400 column (strongly basic type resin) to separate the free base from the amino acid. This procedure was based on the work of Winters and Kunin (35, p. 462) who found that anion exchangers of the strongly basic type in the free base form have the ability to retain quantitatively all amino acids except arginine.

Thus any amino acid (other than arginine) should be adsorbed and the diamine, because of its strong basic properties, should pass through in the effluent. It was observed, however, that the IR4B resin was incapable of quantitatively cleaving the diamine bases from the sulfate ion. Thus the IRA400 picked up the amino acid together with some sulfate ion.

Upon elution of the amino acid with hydrochloric acid one then obtained a mixture of amino acid hydrochloride and sulfate, which created another problem.

Therefore, another passage of the amino acid eluate through the IR4B column was necessary to remove sulfate and chloride ions. This final treatment of the amino acid eluate necessitated a high capacity IR4B column to adsorb the large amount of chloride ions required for the elution.

This procedure was modified by substituting a carboxylic type cation resin for the IRA400 resin. The work of Tiselius, Drake, and Hagdahl (30, pp. 21-26) indicated that only basic amino acids are adsorbed on a carboxylic type resin. Winters and Kunin reported Amberlite IRC50 (carboxylic type resin) to give negligible adsorption of weak bases (pK_B 10) when used in the acid form (35, p. 463). On the other hand, both adrenaline and histamine were reported to have been successfully isolated and purified (14, pp. 734-735 and 5, p. 92) by adsorption on to a carboxylic acid type resin. This modification of procedure was based on the above information. The use of an Amberlite IRC50 column permitted the amino acid to pass through and retained the diamine. The effluent (containing the amino acid) was recycled through an IR4B column to remove the sulfate ion which was cleaved from the diamine by the resin. Since the amount of sulfate ions was small this operation required only a small IR4B column in contrast to the very large column in the original procedure. The diamine was removed by eluting the

IRC50 column with hydrochloric acid. These results are tabulated in Table I, pp. 15-16.

In order to determine the inhibiting effect of an amino group substituted on an aliphatic acid it was proposed to subject β -alanine and γ -aminobutyric acid to the Schmidt reaction. The inhibiting effect of α -amino acids had been known almost as long as the Schmidt reaction itself, but the effect of a more removed amino group had not been investigated.

β -Alanine yielded only 35% of ethylenediamine while γ -aminobutyric acid produced 65% of trimethylenediamine. These results, when compared with the results obtained on the corresponding unsubstituted acids (yields of 65% to 90%) (18, pp. 173-178), indicate that an amino group on the β -carbon atom has considerable inhibiting effect while an amino group on the γ -carbon atom has very little effect on the yield of the diamine. When γ -aminobutyrolactam was used in place of γ -aminobutyric acid the yield of trimethylenediamine was only 10%.

In order to correlate the actual yields with the extent of the reaction, the carbon dioxide evolved was absorbed and determined by precipitation as barium carbonate. These measurements furnished an excellent check on the degree of the reactions in which the yields were small. These data are given in Table II, p. 22.

There have been no reported successful applications of the Schmidt reaction to nitrogen heterocyclic compounds. One experiment carried out in this laboratory confirmed this observation. Another experiment in which the carboxylic acid group was one carbon atom removed from the ring gave a small yield of the amine. These results are given in Table III, p. 23. When furoic acid was subjected to the Schmidt reaction, decomposition occurred resulting in a mixture of volatile amines.

The isolated products were identified by chloride analysis and by synthesis of known derivatives or both. The chloride analysis proved very satisfactory except for the higher molecular weight amino acids which formed insoluble silver salts resulting in a high chloride analysis. The chloride analysis data appear in Table IV, p. 23.

EXPERIMENTAL

Preparation of Hydrazoic Acid Solution. In a 300 milliliter 3-necked flask equipped with a dropping funnel, thermometer, efficient stirrer, and a gas outlet tube a paste was prepared from 16 grams of sodium azide and 16 milliliters of warm water. To the paste 100 milliliters of chloroform was added. While the mixture was stirred and cooled 6.8 milliliters of concentrated sulfuric acid was added dropwise. The temperature was kept below 10° centigrade by the use of an ice bath. After the addition of the acid, the mixture was cooled to 0° centigrade and the chloroform layer was separated. The precipitated sodium sulfate was washed with cold chloroform and the combined washings and chloroform layer were dried for at least 2 hours over anhydrous sodium sulfate.

Preparation of Amines. The general procedure for the preparation of diamines as used throughout the work was as follows. To 0.1 mole of dry carboxylic acid dissolved in 0.7 to 1.0 mole of concentrated sulfuric acid was added, dropwise with stirring, exactly 0.1 mole of hydrazoic acid solution prepared as described above. The hydrazoic acid solution was titrated with standard sodium hydroxide solution of approximately 0.1 normal to determine the volume to be added. A sample of the hydrazoic acid solution was withdrawn with a 1 milliliter pipet and placed

in a small flask containing 10 to 15 milliliters of water. Phenolphthalein indicator was added and the solution was titrated to a faint pink color with the base. The temperature was maintained between 43° to 46° centigrade by means of a heating mantle. The addition of hydrazoic acid took place over a period of 1 to 2 hours. Stirring and heating were continued for an additional four hours or until all carbon dioxide evolution had ceased. At the end of this time the acid layer was separated and diluted to 500 milliliters with water. Any unreacted acid which precipitated was removed by filtration and washed with water. The filtrate and washings contained the products and the combined solution was treated by one of the five procedures listed below. See Table I, pp. 15-16.

Isolation procedure A. The reaction solution was passed downward through an ion exchange column containing Amberlite IR4B resin (a weakly basic resin). The column consisted of a glass tube 35 millimeters inside diameter and 120 centimeters long. The bottom end was fitted with a one hole rubber stopper with a short piece of glass tubing protruding. A small piece of glass wool covered this outlet and 2 centimeters of Ottawa sand covered the glass wool. The ion exchange resin, itself, was 56 centimeters in height. The rate of flow through the column was regulated by a screw clamp on a section of rubber

TABLE I
THE SCHMIDT REACTION WITH ALIPHATIC DICARBOXYLIC ACIDS

Parent acid	Mole ratio HN ₃ :acid	Products ¹	Yield	Isolation procedure	Melting point of derivative (°C.)		
					Observed	Literature	Reference
Succinic	1:1	Diamine	10% ⁵	D	241 ²	244	(12,vol.2,p.502)
		Amino acid	36% ⁵	E	122 ³	123	(12,vol.1,p.130)
Glutaric	1:1	Diamine	35% ⁵	D	147 ²	147-148	(12,vol.4,p.603)
		Amino acid	30% ⁵	C	136 ³	135-136	(12,vol.1,p.76)
Adipic	1:1	Diamine	30%	A	168 ⁴	168	(28,p.234)
		Amino acid	30%	B	104 ²	105-106	(27,p.1558)
Azaleic	1:1	Diamine	34%	D	124 ²	124	(12,vol.2,p.640)
		Amino acid	30%	C	146 ³	147	(11,p.3129)
Sebacic	1:1	Diamine	35%	D	172 ²	173	(12,vol.4,p.8)
		Amino acid	30%	C	117 ³	115-118	(4,p.176)

¹ The diamine produced was of two less carbon atoms than the original acid. The amino acid formed was the ω -amino acid of one less carbon atom than the parent acid.

² The benzoyl derivative was formed.

³ The hydrochloride derivative was formed.

⁴ The phenylthiourea derivative was formed.

⁵ The yields were checked by absorption of CO₂.

TABLE I (Cont'd.)

Parent acid	Mole ratio HN ₃ :acid	Products ¹	Yield	Isolation procedure	Melting point of derivative (°C.)		
					Observed	Literature	Reference
Succinic	2:1	Diamine	18% ⁵	D	243 ²	244	(12, vol. 2, p. 502)
		Amino acid	38% ⁵	C	121 ³	123	(12, vol. 1, p. 130)
Glutaric	2:1	Diamine	77% ⁵	D	147 ²	147-148	(12, vol. 4, p. 603)
		Amino acid	6% ⁵	C	135 ³	135-136	(12, vol. 1, p. 76)
Pimelic	2:1	Diamine	80%	A	149 ⁴	148	(28, p. 234)
Azaleic	2:1	Diamine	85%	A	123 ²	124	(12, vol. 2, p. 640)
Sebacic	2:1	Diamine	84%	A	182 ⁶	182	(28, p. 234)
Glutamic	1:1	2,4-Diamino-butyrac acid	30%	F	182 ⁷	180-181	(2, p. 1565)
dl-Malic	1:1	dl-Isoserine	16% ⁵	F	150 ²	151	(28, p. 246)

⁶ The p-toluene sulfonamide derivative was formed.

⁷ The dipicrate derivative was made.

tubing attached at the outlet. The rate of flow was maintained at approximately 3 milliliters per minute. The sulfuric acid and any unreacted organic acid were removed by this process. A sample of the effluent was tested for sulfate ion with a barium chloride solution and found to contain traces of sulfate. This was due to incomplete cleavage of the sulfate ion from the diamine by the resin.

The effluent was then passed through a strongly basic type resin (Amberlite IRA400) to remove any amino acid which may have formed during the reaction. All traces of sulfate ion were also removed by this operation. The IRA400 column was constructed in the same manner as the IR4B column previously described except that the glass tube was only 30 millimeters inside diameter and contained 62 centimeters of IRA400 resin. The effluent was acidified with hydrochloric acid to a pH of 2 and evaporated in vacuo to dryness. The diamine hydrochloride was washed with ether and identified by synthesis of a known derivative and by chloride analysis.

The IR4B column was regenerated by passing 4% ammonia through it until the effluent was free of sulfate. The column was then washed with water until the effluent was neutral.

Isolation procedure B. The IRA400 column used in isolation procedure A was eluted with 1 liter of 2%

hydrochloric acid solution. The eluate contained a mixture of amino acid hydrochloride and sulfate. The sulfate and chloride ions were removed by passing the solution through an IR4B column 55 millimeters inside diameter containing 75 centimeters of resin. The effluent was acidified with hydrochloric acid to a pH of 2 and evaporated to dryness in vacuo. The solid amino acid hydrochloride was washed with ether and a derivative formed to prove its identity. The IRA400 column was regenerated by passing 4% sodium hydroxide through it until the effluent contained only a trace of chloride ions. The column was then washed with distilled water until the effluent was neutral to litmus.

Isolation procedure C. The bulk of the sulfuric acid was removed from the reaction solution by passing it through an IR4B column as previously described in procedure A. The solution was then passed through an IRC50 column (carboxylic acid type resin) to adsorb the diamine. The IRC50 column consisted of a 120 centimeter piece of glass tubing with an inside diameter of 30 millimeters. The column was constructed in the same manner as those described above with a resin bed of 55 centimeters length. The effluent (containing the amino acid) was freed of the trace of sulfate ion which remained by passing it through a small IR4B column with an 11 centimeter resin bed in a

40 millimeter inside diameter glass tube. The effluent was acidified with hydrochloric acid to a pH of 2 and evaporated in vacuo to dryness. The amino acid hydrochloride was washed with ether and identified by the formation of a suitable derivative and by a chloride analysis.

Isolation procedure D. The IRC50 column used in procedure C was eluted with 1 liter of 4% hydrochloric acid to displace the diamine from the resin. This elution step also regenerated the column. It was necessary only to wash it with distilled water until free of acid to obtain it in its operating form. The acid eluate was evaporated in vacuo to dryness. The amine hydrochloride was washed with ether and its identity was proven by the formation of a derivative and by chloride analysis. The chloride analyses on ethylenediamine and trimethylenediamine were low by several percent. These products were moistened with concentrated hydrochloric acid and washed with absolute ethanol. After being treated in this manner the chloride analyses were satisfactory.

Isolation procedure E. Procedure E was identical to procedure C except that the effluent from IRC50 was found to be sulfate free and therefore the small IR4B column was eliminated.

Isolation procedure F. The product of the reaction

was basic in nature and was obtained by simply passing the reaction solution through the IR4B column described in procedure A. The effluent was tested with barium chloride solution and found to be free of sulfate ion. The effluent was acidified with hydrochloric acid and evaporated to dryness in vacuo. The residue was treated with 20 milliliters of concentrated hydrochloric acid and re-evaporated to dryness in the case of the α -amino acids.

Determination of maximum yield by absorption of carbon dioxide. A 3-necked, 300 milliliter flask was equipped with a dropping funnel, small condenser, magnetic stirrer, and a gas inlet valve. To the condenser was attached a gas absorption tube containing distilled water. The outlet of the tube was attached to an aspirator. The organic acid and sulfuric acid were added to the flask and the magnetic stirrer was started. When solution was complete 50 milliliters of chloroform were added. In order to insure carbon dioxide free air as the sweeping gas, air was passed through an adsorption column containing calcium oxide and bubbled through an absorber containing barium hydroxide solution before entering the reaction flask. The system was checked for leaks by operating the aspirator with the gas inlet closed and observing the gas absorption tube for bubbles. After sweeping the system with the carbon dioxide free air for 15 minutes the water in the

adsorption tube was replaced with carbon dioxide free, 3N sodium hydroxide and the hydrazoic acid solution was added dropwise to the reaction flask over a period of 1 to 2 hours. The temperature of the solution was maintained at 43° by means of an electric heating mantle. Stirring and heating were continued for four hours or until no more gas was evolved. The sodium hydroxide solution was removed from the absorber and barium carbonate was precipitated with an equivalent amount of 1N barium chloride solution containing 53 grams of ammonium chloride per liter. The precipitate was filtered through a tared sintered glass crucible of grade M and washed well with water. The precipitate was dried at 105° centigrade for four hours and weighed. The maximum yield was calculated from the weight of barium carbonate obtained. The isolated yield and maximum yield as determined by this method are compared in Table II.

Reaction of heterocyclic acids. In addition to the dicarboxylic acids, a few heterocyclic acids were subjected to the Schmidt reaction. The reaction was carried out in the same manner as with the aliphatic acids. An equal molar ratio of hydrazoic acid and organic acid was used and the product was isolated by procedure A. Table III, p.23, shows the results of these reactions.

Chloride determination. The standard Volhard

TABLE II

A COMPARISON OF THE PERCENT OF HYDRAZOIC ACID
 REACTING IN THE SCHMIDT REACTION BASED UPON THE
 ISOLATED YIELD AND THE CARBON DIOXIDE ADSORBED

Parent compound	Mole ratio HN ₃ :acid	Products ¹	Isolated yield	Percent of HN ₃ reacting by isolation by CO ₂	
Succinic acid	1:1	Diamine Amino acid	10% 36%	56	57
Glutaric acid	1:1	Diamine Amino acid	35% 30%	100	101
Succinic acid	2:1	Diamine Amino acid	18% 38%	37	38
Glutaric acid	2:1	Diamine Amino acid	77% 6%	80	79
Malic acid	1:1	Isoserine	17%	17	23
-Alanine	1:1	Ethylene- diamine	35%	35	35
-Butyrolactam	1:1	Trimethylene- diamine	10%	10	15
-Aminobutyric acid	1:1	Trimethylene- diamine	65%	65	66

chloride determination was carried out on all products. The results of these determinations appear in Table IV.

TABLE III

THE SCHMIDT REACTION WITH CERTAIN HETEROCYCLIC COMPOUNDS

<u>Parent acid</u>	<u>Product</u>	<u>Yield</u>
Imidazole-4,5-dicarboxylic	None	---
Uracil-4-acetic	Uracil-4-methylamine	10%

TABLE IV

RESULTS OF CHLORIDE ANALYSIS

<u>Product</u>	<u>Percent chloride</u>	
	<u>calc'd.</u>	<u>found</u>
Ethylenediamine•2HCl	53.3	53.0
Trimethylenediamine•2HCl	48.3	47.6
Putrescine•2HCl	44.0	43.7
Cadaverine•2HCl	40.5	40.0
Heptamethylenediamine•2HCl	34.9	34.9
Octamethylenediamine•2HCl	32.7	32.3
β -Alanine•HCl	28.3	27.9
γ -Aminobutyric acid•HCl	25.4	24.9
ω -Aminovaleric acid•HCl	23.1	25.8
ω -Aminocaprylic acid•HCl	18.2	23.0
ω -Aminononanoic acid•HCl	17.0	20.8
2,4-Diaminobutyric acid•2HCl	37.1	37.2

TABLE IV (Cont'd.)

Product	Percent calc'd.	chloride found
Isoserine·HCl	25.1	24.4
Uracil-4-methylamine·HCl	20.1	21.0

SUMMARY

The preparation of ω -amino acids from dicarboxylic acids by the Schmidt reaction has been demonstrated. Furthermore, the reaction produced the corresponding diamine in nearly equal yield if the carboxyl groups were separated by at least three carbon atoms. For example, glutaric acid, adipic acid, azaleic acid, and sebacic acid produced γ -aminobutyric acid, δ -aminovaleric acid, ω -aminocaprylic acid, and ω -aminononanoic acid, respectively. The corresponding diamines were the chief product when the ratio of hydrazoic acid to organic acid was in the order of 2:1. However, succinic acid, with only two carbon atoms separating the acid groups, yielded the amino acid as the chief product with only a small amount of the diamine being produced. The β -alanine produced was hindered from reacting further by the amino group.

The inhibiting effect of the amino group in the Schmidt reaction was shown to be considerable with β -amino acids but only slight if the amino group was further removed from the carboxyl group.

Ion exchange procedures were developed to facilitate the separation of the products and reactants of the Schmidt reaction. The isolated yield, obtained by these procedures, compared favorably with the extent of the reaction as measured by the carbon dioxide evolved.

One nitrogen heterocyclic compound, with the carboxyl one carbon removed from the ring, was found to react with hydrazoic acid to a small extent. Previously there had been no reported successful applications of the Schmidt reaction to nitrogen heterocyclic compounds. In every reported attempt, however, directly substituted heterocyclic acids had been used. This observation suggested that the application of the Schmidt reaction to nitrogen heterocyclic compounds might be possible if the carboxyl group is not attached directly to the ring.

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