

thiamine hydrobromide was 200 mg. (73% based on pyrimidine); m. p. 205–210° (dec.);  $\lambda_{\text{max}}$  in water 238 and 270  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{20}\text{N}_4\text{OBr}_2$ : C, 40.02; H, 4.80; N, 13.34. Found: C, 39.70; H, 5.02; N, 12.99.

**Preparation of Neopyrithiamine Hydrobromide in Acetone.**—Six hundred milligrams of 2-methyl-3-( $\beta$ -hydroxyethyl)-pyridine was dissolved in 10 ml. of acetone, and to this solution was added 240 mg. of 2-methyl-5-bromomethyl-6-aminopyrimidine dihydrobromide. The mixture was shaken until most of the pyrimidine had dissolved. In a few minutes a gummy precipitate had formed. The supernatant liquor was decanted from the gum and was allowed to stand overnight at room temperature. The product separated from solution as a solid. It was centrifuged, washed with fresh portions of acetone and with petroleum ether, and dried. The yield of neopyrithiamine hydrobromide was 150 mg. (55% based on pyrimidine); m. p., 218–220° (dec.);  $\lambda_{\text{max}}$  in water, 238 and 271  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{20}\text{N}_4\text{OBr}_2$ : C, 40.02; H, 4.80; N, 13.34. Found: C, 40.36; H, 5.09; N, 12.92.

**Preparation of Neopyrithiamine Picrate.**—One hundred milligrams of neopyrithiamine hydrobromide was dissolved in 20 ml. of water and added to a solution of 200 mg. of picric acid in 50 ml. of water. The solution was filtered from a small amount of gummy precipitate and was allowed to stand overnight in the refrigerator where the product separated in a crystalline condition. The product was filtered, washed with water and dried. The yield of neopyrithiamine picrate was 70 mg. (40%); m. p. 186–188°.

*Anal.* Calcd. for  $\text{C}_{26}\text{H}_{24}\text{N}_{10}\text{O}_{15}$ : C, 43.58; H, 3.38; N, 19.55. Found: C, 43.52; H, 3.28; N, 19.61.

**Preparation of Neopyrithiamine Hydrochloride.**—Eight hundred and forty milligrams of neopyrithiamine hydrobromide was converted into the picrate as described above. The melting point of a dried sample was 183–184°. The main crop was suspended in water, was acidified with dilute hydrochloric acid, and was extracted with nitrobenzene to remove the liberated picric acid. The aqueous solution was extracted further with ether, and then concentrated to a small volume under reduced pressure and at a low temperature. On addition of isopropyl alcohol to the residue, the product crystallized slowly. It was filtered, washed with isopropyl alcohol, washed with ether and dried. The yield of neopyrithiamine hydrochloride was 260 mg. (40% from the bromide); m. p. 234–236° (dec.);  $\lambda_{\text{max}}$  in water 235 and 273  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{18}\text{N}_4\text{OCl}_2$ : C, 50.76; H, 6.09; N, 16.92. Found: C, 50.69; H, 6.08; N, 16.76.

**Stability of Neopyrithiamine Salts in Solution.**—The ultraviolet absorption spectrum of a freshly prepared methanolic solution of neopyrithiamine hydrobromide changed when the solution was allowed to stand for several days at room temperature. The 235  $\mu$  band shifted to 240  $\mu$  and had a lower intensity, while the 273  $\mu$  band shifted to 267  $\mu$  and was of greater intensity. At the same time the minimum point of the curve at 252  $\mu$  changed to 250  $\mu$  and was of much greater intensity. In short, the two bands seemed to coalesce and to resemble that of pyrithiamine (hydrobromide).

The decomposition was only slight in aqueous solution at room temperature. When the temperature was increased, however, the decomposition was much more rapid. In neutral or alkaline solutions, the decomposition was rapid even at room temperature. Under these conditions the 235  $\mu$  band completely disappeared.

Both neopyrithiamine hydrobromide and neopyrithiamine hydrochloride can lose hydrogen bromide or hydrogen chloride when heated under reduced pressure. The loss was greater with longer heating and with higher temperatures. Conversely, some samples crystallized from solution with varying amounts of hydrogen bromide or hydrogen chloride.

**Acknowledgments.**—The authors wish to express their appreciation and thanks to Dr. Nelson R. Trenner and Dr. Charles Rosenblum for their helpful suggestions on this problem, and for determining and interpreting the physical measurements reported in this paper. The authors also wish to thank Mr. R. N. Boos and his associates for the microanalyses.

### Summary

The previously reported method of preparation of 1-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-2-methyl-3-( $\beta$ -hydroxyethyl)-pyridinium bromide hydrobromide was found to yield a substance that was not analytically in agreement with the desired product. This product has been prepared now, and its analytical and physical properties are described. It has been named neopyrithiamine hydrobromide. Neopyrithiamine hydrobromide has been converted first into the picrate and then into the hydrochloride.

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RECEIVED FEBRUARY 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

## The Schmidt Reaction. I. Conditions and Reaction Mechanism with Primary, Secondary and Tertiary Aliphatic Acids

By CONRAD SCHUERCH, JR.,<sup>1,2</sup> AND ERNEST H. HUNTRESS

Although carboxylic acids react with sulfuric and hydrazoic acids to give primary amines, a recent review<sup>3</sup> indicates only meager information

(1) This paper is constructed from part of a dissertation submitted by Conrad Schuerch, Jr., to the Faculty of the Massachusetts Institute of Technology in June, 1947, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. It was presented before the Division of Organic Chemistry at the 112th meeting of the A. C. S. in New York on September 18, 1947.

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(3) Wolff, "The Schmidt Reaction, Organic Reactions," Vol. 3, John Wiley and Sons, New York, N. Y., 1946, pp. 307–336.

on the behavior of the lower primary, secondary and tertiary representatives, and that for the last group high yields of amine have been obtained only with acids containing a cyclopentyl radical adjacent to the carboxyl. The influence of reaction conditions upon yield of amine has been inadequately characterized, and whether yields less than theoretical were due to incomplete reaction or to diversion into side reactions has rarely been established. The present study adds to our knowledge of acetic, isobutyric and tri-

methylacetic acids, and reports new observations on the reaction products both from these and other secondary and tertiary acids.

The conditions necessary for complete conversion of the acids were determined by allowing a small quantity of organic acid to react with sulfuric acid and sodium azide according to Oesterlin's modification<sup>4</sup> of the original procedure and analyzing the evolved gas for carbon dioxide. From the latter simple calculation gave the amount of carboxylic acid reacting, while direct azide decomposition<sup>5</sup> was measured by nitrogen found in excess of that required for the reaction  $\text{RCOOH} + \text{HN}_3 \rightarrow \text{RNH}_2 + \text{CO}_2 + \text{N}_2$ .

These experiments have shown that a molal ratio of sulfuric acid to organic acid of about 7 or 9:1 is usually required for complete reaction, and that neither trichloroacetic nor phosphoric acids can be used in place of sulfuric acid. It was confirmed that hydroxylic solvents interfere with the reaction but that nitromethane, a solvent which does not ionize in sulfuric acid,<sup>6a</sup> was a satisfactory diluent.<sup>7</sup> Acetic anhydride was found to react somewhat more completely than acetic acid under the same conditions, but chloroacetic and trichloroacetic acids did not give off carbon dioxide under ordinary conditions. These results can all be explained adequately by the ionic mechanism proposed for this reaction by other workers,<sup>8,9,10,11</sup> and indicate the importance of maintaining the organic acid in the form of a positive ion for complete reaction.

A temperature higher than the usual 40° was found to be necessary only in the case of acetic acid. At 60°, good yields of carbon dioxide and methylamine were obtained; at lower temperature there was excessive direct azide decomposition.<sup>12</sup> Most other variables were of minor significance.

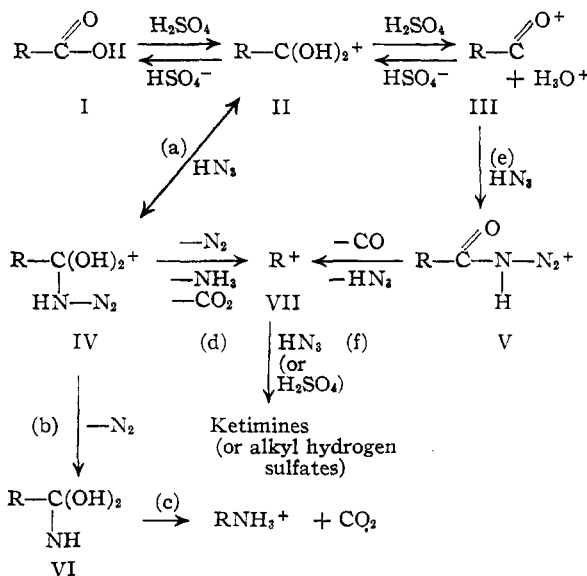
Preparative experiments showed that only acetic acid gave equivalent amounts of carbon dioxide and amine. Isobutyric acid gave quantitative yields of carbon dioxide, 84% of isopropyl-

amine and some isopropyl alcohol. When trimethylacetic acid was allowed to react with sodium azide (1.17 moles), some unchanged acid was recovered, and the reaction products were acetone, methylamine, ammonia, carbon dioxide, carbon monoxide and 33% of *t*-butylamine. By diluting the reaction mixture with nitromethane, the formation of carbon monoxide was completely inhibited, and the yield of *t*-butylamine was raised to 55%, but the cleavage products were still formed.

Dimethylethylacetic acid reacted similarly, forming a larger proportion of carbon monoxide, less *t*-alkylamine (somewhat impure), acetone, ethyl methyl ketone, ammonia, methylamine and impure ethylamine. The reaction of 1-methylcyclohexanecarboxylic acid produced both carbon monoxide and carbon dioxide and a 42% yield of 1-methylcyclohexylamine, but the expected cleavage products were not found. An investigation of other tertiary acids showed that the proportion of carbon monoxide increased as the chain length of the acid increased, and with triethylacetic acid (to be reported later), the proportion of carbon monoxide was found to be greater at the beginning of the reaction than at the end.

No method was found for decreasing the amount of cleavage products formed when carbon dioxide alone was evolved. Under these conditions, the proportion of cleavage products to *t*-alkylamine did not appear to be sensitive to dilution of the reaction medium.

In explanation of these results, these equations are proposed as a tentative mechanism



The organic acid is shown reacting with hydrazoic acid only in the form of a positive ion, since changes in the system which result in decreased ionization of the organic acid, also result in incomplete reaction. In reactions which yield both car-

(4) Oesterlin, *Z. angew. Chem.*, **45**, 536 (1932).

(5) Briggs and Lyttleton, *J. Chem. Soc.*, 421 (1943).

(6) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940; (a) p. 47; (b) p. 55; (c) p. 283.

(7) Samour and Huntress, unpublished results.

(8) Smith, *THIS JOURNAL*, **70**, 320 (1948).

(9) Sanford, Blair, Arroya and Sherk, *ibid.*, **67**, 1941 (1945).

(10) Newman and Gildenhorn, *ibid.*, **70**, 317 (1948).

(11) The reactions of alcohols, olefins and halides with hydrazoic acid to form aldimines or ketimines likewise appear to be best explained by a carbonium ion mechanism, for in the reaction of menthol reported by Schmidt and Klavehn [German Patent 583,565, *Chem. Zentr.*, **105**, I, 946-947 (1934); *C. A.*, **28**, 1047 (1934); *Friedländer*, **20**, 947 (1935); this patent is incompletely abstracted in Wolff's review<sup>1</sup>], there appears to have been a typical carbonium type rearrangement followed by reaction with hydrazoic acid. The products of the reaction seem to have been acetone, 1-acetyl-4-methylcyclohexane, and 4-methylcyclohexylamine, although the authors interpret differently the identity of their products and the nature of the reaction. They fail to account for the second ketone, and designate the amine as "4-methylhexamethylenimine."

(12) The higher temperature may be necessary in this case to cause migration of the methyl radical, which is less mobile than other alkyl groups.

bon monoxide and carbon dioxide, complex ionization of the organic acids is assumed, the dihydroxycarbonium ions (II) reacting to form carbon dioxide and primary amines or cleavage products, the oxocarbonium ions (III) reacting to form carbon monoxide and cleavage products (but no primary amine). This interpretation is chosen to explain the following observations: As reaction conditions are changed to decrease the yield of carbon monoxide, the yield of primary amine is increased. The proportion of carbon monoxide formed is reduced by factors (dilution and accumulation of reaction products) which would reverse the mobile equilibrium shown. The proportion of primary amine to cleavage products was not observed to vary on dilution of the reaction medium, if no carbon monoxide was evolved. The alternative assumption that only one ion (II or III) can react in three different ways, only one of which is sensitive to dilution, appears a less satisfactory explanation.<sup>13</sup>

Reactions (a), (b) and (c) constitute one possible mechanism suggested for the formation of primary amines from carboxylic acids by Newman and Gildenhorn.<sup>10</sup> Equations (d), (e) and (f) are believed to be the most probable mechanism for the formation of isopropyl alcohol from isobutyric acid and the various cleavage products from tertiary acids for the following reasons: Ketones cannot have been present in the reaction mixture since with hydrazoic acid they react more readily than carboxylic acids. They must, therefore, have been in the form of ketimines. From the known reactions of tertiary alcohols and halides,<sup>11</sup> it is most probable that these ketimines are formed by the reaction of a trialkylcarbonium ion (VII) with hydrazoic acid, and that isopropyl alcohol is similarly derived from the dimethylcarbonium ion.

The carbonium ion is almost certainly not formed by decomposition of the *t*-alkylamine, since continued heating of the reaction mixture was not observed to decrease the yield of normal product and since cleavage products are obtained from reactions in which there is still unreacted organic acid. The carbonium ion is, therefore, probably derived from an active complex (IV or V).

Ion III is shown decomposing to form carbon monoxide and a carbonium ion only after reaction with hydrazoic acid and not directly as does triphenylacetic acid<sup>6c</sup> since no gas evolution occurred with these acids until sodium azide was

added to the reaction mixture.<sup>14</sup> The assumption that in complex (V) electron-withdrawal from the alkyl group proceeds in preference to the cleavage of the nitrogen-nitrogen bond does not appear unlikely in view of the tendency for carbonium ion formation when carbon dioxide is evolved. The same carbonium ion (VII) is assumed formed from ions (IV) and (V) since no different cleavage products were isolated when carbon monoxide was evolved.

The fact that no cleavage products were found in the reaction of 1-methylcyclohexanecarboxylic acid is not adequately explained by this mechanism, but the yields of 1-methylcyclohexylamine can probably be improved by dilution of the reaction medium with non-ionizing solvents.

### Experimental

**Method of Gas Analysis.**—The reaction vessel comprised a tube of about 40-ml. capacity, fitted with a 12 mm. diameter horizontal side-arm (A) projecting slightly within the wall of the main reaction tube, and a second smaller side-arm (B) leading through capillary tubing to a separate 600-ml. gas collection tube provided with leveling bulb. In side-arm (A) was arranged a tight-fitting rubber pusher (C) attached to a hollow glass tube (E) which passed through a rubber stopper and was sealed with a pinchcock and rubber tube (F). A mercury-sealed stirrer fitted onto the reaction vessel in the usual manner. The retaining liquid in the gas collection tube was 5% sulfuric acid saturated with sodium sulfate.

The organic acid (0.01 equiv.) together with a measured quantity of concentrated C. P. sulfuric acid was placed in the reaction vessel. Solid finely powdered sodium azide (about 0.012 equiv.) was placed in side-arm (A), the gas collection tube was filled with liquid, and the system closed and tested for leaks. The reaction tube was immersed in a water-bath at the desired temperature, the stirrer started, and the sodium azide gradually pushed into the reaction mixture. The evolved gas was collected under a slight negative pressure. After completion of the reaction and measurement of the corresponding gas, the gas remaining in the reaction vessel was displaced with water added through tube E and the total gas volume determined. The carbon dioxide content of a 100-ml. sample withdrawn to a Hempel buret was determined by absorption in 30% potassium hydroxide. Several individual carboxylic acid/azide reactions were usually run simultaneously.

**Calculation of Results.**—Expressing by  $V_e$  the volume of gas evolved, by  $V_t$  the sum of  $V_e$  plus the gas displaced from the reaction vessel, by  $T_k$  the absolute temperature, by  $P_a$  the pressure in millimeters, and per cent. carbon dioxide as the percentage of gas absorbed by the alkali, then it follows that

$$\text{Maximum yield of amine} = \frac{\text{moles CO}_2 \text{ formed}}{\text{moles R.COOH used}} = \frac{100 \times P_a \times \% \text{ CO}_2 \times V_t \times \text{M. W. acid}}{760 \times 82.07 \times T_k \times \text{wt. acid}}$$

$$\% \text{ NaN}_3 \text{ decomposed} = \frac{100 \times P_a \times (V_a - 0.01 \times 2 \times \% \text{ CO}_2 \times V_t) \times \text{M. W. NaN}_3}{760 \times 82.07 \times T_k \times \text{wt. NaN}_3}$$

If allowance be made for errors in analysis, volume

(14) The authors have recovered triethylacetic acid largely unchanged after treatment with reagent grade sulfuric acid at 50° for one hour, although this compound has been found by Professor Melvin S. Newman to evolve gas with 100% sulfuric acid at 50° (private communication).

(13) Direct evidence for the presence of ions of type (III), which have been postulated to explain the complex ionization of 2,6-disubstituted benzoic acids<sup>6b</sup> and aliphatic esters (Kuhn, *THIS JOURNAL*, **69**, 1974–1976 (1947)) and assumed as possible intermediates in the Schmidt reaction,<sup>10</sup> has not been obtained with trimethylacetic (Treffers and Hammett, *ibid.*, **59**, 1708–1712 (1937)) or triethylacetic acid (private communication from Professor Melvin S. Newman, The Ohio State University). Both have an *i*-factor of 2 at the freezing point of sulfuric acid. At higher temperatures, however, it seems possible that small amounts of oxocarbonium ions are formed.

measurement and the possible presence of small amounts of hydrazoic acid incompletely absorbed by the retaining liquid, the resultant error in maximum yield of amine is probably less than 5%. Inert vapors such as those of water or nitromethane do not interfere but chloroform cannot be used. The calculation of sodium azide decomposition is much less reliable and was used only as a qualitative indication.

**Results with Acetic Acid** (see Table I).—The ratio of sulfuric/carboxylic acids must be high; however, excessive amounts decrease the yield of amine apparently by promoting the proportion of direct sodium azide decomposition (expts. 9, 10, 11, 13; 1, 2, 3). The desired reaction is relatively favored, however, by raising the temperature to about 60° (expts. 13, 14, 15; 2, 9, 16). The reaction is effectively stopped by water, and conversely use of acetic anhydride in place of acetic acid gives a better yield under the same conditions (expts. 10, 12). Nitromethane has no such effect.

TABLE I  
BEHAVIOR OF ACETIC ACID<sup>a,c</sup>

Expt.	Acetic acid, wt. g.	H <sub>2</sub> SO <sub>4</sub>	Mole ratio <sup>b,d</sup> NaN <sub>3</sub>	Temp., °C.	Max. yield amine in %	% NaN <sub>3</sub> dec.
1	0.68	9.33	1.21	40	59	..
2	.68	7.78	1.21	40	77	30
3	.69	6.40	1.19	40	55	39
4	.68	9.90	1.21	40	50	48
5	.69	10.50	1.18	40	53	57
6	.69	9.20	1.19	40	56	58
7	.69	9.22	1.28	40	57	53
8	.69	10.45	1.28	40	49	48
9	.69	7.92	1.28	40	67	44
10	.69	9.52	1.27	40	55	31
11	.69	7.08	1.28	40	66	38
12	<sup>a</sup>	9.12	1.28	40	69	25
13	.68	7.08	1.30	45	73	50
14	.69	7.05	1.28	52	79	28
15	.69	7.06	1.28	60	89	26
16	.50	9.82	1.85	40-55	78	46

<sup>a</sup> Substituted for the acetic acid 0.59 g. of acetic anhydride; mol. wt. calculated as 51, for ratios. <sup>b</sup> Nitromethane was used in certain runs as follows: runs 1, 3-6 and 8 used 3.9 g.; run 2 used 3.3 g.; run 7 used 2.3 g. <sup>c</sup> Ratio of reagent to acetic acid. <sup>d</sup> Time of addition of sodium azide was two and one-half hours for runs 5-8; thirty minutes for runs 1-4; twenty-five minutes for runs 9-16. <sup>e</sup> Three runs (17, 18, 19) on 0.69 g. of acetic acid with 10.3 g. of sulfuric acid (molar ratio = 9.15) and 0.95 g. of sodium azide (molar ratio = 1.27) but using, respectively, 0.84 g., 1.88 g., and 3.60 g. of water (instead of nitromethane) gave in 30 min. only about 70 ml. of gas.

**Results with Isobutyric Acid** (see Table II).—The most significant variable is the sulfuric/isobutyric acid ratio (runs 2, 3, 4, 6, 7, 9). The sodium azide/isobutyric acid ratio need not be much greater than unity (runs 6, 7, 9). The sodium azide/sulfuric acid ratio is not critical. Heating the reaction mixture to a higher temperature after complete addition of azide helps to

complete the reaction, but its maintenance for long periods has little effect (runs 2, 3, 4). When nitromethane is employed as solvent, the reaction is less vigorous and gives excellent yields (runs 1, 2, 6, 7, 8) but excessive amounts diminish the yield. The rate of addition of sodium azide does not appear to be of importance.

TABLE II  
BEHAVIOR OF ISOBUTYRIC ACID<sup>a</sup>

Expt.	Iso-butyric acid wt. g.	H <sub>2</sub> SO <sub>4</sub>	Mole ratio <sup>b,c</sup> NaN <sub>3</sub>	Temp., °C.	Max. yield amine in %	% NaN <sub>3</sub> dec.
1	0.508	6.37	1.10	40	58	13
2	1.00	6.50	1.35	40	74	6
3	1.00	6.48	1.38	40	80	9
4	1.01	6.43	1.34	40	77	35
5	1.02	6.35	1.34	40	86	9
6	1.02	9.11	1.34	40	96	19
7	1.01	9.00	1.35	40	95	16
8	1.00	6.42	1.37	40	86	5
9	1.01	9.20	1.13	40	92	14
10	1.02	7.61	1.11	40	80	30

<sup>a</sup> Nitromethane was used as follows: run 10, 3.3 g.; runs 1-6, 9, 3.9 g.; runs 7 and 8, none. <sup>b</sup> Ratio of reagent to isobutyric acid. <sup>c</sup> Time of addition of sodium azide was eighty minutes for run 2; fifty minutes for runs 3 and 4; forty minutes for run 1; thirty minutes for runs 5-8; twenty minutes for runs 9 and 10.

**Results with Trimethylacetic Acid** (see Table III).—The minimum molar ratio of sulfuric/trimethylacetic acid is about 7.5 (runs 4 and 5); an increase to about 10.0 has little effect (runs 2, 3, 5, 7). The presence of nitromethane raises the carbon dioxide by about 15% (runs 5, 8).

TABLE III  
BEHAVIOR OF TRIMETHYLACETIC ACID<sup>a,c</sup>

Expt.	Tri-methyl-acetic acid wt., g.	H <sub>2</sub> SO <sub>4</sub> <sup>b</sup>	Molal ratio NaN <sub>3</sub> <sup>b,c</sup>	Temp., °C.	Max. yield amine, %
1	0.88	9.16	1.20	40	83.3
2	.89	9.97	1.18	40	85.8
3	.89	7.58	1.18	40	86.8
4	.89	6.45	1.18	40	72.8
5	.90	7.54	1.17	45	83.0
6	.90	8.71	1.17	45	91
7	.90	9.85	1.17	45	85
8	.90	7.50	1.17	45	69

<sup>a</sup> Nitromethane was used as follows: runs 1 and 2, 3.0 g.; run 3, 2.5 g.; runs 4-7, 2.3 g.; run 8, none. <sup>b</sup> Molal ratio of reagent to trimethylacetic acid. <sup>c</sup> The time of addition of sodium azide: runs 1-4, sixty minutes; runs 5-8, thirty minutes.

**Gases Evolved in the Reaction of Secondary and Tertiary Acids.**—In the apparatus previously described a small quantity (*e. g.*, 0.5 g.) of the acid in concentrated sulfuric acid (about 5 ml.) was allowed to react rapidly with excess sodium azide (about 0.5 g.). The air in the apparatus was first displaced with nitrogen and after reaction was complete the gas was analyzed for carbon dioxide (by absorption in 30% potassium hy-

dioxide) and for carbon monoxide (by absorption in acidic cuprous chloride). Table IV summarizes the results obtained with four tertiary acids and two secondary acids.

TABLE IV

Acid	CO <sub>2</sub> , %	CO, %
Trimethylacetic <sup>a</sup>	39.2	0.0
Trimethylacetic	25.9	0.9
Trimethylacetic	25.7	2.1
Dimethylethylacetic	20.5	9.0
Methyldiethylacetic	6.3	26.0
1-Methylcyclohexanecarboxylic	6.2	27.3
Diethylacetic	35.8	0.0
Diphenylacetic	22.2	1.5

<sup>a</sup> Trimethylacetic acid (0.89 g.), sulfuric acid (7.53 g.), sodium azide (0.68 g.), nitromethane (2.0 ml.); slow addition; carbon monoxide analysis by combustion of non-acidic gases. All other reactions without nitromethane.

**Preparation of Methylamine Hydrochloride.**—Acetic acid (20 g., 99.5% purity) dissolved in C. p. concentrated sulfuric acid (232 g.) was allowed to react with sodium azide (27.9 g.) at 60° under conditions essentially those of run 15 of Table I. The amine was collected in concentrated hydrochloric acid, evaporation of which gave 21.5 g. of crude product, m. p. 186–220°. Recrystallization from absolute ethanol gave 19.5 g. of beautiful plates but did not improve the melting point.<sup>15</sup> This yield of 87% is in good agreement with that (89%) of the corresponding carbon dioxide obtained.

**Preparation of Isopropylamine.**—Isobutyric acid (25 g. of b. p. 151.5–152.2°) concentrated sulfuric acid (253 g.) and sodium azide (23 g.) were allowed to react under essentially the conditions of run 7 of Table II. After dilution and distillation of the acid reaction mixture, the distillate was neutralized with sodium bicarbonate and redistilled. The neutral aqueous distillate gave a positive iodoform test (isopropyl alcohol) but was negative for aldehydes (Schiff and Tollens reagents) and for ketones (phenylhydrazine). These tests were checked with authentic samples; and the iodoform test was carried out under conditions which did not respond to ethanol. Acidification and appropriate processing of the sodium bicarbonate solution gave no evidence of any unchanged isobutyric acid.

The main reaction mixture was cautiously made alkaline and distilled into ice-cooled receivers. Refractionation of this distillate through a suitable Podbielniak column gave isopropylamine (14.4 g. = 84% yield, b. p. 31–32°), identified as N,N'-diisopropylamide, m. p. 209–211° uncor., reported 212°.<sup>16</sup>

**Reaction of Trimethylacetic Acid.**—Trimethylacetic acid (30 g.) dissolved in C. p. concentrated sulfuric acid (255 g.) was allowed to react with sodium azide (22.5 g.) under the conditions of run 8 (Table III). Isolation of the products as previously described gave some unreacted trimethylacetic acid (5.0 g.), *t*-butylamine (6 g., 33% b. p. 43–44°, *n*<sub>D</sub><sup>20</sup> 1.3779), acetone (4.2 g., b. p. 56–60°, *n*<sub>D</sub><sup>20</sup> 1.3582), and a mixture of methylamine and ammonia (7.5 g.). The *t*-butylamine was confirmed through its hydrochloride, m. p. 299–300°. The acetone gave a positive iodoform reaction in the cold and yielded a 2,4-dinitrophenylhydrazone, m. p. 121–124° (recorded 126°). The methylamine/ammonia mixture was converted to the hydrochlorides and the two salts separated by crystallization from absolute ethanol. The more soluble methylamine hy-

drochloride was confirmed by conversion to N-methyl-*p*-toluenesulfonamide, m. p. 73–75° (recorded 75°). The less soluble ammonia chloride was reconverted to ammonia which gave a positive Nessler test.

Similar results were obtained using nitromethane as solvent under the conditions of run 6 (Table II) (55% yield *t*-butylamine), while an experiment using less sulfuric acid together with hydrazoic acid and chloroform gave 56% yield.

**Reaction of Dimethylethylacetic Acid.**—Dimethylethylacetic acid (34 g., b. p. 181–183°) dissolved in C. p. concentrated sulfuric acid (260 g.) was allowed to react with sodium azide (22 g., 1.15 molal ratio) at 38–45°. Isolation of the products as before gave some unreacted dimethylethylacetic acid (9.0 g.), a mixture of ketones (5.9 g., b. p. 59–74°), and a mixture of basic materials.

Refractionation of the ketone mixture gave (in addition to an intermediate fraction) lower and higher boiling units of acetone (b. p. 59–61°, Legal test) and ethyl methyl ketone (b. p. 73–74°, semicarbazone, m. p. 134.5–137°). The basic material was separated into gaseous and liquid components; the gaseous base mixture boiled over the range 11–17°, but did not as such derivatize cleanly. However, we were able to separate from it both ammonia (Nessler test) and methylamine (corresponding N-methyl-*p*-nitrobenzamide, m. p. 214.2–214.5°). The liquid bases were twice fractionated and showed a boiling range of 63–75°; this corresponds to *t*-amylamine possibly contaminated with 2-aminobutane but further separation proved impossible. Material balances accounted for about 78% of the initial material.

**Reaction of 1-Methylcyclohexanecarboxylic Acid.**—This acid (14.2 g., b. p. 131–132° at 20 mm.) dissolved in C. p. concentrated sulfuric acid (88–98 g.) was allowed to react with sodium azide (9.0–9.75 g.) at 40–50°. The temperature was maintained for an hour after complete addition of the azide, and less than 0.5 g. of the acid was recovered. The neutral distillate gave only traces of organic material in which no cyclohexanone could be detected. The basic products yielded only a small amount (less than 2 ml.) of gaseous bases together with 1-methylcyclohexylamine (4.8 g., 42%; obs. b. p. 143–146°; recorded 142–142.5°; neut. equiv. observed 112.7, 113.7, calculated 113; benzoyl derivative, observed m. p. 97–99°, recorded,<sup>17</sup> 101–101.5°).

## Summary

1. An experimental technique for the determination of the percentage conversion and optimum conditions in the Schmidt degradation of carboxylic acids to amines has been devised.

A study of the behavior of acetic, isobutyric, and trimethylacetic acids has shown that the most significant variables are the proportion of sulfuric to carboxylic acid, the temperature and the extent of dilution of the sulfuric acid.

2. The yields of primary amine are shown to be less than theoretical from acids with chain-branching in the  $\alpha$ -position. At least two side reactions have been shown to occur, one of which can be inhibited by dilution of the reaction medium. Among the by-products formed from secondary and tertiary acids are carbon monoxide, ketones, primary amines, alcohols and ammonia.

3. A mechanism is proposed for these reactions involving complex ionization of the organic acids, and it is suggested that the reaction of alcohols, olefins and halides with hydrazoic acid involves the intermediate formation of a carbonium ion.

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RECEIVED JUNE 21, 1948

(15) A similar result has been reported in the Curtius degradation of acetic acid and the amine hydrochloride shown to be of good purity by Naegeli, Gruntuch and Lendorff, *Helv. Chim. Acta*, **12**, 249 (1929).

(16) Dermer and Hutcheson, *Proc. Oklahoma Acad. Sci.*, **23**, 60–63 (1943); *C. A.*, **38**, 2006 (1944).

(17) Gutt, *Ber.*, **40**, 2069 (1907).