When 1:2 or 3:4 molar ratios of triethylenetetramine and toluene-2,4-diisocyanate or toluene-2,4,6-triisocyanate were reacted the products were viscous polymers.

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Carbonyl Derivatives of γ-Cyano and γ-Carboxy-α,α-dimethylpentanal

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Although γ-cyano-α,α-dimethylpentanal, also called Ibanitrile, and γ-carboxy-α,α-dimethylpentanal, also called Iba-acid, have been known for some time,[1,2] several of the simple carbonyl derivatives of these compounds have not been previously described. The availability of Ibanitrile from the reaction of isobutyraldehyde with acrylonitrile suggests that the data for these compounds be made available. We have prepared several of these derivatives whose properties are recorded in the table. All were prepared by standard methods. The unusual formation of the hydrazone, rather than the azine, from equimolar quantities of Ibanitrile and hydrazine is noteworthy. Usually the azine is the exclusive product from the reaction of an aliphatic aldehyde with hydrazine. Only the azine was obtained from hydrazine and Iba-acid.

TABLE I

DERIVATIVES OF IBANITRILE AND IBA-ACID

	M.P. or B.P.[a]	Yield, %	Analysis[b] Calcd.	Found
Ibanitrile Derivatives				
Hydrazone	b103/1.5[c]	60	30.19N	29.92N
Azine	m76-78EW	75	68.25C 9.00H	68.52C 9.07H
Methylhydrazone	b104/4[d]	87	27.43N	27.51N
Dimethylhydrazone	b90/3[e]	76	25.13N	25.13N
Semicarbazone	m154W	84	30.75N	30.53N
Thiosemicarbazone	m95MW	62	28.25N	28.36N
Aminoguanidine sulfate	m166M	43	29.81N	29.92N
Iba-acid Derivatives				
Azine	m165MW	95	9.99N 140.1NE	10.07N 143.0NE
Dimethylhydrazone	m73PC	55	15.04N 186.2NE	15.01N 185.4NE
Semicarbazone	m175W	98	20.88N 201.2NE	20.95N 201.9NE
Thiosemicarbazone	m160W	99	19.33N 217.3NE	19.51N 218.4NE
2,4-Dinitrophenylhydrazone	m147E	99	17.27N	17.22N

[a] Solvents for recrystallization: B, benzene; M, methanol; W, water; C, carbon tetrachloride; P, petroleum ether; E, ethanol. [b] C, carbon; H, hydrogen; N, nitrogen; NE, neut. equiv. [c] n_D^{25} 1.4805. [d] n_D^{24} 1.4770. [e] n_D^{24} 1.4660.

EXPERIMENTAL[3]

γ-Carboxy-α,α-dimethylpentanal. This acid was obtained in 75% yield by hydrolysis of the nitrile with 25% aqueous hydrochloric acid; b.p. 130–132°/3 mm.; n_D^{25}, 1.4450.

Derivatives of γ-cyano-α,α-dimethylpentanal. Hydrazone. The nitrile (12.5 g.) was added dropwise to a solution of 10 g. of hydrazine in 50 ml. of benzene. The mixture was refluxed for 1 hr. with azeotropic removal of the water formed in the reaction. The benzene solution was dried and evaporated to leave a residue which was fractionated to give 8.3 g. (60%) of the hydrazone, b.p. 101–103/1.5 mm.; n_D^{25}, 1.4805. Attempted refractionation partially converted this material to the azine. *Azine.* A solution of 4.0 g. of hydrazine and 2.5 g. of nitrile in 100 ml. of benzene was refluxed for 1 hr. with azeotropic removal of the water formed in the reaction. Evaporation of the solvent left a solid residue, 2.9 g. (75%), which was recrystallized from ethanol-water, m.p. 76–78°. The infrared absorption spectrum for this azine shows strong absorption bands at 2250 cm.$^{-1}$ (C≡N stretching frequency); 1630 cm.$^{-1}$ (C=H stretching frequency); 1450 cm.$^{-1}$ (C—H deformation frequency in CH_2); 1380 cm.$^{-1}$ and 1358 cm.$^{-1}$ [C—H deformation frequency in $(CH_3)_2C$]; and 1195 cm.$^{-1}$ and 770 cm.$^{-1}$ [$(CH_3)_2C$ skeletal vibration]. *Methylhydrazone and dimethylhydrazone.* These compounds were prepared by refluxing the aldehyde with methyl- and dimethylhydrazine. Properties are given in the table. *Dinitrophenylhydrazone.* This compound was prepared as previously described,[4] m.p. 139–140°. *Semicarbazone.* This compound precipitated from a solution of the aldehyde, semicarbazide hydrochloride, and sodium acetate in water. *Thiosemicarbazone.* A solution of 12.5 g. of the nitrile and 9.0 g. of thiosemicarbazide in 40 ml. of ethanol was refluxed for 2 hr. The precipitated solid left on evaporation of the ethanol was recrystallized from methanol-water to give 12.4 g. (62%) of the product, m.p. 95–96°. *Aminoguanidine sulfate.* A mixture of 26.5 g. of aminoguanidine sulfate, 25 g. of the aldehyde, and 2 drops of concd. sulfuric acid were agitated to homogeneity. After standing at room temperature for 24 hr., the solvent was evaporated under vacuum at room temperature. The viscous residue solidified on standing and was recrystallized by dissolving in methanol at 45° and cooling to −20°.

Derivatives of γ-carboxy-α,α-dimethylpentanal. Azine. The white solid product separated from a benzene solution of the aldehyde and an equivalent amount of hydrazine. *Dimethylhydrazone, semicarbazone, thiosemicarbazone.* These derivatives were prepared using the procedures given above for the derivatives of the nitrile. *2,4-Dinitrophenylhydrazone.* This compound precipitated from an acidic aqueous solution of the hydrazine and the aldehyde.

Both aldehydes react with phenylhydrazine to give products which could not be recrystallized.

(1) N. E. Thiele and W. Franke, Publication Board Reports **35**, 102; **35**, 103 (1944).

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(3) Analyses by Micro Tech Laboratories, Skokie, Ill.

(4) G. Tschudi and S. Schinz, *Helv. Chim. Acta*, **33**, 1870 (1950).

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Synthesis and Properties of *N*-Acetoxytrimethylammonium Bromide[1]

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N-Acetoxytrimethylammonium bromide, which is the initial member of a homologous series of parasympathomimetic substances including acetyl-*nor*-choline[2] (acetoxymethyltrimethylammonium bromide), acetylcholine, and acetyl-*homo*-choline[3] (3-acetoxy-*n*-propyltrimethylammonium bromide), seems not to have been previously described. This substance may be considered to be an acetylated derivative of trimethylamine-*N*-oxide, or as a quaternary hydroxylammonium salt. It has been found possible to prepare the substance by the reaction of acetyl peroxide with trimethylamine:

$$Ac_2O_2 + Me_3N \longrightarrow (Me_3NOAc)^+ + OAc^-$$

Attempts to make the compound by other routes, such as the reaction of trimethylamine with lead tetraacetate, acetylation of trimethylamine-*N*-oxide with acetyl bromide, and methylation of the *O*-acetyl-*N*-dimethylhydroxylamine with methyl iodide seem to have led to poor yields of highly impure material, since biological assay of the crude products showed only low levels of parasympathomimetic activity.

The assigned structure is supported both by the analytical data, and by the properties of the substance. The presence of a trimethylamino group was indicated by the formation of trimethylamine on both acid and alkaline hydrolysis. Reaction with Hestrin's[4] reagent solutions (alkaline hydroxylamine followed by acidified ferric chloride), which indicates the presence of an ester-like linkage, proceeded somewhat more slowly than with acetylchlorine, 15 minutes being required at 25°. The product had the same molar extinction coefficient at 540 mμ as acetylcholine.

N-Acetoxytrimethylammonium bromide shows parasympathomimetic properties. The substance causes the contraction of guinea pig ileum at $1.7 \times 10^{-6}M$, an action which is prevented by atropine, $4.8 \times 10^{-5}M$. The substance also stimulates eserinized leech dorsal muscle at $1.7 \times 10^{-5}M$, and eserinized frog *rectus abdominis* muscle at $4.3 \times 10^{-6}M$.

N-Acetoxytrimethylammonium bromide is not hydrolyzed by the acetylcholinesterase of guinea pig brain, but is hydrolyzed by horse serum cholinesterase about one-tenth as rapidly as acetylcholine. *N*-Acetoxytrimethylammonium bromide, $1.8 \times 10^{-3}M$, does not inhibit the action of horse serum cholinesterase on acetylcholine.

EXPERIMENTAL

N-Acetoxytrimethylammonium bromide. To 118 g. of a 25% solution of acetyl peroxide (0.25 mole) in dimethyl phthalate,[5] cooled to −5°, was added over 2 hr. 7.4 g. of trimethylamine (0.125 mole) in 25 ml. of sodium-dried ether. (Insufficient cooling has led to explosions.) The reaction mixture was kept at −5° for 48 hr., and was then shaken with 100 ml. of water and 60 ml. of ether. The *p*H of the aqueous layer, originally about 4.6, was adjusted to 3.6 by adding about 12 ml. of concentrated hydrobromic acid, and was reextracted with about ten 50-ml. portions of ether until a test for peroxides with starch-iodide paper was negative. The *p*H was continuously readjusted to 3.6 during this process. The aqueous solution was concentrated under reduced pressure to a crystalline mass, which was dried *in vacuo* over phosphorus pentoxide. The dried solid was refluxed with several 100-ml. portions of dry chloroform, and the extracts were chilled overnight at −5°. The crystals that appeared were filtered off, washed with cold chloroform, and dried *in vacuo* over phosphorus pentoxide. The yield was usually about 3.5 g. The substance (noticeably hygroscopic) melted at 148° with gas evolution.

Anal. Calcd. for $C_5H_{12}O_2NBr$: C, 30.32; H, 6.11; N, 7.07; Br, 40.35. Found:[6] C, 29.65; H, 6.78; N, 6.67; Br, 39.34.

The data indicate the presence of about 2% of water. The chloroplatinate melted at 242°, the chloroaurate at 145°, and the reineckate at 159°. All melting points have been corrected.

Hydrolysis of N-acetoxytrimethylammonium bromide. The substance (0.1 g.) was refluxed with 5.0 ml. of 0.1*M* hydrobromic acid for 1 hr. The hydrolyzate was evaporated to dryness *in vacuo*, and the residue crystallized from alcohol and ether. The product melted at 245°. A mixed melting point with an authentic sample of trimethylamine hydrobromide (melting point, 245°) showed no depression. Treatment of the substance with alkali, and aeration of the gaseous product into dilute hydrobromic acid, yielded the same product.

Anal. Calcd. for $C_3H_{10}NBr$: C, 25.79; H, 7.20; N, 10.00. Found:[6] C, 25.84; H, 7.33; N, 9.94.

Enzyme and pharmacological tests. The tests for susceptibility to acetylcholinesterase and cholinesterase were made manometrically, as described by Augustinsson.[7] The assays with guinea-pig ileum, leech dorsal muscle, and frog *rectus*

(1) Supported by grants from the National Heart Institute (H-2321), and the National Science Foundation (G-2500).

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(6) By Joseph F. Alicino, Box 267, Metuchen, N. J.

(7) K. B. Augustinsson, *Acta Physiol. Scand.*, **15**, Suppl. 52, 37 (1948).