205, granted by the Research Institute of the University of Texas.

Summary

1. The ionization constants of *n*-butyric acid in 5, 10 and 20 weight per cent. isopropyl alcohol have been determined from 0 to 40° by use of cells without liquid junction.

2. The ionization constants and standard thermodynamic quantities have been expressed as functions of temperature.

Austin, Texas Received April 21, 1948

[Contribution from the Research Laboratories of the J. T. Baker Chemical Co.]

Some New Compounds Related to Amidone

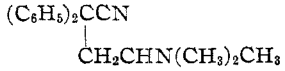
By John H. Gardner, Nelson R. Easton[1] and Joseph R. Stevens

The availability of the two isomeric nitriles prepared as intermediates in the synthesis of the Amidones[2] aroused interest in their application for the synthesis of other compounds of possible value. A number of these substances have now been prepared.

4-Dimethylamino-2,2-diphenylpentanenitrile (I), the higher melting of the two isomeric nitriles, was hydrolyzed with 72% sulfuric acid to the corresponding acid (II). This was isolated first as the bisulfate, from which the free acid was prepared. For the preparation of esters, the bisulfate was treated with thionyl chloride and the crude product brought into reaction with the alcohol. In this way, methyl, ethyl and β-dimethylaminoethyl 4-dimethylamino-2,2-diphenylpentanoates were prepared. These esters were isolated as the hydrochlorides.

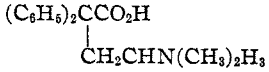
On attempting to prepare the corresponding isopropyl ester, the only product isolated in sufficient quantity and purity for identification was a neutral substance which was indicated by analysis to be 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (III).

The same compound was formed when the free acid was used instead of the bisulfate. It is probable that the pyrrolidone was one of the products formed in the reaction of the acid (II) with thionyl chloride as a similar compound was obtained when 4 - dimethylamino - 2,2 - diphenyl - 3 - methylbutanoic acid (IV) was allowed to react with thionyl chloride, without the addition of an alcohol. Similar compounds were obtained by Blicke and Zambito[3] by hydrolysis of the imides resulting from the action of alcoholic hydrogen chloride on acids closely related to II and IV.



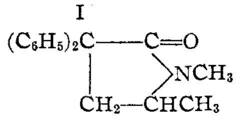
$(C_6H_5)_2C(CN)CH_2CHN(CH_3)_2CH_3$

I

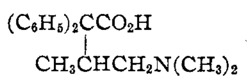


$(C_6H_5)_2C(CO_2H)CH_2CHN(CH_3)_2H_3$

II



III



$(C_6H_5)_2C(CO_2H)CH_3CHCH_2N(CH_3)_2$

IV

Isopropyl 4-dimethylamino-2,2-diphenylpentanoate was prepared by the reaction of the silver salt of the acid with isopropyl iodide. It was isolated as the hydrochloride.

The isomeric acid (IV) was prepared in a similar manner from the corresponding nitrile. Attempts to prepare esters by way of the acid chloride gave only 1,4-dimethyl-3,3-diphenyl-2-pyrrolidone. Ethyl 4-dimethylamino-2,2-diphenyl-3-methylbutanoate was prepared by the reaction of the silver salt of the acid with ethyl iodide. The ester was characterized as the hydrochloride.

In working up the residues from the isolation of 6 - dimethylamino - 4,4 - diphenyl - 5 - methyl-3-hexanone (Isoamidone II) oxalate,[2d] an oxygen-free base was isolated in substantial amounts. This has been identified as 1-dimethylamino-3,3-diphenyl-2-methylpropane (V) through its formation by the decyanation of 4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile (VI) with sodium and isopropyl alcohol.

$$(CH_3)_2NCH_2CH(CH_3)CH(C_6H_5)_2$$

V

$$(CH_3)_2NCH_2CH(CH_3)C(C_6H_5)_2CN$$

VI

Experimental

4-Dimethylamino-2,2-diphenylpentanoic Acid Bisulfate.—A solution of 200 g. of 4-dimethylamino-2,2-diphenylpentanenitrile in a mixture of 240 ml. of concentrated sulfuric acid and 140 ml. of water was heated at 145–150° for about five hours. It was cooled and the crystals which formed were filtered out and washed with absolute alcohol. The yield was 278.5 g., m. p. 221–223° after crystallization from methanol.

Anal. Calcd. for $C_{19}H_{23}NO_2 \cdot H_2SO_4$. C, 57.70; H, 6.37; N, 3.54; S, 8.11. Found: C, 57.85; H, 6.56; N, 3.63; S, 8.27.

4-Dimethylamino-2,2-diphenylpentanoic Acid.—The acid bisulfate was dissolved in sufficient hot 5% sodium hydroxide to give a solution alkaline to phenolphthalein. This was treated with Nuchar W and filtered. The filtrate was acidified with 30% acetic acid, chilled and filtered. The yield of crude acid, m. p. 203–203.5°, was 88%. Crystallization from alcohol and drying at 100° under 2 mm. pressure raised the m. p. to 204–205°.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71. Found: C, 76.80; H, 7.78; N, 4.75.

4-Dimethylamino-2,2-diphenylpentanoyl Chloride Sulfate.—To 50 g. of the acid bisulfate, 75 ml. of thionyl

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[1] Present address, Lehigh University, Bethlehem, Pa.

[2] (a) O. P. B. Report PB 981, p. 96; (b) E. M. Schultz, C. M. Robb and J. M. Sprague, This Journal, **69**, 188 (1947); W. R. Brode and M. W. Hill, *ibid.*, **69**, 724 (1947); N. R. Easton, J. H. Gardner, M. L. Evanick and J. R. Stevens, *ibid.*, **70**, 76 (1948).

[3] F. F. Blicke and A. J. Zambito, abstracts of papers presented at the meeting of the American Chemical Society, Atlantic City, N. J., April, 1947, p. 3K.

chloride was added. After the initial reaction had subsided, the mixture was heated on the steam-bath for two hours. The excess thionyl chloride was distilled. Benzene was added and the solid which separated was filtered out, washed with benzene and with ether and dried in a vacuum desiccator. The yield was 50 g. This was used without purification.

Methyl 4-Dimethylamino-2-diphenylpentanoate Hydrochloride.—A mixture of 20 g. of the acid chloride sulfate and 30 ml. of methanol was refluxed for two hours. It was poured into 200 ml. of water and the solution was made alkaline to phenolphthalein with 10% sodium hydroxide. It was extracted three times with ether and the ether extract was washed with water. It was dried over magnesium sulfate and filtered. A 30% solution of hydrogen chloride in absolute alcohol was added to congo red acidity. An oil separated which soon crystallized on scratching. After chilling overnight, the crystals were filtered out and recrystallized from a mixture of isopropyl alcohol and di-isopropyl ether. The yield was 11.1 g., m. p. 187.5–188.5°.

Anal. Calcd. for $C_{20}H_{25}O_2N{\cdot}HCl$: C, 69.05; H, 7.53; N, 4.03; Cl, 10.19. Found: C, 68.70; H, 7.86; N, 3.94; Cl, 10.30.

Ethyl 4-Dimethylamino-2,2-diphenylpentanoate Hydrochloride.—This was prepared and isolated similarly to the methyl ester; m. p. 151–152°.

Anal. Calcd. for $C_{21}H_{27}NO_2{\cdot}HCl$: C, 69.69; H, 7.80; N, 3.87; Cl, 9.80. Found: C, 69.60; H, 7.84; N, 3.90; Cl, 9.70.

Dimethylaminoethyl 4-Dimethylamino-2,2-diphenylpentanoate Dihydrochloride.—This was prepared and isolated by a procedure similar to that used for the methyl ester; m. p. 207–208°.

Anal. Calcd. for $C_{23}H_{32}N_2O_2{\cdot}2HCl$: C, 62.58; H, 7.76; N, 6.35; Cl, 16.06. Found: C, 62.35; H, 7.67; N, 6.35; Cl, 15.80.

1,5-Dimethyl-3,3-diphenyl-2-pyrrolidone.—A mixture of 20 g. of 4-dimethylamino-2,2-diphenylpentanoic acid and 20 ml. of purified thionyl chloride was refluxed for two hours. The excess thionyl chloride was distilled in partial vacuum and 50 ml. of isopropyl alcohol was added. After refluxing three hours, the mixture, when cooled in the refrigerator overnight, deposited 17.5 g. of crystals, m. p. 120–122°. These were recrystallized from isopropyl alcohol and then from ethyl alcohol and dried at 60° in a vacuum oven; m. p. 121–122°. More of the same compound was isolated from the original mother liquors.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.55; H, 7.27; N, 5.29.

The same substance was isolated also when 4-dimethylamino-2,2-diphenylpentanoic acid bisulfate was used as the starting material.

Silver 4-Dimethyl-2,2-diphenylpentanoate.—To a solution of 0.8 g. of sodium in 25 ml. of absolute alcohol there was added 10 g. of 4-dimethylamino-2,2-diphenylpentanoic acid. The solution was neutralized to Brilliant Yellow paper with glacial acetic acid and, after dilution with 25 ml. of absolute alcohol, was heated to boiling. A solution of 5.8 g. of silver nitrate in 50 ml. of boiling absolute alcohol was added. A white precipitate formed. After cooling, this was filtered out, washed with alcohol and dried in a vacuum desiccator. The yield was 8.5 g. of 88% silver salt (calcd. for $C_{19}H_{22}NO_2Ag$: Ag, 26.69. Found: Ag, 23.60). A solution of the compound in cold, dilute nitric acid gave no precipitate with hydrochloric acid.

Isopropyl 4-Dimethylamino-2,2-diphenylpentanoate Hydrochloride.—To a suspension of 7.7 g. of silver 4-dimethylamino-2,2-diphenylpentanoate in 50 ml. of acetone there was added 5 ml. (8.5 g.) of isopropyl iodide. The mixture was stirred at room temperature an hour and then under reflux a second hour. It was filtered and the filtrate evaporated to dryness on a steam-bath and finally dried in a vacuum desiccator. The residue was a mixture of sirup and a solid. It was dissolved in 15 ml. of acetone and the turbid solution was filtered. To the filtrate 2 ml. of concentrated hydrochloric acid was added. An oily layer separated. Isopropyl alcohol was added, precipitating 0.7 g. of an unidentified yellow, waxy solid, which was filtered out.

Cautious dilution of the hot filtrate with di-isopropyl ether and chilling gave a small quantity of 4-dimethylamino-2,2-diphenylpentanoic acid hydrochloride of m. p. 210–213°, dec., which melted at 212–215°, dec., when mixed with a purified sample, m. p. 217.5°, dec.

The filtrate from the acid hydrochloride was diluted with a large volume of di-isopropyl ether, precipitating an oil which crystallized after a month in the refrigerator. This was crystallized from a mixture of isopropyl alcohol and di-isopropyl ether. The yield was 2.1 g., m. p. 161–162° after drying at 100° in a vacuum.

Anal. Calcd. for $C_{22}H_{29}NO_2{\cdot}HCl$: C, 70.28; H, 8.04; N, 3.73; Cl, 9.43. Found: C, 70.15; H, 8.02; N, 3.71; Cl, 9.44.

4-Dimethylamino-2,2-diphenylpentanoic Acid Hydrochloride.—On attempting the direct esterification of the acid with various alcohols in the presence of hydrogen chloride or sulfuric acid, and working up in the usual way, the only definite product isolated was the acid hydrochloride, m. p. 217°, dec., after crystallization from a mixture of acetone and ethyl alcohol.

Anal. Calcd. for $C_{19}H_{23}NO_2{\cdot}HCl$: N, 4.20; Cl, 10.62. Found: N, 4.13; Cl, 10.61.

4-Dimethylamino-2,2-diphenyl-3-methylbutanoic Acid.—4-Dimethylamino-2,2-diphenyl-3-methylbutanenitrile was hydrolyzed by the procedure used for the isomer. The initial product was presumably the bisulfate but attempts to purify it were unsuccessful. For conversion to the free acid, the procedure described for the isomeric acid was used. The crude acid came down as a gelatinous mass. After repeated crystallization from alcohol, the acid formed firm crystals which melted at 176–178° without decomposition. Less pure material melted at nearly the same temperature but less sharply and with decomposition.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71. Found: C, 76.85; H, 7.74; N, 4.63.

On attempting to esterify the acid with ethyl alcohol in the presence of hydrochloric acid, the only identifiable product was the hydrochloride of the acid, which melted at 205–208° after crystallization from ethyl alcohol and drying at 100° in a vacuum.

Anal. Calcd. for $C_{19}H_{23}NO_2{\cdot}HCl$: N, 4.20; Cl, 10.62. Found: N, 4.08; Cl, 10.5.

1,4-Dimethyl-3,3-diphenyl-2-pyrrolidone.—This was obtained in a quantitative yield by treating 4-dimethylamino-2,2-diphenyl-3-methylbutanoic acid with thionyl chloride and then with ethyl alcohol or with water; m. p. 122–123° after crystallization from dilute alcohol. A mixture with 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone melted at 102–112°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.35; H, 7.06; N, 5.19.

Silver 4-Dimethylamino-2,2-diphenyl-3-methylbutanoate.—This was prepared similarly to the isomer and was obtained as a brown powder which was not purified.

Ethyl 4-Dimethylamino-2,2-diphenyl-3-methylbutanoate Hydrochloride.—To 8.4 g. of the silver salt suspended in 50 ml. of acetone, 3 ml. of ethyl iodide was added. The mixture was stirred an hour at room temperature and then two and a half hours under reflux. It was then filtered and the filtrate evaporated to a mixture of an oil and crystals. This was taken up in anhydrous ether and filtered from a small, yellow residue.

An excess of alcoholic hydrogen chloride was added to the filtrate, followed by dry ether. An oil separated. The upper layer was decanted. The lower layer was dissolved in hot absolute alcohol and di-isopropyl ether was added just short of turbidity. The oil which separated on cooling crystallized on standing two weeks in the refrigerator, with occasional scratching. By diluting the various mother liquors with di-isopropyl ether and seeding with these crystals, more of the same material was obtained.

The combined crystals were recrystallized from a mixture of ethyl alcohol and di-isopropyl ether. The yield was 1.5 g., m. p. 191–192°, after drying at 100° in a vacuum.

Anal. Calcd. for $C_{21}H_{27}NO_2\cdot HCl$: C, 69.69; H, 7.80; N, 3.87; Cl, 9.80. Found: C, 69.5, 69.3; H, 7.72, 7.56; N, 3.57; Cl, 9.54.

1-Dimethylamino-3,3-diphenyl-2-methylpropane and Salts.—After the removal of 6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanone (Isoamidone II) oxalate from the material obtained by the hydrolysis of the crude ketimine, there remained a mixture of oxalates. A solution of 30.5 g. of this mixture in 300 ml. of 20% hydrochloric acid was boiled eight hours. It was made alkaline to phenolphthalein with sodium hydroxide and extracted three times with ether. A solution of 30 g. of oxalic acid in alcohol was added to the ether solution. The crystals which separated on cooling were recrystallized three times from a mixture of acetone and alcohol. The yield was 7.1 g., m. p. 138–140°.

Anal. Calcd. for $C_{18}H_{23}N\cdot H_2C_2O_4$: C, 69.97; H, 7.29; N, 4.08; $H_2C_2O_4$, 26.24; neut. equiv., 171.5. Found: C, 70.00; H, 7.40; N, 4.14, 4.06; $H_2C_2O_4$, 25.90; neut. equiv., 169.5.

The picrate was prepared by the action of picric acid on the base in alcohol; m. p. 127–129° after crystallization from alcohol and drying at 100°.

Anal. Calcd. for $C_{18}H_{23}N\cdot C_6H_3N_3O_7$: C, 59.75; H, 5.39; N, 11.62. Found: C, 59.55; H, 5.43; N, 11.58, 11.58.

The base was liberated from the oxalate; b. p. 144–150° under 2 mm.

Anal. Calcd. for $C_{18}H_{23}N$: C, 85.37; H, 9.09; N, 5.53. Found: C, 85.45; H, 9.08; N, 5.54.

For the preparation of the hydrochloride, 2 g. of the base was dissolved in a mixture of 1.7 ml. of 20% hydrochloric acid and 2 ml. of water. The mixture was evaporated to dryness and the residue crystallized from isopropyl alcohol and dried at 100° in vacuum. The yield was 1.86 g., m. p. 181.5–183°.

Anal. Calcd. for $C_{18}H_{23}N\cdot HCl$: C, 74.61; H, 8.29; N, 4.84; Cl, 12.26. Found: C, 74.60; H, 8.24; N, 4.80; Cl, 12.30.

Preparation of 1-Dimethylamino-3,3-diphenyl-2-methylpropane from 4-Dimethylamino-2,2-diphenyl-3-methylbutanenitrile.—To a solution of 20 g. of the nitrile in 500 ml. of isopropyl alcohol, there was added 50 g. of sodium. After the reaction subsided, the mixture was boiled one and a half hours. Water and alcohol were added to destroy the remaining sodium. The mixture was poured into water and extracted with ether. The extract was washed with water. Treatment with oxalic acid in the usual way gave 15 g. of the oxalate, m. p. 134–137°. A portion was converted into the picrate, m. p. 128–130°. There was no depression on mixing with 1-dimethylamino-3,3-diphenyl-2-methylpropane picrate obtained as described above.

Acknowledgment.—We are indebted to Dr. V. B. Fish for the analyses and to Miss Mary L. Evanick for technical assistance.

Summary

1. A series of acids and esters derived from the nitriles obtained as intermediates in the synthesis of the Amidones has been prepared.

2. Two anomalous reactions of these nitriles have been studied.

PHILLIPSBURG, NEW JERSEY RECEIVED APRIL 6, 1948

[CONTRIBUTION FROM THE LOS ALAMOS SCIENTIFIC LABORATORY OF THE UNIVERSITY OF CALIFORNIA, LOS ALAMOS, N. M.]

Utilization of Nicotinic Acid and its Amide by the Human Erythrocyte in Vitro[1]

BY EDGAR LEIFER, JOHN R. HOGNESS, LLOYD J. ROTH AND WRIGHT LANGHAM

Recent investigations by Hoagland, Ward and Shank,[1a] and Handler and Kohn[2] indicate that nicotinic acid is a precursor of coenzyme in the human erythrocyte *in vivo* and *in vitro*, whereas nicotinamide is not. In view of these reports, it was felt that studies of the utilization of nicotinic acid and its amide, using tracer techniques, would be of value. These compounds "labeled" with C^{14} have recently been synthesized.[3a,b] *In vitro* studies of the transport of nicotinic acid, nicotinamide, as well as *p*-aminobenzoic acid (all "labeled" with C^{14} in the carboxyl group) are discussed in this paper. Previous *in vitro* investigations have given inconclusive results. Axelrod, Spies and Elvehjem[4] report that nicotinamide is effective for coenzyme synthesis; Handler and Kohn[2] find that at best the amide is only one-third as potent as nicotinic acid. *In vivo* determinations (mice) will be reported along with gross metabolism studies.

Procedure

Five cc. lots of whole, sterile, heparinized, human venous blood were pipetted into a number of sterile stoppered flasks; 0.5 cc. of C^{14} "labeled" nicotinic acid solution (approximately 3,000 counts/sec./cc., equivalent to 0.05 mg. of nicotinic acid) were added to one third of the flasks; 0.5 cc. of C^{14} "labeled" *p*-aminobenzoic acid solution (approximately 3,000 counts/sec./cc., equivalent to 0.05 mg. of *p*-aminobenzoic acid) were added to the second third; and 0.5 cc. of C^{14} "labeled" nicotinamide (approximately 3,650 counts/sec./cc., equivalent to 0.05 mg. of nicotinamide/cc.) were added to the remaining flasks. The contents of the flasks were thoroughly mixed and the temperature maintained at 37°. The flasks were shaken slowly and continuously throughout the experiment. An atmosphere of 5% carbon dioxide in oxygen was provided to maintain normal *p*H.

At various intervals, 0.5-cc. aliquots were withdrawn from each flask, introduced into centrifuge tubes and centrifuged; 0.05 cc. of the supernatant plasma from each tube was plated on copper discs and counted using a helium–alcohol filled G. M. tube with a thin mica window (1.7 mg./sq. cm.). The remaining plasma was removed and the cells were laked with distilled water up to 0.5 cc.; 0.05 cc. of the laked cells were plated and the radioactivity

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(1) This document is based on work performed under Contract Number W-7405-eng-36 for the Atomic Energy Project, and the information covered therein will appear in Division V of the National Nuclear Energy Series (Manhattan Project Technical Section) as part of the contribution of the Los Alamos Laboratory.

(1a) Chas. L. Hoagland, S. M. Ward and R. E. Shank, *J. Biol. Chem.*, **151**, 369 (1943).

(2) Philip Handler and Henry I. Kohn, *ibid.*, **150**, 447 (1943).

(3) (a) Arthur Murray, W. W. Foreman and Wright Langham, THIS JOURNAL, **70**, 1037 (1948); (b) Arthur Murray and Wright Langham, unpublished.

(4) A. E. Axelrod, Tom D. Spies and C. A. Elvehjem, *J. Biol. Chem.*, **138**, 667 (1941).