temperature was maintained below 45° until the exothermic reaction stopped. Excess dimethyl sulfate was decomposed by heating to 90° for two hours. The upper layer of the reaction mixture was washed with water, dried, and fractionally distilled at reduced pressure to give a 60% yield of the ether. Calculated for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.37; H, 9.98.

**Cyclohexyl Methyl Ether.**[17]—Anisole (750 g., 7 moles) was hydrogenated in the presence of 75 g. of nickel-on-kieselguhr catalyst at 180° to give 600 g. of ether, 76%.

**Cyclopropyl Methyl Ether.**—Glycerol was brominated, in approximately 18 mole runs, to glycerol $\alpha,\gamma$-dibromohydrin, in 60% yields, following the procedure of Braun.[18] The dibromohydrin (10.8 moles, 2347.5 g.) was treated with 1449 g. (11.5 moles) of dimethyl sulfate according to Krantz and co-workers.[19] A mixture of 212 g. (2 moles) of sodium carbonate, 600 g. (4 moles) of sodium iodide, 390 g. (6 moles) of zinc dust, and 400 g. (6.7 moles) of acetamide was heated to 120–125° and 2 moles (464 g.) of the 1,3-dibromo-2-methoxypropane was added slowly, all according to Krantz and co-workers.[19] A 50% yield (72 g.) of crude ether was obtained. It was found to contain approximately 13% propionaldehyde, presumably formed from unreacted dibromohydrin, which forms an azeotrope (b. p. 43°) with the cyclopropyl methyl ether. It was heated with sodium bisulfite solution and fractionally distilled over sodium hydroxide pellets.

## Summary

The physical constants of 24 pure ethers of various types, together with a description of the preparative method for each ether, have been presented. The synthesis, purification, and physical constants of *t*-butyl methallyl ether and *p*-*t*-butylanisole have been described for the first time.

CLEVELAND, OHIO RECEIVED FEBRUARY 20, 1947

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[17] E. M. van Duzee and Homer Adkins, THIS JOURNAL, **57**, 147 (1935).

[18] Braun, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 308.

[19] J. C. Krantz, Jr., C. J. Carr, S. E. Forman and Wm. E. Evans, Jr., *J. Pharmacol.*, **69**, 207–220 (1940); J. C. Krantz, Jr., and N. L. Drake, U. S. Patent 2,330,979 (October 5, 1944).

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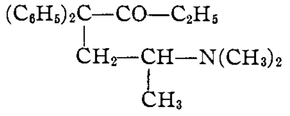
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, MEDICAL RESEARCH DIVISION, SHARP AND DOHME, INC.]

# The Reaction of 1-Dimethylamino-2-chloropropane with Diphenylacetonitrile. The Structure of Amidone

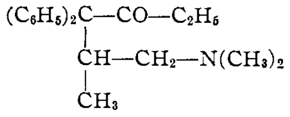
BY EVERETT M. SCHULTZ, CHARLES M. ROBB AND JAMES M. SPRAGUE

In the United States Department of Commerce report[1] that first disclosed the new German analgesic drug, Amidone or No. 10820, in this country, it was noted that the method given by the German chemists for the synthesis would not be expected to lead to the structure I, which was assigned by the Germans, but rather to lead to the isomeric structure II. This uncertainty of the structure is further indicated by recent publications[2] in which the structure I is given for the compound but a chemical name for the structure II is used. In a recent note[3] from this Laboratory, structure I was established for this drug. The present paper describes the details of this structure proof.



$$\begin{array}{l}(C_6H_5)_2C{-}CO{-}C_2H_5\\ \qquad\; |\\ \qquad\; CH_2{-}CH{-}N(CH_3)_2\\ \qquad\qquad\quad |\\ \qquad\qquad\quad CH_3\end{array}$$

I



$$\begin{array}{l}(C_6H_5)_2C{-}CO{-}C_2H_5\\ \qquad\; |\\ \qquad\; CH{-}CH_2{-}N(CH_3)_2\\ \qquad\; |\\ \qquad\; CH_3\end{array}$$

II

The reaction of diphenylacetonitrile with 1-dimethylamino-2-chloropropane either in the presence of sodamide according to the German procedure or in the presence of potassium *t*-butoxide led to a high yield of a semisolid product from which the isomeric nitriles III and IV were isolated in approximately equal amounts. The high-melting nitrile (IV, m. p. 90–91°) reacted smoothly with ethylmagnesium bromide to give Amidone (I). The low-melting nitrile (III, m. p. 66–67°) on treatment with the Grignard reagent did not give the Amidone isomer II but instead a dibasic product that appears to be the corresponding ketimine V. Although analytical data support the ketimine structure, the ordinary condition of hydrolysis failed to give the ketone.[4]

The structures of the isomeric nitriles, and hence the structure of Amidone, were established by decomposition of the quaternary bases derived from the methiodides of the nitriles by treatment with silver oxide. Two isomeric unsaturated nitriles,[5] VI and VII were obtained. Although the analyses and molecular weights support the unsaturated nitrile structure, neither of these compounds exhibited typical unsaturation reactions. They did not absorb bromine in carbon tetrachloride solution and did not decolorize permanganate in neutral acetone solution except on long standing. No uptake of hydrogen was observed when methanolic solutions were shaken with hydrogen and

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[1] Office of the Publication Board, Department of Commerce, Report No. PB-981, page 96-A.

[2] Scott and Chen, *J. Pharmacol.*, **87**, 63 (1946); Scott, Robbins and Chen, *Science*, **104**, 587 (1946); Scott, *et al.*, *Anesthesia and Analgesia*, **26**, 12, 18 (1947).

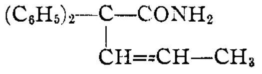
[3] Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188 (1947).

[4] Easton, Gardner and Stevens, *ibid.*, **69**, 976 (1947).

[5] No attempt was made to locate definitely the position of the double bond in VII. The structure indicated seems probable. However, the isomeric structure, 2,2-diphenyl-4-pentenenitrile, is not excluded.

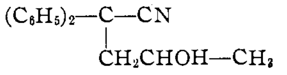
platinum oxide catalyst for several hours. While such behavior was unexpected it may be considered to be in accord with the hindered position of the double bond. 2,2-Diphenyl-4-pentenenitrile, $(C_6H_5)_2C(CH_2{-}CH{=}CH_2)CN$, which is isomeric with VII and differs only in the position of the double bond,[5] was prepared from diphenylacetonitrile and also found to be inert to the above reagents. The hydrogenation of the unsaturated nitriles, VI and VII, at 145° using Raney nickel catalyst in the presence of ammonia yielded the primary amines VIII and IX. These same amines were prepared by hydrogenation of the nitriles X and XI that were prepared by alkylation of diphenylacetonitrile with *n*-propyl or isopropyl iodide. The identity of the amines prepared by the two procedures was established by the comparison of their physical properties and the properties of their derivatives.

In the degradation of the quaternary base derived from the high-melting nitrile IV, two products were isolated in addition to the expected unsaturated nitrile VII. One of these products, m. p. 114–115°, was basic and contained nitrogen. It was distilled under diminished pressure without appreciable decomposition but in contact with dilute mineral acids it readily lost nitrogen as ammonia to give a neutral nitrogen-free substance. This latter compound, m. p. 111–112°, exhibited properties of a lactone. These properties and analytical values together with the results of molecular weight determination pointed to the cyclic imino-ether XII and the corresponding lactone XIII for these compounds. The imino-ether structure is supported further by its formation in good yield in the reaction of propylene oxide with diphenylacetonitrile in the presence of potassium *t*-butoxide.[6] The second product from the degradation of the nitrile quaternary base was isolated in small amounts and was not completely characterized. The analytical values and neutral properties suggest either the amide XIV or the hydroxy nitrile XV. However, the hydroxy-nitrile structure appears unlikely since it would be expected to cyclize to yield the imino-ether XII.



$$(C_6H_5)_2{-}\underset{\displaystyle CH{=}CH{-}CH_3}{\underset{|}{C}}{-}CONH_2$$

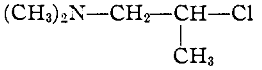
XIV



$$(C_6H_5)_2{-}\underset{\displaystyle CH_2CHOH{-}CH_3}{\underset{|}{C}}{-}CN$$

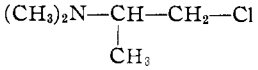
XV

While the results that are discussed above make it apparent that the isomeric nitriles arose as a consequence of a rearrangement, the point at which the rearrangement occurred is not settled. It seems likely that under the influence of alkaline condensing agents, 1-dimethylamino-2-chloropropane gave rise to an ethylenimonium ion XVIII[7] which then reacted with the diphenylacetonitrile to yield the two isomeric nitriles, III and IV. However, Brode and Hill[8] have recently reported data from which they conclude that the isomeric 1,2-dimethylamino-chloropropanes, XVI and XVII, can rearrange during the isolation of the bases from their hydrochlorides. These workers conclude, therefore, that the chloroamine that was prepared from 1-dimethylamino-2-propanol may be either of the two isomeric chloroamines or an equilibrium mixture of the two. The results of our work with these isomeric chloroamines are not in accord with this conclusion. Our data[9] support the conclusion that the chloroamine derived from 1-dimethylamino-2-propanol is in fact 1-dimethylamino-2-chloropropane and that this chloroamine does not undergo rearrangement either during the liberation from the hydrochloride or during distillation. Since this is the chloroamine employed in the reaction with diphenylacetonitrile, it follows that the rearrangement leading to the formation of isomeric nitriles occurred in the condensation reaction, probably through the intermediate imonium ion.



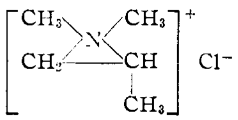
$$(CH_3)_2N{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}Cl$$

XVI



$$(CH_3)_2N{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_2{-}Cl$$

XVII



XVIII

Relatively large amounts of diphenylacetonitrile were needed for this work. While the preparation of this compound by the bromination of benzyl cyanide followed by the reaction with benzene in the presence of aluminum chloride has been reported,[10] complete experimental details were not found in the literature. A satisfactory experimental procedure was developed incidental to this investigation.

## Experimental[11,12]

**Condensation of Diphenylacetonitrile with 1-Dimethylamino-2-chloropropane.**—The chloroamine was prepared from 1-dimethylamino-2-propanol (b. p. 120–125°) by treatment with thionyl chloride in benzene[1] and had the following properties: b. p. 62–63° (100–110 mm.), $n^{20}_D$ 1.4250, hydrochloride m. p. 185–186°.

**A. Using Sodamide.**—A yield of 138.3 g. (79%) of mixed nitriles was obtained from a 0.63-mole run that was carried out by the German procedure.[1]

**B. Using Potassium *t*-Butoxide.**—In a 500-ml., three-necked flask fitted with a reflux condenser, a mechanical stirrer and a gas inlet tube, was placed dry xylene (15 ml.) and dry *t*-butyl alcohol (154 ml.). The flask was placed in a "Glas-Col" heater. Potassium (8.6 g., 0.22 mole) was added in small pieces over a period of ninety minutes while a slow stream of dry nitrogen was led through the flask. The mixture then was refluxed until all the potassium was dissolved (two–four hours).

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[6] Easton, Gardner and Stevens, 111th Meeting, American Chemical Society, Atlantic City, N. J., April, 1947, Abstracts 4 K report similar results with this reaction employing sodamide as condensing agent.

[7] *Cf.* Bergman, Fruton, *et al.*, *J. Org. Chem.*, **11**, 517–591 (1946).

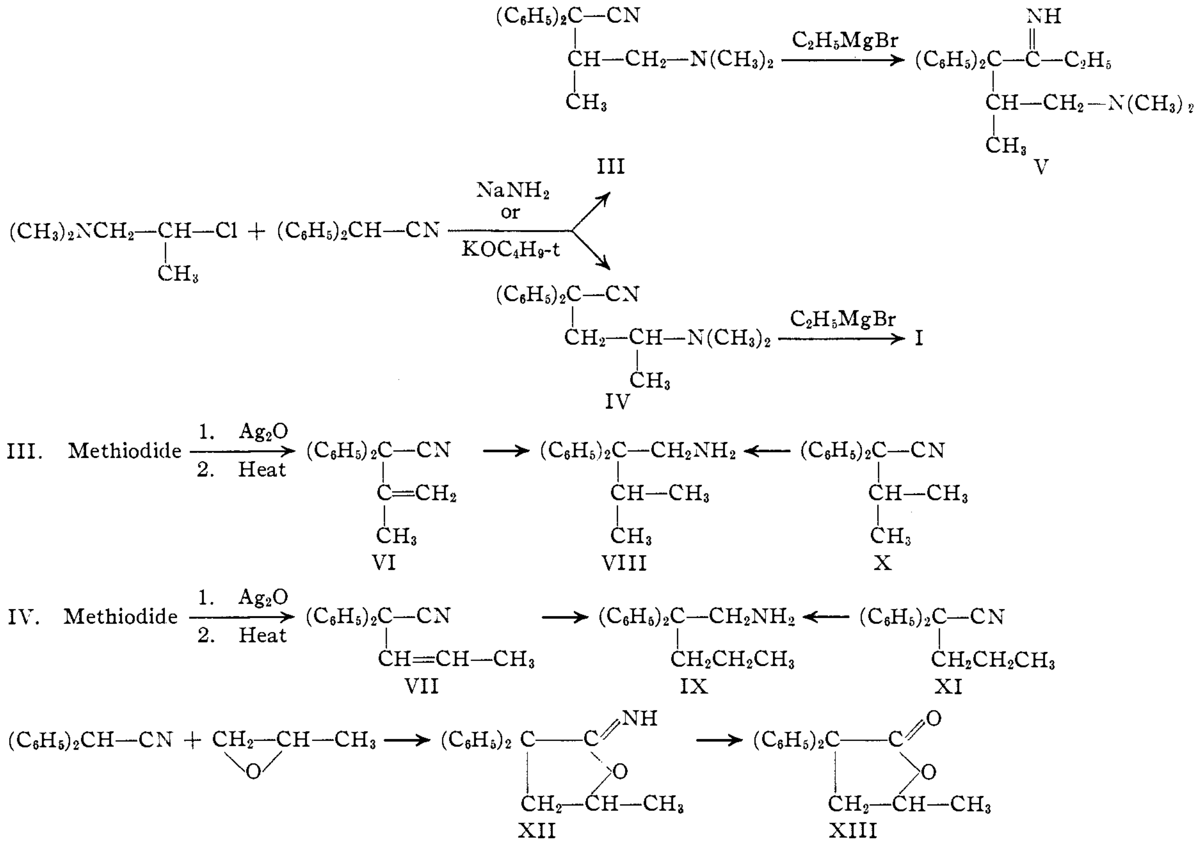
[8] Brode and Hill, THIS JOURNAL, **69**, 724 (1947).

[9] Data to be published.

[10] Hoch, *Compt. rend.*, **197**, 770 (1933).

[11] All melting points and boiling points are uncorrected.

[12] We are indebted to Mr. K. B. Streeter and to the Misses Thelma Plank and Ruth Lynch for the analytical data.



The heat was removed and diphenylacetonitrile (42.5 g., 0.22 mole) was added in one portion with stirring. A deep red solution resulted. The solution was boiled gently and, with stirring, 1-dimethylamino-2-chloropropane (30.4 g., 0.25 mole) was added by means of a dropping funnel which replaced the gas inlet tube. The addition was completed in thirty minutes and heating was continued for two and one-half hours. The color of the reaction mixture changed from red to pale yellow and potassium chloride separated. The alcohol was removed by distillation. Water was added to dissolve the inorganic material and the mixture extracted with ether. The ether layer was extracted with dilute hydrochloric acid. The addition of sodium hydroxide solution (20%) to the acid extract liberated an oil that was taken up in ether and the ether solution dried with anhydrous sodium sulfate. Upon evaporation of the solvent, there was obtained 57.2 g. (92%) of a semi-solid mixture of the two nitriles III and IV.

**2,2-Diphenyl-4-dimethylaminopentanenitrile** (IV).—The semi-solid mixture of the isomeric aminonitriles (57.2 g.) was chilled in an ice-bath and triturated with hexane. The amount of hexane used is not critical since the high-melting nitrile is quite insoluble in cold hexane. The pure white solid was collected by filtration and washed several times with a small amount of cold hexane. After drying, the solid melted at 85–88° (28.5 g.). After crystallization from benzine, it melted at 90–91°.

*Anal.* Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.96; N, 10.06. Found: C, 82.0; H, 8.04; N, 10.00.

The **picrate** was prepared in alcohol. Crystallization from absolute ethanol gave yellow needles, m. p. 145–146°.

*Anal.* Calcd. for $C_{25}H_{25}N_5O_7$: C, 59.16; H, 4.97; N, 13.80. Found: C, 59.19; H, 5.00; N, 13.78.

The **methiodide** was prepared from 25.7 g. of the aminonitrile in 100 ml. of dry ether. Seventy-five ml. of methyl iodide was added slowly and the mixture allowed to stand at room temperature for sixteen hours. After boiling the mixture for forty-five minutes, the solid was collected, washed with ether and recrystallized from methanol; yield, 32.7 g. (82%); m. p. 216–217°.

*Anal.* Calcd. for $C_{20}H_{25}N_2I$: C, 57.2; H, 5.95; N, 6.66. Found: C, 57.17; H, 5.95; N, 6.46.

**2,2-Diphenyl-3-methyl-4-dimethylaminobutanenitrile** (III).—The combined hexane filtrates from the separation of isomeric nitrile IV, were evaporated to dryness on a steam-bath. The oily residue was distilled, b. p. 162–165° (1–2 mm.). The distillate soon solidified, m. p. 48–50° (23.7 g.).

The **picrate** of the distilled material (39 g.) was prepared in alcohol. Crystallization from alcohol gave 32.2 g. of the salt melting at 204–205°.

*Anal.* Calcd. for $C_{25}H_{25}N_5O_7$: C, 59.16; H, 4.97; N, 13.80. Found: C, 59.18; H, 4.92; N, 13.76.

The picrate (32.2 g.) was dissolved in a minimum amount of saturated (13%) lithium hydroxide solution[13] and the free base was extracted with ether. The extract was washed with lithium hydroxide solution until colorless, dried over anhydrous sodium sulfate and the ether removed by evaporation. A solid remained that melted at 66–67° after crystallization from benzine; yield 12.4 g.

*Anal.* Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.89; H, 7.71; N, 10.00; $n^{20}_D$ 1.5555 (on super-cooled liquid).

Reaction of the base with methyl iodide as described for the isomer gave the **methiodide** that crystallized from alcohol as a solvate, m. p. 231–232°, when placed in a melting point bath below 100° and heated slowly. When placed in a bath at about 120° and heated, the compound sintered and foamed at 150–160°, resolidified and remelted at 230–233°.

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(13) Burger, THIS JOURNAL, **67**, 1615 (1945).

*Anal.* Calcd. for $C_{20}H_{25}N_2I\cdot C_2H_5OH$: C, 56.5; H, 6.65; N, 6.00. Found: C, 56.62; H, 6.50; N, 6.21.

**Degradation of Nitrile, IV.**—Moist silver oxide, freshly prepared from 63 g. (0.37 mole) of the silver nitrate and washed free of alkali, was added in small portions with vigorous mechanical stirring to 51.9 g. (0.124 mole) of the methiodide of IV in 1200 ml. of hot water (90°). The reaction mixture was heated for an additional half hour with occasional stirring. After cooling, the silver iodide and excess silver oxide were removed by filtration. The water was removed by vacuum distillation at about 80–90°. The oily residue was then heated to 110° at 25 mm. to remove residual water. After cooling to 100°, 5 g. of solid potassium hydroxide was added. Upon reducing the pressure a vigorous evolution of gas occurred. The temperature was raised slowly to 120° over a period of one-half hour at a pressure of 18 mm. Finally, the temperature was raised to 135–145° for ten minutes. Then the mixture was allowed to cool. Water (50 ml.) was added to dissolve inorganic material, the mixture extracted with 150 ml. of ether and the extract washed with water.

The **basic degradation product** was extracted from the ether with dilute hydrochloric acid. When the acid extract was made basic with 20% sodium hydroxide solution, a solid (6.23 g.) separated at once. It melted at 114–115° after crystallization from a 2:1 hexane-benzine mixture and was identical with the cyclic imino-ether, XII. Heating with dilute hydrochloric acid converted it to the lactone, XIII.

A **solid neutral product** was isolated after the ether solution had been dried over anhydrous sodium sulfate. Evaporation of the ether left an oil that became semi-solid upon cooling. Stirring with hexane dissolved the oil leaving a white solid (4.65 g.). After crystallization from absolute alcohol, the solid melted at 157–158°. It was not characterized further but analytical data agreed with the 2,2-diphenyl-3-penteneamide structure XIV.

*Anal.* Calcd. for $C_{17}H_{17}NO$: C, 81.3; H, 6.84; N, 5.57. Found: C, 80.9; H, 6.52; N, 5.56.

The **2,2-diphenyl-3-pentenenitrile**[5] (VII) remained as a yellow oil (7.5 g.) when the hexane filtrate was evaporated. On distillation, a thick colorless oil resulted, b. p. 127–131° (0.5–1 mm.), $n^{23.5}$D 1.5750.

*Anal.* Calcd. for $C_{17}H_{15}N$: C, 87.55; H, 6.43. Found: C, 87.68; H, 6.43.

**2,2-Diphenyl-*n*-amylamine (IX). A. From 2,2-Diphenyl-3-pentenenitrile (VII).**—The nitrile (15 g.) was dissolved in methanol (100 ml.) and Raney nickel (5 g.) was added. The mixture was placed in a hydrogenation autoclave that was then connected to an ammonia cylinder. After the methanol was saturated with ammonia, hydrogen was admitted to a pressure of 1260 pounds at 28° and the compound hydrogenated at 140–145° in about eight hours. Upon working up in the usual way, there was obtained 10.65 g. of a basic oil, b. p. 137–144° (1.5–2.5 mm.), $n^{20}$D 1.5753, $n^{22.5}$D 1.5749.

*Anal.* Calcd. for $C_{17}H_{21}N$: C, 85.36; H, 8.84; N, 5.86. Found: C, 85.00; H, 8.65; N, 5.82.

**B. From 2,2-Diphenylpentanenitrile (XI).**—The hydrogenation of this nitrile was carried out in the same manner as in A. The product boiled at 123–125° (1 mm.), $n^{20}$D 1.5750; yield 75%.

*Anal.* Calcd. for $C_{17}H_{21}N$: C, 85.36; H, 8.84; N, 5.86. Found: C, 84.75; H, 8.64; N, 5.80.

Reaction of phenyl isothiocyanate with the amine prepared by either procedure gave **1-[(2,2-diphenyl)-*n*-amyl]-3-phenylthiourea.** After crystallization from absolute alcohol this derivative melted at 179–180°.

*Anal.* Calcd. for $C_{24}H_{26}N_2S$: C, 76.96; H, 6.99; N, 7.48. Found: C, 77.04; H, 6.88; N, 7.47.

The amines from the two procedures gave identical **benzoyl derivatives** on reaction with benzoyl chloride in the presence of aqueous alkali. After recrystallization from ethanol, the N-(2,2-diphenyl-*n*-amyl)-benzamide melted at 146–147°.

*Anal.* Calcd. for $C_{24}H_{25}NO$: C, 83.92; H, 7.34; N, 4.08. Found: C, 83.85; H, 7.18; N, 4.07.

**2,2-Diphenyl-3-methylbutenenitrile**[5] **(VI).**—The degradation of the low-melting nitrile was carried out on 30.4 g. of the methiodide (m. p. 231–232°), in the same manner as described for the high-melting isomer. No product except a small amount of oil was isolated upon making the acid extract basic. Evaporation of the dried ether extract yielded 13 g. of waxy solid; m. p. 56–58°. It was taken up in benzine and the solution filtered to remove a small amount of solid. The filtrate was evaporated and the solid residue was crystallized from benzine; 8.4 g., m. p. 56–58°. The material from two such runs (17 g.) was combined and distilled. The product boiled at 132–134° (1.5 mm.), m. p. 62–63°; yield, 15.8 g. After crystallization from benzine, there was obtained 14.7 g. of white crystals that melted at 63–64°.

*Anal.* Calcd. for $C_{17}H_{15}N$: C, 87.55; H, 6.43; mol. wt., 233. Found: C, 87.58; H, 6.56; mol. wt., 231.0.

**2,2-Diphenyl-3-methyl-*n*-butylamine (VIII). A. From 2,2-Diphenyl-3-methyl-3-butenenitrile (VI).**—The nitrile (14 g., 0.064 mole) was reduced to the amine as described for the preparation of 2,2-diphenyl-*n*-amylamine. The product was a viscous oil, b. p. 144–145° (2 mm.); $n^{20}$D 1.5830.

*Anal.* Calcd. for $C_{17}H_{21}N$: C, 85.36; H, 8.84; N, 5.86. Found: C, 85.07; H, 8.78; N, 5.84.

**B. From 2,2-Diphenyl-3-methyl-butanenitrile (X).**—The nitrile (31.43 g., 0.134 mole) (m. p. 46–47°) was subjected to the same hydrogenation conditions as described in A. It proved to be quite resistant to catalytic hydrogenation since only 14.19 g. (44%) of amine was obtained after heating at 140–145° at 133 atm. for eight hours. The amine boiled at 123–125° (1 mm.); $n^{20}$D 1.5825.

*Anal.* Calcd. for $C_{17}H_{21}N$: C, 85.36; H, 8.84; N, 5.86. Found: C, 84.94; H, 8.64; N, 5.77.

The remainder of the nitrile was recovered. However, it now melted at 58–59° after recrystallization. This is actually another crystalline form of the original nitrile as will be shown under the preparation of the nitrile.

**1-[(2,2-Diphenyl-3-methyl)-*n*-butyl]-3-phenylthiourea** was prepared in the usual way from the amines obtained by either A or B and phenyl isothiocyanate. Both samples and a mixture of the two melted at 157–158°. The compound crystallized from absolute alcohol in needles.

*Anal.* Calcd. for $C_{24}H_{22}N_2S$: C, 76.96; H, 6.94; N, 7.48. Found: C, 76.94; H, 6.82; N, 7.38.

**1-(2,2-Diphenyl-3-methyl-*n*-butyl)-3-ethylurea** was prepared by the reaction of amine obtained in either A or B with ethyl isocyanate.[14] Upon crystallization from acetone and then from benzene both samples and a mixture of the two melted at 183–184°.

*Anal.* Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.53; H, 8.34; N, 9.01.

**2,2-Diphenylpentanenitrile (XI).**—To a hot solution of potassium *t*-butoxide, prepared by dissolving potassium metal (7.5 g., 0.19 mole) in *t*-butyl alcohol (156 ml.) containing xylene (12 ml.), diphenylacetonitrile (37 g., 0.19 mole) was added. The mixture was heated to boiling and *n*-propyl iodide (42.5 g., 0.25 mole) was added dropwise with stirring. After the addition, the mixture was refluxed for two hours. The alcohol was distilled. Water was added to dissolve the potassium iodide and the resulting mixture was extracted with ether. The extract was dried over anhydrous sodium sulfate. After evaporation of the ether, the oily residue was distilled, b. p. 125–127° (1 mm.); $n^{23}$D 1.5623; yield, 39.3 g. (88%).

*Anal.* Calcd. for $C_{17}H_{17}N$: C, 86.8; H, 7.24. Found: C, 86.97; H, 7.07.

**2,2-Diphenyl-3-methylbutanenitrile (X).**—This compound was prepared from diphenylacetonitrile and isopropyl iodide in 72% yield in a 0.185 mole run by the

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[14] Slotta and Lorenz, *Ber.*, **58**, 1320–1323 (1925).

same method as was used for the preparation of 2,2-diphenylpentanenitrile. The product boiled at 120–122° (1 mm.), and melted at 46–47° after crystallization from methanol.[15] Crystallization was carried out by dissolving the compound at room temperature and cooling to +5°.

*Anal.* Calcd. for $C_{17}H_{17}N$: C, 86.80; H, 7.24. Found: C, 86.75; H, 7.34.

Upon hydrogenation of this nitrile to the corresponding amine, VIII, considerable non-basic material was recovered in one run. This material melted at 58–59° after crystallization from methanol and then from benzine. That the materials melting at 46–47° and at 58–59° are dimorphic forms of the nitrile was demonstrated by observing the melting behavior of adjacent crystals of the two forms with a hot-stage microscope. At 46° the lower-melting form liquified and flowed onto the unmelted crystal of the higher-melting form. The melt immediately solidified and remelted at 59–60°.

**2,2-Diphenyl-4-pentenenitrile.**[16]—This compound was prepared by the reaction of allyl bromide (26 g., 0.21 mole) with diphenylacetonitrile (35.6 g., 0.185 mole) in the presence of potassium *t*-butoxide following a procedure analogous to the preparation of 2,2-diphenylpentanenitrile. The yield was 43 g. (72%), b. p. 129–131° (1.5 mm.); $n^{20}D$ 1.5744.

*Anal.* Calcd. for $C_{17}H_{15}N$: C, 87.55; H, 6.43. Found: C, 87.49; H, 6.46.

**2-Imino-3,3-diphenyl-5-methyltetrahydrofuran (XII).**—Potassium metal (4.0 g., 0.1 mole) was dissolved in *t*-butyl alcohol (125 ml.) in a 500-ml. round-bottomed flask fitted with a stirrer, reflux condenser and nitrogen inlet tube. To this solution was added diphenylacetonitrile (19.3 g., 0.1 mole). After the color had become deep red, dry propylene oxide (7.0 g., 0.12 mole) was added at 40–45° over a period of twenty minutes. When the temperature began to fall, the mixture was heated at 55–60° for two and one-half hours. After standing at room temperature for sixteen hours, the alcohol was removed by vacuum distillation. Ice and dilute hydrochloric acid was added to the residue which dissolved completely. On making basic with saturated sodium bicarbonate solution a solid separated. This was crystallized from 7:3 hexane–benzene mixture (14.5 g.), m. p. 114–115°. This compound was identical with the basic product from the degradation of the nitrile, IV.

*Anal.* Calcd. for $C_{17}H_{17}NO$: C, 81.3; H, 6.77; N, 5.57. Found: C, 81.15; H, 6.76; N, 5.54.

**$\alpha$,$\alpha$-Diphenyl-$\gamma$-valerolactone (XIII).**—2-Imino-3,3-diphenyl-5-methyltetrahydrofuran (12.35 g.) was dissolved in dilute hydrochloric acid and heated on a steam-bath for one-half hour. The solid that separated was collected by filtration after cooling the reaction mixture; yield, 11.68 g., m. p. 111–112°. Crystallization from hexane yielded long white needles, but did not change the melting point. Upon making the acid filtrate strongly basic with sodium hydroxide, ammonia was evolved.

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39; mol. wt., 252.3. Found: C, 80.78; H, 6.48; mol. wt., 246.0.

The compound dissolves in hot 10% sodium hydroxide solution and precipitates unchanged on addition of acid. It is insoluble in sodium bicarbonate solution and in cold sodium hydroxide solution. It does not react with concentrated ammonium hydroxide solution even when heated at 120° for twenty-four hours. From analyses and chemical properties, it is concluded that this compound is the lactone.

**Reaction of Low-Melting Nitrile, III, and Ethylmagnesium Bromide.**—The reaction of ethylmagnesium bromide (0.072 mole) with a purified sample (10 g., 0.036 mole) of the low-melting nitrile was carried out according in the procedure used in the preparation of Amidone. The reaction mixture was poured into a solution of 20 ml. of concentrated hydrochloric acid in 50 ml. of water. The organic layer was discarded and the aqueous layer was made basic with sodium hydroxide solution. The basic mixture was extracted with ether, the extract dried and the ether evaporated. The pale yellow viscous residue was dried in a vacuum desiccator containing solid potassium hydroxide and concentrated sulfuric acid.

The **dipicrate**, m. p. 135–136°, was prepared in an alcohol solution.

*Anal.* Calcd. for $C_{33}H_{34}N_8O_4$: C, 51.69; H, 4.47; N, 14.6. Found: C, 51.66; H, 4.81; N, 13.80.

The **dihydrochloride** was obtained as a gummy dark precipitate by adding hydrogen chloride gas to an ether solution of the crude base. After digesting with acetone and recrystallizing from isopropyl alcohol, it melted at 194–196°.

*Anal.* Calcd. for $C_{21}H_{30}Cl_2N_2$: C, 66.11; H, 7.92; N, 7.34. Found: C, 65.24; H, 7.79; N, 7.28.

The compound was essentially unchanged by heating to refluxing for three hours in 6 *N* hydrochloric acid.

**Diphenylacetonitrile.**—Benzyl cyanide (117 g., 1 mole) was placed in a dry 500-ml., round-bottomed flask fitted with an air condenser, a glass mechanical stirrer, a dropping funnel and a thermometer. The temperature of the liquid was adjusted to 105–110° and bromine (176 g., 1.1 mole) was added, with stirring, over a period of one hour. After fifteen minutes, the dropping funnel was replaced by a gas inlet tube and dry nitrogen was passed through the apparatus for thirty minutes. The hot reaction mixture was removed and the reaction flask rinsed with 100 ml. of benzene. The benzene was added to the crude $\alpha$-bromo-$\alpha$-phenylacetonitrile. The benzene solution thus obtained was added over a period of two hours to a stirred, boiling mixture of dry benzene (368 g., 4.7 mole) and anhydrous aluminum chloride (133.5 g., 1 mole) contained in a two-liter flask equipped as above. After heating and stirring for an additional hour, the cooled reaction mixture was poured into a mixture of 1 kg. of ice and 100 ml. of concentrated hydrochloric acid. The benzene layer was separated and the aqueous layer extracted with ether. The benzene and ether extracts were combined, and washed with water, saturated sodium bicarbonate solution and finally again with water. After drying over anhydrous sodium sulfate the benzene and ether were removed by vacuum distillation. The dark residue (about 190 g.) was distilled in a flask so constructed that the side arm may be heated, b. p. 122–125° (1–2 mm.); yield, 130–139 g., m. p. 68–70°.

The product was dissolved in hot isopropyl alcohol (1 ml. per gram). The solution was allowed to cool slowly to room temperature. After crystallization was complete, the pure white solid was collected and washed with cold isopropyl alcohol (0.2 ml. per gram). The yield of pure white product melting at 74–75° was 97–100 g. (50–51% based on benzyl cyanide).

## Summary

The reaction of 1-dimethylamino-2-chloropropane with diphenylacetonitrile in the presence of either sodamide or potassium *t*-butoxide gave two isomeric nitriles, 2,2-diphenyl-4-dimethylaminopentanenitrile (IV) and 2,2-diphenyl-3-methyl-4-dimethylaminobutanenitrile (III).

The structure of each nitrile was established by characterization of the products from the exhaustive methylation.

The 2,2-diphenyl-4-dimethylaminopentanenitrile reacted with ethylmagnesium bromide to give Amidone, thus establishing the structure (I) for this drug.

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(15) Ramart-Lucas, *Compt. rend.*, **154**, 1617 (1912), reports a b. p. of 193° (15 mm.) but no m. p. or refractive index is recorded.

(16) Danilov, *J. Russ. Phys.-Chem. Soc.*, **52**, 369 (1920); *C. A.*, **18**, 1489 (1924) prepared this compound by another method and records a boiling point of 192–195° (14 mm.).

2-Imino-3,3-diphenyl-5-methyltetrahydrofuran (XII) was obtained from the reaction of propylene oxide and diphenylacetonitrile.

A procedure for the preparation of diphenylacetonitrile through the bromination of benzyl cyanide followed by reaction with benzene and aluminum chloride is described.

GLENOLDEN, PENNSYLVANIA RECEIVED MAY 15, 1947

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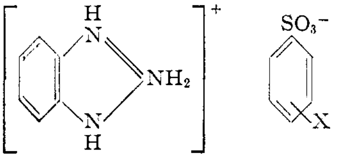
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Sulfonate Salts of Substituted Benzimidazoles[1]

BY NELSON J. LEONARD, DAVID Y. CURTIN[2] AND KARL M. BECK

A generally satisfactory method for the preparation of "sulfa" drugs,[3] when applied to the synthesis of 2-sulfabenzimidazole, led to the formation of a product for which Price and Reitsema[4] have suggested a salt structure. 2-Aminobenzimidazole sulfanilate (I) has now been prepared by direct combination of 2-aminobenzimidazole and sulfanilic acid. This salt corresponds in physical properties to the "sulfabenzimidazole" of Raiziss, Clemence and Freifelder.

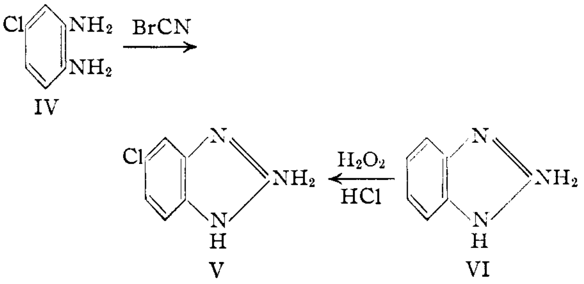


I $X = p\text{-}NH_2$
II $X = m\text{-}NO_2$
III $X = m\text{-}NH_2$

2-Aminobenzimidazole *m*-nitrobenzenesulfonate (II) and 2-aminobenzimidazole metanilate (III) have also been prepared by direct salt formation and have been shown to be identical with these sulfonate salts as obtained by Price and Reitsema by indirect methods. 2-Amino-5-chlorobenzimidazole *m*-nitrobenzenesulfonate has been formed by combination of *m*-nitrobenzenesulfonic acid with 2-amino-5-chlorobenzimidazole (V). Compound V has been shown to be the monochlorination product of 2-aminobenzimidazole and the condensation product of *p*-chloro-*o*-phenylenediamine with cyanogen bromide.

Salts of aromatic amines with *m*-nitrobenzenesulfonic acid were first made by Keyworth[5] for use as derivatives for the identification of certain amines. The salts were prepared by treating sodium or potassium *m*-nitrobenzenesulfonate with the arylamine hydrochloride in aqueous solution. The contrasting use of an organic base to isolate and identify arylsulfonic acids is illustrated by the reaction of S-benzylthiouronium chloride with sodium *m*-nitrobenzenesulfonate in aqueous solution.[6] Many other arylsulfonic acids have been used to identify amines and likewise have been identified by amines through salt formation. Occasionally amine arylsulfonates have been obtained in reactions from which one might be led to expect other products. Rouiller[7] obtained benzamidine benzenesulfonate when benzoic acid and benzenesulfonamide were heated at 225°. Clarke and Gillespie[8] obtained guanidine benzenesulfonate from guanidine carbonate and benzenesulfonyl chloride in aqueous potassium carbonate. Karrer and Epprecht[9] showed that guanidine *p*-nitrobenzenesulfonate was the product of the reaction of guanidine nitrate with *p*-nitrobenzenesulfonyl chloride in aqueous sodium hydroxide by its identity with the salt obtained directly from *p*-nitrobenzenesulfonic acid and guanidine carbonate. Guanidine *m*-nitrobenzenesulfonate was obtained by the same method.[4]

In the present investigation, 2-aminobenzimidazole sulfanilate (I), *m*-nitrobenzenesulfonate (II), and metanilate (III) have been prepared by combination of 2-aminobenzimidazole with the corresponding arylsulfonic acid in aqueous solution. The study initiated by Price and Reitsema on the condensation products of arylsulfonyl chlorides with 2-aminobenzimidazole in pyridine has been extended to chloro-substituted 2-aminobenzimidazole in order to determine the effect of rendering the ring-nitrogen less basic. The reaction of *p*-chloro-*o*-phenylenediamine (IV) with cyanogen bromide produced a compound which had the correct analysis for 2-amino-5-chlorobenzimidazole (V) and also for the substituted cyanamide in which the



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[1] Presented before the Division of Organic Chemistry at the 111th meeting of the American Chemical Society, Atlantic City, New Jersey, April 16, 1947.

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(3) Raiziss, Clemence and Freifelder, THIS JOURNAL, **63**, 2739 (1941).

(4) Price and Reitsema, *J. Org. Chem.*, **12**, 269 (1947).

(5) Keyworth, *J. Soc. Chem. Ind.*, **46**, 20T (1927).

(6) Donleavy, THIS JOURNAL, **58**, 1004 (1936); Chambers and Watt, *J. Org. Chem.*, **6**, 376 (1941).

(7) Rouiller, *Am. Chem. J.*, **47**, 475 (1912).

(8) Clarke and Gillespie, THIS JOURNAL, **54**, 1964 (1932).

(9) Karrer and Epprecht, *Helv. Chim. Acta*, **24**, 310 (1941).