member, oxidized to the corresponding sulfone series.

Preliminary testing indicates that the compounds are inactive against electrically induced convulsions.

DETROIT, MICHIGAN RECEIVED MAY 14, 1947

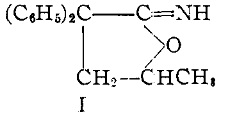
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF J. T. BAKER CHEMICAL CO.]

A New Synthesis and Confirmation of the Structure of Amidone[1]

BY NELSON R. EASTON, JOHN H. GARDNER AND JOSEPH R. STEVENS

The original procedure for the synthesis of the new German analgesic, Amidone or 10820,[2] involves some technical difficulties due to the formation of isomeric aminonitriles in approximately equal amounts.[3] A new synthesis which avoids this difficulty has been developed.

Diphenylacetonitrile was condensed with propylene oxide in the presence of sodium amide to yield 3,3-diphenyl-5-methyltetrahydro-2-furanoneimine (I), which was isolated as the hydrochloride. On treating this compound with phosphorus tribromide, 4-bromo-2,2-diphenylpentanenitrile (II) was formed. The analogous chlorine compound (III) was prepared in a similar manner. Either of these halonitriles, condensed with dimethylamine, gave 4-dimethylamino-2,2-diphenylpentanenitrile (IV), from which Amidone was prepared by the action of ethylmagnesium bromide, as in the original synthesis.[2]



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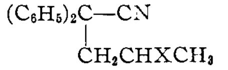


$(C_6H_5)_2C{-}CN$ / CH_2CHXCH_3

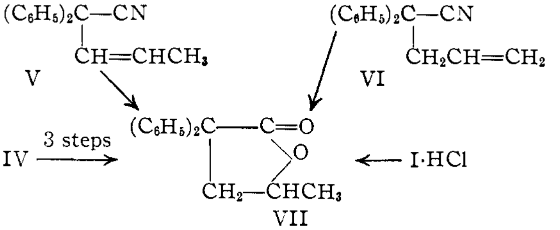
II. X = Br

III. X = Cl

IV. X = $N(CH_3)_2$

The yields in the formation of the aminonitrile from either of the halonitriles under the conditions tried so far have been below 10%. This reaction is being studied further. There was always formed as a major product an unsaturated nitrile, presumably 2,2-diphenyl-3-pentenenitrile (V) or a mixture of that with 2,2-diphenyl-4-pentenenitrile (VI). The product agreed with the latter in all properties except refractive dispersion.

As an incidental part of this work, the structure established for Amidone by Schultz, Robb and Sprague was confirmed by a new series of reactions. 4-Dimethylamino-2,2-diphenylpentanenitrile (IV) was degraded by exhaustive methylation to an unsaturated nitrile[3] (V, VI or a mixture) which was hydrolyzed without purification to the lactone of 2,2-diphenyl-4-hydroxypentanoic acid (VII). The same lactone was also formed by the hydrolysis both of 2,2-diphenyl-4-pentenenitrile (VI) and of the unsaturated nitrile obtained as a by-product in the new synthesis of the aminonitrile (IV). The hydrochloride of 3,3-diphenyl-5-methyltetrahydro-2-furanoneimine (I) gave the same lactone on long standing in aqueous solution. These facts can only be accounted for by a straight chain structure for the aminonitrile (IV).



Experimental

3,3-Diphenyl-5-methyltetrahydro-2-furanoneimine Hydrochloride (I).—To a well-stirred suspension of 20 g. of sodium amide in 100 ml. of benzene there was added 96 g. of diphenylacetonitrile. The mixture was heated to 40–45° for one and a half hours and then cooled to 20°, 29 g. of propylene oxide then was added, with the temperature kept at 20–25°. The mixture was then boiled for fifteen minutes and poured into a large excess of water. The benzene layer was separated and dried over magnesium sulfate. The mixture was filtered and 75 g. of a 38% solution of anhydrous hydrogen chloride in absolute alcohol and 500 ml. of anhydrous ether were added to the filtrate. The mixture was placed in a refrigerator for sixteen hours and then filtered. The yield of material melting at 220–222° with decomposition was 114 g. (80%).

Anal. Calcd. for $C_{17}H_{18}NOCl$: N, 4.87; Cl, 12.32. Found: N, 4.87; Cl, 12.20.

A portion of the hydrochloride was suspended in water and an excess of sodium hydroxide was added. A solid separated which melted at 115–116° after crystallization from methylcyclohexane.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.45; H, 6.81; N, 5.55.

4-Bromo-2,2-diphenylpentanenitrile (II).—A mixture of 112 g. of the hydrochloride (I) and 224 g. of phosphorus tribromide was refluxed for thirty minutes. After cooling, 200 cc. of benzene was added and the mixture was filtered. The filtrate was poured into an excess of water, the benzene layer separated, washed with water and dried over magnesium sulfate. The benzene solution was then evaporated to dryness under reduced pressure, leaving 107.6 g. of material melting at 41–42°. Analysis showed that this material was quite pure.

Anal. Calcd. for $C_{17}H_{16}NBr$: C, 64.98; H, 5.13; N, 4.46. Found: C, 65.05; H, 5.05; N, 4.52.

4-Chloro-2,2-diphenylpentanenitrile (III).—A mixture of 24 g. of the hydrochloride (I), 40 ml. of phosphorus trichloride and 40 ml. of phosphorus oxychloride was heated in sealed tubes at 175° for three hours. The tubes were opened and their contents poured into water. The resulting mixture was extracted with benzene. The benzene layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The yield

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(1) Presented before the Division of Medicinal Chemistry, American Chemical Society, Atlantic City, N. J., April 16, 1947.

(2) Office of the Publication Board, Department of Commerce, Report PB 981, p. 96.

(3) 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).

was 17 g. of material melting at 53-55° after crystallization from petroleum ether, using decolorizing carbon.

Anal. Calcd. for $C_{17}H_{16}NCl$: C, 75.68; H, 5.98; N, 5.19. Found: C, 75.70; H, 6.08; N, 5.22.

4-Dimethylamino-2,2-diphenylpentanenitrile (IV) A.—A mixture of 11 g. of the bromonitrile (II), 20 ml. of alcohol and 20 g. of dimethylamine was heated in a sealed tube at 94° for fourteen hours. After opening the tube, the contents were evaporated to dryness under reduced pressure. After adding 20% hydrochloric acid to the residue, the mixture was extracted with ether. The aqueous layer was separated and made alkaline with 50% sodium hydroxide. It was then extracted with ether, the ether solution dried over magnesium sulfate and evaporated to dryness. On cooling and scratching, the oily residue crystallized. The crystals melted at 89-91° and the melting point was not depressed by the additions of 4-dimethylamino-2,2-diphenylpentanenitrile prepared by the German process.[2] Crystallization from Skellysolve did not change the melting point.

Anal. Calcd. for $C_{19}H_{22}N_2$: N, 10 06. Found: N, 10.06, 10.05.

The material recovered from the first ether extraction agreed in all of its properties with 2,2-diphenyl-4-pentenenitrile (VI), the preparation of which is described below, except in refractive dispersion, and was therefore probably 2,2-diphenyl-3-pentenenitrile (V) or a mixture of the two; b. p. 133-136° under 2 mm.; n_D 1.5748, n_F-n_C 0 0286. For 2,2-diphenyl-4-pentenenitrile, b. p. 134-136° under 2 mm.; n_D 1.5747, n_F-n_C + 0.0183. All refractive index data were at 22.4°.

Anal. Calcd. for $C_{17}H_{15}N$: N, 6.00. Found: N, 6.04, 6.01.

B.—The procedure was repeated using the chloronitrile (III), except that the mixture was heated at 150°. The products were identical.

Amidone.—Amidone prepared from 4-dimethylamino-2,2-diphenylpentanenitrile obtained by either of the procedures above was identical with that obtained by the German process.[2] The yield was about 85%.

Exhaustive Methylation of 4-Dimethylamino-2,2-diphenylpentanenitrile.—The methiodide of this compound was decomposed in the usual way, to yield an oily product which, without purification, was hydrolyzed by heating on the steam-bath with 90% sulfuric acid. After crystallization from Skellysolve C, the white product melted at 112-113°. There was no depression in melting point after mixing with the lactone of 2,2-diphenyl-4-hydroxypentanoic acid prepared from 2,2-diphenyl-4-pentanenitrile.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.00; H, 6.40.

2,2-Diphenyl-4-pentenenitrile (VI).—To a suspension of 39 g. of sodium amide in 180 ml. of dry benzene, there was added 173.4 g. of diphenylacetonitrile during fifteen minutes, with efficient stirring. The mixture was heated to 40-45° for one and a half hours and then cooled to 25°. Then, 78 ml. of allyl chloride was added during thirty minutes, with cooling. The mixture was refluxed for thirty minutes and then poured into water. The benzene layer was separated, dried over magnesium sulfate and filtered. The residue, after evaporation of the solvent, was distilled under reduced pressure. The yield of material boiling at 134-136° under 2 mm. pressure was 159 g. (76%).

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.51; H, 6.48; N, 6.00. Found: C, 87.60; H, 6.33; N, 6.05.

Lactone of 2,2-Diphenyl-4-hydroxypentanoic Acid (VII)—A mixture of 2,2-diphenyl-4-pentenenitrile (VI) and 90% sulfuric acid was heated on a steam-bath for two hours. The solution was poured into water and allowed to stand overnight. The solid which separated was crystallized from Skellysolve C. The white product melted at 112-113°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.90; H, 6.34.

Hydrolysis of 3,3-Diphenyl-5-methyltetrahydrofuranone-2-imine Hydrochloride (I).—An aqueous solution of the hydrochloride was allowed to stand overnight. The precipitate was collected and melted at 112-113° after crystallization from methylcyclohexane. Mixed melting points with samples of the lactone (VII) prepared by each of the methods described above gave no depression.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.95; H, 6.28.

Acknowledgment.—We wish to express our appreciation to Dr. V. B. Fish for the analyses, to Dr. E. C. Larsen for the refractive index data and to Miss Mary L. Evanick for technical assistance.

Summary

1. A new synthesis of amidone has been developed.

2. A confirmation of the structure of amidone has been presented.

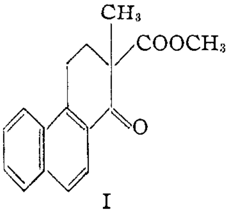
Phillipsburg, N. J. Received April 25, 1947

[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

A New Synthesis of Fused Ring Structures Related to the Steroids. The 17-Equilenones. A Total Synthesis of Equilenin[1,2]

By William S. Johnson, Jack W. Petersen[3] and C. David Gutsche[4]

In the course of studies of the synthesis of steroid-like structures we endeavored to effect a Stobbe condensation with the keto ester I in the hope that by procedures already described,[5] a propionic acid side-chain could be introduced at the site of the keto group to form a product II, known to be convertible to 17-equilenone (3-desoxyequilenin), XI.[6] Preliminary experiments,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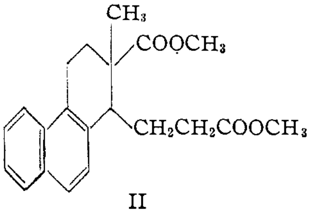
II

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[1] This work was assisted in part by a grant from the Wisconsin Alumni Research Foundation.

[2] A preliminary announcement of this work was reported in a Communication to the Editor, This Journal, **67**, 2274 (1945).

[3] W. A. R. F. Research Assistant, 1943-1945. Present address: Department of Chemistry, University of California, Berkeley, California.

[4] du Pont fellow, September 1946-March 1947; Wisconsin Alumni Research Foundation Post-doctorate fellow March 1947–.

[5] Johnson, Goldman and Schneider, This Journal, **67**, 1357 1945); Johnson, Johnson and Petersen, *ibid.*, **67**, 1360 (1945); Johnson and Petersen, *ibid.*, **67**, 1366 (1945).

[6] Bachmann and Wilds, *ibid.*, **62**, 2084 (1940).