

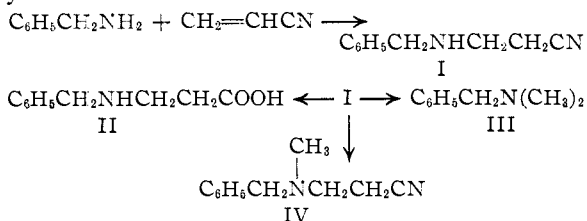
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation and Properties of Some  $\beta$ -Aminopropionic Acid Derivatives

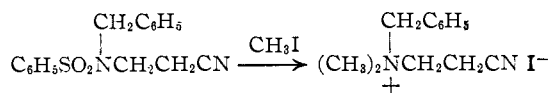
BY JOHN A. KING AND FREEMAN H. McMILLAN

As an intermediate in the synthesis of model substances related to penicillin it was desirable to use  $\beta$ -benzylmethylaminopropionitrile (IV). The present paper reports the preparation and some of the properties of this substance.

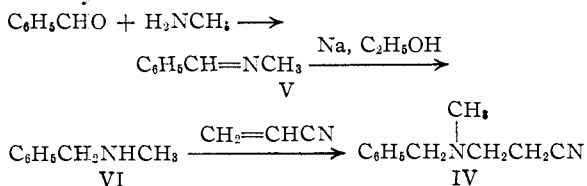
Benzylamine was added to acrylonitrile in 73% yield to produce  $\beta$ -benzylaminopropionitrile (I), which was converted to the corresponding amino acid II by either acid or alkaline hydrolysis. Some difficulty was encountered in the methylation of I. The Eschweiler<sup>1</sup> method, as modified by Clarke, Gillespie and Weisshaus,<sup>2</sup> gave entirely unexpected results: the only identifiable product isolated was dimethylbenzylamine (III). Methylation by means of methyl sulfate gave the desired  $\beta$ -benzylmethylaminopropionitrile (IV) in 26% yield. Better results were obtained using methyl iodide, but even this gave only a 41% yield of IV.



The interesting observation was made that the benzenesulfonamide of I on treatment with methyl iodide lost the benzenesulfonyl group and gave the methiodide of IV.



Because of the low yields attendant to the methylation of  $\beta$ -benzylaminopropionitrile the tertiary amine IV was prepared by another method. Benzaldehyde and methylamine were condensed<sup>3,4</sup> to give the Schiff base V in 91% yield; this was reduced to benzylmethylamine (VI) in 74% yield and the latter was added to acrylonitrile in 93% yield to give the desired tertiary amino nitrile IV.

(1) Eschweiler, *Ber.*, **38**, 880 (1905).(2) Clarke, Gillespie and Weisshaus, *THIS JOURNAL*, **55**, 4571 (1933).(3) Zaunschirm, *Ann.*, **245**, 279 (1888), gave general directions for this.(4) Cromwell, Babson and Harris, *THIS JOURNAL*, **65**, 312 (1943).

This second method of synthesis gave an overall yield of 62.5%, as compared with the first method which gave an over-all yield of 30%, each from available starting materials.

$\beta$ -Benzylmethylaminopropionitrile was converted to ethyl  $\beta$ -benzylmethylaminopropionate by hydrolysis-esterification with ethanolic hydrogen chloride. The ester hydrochloride could be isolated in 71% yield and this could be converted to the pure free base in 80% yield; however, if no attempt was made to isolate the intermediate hydrochloride the pure amino ester could be obtained in 86% yield, as contrasted with the 56% over-all yield when the hydrochloride was isolated.

Hydrolysis of either the tertiary amino ester or the corresponding nitrile gave a derivative of the corresponding acid which could be reconverted to the original ester. We were unable to prepare a bromosubstituted ester or nitrile.

Experimental<sup>5,6</sup>

**$\beta$ -Benzylaminopropionitrile (I).**—Addition in the usual manner of benzylamine (107 g., 1.00 mole) to acrylonitrile (53 g., 1.00 mole) gave 117 g. (73% yield) of a colorless liquid with an amine-like odor, b. p. 184–185° (23 mm.).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{N}_2$ : C, 75.00; H, 7.50; N, 17.50. Found: C, 74.80; H, 7.48; N, 17.20.

The benzoyl derivative, after three recrystallizations from 50% alcohol, melted at 70°.

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$ : C, 77.31; H, 6.07; N, 10.61. Found: C, 76.53; H, 6.16; N, 10.66.

The picrate, after two recrystallizations from ethanol, melted at 128°.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{N}_2 \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$ : C, 49.36; H, 3.85; N, 18.00. Found: C, 49.41; H, 3.93; N, 18.23.

The benzenesulfonamide was recrystallized from petroleum ether (b. p. 140–180°) to give long filaments, m. p. 73°.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ : N, 9.33. Found: N, 9.22.

Two grams of the amino nitrile was dissolved in dry ether and dry hydrogen chloride was passed in until no more white solid precipitated. The material, after recrystallization from methanol-ethanol, melted at 209° and was not the simple hydrochloride of the amino nitrile. The analysis was satisfactory for the dihydrochloride of the amino nitrile with one molecule of methanol of crystallization. That the substance was not the isomeric amino imino-ether dihydrochloride  $\text{C}_6\text{H}_5\text{CH}_2\text{NHCH}_2\text{CH}_2\text{C}(\text{OCH}_3)\text{NH}_2 \cdot 2\text{HCl}$  was shown by the fact that when the material was dissolved in water, the solution made alkaline and then extracted with ether the extracted oil gave the picrate of the original amino nitrile, m. p. and mixed m. p. 128°.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{N}_2 \cdot 2\text{HCl} \cdot \text{CH}_2\text{OH}$ : Cl (ionic), 26.80. Found: Cl (ionic), 27.24.

**$\beta$ -Benzylaminopropionic Acid (II).** **A. Hydrobromic Acid Hydrolysis.**— $\beta$ -Benzylaminopropionitrile (2.5 g.) was refluxed with 48% hydrobromic acid (55 g.) for two

(5) All melting points and boiling points are uncorrected.

(6) Microanalyses are by Misses P. Curran and A. Rainey of these laboratories.

and one-half hours, then most of the hydrobromic acid was removed by distillation. The remaining solution was exactly neutralized, evaporated to dryness and the residue extracted with ethanol. The melting point of the material obtained from the extract varied with the rate of heating; however, this material easily gave a *p*-toluenesulfonamide which had a constant melting point of 138.5° after recrystallization from 40% alcohol.

*Anal.* Calcd. for  $C_{17}H_{19}NO_4S$ : N, 4.21. Found: N, 4.23.

**B. Hydrochloric Acid Hydrolysis.**—A mixture of the amino nitrile (5.0 g.) and concentrated hydrochloric acid (70 cc.) was refluxed five hours, the solution was evaporated to dryness and the residue was recrystallized from absolute alcohol to give 4.2 g. (63% yield) of the amino acid hydrochloride, m. p. 175° (slight dec.).

*Anal.* Calcd. for  $C_{10}H_{13}NO_2 \cdot HCl$ : C, 55.81; H, 6.51; N, 6.51. Found: C, 56.22; H, 6.88; N, 6.79.

**C. Alkaline Hydrolysis.**—A mixture of the amino nitrile (4.8 g.) and 25 cc. of 10% sodium hydroxide was refluxed until clear, then exactly neutralized with hydrochloric acid and evaporated to dryness. Four recrystallizations of the residue from absolute alcohol gave white crystals, m. p. 181°. The analytical data indicated that the material still contained a trace of ammonium chloride.

*Anal.* Calcd. for  $C_{10}H_{13}NO_2$ : C, 67.03; H, 7.26; N, 7.82. Found: C, 67.68; H, 6.56; N, 8.47.

A mixture of one gram of the free amino acid and one gram of aniline yielded a precipitate in benzene solution. This material could be recrystallized from water and melted at 239–240°.

*Anal.* Calcd. for  $C_{10}H_{13}NO_2 \cdot C_6H_5NH_2$ : N, 10.27. Found: N, 10.10.

**Treatment of I with Formaldehyde-Formic Acid.<sup>1,2</sup> Benzylidimethylamine (III).**—The methylation of  $\beta$ -benzylaminopropionitrile (0.50 mole) by the procedure of Clarke and co-workers gave as the only identifiable product 26 g. (38% yield) of a pale yellow oil, boiling at 83–84° (30 mm.). Tiffeneau and Fuhrer<sup>7</sup> gave the boiling point of benzylidimethylamine as 67–68° (14 mm.) and 178° (atm.). The oil gave a picrate which, after recrystallization from ethanol, melted at 93°.

*Anal.* Calcd. for  $C_9H_{13}N \cdot C_6H_5N_3O_7$ : C, 49.44; H, 4.39; N, 15.37. Found: C, 49.56; H, 4.03; N, 16.11.

The oil also gave a methiodide which melted, after four recrystallizations from ethanol, at 178°. Tiffeneau and Fuhrer reported the m. p. as 178–179°.

**$\beta$ -Benzylmethylaminopropionitrile (IV). A. Methyl Sulfate Methylation.**—Treatment of 0.25 mole of  $\beta$ -benzylaminopropionitrile with methyl sulfate in the usual manner gave 11.5 g. (26% yield) of a pale yellow oil, b. p. 172° (23 mm.).

*Anal.* Calcd. for  $C_{11}H_{14}N_2$ : C, 75.88; H, 8.04; N, 16.08. Found: C, 75.75; H, 8.53; N, 15.95.

The picrate, after several recrystallizations from ethanol, had a constant m. p. of 132°.

*Anal.* Calcd. for  $C_{11}H_{14}N_2 \cdot C_6H_5N_3O_7$ : N, 17.37. Found: N, 17.95.

The methiodide, after recrystallization from ethyl acetate-methanol, melted at 128° (effervescence).

*Anal.* Calcd. for  $C_{11}H_{14}N_2 \cdot CH_3I$ : C, 45.55; H, 5.38; N, 8.87. Found: C, 45.61; H, 5.43; N, 9.13.

Two grams of the tertiary amino nitrile was dissolved in dry ether and dry hydrogen chloride was passed in until no more white solid precipitated. This material, after recrystallization from methanol-ethanol, melted at 120°. In agreement with the behavior of the unmethylated amino nitrile (see above), this material was not the simple hydrochloride of the amino nitrile, and the analysis was satisfactory for the dihydrochloride of the amino nitrile with one molecule of methanol of crystallization. This also was shown not to be the isomeric amino imino-ether

dihydrochloride  $C_6H_5CH_2N(CH_3)CH_2CH_2C(OCH_3)NH \cdot 2HCl$  by the fact that when it was dissolved in water, the solution made alkaline and extracted with ether the extract gave the picrate of the original amino nitrile, m. p. and mixed m. p. 131–132°.

*Anal.* Calcd. for  $C_{11}H_{14}N_2 \cdot 2HCl \cdot CH_3OH$ : Cl (ionic), 25.45. Found: Cl (ionic), 25.73.

**B. Methyl Iodide Methylation.**—Treatment of 0.20 mole of  $\beta$ -benzylaminopropionitrile with methyl iodide in the usual manner gave 31.5 g. of yellow oil. This oil was shaken with benzenesulfonyl chloride (35 g., 0.20 mole) and caustic (200 cc. of 17% caustic soda) until no odor of the acid chloride remained; acidification of the solution gave 33.5 g. (56% recovery of secondary amine) of the benzenesulfonamide of the starting material. The filtrate was made alkaline and extracted three times with ether; removal of the solvent from the dried extract gave 14.3 g. (41% yield) of pale yellow oil which on distillation boiled at 174–175° (23 mm.).

**De-acylation of N-Benzenesulfonyl  $\beta$ -Benzylaminopropionitrile.**—A small amount of the sulfonamide was mixed and warmed with an excess of methyl iodide. A violent reaction occurred and recrystallization of the product from ethyl acetate-methanol gave the methiodide of  $\beta$ -benzylmethylaminopropionitrile, m. p. 128°, identical with that prepared directly from  $\beta$ -benzylmethylaminopropionitrile and methyl iodide.

*Anal.* Calcd. for  $C_{11}H_{14}N_2 \cdot CH_3I$ : C, 45.55; H, 5.38; N, 8.87. Found: C, 45.49; H, 5.34; N, 8.98.

**N-Methylbenzalimine (V).**—This was prepared essentially by the described<sup>3,4</sup> method in 91% yield; b. p. 81–82° (21 mm.).

**Benzylmethylamine (VI).**—The imine V was reduced by the general procedure of Fischer<sup>8</sup> in 74% yield; b. p. 83.5–85.5° (21 mm.).

**$\beta$ -Benzylmethylaminopropionitrile (IV).**—Addition of 1.42 moles of benzylmethylamine to acrylonitrile in the usual manner gave 185 g. (75% yield) of colorless liquid, b. p. 163–164° (14 mm.). The forerun (50 g.) was heated thirty-six hours on the steam cone with more (25 g.) acrylonitrile and fractionally distilled (6–8 g. forerun) to give another 46 g. (18% yield) of product, b. p. 164–165° (15 mm.); the total yield was 231 g. (93% based on the amine used).

**Ethyl  $\beta$ -Benzylmethylaminopropionate Hydrochloride.**— $\beta$ -Benzylmethylaminopropionitrile (44 g., 0.25 mole) was dissolved in absolute alcohol (100 cc.) containing the requisite amount (4.2 g., 0.25 mole) of water for hydrolysis. The solution was refluxed on the steam cone for six hours while dry hydrogen chloride was bubbled in; then refluxing was continued for two hours longer. The precipitated ammonium chloride was removed by filtration and the chilled filtrate was diluted with dry ether (400 cc.) and refrigerated. There were obtained hygroscopic crystals (45 g., 71% yield) which melted, after two recrystallizations from 3:1 petroleum ether-ethanol, at 145°.

*Anal.* Calcd. for  $C_{12}H_{16}NO_2 \cdot HCl$ : Cl (ionic), 13.83. Found: Cl (ionic), 13.96.

**Ethyl  $\beta$ -Benzylmethylaminopropionate. A. From the Hydrochloride.**—The hydrochloride of the amino ester (32 g., 0.12 mole) was dissolved in ice water (60 cc.) and cautiously made alkaline with ice-cold sodium hydroxide (8 g. caustic in 80 cc. water). The resultant oil was extracted with ether, the extract was dried, the solvent was removed and the residue was distilled to give the ester (22 g., 80% yield), b. p. 163–164° (10 mm.).

*Anal.* Calcd. for  $C_{13}H_{18}NO_2$ : C, 70.54; H, 8.60. Found: C, 70.87; H, 8.79.

**B. From the Nitrile.**—The alcoholic solution in which the ester hydrochloride was prepared (from 132 g., 0.75 mole, nitrile; 13.5 g., 0.75 mole, water; 450 cc. ethanol) was filtered to remove the ammonium chloride and most of the alcohol was removed from the filtrate by distillation. The residue was dissolved in ice water, made alkaline

(7) Tiffeneau and Fuhrer, *Bull. soc. chim.*, (4) **15**, 168 (1914).

(8) Fischer, *Ann.*, **241**, 328 (1887).

with ice-cold caustic solution and rapidly extracted with ether. The dried extract gave 143 g. (86% yield) of ester, b. p. 159–160° (16 mm.).

The methiodide came out as an oil which would not crystallize on trituration with ethyl acetate. It was suspended in boiling ethanol and methanol was added dropwise until complete solution occurred. Refrigeration of the solution produced crystals which, after recrystallization, melted at 103°.

*Anal.* Calcd. for  $C_{13}H_{19}NO_2 \cdot CH_3I$ : C, 46.28; H, 6.07; N, 3.85. Found: C, 46.14; H, 6.16; N, 3.97.

The picrate also came out as an oil but crystallized on refrigeration. After recrystallization from ethanol it melted at 96°.

*Anal.* Calcd. for  $C_{13}H_{19}NO_2 \cdot C_6H_3N_3O_7$ : C, 50.67; H, 4.88. Found: C, 51.06; H, 4.83.

**Hydrolysis of Ethyl  $\beta$ -Benzylmethylaminopropionate.**—Hydrolysis of either the ester or the corresponding nitrile yielded a crystalline solid with the empirical formula  $C_{17}H_{29}N_2O_5Cl_3$ ; this could be reconverted to the original ester by esterification (see paragraph D, below).

**A. Acid Hydrolysis.**—Ethyl  $\beta$ -benzylmethylaminopropionate (4.4 g.) was refluxed six hours with concentrated hydrochloric acid (20 cc.) and then allowed to stand at room temperature for forty-eight hours. The crystalline solid (2.5 g.), after recrystallization from ethanol, melted at 187–188°.

*Anal.* Found: C, 45.83, 45.59; H, 6.61, 6.47; N, 6.25, 6.24; Cl (ionic), 23.85, 23.79. Calcd. for  $C_{17}H_{29}N_2O_5Cl_3$ : C, 45.59; H, 6.48; N, 6.25; Cl, 23.80.

**B. Alkaline Hydrolysis.**—The same ester (4.4 g.) was refluxed with a solution of sodium hydroxide (20 cc., 10% solution) until it dissolved completely. The solution was exactly neutralized with hydrochloric acid, evaporated to dryness, and the residue leached with ethanol. Evaporation of the ethanol left an oil which changed to an hygroscopic solid; the latter was treated with a few cc. of concentrated hydrochloric acid and evaporated to dryness. The residue, after recrystallization from ethanol, melted at 185–186°; mixed with the material obtained by procedure A, m. p. 182–183°.

**C.  $\beta$ -Benzylmethylaminopropionitrile** (3.5 g.) was refluxed six hours with concentrated hydrochloric acid (20 cc.) and the solution was evaporated to dryness. The residue, after recrystallization from ethanol, melted at 186–188°, alone or when mixed with the material obtained by Procedure A.

The nitrile (5.2 g.) was refluxed with 25 cc. of 10% caustic until the solution was clear (two hours). The chilled solution was exactly neutralized with hydrochloric acid and evaporated to dryness. The residue was extracted with hot absolute alcohol, from which there was obtained 5.0 g. of extremely viscous oil. Crystallization of this oil from acetone-ethanol yielded the free amino acid,  $\beta$ -benzylmethylaminopropionic acid, m. p. 112–112.5°.

*Anal.* Calcd. for  $C_{11}H_{15}NO_2$ : C, 68.41; H, 7.77; N, 7.25. Found: C, 67.85; H, 7.82; N, 7.29.

**D.  $\beta$ -Benzylmethylaminopropionitrile** (34.8 g., 0.20 mole) was refluxed sixteen hours with concentrated hydrochloric acid (200 cc.), the solution was evaporated to dryness and the residue was recrystallized from ethanol. The solid was then dissolved in water, exactly neutralized and extracted with chloroform. The dried chloroform extract was refluxed with red phosphorus (2 g.) as bromine (48 g., 0.30 mole) in chloroform (100 cc.) was dropped in. Most of the bromine was rapidly absorbed, hydrogen bromide being evolved after about one-third of the bromine had been added; the mixture was refluxed two hours after the addition was complete (very little hydrogen bromide still being evolved), then ethanol (15 g., 0.32 mole) was dropped in and the mixture was refluxed one hour. The solution was decanted from the phosphorus compounds and the solvent was removed under vacuum to leave a viscous oil which on crystallization from ethanol-ether proved to be the hydrobromide of ethyl  $\beta$ -benzylmethylaminopropionate, m. p. and mixed m. p. 151° (see following paragraph); picrate, m. p. and mixed m. p. 96°.

**Bromination Experiments.**—Attempted bromination of ethyl  $\beta$ -benzylmethylaminopropionate with bromine in chloroform solution under six sets of conditions yielded as the only identifiable product the hydrobromide of the starting material, m. p. 152° from ethanol-ether.

*Anal.* Calcd. for  $C_{13}H_{19}NO_2 \cdot HBr$ : C, 51.65; H, 6.62; N, 4.63. Found: C, 51.84; H, 6.34; N, 4.71.

This material gave the picrate of the starting material, m. p. and mixed m. p. 95–96°.

Similar attempted bromination of  $\beta$ -benzylmethylaminopropionitrile gave back starting material also as the only identifiable product; picrate m. p. and mixed m. p. 129°; methiodide m. p. and mixed m. p. 127° (effervescence).

In each case about half of the theoretical amount of bromine was rapidly taken up<sup>9</sup> and several hours were required for consumption of the last half, which was accompanied by evolution of hydrogen bromide.

### Summary

$\beta$ -Benzylaminopropionitrile has been prepared by the addition of benzylamine to acrylonitrile. This substance has been methylated to give  $\beta$ -benzylmethylaminopropionitrile, which has also been prepared by the addition of benzylmethylamine to acrylonitrile. Some of the reactions of these substances, and of various of their transformation products, have been studied.

RENSELAER, NEW YORK RECEIVED MARCH 26, 1946

(9) It is quite possible that this rapid uptake of bromine without evolution of hydrogen bromide is due to the formation of a mol-bromide type of compound, involving the unshared electron-pair of the amino nitrogen atom.