of ether and again filtered. Acidification with concentrated hydrochloric acid precipitated an oil which solidified on cooling. It was separated by filtration and dried over phosphorus pentoxide to yield 3.2 g. (59%) of crude 5-oxo-3-phenylcaproic acid. After one crystallization from hexane it melted at 81–83° (84–85°).[12]

(12) Knoevenagel and Fries, *Ber.*, **31**, 761 (1898).

Summary

α,β-Unsaturated carbonyl compounds have been found to add vinyl ethers to the 1,4-conjugated system. Fourteen 2-alkoxy-3,4-dihydro-1,2-pyrans have been synthesized in this manner.

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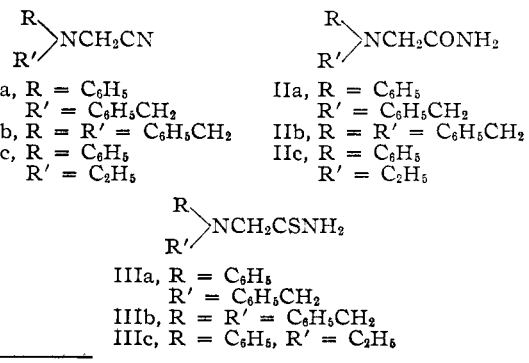
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Preparation and Derivatives of N-Substituted Glycinonitriles

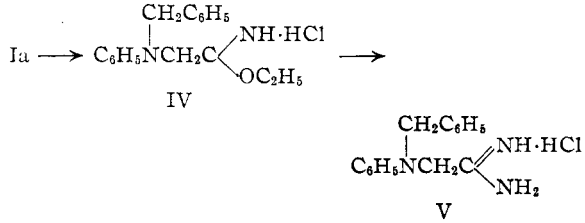
BY ROBERT A. TURNER[1a] AND CARL DJERASSI[1b]

In an earlier article[2] was described a convenient preparation of N,N-dimethylglycinonitrile from dimethylamine, formaldehyde and hydrocyanic acid. Since substituted glycinonitriles were required as starting materials for some projected syntheses, the cyanomethylation procedure was extended to several secondary amines. It was found that when secondary amines other than dimethylamine were employed, particularly aromatic amines, it was necessary to limit the amounts of formaldehyde and cyanide, else resinification became extensive; elevated temperature and a solvent also were necessary. In this manner an apparently general and simple procedure for the cyanomethylation of secondary amines was developed, and its use is illustrated in the experimental section with benzylaniline, dibenzylamine and ethylaniline.

All of the glycinonitriles (I) were readily converted into the corresponding amides (II) by treatment with concentrated sulfuric acid at low temperature, or to the thioamides (III) by reaction with ammonia and hydrogen sulfide. While the nitriles (I) were converted to the corresponding hydrochlorides in anhydrous ether, their behavior differed under other conditions. For instance, when a solution of N-benzyl-N-phenylglycinonitrile (Ia) in commercial ether was treated with hydrogen chloride gas, the only pure product isolated was benzylaniline hydrochloride. Similar results were observed with concentrated hydrochloric acid at 0°, while at a higher temperature some of the amide IIa was also formed. N-Ethyl-N-phenylglycinonitrile (Ic) yielded the nitrile hydrochloride with concentrated hydrochloric acid at 0°, but it gave chiefly the amide IIc on warming. The corresponding dibenzyl derivative Ib, on the other hand, afforded the nitrile hydrochloride under either set of conditions.



In view of the high antihistaminic activity of Antergan[3] and Antistin[4] it was of interest to convert the now readily available nitrile Ia into derivatives of potential value as histamine antagonists. Reaction of the nitrile Ia with hydrogen chloride in chloroform solution with the calculated amount of ethanol led to the corresponding imidic ester hydrochloride IV, which on treatment with ethanolic ammonia gave the hydrochloride of N-benzyl-N-phenylaminoacetamidine (V), an "open analog" of Antistin.[4] The amidine exhibited appreciable antihistaminic activity *in vitro*, but proved to be fairly unstable in aqueous solution. The antihistaminic activity is in agreement with observations made in another series,[5] where replacement of the dimethylamino group by an acetamidine moiety did not adversely affect the pharmacological properties.



Condensation of the thioamide IIIa with two N-substituted 1-bromo-4-aminobutanone-2 hydrobromides (VI)[6] very readily afforded the 4-

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(2) Turner, THIS JOURNAL, **68**, 1607 (1946).

(3) N,N-Dimethyl-N′-benzyl-N′-phenylethylenediamine; *cf.* Halpern, *Arch. Internat. Pharmacodynamie*, **68**, 339 (1942).

(4) 2-(N-Benzyl-N-phenylaminomethyl)-imidazoline; *cf.* Meier and Bucher, *Schweiz. Med. Wochschr.*, **76**, 294 (1946).

(5) Djerassi and Scholz, THIS JOURNAL, **69**, 1688 (1947).

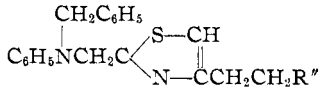
(6) Prepared by bromination of the corresponding "Mannich bases" in hydrogen bromide–acetic acid solution; *cf.* Land, Ziegler and Sprague, *ibid.*, **69**, 125 (1947).

substituted 2-(N-benzyl-N-phenylaminomethyl)-thiazoles (VII), which, while stable in aqueous solution, showed only low antihistaminic activity *in vitro*.

IIIa + $R''CH_2CH_2COCH_2Br \cdot HBr$ ⟶

VIa, $R'' = C_4H_8NO$

VIb, $R'' = (C_2H_5)_2N$



VIIa, $R'' = C_4H_8NO$

VIIb, $R'' = (C_2H_5)_2N$

Acknowledgment.—The technical assistance of Miss Jean Rogers and Mrs. Catherine Oney is gratefully acknowledged.

Experimental[7]

N-Benzyl-N-phenylglycinonitrile (Ia).—To a solution of 92 g. (0.50 mole) of benzylaniline[8] in 150 cc. of ethanol were added with stirring, and at such a rate that the temperature never exceeded 35°, 48 g. (0.59 mole) of 37% formaldehyde solution, 25 g. (0.56 mole) of 96% sodium cyanide and 42 cc. (0.49 mole) of concentrated hydrochloric acid. The mixture was tested with litmus to ascertain that it was alkaline. After stirring for two hours at 25°, the solution was refluxed for six hours, whereupon it turned light reddish-brown in color. After cooling and diluting with water, the layers were separated and the upper layer was extracted with benzene or chloroform. The combined organic solutions were washed with water, dried over magnesium sulfate, and distilled. On fractionation of the residual oil *in vacuo* 80 g. (72%) of N-benzyl-N-phenylglycinonitrile (Ia) was obtained as a light yellow oil; b. p. 167–171° at 0.07 mm.; d^{25}_4 1.0962; $n^{25}D$ 1.5970; M_D (calcd.), 69.47; M_D (obs.) 69.09. The compound has been mentioned[9] but no constants, analyses or derivatives were reported.

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.61. Found: C, 81.06; H, 6.22; N, 12.65.

When a larger excess of sodium cyanide or formaldehyde was used, the yield dropped sharply. Elimination of the solvent resulted in extensive resinification.

The **hydrochloride** was prepared by treating an anhydrous ether solution of the nitrile at 0° with the calculated amount of hydrogen chloride. The colorless precipitate was filtered immediately, washed thoroughly with dry ether and dried in a vacuum desiccator at room temperature over potassium hydroxide and phosphorus pentoxide. The yield of hydrochloride, melting at 111–113°, was nearly quantitative.

Anal. Calcd. for $C_{15}H_{15}N_2Cl$: C, 69.62; H, 5.84; N, 10.83; HCl, 14.08. Found: C, 69.55; H, 5.55; N, 10.86; HCl,[10] 13.71.

When commercial ether was used, a mixture resulted from which benzylaniline hydrochloride could be isolated as the only pure product. An aqueous solution of the hydrochloride became turbid quickly as the aminonitrile was released. When a sample of the hydrochloride was dried *in vacuo* at 76° over phosphorus pentoxide for four hours, the product turned to an oil, $n^{20}D$ 1.5987, which contained no chlorine; the loss in weight corresponded to one mole of hydrogen chloride.

Acid Treatment of N-Benzyl-N-phenylglycinonitrile (Ia).—When 1 g. of the nitrile was treated with 2 cc. of concentrated hydrochloric acid at 0° for ten minutes, the product filtered, dried over potassium hydroxide in a vacuum desiccator and recrystallized from ethanol–ether, there was obtained 15% of benzylaniline hydrochloride, m. p. 213–215°, alone or on admixture with an authentic specimen.

Anal. Calcd. for $C_{13}H_{17}NCl$: HCl, 16.60. Found: HCl, 16.25.

Treatment with potassium carbonate solution gave benzylaniline, m. p. 34.5–36°. When the temperature during the treatment of the nitrile with concentrated hydrochloric acid was 35 to 40°, the amide IIa (yield, 23%) was also identified in the product.

N-Benzyl-N-phenylglycinamide (IIa). (a) **From the Nitrile Ia.**—To 18 cc. of concentrated sulfuric acid cooled to −8° was added dropwise 10 g. of the cold nitrile Ia. After standing at room temperature for seventy-two hours, the reddish solution was poured upon crushed ice, made alkaline with ammonium hydroxide, and extracted with hot benzene. The benzene solution was washed with salt solution, filtered, and evaporated. The residue weighed 9.7 g. (90%) and melted at 129–130.5°. After sublimation *in vacuo* and two recrystallizations from benzene–petroleum ether, the analytical sample had m. p. 131–131.5°.

Anal. Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.87; H, 6.71; N, 11.74.

(b) **From the Imidic Ester IV.**—Two hundred milligrams of the imidic ester hydrochloride IV was heated in an oil-bath at 130–150° for five minutes. The product was dissolved in benzene, filtered, and the filtrate was evaporated under reduced pressure. On treatment of the residue with petroleum ether, there was obtained 120 mg. (76%) of crude N-benzyl-N-phenylglycinamide (IIa), m. p. 112–118°. After sublimation at 0.04 mm., the product melted at 128.5–130°.

N-Benzyl-N-phenylglycinamide hydrochloride, m. p. 139–141°, was prepared by treating the amide with methanolic hydrogen chloride solution and diluting with ether. Addition of water to the hydrochloride regenerated the free amide.

Anal. Calcd. for $C_{15}H_{17}ON_2Cl$: N, 10.13; HCl, 13.18. Found: N, 10.19; HCl, 13.57.

Ethyl N-Benzyl-N-phenylaminoacetimidate Hydrochloride (IV).—A solution of 4.4 g. of N-benzyl-4-phenylglycinonitrile (Ia) and 1.27 cc. of absolute ethanol in 20 cc. of dry chloroform was treated in an ice-bath with 1.5 g. of hydrogen chloride gas, and the clear solution was allowed to stand at 0° for twenty hours. After evaporation of the chloroform under reduced pressure, the residue crystallized on treatment with dry ether; yield, 4.41 g. (72%), m. p. 113–114.5° (gas).

Anal. Calcd. for $C_{17}H_{21}ON_2Cl$: C, 66.98; H, 6.95; N, 9.19; HCl, 11.96. Found: C, 66.75; H, 6.83; N, 8.85; HCl, 12.35.

When the reaction was carried out with ether as the solvent instead of chloroform, the hydrochloride of the nitrile precipitated.

N-Benzyl-N-phenylaminoacetamidine Hydrochloride (V).—A suspension of 1.534 g. of the imidic ester hydrochloride IV in 1.83 cc. of ethanolic ammonia solution (containing 0.0935 g. of ammonia) was shaken in a closed vessel for sixty-eight hours at room temperature. After removal of some ammonium chloride, dilution with ether and chilling, there was obtained 0.585 g. (43%) of crude amidine hydrochloride, m. p. 154–160°. Recrystallization from a mixture of ethanol and methyl ethyl ketone gave colorless rosettes of small needles, m. p. 166–167°.

Anal. Calcd. for $C_{15}H_{18}ClN_3$: N, 15.24; HCl, 13.23. Found: N, 15.50; HCl, 13.14.

N-Benzyl-N-phenylaminoacetothioamide (IIIa).—A solution of 4 g. of the nitrile Ia, 2 g. of ammonia and 4 g. of hydrogen sulfide in 20 cc. of methanol in a pressure bottle was heated for one hour at 70°. The mixture was cooled, diluted with water, and the product was filtered

(7) All melting points are corrected and were determined in sealed capillaries. Microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, New Jersey.

(8) "Organic Syntheses," Coll. Vol. I, 1941, p. 102.

(9) Knoevenagel, *Ber.*, **37**, 4073 (1904).

(10) The hydrogen chloride determinations were carried out on 10 mg. samples by the method of Dubsky and Trtilek, *Mikrochemie*, **12**, 315 (1933).

and recrystallized from ethanol; colorless needles (4.43 g., 97%), m. p. 176–178°.

Anal. Calcd. for $C_{15}H_{16}N_2S$: N, 10.93; S, 12.51. Found: N, 11.35; S, 12.13.

2-(N-Benzyl-N-phenylaminomethyl)-4-(β-morpholinoethyl)-thiazole Dihydrobromide (VIIa).—The above thioamide IIIa (0.51 g.) was dissolved in 20 cc. of boiling ethanol, 0.64 g. of bromide hydrobromide VIa[6] was added in one portion and heating was continued for one minute. The yellowish-orange solution was cooled and the thiazole VIIa was collected; yield, 0.68 g. (61%), m. p. 192–193°. Recrystallization from ethanol raised the m. p. to 194–196°.

Anal. Calcd. for $C_{23}H_{29}Br_2N_3OS$: C, 49.74; H, 5.26; N, 7.57. Found: C, 50.04; H, 5.55; N, 7.59.

2-(N-Benzyl-N-phenylaminomethyl)-4-(β-diethylaminoethyl)-thiazole Dihydrobromide (VIIb).—The above procedure was followed, except that 0.61 g. of the brominated "Mannich base" VIb[6] was employed and the product was isolated by dilution with ether and recrystallization from a mixture of ethanol and acetone; yield, 0.53 g. (49%), m. p. 173–175°.

Anal. Calcd. for $C_{23}H_{31}Br_2N_3S$: C, 51.02; H, 5.77; N, 7.76. Found: C, 50.72; H, 5.94; N, 7.99.

N,N-Dibenzylglycinonitrile (Ib).—The cyanomethylation of dibenzylamine, carried out as for benzylaniline, resulted in an 82% yield of N,N-dibenzylglycinonitrile (Ib), with b. p. 140° at 0.07 mm. The following constants were determined on the supercooled liquid: d^{25}_4 1.0514; $n^{25}D$ 1.5608; M_D (calcd.) 72.75; M_D (obs.) 72.76. The product crystallized from petroleum ether as colorless, prismatic needles, m. p. 46–48°.

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83; N, 11.86. Found: C, 81.19; H, 6.78; N, 11.94.

On treating 1 g. of the nitrile with 2.5 cc. of concentrated hydrochloric acid for one-half hour, in an ice-bath or on the steam-bath, 0.98–1.06 g. (85–92%) of **N,N-dibenzylglycinotrile hydrochloride**, m. p. 183.5–184°, was obtained.

Anal. Calcd. for $C_{16}H_{17}N_2Cl$: HCl, 13.37. Found: HCl, 13.76.

Treatment with water immediately regenerated the free nitrile. The hydrochloride slowly lost hydrogen chloride when kept under vacuum for long periods of time.

N,N-Dibenzylglycinamide (IIb).—The amide was obtained in 90% yield on shaking the nitrile with concentrated sulfuric acid for sixty-eight hours at room temperature. The analytical sample crystallized from petroleum ether–acetone as colorless needles, m. p. 100–101°.

Anal. Calcd. for $C_{16}H_{18}ON_2$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.27; H, 7.09; N, 10.91.

N,N-Dibenzylaminoacetothioamide (IIIb).—The reaction was carried out as in the case of the thioamide IIIa, except that the heating period was extended to two hours; yield, 87%, m. p. 96–98° (from ethanol).

Anal. Calcd. for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; N, 10.36; S, 11.86. Found: C, 71.39; H, 6.66; N, 10.32; S, 12.06.

N-Ethyl-N-phenylglycinonitrile (Ic).—Knoevenagel[9] prepared this substance by a method involving formaldehyde bisulfite[11] and reported b. p. 150° at 13 mm., m. p. 21°, but no analysis or yield was given. Using the method described above for the nitrile Ia, N-ethyl-N-phenylglycinonitrile was obtained in 60% yield; b. p. 112–115° at 0.04 mm., m. p. 21°, $n^{25}D$ 1.5480, d^{25}_4 1.0162, M_D (obs.) 50.08, M_D (calcd.) 49.98.

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49. Found: C, 74.83; H, 7.60; N, 17.44.

Treatment of the nitrile Ic at 0° with concentrated hydrochloric acid resulted in formation of the hydrochloride, while at 100° the amide IIc was obtained; yield of crude product, 59%.

The **hydrochloride** of Ic, m. p. 138.5–140.5°, was isolated in 92% yield by passing the calculated amount of hydrogen chloride gas through a dry ether solution of the nitrile.

Anal. Calcd. for $C_{10}H_{13}ClN_2$: N, 14.25; HCl, 18.54. Found: N, 14.41; HCl, 18.71.

N-Ethyl-N-phenylglycinamide (IIc).—The compound was obtained in 98% yield when prepared by the procedure described for IIa. The analytical sample melted at 114–115°[11] after sublimation *in vacuo* and recrystallization from benzene.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.31; H, 7.64; N, 15.89.

N-Ethyl-N-phenylaminoacetothioamide (IIc).—Yield, 90%, m. p. 139–140°.[11]

Anal. Calcd. for $C_{10}H_{14}N_2S$: C, 61.81; H, 7.26; N, 14.42; S, 16.50. Found: C, 61.70; H, 7.05; N, 14.66; S, 17.02.

Summary

An improved procedure for the cyanomethylation of secondary amines has been described, and the behavior of the resulting N,N-disubstituted glycinonitriles toward acid has been investigated.

N-Benzyl-N-phenylglycinonitrile was converted into the corresponding amidine, and *via* the thioamide into thiazole derivatives.

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(11) A similar procedure is described in German Patent 156,760; the amide IIc (m. p. 114–115°) and thioamide IIIc (m. p. 140°) are also mentioned, without indicating the yield or analysis.