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

The Synthesis of β-Carbolines. V. 1-Amino-β-carboline[1]

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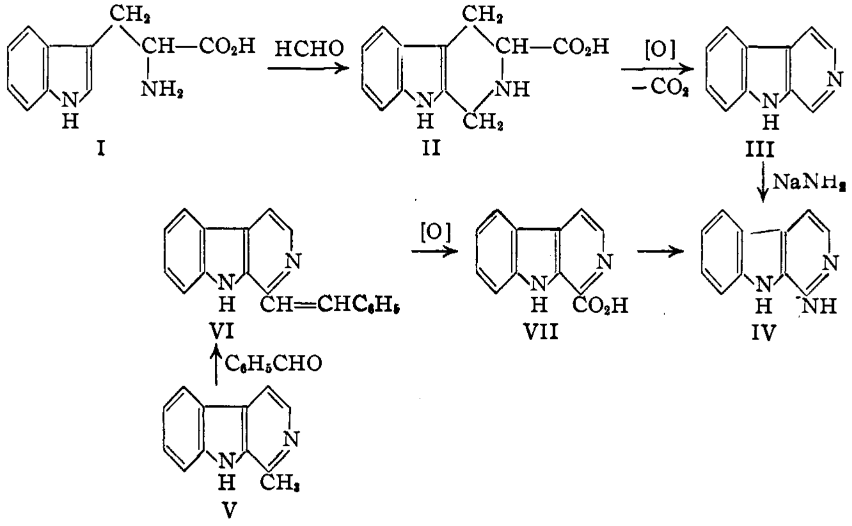
In preceding papers[1,4] syntheses of the isomeric 3- and 6-amino derivatives of harman were reported. These amines were prepared by the degradation of an acid (Curtius reaction) and the reduction of a nitro compound, respectively. Although the direct amination, by alkali amides, of higher heterocyclic bases containing the pyridine nucleus has been found to have only limited applicability,[5] it was of interest to test the possible use of the reaction in the β-carboline series. Accordingly, norharman (III) has been subjected to the action of sodium amide; reaction occurred readily, and the product has been shown to be 1-amino-β-carboline (IV).

The preparation of norharman (III) was carried out according to Harvey, Miller and Robson[6] in direct analogy to the synthesis of harman,[4] without isolation of the intermediate tetrahydrocarboxylic acid (II). *dl*-Tryptophan (I) was condensed with formaldehyde and the 1,2,3,4-tetrahydronorharman - 3 - carboxylic acid so formed (II) was converted directly to III by dehydrogenation and decarboxylation with aqueous potassium dichromate. Amination of III with sodium amide proceeded in 89% yield to give 1-amino-β-carboline (IV). Acetylation of IV with acetic anhydride in pyridine solution produced a diacetyl derivative, the detailed structure of which has not yet been elucidated.



Chichibabin and Oparina[7] have shown that 1-aminoisoquinoline is obtained by direct amination of isoquinoline. It thus seemed reasonable to assume that the β-carboline nucleus would be attacked at the 1-position. All approaches to the structure proof were based on this assumption. Diazotization followed by hydrolysis, or direct hydrolysis of the amine with acid or base, might be expected to lead to the 1-hydroxy-β-carboline prepared by Elderfield and Hageman.[8] All attempts in this direction were unsuccessful, however. 9 - Methyl - 1 - hydroxy - β - carboline[9] might be prepared by methylation and subsequent diazotization of the amine, but methylation with diazomethane failed, so that this approach was abandoned. Similarly, no identifiable products were obtained in attempts to replace the amino group with bromine, nor was it found possible to hydrolyze any of the resulting crude reaction products to the hydroxy compound.

An unequivocal synthesis of 1-amino-β-carboline has been carried out by the method shown in the accompanying diagram. Harman (V) was oxidized to β-carboline-1-carboxylic acid (VII) essentially by the method of Kermak, Perkin and Robinson,[9] who condensed harman with benzaldehyde and oxidized the condensation product (VI) with potassium permanganate. The acid (VII) could be degraded to 1-amino-β-carboline by application of the Curtius reaction.[10] Preliminary experiments indicated that the more direct route to the carbonylazide—treatment of the acid chloride with sodium azide—was not feasible because of the extreme insolubility of the acid, which made conversion to the acid chloride unsatisfactory. The acid was readily esterified, however, and the methyl ester reacted with hydrazine almost instantaneously, without application of heat. Although the hydrazide was very insoluble it was readily transformed into the azide by treatment with nitrous acid in a large

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(1) For the preceding paper see Snyder, Parmerter and Walker, THIS JOURNAL, **70**, 237 (1948).

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(4) Snyder, Parmerter and Katz, THIS JOURNAL, **70**, 222 (1948).

(5) Leffler, in Adams, "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, pp. 91-104.

(6) Harvey, Miller and Robson, *J. Chem. Soc.*, 153 (1941).

(7) Chichibabin and Oparina, *J. Russ. Phys.-Chem. Soc.*, **50**, 543 (1920).

(8) Elderfield and Hageman, private communication.

(9) Kermak, Perkin and Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

(10) See Smith, in Adams, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y., 1946, p. 337 ff.

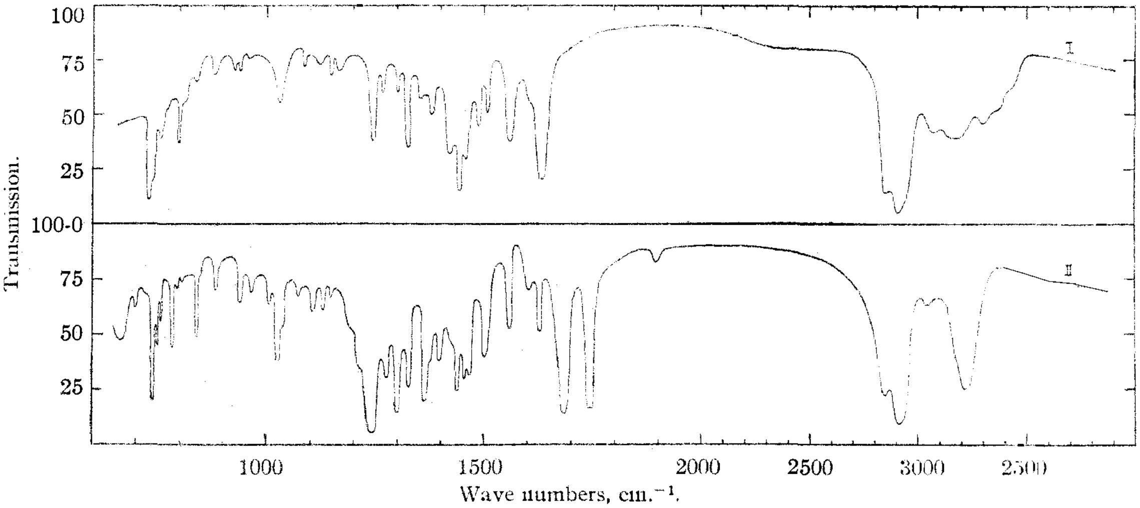

Fig. 1.—I, 1-Amino-β-carboline, suspended in mineral oil; II, diacetyl derivative of 1-amino-β-carboline, suspended in mineral oil.

volume of water. The azide was quite stable at room temperature. Attempted conversion to the amine in dilute acetic acid gave the *sym*-urea, which could be converted to the amine by hydrolysis with concentrated aqueous potassium hydroxide, but only in low yields. Conversion to the amine by preparation and hydrolysis of the ethyl carbamate was the most successful of the methods tried. The amine (IV) thus obtained melted two degrees lower than that formed by direct amination of norharman, but a mixture of the two samples melted at an intermediate temperature. Infrared absorption[11] spectra of the two amines were identical (see Fig. 1).

The diacetyl derivative of the amine obtained by the indirect route was also prepared; this substance and the compound derived from the direct-amination product melted at the same point, alone or mixed, and their infrared absorption curves were identical in every detail (Fig. 1).

Experimental[12]

Norharman.—The general procedure of Harvey, Miller and Robson[6] was followed. Ten grams (0.049 mole) of *dl*-tryptophan was dissolved in 500 ml. of 0.1 *N* sodium hydroxide containing 5.6 ml. (0.07 mole) of aqueous formalin (40%). The solution was incubated at 37° for forty-six hours. It was neutralized with 4 ml. of glacial acetic acid, transferred to a 5-l. flask, and diluted with water to a volume of 2.5 l. The suspension was heated to boiling, and most of the 3-carboxy-1,2,3,4-tetrahydro-β-carboline dissolved. A mixture of 500 ml. of 10% aqueous potassium dichromate and 100 ml. of glacial acetic acid was added to the slowly boiling solution, with stirring, over a period of forty-five minutes. The solution darkened, carbon dioxide was evolved, and a brown precipitate appeared soon after the addition was started. Boiling was continued for two minutes after the addition was complete. The mixture was cooled and the excess dichromate was destroyed with sodium bisulfite. Sodium carbonate was added to definite alkalinity and the product was extracted exhaustively with about 2.5 l. of ether. The extracts were dried over magnesium sulfate and the solvent removed. After one recrystallization from aqueous methanol the slightly yellow, crystalline norharman weighed 2.80 g. (34%), m.p. 199–201°.

1-Amino-β-carboline.—Sodium amide was prepared according to the standard procedure,[5] from 1.81 g. (0.0788 mole) of sodium and 30 ml. of liquid ammonia in a 200-ml. three-necked flask fitted with mercury-sealed stirrer and reflux condenser. After the ammonia had evaporated, 3.31 g. (0.0197 mole) of norharman and 90 ml. of dimethylaniline were added, and the mixture was stirred and heated at 140–150° for twenty-four hours. The contents of the flask were allowed to cool, and 50 ml. of 5% sodium hydroxide solution and 100 ml. of water were added cautiously. Low-boiling petroleum ether was added to precipitate all material in the organic layer, the mixture was cooled in an ice-bath, and the crystalline product was collected. It was washed with low-boiling petroleum ether and dried in a vacuum desiccator; there was obtained 3.31 g. (89%) of material, m.p. 193–197°. Recrystallized from a methanol–water mixture it melted at 198–200°. A mixture of the crude reaction product and norharman melted at 142–159°. A sample of the product was recrystallized once more from methanol–water, yielding white platelets, m.p. 199.5–200.5° (dec.).

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95. Found: C, 72.22; H, 4.79.

The diacetyl derivative was prepared according to a standard method of acetylation.[13] Recrystallized four times from benzene, it melted at 196–197.5°. A sample mixed with 1-amino-β-carboline melted at 135–150°.

Anal. Calcd. for $C_{15}H_{13}O_2N_3$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.56; H, 4.58; N, 15.59.

Benzalharman.[9,14]—**Harman,**[4] 9.94 g. (0.055 mole), and 55 ml. of distilled benzaldehyde were placed in a 500-ml. round-bottomed flask and the mixture was refluxed gently for four hours, with a condenser short enough to permit the slow evaporation of the water formed in the reaction. After cooling, the brown mixture was diluted with 200 ml. of ether, and dilute hydrochloric acid was added to precipitate the yellow hydrochloride of benzalharman. It was separated, washed with ether and water, and recrystallized from 95% ethanol. The hydrochloride

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(11) We are indebted to Mrs. Agatha R. Johnson for the infrared absorption data.

(12) All melting points are corrected. Microanalyses by Miss Theta Spoor and Mr. H. S. Clark.

(13) Shriner and Fuson, "Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, New York, N. Y., 1948, p. 165, Procedure B.

(14) Barger and Scholtz, *J. Chem. Soc.*, 614 (1933); Leonard and Elderfield, *J. Org. Chem.*, 7, 556 (1942).

was suspended in 40 ml. of 95% ethanol, neutralized with dilute aqueous ammonia (1:5 ammonium hydroxide-water), and the free base was collected. The yield of yellow crystalline benzalharman was 12.6 g. (84%), m.p. 197–199°.

β-Carboline-1-carboxylic Acid.—The permanganate oxidation method of Kermak, Perkin and Robinson[9] was used. Benzalharman, 12.7 g. (0.046 mole) was dissolved in 50 ml. of pyridine, the solution was cooled in ice and stirred during the dropwise addition of enough saturated aqueous potassium permanganate to leave a pink color for one hour (approx. 300 ml.). The exact amount added depends on rapidity of addition, temperature and other factors. Five ml. of 95% ethanol was added and the mixture was heated on the steam-bath to destroy excess permanganate. The dark suspension was filtered hot and the filtrate was concentrated to a volume of 100 ml. and acidified with dilute hydrochloric acid. The canary-yellow hydrochloride was collected. The manganese dioxide residue was suspended in 100 ml. of water and acidified with hydrochloric acid; the mixture was treated with sodium bisulfite to dissolve the manganese dioxide, and the additional hydrochloride precipitate was collected. (Direct treatment of the original mixture with sodium bisulfite, to circumvent the necessity for removal of the manganese dioxide by filtration, resulted in lower yields.) The combined hydrochloride precipitates were dissolved in 1500 ml. of hot 5% aqueous potassium hydroxide, the solution was filtered, cooled, and the free acid was precipitated with acetic acid. The material was collected, washed with water, and dried; it weighed 3.4 g., m. p. 235°. The acidic mother liquor yielded an additional 0.9 g. of product (total crude yield, 43%). β-Carboline-1-carboxylic acid is a bright yellow, crystalline powder whose insolubility in all solvents tried made recrystallization impossible.

1-Carbomethoxy-β-carboline.—β-Carboline-1-carboxylic acid, 3.9 g., was suspended in 300 ml. of anhydrous methanol saturated with hydrogen chloride. The mixture was refluxed for twenty hours and concentrated to a volume of 100 ml. under reduced pressure and at room temperature. It was diluted with an equal volume of ice water, made barely alkaline with sodium bicarbonate, and extracted with chloroform. The extract was dried over magnesium sulfate and the solvent was removed. The yield of crude ester was 1.50 g., m.p. 152–157°. A small sample was sublimed *in vacuo* and recrystallized three times from dilute methanol; m.p. 165.3–166.0°.

Anal. Calcd. for $C_{13}H_{10}O_2N_2$: C, 69.02; H, 4.46; N, 12.39. Found: C, 69.02; H, 4.18; N, 12.41.

The magnesium sulfate residue was combined with the extracted water solution, and the mixture was concentrated and acidified with acetic acid. One and one-half grams of β-carboline-1-carboxylic acid was recovered.

β-Carboline-1-carbonyl Hydrazide.—The remainder of the crude ester from the previous preparation, 1.35 g., was dissolved in a mixture of methanol and water and the solution was slowly added to 7 ml. of 85% hydrazine hydrate. Precipitation of the hydrazide started immediately and was allowed to go to completion in the refrigerator overnight. The product was collected, m.p. 215–236°. One recrystallization from dioxane gave 1.20 g. of hydrazide, m.p. 265–267°. A sample recrystallized repeatedly from dioxane melted at 268–269.5° (dec.).

Anal. Calcd. for $C_{12}H_{10}ON_4$: C, 63.71; H, 4.46. Found: C, 63.47; H, 4.30.

β-Carboline-1-carbonyl Azide.—β-Carboline-1-carbonyl hydrazide, 0.95 g., was added to 146.1 ml. of dilute hydrochloric acid (6.1 ml. of the concentrated acid in 140 ml. of water), and the suspension was filtered to remove the insoluble residue. The filtrate was cooled to 0° in an ice-salt-bath, and 0.33 g. of sodium nitrite in 5 ml. of water was added over a period of five minutes. The suspension of azide-hydrochloride was allowed to stand in the cooling bath for two hours, made definitely alkaline with saturated aqueous sodium carbonate, and the solid was collected and washed with water. After drying to constant weight in a vacuum desiccator the product weighed 0.86 g.; it was quite stable at room temperature, but slowly decomposed at temperatures of 70–100°.

Ethyl β-Carboline-1-carbamate.—The crude azide, 0.86 g., was refluxed for three hours in 13 ml. of absolute ethanol diluted with 4 ml. of dry xylene. The mixture was filtered hot and the residue was washed with hot 95% ethanol. The combined filtrate and washings were concentrated to a volume of 15 ml., and 0.38 g. of fluffy yellow needles was collected, m.p. 283–285° (dec.), with characteristic shrinking at 181–183°. Examination of the residue from the hot reaction mixture, weighing 0.16 g., revealed it to be a less soluble crystalline modification of the major reaction product. Its melting point and infra-red-absorption curve were identical with those of the ethanol-soluble portion, and mixtures of the two samples showed no melting point depression. A small amount of the soluble modification, recrystallized repeatedly from ethanol, melted at 285–288° (dec.), shrinking at 184–186°.

Anal. Calcd. for $C_{14}H_{13}O_2N_3$: N, 16.46: Found: N, 16.36.

1-Amino-β-carboline.—A suspension of 0.33 g. of crude carbamate in 7 ml. of 20% aqueous potassium hydroxide was refluxed for two hours. The mixture was allowed to cool, and the crude amine was collected and washed with cold water. After one recrystallization from dilute ethanol (Norite) there was obtained 0.21 g. of colorless needles, m.p. 199–201 (dec.). A sample recrystallized to constant melting point melted at 196.5–198.5° (dec.). Mixed with the amine prepared by direct amination of norharman it melted at 198–200°.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95. Found: C, 72.32; H, 5.14.

The diacetyl derivative was prepared[13] and recrystallized repeatedly from benzene. It melted at 195.5–197.5°, alone or mixed with a sample derived from the amination product of norharman.

Anal. Calcd. for $C_{15}H_{13}O_2N_3$: N, 15.72. Found: N, 15.54.

Summary

1-Amino-β-carboline has been prepared by direct amination of norharman, and the structure of the product has been proved by an independent synthesis.

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