

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

The Synthesis of Derivatives of  $\beta$ -Carboline. III. The Nitration of Harman<sup>1</sup>By H. R. SNYDER, STANLEY M. PARMERTER<sup>2</sup> AND LEON KATZ<sup>3</sup>

The preparation of harman (III) by the condensation of tryptophan (I) with acetaldehyde, followed by aromatization, oxidation and decarboxylation in a single step through the action of potassium dichromate,<sup>4</sup> becomes a practical synthetic method when the readily available *dl*-tryptophan is employed as the raw material.<sup>1</sup>

sumably 8-nitroharman, was isolated in a yield of about 20%.

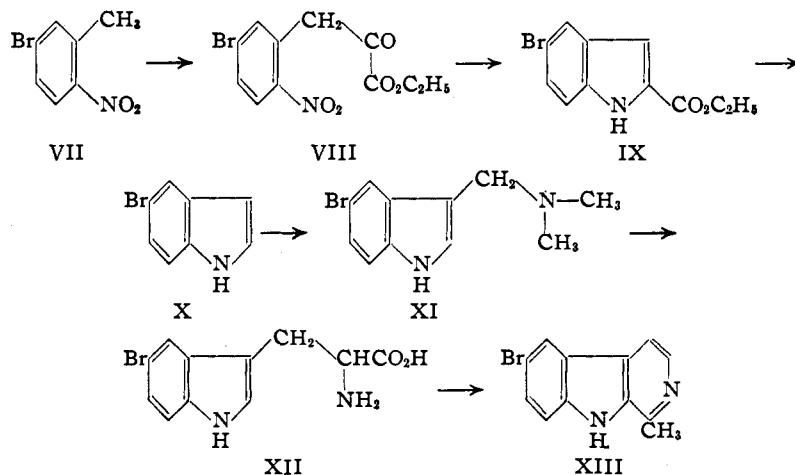
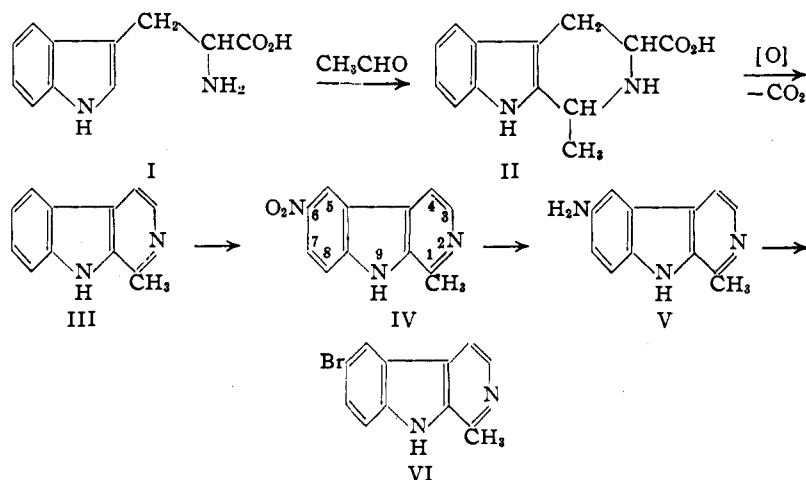
The higher-melting nitro compound (IV) was reduced to the amine (V) which proved not to be identical with the known 7-aminoharman.<sup>5</sup> Diazotization of the amine (V) was accomplished, and since both 6- and 8-methoxyharman are known, the conversion of the diazonium compound to the methyl ether should have sufficed to demonstrate the structure of IV. However, attempts to replace the diazonium group by methoxyl, either directly or by way of the hydroxy compound, have been unsuccessful.

It was possible to convert the diazonium compound to the bromo compound (VI), so an unequivocal synthesis of any of the compounds IV, V or VI would serve to confirm the identity of the high-melting nitro compound. The bromoharman (VI) was syn-

It is therefore desirable to examine the substitution reactions of harman, some of which might be expected to lead to compounds of physiological interest. The present report is concerned with the preparation of two isomeric nitroharmanes by direct nitration and with the proof of the structure of one of them (IV).

The preparation of harman (III) was carried out according to the method of Harvey and Robson,<sup>4</sup> except for the use of the racemic amino acid, without isolation of any of the intermediates and in 67% yield. The nitration was effected with the aid of concentrated nitric acid at temperatures of 40° or below. The higher-melting nitro derivative, now shown to be 6-nitroharman (IV), was formed in the larger amount (57%); the lower-melting isomer, pre-

thesized by the series of reactions shown in the accompanying chart. The 2-nitro-5-bromotol-



ene condensed readily with ethyl oxalate in the presence of potassium ethoxide to give the potassium salt of VIII, and this salt was reduced directly to the bromoindolecarboxylic ester (IX). The acid obtained by saponification of the ester IX proved unexpectedly resistant to decarboxylation. Of a number of decarboxylation procedures tested only vigorous heating with copper

(1) For the preceding paper see Snyder, Hansch, Katz, Parmertter and Spaeth, *THIS JOURNAL*, **70**, 219 (1948).

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(4) Harvey and Robson, *J. Chem. Soc.*, 97 (1938).

(5) Fischer, *Ber.*, **47**, 99 (1914).

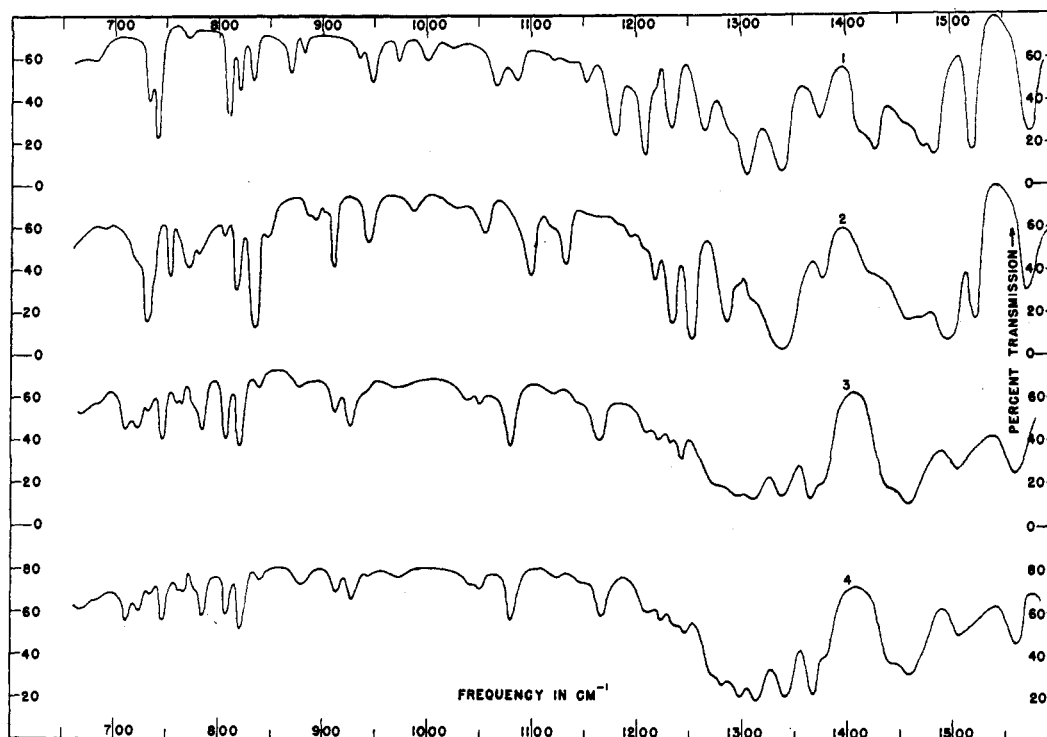


Fig. 1.—1, Nitroharman; m. p. 210°; 2, nitroharman; m. p. 301°; 3, picrate of 6-bromoharman; 4, picrate of bromoharman prepared from high-melting nitro isomer.

and copper chromite catalyst gave yields (ca. 20%) high enough to permit continuation of the projected series of reactions. This treatment apparently resulted in removal of bromine from some of the product, and the 5-bromoindole (X) so prepared could not be purified sufficiently for a satisfactory combustion analysis. 5-Bromoindole (X) of high purity could be obtained, but in very poor yield, by heating the ammonium salt of the acid in glycerol. It was found that the picrate of 5-bromogramine, prepared from the crude 5-bromoindole, could be obtained in the analytically pure state, so the synthesis was continued and the picrate of the 6-bromoharman (XIII) was prepared. This picrate was obtained in analytically pure state. The melting point of the picrate of the 6-bromoharman so obtained was identical with that of the picrate of the bromoharman prepared from the nitro compound (IV). A much more striking proof of the identity of the two picrates was obtained by comparison of the infrared absorption spectra of the two samples. The absorption curves<sup>6</sup> (Figs. 1 and 2) were identical in every detail.

#### Experimental

**Harman (2-Methyl- $\beta$ -carboline) (III).**—The general procedure of Harvey and Robson<sup>4</sup> was followed. Twenty-five grams of *dl*-tryptophan and 50 ml. of freshly distilled acetaldehyde were added to 1 liter of water. The suspension was heated at 50–60° in a loosely-stoppered flask

for three hours and then left at room temperature overnight. The resulting suspension was heated on a steam-bath to remove excess acetaldehyde, diluted to a volume of 6 l. and heated to boiling. To the hot solution was added 1200 ml. of 10% aqueous potassium dichromate and 240 ml. of glacial acetic acid. The brown suspension was heated for two to three minutes and then cooled under the tap. After treating the cold solution with sodium sulfite to remove the excess oxidizing agent, the mixture was made definitely alkaline with solid sodium carbonate. The solution was extracted exhaustively with ether (5–6 liters), the extracts dried over magnesium sulfate, and the solvent removed. The residue of crystalline harman, m. p. 228–230°, weighed 15.1 g. (67%).

**6-Nitroharman (IV).**—Crude harman was added slowly with stirring to concentrated nitric acid (10 ml. per g.). The temperature was held below 40° by occasional cooling. Most of the harman dissolved, and a light yellow solid separated. The mixture was stirred for one hour and filtered. The solid was suspended in dilute ammonium hydroxide to neutralize the nitric acid. The crude nitroharman was collected and dissolved in the minimum amount of hot pyridine. As the pyridine cooled, yellow needles separated. Concentration of the pyridine solution to half its original volume yielded an additional crop of needles. The total yield of nitroharman, m. p. 293–295°, was 57.1%. A sample recrystallized from 95% ethanol separated as clusters of yellow needles, m. p. 299–300°. The compound was soluble in acetic acid and pyridine, somewhat soluble in methanol and ethanol, and insoluble in water.

*Anal.* Calcd. for  $C_{12}H_9N_2O_2$ : C, 63.45; H, 3.99. Found: C, 63.66; H, 4.09.

Addition of water to the nitric acid used in the nitration gave additional quantities of yellow solid. This was collected and treated with ammonia to yield a lower-melting nitroharman. After recrystallization from 95% ethanol, it melted at 209–210°. It separated as octahedra or short needles. Dilution of the pyridine mother liquor

(6) The authors are indebted to Mrs. Agatha Roberts Johnson for the infrared study.

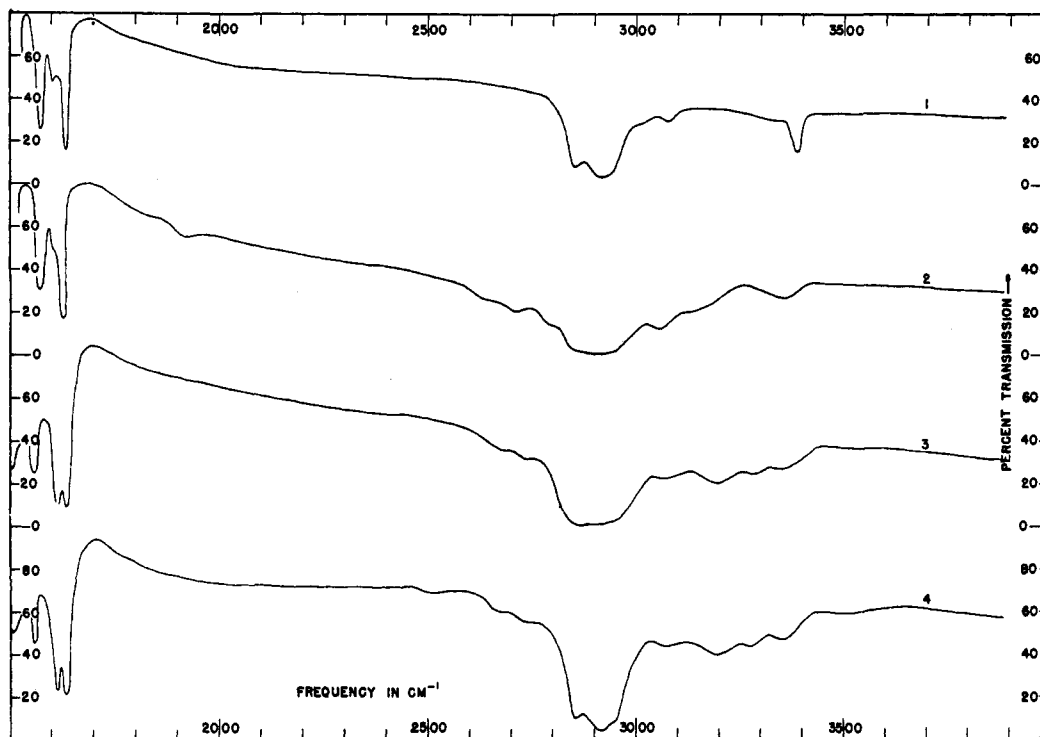


Fig. 2.—1, Nitroharman; m. p. 210°; 2, nitroharman; m. p. 301°; 3, picrate of 6-bromoharman; 4, picrate of bromoharman prepared from high-melting nitro isomer.

yielded additional amounts of this isomer, the total yield being 19.5%.

*Anal.* Calcd. for  $C_{12}H_9N_3O_2$ : C, 63.45; H, 3.99. Found: C, 63.59; H, 4.27.

**6-Aminoharman (V).**—To a solution of 2.2 g. of stanous chloride dihydrate in 2.5 ml. of concentrated hydrochloric acid and 10 ml. of water was added 0.5 g. of high-melting nitroharman. The solution was refluxed two hours and cooled in ice. The yellowish-green salt was collected and suspended in excess 10% aqueous sodium hydroxide to free the base. The solid was collected and washed with water. The yield of crude amine melting at 265–267° was 0.35 g. or 80% of the theoretical amount. After a second recrystallization, the light tan crystals melted at 269–271°. The base slowly darkens on exposure to air, and its solutions rapidly become deep red in color.

*Anal.* Calcd. for  $C_{12}H_{11}N_3$ : C, 73.09; H, 5.62. Found: C, 73.12; H, 5.57.

**6-Bromoharman (VI).**—A cold solution of 0.394 g. of aminoharman in 1.5 ml. of water and 1 cc. of 40% hydrobromic acid was diazotized by the addition of a solution of 0.15 g. sodium nitrite in 0.5 ml. of water. The diazonium salt partially crystallized. The suspension of diazonium salt was transferred to a hot solution of 0.158 g. of cuprous bromide in 0.3 ml. of 40% hydrobromic acid. Heating on a steam-bath for ten minutes caused evolution of gas and the separation of a green solid, which was collected and suspended in dilute ammonium hydroxide. The free amine was then recrystallized from 25 ml. of 50% ethanol. Pale yellow needles melting at 241–244° separated. When these were recrystallized from benzene, they separated as needles which slowly changed to pale yellow plates. Both crystalline forms melted at 246–247°.

*Anal.* Calcd. for  $C_{12}H_9N_2Br$ : C, 55.20; H, 3.47. Found: C, 55.40; H, 3.69.

The picrate, prepared for analysis by recrystallization from absolute ethanol, melted at 291–293° (dec.).

*Anal.* Calcd. for  $C_{12}H_9N_2Br \cdot C_6H_3N_3O_7$ : C, 44.08; H, 2.45. Found: C, 44.39; H, 2.73.

**2-Nitro-5-aminotoluene.**—The procedure of Fieser<sup>7</sup> for acetylation, nitration and deacetylation of aniline was followed, with *m*-toluidine obtained from Eastman Kodak Company. From 102 g. of *m*-toluidine, 79.5 g. of 2-nitro-5-aminotoluene, m. p. 130–132° (lit.,<sup>8</sup> 137–138°) was obtained.

**2-Nitro-5-bromotoluene (VII).**—A modification of the method of Geerling and Wibaut<sup>9</sup> was employed. To a finely divided suspension of 25 g. of 2-nitro-5-aminotoluene in a cold solution of 80 ml. of 48% hydrobromic acid and 150 ml. of water, was added a solution of 11.5 g. of sodium nitrite in 30 ml. of water. The solution of the diazonium salt was filtered and run rapidly into a hot (75°) cuprous bromide solution prepared by boiling 20 g. of copper oxide, 20 g. of copper powder, 100 ml. of 48% hydrobromic acid and 80 ml. of water. The solution was stirred manually and then heated on a steam-bath for one-half hour. The 2-nitro-5-bromotoluene was isolated by steam distillation. The yield was 26 g. (75%); m. p. 55–56° (lit.,<sup>10</sup> 56°).

**Potassium Salt of Ethyl 2-Nitro-5-bromophenylpyruvate (VIII).**—A strong solution of potassium ethoxide was prepared by cautiously adding 3.2 g. of crust-free potassium to a mixture of 5 ml. of dry ether and 10 ml. of absolute alcohol; when the first violent reaction had subsided, 17 ml. of absolute alcohol was added and the solution was heated gently, if necessary, to effect complete solution of the metal. The solution was then cooled and diluted with 125 ml. of dry ether, and to this solution was added 12.3 g. of ethyl oxalate, followed fifteen minutes later by 15 g. of 2-nitro-5-bromotoluene. The solution was shaken gently and allowed to stand overnight. The red salt was collected, washed with dry ether, and used immediately. The yield was almost quantitative (24.5 g.).

(7) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, pp. 163–170.

(8) Noeltling and Stocklin, *Ber.*, **24**, 564 (1891).

(9) Geerling and Wibaut, *Rec. trav. chim.*, **63**, 1012 (1934).

(10) Gibson and Johnson, *J. Chem. Soc.*, 1229 (1929).

**5-Bromoindole-2-carboxylic Acid.**—The above salt, 28 g., was suspended in a solution of 170 ml. of concentrated aqueous ammonia (sp. gr., 0.880) and 200 ml. of water. To the bright red suspension was added, with stirring, a hot solution of 180 g. of ferrous sulfate heptahydrate in 200 ml. of water. The mixture was heated on a steam-bath for one-half hour and then boiled for one-half hour. The suspension was filtered while hot, and the sludge was extracted three times by boiling the filter cake with 500 ml. of water and filtering. The filtrates were cooled and acidified with concentrated hydrochloric acid. A voluminous white precipitate was formed, but the solution was allowed to stand in a refrigerator at 5° overnight before filtration. The yield of white solid, m. p. 270–273°, was 9 g., 42.5%. A sample was sublimed for analysis; m. p. 279–280°.

*Anal.* Calcd. for  $C_9H_6NO_2Br$ : C, 44.98; H, 2.53. Found: C, 44.71; H, 2.73.

The ethyl ester (IX) was obtained by extraction of the dried ferric oxide sludge with ether in a Soxhlet extractor for seventy-two hours. Removal of the solvent yielded 2.7 g. of material; m. p. 162–164°. A sample was prepared for analysis by recrystallization from 95% ethanol; m. p. 165°.

*Anal.* Calcd. for  $C_{11}H_{10}NO_2Br$ : C, 49.25; H, 3.76. Found: C, 49.42; H, 3.75.

**5-Bromoindole (X).**—Two grams of 5-bromoindole-2-carboxylic acid, 1 g. of copper bronze and 1 g. of copper chromite catalyst were intimately mixed and placed in a large test-tube. The test-tube was flushed three times with nitrogen, placed in a metal block, and heated at  $247 \pm 10^\circ$  for one and one-half to two hours. A white sublimate of fine needles collected in the upper portion of the tube which was kept cool throughout the heating period. The yield of 5-bromoindole, m. p. 77–82°, was 0.35–0.4 g. (21–24%). Small amounts of sublimed acid were present as an impurity. The use of amounts larger than 3 g. resulted in lowered yields. A sample was resublimed for analysis; m. p. 85.5–86°.

*Anal.* Calcd. for  $C_8H_6NBr$ : C, 48.98; H, 3.06. Found: C, 50.75; H, 3.22.

When the ammonium salt was decarboxylated by heating in glycerol, a small amount of material sublimed into the condenser. This was collected and recrystallized from 50% ethanol; m. p. 88.5–89°.

*Anal.* Calcd. for  $C_8H_6NBr$ : C, 48.98; H, 3.06. Found: C, 49.34; H, 3.29.

**5-Bromogranine (XI).**—To 7.6 g. of dimethylamine (25%) at 5° was added 6 g. of glacial acetic acid. To this solution, cooled to 5°, was added 3.2 g. of formalin (40%). The solution was agitated mildly and added to 7.5 g. of crude 5-bromoindole. A slight exothermic reaction occurred. The resulting straw-colored solution was kept at room temperature for ten hours and poured into 40 ml. of 10% sodium hydroxide, cooled in an ice-bath. The white precipitate was filtered, yielding 7.8 g. (79%) of crude XI; m. p. 143–145°. A sample sub-

jected to repeated recrystallization from acetone–water melted sharply at 149.5–150°, but still evidently contained bromine-free impurities.

*Anal.* Calcd. for  $C_{11}H_{13}N_2Br$ : C, 52.17; H, 5.18. Found: C, 54.12; H, 5.28.

The picrate prepared from the crude 5-bromogranine was purified by recrystallization from ethanol; it melted at 174°.

*Anal.* Calcd. for  $C_{11}H_{13}N_2Br \cdot C_6H_3N_3O_7$ : C, 42.32; H, 3.33. Found: C, 42.52; H, 3.42.

**Condensation of the Crude 5-Bromogranine with Acetamidomalonic Ester.**—The condensation was run in xylene according to the procedure of Howe, Zambito, Snyder and Tishler,<sup>11</sup> and the condensation product was converted to the amino acid by the method of Snyder and Smith.<sup>12</sup> The carbon and hydrogen contents of the intermediates and of the 5-bromotryptophan all were high (see the analysis of the bromogranine above).

**6-Bromoharman.**—Sixty-five milligrams of 5-bromotryptophan (m. p. 264–267°, dec.) was suspended in 7 ml. of hot water and treated with 20 drops of freshly distilled acetaldehyde and 3 drops of 6 *N* sulfuric acid. The solution was heated on a water-bath for one hour, cooled, treated with 5 drops of acetaldehyde and left at room temperature for twelve hours. The cloudy solution was concentrated on a steam-bath and cooled. Opaque crystals, m. p. 218–220°, were deposited. This acid was dissolved in 15 cc. of hot water and treated with 3.5 cc. of 10% potassium dichromate and 0.5 cc. of glacial acetic acid. The solution was boiled for two minutes, made alkaline with solid sodium carbonate, and extracted with ether. Removal of ether yielded 35 mg. of solid; m. p. 227–230°. Repeated crystallization from benzene raised the melting point to 234–235°.

The picrate was prepared and recrystallized repeatedly from absolute ethanol. The analytical sample thus prepared melted with decomposition at 291–293°, alone or mixed with the picrate of 6-bromoharman (VI) prepared from the nitroharman (IV).

*Anal.* Calcd. for  $C_{12}H_9N_2Br \cdot C_6H_3N_3O_7$ : C, 44.08; H, 2.45. Found: C, 44.29; H, 2.76.

### Summary

Harman is conveniently prepared by the condensation of *dl*-tryptophan with acetaldehyde, followed by aromatization and decarboxylation of the condensation product. The nitration of harman by concentrated nitric acid at moderate temperatures leads to two isomeric mononitro derivatives; the nitro derivative produced in the larger amount is shown to be 6-nitroharman.

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(11) Howe, Zambito, Snyder and Tishler, *THIS JOURNAL*, **67**, 38 (1945).

(12) Snyder and Smith, *ibid.*, **66**, 350 (1944).