MONONITRO-β-CARBOLINES

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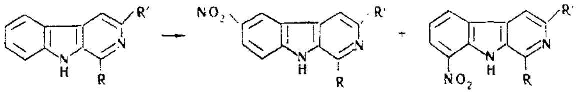
By the direct nitration of harmane and 1,3-dimethyl-, 1-ethyl-, 1-n-propyl-, and 1-isopropyl-β-carbolines with concentrated nitric acid or a mixture of nitric and acetic acids, 6- and 8-nitro-1-alkyl-β-carbolines have been obtained. A chromatographic method for separating the nitration products on alumina is proposed.

In the indole series, electrophilic substitution in the benzene part of the molecule has been studied fairly widely [1]. A limited number of investigations has been devoted to substitution in the benzene ring of the β-carbolines and the laws of orientation in this case have not yet been established. It is known that the nitration of the β-carbolines in conc HNO_3 forms mainly 6-nitro derivatives [2]. Structure of the isomeric compound was not established. There is no information in the literature on the nitration of β-carbolines in acetic acid.

In order to study this reaction in detail, we have subjected to nitration with conc HNO_3 or a mixture of HNO_3 and acetic acids, harmane (**Ia**), 3-methylharmane (**Ib**), 1-ethyl-β-carboline (**Ic**), 1-isopropyl-β-carboline (**Id**), and 1-n-propyl-β-carboline (**Ie**). To nitrate compound **Ia** with HNO_3 at 40° C requires prolonged heating (up to 5 hr), possibly because of the heterogeneous nature of the reaction. The yield of nitration products amounts to 80%. In all cases the separation of the nitrocarbolines on alumina could be effected with satisfactory results in chloroform or the chloroform—ether (3 : 1) system. In the case of the nitroharmanes, the mixture was separated into three substances, with R_f 0.21, 0.35, and 0.54 (chloroform—ether) and R_f 0.19, 0.27, and 0.31 (chloroform). The compounds with R_f 0.21 and 0.35 were identified, respectively, as 6-nitroharmane [2] and the starting material. The compound with R_f 0.54 proved to be identical with the 8-nitroharmane obtained by condensing 7-nitrotryptophan with acetaldehyde [3] and subsequent oxidation by Snyder's method [2]. The 6-nitroharmane was obtained with a yield of 50% and the 8-nitro isomer with a yield of 20%. Carrying out the reaction at 50° C (5 hr) or at 80° C (4 hr) did not lead to an increase in the yield of nitroharmanes. On chromatography in a thin layer of alumina, none of the starting material was detected, but a considerable zone of an unidentified yellow substance remained.

The β-carbolines Ic–Ie nitrate even at 40° C in 2 hr with a yield of mixtures of nitration products of 80–85%. By chromatography in a thin layer of alumina, the mixture was separated in each case into the starting material and two mononitro-β-carbolines. The chloroform—ether system was used for the preparative separation of the nitration products, giving IIc–IIe with yields of 40, 45, and 47% and IIIc–IIIe with yields of 20, 21, and 22%, respectively:



Ia–e IIa–e IIIa–e

a R = CH_3, R' = H; b R = CH_3, R' = CH_3; c R = C_2H_5, R' = H; d R = i-C_3H_7, R' = H; e R = n-C_3H_7, R' = H

In contrast to carbazole [4], the β-carbolines do not undergo nitration on being heated in a mixture of acetic and nitric acids at 60° C (8 hr), which is apparently due to the protonation of the pyridine nitrogen leading to a decrease in the nucleophilic capacity of the benzene nucleus of the β-carboline. When the reaction mixture was boiled for 5 hr, **IIa–IIe** and **IIIa-IIIe** were formed with yields of 60 and 28%, respectively.

The 6-nitro-β-carbolines are pale yellow crystalline substances readily crystallizing from toluene. The 8-nitro-β-carbolines form yellow needles. They are readily soluble in organic solvents and melt considerably lower than the 6-nitro isomers. The constants and results of elementary analysis of the mononitrocarbolines are given in the table.

The IR spectra* of the 6- and 8-nitro-β-carbolines show absorption bands at 1340–1330 and 1510–1480 cm^{-1} characteristic for the symmetrical and asymmetrical vibrations of the nitro group which, however, are displaced considerably to the low-frequency region, possibly because of the electron-donating influence of the indole nitrogen. Bands at 830–810 cm^{-1} relate to CH deformation vibrations of the aromatic skeleton of the β-carbolines. The 3600–2600 cm^{-1} region is characterized by only one strong band at 3400–3380 cm^{-1} (NH vibrations), while in the initial β-carbolines a group of bands at 2800–3090 cm^{-1} characteristic for the CH stretching virbations of an aromatic ring is observed and the NH absorption is strongly displaced in the low-frequency direction (3150 cm^{-1}) [5].

Characteristic of the electronic spectra** of the nitro-β-carbolines studied is a considerable increase in the intensity of the absorption maxima as compared with the initial compounds, obviously because of the lengthening of the chain of conjugation. They differ substantially from one another and can be used to characterize the absorption of the nitro group. The

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*The IR spectra were recorded on a UR-10 spectrophotometer, the 1650–710 cm^{-1} region in paraffin oil and the 3600–2600 cm^{-1} region in M-1 fluorinated oil.

** The UV spectra were taken on an SF-4 instrument in ethanol.

Mononitro-β-carbolines

Compound	Mp, °C	Solvent for crystallization	Found, %			Yield, %
			C	H	N	
IIb	305—308	Ethanol	64.55*	4.62	—	50
IIIb	224—226	Ethanol	64.41*	4.48	—	20
IIe	230—232	Toluene	64.61*	4.50	—	40
IIIe	146—147	Isooctane	64.49*	4.68	—	20
IId	218—219	Toluene	65.69**	5.06	16.42	45
IIId	160—162	Isooctane	65.72**	5.21	16.31	22
IIe	267—268	Toluene	65.59**	4.88	—	50
IIIe	117—118	Petroleum ether	65.71**	5.11	—	22

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*Calculated for $C_{13}H_{11}N_3O_2$, %: C 64.72; H 4.59.

**Calculated for $C_{14}H_{13}N_3O_2$, %: C 65.87; H 5.13; N 16.46.

8-nitro-β-carbolines have three maxima: λ 229, 300, and 393 nm (log ε 4.75, 3.99, and 3.89), while the spectrum of the 6-nitro isomers is characterized by four maxima: λ 230, 270, and 345 nm (log ε 4.68, 4.49, 4.36, and 4.13). In the spectra of IIIa–IIIe there is a considerable bathochromic displacement of the long-wave band as compared with the spectra of IIa–IIe.

EXPERIMENTAL

1-Methyltetrahydro-β-carboline-3-carboxylic acid [6]. A mixture of 1.0 g (4.9 mM) of tryptophan [7], 10 ml of a 0.4% solution of H_2SO_4, and 2 ml of acetaldehyde was left overnight. Then the precipitate was filtered off. Yield 0.8 g (80%).

3-Methylharmane (Ib). A mixture of 0.1 g (0.51 mM) of 3,4-dihydro-3-methylharmane [8], 0.1 g of 13% Pd/C, and 1 g of biphenyl was heated at 290–295° C for 1 hr 30 min. The reaction product was isolated in a similar manner to that reported in the literature [8]. Colorless crystals with mp 173–174° C (from ethanol). Yield 71%.

1-Isopropyl-β-carboline (Id). A mixture of 0.5 g (2.4 mM) of tryptophan, 5 ml of 2% H_2SO_4, and 1 ml of isobutyraldehyde was left overnight. The solution was made alkaline with ammonia and extracted with ether. The ammoniacal solution was neutralized, water was added to bring the volume up to 100 ml, and it was oxidized with potassium bichromate [2]. Yield 0.4 g (80%). Colorless crystals with mp 159–160° C (from n-hexane), readily soluble in ether, chloroform, and benzene. Found, %: C 80.14; H 6.68; N 13.11%. Calculated for $C_{14}H_{14}N_2$, %: C 80.00; H 6.66; N 13.33.

The condensation of tryptophan with isobutyraldehyde in the presence of 0.4% H_2SO_4 under similar conditions gave Id with a yield of 5–8%.

1-n-Propyl-β-carboline (Ie). This was obtained in a similar manner to 1-isopropyl-β-carboline. Colorless needles with mp 209–210° C (from isoctane). Found, %: C 80.22; H 6.57; N 13.49%. Calculated for $C_{14}H_{14}N_2$, %: C 80.00; H 6.66; N 13.33.

1-Ethyl-β-carboline (Ic). This was obtained in a similar manner to 1-isopropyl-β-carboline. Colorless needles with mp 190–191° C (from isoctane).

6- and 8-Nitroharmanes (IIa and IIIa). A) A suspension of 0.1 g (0.55 mM) of harmane [2] in 2 ml of conc HNO_3 was heated with stirring to 80° C and kept at this temperature for 3 hr. The cooled solution deposited a pale yellow precipitate of the nitrate, which was filtered off, washed on the filter with acetone, triturated with 25% ammonia solution, and filtered off again. Yield 0.1 g. A mixture of 0.1 g of the nitration product and 0.5 g of alumina was transferred to a column filled with 9.5 g of alumina in 10 ml of the chloroform–ether system and was eluted with 120 ml of the same system and then with 40 ml of methanol. The following fractions were collected: I (20 ml), did not contain β-carbolines; II (50 ml), contained 20 mg (20%) of a chromatographically homogeneous substance with mp 209–210° C (from methanol) [2], identical with 8-nitroharmane (IIIa); III (10 ml), contained 8 mg of a mixture of IIa and IIIa; IV (70 ml), contained 60 mg of chromatographically homogeneous 6-nitroharmane (IIa).

B) A mixture of 0.1 g (0.55 mM) of harmane, 0.5 ml of glacial acetic acid, and 0.1 ml of conc HNO_3 was boiled for 5 hr. The solution was cooled, poured into ice water, and made alkaline with ammonia, and the precipitate was filtered off. Yield 0.1 g. Chromatography of the mixture in a thin layer of alumina showed the presence of IIa and IIIa and a substance with R_f 0.35, identified as harmane. The yield of IIa was 60% and of IIIa 23%.

6- and 8-Nitro-3-methylharmanes (IIb and IIIb). The nitration of 0.2 g (0.51 mM) of 3-methylharmane in acetic acid was carried out as for harmane. Yield 80 mg. Chromatography of the mixture on 16 g of alumina in the chloroform–ether system gave 20 mg of IIIb and 50 mg of IIb.

6- and 8-Nitro-1-ethyl-β-carbolines (IIc and IIIc). These were obtained similarly to the 6- and 8-nitroharmanes by heating 0.1 g (0.51 mM) of 1-ethyl-β-carboline with 1 ml of conc HNO_3. Yield 0.1 g. The mixture of substances was separated by chromatography on alumina (7 g) in the chloroform–ether (30 ml) system. The yield of IIc was 40% and of IIIc 20%.

6- and 8-Nitro-1-isopropyl-β-carbolines (IId and IIId). A mixture of 0.1 g (0.47 mM) of 1-isopropyl-β-carboline and 2 ml of conc HNO_3 was heated with stirring to 40° C. After 2 hr, the mixture was treated in a similar manner to the production of the nitroharmanes. Yield 0.1 g. The product (0.1 g) was chromatographed on alumina (15 g) and eluted with 30 ml of the chloroform–ether system. Three fractions were collected: I (30 ml), discarded; II (6 ml), contained 22 mg of chromatographically homogeneous IIId; III, contained 10 mg of a mixture of IId and IIId; IV (10 ml), 45 mg of chromatographically homogeneous IId.

6- and 8-Nitro-1-n-propyl-β-carbolines (IIe and IIIe) were obtained under the same conditions as IId and IIId from 0.4 g (1.88 mM) of Ie and 4 ml of conc HNO_3. Yield 0.4 g. The mixture was chromatographed on 20 g of alumina in the same system. The following fractions were collected: I (20 ml), discarded; II (11 ml), contained 87 mg of chromatographically homogeneous IIIe; III (34 ml), contained 0.2 g of a mixture of IIe and IIIe. By crystallizing the latter from toluene, 0.18 g of chromatographically homogeneous IIe was obtained.

REFERENCES

1. W. E. Noland, L. R. Smith, and D. C. Johnson, J. Org. Chem., 28, 2262, 1963.
2. H. R. Snyder, J. Am. Chem. Soc., 70, 222, 1948.
3. J. Casini, and L. Joodman, Can. J. Chem., 42, 1235, 1964.
4. H. M. Grotta, C. J. Riggle, and A. E. Bearse, J. Org. Chem., 29, 2474, 1964.
5. L. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], IL, Moscow, 1963.
6. D. J. Harvey, and W. Robson, J. Chem. Soc., 97, 1938.
7. J. Houben, Die Methoden der organischen Chemie, Vol. 4, Part 2 [Russian translation], GKhI, Moscow, p. 1266, 1949.
8. A. G. Terzyan, Zh. G. Akopyan, and G. T. Tatevozyan, Izv. AN Arm. SSR, khim. nauka, 16, 1, 87, 1963.

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