INDOLE DERIVATIVES

XLV. A New Case of Halogen Migration in the Fischer Reaction

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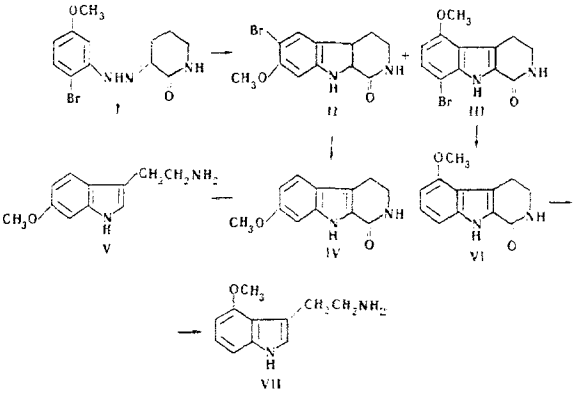
In the Fischer cyclization of the 3-(2'-bromo-5'-phenylhydrazone) of piperidine-2,3-dione, two isomeric carbolines were isolated—8-bromo-5-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline and 6-bromo-7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline. The formation of the latter shows that cyclization is accompanied by the migration of the bromine.

Indole derivatives with substituents in position 4 are of great interest, since some of them possess a high physiological activity (psilocine and psilocybin). However, because of the poor availability of the starting material (2,6-dinitrotoluene) and the multistage nature of the process, the synthesis of these compounds is fairly complex. In this case, the classical method of obtaining indole derivatives, the Fischer reaction, usually leads to a difficultly separable mixture of 4- and 6-substituted derivatives.

It has been reported previously that the synthesis of 4-methoxytryptamine was attempted by the Fischer cyclization of the 3-(2'-bromo-5'-methoxyphenylhydrazone) of piperidine-2,3-dione (I), i.e., a compound in which one of the ortho positions is blocked by bromine so that the formation of only the required isomer was to be expected. However, in a detailed study of this reaction we isolated two isomeric 1-oxo-1,2,3,4-tetrahydro-β-carbolines containing bromine and a methoxyl group in the benzene nucleus, with mp 262° C (II) and 223° C (III). The cyclization reaction took place with pronounced resinification (in spite of the use of various cyclizing agents), and the yields of the two isomers were small. They amounted to 19–22% of II and about 5% of III, the latter being isolated by the chromatography of resinous residue obtained from the mother solution. In the present work, the hydrazone I was isolated in the form of two stereoisomers (syn and anti), which were subjected to Fischer cyclization separately. The structures of the syn- and anti- forms of I were assigned on the basis of their solubilities and IR spectra of these compounds, following Preobrazhenskaya et al. [2]. For the syn- form in the region of the frequencies of >NH bonds a single band was found at 3170 cm^{-1}, while for the anti- form there were two bands at 3170 and 3210 cm^{-1}. In ethylcellosolve it was impossible to find the characteristics of the —CO group in these compounds described by Preobrazhenskaya et al. On Fischer cyclization, both the syn- and the anti-forms of the hydrazone I gave a mixture of the carbolines II and III. The formation of two isomeric bromomethoxycarbolines instead of one was unexpected and required explanation. To determine the structure of the compounds obtained, both isomers were subjected to debromination by being boiled in ethanol with hydrazine hydrate in the presence of a palladium catalyst. The debromination of II gave the carboline IV, which proved to be identical with the known [3] 7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline. The carboline IV was subjected to further transformation by the opening of the lactam ring and decarboxylation [3] to give 6-methoxytryptamine (V). The structure of V was confirmed by comparison with the 6-methoxytryptamine obtained by published methods [3,4]. Both the tryptamine obtained by published methods [3,4]. Both the tryptamine bases and their picrates and N-acetyl derivatives proved to be identical.



All that has been said above indubitably shows that in the bromomethoxycarboline II the OCH_3 group occupies position 7. The debromination of the isomer III gave the known [3] 5-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (VI). Compound VI was converted further into the known [5] 4-methoxytryptamine.

The position of the bromine atom in carboline II was confirmed by means of PMR spectra. In the spectrum of II in the region of aromatic protons there are two singlets at 6.95 and 7.68 ppm which can correspond only to para protons. Since it had been established previously that the methoxy group occupies position 7, the signals of the PMR spectrum correspond to protons in positions 5 and 8 and, therefore, the bromine occupies position 6.

In the region of aromatic protons, the PMR spectrum of carboline III has two doublets at 6.34 and 7.19 ppm with a spin-spin coupling constant J = 9 Hz, which can correspond only to ortho protons in positions 6 and 7.

The results obtained show that the Fischer cyclization of the hydrazone I takes place mainly in the ortho position occupied by the bromine (in the para position to the methoxy group) and is accompanied by the simultaneous migration of the bromine into another position on the benzene nucleus. The "normal" reaction product is formed in considerably smaller amounts.* Cases of halogen migration in the Fischer cyclization of phenylhydrazones in which both ortho positions are occupied by substituents have been described previously [6–8].

EXPERIMENTAL

The initial compound for the preparation of the hydrazone I was p-anisidine, which was converted through a number of intermediate stages into 3-amino-4-bromoanisole hydrochloride [1]. The latter, and also all the intermediate products in the preceding stages were subjected to careful purification and were analytically pure. Chromatography was carried out on plates with a thin layer of KSK silica gel fixed with gypsum in the chloroform–acetone (1 : 1) system. Unless stated otherwise, these spots were revealed in UV light.

The PMR spectra were taken on a INM 4H-100 instrument in a mixture of dimethyl sulfoxide and carbon tetrachloride by L. A. Alekseeva.

The 3-(2'-bromo-5'-methoxyphenylhydrazone) of piperidine-2,3-dione (I). 3-Ethoxycarbonylpiperid-2-one (23.2 g; 0.14 mole) was saponified with a solution of 8.16 g (0.14 mole) of caustic potash in 230 ml of water at room temperature for 30 min. To the resulting solution of 3-carboxypiperid-2-one, cooled to −2° C, was added a diazonium solution prepared by the treatment of 3-amino-4-bromoanisole with sodium nitrite in dil HCl at from −2 to −4° C and brought to pH 4 with a solution of sodium acetate [32.4 g (0.14 mole) of 3-amino-4-bromoanisole hydrochloride, 164 ml of water, 36 ml of HCl, and 9.6 g (0.14 mole) of sodium nitrite in 30 ml of water]. The mixture was stirred at 0–2° C for 6 hr and was left at 0° C for 12 hr, after which the precipitate was filtered off, washed with water, and boiled with 1400 ml of aqueous ethanol (1 : 3). This gave 18.3 g (43%) of the syn-isomer of I. Mp 159–160° C (from a ten-fold volume of benzene). Found, %: C 46.43; H 4.80; Br 25.46; N 13.59. Calculated for $C_{12}H_{14}BrN_3O_2$, %: C 46.14; H 4.52; Br 25.59; N 13.45. The anti-isomer of I was filtered off from the ethanolic solution after cooling. Yield 18.12 g (42.5%). Mp 191–192° C (from a 100-fold volume of the benzene). Found, %: C 46.48; H 4.77; Br 25.62; N 13.67. Calculated for $C_{12}H_{14}BrN_3O_2$, %: C 46.14; H 4.52; Br 25.59; N 13.45.

Fischer cyclization of the stereoisomeric hydrazones I. A mixture of 2.5 g of the anti-hydrazone, 12 ml of glacial acetic acid, and 6 ml of conc HCl was boiled for 3 hr. The solution was left at 0° C for 12 hr, and the precipitate of the carboline II was filtered off, and washed with water and ethanol. Yield 0.52 g (22%). Mp 262° C (decomp., from ethanol). Found, %: C 49.06; H 3.80; Br 26.85; N 9.30. Calculated for $C_{12}H_{11}BrN_2O_2$, %: C 48.83; H 3.76; Br 27.08; N 9.49. R_f 0.08 (revealing agent–phosphomolybdic acid at 100° C). After the separation of the II, the acetic acid mother solution was evaporated to dryness in vacuum. The resinous residue (1.97 g) was dissolved in 10 ml of ethanol and the solution was mixed with 10 g of silica gel and dried to constant weight, after which it was deposited on a column of KSK silica gel (20.0 g). Chloroform eluted 0.7 g of a substance which, after rechromatography under the same conditions, was crystallized from benzene. This gave 0.13 g of III (5.5%). Mp 223–225° C (decomp.). Found, %: C 48.15; H 3.70; Br 26.99; N 9.46. Calculated for $C_{12}H_{11}BrN_2O_2$, %: C 48.83; H 3.76; Br 27.08; N 9.49. R_f 0.32 (spot fluorescing blue in UV light).

The cyclization of the syn-hydrazone was carried out similarly. From 5 g of the hydrazone was obtained 0.93 g of II with mp 247–248° C. After crystallization from ethanol, mp 262° C (decomp.). The mother liquor, after chromatography in a column yielded 0.22 g of III, mp 222–223° C (decomp.).

7-Methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (IV). A mixture of 1.79 g of II, 10 ml of hydrazine hydrate, 100 ml of ethanol and 0.5 g of Pd/C (10%) was boiled with stirring for 5 hr. The solution was filtered from the catalyst, the ethanol was evaporated off to dryness in vacuum, and the residue was washed with water and crystallized from ethanol. The yield of IV was 1.23 g. Mp 199–200° C. Substance IV gave no depression of the melting point in admixture with 7-methoxy-1-oxo-1,2,3,4-tetrahydrocarboline obtained by a published method [3]. The IR spectra of the two substances were identical. Found, %: C 66.12; H 5.67; N 13.40. Calculated for $C_{12}H_{12}N_2O_2$, %: C 66.65; H 5.59; N 12.95. R_f 0.14 (dark violet spot in UV light).

6-Methoxytryptamine (V). A mixture of 1.23 g of IV, 3.86 g of KOH, 14 ml of water, and 21 ml of ethanol was boiled with stirring for 5 hr. The solution of potassium 6-methoxytryptamine-2-carboxylate was acidified with acetic acid and the acid that deposited was filtered off, washed with water, and crystallized from aqueous ethanol. Yield 1 g, mp 250–252° C (decomp.). 0.8 g of the acid was boiled with 8 ml of 5% aqueous HCl solution for 30 min and the solution was cooled, made alkaline with caustic soda, and extracted with ether. The ether was distilled off and the V was crystallized from ethyl acetate. Mp 142–143° C. Found, %: C 69.20; H 7.30; N 14.60. Calculated for $C_{11}H_{14}N_2O$, %: C 69.45; H 7.42; N 14.73. Picrate of V — mp 215° C (decomp.). It melted without depression in admixture with the 6-methoxytryptamine picrates obtained by published methods [3, 4].

N-Acetyl derivative of V — mp 136° C, melting without depression in admixture with N-acetyl-6-methoxytryptamine [9].

5-Methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (VI). A mixture of 0.8 g of III, 8 ml of hydrazine hydrate, 80 ml of ethanol, and 2 g of Pd/C was boiled with stirring for 10 hr. After the catalyst had been filtered off and the solvent had been distilled off, the residue was mixed with water, filtered off, and crystallized twice from aqueous ethanol (1 : 1). Mp 210–211° C. Found, %: C 66.25; H 5.68; N 12.53. Calculated for $C_{12}H_{12}N_2O_2$, %: C 66.65; H 5.59; N 12.95. R_f 0.27 (spot fluorescing green).

4-Methoxytryptamine (VII). A mixture of 0.3 g of VI, 0.9 g of KOH, 3.6 ml of water, and 5.4 ml of ethanol was boiled with stirring for 5 hr. The ethanol was distilled off in vacuum, the residue was treated with water, and 4-methoxytryptamine-2-carboxylic acid was isolated from the solution of its salt by acidification in acetic acid. Yield 0.3 g (mp 240° C, decomp.). 0.3 g of the acid was boiled with 12 ml of 7% HCl for 2 hr. After the mixture had been made alkaline, the VII was extracted with ether. Distillation of the ether yielded 0.15 g of VII. Mp 136–137° C. It was crystallized from ethyl acetate. Mp 139–140° C. Found, %: C 69.09; H 7.29; N 14.47. Calculated for $C_{11}H_{14}N_2O$, %: C 69.45; H 7.42; N 14.73. A mixture with 6-methoxytryptamine melted at 108–110° C. The hydrochloride of VII had mp 210–212° C. A mixture with 6-methoxytryptamine hydrochloride (mp 219–221° C) melted at 195–205° C.

*6-Methoxytryptamine was described in a previous paper [1] but we erroneously regarded it as the 4-isomer.

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