BENZINDOLES

III.* SYNTHESIS OF γ-(6,7-BENZINDOL-3-YL)-BUTYRIC ACID AND ITS DERIVATIVES

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The synthesis of γ-(6,7-benzindol-3-yl)butyric acid and its derivatives has been effected. It has been shown that the Fischer cyclization of the α-naphthylhydrazone of γ-formylvaleric acid leads to the formation of considerable amounts of esters of ω,ω-di[3-(3'-alkoxycarbonylpropyl)-6,7-benzindol-2-yl]caproic acid, in addition to the desired product.

In the previous communication [1] we described the synthesis of γ-(4,5-benzindol-3-yl)butyric acid and some of its derivatives. During the Fischer cyclization in ethanol, in addition to the main product it was possible to isolate by-products which we identified as methyl and ethyl ω,ω-di[3-(3'-alkoxycarbonylpropyl)-4,5-benzindol-2-yl]caproates. In the present work we aimed at synthesizing γ-(6,7-benzindol-3-yl)butyric acid (I).

The cyclization of the initial α-naphthylhydrazone of ethyl ω-formylvalerate (II) was effected by the action of solutions of orthophosphoric acid in ethyl cellosolve and by sulfosalicylic acid (SSA) in methanol and ethanol. In the first case, the reaction was not accompanied by transesterification and led to ethyl γ-(6,7-benzindol-3-yl)butyrate (IIIb) with a yield of 58%. No by-products were found. In cyclization under the action of SSA, the products isolated corresponded to methyl or ethyl esters, according to which alcohol was used as solvent. The yield of the methyl ester (IIIa) was 49%, and that of the ethyl ester (IIIb) 76%. In both cases by-products were found (in yields of 19.7 and 5.4%, respectively) to which structures VIa and b were ascribed on the basis of the results obtained in a study of the by-products isolated in the synthesis of γ-(4,5-benzindol-3-yl)butyric acid [1].

Under the action of hydrazine hydrate, the esters IIIa and b were readily converted into the hydrazide V and were smoothly saponified with ethanolic alkali into the initial acid I which, in its turn, was reduced with lithium aluminum hydride to the corresponding indol-3-ylbutanol (IV). The structures of all compounds obtained were confirmed by their IR and UV spectra, in addition to elementary analysis. The esters IIIb and VIa and b were also studied by nuclear magnetic resonance. The NMR spectra of these compounds did not contradict the structure assigned to them and were very close to the analogous spectra of the 4,5-benzo isomers [1], with the exception of the signals corresponding to the protons of the naphthalene ring.

It is interesting to observe that, in agreement with modern ideas of the structure of monosubstituted naphthalene derivatives [2,3] and on the mechanism of the Fischer reaction [4], the cyclizations of the β- and of α-naphthylhydrazones take place approximately equally readily, although the closure of the ring in the first case takes place in the α and in the second case in the β position of the naphthylene nucleus. (See scheme, page 615.)

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer and the UV spectra on an SF-4M spectrophotometer. The NMR spectra were obtained on a JNM-4H-100 spectrometer with a working frequency of 100 MHz with deuterochloroform as the solvent and tetramethylsilane as the internal standard.

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*For Communication II, see [1].

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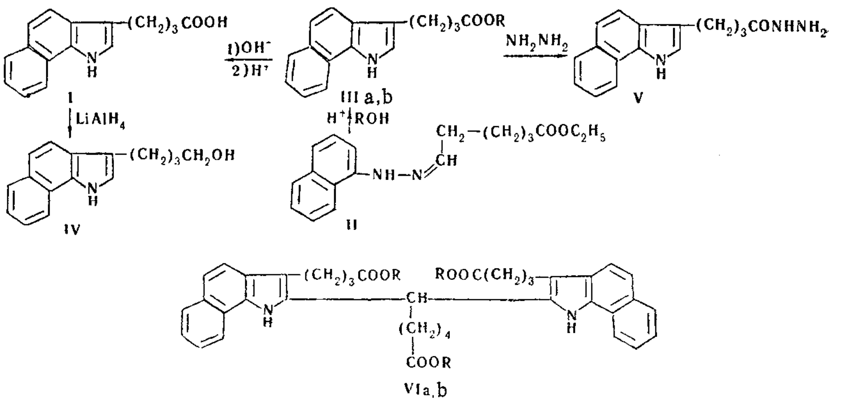

IIIa R = CH_3, b R = C_2H_5; VIa R = CH_3, b R = C_2H_5

α-Naphthylhydrazone of Ethyl γ-Formylvalerate (II). A mixture of 8 g (51 mmoles) of α-naphthylhydrazine and 8 g (51 mmoles) of ethyl δ-formylvalerate in 250 ml of absolute methanol was boiled for 45 min. Then it was evaporated in vacuum to 40 ml and cooled, and the precipitate was filtered off. Yield 10.5 g (68%), mp 69.5-70°C (from methanol). UV spectrum, λ_{max}, nm: 252, 282, 335; log ε 4.20, 3.65, 4.00 (in ethanol). IR spectrum, ν_{max}, cm^{-1}: 3340 (N–H), 1705 (C=O), 1580 (C=C arom.). Found %: C 72.57; H 7.48; N 9.51. $C_{18}H_{22}N_2O_2$. Calculated %: C 72.50; H 7.40; N 9.40.

Cyclization of the α-Naphthylhydrazone of Ethyl γ-Formylvalerate (II). a. With Orthophosphoric Acid. A mixture of 3 g (10 mmoles) of II and 2.2 g of crystalline orthophosphoric acid was boiled in 25 ml of ethyl cellosolve for 2 h. Then it was cooled and poured onto ice. The precipitate was filtered off, carefully washed with water, and dried. The yield of unpurified product was 2.80 g, mp 120-125°C. After crystallization from a mixture of chloroform and petroleum ether (bp 60-70°C), 1.47 g (58%) of ethyl γ-(6,7-benzindol-3-yl)butyrate (IIIb) with mp 134.5-135°C was obtained. R_f * 0.54 [benzene–methanol (30 : 1)]; 0.57 [benzene–ether (1 : 1)]. UV spectrum λ_{max}, nm: 266, 288 (inflection), 322-328 (plateau); log ε 4.62, 3.88, 3.19 (in ethanol). IR spectrum, ν_{max}, cm^{-1}: 3340 (N–H), 1718 (C=O). Found %: C 76.97; H 6.76; N 4.99. $C_{18}H_{19}NO_2$. Calculated %: C 76.90; H 6.76; N 4.98.

b. With SSA in Methanol. A mixture of 3.0 g (10 mmoles) of II and 6 g (27.5 mmoles) of SSA in 60 ml of absolute methanol was boiled for 4 h, cooled, and poured onto ice. The precipitate was filtered off (2.73 g, mp 104-110°C). Treatment with a small amount of methanol gave 1.37 g (49%) of methyl γ-(6,7-benzindol-3-yl)butyrate (IIIa), mp 130°C (from benzene). R_f 0.41 [benzene–ether (2 : 1)]. UV spectrum, λ_{max}, nm: 266, 288 (inflection), 322-328 (plateau), 344; log ε 4.66, 3.88, 3.18, 2.76 (in ethanol). IR spectrum, ν_{max}, cm^{-1}: 3340, 1725.

After the evaporation of the methanolic solution, 0.5 g (19.7%) of methyl ω,ω-di[3-(3'-methoxycarbonylpropyl)-6,7-benzindol-2-yl]caproate (VIa) was obtained with mp 156-157°C (from aqueous methanol). R_f 0.47 [benzene–ether (1 : 1)]. UV spectrum: λ_{max}, nm: 263, 273, 296 (inflection), 330; log ε 4.45, 4.45, 3.98, 3.20 (in ethanol). IR spectrum, ν_{max}, cm^{-1}: 3430, 3420 (N–H), 1740, 1715 (C=O), 1605 (C=C arom.). Found %: C 74.08; H 6.52. $C_{41}H_{44}N_2O_6$. Calculated %: C 74.53; H 6.56.

c. With SSA in Ethanol. Similarly, 10.8 g (36 mmoles) of II was cyclized in 220 ml of absolute ethanol by the action of 21.6 g (100 mmoles) of SSA. The yield of IIIb was 5.36 g, mp 134°C (from methanol). The methanol was distilled off in vacuum from the filtrate remaining after the separation of the IIIb, and the residue was poured onto ice and extracted with ether. The solid residue after the evaporation of the ether was crystallized from methanol, giving another 1.7 g of IIIb, mp 134-135°C. The total yield was 7.06 g (76%). The evaporation of the methanolic mother liquor gave 0.5 g (5.4%) of ethyl ω,ω-di[3-(3'-ethoxycarbonylpropyl)-6,7-benzindol-2-yl]caproate (VIb), mp 122°C (from methanol). R_f 0.52 [benzene–ether (1 : 1)]; 0.38 [benzene–ether (2 : 1)]. UV spectrum, λ_{max}, nm: 261, 270-274, 324-330, 342-346; log ε 4.47, 4.47, 3.25, 3.02 (in ethanol). IR spectrum, ν_{max}, cm^{-1}: 3405, 3380, 1722, 1696. Found %: C 75.33; H 7.55; N 3.74. $C_{44}H_{50}N_2O_6$. Calculated %: C 75.19; H 7.17; N 3.98.

γ-(6,7-Benzindol-3-yl)butyric Acid (I). This was obtained by the saponification of 0.75 g of IIIa with ethanolic alkali. Yield 0.58 g (87%). mp 190.5-191°C (from aqueous methanol). Found %: C 75.54; H 6.10; N 5.44. $C_{16}H_{15}NO_2$. Calculated %: C 75.80; H 5.92; N 5.53.

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*Here and below, the R_f values are given for alumina of activity grade 2. The spots were revealed with iodine.

4-(6',7'-Benzindol-3'-yl)butan-1-ol (IV). 0.24 g (0.95 mole) of γ-(6,7-benzindol-3-yl)butyric acid (I) was reduced with 0.15 g (4 mmoles) of $LiAlH_4$ in 75 ml of absolute ether. This gave 0.18 g (96.5%) of IV with mp 136-137°C (from a mixture of benzene and petroleum ether). R_f 0.37 [chloroform–ethylacetate (4 :1)]. UV spectrum, λ_{max}, nm: 266, 284 (inflection), 328; log ε 4.63, 3.95, 3.05 (in ethanol). IR spectrum, ν_{max}, cm^{-1}: 3420. Found %: N 5.85. $C_{16}H_{17}NO$. Calculated %: N 5.85.

Hydrazide of γ-(6,7-Benzindol-3-yl)butyric Acid (V). A mixture of 0.5 g (1.8 mmole) of IIb, 1 ml of hydrazine hydrate, and 3 ml of ethyl cellosolve was boiled for 3 h. After cooling, 0.33 g of the hydrazide V was isolated by the addition of water. mp 169.5-170°C (from ethanol). Yield 70%. Found %: C 72.01; H 6.25; N 15.4. $C_{16}H_{17}NO_3$. Calculated %: C 72.0; H 6.37; N 15.7.

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