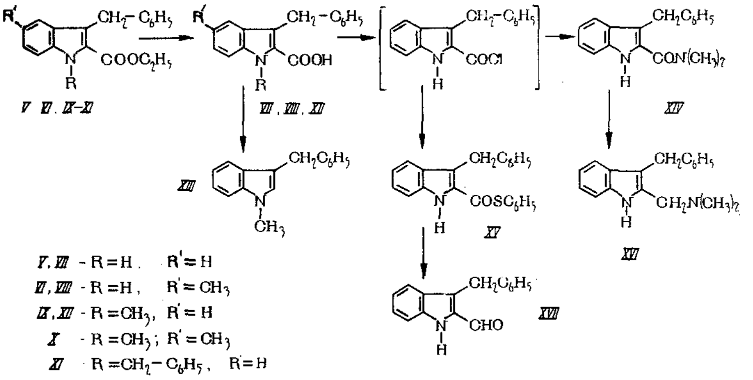
SYNTHESIS OF DERIVATIVES OF 3-BENZYLINDOLE

V. I. Shvedov, G. N. Kurilo,
and A. N. Grinev

UDC 615.31:547.567.5]012.1:542.9

Among indole derivatives several effective medicinal compounds are known such as reserpine, serotonin, indopan, dimecarbine, etc. [1].

With the aim of synthesizing structural analogs of the compounds mentioned the cyclization of monoarylhydrazones into indole derivatives has been studied. These were obtained by azo coupling of α-phenylethylacetoacetic ester (I) with aryl diazonium chlorides. The monoarylhydrazones of benzylpyruvic acid ethyl ester were converted into the corresponding acids (II-IV) or cyclized, without isolation or further purification, into esters of 3-benzylindole 2-carboxylic acid (V, VI). One of these (V) has been obtained previously by another method [2]. Esters (V, VI) were converted by hydrolysis into 3-benzylindole 2-carboxylic acids (VII, VIII). The latter were also formed, but in reduced yield, from monoarylhydrazones of benzylpyruvic acid (II-IV). Esters of 3-benzylindole 2-carboxylic acids (IX-XI) substituted on the nitrogen atom were obtained by the alkylation of indole derivatives (V, VI), and by the hydrolysis of ester (IX), 1-methyl-3-benzylindole 2-carboxylic acid (XII) was obtained which had been synthesized earlier by another method [3]. On heating above the melting point (XII) was decarboxylated forming the known [4] 1-methyl-3-benzylamide (XIV) and thiophenyl ester of 3-benzylindole 2-carboxylic acid (XV). Amide (XIV) was converted by reduction with lithium aluminum hydride into 2-dimethylaminomethyl-3-benzylindole (XVI). On heating thiophenyl ester (XV) with Raney nickel in aqueous dioxane 2-formyl-3-benzylindole (XVII) was formed by reductive desulfuration.



V, VII - R = H, R' = H
VI, VIII - R = H, R' = CH_3
IX, XII - R = CH_3, R' = H
X - R = CH_3; R' = CH_3
XI R = $CH_2-C_6H_5$, R = H

Several very intense characteristic absorption bands were found in the IR spectra of the monoarylhydrazones of benzylpyruvic acid which we obtained. The absorption maximum in the 3320-3290 cm^{-1} region is due to the stretching vibration of the NH group, and in the 1680-1665 cm^{-1} region to the stretching vibration of the carbonyl group. A band in the 1610-1600 cm^{-1} region is explained by the stretching vibration of an unsaturated carbon-nitrogen bond (C=N). The various substituents in the aryl nucleus of the monoarylhydrazones did not show a significant effect on the characteristic absorption bands.

Three absorption maxima were observed in the UV spectra of the arylhydrazones, viz., 237-245 mμ (log ε 3.83-3.86), 293-313 mμ (log ε 4.05-4.11), and at 319-343 mμ (log ε 4.15-4.24).

In the IR spectra of the 3-benzylindole 2-carboxylic acids (VII and VIII) and of their derivatives (V and VI), absorption bands were observed in the 3440-3330 cm^{-1} (NH) and 1690-1670 cm^{-1} (C=O) regions, which are displaced towards low frequency due to the formation of hydrogen bonds. Transfer to the N-methyl derivatives (IX-XI) is accompanied by a displacement of the carbonyl absorption bands to a higher

---

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute, Moscow.
Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 7, pp. 10-15, July, 1969. Original article submitted November 20, 1968.

frequency region, viz., 1710-1700 cm^{-1}. A similar effect has been noticed previously for derivatives of 2- and 3-acylindoles [5]. The structure of 2-formyl-3-benzylindole was confirmed by IR spectral data: 3310 cm^{-1} (NH) and 1660 cm^{-1} (C=O) which concur well with the IR spectral data of 2-acetyl-3-methylindole: 3311 cm^{-1} (NH) and 1631 cm^{-1} (C=O) [5].

Two absorption maxima of high intensity appear in the UV spectra of the indole derivatives obtained in the regions of 227-236 mμ (log ε 4.38-4.43) and 296-302 mμ (log ε 4.18-4.30) which are characteristic of the UV spectra of indole carbonyl derivatives [5, 6].

EXPERIMENTAL

IR spectra of the substances obtained were taken in Nujol mulls on an UR-10 spectrophotometer and the UV spectra on the recording ultraviolet spectrophotometer EPS-3 in alcohol solution.

α-Phenylethylacetoacetic Ester (I). Sodium (23 g) was dissolved in 360 ml absolute alcohol in a three-necked flask, and to the solution obtained was added with cooling 260 g acetoacetic ester and then 203.5 g phenylethyl bromide. The reaction mixture was boiled, with stirring, on the water bath until a neutral reaction was obtained on universal indicator paper. The mixture was diluted with 1-1.5 volumes water and the alcohol distilled off in vacuum. The oily layer was separated and the aqueous layer extracted with benzene. The oil and the benzene extract were combined, washed with water, and dried by azeotropic distillation of the water with a Dean and Stark still-head. Benzene was distilled off and the residue distilled in vacuum. Yield of (I) was 369.5 g (79%), bp 137-142° (1.5 mm), n_D^{20} 1.5003. Found, %: C 72.00, 72.20; H 7.90, 7.91. $C_{14}H_{18}O_3$. Calculated, %: C 71.77; H 7.74.

Phenylhydrazone of Benzylpyruvic Acid (II). To a solution of 23.4 g (I) in 150 ml alcohol was added 12 g sodium hydroxide in 31 ml water maintaining the temperature in the range 0-5°. To a solution was added, at 0° and in one batch, phenyldiazonium chloride, prepared in the usual way from 9.3 g aniline, 50 ml conc. hydrochloric acid, and 6.9 g sodium nitrite. In this way a yellow-brown oil was isolated. This was kept at 0° for 2-3 h and then diluted with 300 ml water, the oil separated, and the aqueous layer extracted with benzene. The oily layer and the benzene extract were treated as indicated above. The oily residue, without being distilled, was added to a solution of sodium hydroxide in 270 ml methanol. The mixture was boiled for 2 h on the water bath and then diluted with 1-1.5 volumes water. Methanol was distilled off, the aqueous solution extracted with ether and acidified with dilute hydrochloric acid to acid reaction. Acid (II), isolated as an oil, quickly crystallized. The solid was filtered off, washed with water, and dried. Yield of (II) was 16.6 g (62%) mp 142-143° (from methanol). According to literature date [2], mp 149-151°.

Benzylpyruvic Acid p-Tolylhydrazone (III) was obtained under the conditions used to synthesize (II). Yield of (III) was 41%, mp 138-139° (from aqueous methanol). Found, %: C 72.30, 72.00; H 6.66, 6.58; N 9.93, 9.83. $C_{17}H_{18}N_2O_2$. Calculated, %: C 72.31; H 6.42; N 9.92.

Benzylpyruvic Acid p-Anisylhydrazone (IV) was obtained under the conditions used to synthesize (II). Yield of (IV) was 60.7%, mp 132-133° (from aqueous methanol). Found, %: C 68.50, 68.57; H 6.06, 5.98; N 9.29, 9.18. $C_{17}H_{18}N_2O_3$. Calculated, %: C 68.43; H 6.08; N 9.39.

3-Benzylindole 2-Carboxylic Acid Ethyl Ester (V). To the phenylhydrazone of benzylpyruvic acid ethyl ester, obtained under the conditions of the previous experiment from 35.1 g (I), 18 g sodium hydroxide, 14 g aniline, 10.35 g sodium, and 75 ml conc. hydrochloric acid, was added a solution of 18.5 ml conc. sulfuric acid in 185 ml absolute alcohol and the mixture boiled on a water bath for 3 h. The solution was cooled, the precipitate filtered off, washed with water, with methanol, and dried. The yield of (V) was 15.8 g (38%) based on ester (I). It had mp 145.5-146.5° (from a mixture of petroleum ether and benzene, 3:4); according to literature data [2], mp 144-146°.

3-Benzyl-5-methylindole 2-Carboxylic Acid Ethyl Ester (VI) was obtained under the conditions for the synthesis of (V). The yield of (VI) was 40.3%, mp 177-178° (from acetone). Found, %: C 77.89, 77.92; H 6.54, 6.68; N 4.93, 5.00. $C_{19}H_{19}NO_2$. Calculated, %: C 77.78, H 6.52; N 4.77.

3-Benzylindole 2-Carboxylic Acid (VII). Ester (V: 14 g) was added to a solution of 2.4 g sodium hydroxide in 200 ml alcohol, the reaction mixture was boiled on a water bath for 1 h, and then 1-1.5 volumes water were added. The alcohol was distilled off under vacuum, and the aqueous solution acidified with acetic acid to acid reaction. The precipitate was filtered off, washed with water, and dried. The yield of (VI) was 12.5 g (99.5%), mp 192-193° (from benzene). Found, %: C 76.60, 76.15; H 5.37, 5.50; N 5.55, 5.66. $C_{16}H_{13}NO_2$. Calculated, %: C 76.47; H 5.21; N 5.57.

3-Benzyl-5-methylindole 2-Carboxylic Acid (VIII) was obtained under the conditions for the synthesis of (VII). The yield of (VIII) was 98.5%, mp 227-227.5° (from aqueous methanol. Found, %: C 76.97, 76.85; H 5.70, 5.45; N 5.17, 5.51. $C_{17}H_{15}NO_2$. Calculated, %: C 76.96; H 5.69; N 5.27.

1-Methyl-3-benzylindole 2-Carboxylic Acid Ethyl Ester (IX). To a suspension of 8.4 g (V) in 30 ml dry dioxane was added a solution of 0.69 g sodium in 17 ml absolute alcohol. The solvent was distilled from the resulting solution, up to 120°, and the remainder of the solvent distilled off in vacuum. To the cooled sodium derivative was added a solution of 5.6 ml methyl iodide in 36 ml dry dimethylformamide. The mixture was heated at 40-50° for 30 min on the water bath, then poured onto ice. The oil isolated in this way then crystallized. The crystals were filtered off, washed with water, with methanol, and dried. Yield of (IX) was 7.3 g (83%), mp 44-45° (from methanol). Found, %: C 77.85, 77.69; H 6.21, 6.20; N 5.08, 5.26. $C_{19}H_{19}NO_2$. Calculated, %: C 77.79; H 6.52; N 4.77.

1,5-Dimethyl-3-benzylindole 2-Carboxylic Acid Ethyl Ester (X) was obtained under the conditions for the synthesis of (IX). The yield of (X) was 86.6%, mp 62-63° (from methanol). Found, %: C 77.98, 78.46; H 7.00, 6.61; N 4.59, 4.91. $C_{20}H_{21}NO_2$. Calculated, %: C 78.14; H 6.89; N 4.55.

1,3-Dibenzylindole 2-Carboxylic Acid (XI). To the sodio derivative, obtained from 1.4 g (V) under the conditions of the previous experiment with 0.115 g sodium, was added a solution of 0.6 ml benzyl chloride in 6 ml dry dimethylformamide. The mixture was boiled for 1 h, then poured onto ice. The crystals were filtered off, washed with water and methanol, and dried. The yield of (XI) was 0.3 g (16.6%), mp 80.5-82° (from methanol). Found, %: C 81.18, 81.17; H 6.30, 6.10; N 3.99, 4.13. $C_{25}H_{23}NO_2$. Calculated, %: C 81.27; H 6.27; N 3.79.

1-Methyl-3-benzylindole 2-Carboxylic Acid (XII). To molten potassium hydroxide, obtained at 155° from 8.4 g potassium hydroxide and 1.5 ml water, was added 4.4 g ester (IX). The melt was stirred 5-10 min at 170-180° until cessation of gas bubbling, then cooled, dissolved with heating in 4-5 volumes water, and acidified with acetic acid to acid reaction. The solid, which had separated, was filtered off, washed with water, and dried. The yield of (XII) was 4 g (quantitative), mp 194-194.5° (from benzene). According to literature data [3], mp 194°.

1-Methyl-3-benzylindole (XIII). (XII) (5.4 g) was heated at 200-205° until termination of bubbling in a flask with an air condenser provided with a Bunsen valve. The resulting oily mass crystallized. The yield of (XIII) was 4.4 g (quantitative), mp 56-57° (from methanol). According to literature data [4], mp 60.5-61°. Found, %: C 86.70, 87.04; H 6.96, 6.78; N 6.33, 6.51. $C_{16}H_{15}N$. Calculated, %: C 86.84; H 6.63; N 6.33.

3-Benzylindole 2-Carboxylic Acid Dimethylamide (XIV). To a suspension of 5 g (VII) in 12 ml dry dioxane was added 0.16 ml dry dimethylformamide, and 1.6 ml thionyl chloride and the mixture heated for 30 min on a boiling water bath. Dioxane and the excess of thionyl chloride were distilled off in vacuum on the water bath. The resulting crystals were dissolved in 60 ml dry dioxane, and to the solution obtained a solution of 1.8 g dimethylamine in 8 ml dry dioxane was added with cooling. The mixture was left in a flask provided with a calcium chloride tube at room temperature overnight, then the reaction mass was diluted with water, the solid filtered off, and dried. The yield of (XIV) was 4.9 g (87.5%), mp 165-166° (from methanol). Found, %: C 77.30, 77.28; H 6.46, 6.44; N 10.00, 10.26. $C_{18}H_{18}N_2O$. Calculated, %: C 77.67; H 6.52; N 10.06.

3-Benzylindole 2-Carboxylic Acid Thiophenyl Ester (XV). To a solution of the acid chloride, obtained under the conditions of the previous experiment from 5 g (VII), in a mixture of 110 ml dry benzene and 20 ml dry dioxane was added 6.6 g thiophenol and then 2.5 ml dry pyridine. The reaction mixture was left overnight in a flask protected from moisture. The precipitate of (XV), which separated, was filtered off, washed on the filter with methanol and water, and dried. An additional quantity of (XV) was isolated from the benzene-dioxane mother liquor after distilling off the solvent. Overall yield of (XV) was 6.3 g (92%), mp 197-197.5° (from a mixture of methanol and dioxane, 1:3). Found, %: C 76.87, 77.30; H 5.15, 5.14; N 4.08, 4.01; S 9.35, 9.37. $C_{22}H_{17}NOS$. Calculated, %: C 76.94; H 4.99; N 4.08; S 9.33.

2-Dimethylaminomethyl-3-benzylindole (XVI). To a suspension of 2.28 g lithium aluminum hydride in 60 ml dry dioxane heated to 90°, was added a solution of 11.2 g (XIV) in 120 ml dry dioxane heated to 70°, such that the dioxane boiled steadily (15-20 min). The suspension was stirred for 10 h at 90-95°, left overnight, then decomposed, under cooling by the addition in turn of 2.3 ml water, 2.3 ml 15% sodium hydroxide solution, and 6.8 ml water. The precipitate of aluminum oxide was filtered off and washed with ether. The combined ether-dioxane extract was dried with magnesium sulfate, and the solvents distilled off in vacuum. The residue was dissolved in dry ether and a small excess of a solution of hydrogen chloride in ether added to the solution obtained. The precipitate of hydrochloride was filtered off and washed with a mixture of acetone and ether (1:1). The yield of (XVI) hydrochloride was 9.8 g (81.7%), mp 191-192° (from a mixture of acetone-methanol, 5:1). Found, %: C 71.80, 72.28; H 7.05, 7.07; N 9.36, 9.38; Cl 11.80, 11.96. $C_{18}H_{21}N_2Cl$. Calculated, %: C 71.86; H 7.03, N 9.31; Cl 11.78. Base (XVI) was obtained from the hydrochloride by the usual method and had mp 81-82° (from aqueous methanol). Found, %: C 81.95, 81.59; H 7.80, 7.55; N 10.51, 10.71. $C_{18}H_{20}N_2$. Calculated, %: C 81.77; H 7.62; N 10.59.

(XVI) Methiodide was obtained by the usual method, mp greater than 220° (with decomposition: from a mixture of methanol-ether, 1:3). Found, %: C 56.56; H 5.64; N 7.00, 6.77; I 30.94, 30.83. $C_{19}H_{23}N_2I$. Calculated, %: C 56.16; H 5.71; N 6.89; I 31.23.

2-Formyl-3-benzylindole (XVII). In order to deactivate the catalyst 17 g Raney nickel in 50 ml acetone was boiled for 1 h with stirring on a boiling water bath. The solvent was then distilled off and to the residue was added 40 ml dioxane, 17 ml water, and a solution of 1.7 g indole in 34 ml dioxane. The reaction mixture was boiled for 5 h, the catalyst was then filtered off, and washed on the filter with dioxane. Aqueous dioxane was distilled off from the filtrate under vacuum on a water bath. The residue was treated with a mixture of 10 ml ether, 9 ml methanol, and 4 ml water. To the mixture of substances obtained 5 ml 47% sodium bisulfate was added and the mixture shaken energetically for 10-15 min. The aqueous layer was separated and acidified with heating with 7 ml 20% sulfuric acid solution. The solid was filtered off, washed with water, and dried. The yield of (XVII) was 0.1 g (9%), mp 115-115.5° (from aqueous methanol). Found, %: C 81.49, 81.37; H 5.76, 5.63; N 5.94, 5.66. $C_{16}H_{13}NO$. Calculated, %: C 81.68; H 5.57; N 5.95.

CONCLUSIONS

1. A series of monoarylhydrazones of benzylpyruvic acid ethyl ester has been obtained by azo coupling of α-phenylethylacetoacetic ester with aryldiazonium chlorides. The corresponding acids were obtained by saponification.

2. Esters of 3-benzylindole 2-carboxylic acid were obtained by cyclizing the monoarylhydrazones of benzylpyruvic acid ethyl ester, and by subsequent conversions a series of other derivatives of 3-benzylindole was prepared.

LITERATURE CITED

1. M. D. Mashkovskii, Medicinal Compounds [in Russian], Moscow (1967).
2. W. Wislicenus and M. Münzesheimer, Ber. dtsch. chem. Ges., 31, 555 (1898).
3. W. Borsche and A. Klein, Justus Liebigs Ann. Chem., 548, 64 (1941).
4. H. R. Snyder, F. L. Eliel, and R. E. Carnahan, J. Am. Chem. Soc., 73, 970 (1951).
5. J. A. Ballantine, C. B. Barrett, R. J. S. Beer et al., J. Chem. Soc., 2227 (1957).
6. K. T. Potts and D. R. Liljegren, J. Org. Chem., 28 (11), 3202 (1963).