SYNTHESIS OF 2-ARYLINDOLE DERIVATIVES

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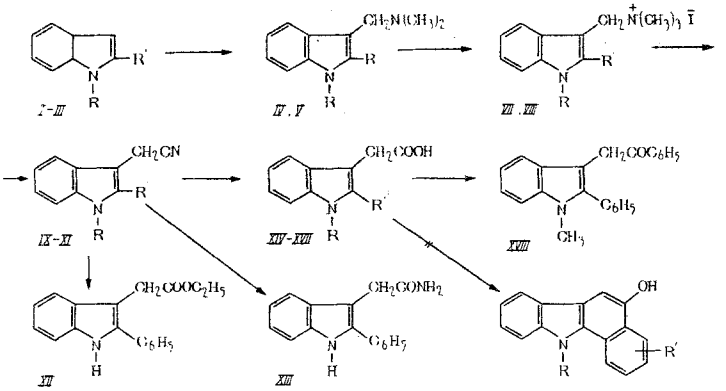
In connection with the fact that carbazole derivatives present interest in the search for new medicinal preparations [1], we have achieved the synthesis of 1,2-benzocarbazole derivatives by intramolecular cyclization of 2-arylindolyl-3-acetic acids. The latter were prepared from 2-arylindoles (I-III) by the general scheme:



I, IV, VII, IX, R=H, R′=C_6H_5
II, XVI R=H, $(CH_3O)_2C_6H_3$
III, V, X, XV R=CH_3, R′=C_6H_5
XI, XVII R=CH_3, R′=3,4 $(CH_3O)_2C_6H_3$

The synthesis of 2-phenylindole (I) was performed by the method described in [2]; and the method of preparing 2-veratrylindole (II) was improved – the yield was 90% instead of 54.4% [3]. By methylation of (I) with dimethyl sulfate we obtained the already known [2, 4, 5] 1-methyl-2-phenylindole (III); here the isolation of the product was improved in the synthesis method of [5]. The yield of 2-phenylgramine (IV) which we obtained was significantly higher than that indicated in the literature [6]. We synthesized the 2-phenylindolyl-3-acetonitriles (IX, X) from the methiodides of the 2-phenylgramines (VII, VIII) by the known method of [3]. 1-Methyl-2-veratryl-3-acetonitrile (XI) was prepared by methylation of 2-veratryl-3-acetonitrile, which has been described in the literature [3], with dimethyl sulfate. From nitrile (IX) we succeeded in obtaining in high yield the ester (XII) and amide (XIII) of 2-phenylindolyl-3-acetic acid, which had previously been synthesized by another method [7]. By hydrolysis of the nitriles (IX-XI) and the amide (XIII) under the action of potassium hydroxide in ethylene glycol, we prepared the 2-arylindolyl-3-acetic acids (XIV-XVII), of which XIV had been previously synthesized by other methods [6, 8]. Attempts at intramolecular cyclization of 2-arylindolyl-3-acetic acid derivatives (XIV-XVII) into 1,2-benzocarbazole derivatives in the presence of polyphosphoric acid, phosphorus pentoxide in benzene, or concentrated sulfuric acid proved fruitless. We also investigated the intramolecular cyclization of 1-methyl-2-phenylindolyl-3-acetyl chloride, which was attempted in benzene in the presence of aluminum chloride; that is, under the

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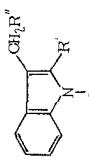
TABLE 1. 2-Arylindole Derivatives, 

Compound	R	R'	R''	Yield (in %)	Mp (in deg)	Recrystallization solvent	Found (in %)			Empirical formula	Calcd. (in %)		
							C	H	N		C	H	N
VI[1]	CH_3	C_6H_5	$N(CH_3)_2 \cdot HCl$	83,0	199—200	Acetone—methanol—ether (6 : 2 : 1)	71,56 71,50	7,15 7,00	9,43 9,50	$C_{18}H_{21}N_2Cl$	71,85	7,03	9,31
VIII[2]	CH_3	C_6H_5	$+N(CH_3)_3$	97,5	185—6 dec.	Methanol—ether (1 : 3)	56,24	5,78	6,58	$C_{19}H_{23}N_2I$	56,16	5,71	6,89
X	CH_3	C_6H_5	CN	95,0	96—7	Methanol	82,49 82,72	5,75 5,48	11,29 11,37	$C_{17}H_{14}N_2$	82,89	5,73	11,37
XV	CH_3	C_6H_5	COOH	92,8	145—6	Glacial acetic acid	76,81 76,70	5,64 5,60	5,38 5,41	$C_{17}H_{15}NO_2$	76,96	5,69	5,28
XVI	H	$3,4(CH_3O)_2C_6H_3$	COOH	93,5	179—80	Same	69,11 69,34	5,67 5,67	4,87 4,88	$C_{18}H_{17}NO_4$	69,44	5,50	4,49
XVII	CH_3	$3,4(CH_3O)_2C_6H_3$	COOH	97,0	156—7	Acetone	70,37 70,36	6,09 6,07	4,31 4,50	$C_{19}H_{19}NO_4$	70,14	5,89	4,30

*Found, %: Cl, 12.09, 12.13. Calculated, %: Cl, 11.80.
†Found, %: I, 31.72. Calculated, %: I, 31.23.

conditions described for intramolecular cyclization in the indole field by [9]. Thereupon, instead of the expected derivative of 1,2-benzocarbazole we obtained 1-methyl-2-phenyl-indolyl-3-acetophenone (XVIII), which was formed as the result of acylation of the solvent. Substitution of the benzene by solvents which could not be acylated, for example, dichloroethane, leads to the formation of resinous products.

In the infrared spectra of the 2-arylindolyl-3-acetonitriles an intense narrow peak is observed in the 2280-2260 cm^{-1} region (C ≡ N frequency). For the 2-arylindoly-3-acetic acids, the absorption maximum in the 1720-1705 cm^{-1} region is connected with the valence stretching of the carbonyl group, and that in the 2800-2600 cm^{-1} range is caused by the hydroxyl group of the carboxyl grouping with a strong hydrogen bond. In the infrared spectra of 2-arylindolyl-3-acetic acids which are not substituted on nitrogen, or of their derivatives, there is a strong absorption in the 3410-3390 cm^{-1} region (NH frequency). Substituents in the aryl nucleus of the 2-arylindoles do not exert an important effect on the position of characteristic bands.

In the ultraviolet spectra of the 2-arylindoles, two intense maxima are observed in the 223-227 mμ region (log ε =4.42-4.60) and the 295-305 mμ region (log ε =4.14-4.32). In some cases a weak inflection appears on the curve at about 240 mμ. Introduction of an aryl chromophore into a position of the indole heterocycle leads to an increase in absorption intensity and a shift of the absorption bands into the long-wavelength region of the spectrum. The character of the substituent in the aryl chromophore does not affect the position of the absorption maxima, which agrees with literature data [10]. Some of the compounds prepared were tested in the laboratory of chemotherapy of infectious diseases of the S. Ordzhonikidze Chemico-Pharmaceutical Research Institute for antiviral activity. It was established that only VI and XV possess virucidal activity in vitro with respect to a type A virus, strain PR-8.

EXPERIMENTAL

Infrared spectra of the compounds prepared were taken in the form of vaseline oil suspensions, on a UR-10 spectrophotometer; ultraviolet spectra, on an EPS-3 recording ultraviolet spectrophometer, in alcoholic solutions.

2-Veratrylindole (II). To 66 g of 100% phosphoric acid solution, at 90°, was gradually added acetoveratrole phenylhydrazone (prepared from 16.2 g of phenylhydrazine and 27 g of acetoveratrole), heated to 80°; here the temperature of the mixture should not exceed 140°. Then the suspension formed was heated for 15 min at 140-145°, cooled to 120-130°,

diluted with 0.5 liter of hot water, and boiled until a uniform precipitate was formed. The precipitate was filtered off, washed with water to a neutral reaction, and dried. The yield of II was 34.5 g (90%), mp 190-191° (from a 3:1 methanol-acetone mixture); lit. [3], mp 190-192°.

1-Methyl-2-phenylindole (III). To a solution of 28.95 g of 2-phenylindole (I) [2] in 180 ml of acetone was added, all at once, a saturated solution of 30 g of sodium hydroxide and then, over a period of 5 min, 37.8 g of dimethyl sulfate; the mixture was stirred for 45 min, and was diluted upon cooling with 2 or 3 volumes of water. The precipitate was filtered off, washed with water, and dried. The yield of III was 31 g (99.5%), mp 99-100° (from methanol); lit. [5], mp. 100-101°.

2-Phenyl-3-dimethylaminomethylindole (IV). To a suspension of 38.6 g of I in 200 ml of dioxane was added a solution of 32.6 g of dimethylamine hydrochloride in 98 ml of water and 30 ml of a 40% formalin solution; the mixture was stirred and warmed at 40° until complete solution occurred. The solution was allowed to stand overnight, then it was diluted with 4 or 5 volumes of distilled water, it was filtered, the filtrate was shaken with acidic charcoal, and it was filtered again. The filtrate was made basic, with ice cooling, by adding 2 N sodium hydroxide solution to a strongly alkaline reaction. The base (IV) precipitated in the form of a dense, viscous oil, which crystallized upon rubbing with methanol. The crystals were filtered off, washed with water, and dried. The yield of IV was 30 g (69%), mp 129-130° (from methanol). Lit. [6], mp 130-130.8°.

1-Methyl-2-phenyl-3-dimethylaminomethylindole (V) was prepared similarly, and was isolated in the form of the hydrochloride (VI). Data on VI are given in Table 1.

2-Phenyl-3-dimethylaminomethylindole methiodide. (VII). To a solution of 10 g of IV in 120 ml of absolute ether was added 7.4 ml of methyl iodide and the mixture was allowed to stand for 2 h. The precipitate was filtered off, washed with ether, and dried. The yield of VII was 15.6 g (99%), mp 200-201° (dec., from a 1:2 methanol–ether mixture). Found, %: C 54.88; H 5.70; N 7.08; I 32.1. $C_{18}H_{21}N_2I$. Calculated, %: C 55.11; H 5.40; N 7.14; I 32.34. Compound VIII was prepared similarly (see Table 1).

2-Phenylindolyl-3-acetonitrile (IX). A solution of 15.8 g of VII and 13 g of potassium cyanide in 80 ml of water and 12 ml of dioxane was boiled under reflux for 2 h. The mixture was cooled, and was diluted with a double volume of water. The precipitate was filtered off, washed with water, and dried. The yield of IX was 8.6 g (92.5%), mp 117-118° (from methanol). Found, %: C 83.03; 83.21; H 5.22, 5.10; N 12.07, 12.13. $C_{16}H_{12}N_2$. Calculated, %: C 82.73; H 5.20; N 12.06. Compound X was prepared similarly (see Table 1).

1-Methyl-2-veratrylindolyl-3-acetonitrile (XI). To a suspension of 5.1 g of 2-veratrylindolyl-3-acetonitrile [3] in 67 ml of dimethylformamide was added a solution of 3.4 g of sodium hydroxide in 3 ml of distilled water. The solution was stirred for 1-2 min and then 3.3 ml (0.034 mole) of dimethyl sulfate was added to it over the course of 5 min. The reaction mixture was stirred for 40-45 min and, upon cooling, was diluted with 4 or 5 volumes of water. The precipitate was filtered off, washed with water, and dried. The yield of XI was 5.18 g (97.7%), mp 139.5-140° (from methanol). Found, %: C 74.28, 74.23; H 5.78, 5.55; N 9.26, 9.58. $C_{19}H_{18}N_2O_2$. Calculated, %: C 74.49; H 5.92; N 9.14.

Ethyl 2-Phenylindolyl-3-acetate (XII). Compound IX (1.8 g) was dissolved in a mixture of 12 ml of absolute ethanol and 8 ml of absolute ether, and dry hydrogen chloride was passed into the solution for 4 h, with stirring. After 4 days the mixture was diluted, after cooling, with 4 or 5 volumes of water. The mixture was heated for 1 h at 50-55°, cooled, and the precipitate was filtered off, washed with water, and dried. The yield of XII was 2 g (91%), mp 82-82.5° (from aqueous methanol). Found, %: C 77.34, 77.17; H 6.04, 6.02 6.02; N 5.42, 5.37. $C_{18}H_{17}NO_2$. Calculated, %: C 77.39; H 6.13; N 5.02.

2-Phenylindolyl-3-acetamide (XIII). To 120 g of polyphosphoric acid was added 4.6 g of IX and, while stirring, the suspension obtained was heated at 50-60° for 4 h. The mixture was cooled, diluted with 5 or 6 volumes of water, the precipitate filtered off and washed with water, and it was dried. The yield of XIII was 3.8 g (76%), mp 198-199° (from acetone). Found, %: C 76.80, 76.49; H 5.60, 5.56; N 11.21, 11.10. $C_6H_{14}N_2O$. Calculated, %: C 76.77; H 5.63; N 11.19.

2-Phenylindolyl-3-acetic Acid (XIV). Compound IX (2.3 g) and 1.12 g of potassium hydroxide were heated together in 4 ml of ethylene glycol for 3 h at 140-150°. The solution was cooled, diluted with 6 or 7 volumes of water, and filtered; the filtrate was acidified with glacial acetic acid. The precipitate was filtered off, washed with water, and dried. The yield of XIV was 1.9 g (76%), mp 177-178°. Found, %: C 76.33, 76.12; H 5.30, 5.44; N 5.59, 5.78. $C_{16}H_{13}NO_2$. Calculated, %: C 76.47; H 5.21; N 5.57. Compound XVI was

prepared similarly (see Table 1). By hydrolysis of X, XI, and XIII, carried out under similar conditions, but at 180-185°, the corresponding acids (XV, and XVII, see Table 1) were prepared, as well as XIV.

1-Methyl-2-phenylindolyl-3-acetophenone (XVIII). To a solution of 2.65 g of XV in 25 ml of dry benzene was added 1.5 ml of thionyl chloride, and the mixture was boiled on a water bath for 2 h. The benzene and excess thionyl chloride were stripped off, and the 1-methyl-2-phenylindolyl-3-acetyl chloride, without isolation, was dissolved in 25 ml of dry benzene; to the solution was added, with stirring, 2.6 g of anhydrous aluminum chloride. The mixture was heated for 6 h at 50°, it was allowed to stand overnight, and then it was poured onto 30 g of ice containing 5 ml of concentrated hydrochloric acid. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene extracts were washed with water, dried by azeotropic distillation with a Dean-Stark adapter, and the benzene was stripped off under vacuum. The residue was dissolved in 45 ml of a 3 : 1 benzene — petroleum ether mixture and was chromatographed on aluminum oxide. The yield of XVIII was 1.3 g(40.6%), mp 118-119° (from ethyl acetate).

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