SYNTHESIS OF PYRROLO[3,2-b]INDOLE DERIVATIVES

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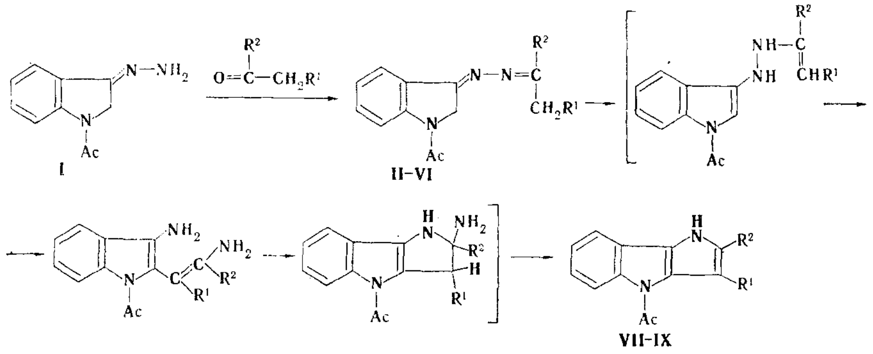
The reaction of N-acetylindoxyl hydrazone with ketones in alcohol gave N-acetylindoxyl alkylindenehydrazones, which were converted to pyrrolo[3,2-b]indole derivatives by treatment with glacial acetic acid. Pyrrolo[3,2-b]indole derivatives were also obtained in the reaction of N-acetylindoxyl hydrazone with ketones in glacial acetic acid. The structures of the synthesized products were confirmed by data from the IR, UV, PMR, and mass spectra.

Despite the fact that pyrrolo[2,3-b]indole derivatives have been studied extensively and their heterocyclic fragment lies at the foundation of many alkaloids [1-3], pyrrolo[3,2-b]-indoles have thus far been virtually inaccessible. Only one representative of this class, viz., 1-(o-acetylphenyl)-3,3a,4,8b-tetrahydro-3aa,8ba-dimethylpyrrolo[3,2-b]indole, has been isolated in the case of oxidation of a indolobenzopyrrolizine derivative [4].

In the present research we studied the reaction of N-acetylindoxyl hydrazone (I) [5] with ketones. As a result, we obtained the previously unknown N-acetylindoxyl alkylidenehydrazones II-VI. Absorption bands at 1630-1650 ($C{=}O$) and 1660-1670 cm^{-1} ($2C{=}N$) are observed in the IR spectra of II-VI, and absorption bands of amino groups at 3100-3400 cm^{-1} are absent.

It is apparent that the alkylidenehydrazones (unsymmetrical azines) II-VI obtained can be used as starting compounds for the synthesis of pyrrolo[3,2-b]indoles by the Piloty method. Using this method we accomplished for the first time the synthesis of completely aromatic pyrrolo[3,2-b]indoles (VII-IX) by the action of glacial acetic acid on N-acetylindoxyl alkylidenehydrazones (III-V).



II R^1andR^2 = $(-CH_2-)_3$; III, VII R^1andR^2 = $(-CH_2-)_4$; IV, VIII R^1andR^2 = $(-CH_2-)_5$; V, IX $R^1 = C_6H_5$, $R^2 = CH_3$; VI $R^1 = COOC_2H_5$, $R^2 = CH_3$

As compared with the IR spectra of II-VI, the IR spectra of pyrrolo[3,2-b]indoles VII-IX do not contain absorption bands at 1660-1670 cm^{-1} ($2C{=}N$); however, the absorption band of an acetyl carbonyl group is retained at 1650-1660 cm^{-1}. In addition, an absorption band due to stretching vibrations of the NH group of the pyrrole ring is observed at 3230-3300 cm^{-1}.

We found that the previously described [5] 7-methyl-13-acetamidopyrimido[3,4-a:5,6-b']-diindole (X) is formed as a side product in the cyclization of N-acetylindoxyl alkylidenehydrazones to pyrrolo[3,2-b]indoles and when other cyclizing agents such as hydrochloric acid in acetic acid, concentrated sulfuric acid in absolute ethanol, and formic acid are used for this reaction; this side product is formed as a result of disproportionation of the alkylidenehydrazones.

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TABLE 1. N-Acetylindoxyl Alkylidenehydrazones II-VI

Compound	mp,* °C (dec.)	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm†	IR spectrum, cm^{-1}		Found, %			Empirical formula	Calc., %			Yield, %
				2C=N	C=O	C	H	N		C	H	N	
II	136	213 (4,13), 252 (4,37), 259 (4,35) shoulder, 264 (4,25), 340 (4,05)	1,54—2,31 (methylene protons of a cyclopentane ring); 2,01 (s, $COCH_3$); 4,42 (s, 2H—C_2); 6,90, 7,20 (2 t 2H—$C_{5,6}$); 7,58, 8,21 (2 d, 2H—$C_{4,7}$)	1670	1650	70,4	6,5	16,7	$C_{15}H_{17}N_3O$	70,6	6,7	16,5	74
III	127—129	205 (4,19), 252 (4,36), 256 (4,33) shoulder, 273 (4,22), 338 (4,02)	1,64—2,62 (methylene protons of a cyclohexane ring); 2,18 (s, $COCH_3$); 4,64 (s, 2H—C_2); 7,01, 7,33 (2 t, 2H—$C_{5,6}$), 7,66, 8,22 (2 d, —$C_{4,7}$)	1680, 1670	1640	72,0	7,1	15,9	$C_{16}H_{19}N_3O$	71,4	7,1	15,6	75
IV	104—106	206 (4,15), 252 (4,38), 275 (4,24), 335 (4,04)	2,32—2,50 (methylene protons of a cycloheptane ring); 2,48 (s, $COCH_3$); 4,71 (s, 2H—C_2); 7,14—7,68 (aromatic ring protons)	1660	1630	72,0	7,2	14,8	$C_{17}H_{21}N_3O$	72,1	7,5	14,8	70
V	120—125	250 (4,28), 256 (4,26) shoulder, 275 (4,20), 335 (4,01)	—	1660	1635	75,0	6,5	13,6	$C_{19}H_{19}N_3O$	74,7	6,3	13,8	67
VI	126—128	222 (4,13), 266 (4,22), 276 (4,26), 305 (3,95), 318 (4,10), 357 (4,52), 373 (4,51)	—	1660	1640	63,6	6,2	13,9	$C_{16}H_{19}N_3O_3$	63,8	6,4	14,0	87

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*Crystallization solvents: methanol for II-IV and VI and dioxane for V.

†Solvents: $CDCl_3$ for II, d_6-DMSO—CCl_4 for III, and d_6-DMSO for IV.

TABLE 2. 4-Acetylpyrrolo[3,2-b]indoles VII-IX

Compound	mp, °C (methanol)	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm*	IR spectrum, cm^{-1}		Found, %			Empirical formula (M, from the mass spectrum)	Calc., %			Yield, %	
				NH	C=O	C	H	N		C	H	N	A	B
VII	200—201	237 (4,16), 280 (4,87), 304 (4,12)	2,70 (s, $COCH_3$). 2,05—2,95 (methylene protons), 7.92-7,54 (aromatic ring protons), 10.99 (s, NH)	3250	1650	76,1	6,2	11,3	$C_{16}H_{16}N_2O$ (252)	76,2	6,4	11,1	47	70
VIII	223—224	204 (4,23), 240 (4,09), 273 (4,00) shoulder, 282 (4,01), 315 (4,09)	2,69 (s, $COCH_3$), 2,00—2,92 (methylene protons), 7.12-7,85 (aromatic ring protons), 10.99 (s, NH)	3230	1650	76,6	6,7	10,4	$C_{17}H_{18}N_2O$ (266)	76,7	6,8	10,5	56	70
IX	221—223	233 (4,29), 268 (4,17), 310 (4,20)	1,97 (c, $COCH_3$), 2,25 (s, CH_3), 7,13—7,9 (aromatic ring protons)	3300	1660	79,2	5,5	9,9	$C_{19}H_{16}N_2O$ (288)	79,1	5,6	9,7	33	49

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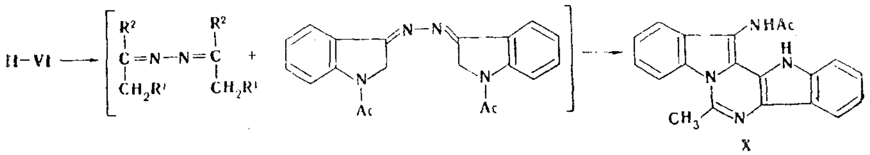
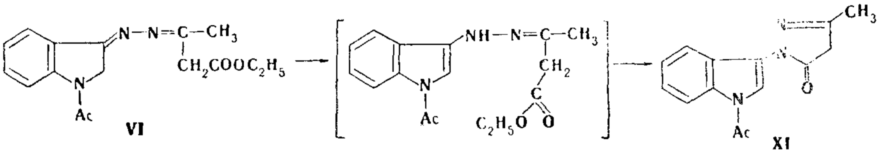
*Solvents: d_6-DMSO for VII and VIII and d_6-DMSO—$CDCl_3$ for IX.

The N-acetylindoxyl alkylidenehydrazones remain unchanged when polyphosphoric acid is used as the cyclizing agent. However, N-acetylindoxyl is formed as a result of hydrolysis in some cases when the reaction mixture is treated with water.



N-Acetylindoxyl carbethoxyisopropylidenehydrazone (VI) is converted to N-acetyl-3-(3'-methylpyrazol-5'-on-1'-yl)indole (XI) when it is heated to 90°C in polyphosphoric acid.



Thus pyrrolo[3,2-b]indole derivatives VII-IX are formed only by the action of glacial acetic acid on N-acetylindoxyl alkylidenehydrazones III-V. We proposed to obtain these compounds by bypassing the step involving the synthesis of N-acetylindoxyl alkylidenehydrazones by the reaction of N-acetylindoxyl hydrazone I with ketones in acetic acid. We found that pyrrolo[3,2-b]indoles VII-IX are formed if N-acetylindoxyl hydrazone is added to a solution of the ketone in glacial acetic acid. If this reaction is carried out with equimolar amounts of reagents the yields of pyrrolo[3,2-b]indoles range from 37 to 41%. When the reaction is carried out with a twofold to threefold excess of the ketone the yields of pyrrolo[3,2-b]indoles increase to 49-70%. When the order of mixing of the reagents is changed, i.e., in the case of prior dissolving of the N-acetylindoxyl hydrazone in acetic acid, only a side process, which leads to X, is observed.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with UR-10 and Perkin-Elmer spectrometers. The UV spectra of solutions of the compounds in alcohol were recorded with Hitachi EPS-3T and Perkin-Elmer 575 spectrophotometers. The PMR spectra were recorded with C-60HL (with hexamethyldisiloxane as the internal standard) and JNM-4H-100 (with tetramethylsilane as the internal standard) spectrometers. The mass spectra were recorded with a Varian MAT-112 mass spectrometer (70 eV) by direct introduction of the samples into the ion source. The course of the reaction and the individuality of the substances were monitored on Silufol UV-254 plates in a benzene—methanol system (9:2) with development in UV light.

N-Acetylindoxyl Alkylidenehydrazones (II-VI). A mixture of 0.01 mole of N-acetylindoxyl hydrazone I, 0.02 mole of the ketone, and 40 ml of absolute alcohol was refluxed for 2 h, after which the reaction solution was evaporated to half its original volume,* and the residue was cooled. The precipitate was removed by filtration, washed with methanol, and dried. Data on II-VI are presented in Table 1.

Pyrrolo[3,2-b]indoles (VII-IX). A) A mixture of 1 mmole of N-acetylindoxyl alkylidenehydrazone III-V and 3 ml of glacial acetic acid was heated to the boiling point, after which it was cooled to room temperature, and the resulting precipitate was removed by filtration and washed with acetic acid and methanol.

B) A 2-mmole sample of the N-acetylindoxyl hydrazone was added to a solution of 6 mmole of the ketone in 4 ml of glacial acetic acid, and the mixture was stirred at 20°C until the solid material dissolved. The solution was heated to the boiling point, after which it was cooled, and the resulting precipitate was removed by filtration and washed with glacial acetic acid and methanol. Data on VII-IX are presented in Table 2.

N-Acetyl-3-(3'-methylpyrazol-5'-on-1'-yl)indole (XI). A 72-g sample of phosphorus pentoxide was added with stirring and cooling to 48 ml of phosphoric acid, and the mixture of substances was heated on an oil bath at 100°C for 1 h. It was then cooled to 20°C, and 4 g (13 mmole) of N-acetylindoxyl carbethoxyisopropylidenehydrazone (VI) was added to the resulting

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*In the preparation of II the reaction solution was not evaporated.

polyphosphoric acid. The reaction mixture was stirred at 20°C for 2 h, after which it was heated to 90°C. The heater was removed, and the mixture was allowed to cool spontaneously to 40°C. The reaction mass was poured over ice (~1200 g), and the resulting mixture was neutralized with ammonium hydroxide. The precipitate was removed by filtration, washed with water, air dried, and recrystallized from methanol to give 2 g (59%) of XI with mp 178-180°C (from methanol). IR spectrum: 1715, 1680 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 238 (4.34) and 302 nm (3.90). PMR spectrum ($CDCl_3$): 2.17 (s, $COCH_3$), 2.55 (s, CH_3), 3.30 (s, 2H-C_4), 7.94 (s, H-C_2), 7.36, 8.18, 8.58 ppm (3m, aromatic ring protons). Found: C 65.8; H 5.1; N 16.6%; M$^+$ 255. $C_{14}H_{13}N_3O_2$. Calculated: C 65.9; H 5.1; N 16.5%; M 255.

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PYRROLOINDOLES.

5.[*] ACETYLATION OF 1H,6H-PYRROLO[2,3-e]INDOLE BY MEANS OF THE VILSMEIER—HAACK REACTION

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The Vilsmeier—Haack reaction with 1H,6H-pyrrolo[2,3-e]indole with the participation of dimethylacetamide was studied. 3-Acetyl, 8-acetyl, 2-acetyl, and 3,8-diacetyl derivatives (with great preponderance of the 3-acetyl derivative) were obtained. The formation of a 2-substituted product does not have an analogy in the chemistry of indole. On the basis of data from the IR and PMR spectra it was established that an intramolecular hydrogen bond between 1-H and the C=O group in the 8 position exists in the 8-acetylpyrroloindole molecule. This bond also affects the mass-spectral fragmentation of the 8-acetyl derivative.

The aim of the present research was to determine the positions of the centers of electrophilic attack in the 1H,6H-pyrrolo[2,3-e]indole (I) molecule by means of the Vilsmeier—Haack reaction.

We have previously reported [2] that Vilsmeier formylation of 1H,6H-pyrrolo[2,3-e]indole gives its 3,8-diformyl derivative. In the present research we studied acetylation. The interest in this reaction is due to the fact that the complex based on dimethylacetamide (DMAA) and phosphorus oxychloride reacts only with sufficiently highly nucleophilic substances. Some indole-containing polycyclic systems virtually do not react with it [3], while the degree of reaction of indole is only 22% at 85°C [4].

The acetylation of 1H,6H-pyrrolo[2,3-e]indole was carried out in analogy with the acetylation of indole [4]. Four compounds that differed with respect to their R_f values and melting points but were similar in that their IR spectra contained bands of a C=O bond at 1620-1660 cm^{-1} were isolated from the reaction products. The structures of acetylpyrroloindoles II-V were established on the basis of data from the PMR, IR, UV, and mass spectra. The principal

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[*] See [1] for communication 4.

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