Pyrrolyl- and Indolyl(1,3-dioxo-2-indanylidene)acetonitriles (IIa-e). A solution of 0.5 mmole of reaction product I in 50 ml of acetonitrile was irradiated from above with the full light of the UV lamp, which was situated at a distance of 10 cm from the surface of the solution. The corresponding dye, which precipitated in the form of a finely crystalline substance, was removed periodically by filtration and was recrystallized from acetonitrile. Irradiation was carried out for 20-30 h until I was converted almost completely to the dye, which was verified by chromatography. The dyes were obtained in 44-61% yields.

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PYRROLOINDOLES.

6.* NEW SYNTHESIS OF 1H,5H-PYRROLO[2,3-f]INDOLE AND 3H,6H-PYRROLO[3,2-e]INDOLE

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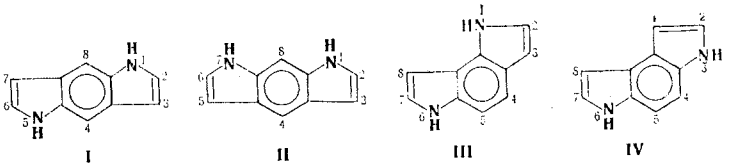
Ethyl pyruvate 1-acetyl-5-indolinylhydrazone was obtained by diazotization of 1-acetyl-5-aminoindoline with subsequent reduction of the diazonium salt and condensation of the hydrazine with ethyl pyruvate. A mixture of hydrogenated derivatives of linear and angular pyrroloindoles is formed as a result of cyclization of the hydrazone in polyphosphoric acid esters. Subsequent hydrolysis, decarboxylation, and dehydrogenation lead to 1H,5H-pyrrolo[2,3-f]indole and 3H,6H-pyrrolo[3,2-e]indole.

Unsubstituted linear pyrroloindoles are difficult to obtain, and little study has therefore been devoted to them. The literature contains only two reports describing the synthesis of 1H,5H-pyrrolo[2,3-f]indole (I) [2] and 1H,7H-pyrrolo[3,2-f]indole (II) [3], which were obtained by closing of two pyrrole rings with the benzene ring. Pyrroloindole II is formed only as an impurity in angular 1H,6H-pyrrolo[2,3-e]indole (III) in the cyclization of the corresponding hydrazone obtained from m-phenylenediamine (with subsequent hydrolysis and decarboxylation) [3]. Only angular 3H,6H-pyrrolo[3,2-e]indole (IV) was synthesized by the same method when p-phenylenediamine was used as the starting amine [4]. Pyrroloindole I is obtained as the principal product in the cyclization of 2,5-bis(β-aminoethyl)hydraquinone hydrobromide (with subsequent dehydrobromination [2]. However, the difficulty with which starting hydroquinone V is obtained, the large number of steps, and the low overall yield make this method unsuitable for the synthesis of pyrroloindole I.



I II III IV

*See [1] for Communication 5.

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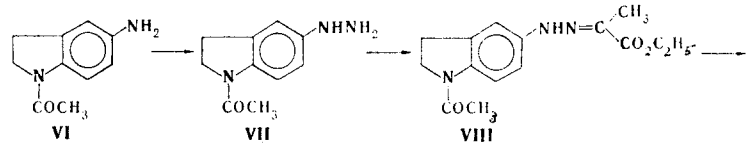
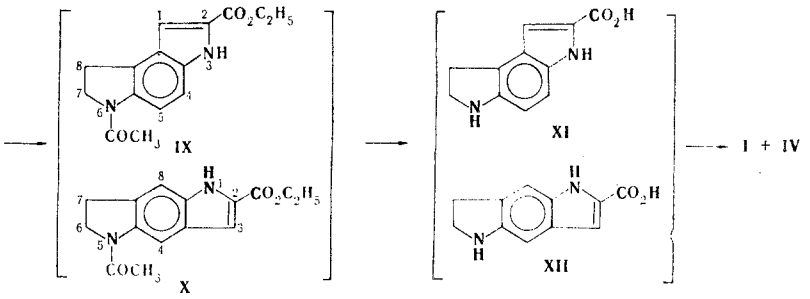
We have accomplished a new synthesis of linear pyrroloindole I via an alternative scheme, viz., by rearrangement of the pyrrole ring to an indoline ring.

For the synthesis of hydrazine VII, 5-amino-N-acetylindoline VI was diazotized by the usual method with subsequent reduction of the diazonium salt with stannous chloride. However, the isolation of the hydrazine in individual form presented considerable difficulties and was accompanied by great losses, and hydrazine VII was therefore condensed without isolation with ethyl pyruvate to give a mixture of syn and anti isomers of hydrazone VIII (in 80% yield). A characteristic bathochromic shift of 22 nm, which is in good agreement with the literature data [5], is observed in the UV spectra of the syn form. In the IR spectra of the syn isomer the absorption band of the carbonyl group is shifted 70 cm^{-1} to the low wave-number region as compared with the absorption band of the carbonyl group for the anti isomer. A weak-field shift of the proton of the NH group tied up in an intramolecular hydrogen bond (12.0 ppm) is observed in the PMR spectrum of the syn isomer. Unfortunately, the signal of the NH group of the anti isomer is not observed in the spectrum in view of exchange broadening. However, as expected, the chemical shift of the 4-H proton differs substantially for the anti (7.64 ppm) and syn (7.07 ppm) isomers.



VI VII VIII



IX X XI XII I + IV

An alcohol solution of hydrogen chloride, a solution of sulfuric acid in acetic acid, and polyphosphoric acid esters were used as cyclizing agents for the indolization of hydrazone VIII; the best results (73%) were obtained in the case of polyphosphoric acid esters. According to the PMR spectral data, two isomers, viz., angular ester IX and linear ester X in a ratio of 1:4, are formed as a result of the cyclization of hydrazone VIII.

All attempts to separate the mixture obtained were unsuccessful. However, for identification we were able to isolate ester X by column chromatography.

Three signals that are split due to small spin–spin coupling constants, the greatest of which J_{13} = 2 Hz, are observed in the PMR spectrum for linear isomer X in the aromatic region, whereas the AB system that is characteristic for the ortho protons of the benzene ring is observed in the spectrum of angular isomer IX (see the experimental section).

Attempts to separate acids XI and XII, as well as their N-acetylated derivatives, were also unsuccessful, and the mixture of acids XI and XII was therefore also subjected to dehydrogenation–decarboxylation in the presence of Pd on carbon, as a result of which we obtained a mixture of pyrroloindoles I and IV in a ratio of ~1:1, which was separated by column chromatography. The structures of pyrroloindoles I and IV were established on the basis of the results of elementary analysis and the NMR and IR spectral data and by comparison with the literature data [2, 4].

This disparity in the ratio of cyclization products IX and X and the isolated pyrroloindoles I and IV is evidently explained by the lower thermal stability of linear pyrroloindole I and its intermediates as compared with angular pyrroloindole IV.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with a

Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian CFT-20 spectrometer (80 MHz) with tetramethylsilane as the internal standard. The course of the reaction and the purity of the compounds were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates.

Stereomers of Ethyl Pyruvate 1-Acetyl-5-indolinylhydrazone (VIII). A solution of 54 g (0.3 mole) of 1-acetyl-5-aminoindoline in 250 ml of 18% hydrochloric acid was cooled to −5°C, and a solution of 23.1 g (0.33 mole) of sodium nitrite in 150 ml of water was added at such a rate that the temperature of the reaction mixture did not rise above 0°C. The reaction mixture was then stirred at 0°C for 0.5-1 h, after which it was poured into a cooled (to −15°C) solution of 180 g (0.79 mole) of stannous chloride in 250 ml of 18% hydrochloric acid at such a rate that the temperature of the reaction mixture did not exceed −10°C. The mixture was then stirred at 0°C for 2-3 h, after which 2 liters of water were added, and the mixture was heated to 80°C and made alkaline to pH 3-3.5 with sodium acetate. The resulting precipitate of tin salts was removed by filtration at 70-80°C, the filtrate was cooled to 20°C, and a solution of 34.8 g (0.3 mole) of ethyl pyruvate in 35 ml of isopropyl alcohol was added to it with vigorous stirring. The mixture was stirred for 2 h, after which the precipitate was removed by filtration, washed with water, and dried to give 70 g (80%) of a mixture of isomers of hydrazone VIII. For identification, the mixture of hydrazones VIII was separated with a column filled with 100/250 μ silica gel (elution with benzene and ether) to give the syn and anti forms. The syn isomer had mp 188-189°C (from benzene). UV spectrum, λ_{max} (log ε): 206 (3.03), 269 (2.79), 319 sh (2.58), and 370 nm (3.01). IR spectrum: 3250 (NH), 3010 (C—H), 1665 (CO), and 1645 cm^{-1} (CO). PMR spectrum (in $CDCl_3$): 2.18 (3H, s, 1-CH_3); 4.08 and 3.14 (2H, t, 2-H and 2H, t, 3-H, J_{23} = 8.5 Hz); 7.07 (1H, d, 4-H, J_{46} = 2.0 Hz); 6.80 and 8.06 (AB system, 6-H and 7-H, J_{67} = 8.7 Hz); 12.0 (NH); side chain 2.13 (3H, s, CH_3); 4.22 (2H, q, CH_2CH_3); 1.34 ppm (3H, t, CH_2CH_3). Found: C 62.0; H 7.0; N 14.8%. $C_{15}H_{19}N_3O_3$. Calculated: C 62.3; H 6.6; N 14.5%.

The anti isomer has mp 233-234°C (from benzene). UV spectrum, λ_{max} (log ε): 205 (3.04), 264 (2.57), 312 (2.91), and 348 nm (3.13). IR spectrum: 3250 (NH), 1715 (CO), and 1645 cm^{-1} (CO). PMR spectrum (in $CDCl_3$): 2.19 (3H, s, 1-CH_3); 4.04 and 3.16 (2H, t, 2-H and 2H, t, 3-H, J_{23} = 8.8 Hz); 7.64 (1H, d, 4-H, J_{46} = 2.4 Hz); 6.82 and 8.08 (AB system, 6-H and 7-H, J_{67} = 8.6 Hz); side chain 2.08 (3H, s, CH_3); 4.30 (2H, q, CH_2CH_3); 1.37 ppm (3H, t, CH_2CH_3). Found: C 62.4; H 6.6; N 14.4%. $C_{15}H_{19}N_3O_3$. Calculated: C 62.3; H 6.6; N 14.5%.

Mixture of 2-Ethoxycarbonyl-6,7-dihydro-1H,5H-pyrrolo[2,3-e]indole (X) and 2-Ethoxycarbonyl-7,8-dihydro-3H,6H-pyrrolo[3,2-e]indole (IX). A 45-g (0.156 mole) sample of hydrazone VIII was suspended with vigorous stirring in 450 g of polyphosphoric acid esters, during which the reaction mixture warmed up spontaneously to 60-70°C. It was then heated up to 90°C and stirred at this temperature for 1 h. It was then cooled and poured over ice, and the resulting precipitate was removed by filtration and dried to give 31 g (73%) of a mixture of esters IX and X. For identification, ester X, with mp 261-262°C, was isolated by chromatography with a column filled with 100/250 μ silica gel (elution with benzene and ether). IR spectrum: 3200 (NH), 1680 (CO), and 1650 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 204 (4.17), 257 (4.56), 303 (4.31), and 345 nm (3.96). PMR spectrum (in d_6-DMSO, 60°C): 11.4 (NH), 7.23 (1H, d, 3-H, J_{13} = 2.2 Hz), 8.17 (1H, m, 4-H, $J_{14} \approx J_{48}$ = 0.7 Hz), 2.16 (3H, s, 5-CH_3), 4.07 and 3.28 (2H, t, 6-H and 2H, t, 7-H, J_{67} = 8.0 Hz), 6.99 (1H, m, 8-H), side chain 4.29 and 1.32 ppm (2H, q, CH_2CH_3 and 3H, t, CH_2CH_3, $J_{CH_2CH_3}$ = 7.0 Hz). Found: C 66.5; H 6.0; N 10.1%. $C_{15}H_{16}N_2O_3$. Calculated: C 66.2; H 5.9; N 10.3%. PMR spectrum of IX (in d_6-DMSO, 60°C): 6.98 (1H, m, 1-H, J_{13} = 2.0 Hz), 11.5 (NH), 7.23 and 8.06 (AB system, 4-H, 5-H, J_{45} = 8.8 Hz, J_{14} = 0.7 Hz), 2.14 (3H, s, 6-CH_3), 4.14 and 3.26 (2H, t, 7-H and 2H, t, 8-H, J_{78} = 8.5 Hz), side chain 4.32 and 1.33 ppm (2H, q, CH_2CH_3 and 3H, t, CH_2CH_3, $J_{CH_2CH_3}$ = 7.1 Hz).

Mixture of 2-Carboxy-6,7-dihydro-1H,5H-pyrrolo[2,3-f]indole (XII) and 2-Carboxy-6,7-dihydro-3H,6H-pyrrolo[3,2-e]indole (XI). A 2.5-g sample of sodium hydrosulfite and 50 g of a mixture of esters IX and X were added to a solution of 140 g of potassium hydroxide in 250 ml of water, and the mixture was refluxed with stirring in a stream of nitrogen for 1 h. It was then cooled to −25°C, filtered, and acidified with acetic acid to pH 5 at no higher than −10°C. The resulting precipitate was removed by filtration, washed with water, and dried to give 26 g (70%) of a mixture of acids XI and XII, which was used for the next step without additional purification.

1H,5H-Pyrrolo[2,3-f]indole (I) and 3H,6H-Pyrrolo[3,2-e]indole (IV). A thoroughly blended mixture of 0.5 g of acids XI and XII and 0.7 g of 10% Pd on carbon was placed in a wide test

tube, and the test tube was heated for ~5 min in a burner flame until the evolution of white vapors ceased. The tube was then cooled, and the reaction mixture was extracted with acetone. The extract was applied to silica gel, and linear isomer I and angular isomer IV were separated with a column filled with 100/250 μ silica gel (elution with benzene). Workup gave 0.12 g (8%) of indole I with mp 206°C (mp > 200°C [2]) and 0.11 g (7%) of indole IV with mp 86°C (mp 86°C [3]). The PMR spectra of I and IV were in agreement with symmetrical structures. PMR spectrum of I (in d_6-acetone): 9.7 (NH), 7.20 (1H, dd, 2-H, J_{13} = 2.4 Hz, $J_{23} \approx J_{12} \approx$ 2.7 Hz), 6.36 (1H, dd, 3-H), and 7.46 ppm (1H, s, 4-H). PMR spectrum of IV (in d_6-acetone): 6.64 (1H, dd, 1-H, J_{13} = 2.2 Hz, J_{12} = 2.9 Hz), 7.21 (1H, dd, 2-H, J_{23} = 2.5 Hz), 10.0 (NH), and 7.20 ppm (1H, s, 4-H). These data are in agreement with the data obtained in [3].

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SYNTHESIS OF 3-OXOISOTHIAZOLO[5,4-b]PYRIDINES

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3-Oxoisothiazolo[5,4-b]pyridines were synthesized for the first time by the reaction of 3-cyanopyridine-2-thiones or bis(3-cyanopyridyl) disulfides with concentrated sulfuric acid. It is demonstrated that 3-carbamoylpyridine-2-thiones are formed as intermediates. The 3-oxoisothiazolopyridines were converted to 3-bromoisothiazolopyridines and pyridine-2-thiones. The bromination of pyridine-2-thione was studied.

3-Cyanopyridine-2-thiones react with bromine [1], chloranil [2], and sulfamide [3] with the formation of an isothiazole ring to give, respectively, 3-bromo- and 3-aminoisothiazolo-[5,4-b]pyridines.

We have shown that 3-cyanopyridine-2-thiones (I) in concentrated sulfuric acid form the previously undescribed 3-oxo derivatives of isothiazolo[5,4-b]pyridines (III). In contrast to the previously described cyclocondensation of I with bromine, which leads to the formation of 3-bromoisothiazoles [1], treatment of pyridinethiones I with concentrated sulfuric acid leads initially to hydrolysis of the nitrole group to an amide group, after which the resulting 3-carbamoyl-4,6-diphenylpyridine-2-thiones (II) undergo oxidative cyclization to III. The formation of amides II as intermediates is confirmed by the formation of an isothiazole ring when a model compound, viz., 3-carbamoyl-4,6-diphenylpyridine-2-thione (IIa), which was synthesized from 2-bromo-3-carbamoyl-4,6-diphenylpyridine (VI) with thiourea, is treated with concentrated sulfuric acid.

The difference between oxoisothiazolo[5,4-b]pyridine III and the corresponding acylic amide II was proved by spectroscopy.

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