PYRROLOQUINOLINES AND PYRROLOISOQUINOLINES.

3.* SYNTHESIS OF 1H-PYRROLO[2,3-f]ISOQUINOLINE AND SOME OF ITS DERIVATIVES

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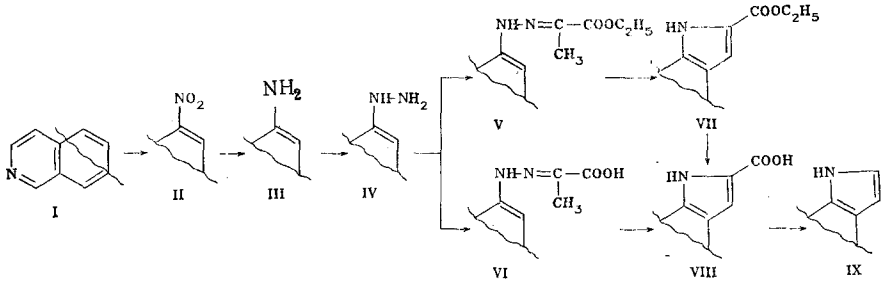
The preparative synthesis of 1H-pyrrolo[2,3-f]isoquinoline is proposed. Electrophilic substitution reactions, viz., the Mannich and Vilsmeier reactions and diazo coupling, were studied for the first time in the pyrroloisoquinoline series.

In a continuation of our systematic research on pyridoindoles we have begun the study of compounds of the pyrroloisoquinoline series.

The literature contains information regarding the preparation of f-, h-, and C-pyrroloisoquinolines by Fischer cyclization of isoquinolylhydrazones of ethyl pyruvate and aliphatic and aromatic ketones with zinc chloride [2-4]. However, the described method makes it possible to obtain unsubstituted pyrroloisoquinolines in low overall yields (4-5%).

We synthesized 1H-pyrrolo[2,3-f]isoquinoline (IX) via the scheme



In order to increase the yield of 1H-pyrrolo[2,3-f]isoquinoline (IX) we attempted to select the optimum conditions for carrying out the reactions for each step individually. Particular attention was directed to the cyclization of the isoquinolylhydrazones of pyruvic acid and its ethyl ester.

Nitration of isoquinoline (I) under mild conditions gave 5-nitroisoquinoline (II) [5], which was reduced with hydrazine hydrate in the presence of Raney nickel. Diazotization of amine III and reduction of the diazonium salt with $SnCl_2$ led to the hydrochloride of 5-isoquinolylhydrazine (IV) [6]. Direct condensation of the latter with pyruvic acid and its ethyl ester led to the formation of hydrazones VI and V, respectively, in high yields. Zinc chloride, mineral acids, polyphosphoric acid and its ethyl ester, and a mixture of acetic and sulfuric acids can be used for the cyclization of 5-isoquinolylhydrazines V and VI. However, 1H-pyrrolo[2,3-f]isoquinoline-2-carboxylic acid (VIII) was isolated in quantitative yield when hydrazone VI was heated in a mixture of concentrated sulfuric acid and glacial acetic acid (1:3). The cyclization of hydrazone V by means of ethyl polyphosphate made it possible to obtain ethyl 1H-pyrrolo[2,3-f]isoquinoline-2-carboxylate (VII) also in high yield. Thermal decarboxylation of acid VIII led to the formation of 1H-pyrrolo[2,3-f]isoquinoline (IX).

*See [1] for communication 2.

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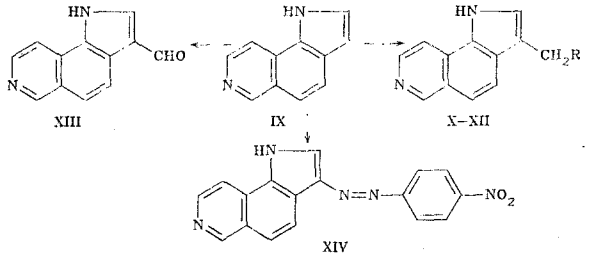
The reactivity of the pyrroloisoquinoline obtained was studied primarily in electrophilic substitution reactions, viz., the Mannich and Vilsmeier reactions and diazo coupling.

Various amines, viz., dimethylamine, morpholine, and piperidine, were used in the classical variant of the Mannich reaction. Aminoalkyl derivatives X-XII were obtained in ∿50% yields. The utilization of a crystalline Mannich reagent [7] made it possible to increase the yield of 3-N,N-dimethylaminomethyl-1H-pyrrolo[2,3-f]isoquinoline (X) to 93%.



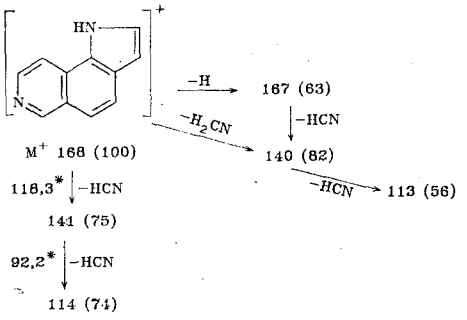
X R=N(CH$_3$)$_2$, XI R=morpholyl, XII R=piperidyl

We were able to accomplish the Vilsmeier reaction only in the case of N,N-dimethylformamide (DMF). 3-Formyl-1H-pyrrolo[2,3-f]isoquinoline (XIII) was isolated in 41% yield. An attempt to obtain an acetyl derivative with N,N-dimethylacetamide was unsuccessful.

The diazo coupling of 1H-pyrrolo[2,3-f]isoquinoline (IX) was carried out with diazonium salts obtained from aniline and p-nitroaniline. We found that the pyrroloisoquinoline reacts only with p-nitrobenzenediazonium chloride. The reaction should be carried out at pH 7 with a 2 M amount of the diazonium salt while maintaining the reaction mixture in the dark for 2 days. Azo product XIV was isolated in 45% yield.

The structures of the unsubstituted pyrroloisoquinoline and its derivatives were confirmed by data from IR, UV, PMR, and mass spectroscopy.

An intense molecular-ion peak (M^+) with m/z 168, which corresponds to its molecular mass, is observed in the mass spectrum of IX. The fragmentation of 1H-pyrrolo[2,3-f]isoquinoline is similar to the fragmentation of indole and quinoline [8]. The fragmentation processes were confirmed by metastable transformations.*



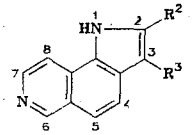
Ethyl pyruvate hydrazone V was separated into syn and anti isomers by means of column chromatography. According to the PMR spectral data (see the Experimental section), the signal of the NH proton for the syn form is observed at weaker field (12.8 ppm) as compared with the signal of the NH proton of the anti form (8.10 ppm); this is due to the existence of an intramolecular hydrogen bond.

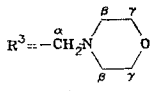
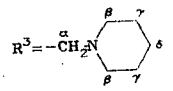
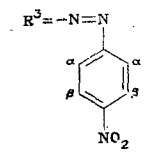
It is apparent from Table 1 that chemical shifts and spin-spin coupling constants (SSCC) that are characteristic for the protons of both the indole and pyridine parts of the molecule are observed in the PMR spectrum of 1H-pyrrolo[2,3-f]isoquinoline (IX).

The signal of a proton that is characteristic for the β-H position of unsubstituted 1H-pyrrolo[2,3-f]isoquinoline is absent in the PMR spectra of aminoalkyl derivatives of pyrroloisoquinoline X-XII, and spin–spin coupling with this proton vanishes; signals of the protons of the corresponding substituents appear in the spectra.

*The m/z values are presented in the scheme; the relative intensities of the ion peaks in percent relative to the maximum peak are given in parentheses.

TABLE 1. Chemical Shifts (δ, ppm) and Spin–Spin Coupling Constants (J, Hz) of Pyrroloisoquinolines in d_6-DMSO at 80°C



Compound	R^2; R^3	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	J, Hz
VII	R^2=—$COOCH_2CH_3$; R^3=H	12,8	4,38 (CH_2); 1,37 (CH_3)	7,28	7,79	7,57	9,18	8,53	8,53	J_{13}=2,3; J_{45}=8,1; $J_{CH_2CH_3}$=7,3
VIII*	R^2=—COOH; R^3=H	12,8	5,3	7,25	7,83	7,60	9,22	8,56	8,56	J_{45}=8,3
IX	R^2=R^3=H	12,3	7,55	6,65	7,80	7,55	9,17	8,49	8,17	J_{12}=2,4; J_{13}=1,9; J_{23}=3,1; J_{14}=J_{58}=J_{68}≤0,5; J_{45}=8,5; J_{78}=5,8
X	R^2=H; R^3=—CH_2—$N(CH_3)_2$	12,2	7,44	3,62 (CH_2); 2,17 (CH_3)	7,87	7,54	9,17	8,49	8,17	J_{12}=1,7; J_{45}=8,8; J_{78}=5,8
XI	R^2=H; 	12,2	7,41	3,70 (CH_2)$^\alpha$; 2,47 (CH_2)$^\beta$; 3,55 (CH_2)$^\gamma$	7,89	7,53	9,13	8,45	8,12	J_{12}=2,0; J_{14}≤0,5; J_{45}=8,6; J_{78}=5,5; $J_{\beta,\gamma}$=4,5.
XII	R^2=H; 	11,5	7,36	3,66 (CH_2)$^\alpha$; 2,36 (CH_2)$^\beta$; 1,42 (CH_2)$^{\gamma=\delta}$	7,88	7,50	9,13	8,44	8,11	J_{12}=2,2; J_{45}=8,5; J_{78}=6,1
XIII*	R^2=H; R^3=—CHO	13,0	8,34	10,04	8,20	7,77	9,23	8,54	8,20	J_{14}≤0,5; J_{45}=8,6; J_{78}=6,1
XIV*	R^2=H; 	12,2	8,58	7,97 (CH_2)$^\alpha$; 8,35 (CH)$^\beta$	8,54	7,84	9,27	8,57	8,20	J_{45}=8,7; J_{78}=5,7; $J_{\alpha,\beta}$=9,0

*Spin–spin coupling with NH is not observed because of rapid NH → ND exchange.

A signal of an aldehyde proton (10.04 ppm) is observed in the spectrum of formyl derivative XIII, and the signal of the 2-H proton is correspondingly shifted 0.8 ppm to weak field. Replacement of the proton in the β position of the pyrrole ring by an aldehyde group is also confirmed by the shift of the signal of the aromatic 4-H proton as a result of the anisotropic effect of the aldehyde group.

The IR spectrum of XIII contains an absorption band at 1660 cm^{-1}, which is characteristic for a conjugated carbonyl group.

The signal of a 3-H proton is absent in the PMR spectrum of azo product XIV, but signals of the AB system of a p-substituted phenyl ring are observed. The signals of the 2-H and 4-H protons are shifted to weak field because of the electronic and anisotropic effects of the azo group.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in dimethyl sulfoxide (DMSO) were recorded with a Varian CFT-20 spectrometer (80 MHz) with tetramethylsilane as the internal

standard. The IR spectra of mineral oil suspensions were obtained with a UR-20 spectrometer. The electronic spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source; the cathode emission current was 1.5 mV, the ionizing-electron energy was 50 eV, and the accelerating voltage was 2 kV.

5-Aminoisoquinoline (III). An 8.7 g (0.05 mole) sample of 5-nitroisoquinoline was dissolved with heating and stirring in 100 ml of isopropyl alcohol, 0.5 g of Raney nickel was added, and 25 g (0.5 mole) of hydrazine hydrate was added in the course of an hour. The mixture was stirred at the boiling point of the solution for 3 h, after which the catalyst was removed by filtration, the solvent was removed by vacuum distillation, and the residue was recrystallized from chloroform–petroleum ether (1:1) to give 6.5 g (90%) of light-yellow crystals with mp 127-128°C (mp 128°C [6]).

Pyruvic Acid 5-Isoquinolylhydrazone (VI). A 9.8-g (0.12 mole) sample of sodium acetate and 4.8 g (0.055 mole) of pyruvic acid in 5 ml of isopropyl alcohol were added with stirring to a solution of 11.5 g (0.05 mole) of the hydrochloride of 5-isoquinolylhydrazine (IV) in 100 ml of water, and the mixture was allowed to stand at 20°C for 18 h. The precipitate was removed by filtration, washed with water, dried, and recrystallized from DMF to give 10.4 g (92%) of a product with mp 194-195°C (mp 193-194°C [2]).

Ethyl Pyruvate 5-Isoquinolylhydrazone (V). A 5.7-g (0.05 mole) sample of ethyl pyruvate was added to a solution of 7.9 g (0.05 mole) of 5-isoquinolylhydrazine (IV) in 150 ml of benzene, and the mixture was maintained at 50°C for 1 h. The solvent was removed by vacuum distillation to give hydrazone V in the form of a mixture of syn and anti isomers, which were separated with a column packed with silica gel (elution with chloroform) to give 1.56 g (14.3%) of the syn form, with mp 114-115°C, and 9.34 g (85.7%) of the anti form with mp 123-124°C (mp 123-124°C [2]). PMR spectrum, δ (in $CDCl_3$): syn isomer: 12.8 (NH); 2.22 (CH_3); 4.33, 1.39 (CH_2–CH_3), $J_{CH_2-CH_3}$ = 7.2 Hz; anti isomer: 8.1 (NH); 2.25 (CH_3); 4.34, 1.40 (CH_2–CH_3), $J_{CH_2-CH_3}$ = 7.1 Hz. IR spectrum (in CCl_4): syn isomer: 1685 (C=O) and 3275 cm^{-1} (NH); anti isomer: 1720 (C=O) and 3390 cm^{-1} (NH).

Ethyl 1H-Pyrrolo[2,3-f]isoquinoline-2-carboxylate (VII). A 1.28-g (5 mmole) sample of hydrazone V was added to 12.8 g of ethyl polyphosphate, and the mixture was heated to 140°C and maintained at this temperature for 30 min. It was then cooled and poured over ice, and the pH of the medium was brought up to six with ammonium hydroxide. The precipitate was removed by filtration, washed with water, and dried to give 0.93 g (74%) of a product with mp 205-206°C (from alcohol). Found: C 69.7; H 5.1; N 11.3%. $C_{14}H_{12}N_2O_2$. Calculated %: C 70.0; H 5.0; N 11.7%.

1H-Pyrrolo[2,3-f]isoquinoline-2-carboxylic Acid (VIII). A) A mixture of 6.9 g (0.03 mole) of hydrazone VI, 51 ml of glacial acetic acid, and 17 ml of concentrated sulfuric acid was refluxed for 10 min, after which it was cooled and poured into 300 ml of water. The precipitate was removed by filtration, washed successively with sodium carbonate solution and water until the washwater was neutral, and dried to give 6.2 g (98%) of a product with mp 282-283°C (dec., from alcohol). Found: C 62.2; H 4.3; N 12.2%. $C_{12}H_8N_2O_2 \cdot H_2O$. Calculated: C 62.6; H 4.4; N 12.2%.

B) A mixture of 4.8 g (0.02 mole) of ester VII and 180 ml of 10% sodium hydroxide solution was refluxed for 1.5 h, after which it was cooled and filtered, and the filtrate was acidified to pH 5 with acetic acid. The precipitate was removed by filtration, washed with water, and dried to give 4.1 g (98%) of acid VIII with mp 282-283°C.

1H-Pyrrolo[2,3-f]isoquinoline (IX). A 2.12-g (0.01 mole) sample of acid VIII was heated rapidly to 250-280°C and maintained at this temperature for 10-15 min. The pyrroloisoquinoline was purified with a column (4.5 × 30 cm) packed with aluminum oxide by elution with ether to give 0.67 g (40%) of a product with mp 198-199°C (from benzene) (mp 198-199°C [2]). IR spectrum (in CCl_4): 3485 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 210 (4.48), 267 (4.78), and 294 nm (3.98). Found: C 78.4; H 4.9; N 16.3%. $C_{11}H_8N_2$. Calculated: C 78.6; H 4.8; N 16.7%.

3-N,N-Dimethylaminomethyl-1H-pyrrolo[2,3-f]isoquinoline (X). A) A 1.6-ml sample of glacial acetic acid was added slowly with cooling to 1.36 g (0.01 mole) of a 33% aqueous solution of dimethylamine, after which 0.8 ml of formalin and 0.84 g (5 mmole) of pyrroloisoquinoline IX were added, and the mixture was maintained at 90°C for 1.5 h. It was then

cooled and poured into water, and the aqueous mixture was made alkaline with 10% sodium hydroxide solution. The precipitate was removed by filtration, washed with water, and dried to give 0.61 g (54%) of a product with mp 166-167°C (from benzene). UV spectrum, λ_{max} (log ε): 212.7 (4.12), 268 (4.48), and 299 nm (3.81). Found: C 74.9; H 6.6; N 18.5%. $C_{17}H_{19}N_3$. Calculated %: C 74.7; H 6.7; N 18.7%.

B) A 0.23-g (2.5 mmole) sample of a crystalline Mannich reagent [7] was added to a solution of 0.168 g (1 mmole) of pyrroloisoquinoline IX in 4 ml of absolute ethanol, and the reaction mixture was maintained at 70-75°C for 1.5 h. It was then cooled and poured over ice, and the aqueous mixture was made alkaline with 10% sodium hydroxide solution. The precipitated white crystals were removed by filtration, washed with water, and dried to give 0.23 g (93%) of a product with mp 167-168°C (from benzene).

3-Morpholinomethyl-1H-pyrrolo[2,3-f]isoquinoline (XI). This compound was similarly obtained by method A from 0.84 g (5 mmole) of pyrroloisoquinoline IX and 0.87 g (0.01 mole) of morpholine. Workup gave 0.65 g (49%) of a product with mp 108-109°C (from chloroform–petroleum ether). UV spectrum, λ_{max} (log ε): 2.12 (4.39), 269 (4.58), and 296 nm (4.11). Found: C 71.7; H 6.4; N 15.7%. $C_{16}H_{17}N_3O$. Calculated: C 71.9; H 6.4; N 15.7%.

3-Piperidinomethyl-1H-pyrrolo[2,3-f]isoquinoline (XII). This compound was similarly obtained by method A from 0.84 g (5 mmole) of pyrroloisoquinoline IX and 0.85 g (0.01 mole) of piperidine. Workup gave 0.56 g (42%) of a product with mp 105-106°C (from chloroform–petroleum ether). UV spectrum, λ_{max} (log ε): 214 (4.35), 270 (4.46), and 300 nm (3.82). Found: C 76.9; H 7.3; N 15.6%. $C_{17}H_{19}N_3$. Calculated: C 77.0; H 7.2; N 15.9%.

3-Formyl-1H-pyrrolo[2,3-f]isoquinoline (XIII). A 4.49-g (0.032 mole) sample of phosphorus oxychloride was added slowly to 2.9 g (0.04 mole) of freshly distilled DMF cooled to 0°C, and the mixture was stirred at room temperature for 1 h. A solution of 2.5 g (0.015 mole) of pyrroloisoquinoline IX in 9 ml of DMF was then added dropwise, and the mixture was heated at 90°C for 6 h. It was then cooled and poured over ice, and the aqueous mixture was made alkaline with 10% sodium hydroxide solution. The precipitate was removed by filtration, washed with water, and dried to give 1.19 g (41%) of a product with mp 317-318°C (dec., from alcohol). IR spectrum: 1660 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 204 (4.18), 259.7 (4.66), and 272 nm (4.64). Found: C 73.4; H 4.2; N 14.4%. $C_{12}H_8N_2O$. Calculated: C 73.5; H 4.1; N 14.3%.

3-(4-Nitrophenylazo)-1H-pyrrolo[2,3-f]isoquinoline (XIV). A solution of p-nitrobenzenediazonium chloride (2 mmole) was added slowly with stirring at 5°C to a solution of 0.336 g (2 mmole) of pyrroloisoquinoline IX in 10 ml of dioxane and 10 ml of water while maintaining the pH at 7 by the addition of a 0.1 N solution of sodium hydroxide. At the end of the addition the reaction mixture was allowed to stand at 20°C in the dark for 24 h, after which more (2 mmole) p-nitrobenzenediazonium chloride was added. After 24 h, the red-brown precipitate was removed by filtration, washed with water, and dried to give 0.287 g (45%) of a product with mp 319-320°C (dec., from DMF). IR spectrum (in mineral oil): 1430 (N=N); 1520, 1345, (NO_2); 3140 cm^{-1} (NH). Found: C 64.2; H 3.4; N 21.9%. $C_{17}H_{11}N_5O_2$. Calculated: C 64.4; H 3.5; N 22.1%.

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