PYRROLOQUINOLINES AND PYRROLOISOQUINOLINES.

4.* NUCLEOPHILIC SUBSTITUTION IN THE PYRROLOISOQUINOLINE SERIES

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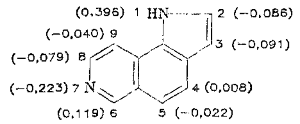
The reactivity of 1H-pyrrolo[2,3-f]isoquinoline with respect to nucleophilic substitution was studied in the case of the Chichibabin reaction and related transformations.

In a continuation of our systematic investigations of unsubstituted 1H-pyrrolo[2,3-f]isoquinoline we decided to study the behavior of the latter in nucleophilic substitution reactions in the case of the Chichibabin reaction and related transformations.

In reviews devoted to the Chichibabin reaction it is noted that isoquinoline is one of the most easily aminated heterocycles and that substitution takes place in the 1 position [2, 3]. The yield of 1-aminoisoquinoline is high when the reaction is carried out in liquid ammonia [4] and dimethylaniline [5]; the use of an inert solvent, viz., toluene, decreases the yield sharply [6].

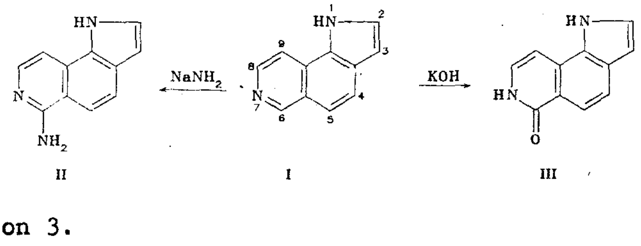
Calculation of the reactivity indexes of 1H-pyrrolo[2,3-f]isoquinoline by the Pariser—Parr—Pople (PPP) method [7] shows that condensation of the isoquinoline system with pyrrole does not have a substantial effect on the electron density distribution in isoquinoline: The highest effective positive charge ($q^+ = 0.119$) is found on the $C_{(6)}$ atom.



The pK_a constant† calculated from the curves of potentiometric titration of a 0.001 M solution of a sample in 50% (by volume) ethanol is 5.68. These parameters lie within the limits considered to be optimal for the Chichibabin reaction.

Liquid ammonia, absolute xylene, and dimethylaniline were used as solvents for the amination of 1H-pyrrolo[2,3-f]isoquinoline (I). When the reaction in liquid ammonia was carried out with excess sodium amide, the formation of amino derivative II was observed only chromatographically. Prolonged refluxing of pyrroloisoquinoline I with excess sodium amide in absolute xylene leads to the formation of 6-amino-1H-pyrrolo[2,3-f]isoquinoline (II) in 55% yield; the starting compound (20%) was also isolated. The use of dimethylaniline as the solvent made it possible to increase the yield of amine II to 90%.

1H,7H-pyrrolo[2,3-f]isoquinol-6-one (III) was isolated when pyrroloisoquinoline I was melted with potassium hydroxide at 260°C. An attempt to obtain the methoxy derivative of the pyrroloisoquinoline by the reaction of the latter with sodium methoxide under various conditions did not lead to the desired result.



II I III

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*See [1] for communication 3.

†We thank I. V. Persianova for determining the pK_a constant.

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TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Found, %			Empirical formula	Calc., %		
				C	H	N		C	H	N
II	231—232 (dec.)	3430 (NH_2), 3190 (NH)	269 (4,84), 310 (3,91)	71,95	4,87	22,71	$C_{11}H_9N_3$	72,12	4,91	22,95
III	304—305 (dec.)	1640 (C=O), 3110 (NH, (pyrrole) 3255 (NH, (pyridine)	206 (3,85), 259 (4,68), 268 (4,68), 296 (3,61), 312 (3,55), 327 (3,71)	71,48	4,39	15,06	$C_{11}H_8N_2O$	71,74	4,34	15,21

TABLE 2. PMR Spectra of II and III in d_6-DMSO at 80°C

Compound	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	J, Hz
II	11,8	7,37	6,55	7,55	7,68	6,30 (NH_2)	—	7,84	7,37	$J_{12}=2{,}4$; $J_{13}=2{,}0$; $J_{23}=3{,}2$; $J_{45}=8{,}8$; $J_{89}=5{,}6$
III	11,7	7,48	6,56	7,55	7,79	—	10,80	6,98	7,19	$J_{12}=2{,}6$; $J_{13}=1{,}8$; $J_{23}=3{,}4$; $J_{45}=8{,}4$; $J_{89}=7{,}0$

The PMR spectrum* of II in DMSO (Table 2) contains a broad signal of protons of an amino group (6.3 ppm) but does not contain the weak-field signal of the 6-H proton. Bands at 3190 and 3430 cm^{-1}, which are characteristic, respectively, for the stretching vibrations of NH and NH_2 groups (see Table 1), are observed in the IR spectrum of this compound. Singlets (10.8 and 11.7 ppm) corresponding to the protons of amido and pyrrole NH groups appear in the PMR spectrum of pyrroloisoquinolone III in DMSO (Table 2); the shift of the proton of the amido NH group depends to a much lesser extent on the solvent (on passing to acetone, $\Delta\delta_{7\text{-}H} \leq 0.4$, whereas $\Delta\delta_{1\text{-}H} = 0.7$ ppm), and this constituted evidence for strong intermolecular H bonding of the 7-H proton, possibly with the formation of a cyclic dimer. Correspondingly, the chemical shifts and spin–spin coupling constants (SSCC) observed in the aromatic part of the molecule are not characteristic for the pyridine part. The IR spectrum of III (Table 1) contains an intense carbamido band at 1640 cm^{-1} and two bands at 3110 and 3255 cm^{-1}, which are due, respectively, to the stretching vibrations of the pyrrole and pyridine NH groups.

The molecular masses of II and III determined by mass spectrometry are in agreement with the calculated values.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in 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 recorded with a UR-20 spectrometer. The electronic spectra of 1-cm-thick layers of solutions of the compounds in ethanol were obtained with a Specord 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 mA, the ionizing-electron energy was 50 eV, and the accelerating voltage was 2 kV. A G 2222B glass electrode was used as the standard electrode in the determination of the basicity constant (pK_a); the reference electrode was a K 4112 calomel electrode, and the RNM-26 pH meter was tuned with respect to aqueous buffer solutions. The pK_a value was calculated over the 20-70% neutralization region. The accuracy in the determination was ±0.06 log pK_a.

6-Amino-1H-pyrrolo[2,3-f]isoquinoline (II). A) A solution of 1.5 g (0.009 mole) of pyrroloisoquinoline I in 45 ml of absolute xylene was added dropwise to a heated (to 120°C) suspension of 1.25 g (0.032 mole) of sodium amide in absolute xylene, after which the temperature was raised to 135-140°C, and the mixture was maintained under these conditions for 25 h. It was then cooled and hydrolyzed with 30 ml of water. The precipitate was removed by filtration, the organic layer was separated from the aqueous layer, and the latter was extracted with ethyl acetate. The mixture of crystals and the oil obtained after removal

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*We thank L. N. Kurkovskaya for interpreting the PMR spectra.

of the xylene and ethyl acetate by distillation was separated with a chromatographic column packed with aluminum oxide [elution with ether and ether—isopropyl alcohol (3:1)] to give 0.9 g (55%) of 6-amino derivative II and 0.3 g (20%) of pyrroloisoquinoline I.

B) A 1.36-g (0.035 mole) sample of sodium amide was added with stirring to a heated (to 100°C) solution of 1.68 g (0.01 mole) of pyrroloisoquinoline I in 25 ml of dimethylaniline, and the mixture was stirred at 135-140°C for 1.5 h. It was then cooled and hydrolyzed with 30 ml of water, and the precipitate was separated, washed with water and benzene, and dried to give 1.65 g (90%) of product.

1H,7H-Pyrrolo[2,3-f]isoquinol-6-one (III). A mixture of 1.68 g (0.01 mole) of pyrroloisoquinoline I and 5.6 g (0.1 mole) of potassium hydroxide was fused at 250-260°C for 6 h, after which it was cooled and treated with 25 ml of water. The aqueous mixture was neutralized with hydrochloric acid, and the precipitate was removed by filtration, washed with water, and dried to give 0.99 g (54%) of product.

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SYNTHESIS OF THIIRANE DERIVATIVES OF DECAHYDROQUINOLINE BY THE REACTION OF α,β-EPOXY ALCOHOLS WITH THIOUREA

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The reaction of α,β-epoxy alcohols of the decahydroquinoline series with thiourea in water in the presence of sulfuric acid leads to 1-alkyl-, 1,2-dimethyl-, and 1,2,2-trimethyl-4-thiiranyl-trans-decahydro-4-quinolol carbamates, the structures of which were established by spectral methods.

It is known that thiiranes are formed in the reaction of epoxides with thiourea, in which the formation of the thiirane ring from the oxirane ring is facilitated as the pH of the medium, the temperature, and the polarity of the solvent are increased [1]. The maximum yields of thiiranes are obtained when the reaction is carried out in aqueous solution with catalysis by acids [2]. In contrast to epoxides, thiirane derivatives could not heretofore be obtained in the reaction of α,β-epoxy alcohols with thiourea [3]. We used the previously synthesized [4] 1-alkyl-, 1,2-dimethyl-, and 1,2,2-trimethyl-4-oxiranyl-trans-decahydro-4-quinolols (I-VIII) as the starting compounds. As we demonstrated in [5], the reaction of epoxy alcohols I-VIII with thiourea in aqueous solution, which is accompanied by an increase in the pH of the medium, gives rise to migration of the epoxide ring to give the corresponding spirooxiranyloxymethyl-trans-decahydroquinolines, which were not altered further under the influence of thiourea. In the reaction of epoxy alcohols I-VIII with

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