PYRROLOQUINOLINES

I. SYNTHESIS OF 1H-PYRROLO[3,2-h]QUINOLINE AND SOME OF ITS HOMOLOGS

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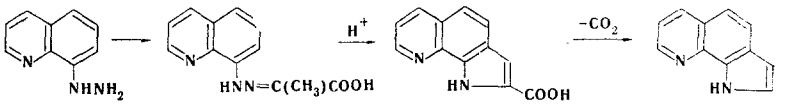
Preparative methods for the synthesis of 1H-pyrrolo[3,2-h]quinoline and its 2-methyl- and 2,3-dimethyl-substituted derivatives are proposed.

In order to search for new biologically active preparations we began a systematic study of pyrroloquinolines and pyrroloisoquinolines for which no practicable preparative methods were available.

An examination of the possible methods for the synthesis of 1H-pyrrolo[3,2-h]quinoline (III) and its 2-methyl- and 2,3-dimethyl-substituted derivatives (V and VI) leads to a scheme based on the Fischer reaction:



I II III

Pyruvic acid 8-quinolylhydrazone (I) was obtained as a mixture of the syn and anti isomers by refluxing hydrated 8-quinolylhydrazine hydrochloride with pyruvic acid and ammonium acetate in isopropyl alcohol.

Polyphosphoric acid (PPA), concentrated hydrochloric acid, and a mixture of glacial acetic and sulfuric acids are suitable as catalysts for cyclization of hydrazone I. 1H-Pyrrolo[3,2-h]quinoline-2-carboxylic acid (II) was obtained in quantitative yield by cyclization of hydrazone I in glacial acetic acid–sulfuric acid (3:1). In earlier papers [1] it was noted that this hydrazone does not undergo indolization under acid-catalysis conditions.

Unsubstituted 1H-pyrrolo[3,2-h]quinoline (III) is formed in 85% yield by thermal decarboxylation of acid II. Compound III was obtained for the first time in 1891 in very low yield [1]. Acetone 8-quinolylhydrazone is cyclized in better yield (87%) in PPA. Other catalysts lead to resinification of the reaction products. In an earlier paper [2] it was proposed that this hydrazone be cyclized by prolonged heating in the presence of $ZnCl_2$ with subsequent decomposition of the resulting complex, but this reduces the yield of 2-methyl-1H-pyrrolo-[3,2-h]quinoline (V).

2,3-Dimethyl-[1H]-pyrrolo[3,2-h]quinoline (VI) was previously obtained from methyl ethyl ketone 8-quinolylhydrazone by refluxing for 3 h in a mixture of acetic and concentrated hydrochloric acid [3]. We did away with the step involving the isolation of the hydrazone, and quinoline VI was easily obtained in 89% yield by brief refluxing of methyl ethyl ketone with hydrated 8-quinolylhydrazine hydrochloride in alcohol–hydrochloric acid. Pyrroloquinolines III and V either were not obtained by this method or were obtained in low yields.

Two intense absorption bands at 215–223 and 268–277 nm are observed in the UV spectra of the pyrroloquinolines (Table 1). An intense absorption band at 268–277 nm is not observed in the UV spectra of either indole or quinoline [4, 5]. An absorption band at 3220–3230 cm^{-1}, which is related to the stretching vibrations of the NH group, is present in the IR spectra.

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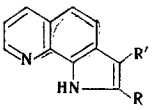
TABLE 1



Compound	R	R′	mp, °C (from alcohol)	UV spectra (in 95% alcohol)		IR spectra, ν, cm^{-1} (in mineral oil)		pK_a	
				λ_{max}, nm	lg ε	NH	ring	in CH_3NO_2	in H_2O
III	H	H	99,5—100,5 (94—96)[1]	223 277	4,53 4,62	3220	1610 1465 1390	11,21	4,73
V	CH_3	H	154—155 (155—157)[2]	217 272	4,45 4,61	3220	1580 1465 1330	11,51	4,97
VI	CH_3	CH_3	157—158 (156—158)[3]	215 268	4,22 4,60	3220	1570 1465 1375	11,88	5,29

TABLE 2. PMR Spectra of Pyrroloquinolines

Compound	Solvent	δ, ppm								J, Hz
		1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	
III	d_6-DMSO	12,16	7,37	6,57	7,69	7,37	8,21	7,33	8,73	$J_{1,2}=2,8$; $J_{1,3}=2,0$; $J_{2,3}=2,9$; $J_{4,5}=8,0$; $J_{6,7}=8,0$; $J_{6,8}=1,6$; $J_{7,8}=4,0$
Va	d_6-DMSO	11,94	—	6,25	7,57	7,33	8,20	7,30	8,73	$J_{1,3}=0,5$; $J_{3\text{-H, CH}_3}=1,0$; $J_{4,5}=8,0$; $J_{6,7}=8,0$; $J_{6,8}=1,6$; $J_{7,8}=4,2$
VI[b]	CCl_4 (acetone for the CH_3 group)	10,87	—	—	7,51	7,37	8,13	7,19	8,66	$J_{4,5}=8,4$; $J_{6,7}=8,2$; $J_{6,8}=1,6$; $J_{7,8}=4,2$

[a] $\delta_{2\text{-}CH_3}$ 2.44 ppm. [b] $\delta_{2\text{-}CH_3}$ 2.18, $\delta_{3\text{-}CH_3}$ 2.35 ppm.

A comparison of the pK_a values of III, V, and VI with the pK_a value of quinoline (11.40 in CH_3NO_2; 4.90 in H_2O) [6] indicates a slight change in the basicity of the nitrogen atom of the quinoline ring on condensation with the pyrrole ring, and the introduction of methyl groups in the latter increases the basicity somewhat (Table 1).

The signals of the 1-H, 2-H, and 3-H protons in the PMR spectra of the pyrroloquinolines (Table 2) are close to the signals of the corresponding protons in the spectrum of 6,7-benzindole. As compared with the latter, the heteroatom of the pyridine ring has only a slight effect on the magnitude of the chemical shifts of the pyrrole ring protons [7]. The signals of the 4- and 5-H protons were assigned in analogy with 6,7-benzindole. The sequence of the chemical shifts in the six-membered heterocyclic ring is in agreement with the sequence determined for pyridine [8].

The molecular weights of III, V, and VI determined by mass spectrometry are in agreement with the calculated values. The mass spectrum of III contains an intense [M^+] 168 molecular ion peak, the fragmentation of which is accompanied by elimination of a hydrogen atom to give a fragment ion with m/e 167 and ejection of an H_2CN particle to give an intense peak of a fragment ion with m/e 140. The latter ion can also be formed by elimination of an HCN particle from the ion with m/e 167. The peak with m/e 140 forms an ion with mass 114 by ejection of a CN particle. The ejections of H_2CN and CN particles from the corresponding fragment ions were confirmed by metastable transitions. The mass spectrum also contains a peak with mass 128, which is formed by fragmentation of the molecular ion with cleavage of the C=N and C–C bonds and removal of C_2NH_3.

The biological activity of III and VI was investigated in the Chemotherapy Division of the S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute by senior scientific co-worker T. V. Zykova under the supervision of Corresponding Member of the Academy of Medical Sciences of the USSR Professor G. N. Pershin. Compounds III and VI have moderate tuberculostatic activity in vitro with respect to strain H-37Rv in doses of 4 and 8 μg/ml, respectively.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of 1-cm thick layers of alcohol solutions of the compounds were obtained with a Specord spectrophotometer. The pK_a values (in CH_3NO_2) were determined by potentiometric titration with glass and calomel electrodes [6]. The pK_a values in H_2O were calculated from the equation for aza heterocycles [6]. The PMR spectra of d_6-DMSO and CCl_4 solutions of the compounds were recorded with an HA-100D spectrometer with hexamethyldisiloxane as the internal standard.

The mass spectra were recorded with an MKh-1303 spectrometer with a modified system for introduction of the samples into the ion source and a recording system at an ionizing-electron energy of 50 eV, a cathode emission current of 1.5 mA, and an accelerating voltage of 2 kV.

Pyruvic Acid 8-Quinolylhydrazone (I). A solution of 21 g (0.24 mole) of sodium acetate in 100 ml of water and 8.8 g (0.1 mole) of pyruvic acid was added all at once to a solution of 25.2 g (0.1 mole) of 8-quinolylhydrazine hydrochloride hydrate [9] in 150 ml of isopropyl alcohol, after which the mixture was refluxed for 40 min. It was then cooled, and the resulting orange crystals were removed by filtration to give 19.9 g (87%) of a mixture of the syn- and anti-hydrazones of I with mp 174.5-175°. Found %: N 18.40. $C_{12}H_{11}N_3O_2$. Calculated %: N 18.33.

1H-Pyrrolo[3,2-h]quinoline-2-carboxylic Acid (II). A 22.9-g (0.1 mole) sample of hydrazone I was refluxed for 40 min in a mixture of 210 ml of glacial acetic and 70 ml of concentrated sulfuric acid, after which the solution was poured into 1 liter of cold water, and the grayish-yellow precipitate was removed by filtration, washed with sodium carbonate solution and water to neutrality, and dried to give II with mp 297-299° (dec., from alcohol) in quantitative yield. Found %: C 62.5; H 4.3; N 12.5. $C_{12}H_8N_2O_2 \cdot H_2O$. Calculated %: C 62.6; H 4.4; N 12.2. Acid II was subsequently decarboxylated without additional purification.

1H-Pyrrolo[3,2-h]quinoline (III). An 11.5-g (0.05 mole) sample of acid II was heated rapidly to 240-280° and held at this temperature for 20 min. Pyrroloquinoline III was purified by chromatography with a column filled with Al_2O_3 (elution with ether) to give 7.1 g (84%) of a product with mp 99.5-100.5° (from alcohol). Found %: N 16.6. $C_{11}H_8N_2$. Calculated %: N 16.7. The hydrochloride had mp 258-259° (from alcohol). A rose coloration was produced on treatment of III with a hot solution of Erlich's reagent.

2-Methyl-1H-pyrrolo[3,2-h]quinoline (V). A solution of 19.9 g (0.1 mole) of acetone 8-quinolylhydrazone (IV) [3] in 180 ml of polyphosphoric acid (PPA) was heated to 120°, during which the temperature rose spontaneously to 150°. The mixture was held at 150° for 1 h, after which 200 ml of 40% sodium hydroxide solution was added, and the mixture was allowed to stand overnight. The resulting light-green precipitate was removed by filtration, washed with water, and dried. The product was purified by column chromatography with aluminum oxide (elution with ether) to give 15.85 g (87%) of a substance with mp 154-155° (from alcohol). Found %: N 15.2. $C_{12}H_{10}N_2$. Calculated %: N 15.4. The hydrochloride had mp 257-258° (from alcohol–ether). A rose coloration was produced when V was treated with a hot solution of Erlich's reagent.

2,3-Dimethyl-1H-pyrrolo[3,2-h]quinoline (VI). A 1.5-g (0.02 mole) sample of methyl ethyl ketone was added to a mixture of 5 g (0.02 mole) of 8-quinolylhydrazine hydrochloride hydrate, 40 ml of alcohol, and 30 ml of concentrated hydrochloric acid, after which the mixture was refluxed for 30 min and poured into 200 ml of 10% ammonium hydroxide. The resulting yellow crystals were removed by filtration, washed with water, and dried to give 3.5 g (89%) of a product with mp 157-158° (from alcohol). Found %: N 14.5. $C_{13}H_{12}N_2$. Calculated %: N 14.3. The hydrochloride had mp 307-309° (from water). No coloration was produced when VI was treated with Erlich's reagent.

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SYNTHESIS OF NAPHTHYRIDINES

I. NEW METHOD FOR THE PREPARATION OF 2,3-DIHYDROBENZO[h][1,6]NAPHTHYRIDIN-4-(1H)-ONES

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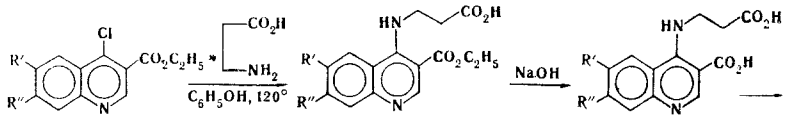
A new method for the synthesis of 2,3-dihydrobenzo[h][1,6]naphthyridin-4-(1H)-ones, which consists in cyclization of 4-(β-carboxyethylamino)quinoline-3-carboxylic acids by heating them in acetic anhydride in the presence of potassium acetate, is proposed.

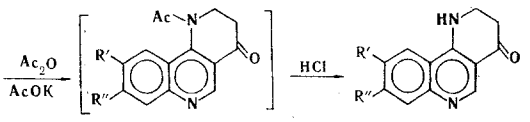
In the development of our research on the synthesis of heterocyclic ketones by cyclization of the corresponding dicarboxylic acids by heating them with acetic anhydride in the presence of potassium acetate [1-3] we accomplished the synthesis of 2,3-dihydrobenzo[h][1,6]naphthyridin-4-(1H)-ones (Va-c).

The only described representatives of the benzo[h][1,6]naphthyridin-4-ones – 2,3-dihydro-8,9-dimethoxybenzo[h][1,6]naphthyridin-4(1H)-one – was obtained in 41% yield by cyclization of 4-(β-carboxyethylamino)-6,7-dimethoxyquinoline [4] – the product of multistep synthesis by the method in [4, 5] – in polyphosphoric acid (PPA).

We synthesized the same compound on the basis of the reaction of the more accessible ethyl 4-chloroquinoline-3-carboxylates (Ia, b) [6-8] with β-alanine via the scheme



I a-c II a-c III a-c



IV a-c V a-c

I-V a R′=R″=H; b R′=H, R″=Cl; c R′=R″=OCH_3

The 4-(β-carboxyethylamino)quinoline-3-carboxylates (IIa-c) formed in the reaction of Ia-c with β-alanine were hydrolyzed and converted to dicarboxylic acids IIIa-c, which were then subjected to cyclization to N-acetyl derivatives IVa-c, which in turn were hydrolyzed, without isolation, to Va-c. We were able to purify Vc only in the form of its hydrochloride, inasmuch as base Vc is a highly insoluble compound.

The presence of an oxo group in Va-c is confirmed by the IR spectra ($\nu_{C=O}$ 1663-1676 cm^{-1}) and also by the formation of hydrazones (in the case of Va).

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