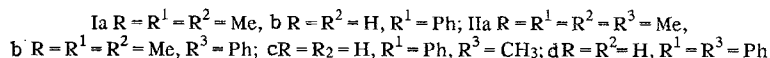
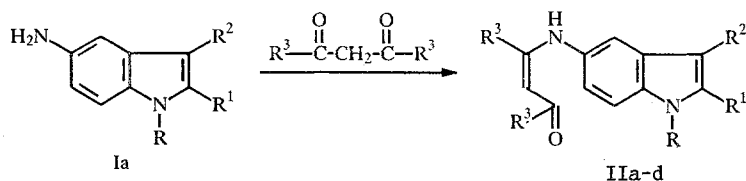


PYRROLOQUINOLINES

S. A. Yamashkin

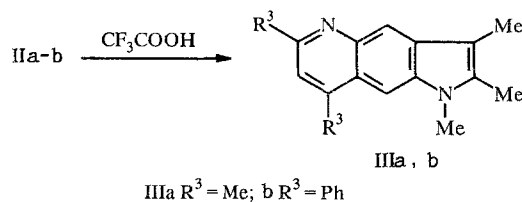
The Combes reaction using 1,2,3-trimethyl- and 2-phenyl-5-aminoindoles gave the corresponding pyrroloquinolines with N-CH₃ and 2-C₆H₅ groups in the pyrrole ring. General patterns in the spectral characteristics of the [2,3-g]- and [3,2-f]pyrroloquinolines that were found in an analysis of published data enabled unambiguous determination of the structure of the newly obtained compounds.

Pyrroloquinolines are known as compounds with pronounced biological activity. The present paper is a continuation of investigations carried out in this field [1]. The possibility was studied of the use of 1,2,3-trimethyl- and 2-phenyl-5-aminoindoles for the preparation of N-methyl- and 2-phenyl-substituted pyrroloquinolines. The condensation of these amines with acetylacetone and dibenzoylmethane affords the corresponding enamino ketones.



In the PMR spectra, the presence of peaks of the imine group NH (13.02, 12.43, and 12.99 ppm) and a vinyl-proton peak (5.85, 6.10, and 5.18 ppm) for compounds IIb, IIc, and IId, respectively, indicated their enamino ketone structure.

During cyclization of the obtained enamino ketones in the presence of acid, we would expect the formation of pyrroloquinolines with linear or angular linkage of rings (occurrence of closure of the pyridine ring at the 6 or 4 position of indole, respectively). However, it was determined that, like enamines without the N-CH₃ group [2], compounds IIa and IIb cyclize to linear pyrroloquinolines III during heating in trifluoroacetic acid.



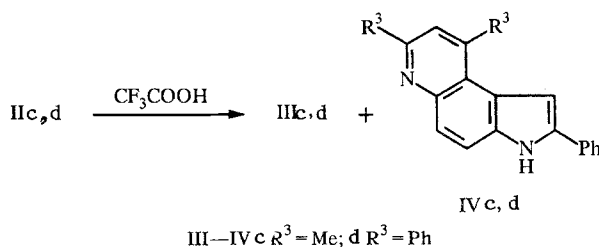
Such linkage of the rings in compound IIIa is supported by the presence of three singlet peaks of protons of the benzene and pyridine rings in the PMR spectrum. For compounds IIIb, in the PMR spectrum the benzene-ring protons could not be detected because of the superposition of peaks of protons of two phenyl groups. But the criterion for evaluation of linearity in this case is the chemical shift of the 3-CH₃ group. In the alternative angular structure, the peak of these protons should be shifted by more than 1 ppm toward stronger fields. The electronic spectra of pyrroloquinolines III also support a linear structure (see Table 1).

TABLE 1. Spectral Characteristics of Isomeric Pyrroloquinolines III and IV

Com- pound	R								Chem. shifts δ ,			UV spectrum: λ_{\max} (log ϵ), nm
	1	2	3	4	5	6	7	8	4- \rightarrow 5-H	1-H	3-H	
IIIa	Me	Me	Me	H	H	Me	H	Me	6,70; 7,08	3,42 (Me)	2,17 (Me)	230(4,41); 280(4,47); 348(4,32)
b	Me	Me	Me	H	H	Ph	H	Ph		3,42 (Me)	2,17	240(4,45); 310(4,61); 370(4,40)
c	H	Ph	H	H	H	Me	H	Me		11,92	7,20	260(4,36); 285(4,50); 310(4,42); 370(4,13)
d	H	Ph	H	H	H	Ph	H	Ph		11,70	7,15	285(4,50); 310(4,42); 370(4,13)
e	H	Me	Me	H	H	Me	H	Me	7,80; 7,65	10,66	2,19	225(4,49); 266(4,81); 340(4,03); 375(3,64)
f	H	Me	Me	H	H	Ph	H	Ph		10,53	2,28	246(4,61); 295(4,77); 358(4,08); 400(3,56)
g	H	Me	H	H	H	Ph	H	Ph		10,70	6,20	243(4,58); 290(4,82); 355(4,14); 390(3,77)
h	H	Me	Me	H	H	Me	H	Ph		10,64		235(4,61); 272(4,76); 344(4,02); 385(3,68)
i	H	Me	Me	H	H	O	H	Me	7,50; 7,23	10,76	2,15	210(4,24); 237(4,62); 287(4,17); 350(4,20)
j	H	Me	Me	H	H	H	NO ₂	H	8,13; 8,10	11,30		233(4,22); 248(4,37); 323(4,29); 365(3,74); 473(3,76)
k	H	H	H	H	H	Me	H	Me	8,33; 7,88	10,95	6,61	
IVc	H	Ph	H	H	H	Me	H	Me		12,30	7,31	228(4,37); 265(4,26); 305(4,36); 350(4,13)
d	H	Ph	H	H	H	Ph	H	Ph		12,27	5,69	245(4,48); 320(4,90); 350(4,30)
e ¹	H	Me	H	H	H	Me	H	Me	7,64; 7,48	11,41	6,71	222(4,49); 260(4,44); 334(3,98)
e ²	H	Me	Me	H	Me	Me	H	Me	7,46	10,96		232(4,56); 274(4,36); 345(3,85)
f	H	Me	Me	H	H	Ph	H	Ph		11,17	1,20	250(4,53); 305(4,65); 360(3,91)
f ¹	H	Me	Me	H	Me	Ph	H	Ph		11,02	1,02	263(4,38); 310(4,59); 346(3,82)
g	H	Me	H	H	H	Ph	H	Ph		11,18	5,19	242(4,49); 394(4,72); 346(4,00)
i	H	Me	Me	H	H	O	H	Me	7,40; 7,05	11,25	2,28	
j	H	Me	Me	H	H	H	NO ₂	H	7,99; 7,73	11,66		225(4,16); 256(4,34); 319(3,85); 380(3,53); 447(4,76)
k	H	H	H	H	H	H	H	H	7,80; 7,68	11,60	7,03	

Compounds III were also obtained by methylation of the corresponding known 1H-pyrroloquinolines. A methyl group was readily introduced by dimethyl sulfate in acetone in the presence of KOH.

In the presence of trifluoroacetic acid, enamino ketones IIc and II d were converted to a mixture of pyrroloquinolines (III-IVc and IVd with angular and linear linkage of rings in a IIIc:IVc ratio of 1:4 according to the integrated intensity of peaks of N-H protons in the PMR spectrum of the reaction mixture), III d:IV d ratio 1:7 (preparatively on aluminum oxide).

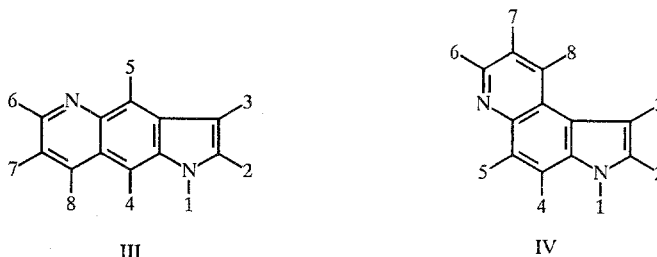


Approximately the same ratio of the corresponding isomeric pyrroloquinolines was also formed under similar conditions from enamino ketones with a 2-CH₃ group [2].

The difference of the isomer pairs in the PMR spectra was in the chemical shift of the β -proton of the pyrrole ring (7.15 ppm for III d and 5.69 ppm for IV d) because of peri interaction in the angular systems. The electronic spectra of isomers III-IV c and IV d agree with similar structures described previously (see Table 1).

Thus, aminoindoles II a and II b can be used for preparation of the corresponding pyrroloquinolines. The methyl group at the pyrrole nitrogen atom and the phenyl group in the 2 position in 5-aminoindoles do not exert a significant effect on the direction of closure of the pyridine ring by the Combes reaction.

LINKAGE OF RINGS IN PYRROLOQUINOLINES [1, 2, 3, 4, 5, 6]



Such numbering of the atoms in compounds III and IV is accepted for convenience of consideration.

The question of the structure of pyrroloquinolines, i.e., the linkage of the rings, is mainly solved by PMR and UV spectroscopy and mass spectrometry. Here the PMR spectra are the most informative. For isomers IV (Table 1), the peaks of the 4-H and 5-H protons of the benzene ring were manifested as two doublets of the AB system ($J = 9$ Hz), unlike in the case of spectra of linear isomers of type III, where they gave two peaks, somewhat shifted to weak fields. However, the criterion for evaluation of the linearity and angularity according to the 4- and 5-H AB system is applicable only for pyrroloquinolines with aliphatic substituents. In the case of compounds with phenyl groups, it is difficult to detect these peaks. The difference of the linear isomers from angular ones in this case was manifested in the difference of the chemical shifts of β -protons (3-H and 3-CH₃) of the pyrrole ring. In the case of structures IV, because of peri interaction with the γ -pyridine substituent, the β -protons underwent screening or descreening in relation to the nature of the group. Thus, the phenyl group contributed to a strong-field shift, but the methyl group, on the other hand, shifted the peaks to weak fields. In isomers III, the peaks of the analogous protons have virtually the same chemical shifts as in the corresponding indole structures.

Within one pair of isomers, the linear isomer could be distinguished from the angular one according to the chemical shift of the 1-H proton, which was manifested in weaker fields in the case of structures IV than in the case of compounds III.

In relation to structure, the UV spectra of the pyrroloquinolines were characterized by three or four absorption bands. The difference of isomers III from IV was manifested in the different intensity of the two short-wave absorption bands, i.e., 220-260 and 260-310 nm. In linear systems, the band at 260-310 nm was always stronger than the band at 220-260 nm, unlike in the case of angular ones, where everything was the opposite.

TABLE 2

Compound	W_{M^+}	$W_{M^{++}}$	$\frac{J_{[M-H]^+}}{J_{M^+}}$	$\frac{J_{[M-H]^{++}}}{J_{M^{++}}}$	$\frac{J_{[M-Me]^+}}{J_{M^+}}$	$\frac{J_{[M-Me]^{++}}}{J_{M^{++}}}$
IIIh	80,0	40,0	0,24	0,22	0,01	0,43
IVh	86,0	19,0	0,21	0,32	0,04	2,40
IIIg	75,0	18,0	0,27	0,22	0,05	1,15
IVg	64,5	11,2	0,28	0,26	0,14	2,90

The UV spectra of compounds III with phenyl substituents were characterized by the appearance of long-wave absorption in the form of a shoulder, unlike in the case of angular isomer systems. With decreasing steric requirements of the peri substituents, the differences in the spectra of compounds III and IV virtually disappeared. The pyrroloquinolines had high electron-impact resistance. As a rule, the molecular-ion peak was the strongest peak in the mass spectra of all the investigated compounds. The values of W_M changed in the range 45-905, with an increase of the number of substituting methyl groups decreasing the stability of the molecule toward electron impact and with phenyl substituents increasing it. The decomposition of both linear and angular pyrroloquinolines under electron impact consisted in elimination (characteristic of compounds containing a mono- or polymethylated indole fragment) of H^{\cdot} and CH_3 radicals accompanied by rearrangement to a quinoline structure. Analogous decomposition was also undergone by doubly charged molecular ions with formation of $[M-H]^{++}$ and $[M-CH_3]^{++}$ ions. It is precisely in this state of the decomposition that we observed some difference of the linear pyrroloquinolines from angular ones, consisting in different values of W_M and different intensities of peaks of fragment ions. Table 2 gives values of W_{M^+} and $W_{M^{++}}$ and the ratio of the intensities of peaks of characteristic ions to molecular ones for two isomer pairs.

As is evident from Table 2, for angular pyrroloquinolines of type IV the value of $J_{[M-CH_3]^{++}}/J_{M^+}$ is always higher than for linear IV. Correspondingly, $W_{M^{++}}$ is higher for III than for IV. These differences can serve as an additional criterion for evaluation of the linkage of the rings of pyrroloquinolines.

EXPERIMENTAL

The UV spectra were measured with a Specord instrument in ethanol. The PMR spectra were recorded on Bruker (200 MHz) and BS-467 (60 MHz) instruments in DMSO- D_6 with respect to TMS. The course of the reaction was monitored by thin-layer chromatography. The adsorbent for purification of the compounds was Al_2O_3 (neutral with Brockmann activity II), and the solvent was chloroform.

The data of elemental analysis for C and H corresponded to the calculated data. The PMR and UV spectra for compounds IIIa-d, IVc, and IVd are given in Table 1.

1,3-Diphenyl-3-(1,2,3-trimethyl-5-indolylamino)-2-propen-1-one (IIb, $C_{26}H_{24}N_2O$). A mixture of 0.65 g (3.5 mmoles) of 1,2,3-trimethyl-5-nitroindole and 4 ml (70 mmoles) of hydrazine hydrate in 50 ml of methanol with a catalytic amount of active Raney nickel was boiled for 1.5 h. The hot solution was filtered, and methanol and excess hydrazine hydrate were evaporated from the filtrate. To the obtained oily residue was added 0.9 g (4 mmoles) of dibenzoylmethane, and the whole was heated for 2 h at 160-165°C. The obtained compound IIb was purified preparatively in a thick layer of Al_2O_3 . The yield was 300 mg (23%), and the mp was 183-185°C. UV spectrum, λ_{max} (log ϵ): 262 (4.36); 293 (4.06); 304 (4.26) nm. PMR spectrum (CCl_4): 2.09 (3H, s, 3- CH_3); 2.20 (3H, s, 2- CH_3); 3.48 (3H, s, 1- CH_3); 5.85 (1H, s, H_{vin}); 6.40-8.00 (13H, m, H_{arom}); 13.02 ppm (1H, s, N- H_{imine}).

1,3-Diphenyl-3-(2-phenyl-5-indolylamino)-2-propen-1-one (IIc, $C_{29}H_{22}N_2O$). A mixture of 0.6 g (2.8 mmoles) of 2-phenyl-5-aminoindole and 0.94 g (4 mmoles) of dibenzylmethane was heated for 1 h at 170-175°C. The obtained substance was purified on a column with Al_2O_3 . The yield was 1.084 g (59%), and the mp was 226-228°C. UV spectrum, λ_{max} (log ϵ): 245 (4.56); 315 (4.54); 390 nm (4.50). PMR spectrum: 6.10 (1H, s, H_{vin}); 6.68-7.98 (19H, m, H_{arom}); 11.58 (1H, s, N- H_{ind}); 12.99 ppm (1H, s, N- H_{imine}).

4-(2-Phenyl-5-indolylamino)-3-penten-2-one (IIc, C₁₉H₁₈N₂O). A mixture of 0.75 g (3 mmoles) of 2-phenyl-5-aminoindole and 5 g (10 mmoles) of acetylacetone was boiled for 1.5 h. The excess acetylacetone was evaporated in vacuo. The obtained compound was purified on a column with Al₂O₃ in the benzene-ethyl acetate system, 2:1. The yield was 0.8 g (80%), and the mp was 104-106°C. UV spectrum: λ_{max} (log ε): 230 (4.0); 330 nm (4.33). PMR spectrum: 1.92 (3H, s, CH); 1.96 (3H, s, CH₃), 5.18 (1H, s, H_{vin}); 6.87-7.83 (9H, m, H_{arom}), 11.67 (1H, s, N-H_{ind}); 12.43 ppm (1H, s, N-H_{imine}).

1,2,3,6,8-Pentamethylpyrrolo[2,3-g]quinoline (IIIa, C₁₆H₁₈N₂). This compound was obtained from 1,2,3-trimethyl-5-nitroindole by reduction similarly to IIb with subsequent condensation of the obtained aminoindole with acetylacetone, as in the case of IIc. To the reaction mixture obtained after evaporation of acetylacetone was added 5 ml of trifluoroacetic acid, and the whole was boiled for 1 h. The cooled mixture was poured into a dilute (10%) aqueous ammonia solution. The precipitate was filtered and dried in air. The obtained pyrroloquinoline was purified preparatively in a thick layer of Al₂O₃. From 0.65 g (3.5 mmoles) of nitroindole was obtained 130 mg (16%) of pyrroloquinoline IIIa with mp 163-164°C.

1,2,3-Trimethyl-6,8-diphenylpyrrolo[2,3-g]quinoline (IIIb, C₂₆H₂₂N₂). This compound was obtained by boiling 0.15 g (0.4 mmole) of enamino ketone IIb in trifluoroacetic acid, and the yield of pyrroloquinoline IIIb was 90 mg (90%). It was recovered similarly to the preceding compound. The mp was 178°C.

2,6,8-Triphenylpyrrolo[2,3-g]quinoline (IIIc, C₂₉H₂₀N₂) and 2,7,9-Triphenylpyrrolo[3,2-f]quinoline (IVd, C₂₉H₂₀N₂). These compounds were similarly obtained from 0.35 g (0.9 mmole) of compound IIc. The isomeric pyrroloquinolines were separated preparatively in a thick layer of Al₂O₃. Compound IVd was obtained in a yield of 140 mg (42%) with mp 250-252°C. Compound IIIc was obtained in a yield of 20 mg (6%) with mp 205°C.

2-Phenyl-4,6-dimethylpyrrolo[2,3-g]quinoline (IIIc, C₁₉H₁₆N₂) and 2-Phenyl-7,9-dimethylpyrrolo[3,2-f]quinoline (IVc, C₁₉H₁₆N₂). These compounds were similarly obtained. The yield of the mixture of the isomers was 85%. The IVc:IIIc isomer ratio was 4:1 (according to the integrated intensity of peaks of indole NH groups in the PMR spectrum).

Pyrroloquinoline IVc was separated from isomer IIIc by recrystallization from ethyl acetate with methanol (10:1). Its mp was 239-241°C. Compound IIIc was not recovered in pure form.

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