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STERIC EFFECTS IN THE SYNTHESIS OF PYRROLOINDOLES FROM 5-AMINOINDOLES

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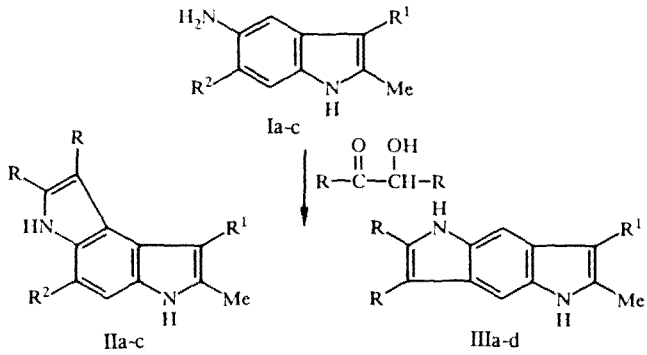
The formation of angular pyrroloindoles from 5-aminoindoles substituted in the pyrrole ring depends both on the steric requirements of the substituent at the β-position of the pyrrole ring, and on the structure of the α-hydroxyketone. Significant amounts of the angular pyrroloindole are only formed together with the linear pyrroloindole in the reaction of 2-methyl-5-aminoindole with benzoin. In the remaining cases, the linear ring closure of the pyrrole ring predominates.

In the study of the route of formation of the pyrridine ring based on substituted 5-aminoindoles with two free ortho-positons in relation to the amino group, it was established that the ratio of the angular and linear pyrroloquinoline isomers formed depends on the steric requirements of the substituent at the β-position of the pyrrole ring and the structure of the dicarbonyl compound [1].

The object of the present investigation is to show the role of steric factors for the regioorientation of the ring closure of the pyrrole ring to the indole in the reaction of 5-aminoindoles with acyloins. The proposition was made in a single known publication [2] that the preferred formation of linear pyrroloindoles in the reaction of 2,3-dimethyl-5-aminoindole with benzoin and α-hydroxycyclohexanone is explained by steric hindrance arising with the closing of the pyrrole ring at the position 4.

In order to verify this assertion, we utilized 2-methyl-5-aminoindole instead of 2,3-dimethyl-5-aminoindole, having thereby excluded steric hindrance at the position of 3 of indole. Moreover, we chose acetoin, which has a more bulky methyl group by comparison with the phenyl in benzoin, as the carbonyl component.



Ia R^1 = Me, R^2 = H; b R^1 = R^2 = Me; c R^1 = R^2 = H; IIa R^1 = Me, R^2 = H, R = Ph; b R^1 = R^2 = Me, R = Ph; c R^1 = R^2 = H, R = Ph; IIIa R^1 = Me, R = Ph; b R^1 = R = Me; c R^1 = H, R = Ph; d R^1 = H, R = Me

The experiment conducted in the work [2] was repeated for comparison. In fact, when 2,3-dimethyl-5-aminoindole (Ia) is heated with benzoin in the presence of catalytic amounts of HCl, the mixture of the angular and the linear pyrroloindoles (IIa) and (IIIa) respectively, is formed with the predominance of the latter. The UV spectra of the angular and linear isomers have characteristic features according to the data of the work [2], confirmed by us (Table 1). Thus, the UV spectra of the linear isomers (III) are characterized by three intense absorption maxima in the regions of 230, 255-298, and 310-340 nm, whereas only two maxima are observed for the angular isomers (II) at 250-270 and 330-357 nm.

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TABLE 1. Pyrroloindoles (II) and (III)

Compound	Empirical formula	mp, °C	M_{calc}	M	UV spectra, λ_{max}, (log ε)	R_f
IIa	$C_{24}H_{20}N_2$	268...270	336	336	270 (4,32); 357 (4,40)	0,48
IIIa	$C_{24}H_{20}N_2$	283...285	336	336	230 (4,47), 260 (4,38), 338 (4,59)	0,23
IIc	$C_{23}H_{18}N_2$	254...255	322	322	258 (4,18), 331 (4,29)	0,25
IIIc	$C_{23}H_{18}N_2$	242...244	322	322	230 (4,35), 255 (4,23), 343 (4,48)	0,44
IIIb	$C_{14}H_{16}N_2$	230	212	212	230 (4,12), 298 (3,97), 310 (4,0)	0,25
IIId	$C_{13}H_{14}N_2$	182...186	198	198	230 (3,92), 298 (3,84), 310 (3,88)	0,26
IIb	$C_{25}H_{22}N_2$	290...292	350	350	250 (3,84), 340 (3,80)	0,46

The formation of two isomers is also observed in the conversion to the 3-unsubstituted 5-aminoindole (Ic) for the reaction with benzoin, but the angular isomer (IIc) predominates in this case. This indicates the strong influence of steric inhibition, produced by the substituent at the position 3 of the 5-aminoindole, on the route of cyclization. The UV spectra of the isomers (IIc) and (IIIc) comply with the principles noted above.

The utilization of acetoin, having a more bulky methyl substituent than benzoin, as the carbonyl component leads to the situation where both 2,3-dimethyl- and 2-methyl-5-aminoindole, (Ia) and (Ic) respectively, form the linear pyrroloindoles (IIIb, d) exclusively. Besides the data of the UV spectra, the structure of the linear isomers (IIIb, d) is confirmed unambiguously by the PMR spectra. Thus, the symmetrical structure (IIIb) is characterized by two singlet of four methyl groups at 1.89 and 2.69 ppm, the position of which agrees with the position of the signals of the methyl grous of 2,3-dimethylindoles. The two equivalent protons of the benzene ring appear in the form of a two-proton singlet signal at 7.6 ppm. Two singlet signals of protons of the 2- and 3-CH_3 groups appear at 2.27 and 2.10 ppm in the PMR spectrum of the pyrroloquinoline (IIId). The signal of the protons of the 6-CHD_3 group at 1.98 ppm is a doublet (J = 3.5 Hz) on account of the spin–spin interaction with the 7-H proton, the quadrupole signal of which is situated at 6.6 ppm. As in the case of the compound (IIIb), the protons of the benzene ring are equivalent and appear in the form of a singlet at 7.3 ppm.

The absence of angular isomers in the condensation of both 3-substituted and 3-unsubstituted 5-aminoindoles (Ia) and (Ic) with acetoin is probably also determined by steric hindrance for the closing of the pyrrole ring at the position 4, produced in this case by the bulky methyl substituent in acetoin.

Confirmation of this is given by the utilization of 2,3,6-trimethyl-5-aminoindole (Ib), having a single possibility for the formation of angular isomers in the condensation with acyloins, in the reaction. In fact, it was found that the angular pyrroloindole (IIb) was isolated and characterized in the case of benzoin, whereas the condensation does not proceed at all when the more bulky acetoin is utilized. The formation of the pyrroloindole with two peri-methyl groups is probably sterically very hindered or impossible.

The investigation carried out obviously demonstrate the influence of steric effects on the route of ring closure of the five-membered ring to the molecule of indole. It should be noted that the forming of the ring-closed five-membered ring presents more rigid steric requirements than those for the six-membered ring since pyrroloquinolines with two peri-methyl substituents are formed, although this is also with great difficulty [1].

EXPERIMENTAL

The PMR spectra were registered on the Varian T60C instrument using HMDS as the external standard. The UV spectra were obtained on the Cary-15 spectrophotometer in ethanol. The purity of the compounds synthesized was monitored by the method of TLC on Silufol type UV-254. Preparative separation was performed on plates with the loose layer of silica gel L 5/40 in benzene. The mass spectra were taken on the MX 1303 instrument with a modified system for the introduction of the sample into the ion source at the 50 eV energy of the ionizing electrons.

The data of the elemental analysis of the compounds synthesized for C and H correspond with the calculated data.

6,7-Dimethyl-2,3-diphenyl-1H,5H-pyrrolo[2,3-f]indole (IIIa) and 7,8-Dimethyl-1,2-diphenyl-3H,6H-pyrrolo[3,2-e]indole (IIa). The mixture of 0.7 g (4.4 mmole) of 2,3-dimethyl-5-aminoindole (Ia), 0.9 g (4.4 mmole) of benzoin, and 2 drops of concentrated HCl is heated at 205°C until the complete melting of the mixture is effected (~5 min). The reaction mass

is diluted with 5 ml of ethanol and 10 ml of 10% aqueous ammonia. The precipitated residue is filtered off and dried in air. The yield of the mixture of isomers is 0.89 g (62%). The isomers are divided by preparative TLC. The yield of compound (IIIa) is 0.19 g (15%): the yield of compound (IIa) is 0.06 g (5%).

6-Methyl-1,2-diphenyl-1H,5H-pyrrolo[2,3-f]indole (III) and 7-Methyl-1,2-diphenyl-3H,6H-pyrrolo[3,2-e]indole (IIc). These compounds are obtained analogously from 0.6 g (4.1 mmole) of 2-methyl-5-aminoindole (Ic) and 0.84 g (4.1 mmole) of benzoin. The yield of the mixture of isomers is 0.78 g (60%). The yield of compound (IIIc) is 0.05 g (4%), and the yield of compound (IIc) is 0.21 g (16%).

2,3,6,7-Tetramethyl-1H,5H-pyrrolo[2,3-f]indole (IIIb). The mixture of 0.6 g (4.1 mmole) of 2,3-dimethyl-5-aminoindole (Ia), 0.35 g (4.1 mmole) of freshly distilled acetoin, and catalytic amounts of triethylamine hydrochloride is heated at 130°C for 30 min. Separation is performed by analogy with compound (IIIa). The yield is 0.5 g (63%). The compound is purified by preparative TLC. The mp is 230°C. The PMR spectrum in CF_3COOH is as follows: 1.89 ppm (6H, s, 2- and 6-CH_3) and 7.6 ppm (2H, s, 4- and 8-H).

2,3,6-Trimethyl-1H,5H-pyrrolo[2,3-f]indole (IIId). This compound is obtained by analogy with the preceding one from 0.5 g (3.4 mmole) of 2-methyl-5-aminoindole (Ic) and 0.3 g (3.4 mmole) of acetoin. The yield is 0.4 g (60%). The PMR spectrum in DMSO-D_6 is as follows: 6.6 ppm (1H, q, J = 3.5 Hz, 7-H) and 7.3 ppm (2H, s, 4- and 8-H). The PMR spectrum is pyridine-D_5 is as follows: 1.98 ppm (3H, d, J = 3.5 Hz, 6-CH), 2.1 ppm (3H, s, 3-Ch_3), and 2.27 ppm (3H, s, 2-Ch).

4,7,8-Trimethyl-1,2-diphenylpyrrolo]3,2-e]indole (IIb). This compound is obtained by analogy from 1 g (6 mmole) of 2,3,6-trimethyl-5-aminoindole (Ib) and 1.4 g (6 mmole) of benzoin. The yield is 1.1 g (50%). The PMR spectrum in acetone-D_6 is as follows: 1.5 ppm (3H, s, 8-CH), 2.2 ppm (6H, s, 4- ad 7-CH_3), and 7.8-8.3 ppm (11H, m, 5-H and 1-, 2-C_6H_5).

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