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REACTIONS OF SUBSTITUTED 7-AMINOINDOLES WITH 1,3-DIKETONES

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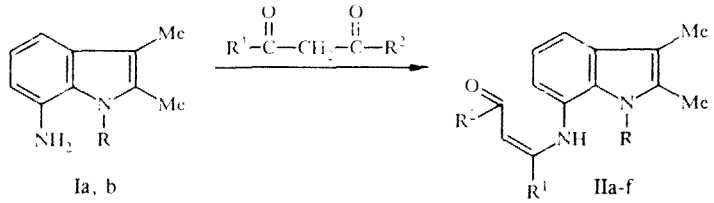
The condensation of 2,3-dimethyl and 1,2,3-trimethyl-7-aminoindoles with β-dicarbonyl compounds leads to enaminoketones, which undergo cyclization by the action of trifluoroacetic acid giving substituted pyrrolo[3,2-h]quinolines.

In the continuation of investigations on the utilization of aminoindoles as starting compounds in the synthesis of pyrroloquinolines [1], we studied the possibility of applying 2,3-dimethyl- and 1,2,3-trimethyl-7-aminoindoles for this purpose.

In the first stage of the process, the condensation of the aminoindoles (Ia, b) with β-diketone leads to the formation of the enaminoketones (IIa-f).



Ia, b IIa-f

I a R = H, b R = Me; II a R = H, $R^1 = R^2 = Me$; b R = H, R^1 = Me, R^2 = H; c R = H, $R^1 = R^2$ = Ph; d R = $R^1 = R^2$ = Me; e R = R^1 = Me, R^2 = Ph; f R = Me, $R^1 = R^2$ = Ph

The reaction of the 1-unsubstituted indole (Ia) with acetylacetone terminates completely after 1.5-2 h. The analogous reaction for 5- and 6-aminoindoles was previously conducted without a solvent using 30 times the excess of acetylacetone [2]. It was found that it is significantly more convenient to perform this condensation in toluene at 100°C with a low (15%) excess of the diketone. In this case, the crystalline mass obtained after the distillation of the solvent is well separated chromatographically. Moreover, there is the possibly of performing the cyclization of the enaminoketone obtained at once in trifluoroacetic acid without its additional purification. The appropriate enamines from the reaction of all diketones with the N-methylindole (Ib) are obtained with more difficulty than in the case of the NH-analog (Ia). This is probably determined by the steric influence of the N-methyl group. The reaction with dibenzoylmethane does not successfully go to completion, even with prolonged heating. The unreacted aminoindole is detected chromatographically [approximately 20% for compound (Ia) and 30-35% for compound (Ib)], i.e., as in the case of other aromatic amines, acetylacetone reacts more easily than dibenzoylmethane in full agreement with differences in the reactivity of alkyl and aryl carbonyl groups. In the case of benzoylacetone, the presence of the active acetyl fragment guarantees the full course of the reaction with the formation of the enaminoketone (IIe) in 30 min at 100°C. The mass spectrum of the enaminoketone (IIe) contains the intense peak of the ion with the *m/z* 105 (benzoyl); this confirms the condensation of the aminoindole at the acetyl group and agrees with the data of the work [2].

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TABLE 1. Spectral Characteristics of the Enaminoketones (II)

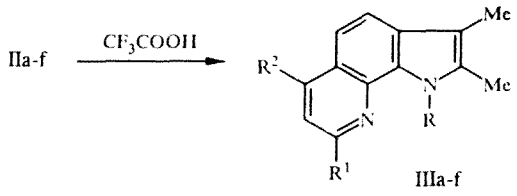
Compound	Empirical formula	Mass spectrum, *m/z* (I_{rel}, %)	PMR spectrum, δ, ppm	UV spectrum, λ_{max} (log ε)	IR spectrum, cm^{-1}
IIa	$C_{15}H_{18}N_2O$		5,2 (1H, s, =CH); 6,5...7,1 (3H, m, 4-, 5-, 6-H); 10,5 (1H, s, NH-pyrr.); 12,1 (1H, s, NH-imine). DMSO-D_6	225 (4,55), 320 (4,30)	1620
IIb	$C_{20}H_{20}N_2O$	304 (M^+, 100), 289 (17), 287 (11), 286 (10), 199 (39), 184 (33), 183 (30), 160 (28), 159 (27), 144 (32), 143 (10), 115 (21), 105 (82), 77 (79)	6,0 (1H, s, =CH); 6,8...7,5 (5H, m, 1-C_6H_5); 7,8...8,1 (3H, m, 4-, 5-, 6-H); 10,5 (1H, s, NH-pyrr.); 13,1 (1H, s, NH-imine). Acetone-D_6	224 (4,32), 280 (3,80), 346 (4,10)	1600
IIc	$C_{25}H_{22}N_2O$		6,0 (1H, s, =CH); 6,8...7,5 (10H, m, 1-, 3-, 3-C_6H_5); 7,8...8,0 (3H, m, 4-, 5-, 6-H); 10,3 (1H, s, NH-pyrr.); 12,8 (1H, s, NH-imine). Acetone-D_6	220 (4,51), 365 (4,13)	1600
IId	$C_{16}H_{20}N_2O$	256 (M^+, 100), 241 (11), 239 (8), 238 (9), 237 (20), 223 (8), 188 (67), 184 (30), 159 (17)	5,2 (1H, s, =CH); 6,6...7,2 (3H, m, 4-, 5-, 6-H); 12,1 (1H, s, NH-imine). DMSO-D_6	230 (4,33), 314 (4,17)	1620
IIe	$C_{21}H_{22}N_2O$	318 (M^+, 77), 303 (5), 213 (69), 198 (100), 184 (33), 173 (9), 159 (35), 158 (30), 144 (9), 143 (16), 105 (80)	6,0 (1H, s, =CH); 6,8...7,5 (5H, m, 1-C_5H_6); 7,8...8,1 (3H, m, 4-, 5-, 6-H); 13,0 (1H, s, NH-imine). Acetone-D_6	227 (4,62), 285 (3,88), 340 (4,38)	1600
IIf	$C_{26}H_{24}N_2O$	380 (M^+, 23), 365 (6), 297 (8), 275 (48), 258 (41), 158 (15), 144 (6), 143(7), 115 (13), 105 (86), 77 (100)	2,2 (3H, s, 3-CH_3); 2,3 (3H, s, 2-CH_3); 4,0 (3H, s, 1-CH_3); 6,0 (1H, s, =CH); 6,1...7,5 (10H, m, 1-, 3-C_6H_5); 7,7...8,0 (3H, m, 4-, 5-, 6-H); 13,5 (1H, s, NH-imine). CCl_4	228 (5,17), 350 (4,58)	1600

TABLE 2. Spectral Characteristics of the Pyrroloquinolines (III)

Compound	Empirical formula	Mass spectrum, *m/z* (I_{rel}, %)	PMR spectrum, δ, ppm.	UV spectrum, λ_{max} (log ε)
IIIa	$C_{15}H_{16}N_2$		7,1 (1H, s, 7-H); 7,5 (2H, s, 4-, 5-H), 11,4 (1H, s, NH-pyrr.). DMSO-D_6	228 (4,09), 276 (3,96), 328 (4,02)
IIIb	$C_{20}H_{18}N_2$	286 (M^+, 100), 285 (86), 271 (8), 145 (5), 137 (8)	2,1 (6H, s, 2-, 3-CH_3); 2,7 (3H, s, 8-CH_3); 7,0 (1H, s, 7-H); 7,1...7,3 (7H, 4-, 5-H, 6-C_6H_5); 10,8 (1H, s, NH-pyrr.). CCl_4	236 (4,94), 282 (5,15), 355 (4,25)
IIIc	$C_{25}H_{20}N_2$		1,8 (3H, s, 2-, 3-CH_3); 2,1 (3H, s, 2-CH_3); 7,0...7,4 (10H, m, 6-, 8-C_6H_5); 7,6 (1H, s, 7-H); 8,1...8,3 (2H, m, 4-, 5-H); 10,5 (1H, s, NH-pyrr.). CCl_4	245 (5,38), 295 (5,23), 355 (4,58)
IIId	$C_{16}H_{18}N_2$		7,1 (1H, s, 7-H); 7,5 (2H, s, 4-, 5-H). DMSO-D_6	225 (5,82), 275 (6,05), 323 (5,03)
IIIe	$C_{21}H_{20}N_2$	300 (M^+, 100), 285 (23), 142 (8), 135 (5)	2,1 (3H, s, 3-CH_3); 2,2 (3H, s, 2-CH_3); 2,6 (3H, s, 8-CH_3); 4,4 (3H, s, 1-CH_3); 6,9 (1H, s, 7-H); 7,1...7,3 (7H, m, 4-, 5-H, 6-C_6H_5). CCl_4	234 (5,50), 281 (5,60), 345 (4,80)
IIIf	$C_{26}H_{22}N_2$		6,9...7,2 (10H, m, 6-, 8-C_6H_5); 7,4 (1H, s, 7-H); 7,8...8,0 (2H, s, 4-, 5-H). Acetone D_6	248 (5,15), 291 (5,25), 350 (4,58)

The PMR spectra of the enaminoketones (IIa-c) (Table 1) reveal signals of the imine group (N–H) and the olefinic proton; this indicates their enaminoketone structure. The absorption band in the region of 1600-1620 cm^{-1} in the IR spectra, corresponding to the conjugated carbonyl group, is confirmed by the data of the PMR spectra. Data on the UV spectra of the compounds (IIa-f) are in agreement with data presented in the literature [2].

In the cyclization of the enamines (IId-f), it was only possible to expect the formation of the corresponding pyrrolo[3,3-h]quinolines, whereas, for the enamines (IIa-f) not having a substituent at the indole nitrogen atom, the alternative possibility of the closing of the ring on the pyrrole fragment with the formation of tricyclic structures with the angular nitrogen atom was not excluded. However, the last was not found in a single case. All the enaminoketones (IIa-f) utilized in the reactions are converted by the action of trifluoroacetic acid into substituted pyrrolo[3,2-h]quinolines (IIIa-f), i.e., the heterocyclization only proceeds at the position 6 of the benzene ring of indole.



IIIa-f

IIIa R = H, $R^1 = R^2$ = Me; b R = H, R^1 = Me, R^2 = Ph; c R = H, $R^1 = R^2$ = Ph; d R = $R^1 = R^2$ = Me; e R = R^1 = Me, R^2 = Ph; f R = Me, $R^1 = R^2$ = Ph

In favor of this is the identity of the UV spectra of the 1-H- and 1-methylpyrroloquinolines, (IIIa-c) and (IIId-f) respectively, obtained (Table 2); this is also in agreement with the data previously obtained for similar structures [3]. The PMR spectra of the pyrroloquinolines (IIIa-c) are characterized by the broad signal of the proton of the pyrrole NH group, and the PMR spectra of the N-methyl analogs (IIId-f) are characterized by the signal of the protons of the N–CH_3 group. The signals of the aromatic protons are mostly poorly resolved in the PMR spectra of the investigated pyrroloquinolines. An exception comprises the compounds (IIIa, d), for which the AB-system of the 4-H and 5-H protons degenerates into a singlet. The 7-H proton is situated in the region of higher field, which is characteristic of the β-H protons of pyridine.

The mass spectra of the pyrroloquinolines (IIIa-f) provide little information. The molecular ion peak has the greatest intensity in them.

Therefore, 2,3-dimethyl- and 1,2,3-trimethyl-7-aminoindoles may be utilized for the isolation of substituted pyrrolo[3,2-h]quinolines. Ring closure at the nitrogen atom of the pyrrole ring is not realized for the enaminoketones (IIa-c) under conditions of the Combes reaction.

EXPERIMENTAL

The PMR spectra were registered on a Varian T60 instrument (the solvent was indicated in each individual case); the internal standard was TMS. The UV spectra were obtained on a Cary-15 spectrophotometer in ethanol. The IR spectra were obtained on a UR-20 instrument in mineral oil. The mass spectra were obtained on a 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 monitoring of the purity of the substances were performed by the method of TLC. The adsorbent utilized for preparative TLC was Al_2O_3 (neutral, activity grade II according to Brockman) and silica gel 40/100.

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

The data of the UV, PMR, IR, and mass spectra are presented in Table 1 for compounds (IIa-f), and in Table 2 for compounds (IIIa-f).

4-(2,3-Dimethylindol-7-yl)aminopent-3-en-2-one (IIa). The mixture of 0.5 g (3.1 mmole) of 2,3-dimethyl-7-aminoindole (Ia) and 0.4 g (4.0 mmole) of acetylacetone in 3 ml of toluene is boiled for 1.5-2 h with chromatographic monitoring. The residue obtained after the distillation of the toluene is purified by preparative TLC on silica gel in the 5:1 system of benzene–ethyl acetate. The yield is 0.41 g (55%). The mp is 172-174°C (from hexane).

4-(1,2,3-Trimethylindol-7-yl)aminopent-3-en-2-one (IId). This compound is obtained by analogy with compound (IIa) from 1,2,3-trimethyl-7-aminoindole (Ib). The enaminoketone is purified by preparative TLC on silica gel in the 7:1 system of benzene–ethyl acetate. The yield is 52%. The mp is 87-89°C (from hexane).

1-Phenyl-3-(2,3-dimethylindol-7-yl)aminobut-2-en-1-one (IIb). The mixture of 0.5 g (3.1 mmole) of the aminoindole (Ia) and 0.65 g (4 mmole) of benzoylacetone is heated for 30 min at the temperature of 160-165°C. The substance obtained is purified by preparative TLC on a plate with Al_2O_3 in the 4:1 system of benzene–chloroform. The compound is obtained in the form of a yellowish oil. The yield is 0.61 g (65%).

1-Phenyl-3-(1,2,3-trimethylindol-7-yl)aminobut-2-en-1-one (IIe). This compound is obtained by analogy with compound (IIb) from the aminoindole (Ib). It is purified by preparative TLC on plates with Al_2O_3 in the 7:1 system of benzene–chloroform. It is an oil, and is obtained with the yield of 61%.

1,3-Diphenyl-3-(2,3-dimethylindol-7-yl)aminoprop-2-en-1-one (IIc). The mixture of 0.4 g (2.5 mmole) of the aminoindole (Ia) and 0.9 g (4 mmole) of dibenzoylmethane is headed for 2-3 h at the temperature of 160-170°C. The substance obtained is purified by analogy with the preceding account. The yield is 0.55 g (60%). The mp is 208-209°C (from hexane).

1,3-Diphenyl-3-(1,2,3-trimethylindol-7-yl)aminoprop-2-en-1-one (IIf). This compound is obtained by analogy with the enaminoketone (IIc) from the aminoindole (Ib). It is purified by preparative TLC on a plate with Al_2O_3 in the 10:1 system of benzene–chloroform. The yield is 51%, and the product is a clear yellow oil.

2,3,6,8-Tetramethylpyrrolo[3,2-h]quinoline (IIIa). The solution of 0.41 g (1.7 mmole) of the enaminoketone (IIa) in 3 ml of trifluoroacetic acid is boiled for 3 h. The cooled mixture is poured into 30 ml of 10% aqueous ammonia solution. The residue is filtered off, dried in air, and then purified by preparative TLC on a plate with silica gel in the 5:1 system of benzene–either. The yield is 0.28 g (69%). The mp is 217-219°C (from ether).

1,2,3,6,8-Pentamethylpyrrolo[3,2-h]quinoline (IIId). This compound is obtained by analogy with compound (IIIa) from the enaminoketone (IId). It is purified on a plate with silica gel in the 2:1 system of benzene–ethyl acetate. The yield is 65%. The mp is 154-156°C.

2,3,8-Trimethyl-6-phenylpyrrolo[3,2-h]quinoline (IIIb). This compound is obtained by analogy with compound (IIIa) from the enaminoketone (IIb). It is purified on a plate with Al_2O_3 in the 3:1 system of benzene–ether. The yield is 70%. The mp is 110-112°C (from hexane).

1,2,3,8-Tetramethyl-6-phenylpyrrolo[3,2-h]quinoline (IIIe). This compound is obtained by analogy with the enaminoketone (IIe). It is purified on a plate with Al_2O_3 in the 4:1 system of benzene–chloroform. The yield is 67%. The mp is 164-166°C.

2,3-Dimethyl-6,8-diphenylpyrrolo[3,2-h]quinoline (IIIc). This compound is obtained from the enaminoketone (IIe), an is purified by analogy with the preceding account in the 15:1 system of benzene–chloroform. The yield is 60%. The mp is 133-135°C (from hexane).

1,2,3-Trimethyl-6,8-diphenylpyrrolo[3,2-h]quinoline (IIIf). This compound is obtained and purified by analogy wit the preceding account from the enaminoketone (IIf). The yield is 54%. The mp is 153-156°C.

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