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FORMATION OF PYRROLO[2,3-*f*]QUINOLINES FROM SUBSTITUTED 5-METHYL-6-AMINOINDOLES BY THE COMBES REACTION

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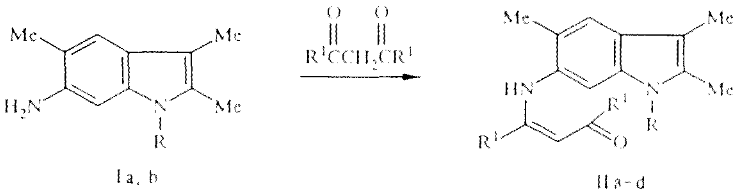
It is shown that the reaction of 2,3,5-trimethyl-6-amino-indole with 1,3-diketones is a convenient method for the preparation of angular 1H-pyrrolo[2,3-f]quinolines, while the presence of a methyl group on the pyrrolic nitrogen atom of the initial indole as a result of steric hindrance completely blocks cyclization to the corresponding pyrroloquinolines.

In research on the annelation of a pyridine ring to an indole ring the main problem is to develop regiospecific methods for the synthesis of angular and linear isomers of the condensed structures. For the directed preparation of angular isomers of pyrroloquinolines, we have selected as models substituted 5-methyl-6-aminoindoles which by interaction with 1,3-diketones under Combes reaction conditions should form a single pyrrolo[2,3-*f*]quinoline isomer.

Like the other benzaminoindoles [1], the reaction takes place in stages, and on heating 2,3,5-trimethyl- (Ia) and 1,2,3,5-tetramethyl-6-aminoindoles (Ib) with acetylacetone or dibenzoylmethane the corresponding enaminoketones IIa-d are first formed.



Ia, b

IIa-d

Ia R = H; b R = Me; IIa R = H, R^1 = Me; b R = H, R^1 = C_6H_5; c R = R^1 = Me; d R = Me, R^1 = C_6H_5

In the PMR spectrum of enaminoketone IIa there are signals due to the proton of the pyrrole NH group (10.56 ppm), singlets due to the 4-H (7.16 ppm) and 7-H (6.92 ppm) aromatic protons and the vinyl proton (5.13 ppm), and unresolved signals due to five methyl groups (1.73-2.30 ppm), which fully supports the structure of this compound. In the spectra of compounds IIb and IId (R^1 = C_6H_5) the signal due to the vinyl proton (6.08 ppm) is shifted downfield by the effect of the ring currents from the phenyl substituents. In the spectra of the N-methyl-substituted enaminoketones IIc and IId there are no signals due to a 1-H proton on the pyrrole nitrogen atom, and singlet signals from the protons of the N-CH_3 groups occur at 3.56 and 3.18 ppm respectively.

The UV spectra of enaminoketones II are dependent to a significant degree on the nature of substituent R^1. Thus, for compounds IIa and IIc (R^1 = CH_3) two absorption maxima (at 230 and 315 nm) occur in the UV spectra, while for enaminoketones IIb and IId (R^1 = C_6H_5) there are three bands (at 220, 295, and 405 nm), which is in agreement with the literature data for similar structures [1].

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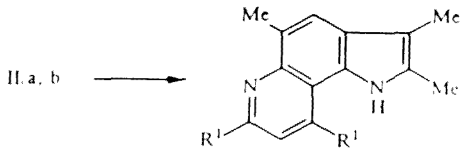
It was to be expected that cyclization of the enaminoketones II in an acid medium would lead to pyrroloquinolines with rings joined up in a previously familiar angular configuration. In fact, on refluxing compounds IIa and IIb in trifluoroacetic acid, pyrroloquinolines IIIa and IIIb are isolated.

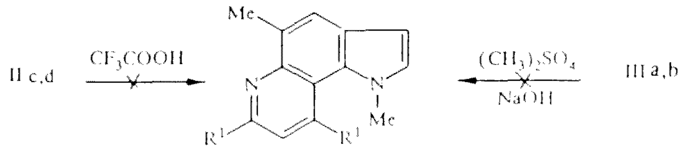


III a, b

IIIa R^1 = Me, b R^1 = C_6H_5

In the PMR spectrum of compound IIIa there are signals due to the NH (10.32 ppm), 4-H (7.53 ppm), and 8-H (7.03 ppm) protons and five methyl groups (2.87, 2.66, 2.36, 2.53, and 2.16 ppm). Taking into account the different R^1 substituent, the spectrum of compound IIIb is also fully consistent with the proposed structure. The UV spectra of compounds IIIa and IIIb (see experimental section) are typical of angular pyrroloquinolines [2].

Enaminoketones IIc and IId, which contain a methyl substituent on the pyrrolic nitrogen atom, do not undergo cyclization even on prolonged heating (~10 h) in trifluoroacetic acid and remain unchanged from reaction.



III c, d

IIIc R^1 = Me, d R^1 = C_6H_5

Thus, the experimental results confirm the proposal previously advanced about the steric requirements of the substituent on the pyrrolic nitrogen atom in the formation of a pyridine ring at the 7-position of indole by the Combes reaction [2].

Evidence for steric obstruction of the pyrrolic nitrogen atom by the γ-substituent of the pyridine ring in the angular pyrroloquinolines IIIa and IIIb is provided by the failure of dimethyl sulfate to methylate the indole nitrogen atom, while pyrroloquinolines that are joined in a linear manner are readily methylated [3].

EXPERIMENTAL

The UV spectra were recorded in ethanol on a Specord instrument. The PMR spectra were recorded on a Varian S-60T instrument in DMSO-d_6 relative to HMDS. The course of the reactions and purity of the compounds synthesized were monitored on Silufol UV-254 plates in the solvent systems indicated for each specific case.

The elemental analysis data for C and H corresponded to the calculated values.

4-(2,3,5-Trimethyl-6-indolyl)aminopent-3-en-2-one (IIa, $C_{16}H_{20}N_2O$). A solution of 1 g (5.7 mmole) of 2,3,5-trimethyl-6-aminoindole in 2.9 g (29 mmole) of acetylacetone was refluxed for 1 h until the initial indole had disappeared (monitored by TLC). The excess acetylacetone was distilled off under vacuum. The solid yellowish residue was crystallized from aqueous ethanol. Yield 1.3 g (88%) of enaminoketone IIa, mp 146-148°C, R_f 0.31 (benzene–ethyl acetate, 10:1). PMR spectrum: 10.56 (1H, s, 1-H), 7.16 (1H, s, 4-H), 6.92 (1H, s, 7-H), 5.13 (1H, s, H_{vin}), 1.73-2.30 ppm (15H, 5 s, 2-CH_3, 3-CH_3, and 5-CH_3 of indole and 2-CH_3 of enamine residue). UV spectrum (λ_{max}, log ε): 230 nm (4.13), 315 nm (4.09).

4-(1,2,3,5-Tetramethyl-6-indolyl)aminopent-3-en-2-one (IIc), ($C_{17}H_{22}N_2O$). This was obtained in a similar manner from 1,2,3,5-tetramethyl-6-aminoindole as a white crystalline compound. Yield 76%, mp 124-126°C (from petroleum ether). R_f 0.62 (benzene – ethyl acetate, 10:1). PMR spectrum: 7.23 (1H, s, 4-H), 7.13 (1H, s, 7-H), 5.13 (1H, s, H_{vin}), 3.56 (3H, s, 1-CH_3), 2.23-1.76 ppm (15H, 5 s, 2-CH_3, 3-CH_3, and 5-CH_3 of indole and 2-CH_3 of the enamine residue). UV spectrum (λ_{max}, log ε): 235 nm (4.17), 315 nm (4.16).

1,3-Diphenyl-3-(2,3,5-trimethyl-6-indolyl)aminoprop-2-en-1-one (IIb, $C_{26}H_{24}N_2O$). A mixture of 0.8 g (4.6 mmole) of 2,3,5-trimethyl-6-aminoindole and 1.3 g (5.8 mmole) of dibenzoylmethane was heated for 1 h at 160-165°C. The resulting condensation product was purified by preparative thin-layer chromatography on alumina (neutral grade II Brockman activity). Yield 0.75 g (43%) of enaminoketone IIb, mp 203-204°C (from petrol ether). R_f 0.87 (benzene – ethyl acetate, 10:1). PMR spectrum: 10.30 (1H, s, 1-H), 6.44-8.00 (12H, m, H_{arom}), 6.08 (1H, s, H_{vin}), 2.00-2.34 ppm (9H, 3 s, 2-CH_3, 3-CH_3, and 5-CH_3). UV spectrum (λ_{max}, log ε): 220 nm (4.20), 295 nm (3.84) and 405 nm (4.03).

1,3-Diphenyl-3-(1,2,3,5-tetramethyl-6-indolyl)aminoprop-2-en-1-one (IId, $C_{27}H_{26}N_2O$). This was obtained in a similar manner to the previous compound from 1,2,3,5-tetramethyl-6-aminoindole. Yield 47%, mp 157-158°C (from petrol ether). R_f 0.62 (benzene – ethyl acetate, 100:1). PMR spectrum: 6.44-8.00 (12H, m, H_{arom}); 6.08 (1H, s, H_{vin}), 3.18 (3H, s, 1-CH_3), 2.00-2.34 ppm (9H, 3 s, 2-CH_3, and 5-CH_3). UV spectrum (λ_{max}, log ε): 220 nm (4.24), 2.95 nm (3.93), and 405 nm (4.18).

2,3,4,7,9-Pentamethylpyrrolo[2,3-*f*]quinoline (IIIa, $C_{16}H_{18}N_2$). To 0.5 g (2 mmole) of enaminoketone IIa was added 3 ml of CF_3COOH, and the mixture was refluxed for 1 h. The reaction mixture was poured into dilute ammonia, and the precipitate that formed was filtered off and recrystallized from aqueous ethanol. Yield 0.43 g (93%), mp 192-194°C (from petrol ether). R_f 0.38 (benzene – ethyl acetate, 10:1). PMR spectrum: 10.32 (1H, s, 1-H), 7.53 (1H, s, 4-H), 7.03 (1H, s, 8-H), 2.82, 2.66, 2.53, 2.36, and 2.16 ppm (15H, 5 s, 2-CH_3, 3-CH_3, 5-CH_3, 7-CH_3, and 9-CH_3). UV spectrum (λ_{max}, log ε): 225 nm (4.28), 275 nm (4.12).

7,9-Diphenyl-2,3,5-trimethylpyrrolo[2,3-*f*]quinoline (IIIb, $C_{26}H_{22}N_2$). This was obtained in a similar manner from enaminoketone IIb, yield 88%, mp 191-192°C (from petrol ether). R_f 0.95 (benzene – ethyl acetate, 100:1). PMR spectrum: 7.30-8.30 (12H, m, H_{arom}), 2.40-2.50 ppm (9H, 3 s, 2-CH_3, 3-CH_3, and 5-CH_3). UV spectrum (λ_{max}, log ε): 220 nm (4.35), 270 nm (4.26), 305 nm (4.51).

Enaminoketones IIc and IId were recovered unchanged after refluxing for 10 h in trifluoroacetic acid.

Pyrroloquinolines IIIa and IIIb were recovered unchanged after refluxing for 4 h in acetone with excess dimethyl sulfate.

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