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SYNTHESIS OF PYRROLOQUINOLINES FROM ALKYL-SUBSTITUTED 6-AMINOINDOLES, ACETOACETIC ESTER, AND ETHOXYMETHYLENEMALONIC ESTER

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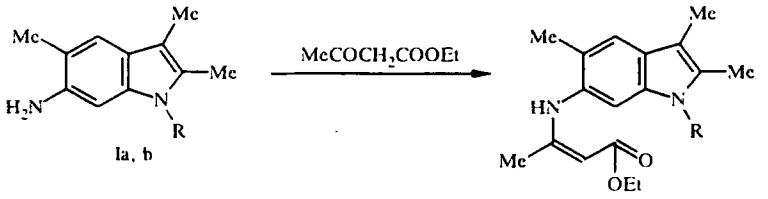
Under the conditions of the Vilsmeier reaction and also when boiled in biphenyl aminocrotonates, obtained from 2,3,5-trimethyl- and 1,2,3,5-tetramethyl-6-aminoindoles, are easily converted into the corresponding pyrroloquinolines. Similarly, pyrroloquinolines with structures known to be angular are formed during the thermal cyclization of the products from the reaction of these amines with ethoxymethylenemalonic ester.

As previously reported [1], during the synthesis of pyrroloquinolines with angularly fused rings from alkyl-substituted 6-aminoindoles under the conditions of the Combes reaction, the determining factor is the steric effect of the substituents at the pyrrole nitrogen atom of the indole. The main steric hindrances probably arise between this substituent and the substituent at the χ position of the pyridine ring in the pyrroloquinoline that forms. Consequently, the steric character of the γ-substituent in the pyridine fragment must also have an effect on the possibility of the formation of the pyrroloquinoline system. For this reason we investigated the cyclization of the aminocrotonates (IIa, b) under the conditions of the Vilsmeier reaction. The initial aminocrotonates were obtained by the condensation of the aminoindoles (Ia, b) with acetoacetic ester.

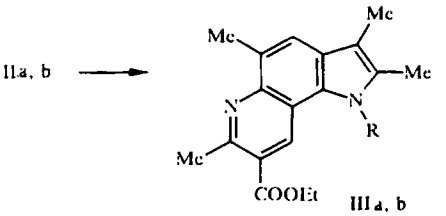


Ia, b

I, II a R = II, b R = Me

IIa, b

The spectral characteristics of compounds (IIa, b), given in Table 1, agree well with investigated structures of similar type [2]. (In the case of compound (IIa) the data are given for a mixture of *cis* and *trans* isomers, which according to the PMR spectra are formed in a ratio of 1:1.) It was expected that the aminocrotonates (IIa, b) would be transformed into the respective pyrroloquinolines with angular fusion of the rings and with the γ position of the pyridine ring free when boiled with the Vilsmeier reagent. In fact, both compound (IIa) and compound (IIb) form pyrroloquinolines (IIIa, b) readily and with good yields under these conditions. The data from the UV and PMR spectra are given in Table 2.



IIIa, b

IIIa R = II, b R = Me

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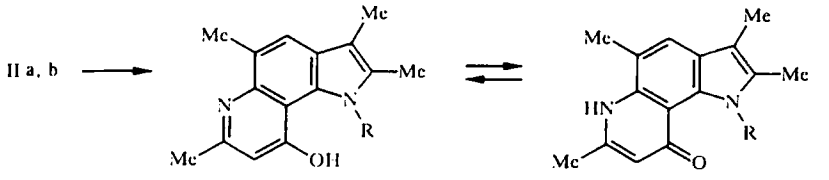
TABLE 1. Aminocrotonates and Aminomethylenemalonates

Compound	mp, °C	R_f (system)	UV spectrum		PMR spectrum, δ, ppm	Molecular formula	Found % / Calculated %		Yield, %
			λ_{max}	lg ε			C	H	
IIa	150...151	0,48 (A)	208 235 300	4,15 4,25 3,90	*cis* isomer 1,22 (3H, m, J = 7 Hz, $CH_2\underline{CH_3}$); 1,75 (3H, s, β-CH_3); 2,18 (3H, s, 3-CH_3); 2,30 (3H, s, 2-CH_3); 2,35 (3H, s, 5-CH_3); 4,10 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 4,62 (1H, s, H vinyl.); 7,21 (2H, s, 4- and 7-H); 10,02 (1H, s, NH imine); 10,40 (1H, s, 1-H); *trans* isomer : 1,10 (3H, m, J = 7 Hz, $CH_2\underline{CH_3}$); 2,18 (3H, s, 3-CH_3); 2,22 (3H, s, β-CH_3); 2,25 (3H, s, 2-CH_3); 2,30 (3H, s, 5-CH_3); 3,86 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 4,22 (1H, s, H vinyl); 6,93 (1H, s, 7-H); 7,00 (1H, s, 4-H); 8,00 (1H, s, NH imine); 10,40 (1H, s, 1-H)	$C_{17}H_{22}N_2O_2$	69,91 71,30	7,32 7,74	51
IIb	134...135	0,64 (A)	208 230 300	4,29 4,37 4,37	1,27 (3H, t, J = 7 Hz, $\underline{CH_2}CH_3$); 1,73 (3H, s, β-CH_3); 2,20 (3H, s, 3-CH_3); 2,33 (6H, s, 2- and 5-CH_3); 3,51 (3H, s, 1-CH_3); 4,03 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 4,46 (1H, s, H vinyl); 6,78 (1H, s, 7-H); 7,07 (1H, s, 4-H); 9,97 (1H, s, NH)	$C_{13}H_{24}N_2O_2$	71,59 71,97	7,87 8,05	64
Va	164...165	0,18 (A)	227 290 356	4,19 3,92 4,00	1,25 (6H, m, J = 7 Hz, $2\underline{CH_2}CH_3$); 2,10 (3H, s, 3-CH_3); 2,30 (3H, s, 2-CH_3); 2,35 (3H, s, 5-CH_3); 4,20 (4H, q, J = = 7 Hz, $2\underline{CH_2}CH_3$); 7,14 (1H, s, 4-H); 8,40 (1H, d, J = = 16 Hz, H vinyl); 10,41 (1H, s, 1-H); 10,85 (1H, s, J = = 16 Hz, NH)	$C_{19}H_{24}N_2O_4$	66,49 66,26	7,08 7,02	73
Vb	148...149	0,35 (A)	230 294 355	4,20 4,00 4,00	*1,27 (6H, m, $2CH_2\underline{CH_3}$); 2,10 (3H, s, 3-CH_3); 2,28 (3H, s, 2-CH_3); 2,33 (3H, s, 5-CH_3); 3,57 (3H, s, 1-CH_3); 4,20 (4H, m, $\underline{CH_2}CH_3$); 7,12 (1H, s, 7-H); 7,18 (1H, s, 7-H); 8,53 (1H, s, H vinyl.)	$C_{20}H_{26}N_2O_4$	67,13 67,02	7,22 7,31	69

*In methanol-d_4.

The experimental data fully support our suggestion above about the deciding effect of the steric interactions of the substituents at the pyrrole nitrogen atom and at the γ position of the pyridine ring that forms on the possibility of cyclization. In fact, such cyclization only takes place successfully in the absence of a substituent at one of these positions (at the pyrrole nitrogen atom or at position 9 of the pyrroloquinoline that forms). As shown earlier [1], cyclization does not occur when there are substituents (two methyl groups or methyl and phenyl groups) at both positions. These factors also explain the ease of methylation of compound (IIIa) by dimethyl sulfate with the formation of pyrroloquinoline (IIIb), in contrast to the situation with the 9-methyl-substituted analog [1], where such methylation is impossible on account of steric hindrances.

We also investigated the behavior of the aminocrotonates (IIa, b) under the conditions of thermal cyclization and established that both compound (IIa) and compound (IIb) are transformed with good yields into the respective pyrroloquinolines (IVa, b) when heated in boiling biphenyl.

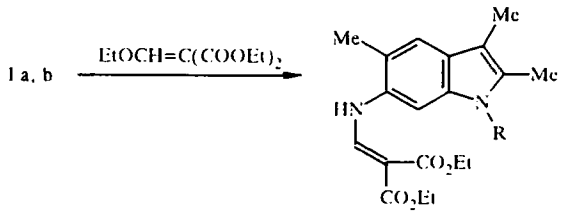


IV a, b

IV a R = H, b R = Me

From the PMR (Table 2) it is not possible to judge unambiguously in which form (hydroxypyrroloquinoline or pyrroloquinolone) the obtained compounds exist. From the presence of a broad signal in the region of 10 ppm it is only possible to establish the presence of an NH or OH group capable of proton exchange. In other respects the spectral characteristics support the proposed structures (IV).

Compounds (Va, b), obtained from diethyl ethoxymethylenemalonate and aminoindoles (Ia, b), behave similarly at high temperature.

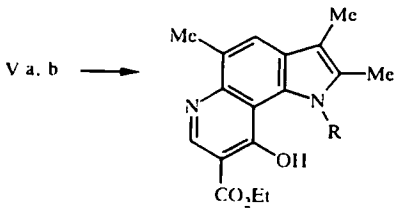


V a, b

Va R = H, b R = Me

In the PMR spectrum of compounds (Va, b) in DMSO-d_6 the signal of the vinyl proton appears in the form of a doublet (J = 16 Hz) (Table 1) on account of spin—spin coupling with the NH proton of the enamine fragment. If deuteromethanol is used as solvent, this signal is transformed into a singlet, while the signals of the protons of the NH groups in the enamine [compounds (Va, b)] and indole [compound (Va)] fragments disappear on account of deuteroexchange.

When compounds (Va, b) were boiled in Dowtherm, the pyrroloquinolines (VIa, b) were isolated and identified.



VI a, b

VI a R = H, b R = Me

In contrast to compounds (IV), the PMR spectra (Table 2) confirm unambiguously the hydroxypyrroloquinoline structure for the tricyclanes (VI). This is demonstrated by a clear singlet for the α-proton of the pyridine ring. In the case of the quinolone form, the signal of the 7-H proton would be a doublet, as seen in the structures (V).

Thus, the thermal cyclization of the aminocrotonates (IIa, b) and aminomethylenemalonates (Va, b) both with and without a methyl group at the indole nitrogen atom takes place readily and provides a convenient method for the production of pyrroloquinolines with known angular structure and with functional substituents in the pyridine ring.

TABLE 2. Pyrroloquinolines

Compound	mp, °C	R_f (system)	UV spectrum		PMR spectrum, δ, ppm	Molecular formula	Found % / Calculated %		Yield, %
			λ_{max}	lg ε			C	H	
IIIa	195...197	0,38 (A)	235 252 298 356	4,11 4,09 4,28 3,27	1,43 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); 2,23 (3H, s, 3-CH_3); 2,41 (3H, s, 2-CH_3); 2,71 (3H, s, 5-CH_3); 2,88 (3H, s, 7-CH_3); 4,41 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 7,73 (1H, s, 4-H); 9,19 (1H, s, 9-H); 11,67 (1H, s, 1-H)	$C_{18}H_{20}N_2O_2$	72,55 72,95	6,71 6,80	60
IIIb	149...151	0,57 (A)	238 255 298 362	4,26 4,23 4,45 3,23	1,40 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); 2,26 (3H, s, 3-CH_3); 2,41 (3H, s, 2-CH_3); 2,72 (3H, s, 5-CH_3); 2,89 (3H, s, 7-H); 4,04 (3H, s, 1-CH_3); 4,42 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 7,80 (1H, s, 4-H); 9,27 (1H, s, 9-H)	$C_{19}H_{22}N_2O_2$	73,21 73,52	7,01 7,14	64
IVa	>300	0,45 (B)	223 260 285 356	4,30 4,19 4,31 3,62	2,20 (3H, s, 3-CH_3); 2,39 (3H, s, 2-CH_3); 2,45 (3H, s, 7-CH_3); 2,59 (3H, s, 5-CH_3); 6,02 (1H, s, 8-H); 7,49 (1H, s, 4-H); 10,15 (1H, s, NH or OH); 10,79 (1H, s, 1-H)	$C_{15}H_{16}N_2O$	75,10 74,97	6,85 6,71	88
IVb	279...280	0,45 (B)	228 263 294 358	4,18 3,86 4,20 3,24	2,20 (3H, s, 3-CH_3); 2,31 (3H, s, 2-CH_3); 2,40 (3H, s, 7-CH_3); 2,54 (3H, s, 5-CH_3); 3,95 (3H, s, 1-CH_3); 5,94 (1H, s, 8-H); 9,78 (1H, s, NH or OH)	$C_{16}H_{18}N_2O$	75,32 75,56	6,98 7,13	52
VIa	251...252	0,47 (B)	215 250 303 355	4,27 3,80 (sh.) 4,24 3,52	1,32 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); 2,22 (3H, s, 3-CH_3); 2,41 (3H, s, 2-CH_3); 2,56 (3H, s, 5-CH_3); 7,62 (3H, s, 4-H); 4,26 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 8,40 (1H, s, 7-H); 11,18 (1H, s, OH); 11,44 (1H, s, 1-H)	$C_{17}H_{18}N_2O_3$	68,51 68,44	6,00 6,08	92
VIb	240...241	0,52 (B)	220 250 310 355	4,33 3,86 (sh.) 4,23 3,53	1,31 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); 2,22 (3H, s, 3-CH_3); 2,33 (3H, s, 2-CH_3); 2,52 (3H, s, 5-CH_3); 3,85 (3H, s, 1-CH_3); 4,24 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 7,60 (1H, s, 4-H); 8,30 (1H, s, 7-H); 11,09 (1H, s, OH)	$C_{18}H_{20}N_2O_3$	69,01 69,21	6,15 6,45	23

EXPERIMENTAL

The PMR spectra were recorded in DMSO-d_6 on a Bruker AC-200P instrument with reference to TMS. The IR spectra were measured in ethanol on a Specord instrument. The reactions and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates in 10:1 benzene—ethyl acetate (A) and 10:1 ethyl acetate—methanol (B) systems. The spectral and other characteristics of the obtained compounds are given in Tables 1 and 2.

Ethyl β-(2,3,5-Trimethyl-6-indolylamino)crotonate (IIa). A solution of 0.6 g (3.4 mmole) of 2,3,5-trimethyl-6-aminoindole (Ia) and 0.5 g (3.8 mmole) of acetoacetic ester in absolute benzene with traces of hydrogen chloride was heated for 14-15 h (monitored by chromatography) with a Dean—Stark tube. At the end of the reaction the benzene was distilled. The product was recrystallized from petroleum ether.

Ethyl β-(1,2,3,5-Tetramethyl-6-indolylamino)crotonate (IIb). The product was obtained by a similar method from the aminoindole (Ib).

2,3,5,7-Tetramethyl-8-ethoxycarbonylpyrrolo[2,3-*f*]quinoline (IIIa). To a solution of 0.5 g (1.7 mmole) of the aminocrotonate (IIa) in chloroform we added the Vilsmeier reagent, prepared from 1 ml of phosphorus oxychloride and 1 ml of DMFA. The mixture was boiled for 6 h. The residue after distillation of the chloroform was treated with aqueous ammonia. The precipitate was filtered off, washed with water, and purified by preparative TLC on aluminum oxide (Brockman, neutral) in 1:1 benzene—ethyl acetate.

1,2,3,5,7-Pentamethyl-8-ethoxycarbonylpyrrolo[2,3-*f*]quinoline (IIIb). The product was obtained by a similar method from the aminocrotonate (IIb).

2,3,5,7-Tetramethyl-9-hydroxypyrrolo[2,3-*f*]quinoline (IVa). To 5 ml of boiling biphenyl we added 0.2 g (0.7 mmole) of the aminocrotonate (IIa). The mixture was boiled for a further 15 min. The warm reaction mass was poured into 50 ml of petroleum ether. The precipitate was filtered off and washed repeatedly with petroleum ether. The product was recrystallized from alcohol.

1,2,3,5,7-Pentamethyl-9-hydroxypyrrolo[2,3-*f*]quinoline (IVb). The product was obtained by a similar method from the aminocrotonate (IIb).

Diethyl 2,3,5-Trimethyl-6-indolylaminomethylenemalonate (Va). A mixture of 1 g (5.7 mmole) of the aminoindole (Ia) and 1.24 g (5.7 mmole) of diethyl ethoxymethylenemalonate in 20 ml of ethanol was boiled for 2 h. After cooling, the precipitate was filtered off and the product was recrystallized from alcohol.

Diethyl 1,2,3,5-Tetramethyl-6-indolylaminomethylenemalonate (Vb). The product was obtained by a similar method from the aminoindole (Ib).

2,3,5-Trimethyl-9-hydroxy-8-ethoxycarbonylpyrrolo[2,3-*f*]quinoline (VIa). To 5 ml of boiling Dowtherm we added 0.5 g (1.5 mmole) of the aminomethylenemalonate (Va). The mixture was heated for 20 min, and the product was isolated by the method used for the preparation of compound (IVa).

1,2,3,5-Tetramethyl-9-hydroxy-8-ethoxycarbonylpyrrolo[2,3-*f*]quinoline (VIb). The product was obtained similarly from the aminomethylenemalonate (Vb).

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