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2,3-DIMETHYL-7-METHOXY-6-AMINOINDOLE IN THE SYNTHESIS OF LINEAR PYRROLOQUINOLINES

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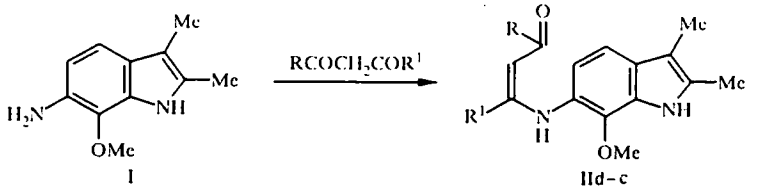
The possibility of using 2,3-dimethyl-7-methoxy-6-aminoindole for the production of pyrroloquinolines was studied. It was established that the methoxy group at position 7 activates the closure of the pyridine ring with the formation of linearly fused pyrroloquinolines in the Combe reaction, under the conditions of the Vilsmeier reaction and of the thermal cyclization of aminocrotonate, and in the high-temperature cyclization of aminomethylenemalonate.

It is well known that the use of 6-aminoindoles with two free *ortho* positions in relation to the amino group in the reactions leading to the formation of pyrroloquinolines leads to a mixture of the linear and angular isomers (acid conditions) [1] or to the angular isomer alone (thermal cyclization) [2].

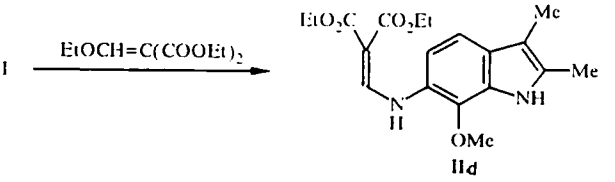
In order to obtain the linear pyrroloquinolines we studied the reaction of 2,3-dimethyl-7-methoxy-6-aminoindole (I) with the diketones acetoacetic and malonic esters. It was established that the condensation of the aminoindole (I) with acetylacetone and dibenzoylmethane took place more readily than in the case of 6-aminoindoles without the methoxyl group in the benzene ring. This is obviously explained by the higher nucleophilicity of the employed amine.



I IId–c

IIa $R = R^1 = Me$; b $R = R^1 = Ph$; c $R = Me$, $R^1 = OEt$

The aminocrotonate (IIc) and aminomethylenemalonate (IId) are formed just as readily from compound (I).



IId

It was to be expected that the presence of the methoxy group at the *meta* position to the point of cyclization would deactivate the formate of the corresponding pyrroloquinolines. It is known that a methoxy group at the *ortho* position to the enamine group blocks or completely excludes the formation of the quinoline system under the conditions of acid cyclization in the case of the corresponding anilines [3]. Despite this, the enamino ketones (IIa, b) in trifluoroacetic acid are transformed very smoothly into the corresponding linear pyrroloquinolines (IIIa, b).

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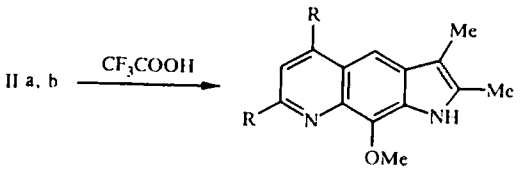
TABLE 1. Enamines

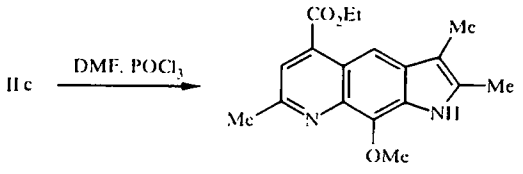
Compound	mp, °C	R_f (system)	UV spectrum		PMR spectrum, δ, ppm	Molecular formula	Found % / Calculated %		Yield, %
			λ_{max}	lg ε			C	H	
IIa	175...176	0,24 (A)	230 315	4,37 4,08	1,76 (3H, s, CH_3C=); 2,01 (3H, s, CH_3CO); 2,09 (3H, s, 3-CH_3); 2,25 (3H, s, 2-CH_3); 3,90 (3H, s, OCH_3); 5,17 (1H, s, H vin); 6,58 (1H, d, J = 11 Hz, 5-H); 6,66 (1H, d, J = = 11 Hz, 4-H); 10,78 (1H, s, 1-H); 12,24 (1H, s, NH imine .)	$C_{16}H_{20}N_2O_2$	70,23 70,56	7,59 7,40	69
IIb	225...227	0,59 (A)	220 278 350	4,42 3,86 4,02	2,31 (3H, s, 3-CH_3); 2,40 (3H, s, 2-CH_3); 3,80 (3H, s, OCH_3); 6,10 (1H, s, H vin .); 6,14 (1H, d, J= 11 Hz, 5-H); 6,29 (1H, d, J = 11 Hz, 4-H); 7,62 (10H, m, $2C_6H_5$); 10,73 (1H, s, 1-H)	$C_{26}H_{24}N_2O_2$	78,60 78,76	5,93 6,10	38
IIc	145...146	0,62 (A)	230 295	4,32 4,11	1,21 (3H, m, J = 7 Hz, $CH_2\underline{CH_3}$); 1,71 (3H, s, CH_3C=); 2,15 (3H, s, 3-CH_3); 2,26 (3H, s, 2-CH_3); 3,91 (3H, s, OCH_3); 4,09 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 4,61 (1H, s, H vin); 6,54 (1H, d, J = 11 Hz, 5-H); 6,63 (1H, d, J = 11 Hz, 4-H); 10,10 (1H, s, 1-H); 10,80 (1H, s, NH imine)	$C_{17}H_{22}N_2O_3$	67,79 67,53	7,10 7,33	46
IId	180...181	0,33 (A)	225 270 345	4,11 3,92 3,76	1,27 (6H, m, $2CH_2\underline{CH_3}$); 2,35 (3H, s, 3-CH_3); 2,39 (3H, s, 2-CH_3); 3,92 (3H, s, OCH_3); 4,20 (4H, m, $\underline{CH_2}CH_3$); 6,60 (1H, d, J = 11 Hz, 5-H); 6,77 (1H, d, J = 11 Hz, 4-H); 8,35 (1H, d, J = 16 Hz, H vin .); 10,90 (1H, s, 1-H); 11,10 (1H, d, J = 16 Hz, H vin .)	$C_{19}H_{24}N_2O_5$	63,22 63,32	6,80 6,71	32



III a, b

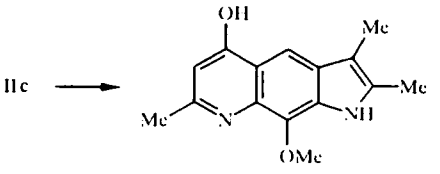
III a R = Me, b R = Ph

The experimental data indicate a unique distribution of electron density in the indole structure. Like the enamino ketones, the aminocrotonate (IIc) is easily transformed into the pyrroloquinoline (IIIc) under the conditions of the Vilsmeier reaction.



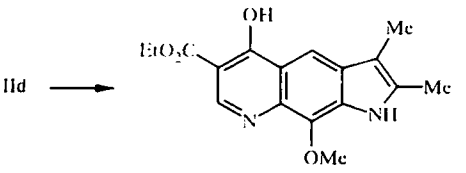
IIIc

As mentioned above, in the case where there are two free *ortho* positions in the aromatic ring, the cyclization of aminocrotonates and aminomethylenemalonates leads to the formation of only the corresponding pyrroloquinolines with angular fusion of the rings [2]. It was interesting to determine whether the formation of a linear pyrroloquinoline system was possible under conditions where angular cyclization is impossible on account of a substituent at position 7 of 6-aminoindole. We showed that the linear pyrroloquinoline (IIId) was formed readily with a good yield when the aminocrotonate (IIc) was boiled in biphenyl.



III d

The aminocrotonate undergoes analogous cyclization to the pyrroloquinoline (IIIe) in boiling Dowtherm.



III e

The spectral and other characteristics of the obtained compounds agree with published data and are given in Tables 1 and 2.

Thus, irrespective of the presence of a methoxyl group in the benzene ring, the cyclization of the enamino ketones (IIa, b) in an acidic medium and of the aminocrotonate under the conditions of the Vilsmeier reaction takes place readily with the formation of pyrroloquinolines with linear fusion of the rings. Thermal cyclization of the crotonate (IIc) and of the aminomethylenemalonate (IId) is a convenient method for the production of pyrroloquinolines with functional groups in the pyridine ring.

EXPERIMENTAL

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

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	
III a	198...199	0,40 (B)	212 235 264 340	4,20 4,37 4,34 3,84	2,36 (3H, s, 3-CH_3); 2,60 (3H, s, 2-CH_3); 2,61 (3H, s, 5-CH_3); 2,68 (3H, s, 7-CH_3); 4,02 (3H, s, OCH_3); 6,83 (1H, s, 6-H); 7,05 (1H, s, 4-H); 11,08 (1H, s, 1-H)	$C_{16}H_{18}N_2O$	75,71 75,56	6,92 7,13	60
III b	194...195	0,70 (A)	215 250 295 360	4,34 4,44 4,33 3,97	2,41 (3H, s, 3-CH_3); 2,80 (3H, s, 2-CH_3); 3,88 (3H, s, OCH_3); 6,80 (1H, s, 6-H); 7,85 (11H, m, 4-Hand5-, 7-C_6H_5); 11,30 (1H, s, 1-H)	$C_{20}H_{22}N_2O$	82,30 82,51	5,63 5,86	40
III c	188...189	0,50 (A)	205 240 285	4,05 4,23 4,41	1,40 (3H, m, J = 7 Hz, $CH_2\underline{CH_3}$); 2,40 (3H, s, 3-CH_3); 2,69 (3H, s, 2-CH_3); 2,95 (3H, s, 7-CH_3); 4,02 (3H, s, OCH_3); 4,39 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 7,00 (1H, s, 4-H); 8,68 (1H, s, 5-H); 11,39 (1H, s, 1-H)	$C_{18}H_{20}N_2O_3$	69,50 69,21	6,21 6,45	39
III d	>300	0,75 (C)	208 230 260 340	4,18 4,41 4,39 3,97	2,34 (3H, s, 7-CH_3); 2,40 (3H, s, 3-CH_3); 2,51 (3H, s, 2-CH_3); 4,02 (3H, s, OCH_3); 5,91 (1H, s, 6-H); 7,18 (1H, s, 4-H); 9,32 (1H, s, OH); 11,20 (1H, s, 1-H)	$C_{15}H_{16}N_2O_2$	70,45 70,29	6,02 6,29	47
III e	241...242	0,32 (B)	210 222 233 250 339	4,26 4,25 4,38 4,45 4,65	1,31 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); 2,39 (3H, s, 3-CH_3); 2,56 (3H, s, 2-CH_3); 4,02 (3H, s, OCH_3); 4,30 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 7,28 (1H, s, 4-H); 7,40 (1H, s, 7-H); 8,50 (1H, s, OH); 11,49 (1H, s, 1-H)	$C_{17}H_{18}N_2O_4$	64,65 64,96	6,00 5,77	57

4-(2,3-Dimethyl-7-methoxy-6-indolylamino)-3-penten-2-one (IIa). The compound was obtained from 2,3-dimethyl-7-methoxy-6-aminoindole and acetylacetone, as described in [4]. It was purified by recrystallization from petroleum ether.

1,3-Diphenyl-3-(2,3-dimethyl-7-methoxy-6-indolylamino)-2-propen-1-one (IIb). The compound was obtained from 2,3-dimethyl-7-methoxy-6-aminoindole and dibenzoylmethane by the method in [4]. The product was purified by preparative TLC on aluminum oxide (Brockman neutral) with chloroform as eluant.

Ethyl β-(2,3-Dimethyl-7-methoxy-6-indolylamino)crotonate (IIc). A solution of equimolar amounts of 2,3-dimethyl-7-methoxy-6-indole and acetoacetic ester was boiled in absolute benzene in the presence of traces of glacial acetic acid for 6 h with a Dean—Stark tube. At the end of the reaction the benzene was distilled. The crotonate was purified by recrystallization from a mixture of benzene and petroleum ether.

Diethyl 2,3-Dimethyl-7-methoxy-6-indolylaminomethylenemalonate (IId). A solution of equimolar amounts of 2,3-dimethyl-7-methoxy-6-aminoindole and ethoxymethylenemalonic acid in alcohol was boiled for 1.5-2 h. The solution was evaporated a little and cooled, and the precipitate was filtered off.

2,3,5,7-Tetramethyl-9-methoxypyrrolo[3,2-*g*]quinoline (IIIa). The compound was obtained by boiling the enamino ketone (IIa) in a 20-fold excess of trifluoroacetic acid for 30 min. The cooled solution was poured into a dilute aqueous solution with ice. The precipitate was filtered off and purified by recrystallization from petroleum ether.

2,3-Dimethyl-5,7-diphenyl-9-methoxypyrrolo[3,2-*g*]quinoline (IIIb). The compound was obtained similarly from the enamino ketone (IIb).

2,3,7-Trimethyl-9-methoxy-6-ethoxycarbonylpyrrolo[3,2-*g*]quinoline (IIId). The compound was obtained by boiling the aminocrotonate (IIc) with a fivefold excess of the Vilsmeier reagent in chloroform for 4 h. After distillation of the chloroform, the solid residue was treated with aqueous ammonia. The precipitate was filtered off and purified by recrystallization from a mixture of benzene and petroleum ether.

2,3-Dimethyl-5-hydroxy-9-methoxy-ethoxycarbonylpyrrolo[3,2-*g*]quinoline (IIIe). The aminomethylene malonate was added to boiling Dowtherm (a 10-fold excess), and the reaction was conducted as in the case of the production of the pyrroloquinoline (IIId). The product was purified by recrystallization from a mixture of benzene and petroleum ether.

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