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1,2,3-TRIMETHYL-5-AMINOINDOLE IN REACTIONS WITH ACETOACETIC ESTER AND ETHOXYMETHYLENE-MALONIC ESTER

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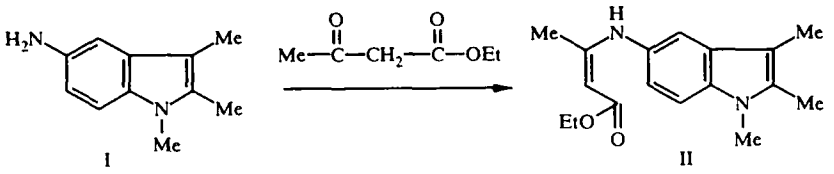
A method is proposed for obtaining N-methylpyrrolo[3,2-f]quinolines with functional groups on the pyridine ring.

We had reported previously that 1,2,3-trimethyl-5-aminoindole (I) in the Combes reaction with acetylacetone and dibenzoylmethane, through a stage of formation of enaminoketones, is converted to the corresponding pyrroloquinolines with linear joining of the rings [1]. The work reported here was aimed at following the influence of the N–Me group on the direction of cyclization to pyrroloquinolines in the case of an aminocrotonate (under conditions of the Vilsmeier reaction) and an aminomethylmalonate (thermal), obtained on the basis of the aminoindole I.

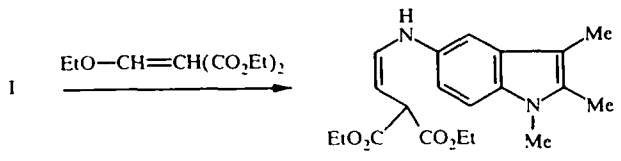
The aminocrotonate of 1,2,3-trimethyl-5-aminoindole (II) was obtained by a standard method, in which the aminoindole I is refluxed in benzene with acetoacetic ester



I II

In the PMR spectrum of the enamine II, singlet signals of the imine and vinyl protons are observed at 10.13 and 4.48 ppm, which is evidence of the enaminocrotonate form of this compound. According to [2], such a value of the chemical shift of the signal of the imine proton in the PMR spectra is characteristic for enaminocrotonates in the molecules of which the ethoxycarbonyl and NH groups are in the cis position relative to each other. This is further supported by the position of the signal from protons of the β-Me group, manifested in strong fields (1.76 ppm), indicating that this group is at a distance from the ethoxycarbonyl group. It should be noted that for the isomeric trans structures, the signal of the proton of the NH_{imine} group is shifted 2 ppm upfield, while the signal of the β-methyl protons, in contrast, is shifted 0.3 ppm downfield [2].

When the aminoindole I is refluxed in alcohol with the ethoxymethylenemalonic ester, the aminomethylenemalonate III is formed:



III

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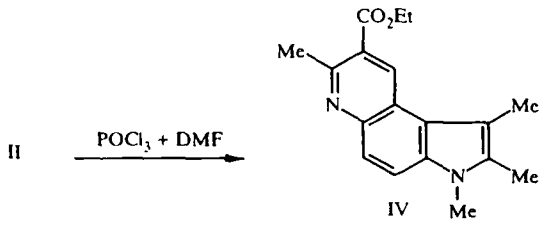
TABLE 1. Characteristics of Enamines II and III and Pyrroloquinolines IV and V

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	R_f (and system)	UV spectrum		PMR spectrum, δ, ppm	Yield, %
		C	H			λ_{max}	lg ε		
II, ethyl ester of β-(1,2,3-trimethyl-5-aminoindolyl)-crotonic acid	$C_{17}H_{22}N_2O_2$	69,85 / 71,30	7,51 / 7,74	56...57	0,43 (A)	205 228 294	4,00 4,11 4,22	1,17 (3H, t, $OCH_2\underline{CH_3}$, J = 7 Hz); 1,78 (3H, s, β-CH_3); 2,15 (3H, s, 3-CH_3); 2,28 (3H, s, 2-CH_3); 3,62 (3H, s, 1-CH_3); 4,05 (2H, q, $O\underline{CH_2}CH_3$, J = 7 Hz); 4,48 (1H, s H_{vin}); 6,68 (1H, d, 6-H, J_{67} = 9 Hz); 6,93 (1H, d, 7-H, J_{76} = 9 Hz); 7,08 (1H, s, 4-H); 10,13 (1H, s, NH vin)	49
III, diethyl ester of N-(1,2,3-trimethyl-indolyl-5)aminomethyl-enemalonic acid	$C_{19}H_{24}N_2O_4$	66,01 / 66,26	7,19 / 7,02	115...116	0,36 (A)	206 230 309 340	4,32 4,29 4,24 4,18	1,28 (6H, m, $OCH_2\underline{CH_3}$); 2,23 (3H, s, 3-CH_3); 2,36 (3H, s, 2-CH_3); 3,64 (3H, s, 1-CH_3); 4,20 (4H, m, $O\underline{CH_2}CH_3$); 7,04 (1H, d, 7-H, J_{67} = 6 Hz); 7,35 (2H, d, 4- & 6-H, J_{76} = 6 Hz); 8,45 (1H, d, J = 16 Hz, H vin); 10,84 (1H, d, J = 16 Hz, NH vin)	35
IV, 1,2,3,7-tetramethyl-8-ethoxycarbonylpyrrolo-[3,2-f]quinoline	$C_{18}H_{20}N_2O_2$	72,59 / 72,98	6,71 / 6,80	188...189	0,80 (B)	205 244 294 (sh) 385	4,14 4,38 3,93 3,55	1,46 (3H, t, $OCH_2\underline{CH_3}$, J = 7 Hz); 2,41 (3H, s, 1-CH_3); 2,50 (3H, s, 2-CH_3); 2,80 (3H, s, 7-CH_3); 3,63 (3H, s, 3-CH_3); 4,36 (2H, q, $O\underline{CH_2}CH_3$, J = 7 Hz); 7,53 (1H, d, J_{45} = 9 Hz, 4-H); 7,28 (1H, d, J_{54} = 9 Hz, 5-H); 9,06 (1H, s, 9-H)	51
V, 1,2,3-trimethyl-9-hydroxy-8-ethoxycar-bonylpyrrolo[3,2-f]-quinoline	$C_{17}H_{18}N_2O_3$	68,33 / 68,44	6,00 / 6,08	262...264	0,14 (B)	228 266 (sh) 307 350 (sh)	4,18 3,78 4,00 3,70	1,31 (3H, t, $OCH_2\underline{CH_3}$, J = 7 Hz); 2,40 (3H, s, 1-CH_3); 2,66 (3H, s, 2-CH_3); 3,74 (3H, s, 1-CH_3); 3,63 (3H, s, 3-CH_3); 4,23 (2H, q, $O\underline{CH_2}CH_3$, J = 7 Hz); 7,22 (1H, d, J_{45} = 9 Hz 4-H); 7,28 (1H, d, J_{54} = 9 Hz, 5-H); 8,71 (1H, s 7-H)	46

The PMR spectrum of compound III is slightly different from that of the enamine II. The signal of the vinyl proton undergoes a downfield shift by 4 ppm, related to the influence of the cis-positioned ethoxycarbonyl group. Analogously, but to a lesser degree, the doublet signal of the proton of the NH_{imine} group is shifted downfield. The multiplicity of this signal is due to spin-spin coupling with the vinyl proton (J = 17 Hz).

In the UV spectra of the enamine II, three absorption bands are manifested, approximately equal in intensity, at 205, 228, and 294 nm. The two short-wave bands are apparently related to $\pi-\pi^*$ transitions in the pyrrole part of the molecule, while the long-wave band is related to transitions in the benzene ring containing the enamine fragment. For comparison: in the spectrum of the original amine I, the long-wave band has a considerably lower intensity. In the electronic spectrum of the enamine III there is still another long-wave band (340 nm), apparently due to the presence of the second ethoxycarbonyl group.

For the enamines II and III, we could expect cyclization to form pyrroloquinolines, with the participation of positions 4 and 6 of the indole molecule. However, we have established that the enaminocrotonate II, under conditions of the Vilsmeier reaction, is converted to the pyrroloquinoline IV with angular joining of the rings (i.e., the cyclization takes place only through position 4).

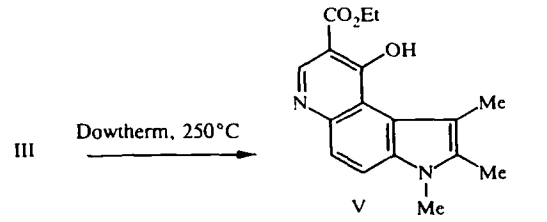


As already reported [3], in the case of such an enamine without a methyl group at the indole nitrogen atom, we observe the formation of a small quantity of the linear pyrroloquinoline, along with predominant formation of the angular isomer.

Formation of the angular isomer is confirmed by the PMR spectrum of the pyrroloquinoline IV, which exhibits two doublet signals of ortho-protons (4-H and 5-H) of the benzene ring at 7.53 and 7.70 ppm.

The relative intensities of the absorption bands at 244 and 294 nm (4.38 and 3.93) in the UV spectrum of compound IV are characteristics for angular-jointed pyrroloquinolines. For the linear isomers, the ratio of intensities of these bands is the opposite [3].

Annelation of the pyridine ring upon thermolysis of compound III in boiling Dowtherm also proceeds with participation of the $C_{(4)}$ atom of the indole molecule, and it leads to the formation of the angular pyrroloquinoline V.



This is evidenced, the same as in the case of the pyrroloquinoline IV, by the presence of two doublet signals of the protons 4-H and 5-H at 7.22 and 7.75 ppm in the PMR spectrum of the pyrroloquinoline V. The distinct singlet of the α-H proton of pyridine (8.71 ppm) suggests that this compound exists in the hydroxyquinoline form.

The characteristics of compounds II-IV are listed in Table 1.

Thus, the introduction of a methyl group onto the indole nitrogen atom of 2,3-dimethyl-5-aminoindole does not have any substantial effect on the course of reactions with acetoacetic ester or ethoxymethylenemalonic ester, in either the condensation stage of the cyclization stage; i.e., this method can be used to obtain N-methylpyrrolo[3,2-f]quinolines with functional substituents on the pyridine ring.

EXPERIMENTAL

The PMR spectra of compounds II and IV were registered in a Tesla BS-467 instrument with a working frequency of 60 MHz, in CCl_4, relative to HMDS; the spectra of compounds III and V were registered in a Bruker AC-200P instrument, in DMSO-d_6, relative to TMS. The course of the reaction and the purity of the compounds that were obtained were monitored by means of TLC on Silufol UV-254 plates in the following systems: *A*) benzene–ethyl acetate, 10:1; *B*) ethyl acetate–methanol, 2:1. Spectral characteristics and other characteristics of the compounds that were obtained are listed in Table 1.

Ethyl ester of β-(1,2,3-trimethyl-5-aminoindolyl)crotonic acid (II) was obtained from the aminoindole I by a procedure described in [4]. The product was purified by passing through a layer of aluminum oxide, in heptane heated to the boiling point.

Diethyl ester of N-(1,2,3-trimethyl-5-indolyl)aminomethylenemalonic acid (III) was synthesized by refluxing equimolar quantities of the aminoindole I and ethoxymethylenemalonic ester in ethanol for 1.5 h. The product was purified by recrystallization from aqueous alcohol.

1,2,3,7-Tetramethyl-8-ethoxycarbonylpyrrolo[3,2-f]quinoline (IV) was obtained from the aminocrotonate II as described in [3]. The product was purified by passing through a layer of aluminum oxide in a mixture of benzene and ethyl acetate, heated to the boiling point. The product was recrystallized from heptane or aqueous ethanol.

1,2,3-Trimethyl-9-hydroxy-8-ethoxycarbonylpyrrolo[3,2-f]quinoline (V) was obtained by refluxing compound III in Dowtherm for 20 min. The product was precipitated from the reaction mixture by heptane, and purified by recrystallization from heptane.

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