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SYNTHESIS OF SUBSTITUTED PYRROLO[3,2-*f*]QUINOLINES

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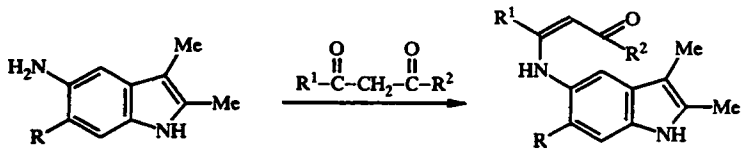
Reactions of 2,3,6-trimethyl- and 2,6-dimethyl-6-methoxy-5-aminoindoles with 1,3-dicarbonyl compounds represent a convenient route for obtaining substituted pyrrolo[3,2-f]quinolines, even though the presence of a methoxy group on the benzene ring sometimes lowers the reactivity of the amine, thus increasing the required reaction time and reducing the yield.

As reported previously [1], enamines obtained from 5-aminoindoles, under conditions of acid cyclization, are converted to pyrroloquinolines with the rings joined either linearly or at an angle. The direction taken by the ring formation reaction is greatly influenced by the steric requirements of the substituent in position 3 of the indole, and also by the character of the enamine fragment. Thus, a methyl group in the β-position of the pyrrole ring completely blocks the formation of angular pyrroloquinolines in the case of cyclization of enaminoketones obtained from 2,3-dimethyl-5-aminoindoles.

With the aim of obtaining pyrroloquinolines with a predetermined angular joining of the rings, we investigated the possibility of using 6-substituted 5-aminoindoles, in particular 2,3,6-trimethyl-5-aminoindole (I) and 2,3-dimethyl-6-methoxy-5-aminoindole (II). The latter compound is of particular interest, since in the previously studied 5- and 7-methoxy-6-aminoindoles, the methoxy group was found to have an ambiguous influence on the process of forming the pyridine ring under various conditions of cyclization [2].

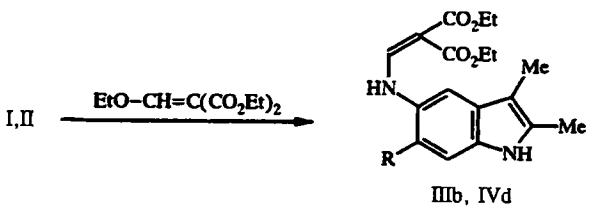
In the present work, the syntheses of enamines based on the aminoindoles I and II were performed by methods described in [1, 2]. Reactions with acetylacetone and dibenzoylmethane gave the corresponding enaminoketones IVa,b, and with acetoacetic ester the aminocrotonates IIIa and IVc.



I, II IIIa, IVa-c

I,III) R = Me; II, IV R = OMe; IIIa) R^1 = Me, R^2 = OEt; IVa) R^1 = R^2 = Me; IVb) R^1 = R^2 = Ph; IV) R^1 = Me, R^2 = OEt

Upon interaction of the aminoindoles I and II with ethoxymethylenemalonic ester, we recovered the corresponding enaminomethylenemalonates IIIb and IVd.



IIIb, IVd

IIIb R = Me; IVd R = OMe

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TABLE 1. Synthesis Conditions and Characteristics of Enamines III and IV

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (and system)	UV spectrum		PMR spectrum, δ, ppm	Reaction conditions and duration	Yield, %
		C	H	M+			λ_{max}	lg ε			
1	2	3	4	5	6	7	8	9	10	11	12
IIIa, ethyl ester of β-(2,3,6-trimethyl-5-indolyl)-aminocrotonic acid	$C_{17}H_{22}N_2O_2$	69,78 / 71,30	7,51 / 7,74	— / 286	166,5...167	0,53 (A)	204, 230, 292	4,20, 4,32, 4,36	1,25 (3H, t, $OCH_2\underline{CH_3}$, J = 7 Hz); 1,75 (3H, s, β-CH_3); 2,12 (3H, s, 3-CH_3); 2,25 (3H, s, 2-CH_3); 2,30 (3H, s, 6-CH_3); 4,08 (2H, q, $O\underline{CH_2}CH_3$, J = 7 Hz); 4,62 (1H, s, H_{vin}); 7,12 (2H, s, 4-H, 7-H); 9,95 (1H, s, 1-H); 10,46 (1H, s, NH_{imine})	C, 8 h	60
IIIb, diethyl ester of (2,3,6-trimethyl-5-indolyl)-aminomethylenemalonic acid	$C_{19}H_{24}N_2O_4$	66,20 / 66,26	6,94 / 7,02	344 / 344	165,5...166,5	0,21 (A)	206, 232, 298, 345	4,22, 4,18, 4,17, 4,13	1,30 (6H, m, $2OCH_2\underline{CH_3}$); 2,20 (3H, s, 2-CH_3); 2,40 (3H, s, 6-CH_3); 4,20 (4H, m, $2O\underline{CH_2}CH_3$); 7,12 (1H, s, 7-H); 7,28 (1H, c, 4-H); 8,44 (1H, d, H_{vin}, J = 16Hz); 10,47 (1H, s, 1-H); 10,88 (1H, d, NH_{imine})	D, 1 h	90
IVa, 4-(2,3-dimethyl-6-methoxy-5-indolyl)-amino-3-penten-2-one	$C_{16}H_{20}N_2O_2$	70,11 / 70,56	7,19 / 7,40	— / 272	202...203	0,07 (A)	208, 233, 323	4,20, 4,22, 4,17	1,88 (3H, s, β-CH_3); 1,98 (3H, s, α-CH_3); 2,13 (3H, s, 3-CH_3); 2,30 (3H, s, 2-CH_3); 3,79 (3H, s, OCH_3); 5,18 (1H, s, H_{vin}); 6,89 (1H, s, 7-H); 7,13 (1H, s, 4-H); 10,41 (1H, s, 1-H); 12,07 (1H, s, NH_{imine})	A, 8 h	52

TABLE 1 (continued)

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (and system)	UV spectrum		PMR spectrum, δ, ppm	Reaction conditions and duration	Yield, %
		C	H	M*			λ_{max}	lg ε			
1	2	3	4	5	6	7	8	9	10	11	12
IVb, 1,3-biphenyl-3-(2,3-dimethyl-6-methoxy-5-indolyl)-amino-3-propen-1-one	$C_{26}H_{24}N_2O_2$			—/396	100...101	0,30 (A)	206, 244 (sh), 303, 435	4,30, 4,20, 3,97, 3,86	1,83 (3H, s, 3-CH_3); 2,20 (3H, s, 2-CH_3); 3,80 (3H, s, OCH_3); 6,07 (1H, s, Hvin); 6,50 (1H, s, 7-H); 6,80 (1H, s, 4-H); 7,70 (10H, m, $2C_6H_5$); 10,35 (1H, s, 1-H); 12,75 (1H, s, NH_{imine})	B, 5 h	24
IVc, ethyl ester of β-(2,3-dimethyl-6-methoxy-5-indolyl)aminocrotonic acid	$C_{17}H_{22}N_2O_3$			—/302	149...151	0,36 (A)	208, 230, 310	4,21, 4,25, 4,07	1,22* (3H, t, $OCH_2\underline{CH_3}$, J = 7 Hz); 1,79 (3H, s, β-CH_3); 2,10 (3H, s, 3-CH_3); 2,23 (3H, s, 2-CH_3); 3,83 (3H, s, OCH_3); 4,00 (2H, q, $O\underline{CH_2}CH_3$, J = 7 Hz), 4,58 (1H, s, Hvin); 6,87 (1H, s, 7-H); 7,25 (1H, s, 4-H); 9,69 (1H, s, 1-H); 10,21 (1H, s, NH_{imine})	C, 13 h	45
IVd, diethyl ester of N-(2,3-dimethyl-6-methoxy-5-indolyl)aminomethylenemalonic acid	$C_{19}H_{24}N_2O_5$	63,51/63,32	6,43/6,71	360/360	240...241	0,11 (A)	206, 238, 285, 362	4,06, 3,94, 3,92, 4,08	1,32 (6H, m, $2OCH_2\underline{CH_3}$); 2,15 (3H, s, 3-CH_3); 2,30 (3H, s, 2-CH_3); 3,90 (3H, s, OCH_3); 4,20 (4H, m, $2O\underline{CH_2}CH_3$); 6,94 (1H, s, 7-H); 7.33 (1H, s, 4-H); 8,54 (1H, d, Hvin, J = 16 Hz); 10,40 (1H, s, 1-H); 10,95 (1H, d, NH_{imine}, J = 16 Hz)	D, 5 h	61

*In CCl_4, relative to HMDS.

TABLE 2. Synthesis Conditions and Characteristics of Pyrroloquinolines V and VI

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (and system)	UV spectrum		PMR spectrum, δ, ppm	Reaction conditions and duration	Yield, %
		C	H	M*			λ_{max}	lgε			
1	2	3	4	5	6	7	8	9	10	11	12
Va, 1,2,3,7-tetramethyl-8-ethoxycarbonylpyrrolo-[3,2-f]quinoline	$C_{18}H_{20}N_2O_2$	73,09 / 72,98	6,72 / 6,80	296 / 296	242...244	0,89 (B)	204, 241, 294, 357	3,98, 4,26, 3,80, 3,36	1,44 (3H, t, $OCH_2\underline{CH_3}$, J = 7 Hz); 2,40 (3H, s, 1-CH_3); 2,50 (3H, s, 2-CH_3); 2,74 (3H, s, 5-H); 2,80 (3H, s, 7-CH_3); 4,40 (2H, q, $O\underline{CH_2}CH_3$, J = 7 Hz); 7,70 (1H, s, 4-H); 9,17 (1H, s, 9-H); 11,15 (1H, s, 3-H)	F, 4 h	80
Vb, 1,2,5-7-tetramethyl-9-hydroxypyrrolo[3,2-f]-quinoline	$C_{15}H_{16}N_2O$	74,82 / 74,97	6,38 / 6,71	240 / 240	>300	0,86 (B)	217, 246, 255, 293, 350	4,33, 4,18, 4,19, 3,97, 3,94	2,35 (3H, s, 1-CH_3); 2,40 (3H, s, 2-CH_3); 2,53 (3H, s, 5-CH_3); 2,62 (3H, s, 7-CH_3); 5,84 (1H, s, 8-H); 7,35 (1H, s, 4-H); 9,61 (1H, s, 6-H); 10,72 (1H, s, 3-H)	G, 15 min	59
Vc, 1,2,5-trimethyl-9-hydroxy-8-ethoxycarbonylpyrrolo-[3,2-f]quinoline	$C_{17}H_{18}N_2O_3$	67,92 / 68,44	6,01 / 6,08	298 / 298	202...204	0,68 (B)	208 (sh), 229, 307, 357	4,16, 4,21, 4,00, 3,80	1,33 (3H, t, $OCH_2\underline{CH_3}$, J = 7 Hz); 2,40 (3H, s, 3-CH_3); 2,57 (3H, s, 2-CH_3); 2,60 (3H, s, 5-CH_3); 4,25 (2H, q, $O\underline{CH_2}CH_3$, J = 7 Hz); 7,46 (1H, s, 4-H); 8,28 (1H, s, 7-H); 10,98 (2H, s, 3- and OH)	H, 30 min	76

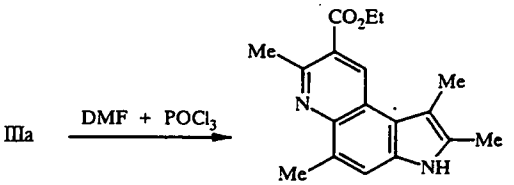
TABLE 2 (continued)

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (and system)	UV spectrum		PMR spectrum, δ, ppm	Reaction conditions and duration	Yield, %
		C	H	M*			λ_{max}	lg ε			
1	2	3	4	5	6	7	8	9	10	11	12
VIa 1,2,7,9-tetramethyl-5-methoxypyrrolo[3,2-f]quinoline	$C_{16}H_{18}N_2O$	74,80 / 75,56	6,90 / 7,13	254 / 254	204...205		230, 284, 360	4,50, 4,20, 3,77		E, 8 h	13
VIb 1,2-dimethyl-7,9-biphenyl-5-methoxypyrrolo[3,2-f]-quinoline	$C_{26}H_{22}N_2O$	— / 82,51	— / 5,86	— / 378	212...214	0,86 (B)	204, 233, 273, 318	4,29, 4,24, 4,16, 4,20	1,10 (3H, s, 1-CH_3); 2,20 (3H, s, 2-CH_3); 4,08 (3H, s, OCH_3); 7,60 (12H, m, 4-, 8-H, $2C_6H_5$); 11,00 (1H, s, 3-H)	E, 10 h	12
VIc 1,2,7-trimethyl-5-methoxy-8-ethoxycarbonylpyrrolo-[3,2-f]quinoline	$C_{18}H_{20}N_2O_3$	69,00 / 69,21	6,31 / 6,45	— / 312	244...246	0,66 (B)	206, 244, 303, 370 (sh),	4,10, 4,24, 3,96, 3,30	1,40 (3H, m, $OCH_2\underline{CH_3}$); 2,45 (6H, s, 1 and 2-CH_3); 2,87 (3H, s, 7-CH_3); 3,99 (3H, s, OCH_3); 4,39 (2H, m, $O\underline{CH_2}CH_3$); 7,28 (1H, s, 4-H); 9,10 (1H, s, 9-H); 11,02 (1H, s, 3-H)	F, 7 h	8
VId 1,2-dimethyl-9-hydroxy-5-methoxy-8-ethoxycarbonyl-pyrrolo[3,2-f]quinoline	$C_{17}H_{18}N_2O_4$	64,50 / 64,96	5,59 / 5,77	— / 314	> 300	0,15 (C)	217, 263 (sh), 306, 357	4,37, 3,86, 4,15, 3,91	1,31 (3H, m, $CH_2\underline{CH_3}$); 2,41 (3H, s, 1-CH_3); 2,60 (3H, s, 2-CH_3); 4,00 (3H, s, OCH_3); 4,24 (2H, m, $\underline{CH_2}CH_3$); 7,22 (1H, s, 4-H); 8,25 (1H, s, 7-H); 10,87 (1H, s, OH); 11,29 (1H, s, 3-H)	H, 30 min	58

Whereas 6-methyl-5-aminoindole reacts with dicarbonyl compounds and ethoxymethylenemalonic ester in the same way as aminoindoles that are not substituted on the benzene ring, the 6-methoxy analog is more inert in these reactions. Thus, a reaction time of 0.5-2 h is required for completion of the condensation of the aminoindole I; this reaction time must be doubled or tripled for the analogous conversions of compound II.

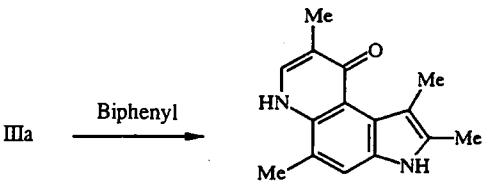
The constants, spectral characteristics, and other characteristics of compounds III and IV are listed in Table 1, along with the reaction times (monitored chromatographically).

We had reported previously [1] that enaminoketones obtained from 2,3,6-trimethyl-5-aminoindole and diketones (dibenzoylmethane and acetylacetone) are converted quite smoothly to the corresponding angular pyrroloquinolines, even though completion of the reaction requires extended heating (6 h) in trifluoroacetic acid, in comparison with the 30-min refluxing that is adequate for linear systems [1]. This difference is explained by the steric requirements of the peri-substituents in the angular structures that are formed. This effect is weaker if there is no substituent in the γ-position of the pyridine ring that is formed. And in fact, we have shown that cyclization of the enaminocrotonate IIIa under conditions of the Vilsmeier reaction proceeds quite readily, with the formation of the pyrroloquinoline Va, within the same time as for the enaminocrotonate without a methyl group in position 6 [2].



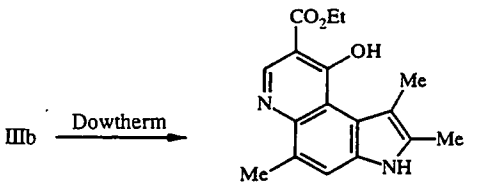
Va

The enaminocrotonate IIIa is cyclized just as easily in a thermal reaction, forming the pyrroloquinoline Vb.



Vb

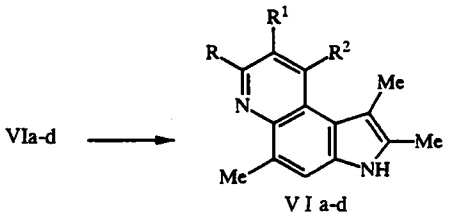
The enamine IIIb, obtained from the aminoindole I and ethoxymethylenemalonic ester, upon refluxing in Dowtherm, is converted to the corresponding angular pyrroloquinoline Vc.



Vc

The ease of cyclization of the enamines III under conditions of the Vilsmeier reaction or high-temperature processes is consistent with our earlier data [2] on the preferential formation of angular pyrroloquinolines for enamines of 5-aminoindoles, even with an open position 6. The influence of a methyl group in the benzene ring comes down merely to a certain increase of electron density on the carbon atom being attacked, and to easier cyclization.

A methoxy group in position 6 of the 2,3-dimethyl-5-aminoindole II has a different effect on the reactivity. We have established that the enamines IV obtained from this aminoindole form the corresponding pyrroloquinolines, but the cyclization requires a much longer reaction time, with concomitant heavy tar formation and lower pyrroloquinoline yields.



VI a-d

VIa) R = R^2 = Me, R^1 = H; VIb) R = R^2 = Ph, R^1 = H; VIc R = Me, R^1 = CO_2Et, R^2 = H; VId R = H, R^1 = CO_2Et, R^2 = OH

When the enamine IVc is used, the methoxy group has such a great deactivating effect on position 4 of the indole ring with respect to cyclization that in the thermal cyclization, we were unable to isolate the corresponding pyrroloquinoline: After refluxing in biphenyl for 30 min, heavy tar formation was observed, and chromatography showed only trace quantities of the pyrroloquinoline and the unreacted aminocrotonate.

Data on the synthesized pyrroloquinolines V and VI are presented in Table 2, along with a listing of the conditions of cyclization.

Thus, the methoxy group in enamines obtained on the basis of 2,3-dimethyl-6-methoxy-5-aminoindole deactivates the meta position relative to this substituent in reactions of electrophilic cyclization, in the same manner as has been described for the 5-methoxy-6-amino analogs [2]; this is also consistent with literature data for derivatives of aniline [3]. Nonetheless, the method that we have developed, the use of cyclization of enamines of 6-substituted-5-aminoindoles, in spite of certain difficulties, can be recommended for the preparation of substituted pyrrolo[3,2-*f*]quinolines.

EXPERIMENTAL

PMR spectra were registered on an AC-200P instrument (Bruker) in DMSO-d_6 relative to TMS. The course of the reactions and the purity of the compounds that were isolated were monitored on Silufol UV-254 plates in the following systems: (A) 10/1 benzene/ethyl acetate; (B) 5/1 ethyl acetate/methanol; (C) 1/1 ethyl acetate/methanol. The enamines III and IV and the pyrroloquinolines V and VI were obtained by procedures described in [1, 2]. The conditions of formation of the enamines from the aminoindoles were as follows: A) refluxing with acetylacetone; B) heating with dibenzoylmethane at 170-180°C; C) refluxing in benzene with acetoacetic ester with a trace of acetic acid; D) refluxing with ethoxymethylenemalonic ester in ethanol. The conditions for cyclization of the enamines were as follows: E) refluxing in trifluoroacetic acid; F) refluxing in chloroform with Vilsmeier reagent; G) refluxing in biphenyl; H) refluxing in Dowtherm.

Compounds IIIa and IVa,c were purified by recrystallization from heptane with activated carbon; IVb was purified by preparative thin-layer chromatography on aluminum oxide in chloroform with subsequent recrystallization from heptane; IIIb, Vb, and IVd were purified by crystallization from alcohol with activated carbon; Vc was purified by crystallization from a 1/1 mixture of benzene and heptane with activated carbon; Va was purified by passing a benzene solution of the compound, heated to boiling with activated carbon, through a bed of aluminum oxide (1.5-2 cm), followed by recrystallization from heptane; VIb was purified by thin-layer chromatography on aluminum oxide in a 5/1 mixture of benzene and ethyl acetate, with subsequent recrystallization from heptane; VIa,c,d were purified by treatment with activated carbon in aqueous alcohol solutions.

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3. C. K. Bradscher, Chem. Rev., **38**, 447 (1946).