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SYNTHESIS OF PYRROLOQUINOLINES FROM 2,3-DIMETHYL-5-METHOXY-6-AMINOINDOLE

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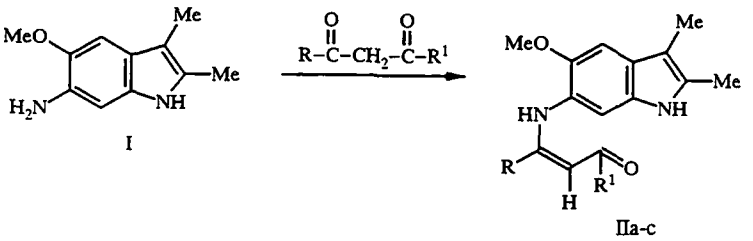
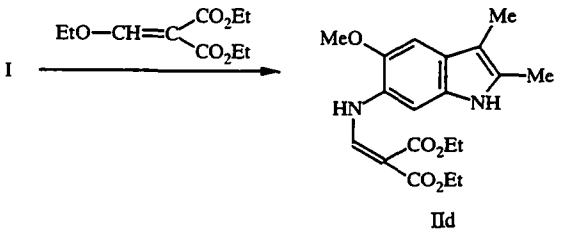
Formation of enaminoketones, enaminocrotonate, and aminomethylenemalonate from 2,3-dimethyl-5-methoxy-6-aminoindole occurs significantly less easily than for the 7-methoxy analog. A similar dependence is observed in the reaction of enamines to the corresponding pyrroloquinolines independently of the cyclization conditions.

In our study of the effect of a methoxy group in the benzene ring of 2,3-dimethyl-6-aminoindoles on the ability of the latter to condense with dicarbonyl compounds and subsequently to cyclize we have found [1] that a 7-methoxy group promotes the formation of both enamines and the corresponding pyrroloquinolines. This leads to an interest in the analogous reactions of 2,3-dimethyl-5-methoxy-6-aminoindole (I). We have shown that heating aminoindole I with diketones gives the corresponding enamines IIa, b, or with acetoacetic ester in benzene and traces of acetic acid, the enaminocrotonate IIc.



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

Similar refluxing of aminoindole I with ethoxymethylenemalonate ester gives the aminomethylenemalonate IId.



In all cases of use of I, completion of the reaction demands more prolonged heating than for the 7-methoxy derivatives. The reaction times, spectral, and other parameters for II are given in Table 1.

In trifluoroacetic acid, the enaminoketones IIa, b are converted to the corresponding pyrroloquinolines IIIa, b with angular ring coupling. In contrast to the enaminoketones with a 7-methoxy group, for which the reaction is complete in 1.5-2 h, cyclization of enamine IIa to pyrroloquinoline IIIa requires refluxing for 14 h (monitored chromatographically).

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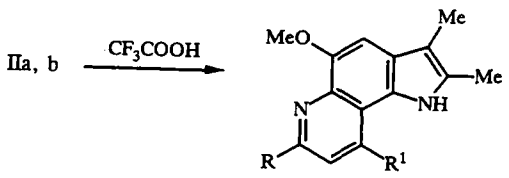
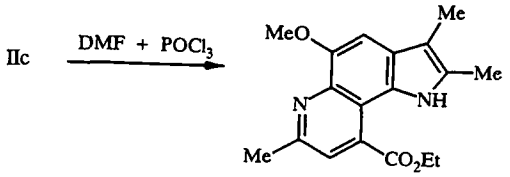


IIIa, b

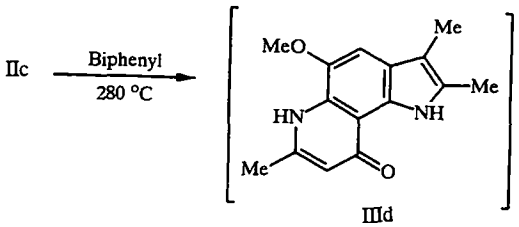
IIIa R = R^1 = Me, b R = R^1 = Ph

Still more prolonged heating (20 h) is required to form the pyrroloquinoline IIIb from enamine IIb. The same dependence is also observed for cyclization of aminocrotonate IIc under Vilsmeier reaction conditions.



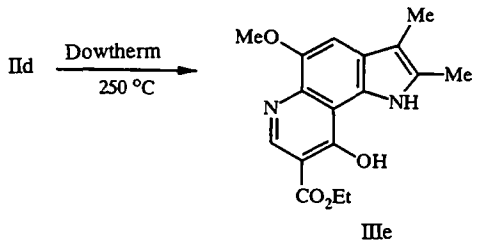
IIIc

It would appear that formation of the angular pyrroloquinolines via thermal cyclization of IIc, d should occur readily since it is favored even in examples with two free ortho positions [2]. By contrast to this, the high temperature cyclization of IIc (refluxing in biphenyl) needs a significantly greater reaction time which leads to much tarring. This hinders the separation of pure pyrroloquinoline IIIc and its formation can only be shown qualitatively from TLC data.



IIId

The enaminomalonate IId also needed more prolonged heating than the corresponding 7-methoxy derivative but it did prove possible to separate the pyrroloquinoline IIId. This is evidently connected to the rather greater reactivity of IId which permits a reduced cyclization temperature (from 280 to 250°C).



IIIe

Physicochemical data confirm the structure of the pyrroloquinolines III and is given in Table 2.

Reviewing the obtained experimental data shows that formation of enaminoketones, aminocrotonate, and aminomethylenemalonate from 2,3-dimethyl-5-methoxy-6-aminoindole is hindered when compared with the 7-methoxy analog, evidently through the decreased nucleophilicity of amine I. To an even greater extent, a methoxy group in position 5 lowers the reactivity of indole position 7 in cyclizations to form a pyridine ring. However, in spite of the more severe conditions needed for the cyclization and the lower yields, it proved possible to use 2,3-dimethyl-5-methoxy-6-aminoindole to prepare the pyrroloquinolines of a known angular structure.

TABLE 1. Preparative Conditions and Parameters for Enamines II

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (system)	UV spectrum		PMR spectrum, δ, ppm	Conditions and duration of reaction	Yield, %
		C	H	M*			λ_{max}	lg ε			
IIa, 4(2,3-Dimethyl-5-methoxyindol-6-yl)amino-pent-3-en-2-one	$C_{16}H_{20}N_2O_2$	70,16 / 70,56	7,10 / 7,40	272 / 272	183,5...184,5	0,07 (A)	207, 225, 323	4,33, 4,29, 4,18	1,94 (3H, s, β-CH_3); 2,01 (3H, s, α-CH_3); 2,19 (3H, s, 3-CH_3); 2,33 (3H, s 2-CH_3); 3,82 (3H, s, O–CH_3); 5,19 (1H, s, H_{vin}); 6,99 (1H, s, 4-H); 7,05 (1H, s, 7-H); 10,37 (1H, s, 1-H); 12,17 (1H, s, H_{imine}	a, 4 h	33
IIb, 1,3-Diphenyl-3-(2-3-dimethyl-5-methoxyindol-6-yl)aminoprop-3-en-1-one	$C_{26}H_{24}N_2O_2$	78,25 / 78,76	6,32 / 6,10	396 / 396	172...173	0,53 (A)	207, 245 (sh), 303, 417	4,39, 4,23, 4,09, 4,02	2,15 (3H, s, 3-CH_3); 2,25 (3H, s, 2-CH_3); 3,90 (3H, s, OCH_3); 6,07 (1H, s, H_{vin}); 6,43 (1H, s, 4-H); 6,93 (1H, s, 7-H); 7,70 (10H, m, $2C_6H_5$); 10,15 (1H, s, 1-H); 12,74 (1H, s, N H_{imine}	b, 4 h	32
IIc, Ethyl β-[2,3-dimethyl-5-methoxy-indol-6-yl)amino]-crotonate	$C_{19}H_{24}N_2O_5$	67,11 / 67,53	7,01 / 7,33	302 / 302	123...124	0,48 (A)	214, 313	4,72, 4,23	† 1,25 (3H, t, $OCH_2\underline{CH_3}$, J = 7Hz); 1,75 (3H, s, β-CH_3); 2,07 (3H, s, 3-CH_3); 2,18 (3H, s, 2-CH_3); 3,66 (3H, s, OCH_3); 4,06 (2H, q, OCH_2CH_3, J = 7Hz); 4,50 (1H, s, H_{vin}); 6,58 (1H, s, 4-H); 6,73 (1H, 7-H); 8,46 (1H, s, NH_{imine}); 9,92 (1H, s, 1-H)	c, 9 h	38
IId, Diethyl N-(2,3-Dimethyl-5-methoxyindol-6-yl)-aminomethylenemalonate	$C_{19}H_{24}N_2O_5$	63,20 / 63,32	6,63 / 6,71	360 / 360	159...160	0,15 (A)	210, 229, 285 (sh), 364	4,28, 4,25, 3,90, 4,28	1,27 (6H, m, $2CH_2\underline{CH_3}$); 2,18 (3H, s, 3-CH_3); 2,32 (3H, s, 2-CH_3); 3,90 (3H, s, OCH_3); 4,20 (4H, m, $2\underline{CH_2}CH_3$); 7,05 (1H, s, 7-H); 7,20 (1H, s, 4-H); 8,50 (1H, d, H_{vin}, J = 16Hz); 10,40 (1H, s, 1-H); 11,02 (1H, d, NH_{imine} J = 16Hz)	d, 4 h	67

*Mass spectrometric.

†In CCl_4 relative to HMDS.

TABLE 2. Conditions for Preparation and Parameters for Pyrroloquinolines III

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (system)	UV spectrum		PMR spectrum, δ, ppm	Conditions and duration of reaction	Yield, %
		C	H	M*			λ_{max}	lg ε			
IIIa, 2,3,7,9-Tetramethyl-5-methoxypyrrolo[2,3-f]quinoline	$C_{16}H_{18}N_2O$	75,70 / 75,56	6,99 / 7,13	254 / 254	256...258	0,20 (B)	210, 244, 286	4,24, 4,00, 4,37	2,24 (3H, s, 3-CH_3); 2,47 (3H, s, 2-CH_3); 2,62 (3H, s, 9-CH_3); 2,91 (3H, s, 7-H); 4,02 (3H, s, OCH_3); 7,19 (1H, s, 8-H); 7,22 (1H, s, 4-H); 10,20 (1H, s, 1-H)	e, 14 h	52
IIIb, 2,3-Dimethyl-7,9-diphenyl-5-methoxypyrrolo-[2,3-f]quinoline	$C_{26}H_{22}N_2O$	82,03 / 82,51	5,40 / 5,86	378 / 378	191...192	0,47 (A)	208, 270, 313	4,32, 4,02, 4,32	2,11 (3H, s, 3-CH_3); 2,19 (3H, s, 2-CH_3); 4,08 (3H, s, OCH_3); 7,85 (12H, m, 4-, 8-H and 7-, 9-C_6H_5)	e, 20 h	25
IIIc, 2,3,7-Trimethyl-5-methoxy-8-carbethoxy-pyrrolo[2,3-f]quinoline	$C_{18}H_{20}N_2O_3$	69,30 / 69,21	6,31 / 6,45	312 / 312	244...245	0,76 (B)	208, 240 (sh), 257, 313	4,34, 4,20, 4,27, 4,23	1,40 (3H, t, $OCH_2\underline{CH_3}$, J = 7Hz); 2,27 (3H, s. 3-CH_3); 2,40 (3H, s, 2-CH_3); 2,90 (3H, s, 7-CH_3); 4,00 (3H, s, OCH_3); 4,41 (2H, q, OCH_2CH_3, J = 7Hz); 7,30 (1H, s, 4-CH_3); 9,13 (1H, s, 9-H); 11,60 (1H, s, 1-H)	f, 12 h	36
IIIe, 2,3-Dimethyl-9-hydroxy-5-methoxy-8-carbethoxy-.pyrrolo[2,3-f]quinoline	$C_{17}H_{18}N_2O_4$	64,51 / 64,96	5,15 / 5,77	314 / 314	235...237	0,52 (B)	210, 233, 260, 333	4,16, 4,29, 4,35, 3,89	1,33 (3H, t, CH_2CH_3, J = 7Hz); 2,34 (3H, s, 3-CH_3); 2,52 (3H, s, 2-CH_3); 4,02 (3H, s, OCH_3); 4,30 (2H, q, $\underline{CH_2}CH_3$, J = 7Hz); 7,28 (1H, s, 4-H); 8,52 (1H, s, 7-H); 11,00 (1H, s, OH); 11,40 (1H, s, 1-H)	g, 30 min	30

*Mass spectrometric.

EXPERIMENTAL

PMR spectra were measured on a Bruker AC-200P Instrument using DMSO-D_6 solvent and TMS internal standard. UV spectra were measured on a Specord spectrophotometer with ethanol solvent. Mass spectra were taken on a Varian MAT-112. The purity of the separated compounds was monitored chromatographically on Silufol UV-254 plates using the systems: benzene–ethyl acetate (10:1, A) or ethyl acetate–methanol (10:1, B). Enamines II and pyrroloqinolines III were prepared by methods reported in [1]. The conditions for preparing the enamines from aminoindole I: a) refluxing with acetylacetone, b) heating with dibenzoylmethane at 170-180°C, c) refluxing with acetoacetic ester in benzene with traces of acetic acid, d) refluxing with ethoxymethylenemalonate ester in alcohol. Conditions for cyclizing the enamines: e) refluxing in trifluoroacetic acid, f) refluxing in chloroform with Vilsmeier reagent, g) refluxing with Dowtherm. Compounds IIa, b, c and IIIb, c, e were recrystallized from a mixture of heptane and benzene and compounds IId, IIIa, d from aqueous alcohol. Constants, spectral, and other parameters and the conditions and times for the reaction are given in Tables 1 and 2.

REFERENCES

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