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SYNTHESIS OF PYRROLOQUINOLONES

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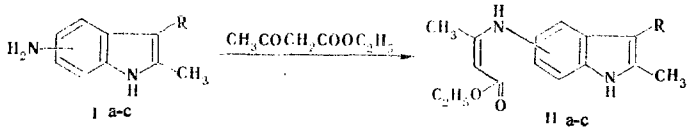
UDC 547.752'836.3:542.953.2:543.422'51

The condensation of 5- and 6-aminoindoles with diketene and acetoacetic ester was realized. A convenient method for the synthesis of pyrrolo[3,2-f]- and pyrrolo-[2,3-f]quinol-9-ones from 5- and 6-aminoindoles was developed. Under the influence of trifluoroacetic acid acetoacetic acid amides gave a mixture of 2,3,8-trimethylpyrrolo[2,3-g]quinol-6-one and 1,2,9-trimethyl-pyrrolo[3,2-f]quinol-7-one (in the case of 5-aminoindole) and a mixture of 2,3,5-trimethylpyrrolo[3,2-g]-quinol-7-one and 2,3,9-trimethylpyrrolo[2,3-f]quinol-7-one.

The interest in research on pyrroloquinolines, which has recently grown, is associated with their biological activity. For example, the pyrroloquinolines obtained from malonic ester have analgesic activity comparable to that of analgine [1]. The problem of the site of ring fusion arises in the formation of the pyrroloquinoline system on the basis of 5- and 6-aminoindoles, the molecules of which contain two free ortho positions relative to the amino group. Thus under acidic cyclization conditions the enamino ketones obtained from the amines and diketones indicated above give either linear or angular isomers [2]. The primary formation of one or the other pyrroloquinoline depends to a considerable extent on the steric requirements of the substituents in the 1 and 3 positions of the indole fragment. However, the thermal cyclization of the products of condensation of aminoindoles with ethoxymethylenemalonic ester proceeds regiospecifically to give pyrroloquinolines with only angular ring fusion, regardless of the nature of the substituent [1].

In a search for convenient methods for the synthesis of pyrroloquinolines that have a functional group in the pyridine ring we investigated the behavior of 5- and 6-aminoindoles in reactions with diketene and acetoacetic ester. The condensation of these amines with the latter may proceed at both the carbonyl group and at the carboxy group, and the formation of aminocrotonates or amides is consequently possible in this case. Crotonates II are readily obtained by refluxing aminoindoles with acetoacetic ester in the presence of traces of glacial acetic acid in absolute benzene. The structure of II was established on the basis of data from the PMR spectra (see Table 1).



I a-c II a-c

I–II a 5-NH_2, R = CH_3; b 5-NH_2, R = H; c 6-NH_2, R = CH_3

*Deceased.

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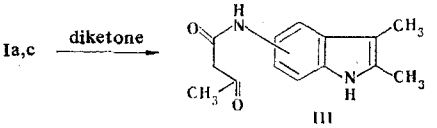
0009-3122/83/1904-0401$07.50

TABLE 1. Aminocrotonates and Amides

Compound	mp, °C	UV spectrum λ_{max}, nm	UV spectrum lg ε	PMR spectrum, δ, ppm	Found element, %	Found M*	Empirical formula	Calc. element, %	Calc. M	Yield, %
IIb	122—123	219 294	4,39 4,51	1,27 (t, 3H, O—CH_2—$\mathbf{CH_3}$, J=6 Hz); 1,95 (s, 3H, 2-CH_3); 2,47 (s, 3H, β-CH_3); 4,13 (q, 2H, O—CH_2); 4,65 (s, α-H); 6,20 (s, 3H); 6,86 (dd, 6-H, J_{67}=9 Hz, J_{64}=2 Hz); 7,28 (d, 4-H); 7,32 (d, 7-H); 10,00 (s, N—H); 10,40 (s, 1-H)	C 69,2 H 7,2	258	$C_{15}H_{18}N_2O_2$	C 69,8 H 7,0	258	85
IIa	124—124,5	227 294	4,36 4,50	1,27 (t, 3H, OCH_2—$\mathbf{CH_3}$, J=6 Hz); 1,95 (s, 3H, 3-CH_3); 2,22 (s, 3H, 2-CH_3); 2,40 (s, 3H, β-CH_3); 4,13 (q, 2H, $\mathbf{OCH_2}$); 4,65 (s, α-H); 6,86 (dd, 6-H, J_{67}=9 Hz, J_{64}=2 Hz); 7,24 (d, 4H); 7,28 (d, 7-H); 9,82 (s, N—H); 10,42 (s, 1-H)	—	272	$C_{16}H_{20}N_2O_2$	—	272	73
IIc	115—116	222 294	4,42 4,39	1,27 (t, 3H, O—CH_2—$\mathbf{CH_3}$, J=6 Hz); 1,97 (s, 3H, 3-CH_3); 2,23 (s, 3H, 2-CH_3); 2,40 (s, 3H, β-CH_3); 4,13 (q, 2H, OCH_2); 4,65 (s, α-H); 6,84 (dd, 5-H, J_{54}=9 Hz, J_{57}=2 Hz); 7,12 (d, 7-H); 7,40 (d, 4-H); 9,80 (s, N—H); 10,50 (s, 1-H)	C 71,0 H 7,2	272	$C_{16}H_{20}N_2O_2$	C 70,6 H 7,4	272	56
IIIa	135—136	245 300	4,45 3,85	2,20 (s, 3H, 3-CH_3); 2,30 (s, 3H, 2-CH_3); 2,36 (s, 3H, β-CH_3); 3,59 (s, 2H, α-CH_2); 7,22 (s, 2H, 6- and 7-H); 7,61 (s, 4-H); 9,20 (s, N—H); 9,68 (s, 1-H)	—	244	$C_{14}H_{16}N_2O_2$	—	244	52
IIIc	221—222	218 247 296	4,29 4,37 4,11	2,20 (s, 3H, 3-CH_3); 2,30 (s, 3H, 2-CH_3); 2,36 (s, 3H, β-CH_3); 3,59 (s, 2H, α-CH_2); 7,07 (dd, 5-H, J_{54}=9 Hz, J_{57}=2 Hz); 7,31 (d, 4-H); 7,93 (d, 7-H); 9,86 (s, N—H); 10,45 (s, 1-H)	C 68,6 H 7,2	244	$C_{14}H_{16}N_2O_2$	C 68,9 H 6,6	244	72

*By mass spectrometry.

We were unable to direct the reaction of 5- and 6-aminoindoles with acetoacetic ester to favor the production of the corresponding amides; however, they are readily formed from aminoindoles and diketone:



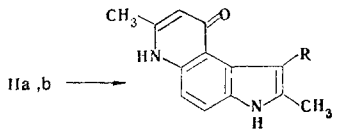
III

III a 5-NH; b 6-NH

Aminoindole Ib reacts with diketene to give a mixture of products of reaction at both the NH_2 group and in the β position of indole; only amides IIIa,c were therefore used for the subsequent transformations.

It is known that the crotonates of aromatic amines undergo cyclization at high temperatures to give quinolones [3]. The formation of a pyridone ring in both the 4 and 6 positions is possible in the case of 5-aminoindole derivatives. However, pyrroloquinolone IVb with angular ring fusion is formed in good yield when aminocrotonate IIb is refluxed in biphenyl, i.e., ring formation proceeds in the 4 position of the indole ring.

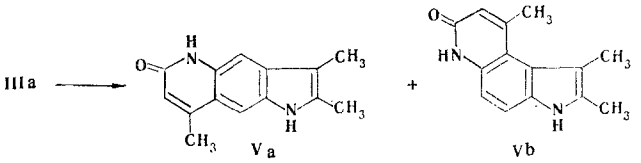
Two doublets of aromatic protons (J = 9 Hz) are observed in the PMR spectrum of IVb. The introduction of an alkyl substituent in the 3 position of the indole fragment does not affect the direction of ring closure to form a pyridone ring, i.e., IIa also gives angular pyrroloquinolone IVa. The PMR spectrum of the latter contains a resolved AB system of benzene ring protons, just as in the case of pyrroloquinolone IVb.



IIa,b → IVa,b

IVa R=CH_3; b R=H

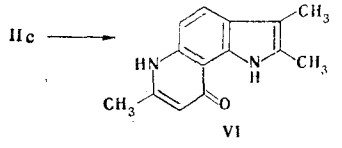
This unambiguous course of the cyclization reaction confirms the higher reactivity of the 4 position as compared with the 6 position. The severe conditions under which the cyclization is carried out exclude the effect of steric hindrance of the β substituent of the pyrrole ring on the direction of the process. It is also completely possible that steric interaction of the oxygen atom of the pyridone ring and the β-methyl group in IVa is virtually absent as a result of partial disruption of the coplanarity of the system. This assumption is also confirmed by the fact that aminocrotonate IIa also forms angular isomer IVa under the acidic cyclization conditions (heating in CF_3COOH in a sealed ampul at 150°C). Amide IIIa, which forms two isomeric pyrroloquinolones Va,b when it is refluxed in trifluoroacetic acid, behaves differently in an acidic medium.



IIIa → Va + Vb

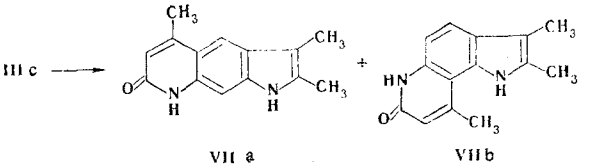
The ratio of the linear and angular isomers (on the basis of the PMR spectra) is 2.5:1. Thus the formation of the Vb system with two methyl groups in the peri positions is hindered, although to a lesser extent than the formation of a pyrroloquinoline with a similar structure from the enamino ketone. A pyrroloquinoline with angular ring fusion is not formed at all in the cyclization of the latter under the same conditions [2]. Attempts to carry out the cyclization of amide IIIa under conditions that decrease the effect of steric factors, i.e, at high temperatures, do not give the expected results. Compound IIIa does not undergo cyclization in refluxing biphenyl.

Aminocrotonate IIc, obtained from 6-aminoindole, behaves like IIa,b. Thus IIc gives only angular pyrroloquinoline VI in good yield under thermal cyclization conditions.



IIc → VI

Two doublets of benzene ring protons (J = 9 Hz) are observed in the PMR spectrum of the reaction product. However, the acidic cyclization of amide IIIc leads to the formation of a mixture of two isomeric pyrroloquinolones VIIa,b with slight preponderance of the latter (1:1.2). Because of their low solubilities and their low mobilities on many sorbents these isomers were not isolated in individual form. Their ratio was estimated from the PMR spectrum of the reaction mixture.



IIIc → VIIa + VIIb

TABLE 2. Pyrroloquinolones

Compound	mp,[a] °C	UV spectrum λ_{max}, nm	UV spectrum lg ε	PMR spectrum, δ, ppm	Found element, %	Found M[b]	Empirical formula	Calc. element, %	Calc. M	Yield, %
IVa	292–294	217 245 254 289 348	4,54 4,24 4,27 4,04 4,06	2,28 (s, 3H, 2-CH_3); 2,32 (s, 3H, 7-CH_3); 2,62 (s, 3H, 1-CH_3); 5,82 (s, 8-H); 7,08 (d, 4-H, J_{45}=9 Hz); 7,50 (d, 5-H); 11,10 (s, 3-H); 11,25 (s, 6-H)	C 74,0 H 6,5	226	$C_{14}H_{14}N_2O$	C 74,4 H 6,2	226	89 53[c]
IVb	279–281	212 243 252 284 347	4,54 4,30 4,30 4,15 4,08	2,36 (s, 3H, 7-CH_3); 2,45 (s, 3H, 2-CH_3); 5,90 (s, 8-H); 7,15 (d, 4-H, J_{45}=9 Hz); 7,25 (s, 1-H); 7,57 (d, 5-H); 11,25 (s, 6-H); 11,45 (s, 3-H)	C 73,4 H 6,2	212	$C_{13}H_{12}N_2O$	C 73,6 H 5,7	212	95
Va	>300	200 237 267 350	4,24 4,62 4,17 4,20	2,15 (s, 3H, 3-CH_3); 2,37 (s, 6H, 2- and 8-CH_3); 6,22 (s, 7-H); 7,23 (s, 9-H); 7,50 (s, 4-H); 10,76 (s, 1-H); 11,25 (s, 5-H)	—	226	$C_{14}H_{14}N_2O$	—	226	62[d]
VI	>300	217 280 343	4,75 4,77 4,04	2,21 (s, 3H, 3-CH_3); 2,40 (s 6H, 2- and 7-CH_3); 6,02 (s, 8-H); 7,15 (d, 4-H, J_{45}=9 Hz); 7,70 (d, 5-H); 11,24 (s, 6-H); 11,65 (s, 1-H)	—	226	$C_{14}H_{14}N_2O$	—	226	90

[a]With decomposition. [b]By mass spectrometry. [c]Acidic cyclization. [d]Overall yield of the mixture of two isomers.

Thus both the thermal and acidic cyclization of alkylindolylaminocrotonates proceed regiospecifically, which ensures a convenient method for the synthesis of pyrrolo[3,2-f]- and pyrrolo[2,3-f]quinol-9-ones from 5- and 6-aminoindoles and acetoacetic ester. Under the influence of trifluoroacetic acid acetoacetic acid amides give mixtures of pyrroloquinolones, i.e., ring formation does not take place regiospecifically. This is in agreement with previously obtained data [2].

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Varian-100 XL spectrometer. The mass spectra were obtained with an MAT-112 mass spectrometer. The UV spectra of solutions in ethanol were recorded with a Cary-219 spectrophotometer.

General Method for the Preparation of Aminocrotonates II (Table 1). A solution of 5 mmole of aminoindole [2] and 5 mmole of acetoacetic ester in absolute benzene was heated in the presence of traces of glacial acetic acid for 8-10 h (with chromatographic monitoring). At the end of the reaction the benzene was removed by distillation, and the resulting crotonate was recrystallized from a mixture of benzene with heptane.

General Method for the Preparation of Amides III (Table 1). A 6-mmole sample of diketene was added to a solution of 3 mmole of aminoindole in absolute ether, and the reaction mixture was refluxed for 1 h. The ether was then removed by distillation, and the amide was recrystallized from aqueous ethanol.

Pyrroloquinolones VI and VII (Table 2). A) A 2.4-mmole sample of the aminocrotonate was added to 40 mmole of refluxing biphenyl, and the mixture was heated for 5-10 min. The still hot solution was diluted with heptane, and the precipitate was removed by filtration and washed repeatedly with heptane and ether. The pyrroloquinolones were purified by recrystallization from ethanol.

B) The acidic cyclization of amides III was carried out as described in [2]. The yield of the mixture of isomers was 62% in the case of IIIa and 56% in the case of IIIc. PMR spectra of the reaction mixtures: a) Va, 6.22 (s, 7-H), 7.23 (s, 9-H), and 7.50 ppm (s, 4-H); Vb, 6.29 (s, 8-H), 7.05 (d, 4-H, J_{45} = 9 Hz) and 7.4 ppm (d, 5-H, J_{54} = 9 Hz) [the ratio of the integral intensity of 9-H (Va) to that of 4-H (Vb) was 2.5:1]; b) VIIa, 6.22 (s, 6-H), 7.20 (s, 4-H), and 7.68 ppm (s, 9-H); VIIb, 6.33 (s, 8-H), 7.08 (d, 4-H,

J_{45} = 9 Hz), and 7.57 ppm (d, 5-H, J_{54} = 9 Hz) [the ratio of the integral intensity of 4-H (VIIb) to that of 4-H (VIIa) was 1.2:1].

Pyrroloquinolone Va was separated from isomer Vb by repeated crystallization from ethanol. Compounds Vb, VIIa, and VIIb were not isolated in individual form.

C) A solution of 2 mmole of the aminocrotonate in trifluoroacetic acid was heated in a sealed ampul at 150°C for 2-3 h. The pyrroloquinolones were isolated by a method similar to that described in [2].

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SYNTHESIS OF 2-ARYL-4-METHYL-9H-INDOLO[2,3-f]QUINOLINES

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T. P. Shulyat'eva, V. M. Adanin,
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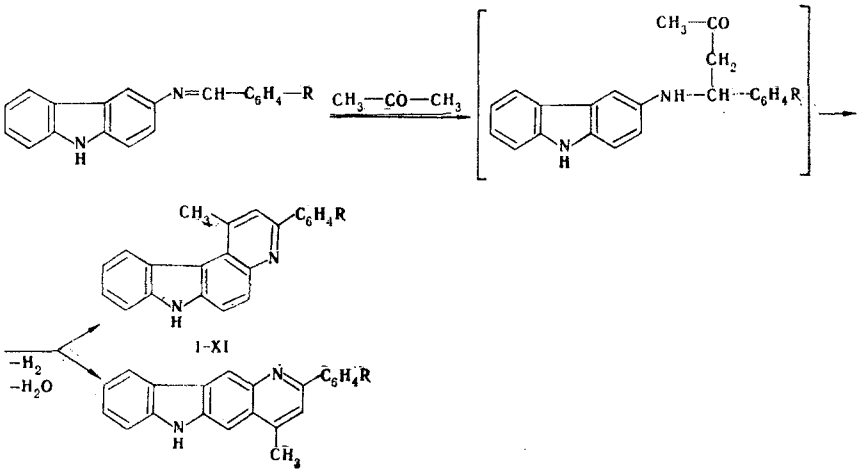
UDC 547.759.32'837.2.607:543.422.51

A new series of indoloquinoline derivatives was obtained by catalytic condensation of carbazole-containing azomethines with acetone. It was shown by means of a combination of physicochemical methods of investigation (UV, IR, NMR, and mass spectroscopy) that the synthesized compounds have angular structures.

We have previously demonstrated the possibility of the synthesis of 2,4-diaryl- and 2-aryl-4-styryl-9H-indolo[2,3-f]quinolines on the basis of carbazole-containing azomethines [1, 2]. 2-Aryl-4-methyl-9H-indolo[2,3-f]quinolines were obtained by the reaction of azomethines of the carbazole series with acetone. The formation of these compounds evidently takes place via the scheme



I R=H; II R=*p*-Cl; III R=*p*-Br; IV R=*p*-F; V R=*p*-NO_2; VI R=*m*-Br; VII R=*m*-Cl; VIII R=*m*-I; IX R=*m*-F; X R=*o*-F; XI R=*p*-OCH_3

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 498-500, April, 1983. Original article submitted June 3, 1982.