Chemistry of Heterocyclic Compounds, Vol. 30, No. 7, 1994

SYNTHESIS OF A NEW HETEROCYCLIC SYSTEM OF 2-AMINO-3-CYANO-5H-4,5-DIHYDROPYRIDO[3′,2′:4,5]-PYRROLO[1,2-a]INDOLE

N. Z. Tugusheva, S. Yu. Ryabova,
N. P. Solov'eva, and V. G. Granik

Alkylation of 2-piperidinomethylene-2H-pyrrolo[1,2-a]indole-3,9-dione with dimethyl sulfate, followed by hydrolysis of the intermediate immonium salts, yielded 2-formyl derivatives, the reaction of which with substances possessing an active methylene unit leads to the formation of 2-substituted vinyl-3-oxo-9-alkoxypyrrolo[1,2-a]indoles. Cyclization of the 9-methoxy derivative yielded a new heterocyclic system of 2-amino-3-cyano-5H-4,5-dihydropyrido[3′,2′:4,5]pyrroloindoledione-4,11.

In our previous work the reaction of 2-piperidinomethylene-3,9-dioxopyrrolo[1,2-a]indole (I) with compounds possessing an active methylene unit was used as the basis for synthesizing a group of 2-vinyl derivatives of this heterocyclic system, and it was shown that their methylation proceeds at the oxygen atom in the 9-position of the tricycles [1]. Continuing this investigation we studied an alternative approach to the synthesis of 2-substituted vinyl-3-oxo-9-alkoxypyrrolo[1,2-a]indoles II and examined the possibility of cyclization of compounds of this type to azaheterotetracyclic derivatives. The first step of the work was a study of the direct alkylation of the enaminocarbonyl compound I by dimethyl sulfate. Compound I contains two related fragments — enaminoketone and dienoaminoketone — and thus we might expect O-alkylation both at the 3-position

TABLE 1. Data of the PMR Spectra of Compounds IIIa, b, IV, V, IX

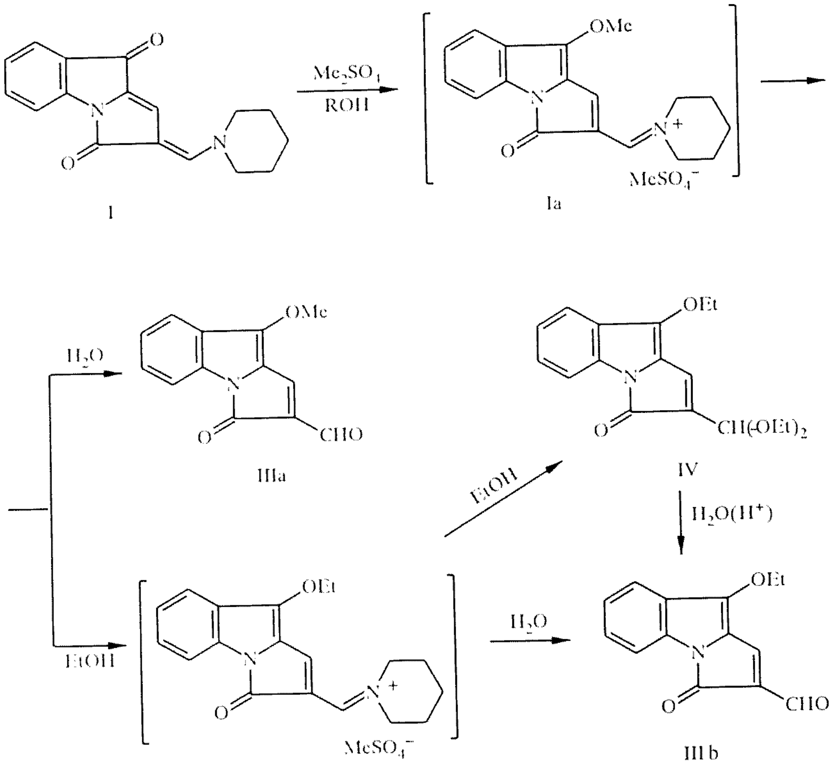
Compound	Chemical shifts, δ, ppm				Solvent
	1-H	2′-H	R, R^1	aromatic protons	
IIIa	7,89	CHO 9,86	OCH_3 4,19	7,15 (t), 7,46...7,80 (m)	$CDCl_3$ NOE 16% (OCH_3,1-H)
IIIb	7,84	CHO 9,86	OCH_2CH_3: 1,60 (t, CH_3), 4,37 (q, CH_2)	7,15 (t), 7,40...7,80 (m)	$CDCl_3$
IV*	7,47	5,26	OCH_2CH_3: 1,43 (t, CH_3), 4,32 (q, CH_2) 2(OCH_2CH_3): 1,15 (t, CH_3), 3,53 (q, CH_2)	7,11 (t), 7,35...7,55 (m)	DMSO-D_6
V*	7,29, 7,89		$^+NH(CH_2CH_3)_2$: 1,17 (t, CH_3), 3,15 (q, CH_2), 8,80 (br.s , NH)	7,16 (t), 7,50...8,00 (m)	DMSO-D_6
IX	8,17	—	NH 12,4 (br. signal), NH_2 6,97 (br. signal)	7,27 (t), 7,51 (t), 7,77 (d), 7,91 (d)	DMSO-D_6

*For compounds IV and V, spin–spin interaction between the protons 1-H and 2′-H [$J_{1,2'}$ 0.7 Hz (V), 0.9 Hz (IV)] was observed in the PMR spectra.

Center for the Chemistry of Drugs, S. Ordzhonikidze All-Russian Scientific Research Institute, Moscow, 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 919-925, August, 1994. Original article submitted June 22, 1994.

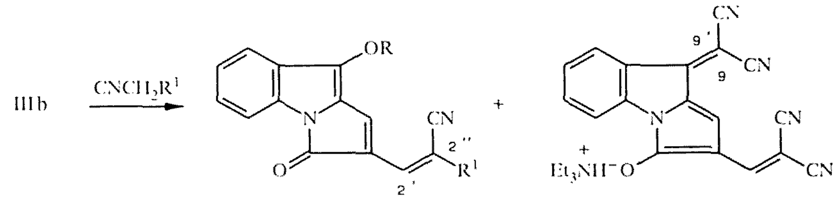
0009-3122/94/3007-0793$12.50

and at the 9-position. It was found that when compound I is alkylated with an excess of dimethyl sulfate in benzene, followed by hydrolysis of the intermediate immonium salt Ia, 2-formyl-3-oxo-9-methoxypyrrolo[1,2-a]indole (IIIa) can be obtained with a satisfactory yield. When methylation was conducted in ethanol at 65°C, the 9-ethoxyaldehyde IIIb was obtained, while at a lower temperature the acetal IV ($M^{+\cdot}$ 315) was isolated in a low yield; in weakly acidic medium it is smoothly converted to the aldehyde IIIb. The formyl group activates the 3-position of the molecule of tricyclics of the III type substantially less than the β-cyano-β-ethoxycarbonylvinyl fragment (see [1]), and replacement of the methoxy group by the ethoxy group evidently occurs at the stage of the intermediate immonium salt — this conclusion follows from the fact that even prolonged boiling of the methoxyaldehyde IIIa in ethanol does not lead to the ethoxyaldehyde IIIb.



In the PMR spectra for compounds IIIa,b (Table 1), the most characteristic signal is the singlet of the aldehyde proton at 9.86 ppm, whereas in the spectrum of the acetal IV the weakly split singlet at 5.26 ppm, belonging to the 2'-H proton ($^4J_{1,2'}$ Hz), is the most characteristic. An experiment on the nuclear Overhauser effect (NOE) in the recording of the PMR spectra for compound IIIa established that the 1'-H proton and the OCH3 group are spatially close together (NOE ~ 16%), which permits compound III to be classified as a 9-alkoxy derivative. Evidently the acetal IV, from which the aldehyde IIIb was obtained by hydrolysis, is also a compound of this type. The ^{13}C NMR spectrum of the aldehyde IIIa (Table 2) is structurally close to the ^{13}C NMR spectrum of 2-(β-ethoxycarbonyl-β-cyano)vinyl-3-oxo-9-methoxypyrrolo[1,2-a]indole, which we described earlier and for which the presence of a OCH3 group in the 9-position has been unambiguously demonstrated [1]. Thus, in the ^{13}C NMR spectrum of the compound IIIa the following signals are characteristic: 137.4 ($C_{(1)}$), 129.1 ($C_{(2)}$, d, $^2J_{C(2),2'-H}$ = 24.9 Hz), 184.0 ($C_{(2')}$ dd, $^1J_{CH}$ = 178.7 Hz, $^3J_{C(2'),1-H}$ = 2.9 Hz), 151.5 ($C_{(9)}$,m), 118.1 m.d, ($C_{(10)}$, d, $^4J_{C(10),2'-H}$ = 7.4 Hz), and the signal in the region of ~ 170 ppm, which might have corresponded to the 9-C=O carbon atom, is absent. In aggregate, the data cited suggest that the alkylation of compound I by dimethyl sulfate proceeds at the oxygen of the carbonyl group in the 9-position.

The reaction of the aldehyde IIIb with cyanoacetic ester and malononitrile leads to the 2-vinyl derivatives IIa,b, the structure of which was studied in detail earlier [1]. We should mention that in the reaction of compound IIIb with malononitrile in the presence of triethylamine, a derivative formed on account of the condensation of the latter at the 2- and 9-positions — the salt V — was also isolated.



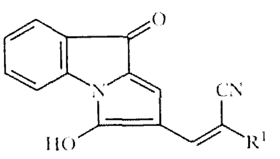
II a–c V

II a R = Et, R^1 = COOEt; b R = Et, R^1 = CN; c R = Me, R^1 = COOEt

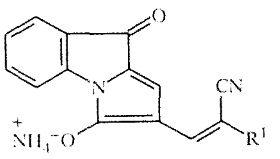
In the PMR spectrum of compound V, the singlets at 7.29 and 7.89 (1-H and 2'-H) and the signals of the HN$^+$Et$_3$ fragment at 1.17, 3.15, and 8.80 ppm (Me, CH$_2$, and N$^+$H, respectively) are characteristic (Table 1). Characteristic signals in the ^{13}C NMR spectra are those of the four CN groups in the region of 117.0-118.6 ppm; two singlets, which were converted to doublets on account of splitting on the 2'-H proton in the system of recording of the spectrum without suppression of spin-spin coupling with protons, were assigned to the 2''-CN groups (117.0, 118.6 ppm). The remaining signals (117.4 and 117.5 ppm) were ascribed to the 9'-CN groups. It is interesting to note the strong-field position of the signals of the C$_{(2'')}$ and C$_{(9')}$ atoms (52.7 and 61.3 ppm, respectively), which is due to the CN groups present at these carbon atoms.

The formation of an analogous salt in the reaction of the aldehyde IIIb with cyanoacetic ester is observed only chromatographically.

It is noteworthy that in compounds of the II type (just as in the previously described 2-vinyl-3-hydroxy-9-oxopyrroloindoles VI [1]), the functional substituents at the C$_{(2'')}$ carbon atom of the vinyl fragment and in the 3-position of the tricycle are close together in space. This creates prerequisites for the possibility of the closing of a new heterocycle at the 2,3-positions of the pyrrole portion of the molecules.*



VI



VIa

Attempts at such cyclization of compound VI by heating it with alcoholic ammonia did not meet with success — in this case its ammonium salt is formed (PMR spectra), which leads to a sharp decrease in the possibility of nucleophilic attack at the 3-position of the molecule (the presence of a whole-number negative charge in the molecule of the salt VIa† also leads to the fact that an amide is not formed at the ethoxycarbonyl group under the conditions selected).

The "reinforced" structures of the II type are a different matter — in this case salt formation is impossible, and it seemed realistic to use them as the basis for pyridine cyclization involving the 2''-ethoxycarbonyl group and the carbon atom in the 3-position. An attempt at such heterocyclization was performed in this work on the basis of the most readily available [1] derivative of 2-vinylpyrrolo[1,2-a]indole IIc. In the ammonolysis of compound IIc we might have expected that the process would occur according to the scheme IIc → VII → VIII.‡

It was found, however, that ammonolysis of compound IIc is complicated by still another process — the addition of ammonia at the 2'-position of the vinyl fragment. As a result, instead of compound VIII we obtained 2-amino-3-cyano-5H-4,5-dihydropyrido[3',2':4,5]pyrrolo[1,2-a]indoledione-4,11 (IX), with a yield of 27%. Just as in the hypothetical case of formation of the tetracycle VIII, the results obtained do not permit any conclusions to be drawn about the relative rate of the processes that occur and about the sequence in which the processes leading to the formation of the tetracycle IX occur. In other words, we have no data on which of the reactions — attack by ammonia at the 3-position, amidation or addition of ammonia at the

---

*A preliminary report on the production of such a tetracyclic system was published in [2]. In this work compounds of the II type were assigned the structure of 3-alkoxy derivatives. In the previous work [1] and in these studies it was reliably established that these compounds have the structure of 2-vinyl-3-oxo-9-alkoxypyrrolo[1,2-a]indoles.

†The structure of salts of the VIa type was examined in detail in the previous work [1].

‡Of course, it cannot be asserted on the basis of the available data that amidation at the ethoxycarbonyl group does not occur at the first step, and the intermediate VII is not formed on account of attack of the amide NH$_2$ group at the 3-position.

TABLE 2. Data of the ^{13}C NMR Spectra of Compounds IIIa, V, IX*

Compound	Chemical shifts, δ, ppm, J_{CH}, Hz										
	$C_{(1)}$	$C_{(2)}$	$C_{(2')}$	$C_{(2'')}$	$C_{(3)}$	$C_{(4a)}$	$C_{(8a)}$	$C_{(9)}$	$C_{(10)}$	R, R^1	CN
IIIa	137,4 dd $^1J_{CH}$ =178,5, $^3J_{CH}$ = 3,7	129,1 d $^2J_{CH}$ = 24.9	HC=O 184,0 dd $^1J_{CH}$ = 178,7 $^3J_{CH}$ = 2,9	—	160,8 q Σ^3J ~9,0	134,3 q Σ^3J ~6,0	125,2 q Σ^3J ~13,0	151,5 m Σ^3J ~10,0	118,1 d $^2J_{CH}$ = 6,0	OCH_3 60,1 q $^1J_{CH}$ = 146,6	—
V	121,6 dd $^1J_{CH}$ =177,9, $^3J_{CH}$ = 8,8	115,5 q Σ^2J ~6,0	145,7 d $^1J_{CH}$ = 157.1	52,7 s	160,6 q Σ^3J ~12,0	141,6 q Σ^3J ~6,0	128,4 q Σ^3J ~10,0	138,0 m Σ^3J ~14,0	128,5 d $^2J_{CH}$ = 4,9	*2	117,0 d $^3J_{CN}$ trans-* 12,8, 118,6 d $^3J_{CN}$ cis-* 7,2

Compound	$C_{(1)}$	$C_{(1a)}$	$C_{(2)}$	$C_{(3)}$	$C_{(5a)}$	$C_{(6a)}$	$C_{(10a)}$	$C_{(11)}$	$C_{(11a)}$	$C_{(4)}$	CN
IX*3	139,9 d $^1J_{CH}$ = 177, 8	86,3 s	157,3 s With sub-splitting	109,2 t ^3J = 6,0	147,2 d ^3J = 7,1	134,1 m $\Sigma\,^3J\,^4J$ = 12,0	126,9 m $\Sigma\,^3J$ ~ 13,0	161,2 d ^2J = 7,2	112,4 s With sub-splitting	C=O 137,4 s With sub-splitting	119,9 s

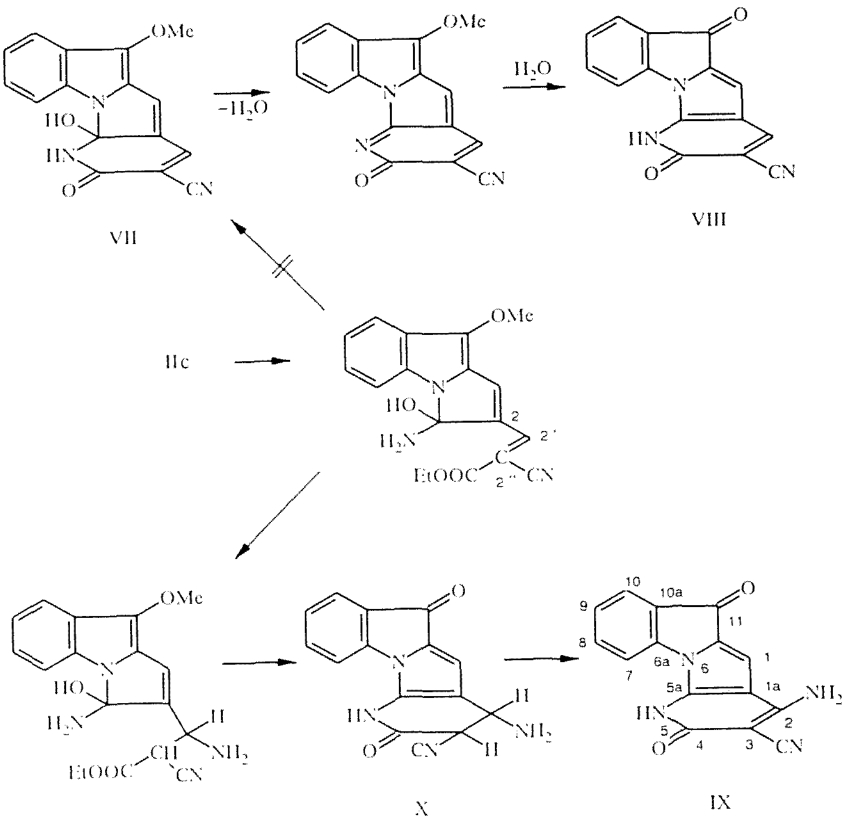
---

*Solvent DMSO-D_2 for compounds IIIa, V, IX. For all the investigated compounds δ $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, $C_{(8)}$ have the values 113.8-135.0 ppm, ^{1}J 162-168 Hz.

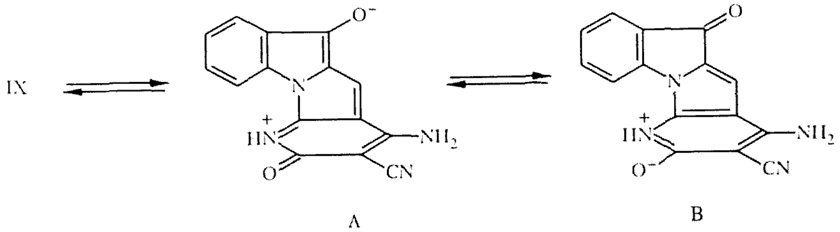
*2 Chemical shifts of the signals of the carbon atoms of the dicyanovinyl fragment at $C_{(9)}$ of compound V: 61.3 (s, $C_{(9')}$), 117.4, 117.5 [s, 2(9'-CN)], 8.9 [tq, ($^+NH(CH_2CH_3)_2$)], $^1J_{CH}$ = 127.8 Hz, 46.1 Hz [tq, ($^+NH(CH_2CH_3)_2$) $^1J_{CH}$ = 143.0 Hz].

*3 For compound IX, for convenience of compilation of the table, numeration of the atoms analogous to the numeration used for compounds I—IX was used. The numbers of the carbon atoms corresponding to the generally accepted numeration of the tetracycle of IX are given in parentheses in each column; this numeration is used in the text of the article in the description of the name of the tetracycle.

2′-position of the substituted acrylic ester — proceeds first. One of the versions of formation of compound IX is shown on the scheme. We should mention that aromatization of the pyridine ring, possibly on account of disproportionation (on the scheme X → IX) occurs in the course of the process.



In the PMR spectrum of compound IX (solvent DMSO-D_6), the following signals are the most characteristic: a narrow singlet at 8.17 (1-H), a broadened two-proton signal at 6.97 ppm (NH_2), and a greatly broadened one-proton signal at 12.10 ppm of the endocyclic NH group (Table 1). Table 2 presents data of the ^{13}C NMR spectrum for the tetracycle IX. As a result of experiments on spin-spin decaplization it was established that the singlets of the $C_{(2)}$ and $C_{(5a)}$ carbon atoms (157.3 and 147 ppm, respectively) are split on account of spin-spin coupling with the 1-H proton; the signal of the $C_{(3)}$ carbon atom is represented by a triplet on account of interaction with the NH_2 protons; the signal of the 4-C=O carbon atom forms a slightly split singlet on account of interaction with the 5-NH proton; the carbon atom of the CN group is a narrow singlet (119.9 ppm). The small strong-field shift of the signals of the 4-C=O and 11-C=O carbon atoms in comparison with the standard values is due to the contribution of resonance structures of types A and B.



In concluding this work, we should mention that compound IX is the first representative of a new heterocyclic system — pyrido[3′,2′:4,5]pyrrolo[1,2-a]indole. Only one study on the synthesis of compounds of this type has been published up to now, namely, the production of derivatives of the isomeric system — pyrido[2′,3′:3,4]pyrrolo[1,2-a]indole [3].

EXPERIMENTAL

The IR spectra of the compounds were obtained on a Perkin-Elmer 457 spectrometer in liquid petrolatum, the mass spectra on a Varian MAT-112 spectrometer with direct introduction of the sample into the ion source. The energy of the ionizing electrons was 70 eV. Temperature of the ionization chamber 180°C. The ^{1}H and ^{13}C NMR spectra of the compounds were recorded on a Varian XL-200 instrument, internal standard TMS. The course of the reaction and individuality of the substances were monitored by thin-layer chromatography on a Silufol UV-254 plate in the system chloroform—methanol, 10:1. Detection in UV light.

The data of elementary analysis correspond to the calculated values.

2-Formyl-3-oxo-9-methoxypyrrolo[1,2-a]indole (IIIa, $C_{13}H_9NO_3$). To a suspension of 2 g (7.2 mmoles) of the enaminoketone I in 70 ml of benzene we added 0.9 g (7 mmoles) dimethyl sulfate and mixed for 3 h at 60°C, then added 0.9 g (7 mmoles) portions of dimethyl sulfate three times more at 3 h intervals. The total time of heating was 12 h. The mixture was cooled, the 2-piperidiniummethylene-3-oxo-9-methoxypyrrolo[1,2-a]indole methylsulfate (Ia) that precipitated was filtered off and dissolved in 50 ml of water at 30°C. The precipitate was filtered off, washed with water, and dried. We obtained 1.2 g of the technical compound IIIa, which was recrystallized from benzene. Yield 0.7 g (43%). mp 229-230°C. IR spectrum: 1700, 1600 cm^{-1}.$M^{+\cdot}$ 227.

2-Formyl-3-oxo-9-ethoxypyrrolo[1,2-a]indole (IIIb, $C_{14}H_{11}NO_3$). A. To a suspension of 2 g (7 mmoles) of the enaminoketone I in 80 ml of absolute alcohol we added 0.9 g (7 mmoles) dimethyl sulfate and mixed at 65°C for 2 h. Then another 0.9 g (7 mmoles) dimethyl sulfate was added, and the mixture was mixed at 65°C for another 1 h. The alcohol was evaporated; the crystalline residue was mixed with acetonitrile and filtered off. Yield of the aldehyde IIIb 1.3 g (76%). mp 234-236°C (from absolute alcohol). IR spectrum: 1700, 1600 cm^{-1}.$M^{+\cdot}$ 241.

B. To a suspension of 8 g (29 mmoles) of the enaminoketone I in 300 ml of absolute alcohol, 9.25 g (73 mmoles) dimethyl sulfate was added with mixing (40°C) in portions at 45 min intervals. The solvent was evaporated, the crystalline residue mixed with acetonitrile, and 6.5 g of a mixture of the aldehyde IIIb with the diethylacetal of 2-formyl-3-oxo-9-ethoxypyrrolo[1,2-a]indole (IV, $C_{18}H_{21}NO_4$) was filtered off. As a result of successive recrystallizations from absolute alcohol and acetonitrile with charcoal, a mixture of compounds IIIb and IV (1:1 according to the PMR data) was obtained. From the mother liquors we isolated 2 g of compound IIIb, and the (1:1) mixture was recrystallized once more from absolute ethanol, yielding an additional 0.2 g of compound IIIb. The total yield of the aldehyde IIIb was 2.3 g (33%). The alcoholic mother liquor was evaporated, the residue was recrystallized from acetonitrile, and we obtained 0.3 g (3%) of the acetal IV. mp 110-112°C. IR spectrum: 3090, 1750, 1730, 1710, 1650, 1610, 1600 cm^{-1}.$M^{+\cdot}$315.

C. One drop of conc. H_2SO_4 was added to a solution of 0.2 g (0.6 mmole) of the acetal IV in 20 ml of water and boiled for 1 h. The mixture was kept at 20°C for 12 h. The precipitate formed was filtered off, washed with water, and 0.1 g (65%) of the aldehyde IIIb was obtained. A mixed melting point test with a sample produced according to method A or B showed no depression.

Ethyl ester of α-cyano-β-(3-oxo-9-ethoxypyrrolo[1,2-a]indol-2-yl)acrylic Acid (IIa, $C_{19}H_{16}N_2O_4$). To a suspension of 0.4 g (1.8 mmoles) of the aldehyde IIIb in 20 ml of absolute alcohol we added 0.1 ml (0.7 mmole) of triethylamine and 0.2 g (1.8 mmoles) of cyanoacetic ester. The mixture was mixed for 3 h at 20°C. The precipitate formed was filtered off and washed with isopropanol and hexane. We obtained 0.35 g of a mixture of compounds IIa and IIIb. The mixture was recrystallized twice from benzene, yielding 0.15 g (27%) of the ester IIa. mp 196-197°C. IR spectrum: 2200, 1720, 1690, 1600 cm^{-1}.$M^{+\cdot}$ 336. A mixed melting point test with a sample produced by the method described in [1] showed no depression.

Nitrile of α-cyano-β-(3-oxo-9-ethoxypyrrolo[1,2-a]indol-2-yl)acrylic Acid (IIb, $C_{17}H_{11}N_3O_2$). From 0.5 g (2.2 mmoles) of the aldehyde IIIb and 0.15 g (2.2 mmoles) malononitrile in 15 ml of absolute alcohol in the presence of 0.2 ml (1.4 mmoles) triethylamine under the conditions of synthesis of the ester IIa we obtained 0.2 g (33%) of compound IIb. Mp 239-240°C (without benzene). IR spectrum: 2200, 1700, 1670, 1650, 1600 cm^{-1}.$M^{+\cdot}$ 289. From the mother liquor we isolated 0.25 g (29%) of the triethylammonium salt of the nitrile of α-cyano-β-(3-hydroxy-9-dicyanomethylenepyrrolo[1,2-a]indol-2-yl)acrylic acid (V, $C_{24}H_{22}N_6O$). mp > 300°C (from isopropanol). IR spectrum: 2200, 1670, 1650, 1600 cm^{-1}.$M^{+\cdot}$ was absent.

2-Amino-3-cyano-5H-4,5-dihydropyrido[3′,2′:4,5]pyrrolo[1,2-a]indole-4,11-dione (IX, $C_{15}H_8N_4O_2$). To a suspension of 0.4 g (1.2 mmoles) of compound IIc [1] in 10 ml of methanol we added 20 ml of a 14% solution of ammonia in methanol. The reaction mass was heated for 5 h in an autoclave at 90-100°C. The mixture was cooled, and the precipitate was filtered off and washed with methanol. Yield 0.1 g (27%) of the tetracycle IX. mp > 300°C (dec., from DMFA). IR spectrum: 3500, 3420, 3300, 3160, 2200, 1690, 1660, 1630 cm^{-1}.M$^{+\cdot}$ 276.

REFERENCES

1. N. Z. Tugusheva, S. Yu. Ryabova, N. P. Solov'eva, and V. G. Granik, Khim. Geterotsikl. Soed., No. 6, 781 (1994).
2. N. Z. Tugusheva, S. Yu. Ryabova, N. P. Solov'eva, and V. G. Granik, Mendeleev Commun., No. 6, 238 (1993).
3. G. Kalaus, N. Malkien, M. Kajtar-Peredy, T. Koritsanzky, A. Kalman, L. Szabo, and O. Szantay, J. Org. Chem., **50**, 3760 (1985).