covered in the form of Bordeaux red crystals with a decomposition temperature equal to 315°C and R_f 0.54 (10:1 benzene–acetone). IR spectrum: 3410, 3340 (NH), 1429 cm^{-1} (N=N). UV spectrum, λ_{max} (log ε): 203.8 (3.87), 260.5 (4.11), 291 (3.63), 526 nm (4.22). Found: N, 19.3%; M 355. Calculated for $C_{20}H_{13}N_5O_2$: N, 19.8%; M 355. The compound produced a violet color with Ehrlich's reagent at room temperature.

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INDOLE DERIVATIVES.

118.* SYNTHESIS OF DERIVATIVES OF PYRROLO[1,2-a]INDOLES ON THE BASIS OF 1-ACETYL-3-INDOLINONE

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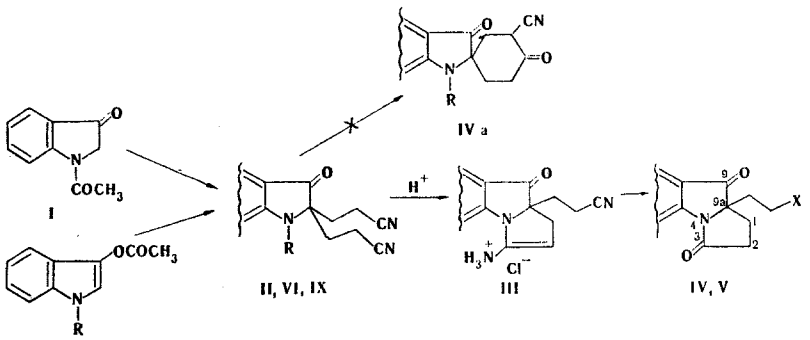
UDC 547.74/75'756.07:542.941.7'951.1

The methods of building up 9-keto-9H-pyrrolo[1, 2-a]indoles on the basis of 1-(o-carboxyphenyl)pyrroles have found application in the synthesis of the antibiotic mitomycin, although they are distinguished by low yields in the cyclization step [2-4].



In the method we propose for constructing the tricyclic system of mytomycin we start out from the condensation product of 1-acetyl-3-indolinone (I) with acrylonitrile, i.e., from 2,2-di-β-cyanoethyl-3-indolinone (II), which is easily cyclized under the action of an ethereal solution of hydrogen chloride to form hydrochloride

*For report 117 see [1].

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0009-3122/79/1509-0994$07.50

TABLE 1. Di-β-cyanoethyl-3-indolinones

Original compounds	Reaction products	mp, °C	Found, %			Empirical formula	Calculated, %			Mole ratio between original compound, acrilonitrile, + sodium ethoxide	Yield, %
			C	H	N		C	H	N		
I	II	110–112[b]	70,1	5,6	17,3	$C_{11}H_{10}N_2O$	70,3	5,4	17,6	1 : 3,8 : 0,13	70
VII	VI	84–85[c]	71,2	6,1	16,5	$C_{15}H_{16}N_2O$	71,1	5,9	16,6	1 : 3,6 : 1	64
VIII	IX	128–130[c]	70,1	5,7	19,5	$C_{17}H_{19}N_4O$	70,0	5,5	18,7	1 : 3,8 : 1,1	51
X	IId	108–110[b]	—	—	—	—	—	—	—	1 : 3 : 1,1	84

[a]The ethanolic solution of sodium ethoxide is prepared on the basis of 100 mg of sodium for every 5 ml of ethanol. [b]From water. [c]From ethanol. [d]Data have been presented previously.

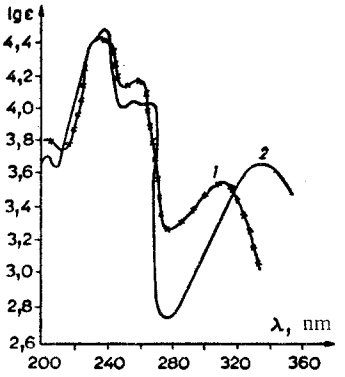

Fig. 1. Ultraviolet spectra of ethanolic solutions of compounds I (1) and IV (2) (the concentration is 3×10^{-4} to 5×10^{-4} M).

Depending on the hydrolysis conditions, hydrochloride III can be converted into lactam IV or V. Lactam IV is obtained by hydrolyzing hydrochloride III with water, and the use of dilute hydrochloric acid results in lactam V.

The IR spectrum of lactam IV does not contain absorption bands of the NH group. Its UV spectrum is practically identical to the UV spectrum of indolinone I (Fig. 1), while the UV spectrum of the alternative isomeric compound IVa should resemble the UV spectrum of ketone II (Table 2).

The possibility of cyclization with the participation of two cyanoethyl groups is also ruled out, since 1-methyl-2,2-di-β-cyanoethyl-3-indolinone (VI) remains unchanged under the cyclization conditions indicated above.

Compound VI was obtained directly from 1-methyl-3-acetoxyindole (VII) [5] (without a step for its conversion into 1-methy-3-indolinone) and acrylonitrile in the presence of sodium ethoxide.

The use of 3-acetoxyindole (VIII) instead of indolinone I for the synthesis of ketone II is not possible, since indigo is obtained from it along with dinitrile II (25% yield) when there is an equimolar amount of acrylonitrile and there is a catalytic amount (1:10) of sodium ethoxide, and the use of a 3- to 3.5-fold excess of acrylonitrile and an equimolar amount of sodium ethoxide produces a tricyanoethylation product (IX).

Instead of indolinone I, for the synthesis of dinitrile II it is better to use 1-acetyl-3-acetoxyindole (X), since a higher yield (84%) is then achieved.

EXPERIMENTAL

The course of the reactions and the purity of the compound obtained were monitored by thin-layer chromatography (Silufol UV-254). The IR spectra were recorded on a UR-10 instrument in liquid petrolatum, the UV spectra were recorded on a Specord UV-vis instrument, the PMR spectra were recorded on a CFT-20 spectrometer in pyridine-d_5, and the internal reference was TMS. The mass spectra were recorded on an MKh-1303 instrument with direct introduction of the sample into the ion source with an energy of the ionizing electrons equal to 50 eV and a cathode emission current equal to 1.25 mA.

TABLE 2. Spectra of the Cyanoethylation Products

Compound	IR spectra, cm^{-1}			UV spectra (in ethanol), λ_{max}, nm (log ε)	PMR spectra		
	C=C	C=O	C≡N		$(CH_2CH_2CN)_2$	aromatic protons	signals of other groups
II	1620	1690	2250	203 (4,35); 307 (4,05); 426 (4,12)	1,96—2,59 (8H, m)	6,69—7,73 (4H, m)	8,13 (1H, s, NH)
VI	1620	1710	2250	235 (4,37); 260 (3,88); 425 (3,68)	2,02—2,58 (8H, m)	6,75—7,70 (4H, m)	2,92 (3H, s, NCH_3)
IX	1605	1700	2245	238 (4,42); 263 (3,76); 404 (3,64)	2,21—2,42 (8H, m)	6,78—7,76 (4H, m)	3,05 (2H, CH_2CN); 3,99 (2H, NCH_2)

Cyanoethylation of I, VII, VIII, and X. Acrylonitrile and an ethanolic solution of sodium ethoxide were successively added to a solution of 10 mmole of the original compound in 30 ml of dioxane, which had been heated to 35°C (Table 1), and then the reaction mass was left to stand at room temperature for 10–12 h. The solvent was driven off, and the residue was treated with water and neutralized with 10% HCl. The precipitate formed was filtered, washed with water, and crystallized.

9a,1-Dihydro-3-amino-9-keto-9H-9a-β-cyanoethylpyrrolo[1,2-a]indole Hydrochloride (III). A suspension of 0.35 g (1.46 mmole) of compound II in 3 ml of ethanol and 6 ml of 7% HCl in ether was stirred to dissolution, and another 2 ml of 7% HCl in ether were added. The precipitate formed after 2–3 h was filtered and washed with dry ether. This yielded 0.4 g (99%) of hydrochloride III, mp 119–120°C (reprecipitation from ethanol by ether). IR spectrum: 1610 (C=C), 1640 ($-\overset{\oplus}{N}H_3$), 1730 (C=O), 2250 (C≡N), 3100–3280 cm^{-1} ($-NH_3$). UV spectrum (in ethanol), λ_{max} (log ε): 207 (4.08), 240 (4.35), 261 nm (3.92). Found: N, 15.2; Cl, 13.2%. Calculated for $C_{14}H_{13}N_3O \cdot HCl$: N, 15.3; Cl, 13.3%.

1,2,3,9,9a-Pentahydro-3,9-dioxi-9H-9a-β-cyanoethylpyrrolo[1,2-a]indole (IV). A solution of 0.35 g (1.27 mmole) of hydrochloride III in 2 ml of water was left to stand at room temperature for 24 h. The precipitate was filtered, and 0.2 g (65.5%) of IV with mp 133–134°C (from ethanol) was obtained. IR spectrum: 1610 (C=C), 1725 (C = O), 2120 cm^{-1} (C ≡ N). IR spectrum ($CHCl_3$): 1610 (C = C), 1720, 1725 (C = O), 2250 cm^{-1} (C ≡ N). UV spectrum (in ethanol), λ_{max} (log ε): 204 (3.81), 238 (4.42), 260 (4.17), 312 (3.56), 357 nm (3.26). PMR spectrum: 7.08–8.04 (4 H, m, aromatic protons); 2.06–2.24 (2 H, m, 1-H); 2.29–2.50 (4 H, m, CH_2CH_2CN); 2.51–3.29 ppm (2 H, m, 2-H). Found: C, 69.9, H, 5.1; N, 11.6%; M^+ 240. Calculated for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7%; M 240. The mother solution was given an addition of 2 ml of conc. HCl and left to stand at room temperature for 2–3 days. The precipitate was filtered, and 0.1 g (30.3%) of V with mp 174–175°C (from ethanol), was obtained. IR spectrum: 1700, 1710 (C=O), 1730 (COOH), 2500–2800 (associated OH), 3250 cm^{-1} (OH). UV spectrum (in ethanol), λ_{max} (log ε): 206 (3.93), 238 (4.38), 260 (3.93), 322 nm (3.28). PMR spectrum: 7.08–8.02 (4 H, m, aromatic CH), 2.02–2.25 (2 H, m, 1-H), 2.34–2.50 (4 H, m, CH_2CH_2CN), 2.51–3.29 ppm (2 H, m, 2-H). Found: C, 64.9; H, 5.3; N, 5.3%; M^+ 259. Calculated for $C_{14}H_{13}NO_4$: C, 64.9; H, 5.0; N, 5.4%; M 259.

1,2,3,9,9a-Pentahydro-3,9-dioxi-9H-9a-β-carboxyethylpyrrolo[1,2-a]indole (V). A solution of 0.35 g (1.27 mmole) of hydrochloride III in 2 ml of water was given an addition of 1 ml of conc. HCl and left to stand for 2–3 days at room temperature. The crystals precipitated were filtered, the mother solution was evaporated, and the residue was filtered and washed with water. The total yield was 0.2 g (59%), and the mp was 174–175°C.

2,2-Di-β-cyanoethyl-3-indolinone (II). A solution of 0.9 g (5 mmole) of 3-acetoxyindole VIII and 0.25 g (5 mmole) of acrylonitrile was given an addition of 2.5 ml of an ethanolic solution of sodium ethoxide [which was prepared from 0.012 g (0.5 mmole) of sodium and 2.5 ml of ethanol] and left to stand at room temperature for 10–12 h. The solvent was evaporated, the residue was boiled with isopropyl alcohol, and the undissolved part was filtered off. This yielded 0.3 g (43%) of indigo, mp 390–391°C, as opposed to 392°C according to the data in [6]. The mother solution was evaporated, and the residue was introduced into a column with 70 g of silica gel and eluted by a 10:1 carbon tetrachloride–acetone mixture. This yielded 0.3 g (25%) of II.

2,2-Di-β-cyanoethyl-3-indolinone (II) and 1,2,2-Tri-β-cyanoethyl-3-indolinine (IX). An ethanolic solution of sodium ethoxide [which was prepared from 0.35 g (16 mmole) of sodium and 17 ml of ethanol] in 50 ml of dioxane was added to a solution of 0.9 g (5 mmole) of indolinone I and 2.6 g (50 mmole) of acrylonitrile, which had been heated to 35°C, and the mixture was left to stand for 16 h. According to the TLC data (1:1 chloroform–acetone), the reaction mass contained a 2:1 mixture of the di- and tricyanoethyl derivatives II and IX (R_f 0.54 and 0.34, respectively).

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ENAMINES.

6.* HYDROLYSIS OF CYCLIC ENAMINO KETONES OF THE PYRROLIDINE, PIPERIDINE, AND HEXAHYDROAZEPINE SERIES

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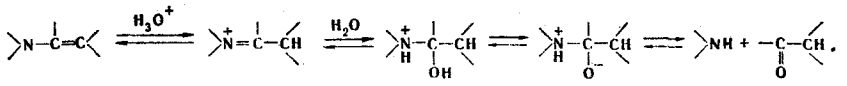
The kinetics and mechanism of the hydrolysis of various enamines have been studied in fairly great detail [2-4], and according to the current ideas, the hydrolysis process takes place in accordance with the following scheme:



At the same time, it has been shown that the rate-limiting step varies as a function of the ambient pH [2-4] and the degree of conjugation between the lone pair of the nitrogen atom and the enamine carbon–carbon double bond [5, 6].

In contrast to the enamines, no systematic investigations of the hydrolysis of enamine ketones have previously been carried out, while in a number of cases, the hydrolysis of enamine ketones is a convenient method for obtaining the corresponding dicarbonyl compounds. Therefore, the study of the features of the hydrolysis of enamine ketones is of definite interest not only in the theoretical respect, but also in the practical respect. In accordance with this goal, the present work was an investigation of the hydrolysis of enamino ketones [in the examples of 1-methyl-2-(2'-benzoylmethylene)pyrrolidine (Ia) [7], -piperidine (Ib) [8], and -hexahydroazepine (Ic) [9]] and of the dependence of the rate of this process on the conditions selected (pH, temperature) and the size of the saturated azaheterocycle. Polarography was selected as the instrumental method, since the half-wave potentials of the original enamino ketones and of their hydrolysis products of type II differ significantly over a broad pH range. As an example, Table 1 presents the values of $E_{1/2}$ for enamino ketones of type I and of the corresponding β-diketones of type II in an acetate buffer solution with pH 4.6.

In moderately acidic media (pH 1-6) the rate of hydrolysis is usually limited by the rate of the addition of water to the immonium cation [2-4]. Thus, already from general considerations it follows that the six-membered enamino ketone (Ib) should undergo hydrolysis most readily. In fact, in this case, in the rate-limiting step there is an sp^2-sp^3 change in the configuration of the $C_{(2)}$ atom of the ring, which, according to the concept of an I strain [10, 11], is most advantageous for a six-membered ring and least advantageous for a five-membered ring. At the same time, as we see from the scheme presented, the hydrolysis of enamino ketones is a reversible process, and its rate should be determined by the ratio between the rate of constants of the forward and reverse reactions. For this reason, it is necessary to take into account the factors which influence

*For report 5 see [1].

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