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LACTAM AND ACID AMIDE ACETALS. 64.* ACYLATION OF ENAMINO KETONES OF THE INDOLIN-3-ONE AND 2-PYRROLIN-4-ONE SERIES AND SYNTHESIS OF 2-INDOLYL- AND 5-PYRROLYLACRYLIC ACID DERIVATIVES

S. Yu. Ryabova, Yu. I. Trofimkin, L. M. Alekseeva, L. S. Khabarova, and V. G. Granik

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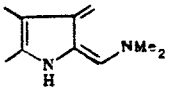
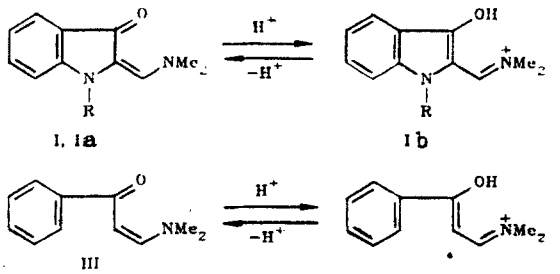
The reaction of 2-(N,N-dimethylaminomethylene)indolin-3-one and 2-methyl-3-ethoxycarbonyl-5-(N,N-dimethyl aminomethylene)-2-pyrrolin-4-one with acyl halides was used to synthesize immonium salts, the aqueous hydrolysis of which leads to 2-formyl-3-hydroxyindole and 4-hydroxy-5 formylpyrrole derivatives. α-Cyano-β-(2-indolyl)- and α-cyano-β-(5-pyrrolyl)acrylic acid derivatives were synthesized by reaction of immonium salts of the pyrrole series, 4 acyloxy-5-formylpyrrole and 2-formyl-3-acyloxyindole derivatives, with compounds that contain an active methylene group.

It is known that, depending on the presence and location of substituents, the acylation of enamino ketones may take place at the oxygen atoms, the β-carbon atom, and the NH group (for primary and secondary enamino ketones) [2; p. 197]. Thus far, however, the question of the acylation of enamino ketones that have a monosubstituted amino group in the β position has not been examined in the literature. Recently, on the basis of reactions of N-acetylindoxyl and 2-methyl-3-ethoxycarbonyl-2-pyrrolin-4-one with DMF diethylacetal, we synthesized tertiary enamino ketones I and II containing, in the β position of the enamine, a secondary amino group conjugated with a benzene ring (I) or making up part of the β-aminodicarbonyl system (II). From an examination of the unusual structural fragment A, which is peculiar to I and II,



A

it follows that the most likely site of attack by electrophilic reagents such as acyl halides are the carbonyl oxygen atom and the secondary amino group; O-acylation is preferable, since an aromatic indole or pyrrole system should be realized



I, Ia — Ib

III

I R=H, ΔpK_a=4,5; Ia R=$COCH_3$, ΔpK_a=6,15; Ib R=H, $COCH_3$; III ΔpK_a=8,12

*See [1] for Communication 63.

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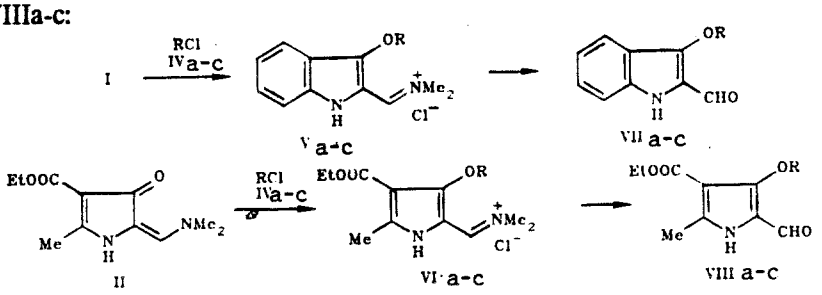
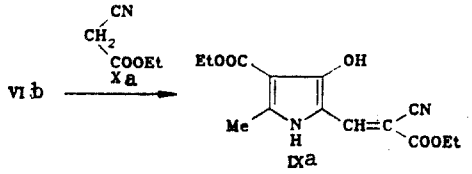
in this case. The degree of this sort of stabilization can be evaluated by measuring the ionization constants of these compounds and of enamino ketones for which O-protonation [2; p. 187] does not lead to aromatization. A comparison of the ΔpK_a values in nitromethane for enamino ketone I, its N-acetyl derivative Ia, and their noncyclic analog — N,N dimethylaminomethyleneacetophenone (III) [3] — shows that the basicity of I is higher than the basicity of enamino ketone III and that even N-acetylated compound Ia is a stronger base than enamino ketone III. This relationship between the basicities of these compounds is undoubtedly associated with aromatization of cations Ib

The results of the acylation of I and II are also in agreement with these considerations. Chloroacetyl chloride (IVa), acetyl chloride (IVb), and p-toluenesulfonyl chloride (IVc) were used as the acylating agents.The reaction of enamino ketone I with IVa yielded immonium salt Va, the structure of which as an O-acyl derivative follows unambiguously from the presence in its IR spectrum of absorption bands at 1790 cm^{-1}, which corresponds to the $OCOCH_2Cl$ group, and at 1670 cm^{-1}, which is related to an immonium fragment. Chloroacetylation in the pyrrolinone series also proceeds similarly: salt VIa (ν1800 and 1670 cm^{-1}) is formed in the reaction of II and IV. Selective O acylation is also observed in the acetylation and tosylation of enamino ketones I and II — the resulting immonium salts Vb,c and VIb,c (just like Va and VIa) are hydrolyzed extremely readily on dissolving in water to give the corresponding aldehydes VIIa-c and VIIIa-c:

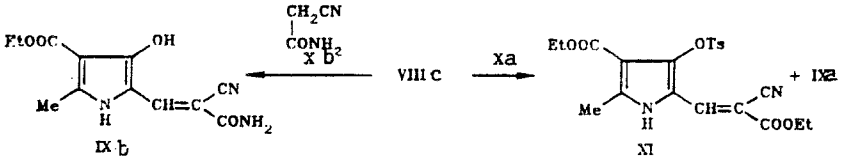


V—VIII [a] R=$ClCH_2CO$; [b] R=$COCH_3$; [c] R=*p*-Ts

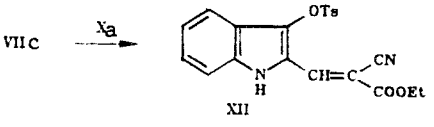
It should be noted that immonium salt VIb can be used to obtain ethyl α-cyano-β-(2-methyl-3-ethoxycarbonyl-4 hydroxy-5-pyrrolyl)acrylate (IXa). The reaction with ethyl cyanoacetate (Xa) proceeds in the presence of piperidine and is accompanied by splitting out of the O-acetyl group:



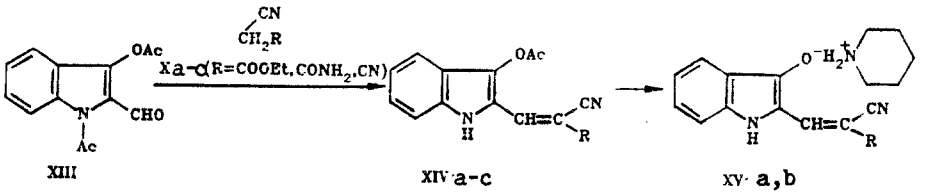
2-Formylpyrrole derivatives VIII can also undergo reaction with X that have an active methylene link; this was demonstrated in the case of the condensation of tosyloxy derivative VIIIc with ethyl cyanoacetate (Xa) and cyanoacetamide (Xb). In both cases the water liberated during the reaction hydrolyzes the O-tosyl grouping, but, whereas only β-(4-hydroxy-5-pyrrolyl)acrylamide (IXb) was isolated in the reaction of VIIIc with cyanoacetamide, a pyrrolylacrylic acid derivative (XI) containing an O-tosyl grouping in the 4 position can be isolated along with IXa in the reaction with ethyl cyanoacetate:



Like 2-formylpyrroles VIIIa-c, 2-formylindoles VIIa-c can be used in the condensation with cyanoacetic acid derivatives. Thus ethyl α-cyano-β-(3-tosyloxy-2-indolyl)acrylate (XII) was obtained in the reaction of tosyloxy aldehyde VIIc with ester Xa:



However, a compound that we previously obtained [1], viz., N-acetyl-2-formyl-3-acetoxyindole (XIII), is a more convenient model for the synthesis of indolylacrylic acids. The condensation proceeds smoothly and is accompanied by hydrolysis of only the N-acetyl group (bands of an acetoxy group at 1750-1780 cm^{-1} are observed in the IR spectra), and β-(2-indolyl)-acrylic acid derivatives XIVa-c are formed in good yields:



XIV [a] R=COOEt; [b] R=$CONH_2$; [c] R=CN

Treatment of acetoxy derivatives XIVa,b with piperidine leads to piperidine salts with β-(3-hydroxy-2-indolyl)acrylic ester (XVa) and -acrylamide (XVb), in the IR spectra of which the absorption bands of acetoxy groups vanish (see Experimental for the IR spectral data).

The structures of the 5-pyrrolyl- and 2-indolylacrylic acid derivatives were established on the basis of a study of the ^{13}C NMR spectra in the case of IXa,b and XIVa,b. It is apparent from Table 1 that splitting by the vinyl β proton of the signals of the carbon atoms of the CN, $CONH_2$, and COOEt groups with different $^3J_{CH}$ values is observed in the spectra of these compounds; this corresponds to data regarding the stereospecificity of carbon-proton spin-spin coupling (SSC) through three bonds [4]. Signals of two isomers relative to the C=C double bond, as evidenced by the presence of paired signals of each of the carbon atoms of the molecule and splitting of the signals of the carbon atom of the cyano group by the β-vinyl proton with constants of 13 and 9 Hz for the trans and cis orientations of the CH and CN groups in these isomers, are observed in the ^{13}C NMR spectrum of IXb (see Table 1). All of these data (in addition to the PMR spectral data — see Experimental) unequivocally confirm the structures of the synthesized compounds.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin—Elmer 457 spectrometer. The mass spectra were obtained with a Varian MAT-112 mass spectrometer with direct introduction of the samples into the ion source; the ionizing-electron energy was 70 eV, and the temperature of the ionization chamber was 180°C. The ^1H and ^{13}C NMR spectra of the compounds were recorded with a Varian XL-200 spectrometer with tetramethylsilane (TMS) as the internal standard. The course of the reactions and the individuality of the substances were monitored by TLC on Silufol UV-254 plates in ethyl acetate (for VII, XII, XII, XIV, and XV) or in benzene—methanol (9:1) (for VIII, IX, and XI) with development in UV light. The ionization constants were determined by potentiometric titration with a Radiometer PHM-26 pH meter with glass (G 2222B) and calomel (K 4112) electrodes in nitromethane at 25°C at a concentration of $1 \cdot 10^{-3}$ mole/liter. A 0.1 N solution of $HClO_4$ in nitromethane was used as the titrant.

The results of elementary analysis were in agreement with the calculated values.

2-Dimethylimmoniamethylene-3-chloroacetoxyindole Chloride (Va, $C_{13}H_{14}Cl_2N_2O_2$). A 0.75-ml (10 mmole) sample of chloroacetyl chloride was added to a solution of 0.94 g (5 mmole) of enamino indolinone I in 20 ml of DMF, and the mixture was stirred for 0.5 h. The resulting precipitate was removed by filtration and washed successively with DMF, acetone, and ether to give a product with mp 195°C. IR spectrum: 1790, 1670, 1620 cm^{-1}. M^+ 264. The yield was 0.8 g (53%).

TABLE 1. ^{13}C NMR Spectra of the Acrylic Fragment of α-Cyano-β-(5-pyrrolyl)- and -(2-indolyl)acrylic Acid Derivatives

Compound*	δ, ppm (J, Hz)			R	δ, ppm (J, Hz)
	β-CH, d	α-C	CN, d		
IXa	136,1 (160)	85,9 [d] (2,5)	120,6 (13)	$COOC_2H_5$	163,7 q t (J_1=6,0; J_2=3,0)
trans-IXb	134,3 (160)	89,7 m	118,6 (13)	$CONH_2$	164,1 m
cis-IXb	134,3 (160)	86,7 m	120,8 (9)		163,9 m
XIV b	135,3 (160)	102 d (2)	116,6 (13,7)	$CONH_2$	162,6 d (J_1=6,4)
XIV c	144,3 (166)	74,4 d (2)	113,8 (13,5)	CN	114,9 d (J_2=8,1)

*For IXb the trans and cis designations pertain to the orientation of the β-vinyl proton and the cyano group.

2-Formyl-3-chloroacetoxyindole (VIIa, $C_{11}H_8ClNO_3$). A 0.4-g (1.3 mmole) sample of chloride Va was dissolved in 20 ml of water, and the precipitate that formed in the course of 0.5 h was removed by filtration, washed with water, and dried to give a product with mp 149-151°C [from hexane—benzene (1:1)]. IR spectrum: 3300, 1780, 1660, 1620 cm^{-1}. M^+ 237. PMR spectrum ($CDCl_3$): 9.93 (1H, s, CHO), 9.02 (1H, br s, NH), 7.16-7.58 (4H, m, arom. protons), 4.17 ppm (2H, s, $OCOCH_2Cl$). The yield was 0.2 g (66%).

2-Formyl-3-acetoxyindole (VIIb, $C_{11}H_9NO_3$). A 0.38-g (2 mmole) sample of enaminoindolinone I was dissolved in 4 ml of acetyl chloride, and the resulting precipitate was removed by filtration, washed with ether, and dissolved in 50 ml of water. The resulting precipitate was removed by filtration and washed successively with water and isopropyl alcohol to give a product with mp 145-147°C [from water—isopropyl alcohol (5:1)]. IR spectrum: 3280, 1770, 1660, 1620 cm^{-1}. M^+ 203. PMR spectrum ($CDCl_3$): 9.90 (1H, s, CHO), 9.17 (1H, br s, NH), 7.12-7.57 (4H, m, arom. protons), 2.48 ppm (3H, s, $OCOCH_3$). The yield was 0.1 g (25%).

2-Formyl-3-tosyloxyindole (VIIc, $C_{16}H_{14}NO_4$). A 0.67-g (3.5 mmole) sample of p-toluenesulfonyl chloride was added to a suspension of 0.56 g (3 mmole) of enaminoindolinone I in 10 ml of pyridine, and the mixture was stirred for 1 h at 20°C. The resulting solution was poured into water (~100 ml), and the resulting precipitate was removed by filtration and washed successively with water, 0.5 N HCl, water, and alcohol to give a product with mp 162-164°C (from benzene). IR spectrum: 3300, 1650, 1620 cm^{-1}. M^+ 315. PMR spectrum ($CDCl_3$): 9.49 (1H, s, CHO), 8.98 (1H, br s, NH), 7.11-7.77 (8H, m, arom. protons), 2.45 ppm (3H, s, $OSO_2C_6H_4CH_3$-p). The yield was 0.7 g (74%).

Ethyl α-Cyano-β-(3-tosyloxy-2-indolyl)acrylate (XII, $C_{21}H_{18}N_2O_5$). A 0.52-ml (4.9 mmole) sample of ethyl cyanoacetate and 0.36 ml (2.5 mmole) of triethylamine were added to a solution of 0.79 g (2.5 mmole) of aldehyde VIIc in 10 ml of benzene, and the mixture was stirred for 3 h at 20°C. The resulting precipitate was removed by filtration and washed with benzene and ether to give a product with mp 178-180°C (from isopropyl alcohol). IR spectrum: 3370 (NH), 2220 (CN), 1720 (CO), 1595 cm^{-1} (C=C). M^+ 410. The yield was 0.9 g (88%).

α-Cyano-β-(3-acetoxy-2-indolyl)acrylic Acid Ethyl Ester and Nitrile (XIVa,c). A 1.43-ml (10 mmole) sample of triethylamine and 1 g (15 mmole) of malonic acid dinitrile or 2.23 g (20 mmole) of ethyl cyanoacetate were added with stirring at 20°C to a solution of 2.44 g (10 mmole) of 2-formylindole XIII in 50 ml of benzene, after which stirring was continued for 1.5-2 h. The resulting precipitate was removed by filtration and washed successively with benzene and ether to give 2.7 g of ester XIVa [$C_{16}H_{14}N_2O_4$, mp 175-177°C (from ethyl acetate). IR spectrum: 3340 (NH), 2240 (CN), 1780 ($COOC_2H_5$), 1760 ($OCOCH_3$), 1600 cm^{-1} (C=C). M^+ 298. PMR spectrum ($CDCl_3$): 2.47 (3H, s, $OCOCH_3$), 1.40 (3H, t, CH_2CH_3), 4.37 (2H, q, CH_2CH_3), 8.09 (1H, s, CH), 9.34 (1H, br s, NH), 7.11-7.47 ppm (4H, m, arom. protons). The yield was 91%] or 2.15 g of nitrile XIVc [$C_{14}H_9N_3O_2$, mp 210-212°C (dec., from acetone). IR spectrum: 3340 (NH); 2240, 2230 (2CN); 1770 ($OCOCH_3$); 1600 cm^{-1} (C=C). M^+ 251. PMR spectrum (d_6 acetone): 2.47 (3H, s, $OCOCH_3$), 8.17 (1H, s, CH), 10.39 (1H, s, NH), 7.19-7.68 (4H, m, arom. protons). ^{13}C NMR spectrum (d_6-DMSO + CD_3OD): 168.5 (q, J ≃ 7 Hz, $OCOCH_3$); 20.7 (q, J = 142 Hz, $OCOCH_3$); 114.9 (d, J = 8.1 Hz, CN); 113.8 (d, J = 13.5 Hz, CN); 74.4 (d, J = 2 Hz, α-C); 144.3 (d, J = 166 Hz, β-CH); 138.8, 138.4 (m, $C_{(2)}$, $C_{(7a)}$); 119.4 (m, $C_{(3a)}$); 121.4 (d, J = 2 Hz, $C_{(3)}$); 128.3, 121.4, 119.8, 113.9 ppm (q, J_1 = 160-165 Hz, J ≃ 8 Hz, $C_{(4)}$, $C_{(5)}$, $C_{(6)}$, $C_{(7)}$). The yield was 86%].

α-Cyano-β-(3-acetoxy-2-indolyl)acrylamide (XIVb, $C_{14}H_{11}N_3O_3$). A mixture of 2.45 g (10 mmole) of 2 formylindole XIII, 0.84 g (10 mmole) of cyanoacetamide, 50 ml of benzene, 1 ml (10 mmole) of acetic anhydride, and 1.44 ml (10 mmole) of triethylamine was refluxed with stirring for 2.5 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed successively with benzene, methanol, and ether to give a product with mp 210-212°C (dec., from acetonitrile). IR spectrum: 3410, 3380, 3280-3340, 3180-3220 (NH, NH_2); 2220 (CN); 1750 ($OCOCH_3$); 1670 ($CONH_2$); 1610 cm^{-1} (C=C). M^+ 269. PMR spectrum ($CDCl_3$ + d_6-DMSO): 2.46 (3H, s, $OCOCH_3$), 7.37 (2H, br s, NH_2), 10.37 (1H, s, NH), 8.12 (1H, s, CH), 7.11-7.57 ppm (4H, m, arom. protons). ^{13}C NMR spectrum (d_6-DMSO + CD_3OD): 168.5 (q, J ≃ 7 Hz, $OCOCH_3$); 20.7 (q, J = 142 Hz, $OCOCH_3$); 162.6 (d, J = 6.4 Hz, $CONH_2$); 116.6 (d, J = 13.7 Hz, CN); 102.1 (d, J = 2 Hz, α-C); 135.3 (d, J = 160 Hz, β-CH); 137.0 (q, J_1 = 10 Hz, J_2 = 7 Hz, $C_{(7a)}$); 119.7 (m, $C_{(3a)}$); 135.3 (s, $C_{(2)}$); 120.7 (d, J = 2 Hz, $C_{(3)}$); 126.4, 120.7, 119.0, 113.4 ppm (qd, J_1 = 160-165 Hz, J_2 ≃ 8 Hz, $C_{(4)}$, $C_{(5)}$, $C_{(6)}$, $C_{(7)}$). The yield was 1.5 g (56%).

Salt (XVa, $C_{19}H_{23}N_3O_3$) of Piperidine with Ethyl α-Cyano-β-(3-hydroxy-2-indolyl)acrylate. A mixture of 0.35 g (1.2 mmole) of ethyl 3-acetoxyindolylacrylate XIVa, 8 ml of acetonitrile, and 0.25 ml (2.5 mmole) of piperidine was stirred for 0.5 h at 20°C, after which the resulting precipitate was removed by filtration and washed successively with acetonitrile and ether to give a product with mp 145-147°C (dec., from acetonitrile). M^+ 256. The yield was 0.2 g (49%).

Salt (XVb, $C_{17}H_{20}N_4O_2$) of Piperidine with α-Cyano-β-(3-hydroxy-2-indolyl)acrylamide. This salt was obtained from 1.3 g (4.8 mmole) of 3-acetoxyindolylacrylamide XIVb, 40 ml of acetonitrile, and 1 ml (10 mmole) of piperidine as in the preparation of XVa and had mp 153-155°C (dec., from acetonitrile). IR spectrum: 3100-3450 (NH, NH_2); 2180 (CN); 1670 ($CONH_2$); 1620, 1600 cm^{-1} (C=C). M^+ 227. The yield was 1.5 g (99%).

2-Methyl-3-ethoxycarbonyl-4-chloroacetoxy-5-dimethylimmoniamethylenepyrrole Chloride (VIa, $C_{13}H_{18}Cl_2N_2O_4$). A solution of 0.7 ml (9.3 mmole) of chloroacetyl chloride in 25 ml of benzene was added to a suspension of 1.5 g (6.7 mmole) of enamino ketone II in 100 ml of dry benzene, and the mixture was refluxed for 30 min. It was then cooled, and the resulting precipitate was removed by filtration and washed with benzene to give a product with mp 223-225°C (from acetonitrile). IR spectrum: 1800, 1720, 1710, 1680 cm^{-1}. M^+ 300. The yield was 2.1 g (93%).

2-Methyl-3-ethoxycarbonyl-4-acetoxy-5-dimethylimmoniamethylenepyrrole Chloride (VIb, $C_{13}H_{19}ClN_2O_4$). This salt was obtained from 3 g (13.4 mmole) of enamino ketone II in 150 ml of benzene and 1.25 g (16.1 mmole) of acetyl chloride in 50 ml of benzene as in the preparation of chloride VIa. The compound did not have a distinct melting point. IR spectrum: 1780, 1700, 1680 cm^{-1}. The yield was 3.2 g (79%).

2-Methyl-3-ethoxycarbonyl-4-chloroacetoxy-5-formylpyrrole (VIIIa, $C_{11}H_{12}ClNO_5$). A 2.1-g (6.2 mmole) sample of chloride VIa was dissolved in 50 ml of water, and the solution was stirred for 30 min. The resulting precipitate was removed by filtration, washed with water, and dried to give a product with mp 182-183°C [from benzene—ethyl acetate (1:1)]. IR spectrum: 3240, 1800, 1680, 1650 cm^{-1}. M^+ 273. The yield was 1.2 g (71%).

2-Methyl-3-ethoxycarbonyl-4-acetoxy-5-formylpyrrole (VIIIb, $C_{11}H_{13}NO_5$). This compound was obtained from 5 g (16 mmole) of chloride VIb in 75 ml of water as in the preparation of 5-formylpyrrole VIIIa and had mp 161-163°C (from benzene) (mp 163°C [5]). IR spectrum: 3220, 1780, 1690, 1640 cm^{-1}. PMR spectrum (d_6-DMSO): 9.46 (1H, s, CHO), 4.16 (2H, q, CH_2CH_3), 1.24 (3H, t, CH_2CH_3), 2.45 (3H, s, 2-CH_3), 2.30 ppm (3H, s, $OCOCH_3$). The yield was 3.3 g (83%).

2-Methyl-3-ethoxycarbonyl-4-tosyloxy-5-formylpyrrole (VIIIc, $C_{16}H_{17}NO_6S$). A 2.34-g (12.3 mmole) sample of p-toluenesulfonyl chloride was added to a suspension of 2.3 g (10.3 mmole) of enamino ketone II in 50 ml of pyridine, and the mixture was stirred for 1 h at 20°C. It was then poured into ice water, and the resulting precipitate was removed by filtration, washed with 1 N HCl solution and water, and dried to give a product with mp 171-172°C (from benzene). IR spectrum: 3220, 1700, 1640, 1620 cm^{-1}. M^+ 351. PMR spectrum (d_6-DMSO): 8.82 (1H, s, CHO), 4.05 (2H, q, CH_2CH_3), 1.21 (3H, t, CH_2CH_3), 2.40 (3H, s, 2-CH_3), 2.43 (3H, s, $OSO_2C_6H_4CH_3$-p), 7.51-7.60 ppm (4H, A_2B_2 system of signals, arom. protons). The yield was 2.85 g (79%).

Ethyl α-Cyano-β-(2-methyl-3-ethoxycarbonyl-4-hydroxy-5-pyrrolyl)acrylate (IXa, $C_{14}H_{16}N_2O_5$). A 0.84-ml (7.9 mmole) sample of ethyl cyanoacetate was added to a suspension of 2 g (6.6 mmole) of chloride Vib in 60 ml of isopropyl alcohol and 0.5 ml of piperidine, and the mixture was refluxed for 7 h. It was then allowed to stand for 10 h at 20°C, and the resulting precipitate was removed by filtration, washed with isopropyl alcohol, and dried to give a product with mp 167-169°C (from isopropyl alcohol). IR spectrum: 3260 (NH, OH); 2220 (CN); 1720, 1680 ($COOC_2H_5$); 1600 cm^{-1} (C=C). M^+ 292. PMR spectrum (d_6-DMSO): 11.07 (br s, NH, OH), 7.93 (1H, s, CH), 4.22 (2H, q, CH_2CH_3), 1.28 (3H, t, CH_2CH_3), 2.52 ppm (3H, s, 2-CH_3). ^{13}C NMR spectrum (d_6-DMSO): 166.3 (br s, 3 $COOC_2H_5$); 163.7 (m, J_1 = 6 Hz, J_2 = 3 Hz, α-$COOC_2H_5$); 61.4, 60.7, 14.6, 14.1 (3-$COOCH_2CH_3$, α-$COOCH_2CH_3$, 2-CH_3); 85.9 (d, J ≃ 2.5 Hz, α-C); 136.1 (d, J ≃ 160 Hz, β-CH); 120.6 (d, J ≃ 13 Hz, CN); 142.8 (oct, J_1 = 7 Hz, J_2 = 2 Hz, $C_{(2)}$); 101.3 (m, $C_{(3)}$); 158.3 (q, d, J_1 = 9 Hz, J_2 = 3 Hz, $C_{(4)}$); 111.1 ppm (q, J_1 = 5 Hz, J_2 = 3 Hz, $C_{(5)}$). The yield was 0.8 g (41%).

α-Cyano-β-(2-methyl-3-ethoxycarbonyl-4-hydroxy-5-pyrrolyl)acrylamide (IXb, $C_{12}H_{13}N_3O_4$). This compound was obtained from 1.5 g (4.3 mmole) of tosyloxy aldehyde VIIIc, 60 ml of isopropyl alcohol, 0.43 g (5.15 mmole) of cyanoacetamide, and 0.5 ml of piperidine as in the preparation of IXa and had mp 248-250°C (dec., from dioxane). IR spectrum: 3430, 3170 (NH, NH_2, OH); 2200 (CN); 1680 ($COOC_2H_5$); 1660 ($CONH_2$); 1620 cm^{-1} (C=C). M^+ 263. PMR spectrum (d_6-DMSO), mixture of cis and trans isomers (1:4): 7.88, 7.37 (2H, 2 s, 2β-CH); 4.21, 4.23 (4H, 2 q, $2CH_2CH_3$); 1.29 (6H, 2 t, $2CH_2CH_3$); 2.49, 2.46 (6H, 2 s, 2-CH_3); 10.9 (br s, NH, OH); 7.36, 7.62 ppm (br s, NH_2). ^{13}C NMR spectrum (d_6-DMSO), trans: 164.3 ($COOC_2H_5$), 164.1 ($CONH_2$), 118.6 (d, J ≃ 13 Hz, CN), 89.7 (α-C), 134.3 (β-CH), 143.5 ($C_{(2)}$), 102.2 ($C_{(3)}$), 154.7 ($C_{(4)}$), 111.2 ($C_{(5)}$); cis: 166.2 ($COOC_2H_5$), 163.9 ($CONH_2$), 120.8 (d, J = 9 Hz, CN), 86.7 (α-C), 134.3 (β-CH), 141.8 ($C_{(2)}$), 101.8 ($C_{(3)}$), 155.8 ($C_{(4)}$), 113.5 ($C_{(5)}$); cis-trans: 59.7, 59.5 ($COOCH_2CH_3$); 14.4, 14.3 ppm ($COOCH_2CH_3$, 2-CH_3). The yield was 0.7 g (62%).

Ethyl α-Cyano-β-(2-methyl-3-ethoxycarbonyl-4-tosyloxy-5-pyrrolyl)acrylate (XI, $C_{21}H_{22}N_2O_7S$). A solution of 1.5 g (4.3 mmole) of tosyloxy aldehyde VIIIc, 0.55 ml (5.2 mmole) of ethyl cyanoacetate, and 0.5 ml of piperidine in 60 ml of isopropyl alcohol was refluxed for 1 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with isopropyl alcohol, and dried to give a product with mp 178-180°C (from isopropyl alcohol). IR spectrum: 3300, 3260 (NH); 2210 (CN); 1720 ($COOC_2H_5$); 1690 ($CONH_2$); 1590 cm^{-1} (C=C). M^+ 446. The yield was 0.65 g (34%).

The mother solution remaining after filtration of ester XI was allowed to stand for 16 h at 5°C, and the resulting precipitate was removed by filtration and washed with isopropyl alcohol to give 0.5 g of (4-hydroxy-5-pyrrolyl)acrylic acid ester IXa. No melting-point depression was observed for a mixture of this product with a sample of IXa obtained by the method described above.

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LACTAM AND ACID AMIDE ACETALS
65.* STUDY OF THE REACTION OF DMF DIETHYLACETAL WITH 5-CARBAMOYL(THIOCARBAMOYL)-6-AMINOPYRROLIZINE DERIVATIVES

A. V. Kadushkin, N. P. Solov'eva, T. V. Golovko, and V. G. Granik

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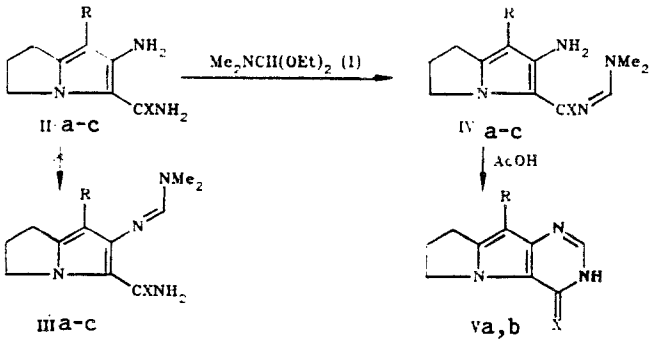
The reaction of DMF diethylacetal with 5-carbamoyl(thiocarbamoyl)-6-aminopyrrolizine derivatives proceeds regioselectively at the amido (thioamido) group without involving the 5-amino group. The synthesized acyl(thioacyl)amidines are starting compounds in the production of pyrimido[5,4-e]pyrrolizine derivatives.

It is known that amide and lactam acetals readily undergo condensation at the amino group of aromatic and heteroaromatic amines to give aryl- and hetarylamidines [2]. The reaction of amide acetals with primary amides and thioamides has also been described — acyl(thioacyl)amidines were isolated in these cases [3]. The presence in a single molecule of amino and amido groupings was a prerequisite for the synthesis of pyrimidine derivatives on the basis of such o-amino amides [3, 4]. Instances in which the condensation of acetals proceeded at both groups to give bisamidines are also known [4].

We have previously shown that the Thorpe—Ziegler reaction is a convenient method for the synthesis of 2 disubstituted 5-cyano-6-aminopyrrolizines from 1-cyanomethylmethylenepyrrolidines; the substituted pyrrolizines synthesized in this way can be easily converted to derivatives of new heterocyclic systems — pyrimido[5,4-e]- and -[4,5-f]pyrrolizine [4, 5].

Considering that it is extremely convenient to use DMF diethylacetal (I) and pyrrolizines that have amino and carbamoyl groupings in adjacent positions as reagents for the formation of a pyrimidine ring, it seemed of interest to attempt to establish through which intermediates — N-arylamidines or N-acylamidines — the pyrimidine cyclization takes place. 5-Carbamoyl(thiocarbamoyl)-6-amino-7-R-pyrrolizines IIa-c and acetal I were selected as the starting compounds. Monodimethylaminomethylene derivatives, which could have N-pyrrolylamidine structure IIIa-c or acyl(thioacyl)amidine structure IVa-c, can be isolated in their condensation under mild conditions (20-40°C, 1 h).



II—V a R=CN, b R=COOEt; a,b X=S; II—IV c R=COOEt, X=O

*See [1] for Communication 64.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021.

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