Synthesis of 1-Acyl-5-pyrazolones and Pyrrolidino[2,3-*c*]pyrazol-3-ones

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The reactivity of acetamidrazones **I** in strong basicity conditions was examined. When compounds **I** are reacted with equivalent quantities of α-haloketones in sodium alcoholate, the pyrrolidino[2,3-*c*]pyrazol-3-ones **IV** were obtained by intermediate formation of 1-acyl-3-amino-5-pyrazolones **III**.

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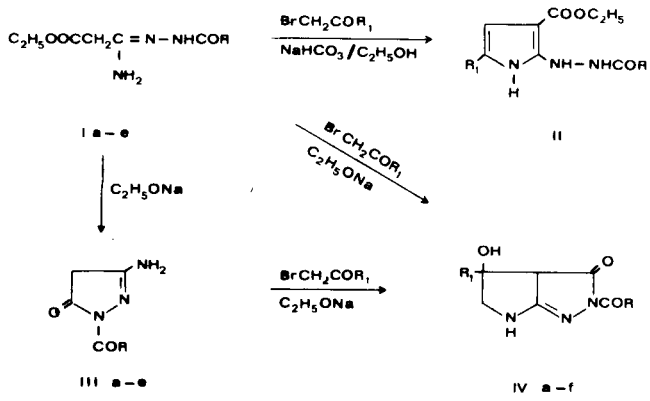
A part of a study on new heterocyclic systems with antimicrobicial activity, we recently synthesized the 2-amino- and 2-(2-acylhydrazino)-3-ethoxycarbonylpyrrole derivatives [1]. Particularly the latter present a very good inhibitory activity against blastomyces and some gram-positive micro-organisms. The 2-(2-acylhydrazino)pyrroles **II** were obtained in satisfactory yields by reaction of N^1-acyl-2-ethoxycarbonylacetamidrazones **I** with α-bromoketones in excess of sodium hydrogencarbonate.

In the present paper we report the reaction of N^1-acyl-acetamidrazones **I** and α-bromo or α-chloroketones in the presence of a stronger base. In this way the pyrrolidino-[2,3-*c*]pyrazol-3-one **IV** is reached by intermediate formation of pyrazol-5-one derivatives **III** (Scheme 1).

Scheme 1



I-III: **a**, R = CH_3; **b**, R = OC_2H_5; **c**, R = C_6H_5; **d**, R $CH_2C_6H_5$; **e**, R = $CH_2C_6H_4Cl$-(p)

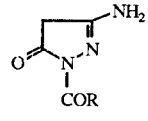
IV: **a**, R = R_1 = CH_3; **b**, R = CH_3, R_1 = C_6H_5; **c**, R = OC_2H_5, R_1 = CH_3; **d**, R = OC_2H_5, R_1 = C_6H_5 **e**, R = $CH_2C_6H_5$, R_1 = CH_3; **f**, R = $CH_2C_6H_4Cl$-(p); R_1 = CH_3

By treatment of an equivalent of sodium ethoxide in anhydrous ethanol, the amidrazones **I** cyclize to give 1-acyl-3-amino-5-pyrozolones **III** (Table 1).

The ^1H nmr spectra of compounds **III** (Table 2), carried out at room temperature in DMSO-d_6, show that they exist only in the enolic form by the presence of only one signal relating to H-5 and of two singlets relating to the OH and

Table I

Physical and Analytical Data of Compounds IIIa-e



Compound	R	Yield %	mp (°C)	Molecular Formula	Analysis Calcd./Found C	H	N
IIIa	CH_3	70	205 [a]	$C_5H_7N_3O_2$	42.56 42.47	5.00 5.03	29.78 29.72
IIIb	OC_2H_5	75	187 [b]	$C_6H_9N_3O_3$	42.10 42.15	5.30 5.27	24.55 24.48
IIIc	C_6H_5	60	164 [b]	$C_{10}H_9N_3O_2$	59.10 59.05	4.46 4.43	20.68 20.62
IIId	$C_6H_5CH_2$	70	168 [a]	$C_{11}H_{11}N_3O_2$	60.84 60.79	5.10 5.11	19.35 19.31
IIIe	4-$ClC_6H_4CH_2$	75	188 [c]	$C_{11}H_{10}ClN_3O_2$	52.49 52.36	4.00 4.03	16.69 16.62

[a] From acetonitrile. [b] From ethanol. [c] From 1-propanol.

Table 2
IR and ^{1}H NMR Spectral Data of Compounds **IIIa-e**

Compound	IR (cm^{-1})	^{1}H NMR [a] δ (ppm)
IIIa	3410, 3120, 1765, 1700, 1655	2.33 (s, 3H, CH_3), 4.17 (s, 1H, H-4), 6.50 (s, 2H, NH_2), 10.16 (s, 1H, OH)
IIIb	3385, 3190, 1775, 1765, 1650	1.15 (t, 3H, CH_3), 3.70 (s, 1H, H-4), 4.10 (q, 2H, CH_2), 5.60 (br s, 2H, NH_2), 8.65 (br s, 1H, OH)
IIIc	3385, 3225, 1670, 1640, 1620	2.94 (s, 1H, H-4), 3.75 (br s, 2H, NH_2), 6.10 (br s, 1H, OH), 7.28 (m, 3H arom), 7.83 (m 2H arom)
IIId	3350, 3280, 1705, 1620	3.55 (br s, 2H, NH_2), 4.24 (s, 2H, CH_2), 4.26 (s, 1H, H-4), 6.59 (s, 1H, OH), 7.23 (s, 5H arom)
IIIe	3560, 3420, 3320, 1730, 1670, 1655	3.34 (br s, 2H, NH_2), 4.21 (s, 3H, CH_2 and H-4), 6.59 (s, 1H, OH), 7.28 (s, 4H arom)

[a] In Hexadeuteriodimethyl sulfoxide.

NH_2 groups, which disappears by deuteration. Moreover the low field position of the OH signal in compounds **IIIa** and **IIIb** respectively at 10.16 and 8.65 ppm, may be considered due to the paramagnetic effect produced by the intramolecular hydrogen bond between the hydroxyl group at position 5 and the COR group on the N-1 position. In compounds **IIIc-e**, where the radical of the acyl group is more bulky, the signal of the OH group is shifted at higher fields (6.59-6.10 ppm). The methyne signals of **IIIa** and **IIIb** at 4.17 and 3.70 ppm respectively disappear after deuteration.

A further confirmation of the structure of these compounds is given by the ^{13}C nmr spectra data (Table 3). On the basis of the characteristic chemical shifts and of the multiplicities, it is possible to assign the resonances due to the ring carbons. The methyne carbon atom appears as a doublet and was shifted very far upfield at 70.53, 71.26 and 72.40 ppm for compounds **IIIa** and **IIIb** and **IIId-e** respectively. This strong shielding of C-4 is due to the (+M)-electron release both by OH in C-5 and by NH_2 in C-3 [2]. In compound **IIIc** the C-4 resonance was observed at lower fields by the deshielding effect of the benzene ring. The shift of C-3 falls in fields between 151.08 and 161.80 ppm, which is typical of the -N=C-N [3] group.

By treatment in sodium ethoxide the α-halogenoketones, compounds **IIIa-b** and **IIId-e** lead to the pyrrolidino[2,3-*c*]pyrazol-3-ones **IV** (Table 4).

The same compounds were obtained when equimolecular amounts of the appropriate N^1-acyl-2-ethoxycarbonylacetamidrazone **I** and α-haloketone in sodium ethoxide solution were allowed to react at room temperature for 12 hours. The reaction mechanism therefore first implies intramolecular cyclization of amidrazone **I** to derivative **III**, which undergoes alkylation of the amino group in C-3 and contemporaneous attack on C-4 of the pyrazolone with formation of the bicondensed system **IV**. On the contrary, at the same conditions compound **IIIc** does not react.

The structure of compounds **IV** is based on the analysis of the nmr spectral data (Table 5 and 6). In compounds **IVa-f** the H-5 protons appear between 3.07 and 3.74 ppm, the OH proton in 4 at 9.91-10.00 ppm, and the NH at 6.12-6.42 ppm. In compounds **IVa-b** the H-8 proton presents the same chemical shift as the H-5 proton.

In the ^{13}C nmr spectra of compound **IVa-b**, four quaternary carbon atoms are present: for compound **IVa**, for example, the more downfield peak (203.91 ppm) is due to

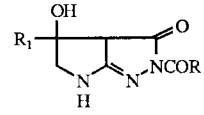
Table 3
^{13}C NMR Spectral data of Compounds IIIa-e [a]

Compound	C-3	C-4	C-5 and NCO	R
IIIa	158.15	70.53	161.18, 161.77	20.21
IIIb	151.08	71.26	159.62, 166.75	14.52, 60.36
IIIc	161.80	94.85	164.03, 170.18	128.20, 127.48, 127.32, 126.78
IIId	160.12	72.40	163.03, 163.52	39.51, 135.00, 129.21, 127.94, 126.29
IIIe	160.32	72.43	163.59, 163.72	39.50, 134.06, 131.18, 127.97

[a] In Hexadeuteriodimethyl sulfoxide

Table 4

Physical and Analytical Data of Compound **IVa-f**



Compound	R	R_1	Yield	mp (C°)	Molecular Formula	Analysis % Calcd./Found C	H	N
IVa	CH_3	CH_3	75	210 [a]	$C_8H_{11}N_3O_3$	48.78 48.71	5.62 5.60	21.31 21.27
IVb	CH_3	C_6H_5	80	215 [b]	$C_{13}H_{13}N_3O_3$	60.22 60.26	5.05 5.07	16.21 16.18
IVc	OC_2H_5	CH_3	70	186 [c]	$C_9H_{13}N_3O_4$	47.57 47.60	5.77 5.75	18.49 18.46
IVd	OC_2H_5	C_6H_5	80	205 [c]	$C_{14}H_{15}N_3O_4$	58.12 58.18	5.23 5.20	14.53 14.55
IVe	$C_6H_5CH_2$	CH_3	80	193 [d]	$C_{14}H_{15}N_3O_3$	61.53 61.49	5.33 5.30	15.38 15.34
IVf	$4\text{-}ClC_6H_4CH_2$	CH_3	85	218 [b]	$C_{14}H_{14}ClN_3O_3$	54.63 54.58	4.58 4.55	13.65 13.61

[a] From dioxane. [b] From 2-ethoxyethanol. [c] From 1-propanol [d] From ethanol.

Table 5

IR and ^1H NMR Spectral Data of Compounds **IVa-f**

Compound	IR (cm^{-1})	^1H NMR [a] δ (ppm)
IVa	3420, 3330, 1705, 1680, 1630	2.00 (s, 3H, CH_3), 2.31 (s, 3H, CH_3CO), 3.07 (s, 3H, NCH_2 and H-8), 6.12 (s, 1H, NH), 9.91 (s, 1H, OH)
IVb	3320, 3120, 1675, 1660, 1630	2.35 (s, 3H, CH_3), 3.74 (s, 3H, NCH_2 and H-8), 6.42 (s, 1H, NH), 7.51 (m, 3H arom), 7.98 (m, 2H arom), 10.00 (s, 1H, OH)
IVc	3395, 3240, 3180, 1730, 1705, 1650	1.20 (t, 3H, CH_3), 1.98 (s, 3H, CH_3), 3.05 (s, 2H, NCH_2), 4.20 (q, 2H, CH_2), 7.00 (br s, 2H, NH and OH), 10.00 (s, 1H, OH)
IVd	3410, 3330, 3200, 1725, 1675, 1645	1.21 (t, 3H, CH_3), 3.72 (s, 2H, NCH_2), 4.20 (q, 2H, CH_2), 6.50 (s, 2H, NH and OH), 7.49 (m, 3H arom), 8.03 (m, 2H arom), 9.60 (s, 1H, OH)
IVe	3410, 3300, 3160, 1690, 1650	2.02 (s, 3H, CH_3), 3.12 (s, 2H, NCH_2), 4.23 (s, 2H, $COCH_2$), 6.52 (s, 2H, NH and OH), 7.22 (s, 5H arom), 10.02 (s, 1H, OH)
IVf	3390, 3280, 3150, 1680, 1650	2.02 (s, 3H, CH_3), 3.12 (s, 2H, NCH_2), 4.22 (s, 2H, $COCH_2$), 6.54 (s, 2H, NH and OH), 7.28 (s, 5H arom), 10.00 (s, 1H, OH)

[a] In Hexadeuteriodimethyl sulfoxide.

C-3, the signals at 161.23 and 156.39 are assigned respectively to amidic carbon and to C-7, and the more upfield shift (76.60 ppm) is attributed to C-4.

Compounds **IVa-b** are present in solution in the ketonic form; while compounds **IVc-f** exist only in the enolic form.

In fact the spectra at ^{13}C nmr are characterized by the presence of a further quaternary carbon at between 148.65-159.00 ppm as a result of the change of C-8 from the sp^3 to sp^2 character.

Table 6
^{13}C NMR Spectral Data of Compounds **IVa-f** [a]

Compound	C-3	C-4	C-5	C-7	C-8	NCO	R	R_1
IVa	203.91	76.60	33.52	159.39	33.52	161.23	20.23	26.69
IVb	195.57	76.56	30.15	157.06	30.15	161.80	20.50	134.96, 131.10, 127.20, 126.04
IVc	205.97	78.87	35.66	159.16	148.84	163.48	14.36, 61.77	28.81
IVd	196.67	78.51	31.41	159.44	148.65	163.48	14.38, 61.78	136.46, 128.5, 128.26, 127.94
IVe	205.98	78.76	35.66	163.39	158.81	164.40	39.98, 135.26, 129.63, 128.35, 126.70	28.85
IVf	206.18	78.82	35.78	163.51	159.00	164.21	39.60, 134.33, 131.66 128.42	28.98

[a] In Hexadeuteriodimethyl sulfoxide.

EXPERIMENTAL

The melting points were determined on Köfler hot stage and are uncorrected. The ir spectra were obtained in nujol with a Perkin-Elmer 325 spectrophotometer. The ^1H nmr spectra were recorded with a Varian FT 80 spectrometer; chemical shifts are reported in ppm from HMS as an internal standard and are given in δ units. The elemental analyses (C,H,N) were carried out with a Carlo Erba model 1106 Elemental Analyzer. The N^1-acyl-2-ethoxycarbonylacetamidrazones **Ia-c** were made by a previously described procedure [1].

N^1-(Phenylacetyl)-2-ethoxycarbonylacetamidrazone (**Id**).

A mixture of ethyl 3-ethoxy-3-iminopropionate (10 mmoles) and 2-phenylacethydrazide (10 mmoles) in 70 ml of anhydrous ethanol was heated at 70-75° for 1-2 minutes and stirred at room temperature for 2 hours. The formed precipitate was collected by filtration and thoroughly washed with ethyl ether, mp 167° (from ethanol); yield 85%; ir (nujol): 3430, 3160, 1720, 1650 cm^{-1}; ^1H nmr (hexadeuteriodimethyl sulfoxide): δ 1.22 (t, 3H, CH_3), 3.07 (s, 2H, CH_2), 3.68 (s, 1H, =CH), 4.03 (q, 2H, CH_2), 6.18 (s, 2H, NH_2), 7.19 (m, 5H, arom), 9.46 (br, 2H, 2NH).

Anal. Calcd. for $C_{12}H_{17}O_3N_3$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.43; H, 6.85; N, 16.69.

N^1-(4-Chlorophenylacetyl)-2-ethoxycarbonylacetamidrazone (**Ie**).

This compound was obtained from ethyl 3-ethoxy-3-iminopropionate and 4-chlorophenylacethydrazide in the same way as for **Id**, mp 170° (from acetonitrile); yield 90%; ir (nujol): 3400, 3150, 1720, 1650 cm^{-1}; ^1H nmr (hexadeuteriodimethyl sulfoxide): δ 1.21 (t, 3H, CH_3), 3.07 (s, 2H, CH_2), 3.67 (s, 1H, =CH), 4.11 (q, 2H, CH_2), 6.17 (s, 2H, NH_2), 7.22-7.25 (m, 4H, arom), 9.49 (br s, 2H, 2NH).

Anal. Calcd. for $C_{13}H_{16}ClN_3O_3$: C, 52.50; H, 5.42; N, 14.13. Found: C, 52.39; H, 5.44; N, 14.10.

1-Acyl-3-amino-5-pyrazolones **III**.

General Method.

N^1-Acyl-2-ethoxycarbonylacetamidrazone **I** (10 mmoles) was added to a cold stirred solution of sodium (0.01 g atom) in absolute ethanol (40 ml). The mixture was stirred at room temperature for 12 hours, then diluted with water and rendered acidic by addition of acetic acid. The solid was filtered, washed with water and crystallized.

2-Acyl-4-hydroxypyrrolidino[2,3-*c*]pyrazol-3-ones **IVa-f**.

Method A.

The α-haloketone (10 mmoles) was added to a solution of 1-acyl-3-amino-5-pyrazolone **III** (10 mmoles) in the presence of sodium ethoxide (10 mmoles) in anhydrous ethanol (50 ml). After standing for 12 hours, the reaction mixture was diluted with water, neutralized with acetic acid, then the resulting solid was collected and crystallized.

Method B.

The N^1-acyl-2-ethoxycarbonylacetamidrazone **I** (10 mmoles) and α-haloketone (10 mmoles) were added to a cold solution of sodium (0.01 g atom) in absolute ethanol (50 ml). The reaction mixture was stirred at room temperature for 12 hours, then diluted with water and neutralized with acetic acid. The solid was collected and crystallized.

Acknowledgements.

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