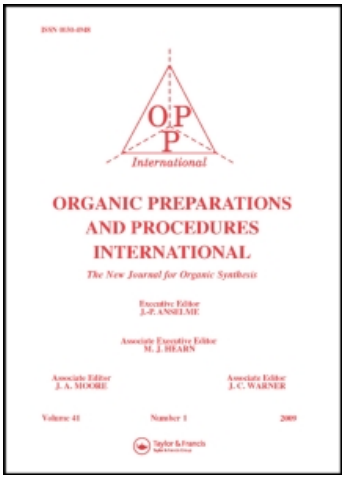

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PREPARATION OF 5-IMINO-2-PYRROLIDINONE DERIVATIVES AND THEIR 5-ALKYLIMINO ANALOGS†

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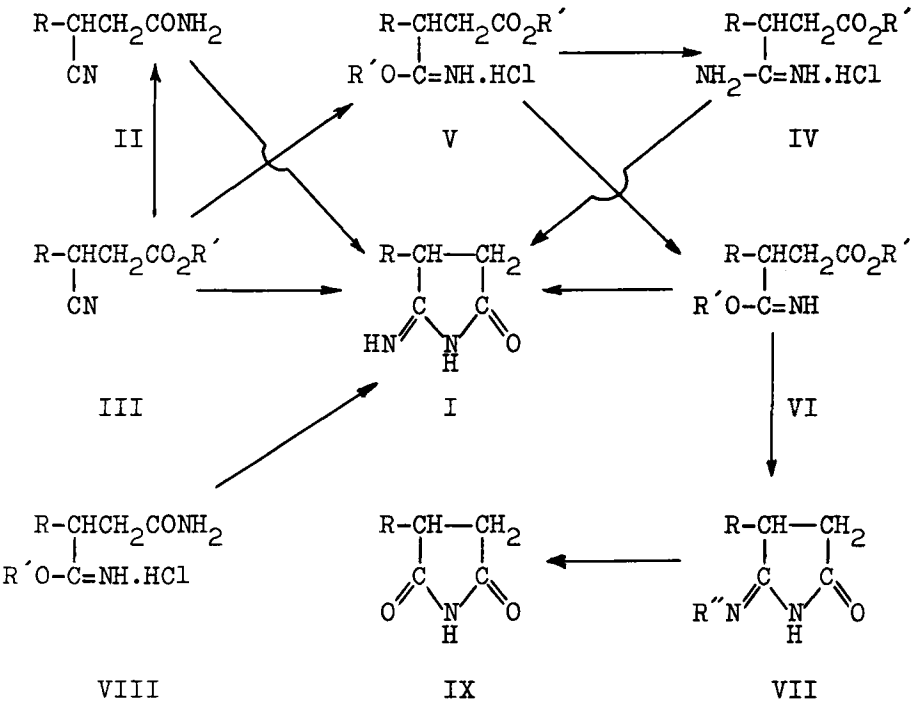
Monoimidic analogs (I) of succinimide have been prepared by alkaline cyclization of 3-cyanopropionamide derivatives[1] (II) and by controlled hydrolysis of the diimidic analog,



a) R = H; b) R = Ph; R´ = Me or Et; R˝, see Table.

succinimidine.[2] However, neither route makes the preparation of I facile and neither may serve for the direct preparation of the N-substituted derivatives (VII) of I.

By employing methyl 3-cyanopropionate (IIIa) and ethyl 3-phenyl-3-cyanopropionate (IIIb) as model compounds, we have observed the formation of both I and II. Since ammonolysis of the ester function is a rapid reaction, the highest yields of II were obtained in homogeneous solutions with ethanol as a solvent. The reaction was complete within a few hours and longer time favored the formation of I. In a heterogeneous system (ester-aqueous ammonia), the rate of the ammonolysis was comparable with that of the cyanoamide cyclization and the main product was I, which precipitated gradually as the ester phase disappeared.

Another possible approach to the synthesis of I is the cyclization of the corresponding 3-carbalkoxypropionamidines (IV) or 3-carbalkoxypropionimidates (V and VI), although two earlier reports[3,4] do not agree with one another in that respect. When Va was treated with an equimolar amount of alcoholic ammonia, ammonium chloride immediately precipitated then gradually dissolved; the product isolated was mostly IVa.[4] Its formation presumably resulted from the interaction of VIa and ammonium chloride. Inferior results were obtained with Vb, from which almost inseparable mixtures of IVb and ammonium chloride were formed.

With an excess of alcoholic ammonia, both Va and Vb gave the cyclic compounds, Ia and Ib, respectively; in the case of Va, some IVa was isolated as a by-product. However, pure Ia

and Ib were prepared when the imidates (VI) were used instead of their hydrochlorides.

The formation of 5-imino-2-pyrrolidinone (I) from V may be interpreted as a 3-step process. In the first step, 3-carbalkoxypropionimidate hydrochloride (V) reacted with ammonia to liberate the imidate (VI); as an ionic reaction, it was completed almost instantly. In the second step, VI reacted with

Table

VII	R″	mp. (°C)	Yield[c], %	Analysis		NMR R″ protons
				Calcd.	Found	
a	Me	105-108	34	C, 53.56 H, 7.19 N, 24.98	53.38 7.28 24.65	3.23 (s)
b	Me	144-147	51	C, 70.19 H, 6.43 N, 14.88	69.97 6.52 14.80	3.25 (s)
a	Me_3C	260[d]	43	C, 62.31 H, 9.15 N, 18.17	62.53 9.22 18.37	1.70 (s)
b	Me_3C	200[d]	25	C, 73.01 H, 7.88 N, 12.16	72.85 7.66 12.21	1.70 (s)
a	Me_2N	135-137	21	C, 51.05 H, 7.85 N, 29.76	50.87 7.94 29.63	2.86 (s) 3.20 (s)
b	CH_2=$CHCH_2$	134-137	39	C, 72.87 H, 6.59 N, 13.07	72.79 6.57 12.98	4.23 (m) 5.40 (m) 5.78 (m)
b	$NH_2(CH_2)_2$	174-177	78	C, 66.34 H, 6.96 N, 19.34	66.18 7.05 19.08	3.75 (s)

Notes: c) Yields refer to products recrystallized from ethanol; d) approximate mp. as charring of the sample occurred well below this temperature; for a and b in the first column, see reaction scheme.

the excess of ammonia to yield 3-carbalkoxypropionamidine (or 3-carbamoylpropionamidine if ammonolysis of the ester function was simultaneous with amidine formation). This step was considered also to be a rather fast one. In the third step, the amidine (or its amide derivative) underwent cyclization to I, the rate of this reaction determining the overall rate of the entire reaction. The reaction of IV with the ammonium chloride formed in the first step and still present in the mixture, gave rise to the formation of IV as the by-product. High basicity of free IV (actually higher than that of ammonia) was regarded as the driving force of this essentially ionic reaction, the rate of which was, however, slow enough because of the heterogeneity of the system.

Under similar conditions, the imidates (VI) and primary aliphatic amines gave cyclic compounds containing one alkyl group derived from the amine. In order to determine the position of that alkyl group (at the exocyclic or endocyclic nitrogen atom), the products were hydrolyzed with dilute sulfuric acid;[5] succinimide (IXa) and 3-phenylsuccinimide (IXb) were isolated from the products obtained from VIa and VIb, respectively, and the appropriate amine was formed in either case. Only the 5-alkylimino-2-pyrrolidinone structure (VII) is in agreement with such results of the hydrolysis experiments.

The results discussed above made it possible to suggest the unstable 3-carbalkoxypropionamidine as the reaction intermediate. Its cyclization in an alkaline medium is spontaneous and involves elimination of a molecule of alcohol.

A similar cyclization leading to Ib was observed upon neutralization of ethyl 2-phenyl-3-carbamoylpropionimidate hydrochloride (VIII). Therefore, both 3-carbalkoxypropionamidines and 3-carbamoylpropionimidates are particularly prone to cyclization and presumably can exist only as salts. For reference purposes, 3-phenyl-5-imino-2-pyrrolidinone was prepared by a similar cyclization of ethyl 3-carbethoxy-3-phenylpropionimidate.

All imidic esters used here were prepared from cyanoesters by the general procedure of Pinner.[6] The free imidates (VI) were remarkably stable and could be purified by vacuum distillation with no sign of decomposition.

EXPERIMENTAL

All mp. values are uncorrected. The NMR spectra were recorded on a JEOL 60 MHz instrument with tetramethylsilane as an internal standard. All chemical shifts are given in the δ scale. The IR spectra were recorded as KBr pellets on a Perkin-Elmer Model 237 spectrophotometer; the IR bands are given in cm^{-1}. Elemental analyses were performed on a Perkin-Elmer C-H-N analyzer.

Preparation of 5-Imino-2-pyrrolidinones.

a) From Imidates. - Ethyl 2-phenyl-3-carbethoxypropionimidate (VIb) (3.5 g, 0.014 mole) was dissolved in 20 ml of anhydrous ethanol and the solution treated with 0.037 g (0.019 mole) of NH_3 in ethanol. After 48 hr, the crystalline product was filtered and washed with ethanol to yield 1.8 g (75 %) of 4-phenyl-5-imino-2-pyrrolidinone (Ib), mp. around 230° with gradual decomposition and marked darkening above 200°.

IR: 3235 (NH); 1705, 1745 (C=O). NMR (CF_3CO_2H): 3.09 (m, CH_AH_B); 3.60 (m, CH_BH_A); 4.80 (m, CH); 7.4 (m, C_6H_5); 9.07 (s, NH=); 9.85 (s, -NH-); $J_{AB} = 19.8$; $J_{AX} = 4.6$; $J_{BX} = 9.3$.

Molecular ion m/e value: 174.

Anal.: Calcd. for $C_{10}H_{10}N_2O$: C, 68.96; H, 5.75; N, 16.09.
Found: C, 69.07; H, 5.88; N, 16.13.

Similarly, methyl 3-carbomethoxypropionimidate (VIa) gave 58 % of 5-imino-2-pyrrolidinone[3] (Ia).

IR: 3325 (NH, broad); 1712, 1755 (C=O). NMR (CF_3CO_2H): 3.28 (m, CH_2CH_2); 9.50 (broad s, both NH). Molecular ion m/e value: 98.

3-Phenyl-5-imino-2-pyrrolidinone, mp. ~230°, was prepared similarly from ethyl 3-carbethoxy-3-phenylpropionimidate in 65 % yield.

IR: 3270 (NH, broad); 1705 (C=O). NMR (CF_3CO_2H): 3.47 (m, CH_AH_B); 3.92 (m, CH_BH_A); 4.36 (m, CH); 7.5 (m, C_6H_5); 9.56 (s, NH=); 9.75 (s, -NH-); J_{AB} = 19.5; J_{AX} = 4.8; J_{BX} = 8.9. Molecular ion m/e value: 174.

Anal.: Calcd. for $C_{10}H_{10}N_2O$: C, 68.96; H, 5.75; N, 16.09.
Found: C, 69.15; H, 5.71; N, 15.97.

b) From Imidate Hydrochlorides. - Methyl 3-carbomethoxypropionimidate hydrochloride (Va) treated with 4 equivalents of NH_3 in anhydrous ethanol and the mixture left standing 3 days at room temp. gave, after removal of NH_4Cl and concentration of the filtrate to approximately one-third of its initial volume, 49 % of Ia. Further concentration of the mother liquors yielded 12 % of 3-carbomethoxypropionamidine hydrochloride[4] (IVa).

An analogous reaction using Vb gave upon evaporation of the solvent a semi-solid mass which was washed with ether. The residue upon trituration with anhydrous ethanol, gave 17% of Ib, purified by repeated recrystallization from ethanol. Attempts to isolate IVb from the mother liquors were unsuccessful.

c) From 3-Cyanopropionates. - A mixture of 5 g (0.025 mole) of ethyl 3-phenyl-3-cyanopropionate[7] (IIIb) and 15 ml of conc. aqueous ammonia was left standing at room temp. until homogeneous (approximately 3 weeks). Filtration yielded 2.6 g (60 %) of Ib. Concentration of the filtrate gave 0.9 g (20 %) of 3-phenyl-3-cyanopropionamide[2] (IIb), mp. 106-108° (MeOH).

IR: 2240 (C≡N). NMR (CF_3CO_2H): 3.28 (m, CH_2); 4.25 (m, CH).

IIb treated with conc. aqueous ammonia and the mixture left standing for a few days yielded quantitatively Ib.

Ia was prepared analogously from ethyl 3-cyanopropionate[4] (IIIa) in the yield of 54 %. No IIa could be isolated from the mother liquors.

When IIIb and aqueous NH_3 were homogeneous by addition of ethanol and the mixture was left standing no more than 3 days, the yield of Ib dropped to 23% and that of IIb rose to 62%.

Preparation of 3-Carbalkoxypropionimidates (VI). - In general, the procedure described for ethyl 3-carbethoxypropionimidate was followed.[4] The conversion of the hydrochlorides (V) into VI was accomplished by rapid shaking with saturated aqueous $NaHCO_3$ and immediate extraction with ether. The imidates were purified by distillation in vacuo. The following new imidates were prepared in this way.

Ethyl 3-carbethoxy-2-phenylpropionimidate (VIb), bp. 110-112° (0.2 mm).

IR: 3330 (NH); 1735 (C=O); 1650 (C=N). NMR (CD_3COCD_3): 1.12 and 1.28 (both t, $CH_2\underline{CH_3}$); 4.02 (q, both $\underline{CH_2}CH_3$); 2.74 (m, $CHC\underline{H_2}$); 6.92 (s, NH); 7.24 (s, C_6H_5); CH of the $CHCH_2$ ABX system was overlapped by the $\underline{CH_2}CH_3$ quartet.

Anal.: Calcd. for $C_{14}H_{19}NO_3$: N, 5.62. Found: N, 5.55.

Ethyl 3-carbethoxy-3-phenylpropionimidate, bp. 120-123° (0.4 mm).

IR: 3325 (NH); 1740 (C=O); 1660 (C=N). NMR (CD_3COCD_3): 1.22

and 1.32 (both t, $CH_2\underline{CH_3}$); 4.20 (q, both $\underline{CH_2}CH_3$); 2.92 (m, $CHC\underline{H_2}$); 6.80 (broad s, NH); 7.32 (s, C_6H_5); CH of the $CHCH_2$ ABX system was overlapped by the $\underline{CH_2}CH_3$ quartet.

Anal.: Calcd. for $C_{14}H_{19}NO_3$: N, 5.62. Found: N, 5.69.

Methyl 3-carbomethoxypropionimidate (VIa), bp. 85-90° (15 mm).

IR: 3325 (NH); 1740 (C=O); 1655 (C=N). NMR (CD_3COCD_3): 2.48 (s, CH_2CH_2); 3.58 (s, OCH_3); 7.00 (broad s, NH).

Anal.: Calcd. for $C_6H_{11}NO_3$: N, 9.65. Found: N, 9.82.

Preparation of 5-Alkylimino-2-pyrrolidinones (VII). - The imidate (VI) and a 10 % excess of a primary amine (or a solution in anhydrous ethanol) were mixed and left standing for 2 days at 0°. Evaporation of the solvent and trituration of the residue with dry ether gave VII.

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