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ON PYRROLE OXIDATION WITH HYDROGEN PEROXIDE

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Abstract—A qualitative study of the influence of the reaction medium on pyrrole oxidation with hydrogen peroxide is reported. In neutral aqueous solution a good yield of a simple oxidation product was obtained of which the isolation, structure, and some aspects of the chemical reactivity are reported. This compound can undergo an acid catalyzed reaction with pyrrole and alkylpyrroles having free α-positions forming derivatives of 5-(2-pyrrolyl)-2-pyrrolidinone.

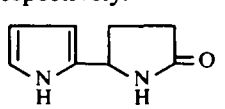
THE OXIDATIVE processes of pyrrole have received little attention, although the autoxidation behaviour of pyrrole and some alkyl- and aryl-pyrroles has been studied.[1] For that concerned with the effect of oxidants on pyrrole itself, only the early work of Angeli and Pieroni has been reported.[2]

In the previous notes[3–6] we studied the behaviour of pyrrole with oxidants, using the same conditions in which pyrrole blacks are formed. The effect of reaction time using a weight ratio of pyrrole:acetic acid:36% hydrogen peroxide of 1:13:2, has already been noted.[4]

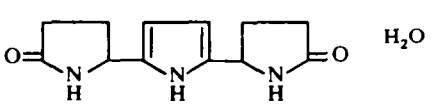
We have studied here the effect of the acidity of the medium when the respective concentrations of pyrrole and hydrogen peroxide are kept constant; we observed several similar oxidation reactions, in formic acid, acetic acid, water and in different buffers having pH values ranging from 1·1 and 11, and followed the reactions proceeding by paper chromatography.

After developing the chromatogram with diazosulphanilic acid, the presence of at most four spots was observed, differing in intensity and colour, according to the reaction conditions. Moreover the quantities of pyrrole blacks precipitated were inversely proportional to the pH of the medium (Table 1).

Products corresponding to the spots with R_f 0·86 and 0·74 were readily isolated from reactions carried out in acidic medium: these have already been identified as I and II respectively.[3, 4]



I



II

On the contrary it was found more difficult to isolate product III, corresponding to the spot with R_f 0·54, because of the small quantity present; the spot, in fact, appeared towards the end of the reaction and was more distinct after I and II had

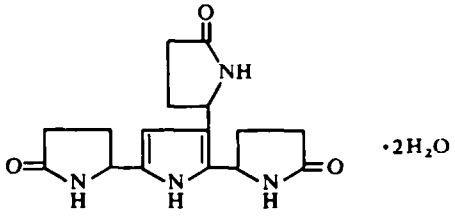
* It is regretted to report that our co-author died on March 3rd 1967.

Table 1. Oxidation of pyrrole with hydrogen peroxide at 20° for 7 days

Medium	pH	Products* I	II	III	IV	Pyrrole blacks
Formic acid		++	++	+	+	+++++
Acetic acid		++++	+++	+	+++	++++
Water		+			+++++	
Sodium citrate/HCl	1·1	++	+		+	+++++
Sodium citrate/HCl	2·0	+++	+		++	++++
Sodium citrate/HCl	3·0	++++	++		+++	+++
Sodium citrate/HCl	4·0	+++	+		+++	++
Sodium citrate/NaOH	5·0	+++	+		++++	+
Sodium citrate/NaOH	6·0	+++			+++++	
Sodium tetraborate/HCl	8·0	+			++++	
Sodium tetraborate/HCl	9·0				+++	

* Spots on Whatman No. 1 filter paper; eluent: n-BuOH:AcOH:H_2O 12:3:5; R_f and colour after developing with diazosulphanilic acid followed by 2N NaOH: I 0·86, red-violet; II 0·74, red-violet; III 0·54, red-violet; IV 0·76, green-yellow.

been isolated. Analysis of III gave the composition: $C_{16}H_{24}N_4O_5$; the UV, IR and NMR investigation (Experimental) has caused us to determine the structure as 2,3,5-ter-(pyrrolidin-2-on-5-yl)-pyrrole with two moles of water of crystallization (III).



III

Compound III readily forms a monoiodo-derivative, in which iodine replaces the last pyrrolic hydrogen. As the chemical behaviour of III does not show anything of particular interest and, because of its similarity to I and II, it was not closely investigated. Furthermore we believe that product III is a mixture of diastereoisomers, as there are three asymmetric centres present, although it appears as one spot on paper and thin layer chromatography in different solvents.

At this point it was evident that the formation of the compounds I, II and III could be attributed to the presence of a simple oxidation product that attacks the free positions of pyrrole, first in the more reactive α-positions.

The product IV, corresponding to the fourth spot with a R_f value of 0·76, could be this intermediate. The intensity of this spot varied according to the pH of the medium, being weak at a pH of 1–2 but very strong at pH 5–6, under which condition the formation of pyrrole blacks is inhibited (Table 1).

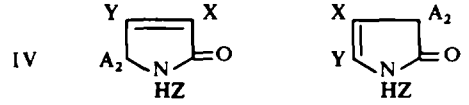
We were able to isolate sufficient IV by carrying out the oxidation of pyrrole in dilute aqueous solution, refluxing for 3–4 hours. It has been isolated as a light yellow,

hygroscopic oil, with a yield 25–30% of the pyrrole used (determining unreacted pyrrole by GLC, the yield on the converted pyrrole was 60–70%). The product was not perfectly pure and even after several subsequent distillations it continued to show the presence of two spots, having different intensities (TLC). Every attempt to separate them by chromatographic techniques has been unsuccessful.

As one of the two components of IV constituted by far the major part of the mixture, we studied the mixture itself: the analysis gives the formula C_4H_5NO and mass spectrum indicates molecular ion at m/e 83. IR spectrum shows very evident bands typical of NH and CO groups, strongly associated. The UV spectrum shows a shoulder at 224 mμ in 95° ethanol and a maximum at 228 mμ in n-hexane, with a very low value of ε in both solvents.

Hydrogenation in the presence of platinum black gave quantitatively 2-pyrrolidinone, identical with an authentic sample (IR and mixed melting point).

Data here reported suggest for IV the structures IVa or IVb



a b

The NMR spectrum (100 MHz, acetone-d6)* of IV shows the product to be a mixture of Δ^3-(IVa) and Δ^4-(IVb) isomers in the ratio 9:1 respectively. The analysis of the patterns of the main component IVa, together with double resonance experiments, gave the following parameters:

Spectrum A_2XYZ

$\delta_A = 4{\cdot}05$	$J_{AX} = -1{\cdot}91$
$\delta_X = 6{\cdot}07$	$J_{AY} = +1{\cdot}72$
$\delta_Y = 7{\cdot}28$	$J_{XY} = +5{\cdot}74$
$\delta_Z = 8{\cdot}3$ (centre of a broad signal)	$J_{AZ} = +1{\cdot}14$
	$J_{XZ} = +1{\cdot}49$
	$J_{YZ} = +1{\cdot}49$

These values confirmed by those obtained from the computed spectrum, are in agreement with the Δ^3-structure IVa.

The ozonolysis of IV in methanol, followed by an oxidative hydrolysis of the ozonide and/or hydroperoxy-ethers, gave high yields of glycine and oxalic acid, again supporting the Δ^3-structure for the main product in the mixture.

Structure IVa had been assigned[7] to a monohydric compound (m.p. 84°), and more recently to a product having m.p. 165° for the anhydrous substance.[8†]

The physical characteristics of IV mainly agree with those of a compound prepared by Grob and Ankli[9] and indicated as IVb: it has been in fact described as a light yellow, viscous, hygroscopic liquid having a b.p. very similar to that found for IV.

We attempted to prepare 4-pyrrolin-2-one (IVb) according to Grob and Ankli,[9] by means of an alkaline hydrolysis of 4-carbetoxy-4-pyrrolin-2-one (VI) and thermal

* NMR spectra, together with discussion of the results will be published elsewhere.

† As our results for the main product present in IV support a Δ^3-structure, either the physical characteristics reported[8] are incorrect, or the small amounts of the isomer IVb prevent, in an unusual way, the solidification of 3-pyrrolin-2-one. Many attempts were made to prepare IVa according to the method described,[8] but were unsuccessful.

decarboxylation of the acid so obtained. The acid shows a remarkable stability and decomposes only at 170–180° (reported 100°) to give a liquid, the chemical composition of which is identical to that of IV, and which on chromatographic analysis shows the same two spots noticed with IV, with analogous intensity.

The NMR spectrum (100 MHz, acetone-d6) shows the product to be a mixture of 3-pyrrolin-2-one (IVa) and 4-pyrrolin-2-one (IVb) in the ratio 2:1.

From the analysis the following parameters were obtained:

3-pyrrolin-2-one (IVa), spectrum A_2XYZ

$\delta_A = 4{\cdot}07$	$J_{AX} = -1{\cdot}95$
$\delta_X = 6{\cdot}10$	$J_{AY} = +1{\cdot}75$
$\delta_Y = 7{\cdot}30$	$J_{XY} = +5{\cdot}75$
$\delta_Z = 8{\cdot}0$ (centre of a broad signal)	$J_{AZ} = +1{\cdot}00$
	$J_{XZ} = +1{\cdot}50$
	$J_{YZ} = +1{\cdot}50$

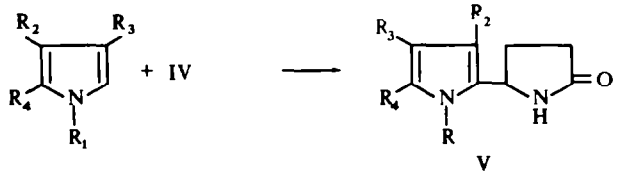
4-pyrrolin-2-one, spectrum A_2XYZ

$\delta_A = 2{\cdot}91$	$J_{AX} = +2{\cdot}44$
$\delta_X = 5{\cdot}19$	$J_{AY} = -2{\cdot}23$
$\delta_Y = 6{\cdot}59$	$J_{XY} = +4{\cdot}93$
$\delta_Z = 8{\cdot}0$ (centre of a broad signal)	$J_{AZ} = 0{\cdot}00$
	$J_{XZ} = +1{\cdot}58$
	$J_{YZ} = +1{\cdot}98$

After the investigation of the nature of this simple oxidation product of pyrrole, we attempted to confirm the hypothesis that IV could be the intermediate reacting with pyrrole in acidic media to give products I–III. The hypothesis was found to be correct: we readily obtained compounds I, II and III from the reaction of pyrrole with IV (mixture 9:1) in acetic acid (yield >60%).

To prove the general character of the reaction, IV was also made to react with several methyl-substituted pyrroles (N-methyl-, 2-methyl-, 2,3-dimethyl-, 2,4-dimethyl-pyrrole) to give compounds of general formula V (Scheme 1).

SCHEME 1

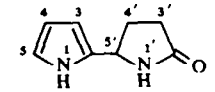
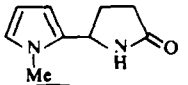
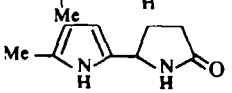
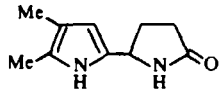
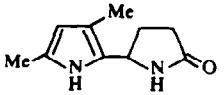
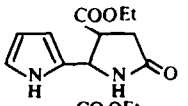
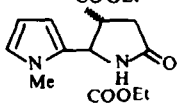
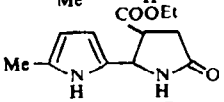
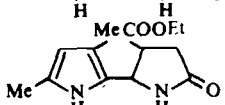


V

The reactions, faster with dimethyl-pyrroles, proceeds giving more than 60% of V. The analysis and spectroscopic data (UV, IR and NMR) confirm the structures assigned for the various compounds obtained (see Table 2). Such compounds may be reduced by LAH to the corresponding 2-(alkylpyrrol-2-yl)-pyrrolidines[10] which in turn can be dehydrogenated to bipyrroles, which are interesting because of their occurrence in Vitamin B_{12}, prodigiosins, corrins and corroles.

The reaction between the same pyrroles and 4-carbetoxy-4-pyrrolin-2-one (VI) under the same experimental conditions, proceeds at a slower rate than in previous

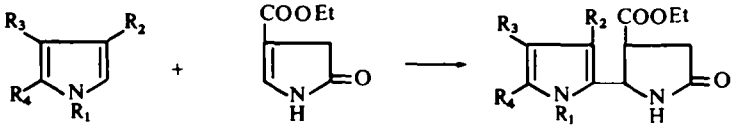
TABLE 2. NMR CHEMICAL SHIFTS AND COUPLING CONSTANTS ($CDCl_3$; 60 MHz)

		H-5	H-4	H-3	H-1	H-1′	H-5′	H-4′	H-3′	Me-1	Me-5	Me-4	Me-3	OEt	$J_{3,4}$	$J_{4,5}$	$J_{3,5}$	$J_{1,3\text{ or }4}$	$J_{4',5'}$	$J_{3',4'}$
		6·70	6·0	6·0	9·70	6·90	4·72	1·8–2·8							3·2[a]	2·5[a]	1·3[a]	2·2[a,a]		
		6·55	6·05	6·05		7·18	4·80	1·9–2·6	3·60							2·3[d]				
			5·77	5·93	9·1	6·55	4·75	1·9–2·6			2·23[b]				3·2			2·3 2·5		
				5·82	8·75	6·60	4·70	1·9–2·6			2·12	1·95						2·7		
			5·64		8·5	5·8	4·80	1·5–2·5			2·20[b]		2·00					2·3[c]		
	*cis*	6·66	6·05	6·05	9·20	6·6	5·10	3·55	2·92 2·42					3·83 1·00		2·2[d]		2·3[e]	8·6	9·5 7·5
	trans	6·70	6·07	6·07	9·5	6·9	4·96	3·20	2·64					4·16 1·23		2·2[d]		2·3[e]	6·5	8·7[f]
	*trans*	6·57	6·07	6·07		6·87	5·06	3·20	2·69 2·64	3·64				4·18 1·27		2·2[d]			5·0	9·0 7·0
	*cis*		5·75	5·92	8·75	6·45	5·05	3·54	2·92 2·44		2·20[b]			3·90 1·03	3·5			2·1 2·0	8·4	9·2 7·5
	*trans*		5·58		9·0	6·03	5·01	3·24	2·67		2·18[b]		2·00	4·18 1·27				2·0	6·5	9·0[f]

[a] coupling constant values are not taken in $CDCl_3$; [b] $J_{4,5Me}$ 0·8 Hz; [c] in DMSO-d_6 soln; [d] $\frac{1}{2} J_{4,5} + J_{3,5}$; [e] $\frac{1}{2} J_{1,3} + J_{1,4}$; [f] $\frac{1}{2} J_{3'a,4'} + J_{3'b,4'}$

experiments, giving another series of compounds of the general formula VII (Scheme 2 and Table 2).

SCHEME 2

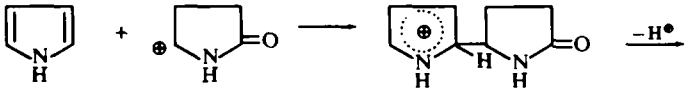


VI VII

Because of the presence in the compounds VII of two asymmetric centres (C-4′ and C-5′), the respective reactions give mixtures of two racemates. Only for VII ($R_1 = R_2 = R_3 = R_4 = H$) were the two racemates separated (column chromatography); in the other cases only the least soluble racemate was isolated by fractional crystallization, analyzed and identified. The total yields of the reactions of Scheme 2 were more than 50%.

The high yields obtained in the reactions illustrated in Scheme 1, and the similarity with the reactions of Scheme 2 suggest that the carbonium ion VIII may be the species attacking pyrrolic substrates according to the Scheme 3.

SCHEME 3



VIII

An hypothesis concerning the formation of VIII from IVa in acidic medium may be illustrated by the following Scheme 4.

Also the alternative pathway, involving a rearrangement due to an hydride shift from C-5 to C-4, has to be considered. Research is in progress to pick out the mechanism responsible for the formation of compounds V.

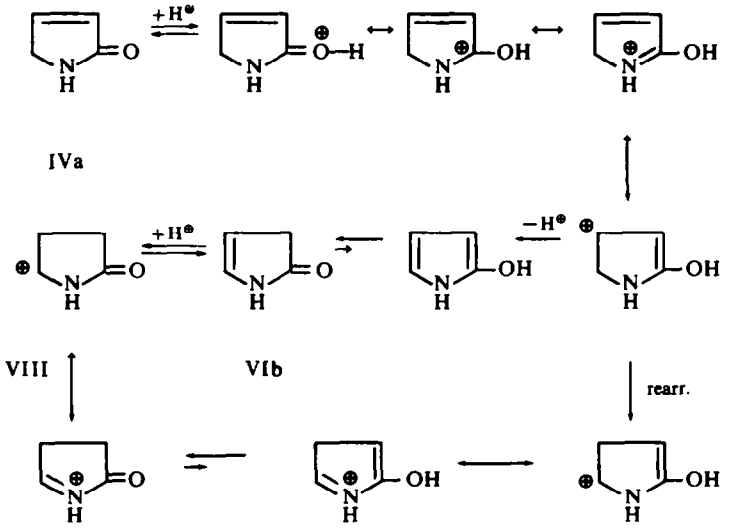
EXPERIMENTAL

M.ps are uncorrected. Unless otherwise stated UV spectra were determined with an Unicam SP 500 spectrophotometer, in EtOH, 95°. IR spectra were recorded on a Perkin–Elmer mod. 137 spectrophotometer. NMR spectra were recorded on a Varian A 60 and HA 100 spectrometers; chemical shifts are measured in ppm (δ) using TMS as an internal standard. The integrals were measured with a Hewlett–Packard 405 CR digital voltmeter.

Pyrrole oxidation with H_2O_2 *in* AcOH, HCOOH *and buffers having* pH *between* 1·1 *and* 11. The different reactions were carried out simultaneously at room temperature, maintaining the weight ratio of pyrrole: solvent: 36% H_2O_2 constant at 1:13:2. The reaction progress was followed by drawing off small samples. Excess oxidant was destroyed by the addition of a small amount of platinum black. After centrifuging, 1 µl of every sample was chromatographed. The chromatograms were developed with diazosulphanilic acid followed by 2N NaOH. Reactions were suspended after seven days, when no further H_2O_2 remained in the mixtures. Qualitative results are reported in Table 1.

Pyrrole oxidation with H_2O_2 *in* H_2O; *Isolation of* IV. Pyrrole (10 g, 0·15 mole) dissolved in H_2O (900 ml) was refluxed in a round-bottomed flask (capacity 1000 ml) with 36% H_2O_2 (14 g, 0·15 mole) for 4 hr in the presence of $BaCO_3$ (3 g). Afterwards the excess oxidant was eliminated by adding to the boiling soln small

SCHEME 4



amounts of finely ground PbO_2. The soln was then filtered and evaporated under vacuum, avoiding heating above 40–50°, until it reached a syrupy consistency. After treatment with dioxane and filtration, the filtrate was evaporated under reduced pressure and the residue, a red liquid, was distilled at 0·5 mm, heating in an air bath at 100–130°. With the best conditions the yield of distilled product reached 30% of the pyrrole weight used. Smaller yields were obtained if the reaction time was longer than 4 hr. After three subsequent distillations the product appeared as a white, viscous, hygroscopic liquid, that was kept in a refrigerator at −25°, at which temp it was solid.

Product IV is very soluble in H_2O, EtOH, Me_2CO, EtAc, dioxane, less soluble in $CHCl_3$, and insoluble in various less polar solvents. (Found: C, 57·51; H, 6·22; N, 16·52. C_4H_5NO requires: C, 57·82; H, 6·07; N, 16·86%). B.p. 90–92° (0·5 mm); d_4^{20} 1·191; n_D^{20} 1·5175. Paper chromatography showed one spot at R_f 0·76 (eluent: n-BuOH:AcOH:H_2O 12:3:5) and two spots at R_f 0·34 and 0·57 (eluent: CCl_4:EtOH 5:1) corresponding respectively to IVa and IVb. Besides diazosulphanilic acid, we obtained good results developing with sodium nitroprusside (1% soln) followed by 2N NaOH (red-brown spots) or with Rydon's reagent[11] (Cl_2 followed by KI in starch soln, violet spots).

λ_{max} 224 mμ (ε 2800) (sh) in 95° EtOH; 228 mμ (ε 1900) in n-hexane. ν_{max} 3250 (NH) and 1680 cm^{-1} (C=O), strongly associated; at a high dilution in $CHCl_3$ soln, the band of free NH lies at 3466 cm^{-1}.

NMR spectrum shows 3-pyrrolin-2-one (IVa) to make up of more than 90% of IV. This percentage was found to be fairly constant for different preparations.

Hydrogenation of IV. 0·124 g (1·5 mmole) of the previous product, freshly distilled, in H_2O (15 ml) and 0·1 g of 10% Pd/C were shaken in an H_2 atmosphere at 20° and at normal pressure for 30 min: one equivalent of H_2 was absorbed. After filtration and evaporation of the solvent, 0·126 g (100%) of the corresponding saturated compound were obtained, which was shown to be identical (IR and mixed m.p.) to an authentic sample of 2-pyrrolidinone.

Ozonolysis of IV. A slow stream of O_3 was bubbled through the soln of IV (0·83 g, 0·01 mole) in MeOH (30 ml) at 25°, until the absorption of O_3 ceased. The soln was then treated with 10N HCl (5 ml) and 10M H_2O_2 (5 ml) at 60° for 30 min, the excess H_2O_2 was eliminated by the addition of small amounts of Pd/C, the soln filtered, evaporated at reduced pres and the residue dissolved in 10 ml of H_2O and chromatographed on a column of ion exchange resin (Dowex 50), eluting with H_2O. The eluate was found to contain oxalic acid (0·68 g, 54%) determined as dimethyl ester by GLC; by washing the column with 2N HCl, and evaporating the eluate, 0·44 g (40%) of glycine hydrochloride were obtained, which was identified by comparison with an authentic sample.

4-Carbetoxy-4-pyrrolin-2-one; Hydrolysis and decarboxylation of the acid obtained. Compound VI was prepared according to Grob and Ankli.[9] Carefully eliminating every trace of moisture, oxygen and CO_2,

the yield obtained was over 50% of pure product (m.p. 143–144° from EtOH). NMR spectrum in $CDCl_3$ shows absorption at the values reported[8] for the same compound.

Alkaline hydrolysis of the ester takes place with 4N NaOH at 0° for 30 min, the pH of the mixture was then adjusted to 2 and the acid slowly precipitated; m.p. 210° (dec) (from H_2O). Every attempt to decarboxylate it under high vacuum at a temp below 160° was unsuccessful; between 170 and 210° slow decomposition takes place, giving a viscous, hygroscopic product that, on paper and thin layer chromatography, showed two spots, in the conditions previously described for IV.

NMR analysis of this mixture shows the presence of the isomers IVa and IVb in a ratio of about 2:1 respectively. The yield from the decarboxylation was about 20%.

2,3,5-*Ter-(pyrrolidin-2-on-5-yl)-pyrrole* (III). (a) *From pyrrole oxidation*: a soln of pyrrole (40 ml) in AcOH (520 ml) was cooled to 5° and 36% H_2O_2 (68 ml) added. Temp was slowly allowed to rise and the mixture was kept at room temp for 20 days. Then the AcOH was removed by warming on a water bath, H_2O added and the soln evaporated until all AcOH was eliminated. Treatment of the residue with boiling EtOH, followed by filtration and evaporation, gave a solid which was dissolved in hot H_2O. Most of II crystallized on standing; some II and III remained in the mother liquor and after evaporation of the solvent were separated by column chromatography (neutral Al_2O_3, eluent dioxane:H_2O 25:1); the fractions containing III were collected, the solvent evaporated and the residue crystallized from H_2O. Yield 0·6 g. III was readily soluble in AcOH and boiling H_2O and did not melt at a temp lower than 260°. (Found: C, 54·58; H, 6·82; N, 16·00. $C_{16}H_{24}N_4O_5$ requires: C, 54·53; H, 6·36; N, 15·87%).

λ_{max} 223 mμ (ε 14,200); ν_{max} 3350 (pyrrolic NH), 3170 (amidic NH) and 1670 cm^{-1} (C=O). NMR (DMSO-d6): doublet at 5·87 δ, which collapses to a singlet with D_2O (β-pyrrolic proton, $J_{H,NH}$ = 2·0 Hz), a large signal at 10·64 δ($w_{1/2}$ ≈ 6 Hz, pyrrolic NH), 3 singlets at 7·83, 7·65 and 7·55δ (3 amidic NH) and finally two complex absorptions at 4·4–4·9 δ (3 protons near amidic nitrogen, —CH—NH—CO), and in the high field region 1·7–2·4δ (12 protons in sequence like —CO—CH_2—CH_2—C—, see 2-pyrrolidinone spectrum).

Dissolved in a 10% soln of K_2CO_3, III reacts with I_2 giving a monoiododerivative, a microcrystalline powder, white after crystallization from H_2O, which does not melt below 260°. (Found: C, 40·32; H, 4·85; I, 26·53. $C_{16}H_{23}IN_4O_5$ requires: C, 40·18; H, 4·84: I, 26·53%)

(b) *from* II *and* IV—Equimolecular quantities of II and IV dissolved in three volumes of AcOH, after refluxing for 6 hr in a N_2 atmosphere, gave a crystalline product that precipitated from the reaction mixture, identical in all aspects with the compound III; yield 67%. The pure product was isolated by removing AcOH under vacuum and crystallizing from H_2O.

5-*(2-Pyrrolyl)-2-pyrrolidinone* (V, $R_1 = R_2 = R_3 = R_4 = H$). 10 mmole of IV and 50 mmole of pyrrole were refluxed in AcOH (5 ml) under N_2 for 1 hr. Then the AcOH and excess pyrrole were removed by evaporating under vacuum; the product was purified by sublimation at 130° (0·5 mm). Yield 80% of pure product, identical to compound I obtained from pyrrole oxidation.

5-*(1-Methylpyrrol-2-yl)-2-pyrrolidinone* (V, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$). 10 mmole of IV, 50 mmole of N-methylpyrrole and AcOH (5 ml) were refluxed for 5 min, yield 67%. It sublimated at 135° (0·5 mm) m.p. 135–136°. (Found: C, 65·79; H, 7·19; N, 16·79. $C_9H_{12}N_2O$ requires: C, 65·83; H, 7·37; N, 17·06%).

λ_{max} 221 mμ (ε 20,500); ν_{max} 3510 (amidic NH) and 1680 cm^{-1} (C=O). NMR ($CDCl_3$) 6·55 δ (t, H—5), 6·05 δ (d, H—3 + H—4): AA'X type, $\delta_A = \delta_3 = \delta_4$, $\frac{1}{2}(J_{3,5} + J_{4,5}) = 2·3$ Hz; 4·80 (centre of a multiplet, 1H, CH—NH—CO); 7·18 δ (broad, NHCO); 3·60 δ (s, 3H, N—Me); 1·9–2·6 δ (m, 4H, —CO—CH_2—CH_2—C—).

5-*(5-Methylpyrrol-2-yl)-2-pyrrolidinone* (V, $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$). 10 mmole of IV, 10 mmole of 2-methyl-pyrrole and AcOH (5 ml) were refluxed for 5 min (or in 5 ml of 20% EtOH for 6 hr). Crystallization from H_2O and subsequent sublimation at 140° (0·5 mm) gave a white product, m.p. 160°, yield 72%. (Found: C, 65·88; H, 7·16; N, 17·04. $C_9H_{12}N_2O$ requires: C, 65·83; H, 7·37; N, 17·06%).

λ_{max} 222 mμ (ε 10,000); ν_{max} 3330 (pyrrolic NH), 3220 (amidic NH) and 1680 cm^{-1} (C=O). NMR ($CDCl_3$) 5·93 δ (t, H—3, $J_{1,3} = 2·3$, $J_{3,4} = 3·2$ Hz); 5·77 δ (H—4, triplet of ca. 2·5 Hz with each line further split by $J \leqslant 1$ Hz with Me—5); 2·23 δ (s, 3H, $w_{1/2}$ = 1·5 Hz, 5—Me, $J_{4,5\text{-Me}} \leqslant 1$ Hz); 4·75 δ (m, centre, 1H, CH—NH—CO); 6·55 δ (broad, NHCO); 9·1 δ (broad, pyrrolic NH); 1·9–2·6 δ (m, 4H, —CO—CH_2 CH_2—C—).

5-*(4,5-Dimethylpyrrol-2-yl)-2-pyrrolidinone* (V, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$). 10 mmole of IV and

10 mmole of 2,3-dimethylpyrrole were warmed in AcOH (5 ml) at 60° for 5 min (or refluxed in 5 ml of 20% EtOH for 5 hr). M.p. 149–150° (sublimation at 160°, 0·5 mm), yield 62% (Found: C, 67·16; H, 7·94; N, 15·77. $C_{10}H_{14}N_2O$ requires: C, 67·39; H, 7·92; N, 15·72%).

λ_{max} 222 mμ (ε 7800) (sh); ν_{max} 3350 (pyrrolic NH), 3210 (amidic NH) and 1670 cm^{-1} (C=O). NMR ($CDCl_3$) 5·82 δ (d, $J_{1,3}$ = 2·7 Hz, H—3); 1·95 and 2·12 δ (2s, Me—4 and Me—5); 8·75 δ (broad, pyrrolic NH); 6·60 δ (broad, NH—CO); 4·70 δ (m, centre, 1H, CH—NH—CO); 1·9–2·6 δ (m, 4H, —CO—CH_2—CH_2—C—).

5-(3,5-*Dimethylpyrrol-2-yl*)-2-*pyrrolydinone* (V, $R_1 = R_3 = H$; $R_2 = R_4 = CH_3$). 10 mmole of IV and 10 mmole of 2,4-dimethylpyrrole were refluxed in 20% EtOH (5 ml) for 5 hr. The product crystallized on standing at the end of the reaction. Sublimation at 150° (0·5 mm) and subsequent crystallization from EtOH gave a substance with a m.p. 220° (dec). Yield 76%. (Found: C, 67·20; H, 7·77; N, 15·90. $C_{10}H_{14}N_2O$ requires: C, 67·39; H, 7·92; N, 15·72%).

λ_{max} 224 mμ (ε 9550); ν_{max} 3330 (pyrrolic NH), 3210 (amidic NH) and 1690 cm^{-1} (C=O). NMR (DMSO-d6) 5·45 δ (d, $J_{1,4} \sim 2·3$ Hz, H—4); 2·10 δ (s, $w_{1/2}$ = 1·8 Hz, $J_{4,5\text{-Me}} \leqslant 1$ Hz, Me—5); 1·92 δ (s, $w_{1/2}$ = 1 Hz, Me—3); 10·15 δ (pyrrolic NH); 7·67 δ (s, NHCO); 4·65 δ (m, centre, 1H, CH—NH—CO); 1·7–2·4 δ (m, 4H, —CO—CH_2—CH_2—C—).

4-*Carbetoxy*-5-(2-*pyrrolyl*)-2-*pyrrolidinone* (VII, $R_1 = R_2 = R_3 = R_4 = H$). 10 mmole of VI and 50 mmole of pyrrole were refluxed in AcOH (5 ml) for 1 hr. After evaporation of the solvent and excess pyrrole under vacuum, H_2O was added and the soln again evaporated until every trace of AcOH was removed. Crystallization of the residue (H_2O) gave white crystals, m.p. 97–105° (mixture of diastereoisomers). Two spots with R_f 0·55 and 0·76 respectively on TLC, eluting with iso-AmOH:CCl_4 1:2 and developing with 1% soln of Na nitroprusside followed by 2N NaOH. The isomers were separated on a SiO_2 column, eluting with iso-AmOH:CCl_4 1:2, and sublimating each isomer at 0·5 mm at a temp near to m.p.

First product eluted: m.p. 109–110°. (Found: C, 59·66; H, 6·37; N, 12·70. $C_{11}H_{14}N_2O_3$ requires: C, 59·45; H, 6·35; N, 12·61%).

ν_{max} 3350, 3230, 1750 and 1700 cm^{-1} (pyrrolic, amidic NH, ester and amidic C=O respectively). NMR ($CDCl_3$)* 6·70 δ (q, H—5), 6·07 δ (t, $H_3 + H_4$): AA'XY type, $\frac{1}{2}(J_{3,5} + J_{4,5}) = 2·2$, $\frac{1}{2}(J_{1,3} + J_{1,4}) = 2·3$ Hz; 9·5 δ (broad, pyrrolic NH); 6·9 δ (NHCO); 4·16 and 1·23 δ (q, resp. t, J = 7·0 Hz, OEt); 2·4–3·5, 4·96 δ (d): 4 protons of an ABCX spectrum, approx. AA'MX, δ_X = 4·96 (H—5'), δ_A = 2·64 (CH_2—3'), δ_M = 3·20 (H—4'), $\frac{1}{2}(J_{AM} + J_{A'M}) = 8·7$, J_{MX} = 6·5 Hz (H—5' and H—4' *trans*).

Second product eluted: m.p. 152–153°. (Found: C, 59·68; H, 6·43; N, 12·78. $C_{11}H_{14}N_2O_3$ requires: C, 59·45; H, 6·35; N, 12·61%).

ν_{max} 3350, 3230, 1750 and 1700 cm^{-1} (for assignment see above). NMR ($CDCl_3$) 6·66 δ (q, H—5, overlapped by NHCO); 6·05 δ (t, $H_3 + H_4$): AA'XY type $\delta_3 = \delta_4 = \delta_A$, $\frac{1}{2}(J_{3,5} + J_{4,5}) = 2·2$, $\frac{1}{2}(J_{1,3} + J_{1,4}) = 2·3$ Hz; 9·20 δ (broad, pyrrolic NH); 6·6 δ (NHCO); 3·83 and 1·00 δ (q, resp. t, J = 7·0 Hz, OEt); 2·1–3·8 δ (16 lines), 5·10 δ (d): 4 protons of an ABCX spectrum, approx. ABMX, δ_X = 5·10 (H—5'), δ_A = 2·42 δ_B = 2·92 (CH_2—3'), δ_M = 3·55 (H—4'), J_{AB} = 17·3, J_{AM} = 9·5, J_{BM} = 7·5, J_{MX} = 8·6 Hz (H—5' and H—4' *cis*).

4-*Carbetoxy*-5-(1-*methylpyrrol*-2-*yl*)-2-*pyrrolidinone* (VII, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$). 10 mmole of VI and 20 mmole of N-methylpyrrole were refluxed in AcOH (5 ml) for 30 min. Work up as in previous case, crystallization of the residue from 50% EtOH and sublimation at 140° (0·5 mm) gave a compound m.p. 150–151°. (Found: C, 61·28; H, 6·74; N, 11·96. $C_{12}H_{16}N_2O_3$ requires: C, 61·00; H, 6·83; N, 11·86%).

λ_{max} 222 mμ (ε 9900); ν_{max} 3210 (NH), 1720 and 1690 cm^{-1} (ester and amidic C=O respectively). NMR ($CDCl_3$) 6·57 δ (t, H—5), 6·07 δ (d, $H_3 + H_4$): AA'X type, $\delta_A = \delta_3 = \delta_4$, $\frac{1}{2}(J_{3,5} + J_{4,5}) = 2·2$ Hz; 3·64 δ (s, N—Me); 6·87 (broad, NHCO); 4·18 and 1·27 δ (q, resp. t, J = 7·0 Hz, OEt); 2·5–3·4 δ (15 lines), 5·06 δ (d): 4 protons of an ABCX spectrum, approx. ABMX, δ_X = 5·06 (H—5'), δ_A = 2·64, δ_B = 2·69 (CH_2—3'), δ_M = 3·20 (H—4'), J_{AM} = 9·0, J_{BM} = 7·0, J_{AB} = 16·4, J_{MX} = 5·0 (H—5' and H—4' *trans*).

4-*Carbetoxy*-5-(5-*methylpyrrol*-2-*yl*)-2-*pyrrolidinone* (VII, $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$). 10 mmole of VI and 10 mmole of 2-methylpyrrole were refluxed in AcOH (5 ml) for 40 min. Work up as in previous cases gave a residue, which by fractional crystallization from H_2O yielded a white product, m.p. 172–173°. (Found: C, 60·83; H, 6·84; N, 11·96. $C_{12}H_{16}N_2O_3$ requires: C, 61·00; H, 6·83; N, 11·86%).

* Data deduced from the spectrum of the mixture of the two isomers.

λ_{max} 224 mμ (ε 8750); ν_{max} 3380, 3220, 1740 and 1700 cm^{-1} (pyrrolic and amidic NH, ester and amidic C=O respectively). NMR ($CDCl_3$) 5·92 δ (t, H—3), 5·75 δ (H—4, triplet with each line further split by Me—5: $J_{3,4}$ = 3·5, $J_{1,3}$ = 2·1, $J_{1,4}$ = 2·0, $J_{4,5\text{-Me}}$ = 0·8 Hz); 2·20 δ (s, $w_{1/2}$ = 1·8 Hz); 8·75 δ (broad, pyrrolic NH); 6·45 δ (NHCO); 3·90 and 1·03 δ (q, resp. t, J = 7·0 Hz, OEt); 2·2–3·8 δ (16 lines), 5·05 δ (d): 4 protons of an ABCX spectrum, approx. ABMX, δ_X = 5·05 (H—5'), δ_A = 2·44, δ_B = 2·92 (CH_2—3'), δ_M = 3·54 (H—5'), J_{AB} = 17·0, J_{AM} = 9·2, J_{BM} = 7·5, J_{MX} = 8·4 Hz (H—5' and H—4' *cis*).

4-*Carbetoxy*-5-(4,5-*dimethylpyrrol*-2-*yl*)-2-*pyrrolidinone* (VII, R_1 = R_2 = H; R_3 = R_4 = CH_3). The experimental conditions were the same as for the previous product. M.p. 171°. (Found: C, 62·55; H, 7·32; N, 11·12. $C_{13}H_{18}N_2O_3$ requires: C, 62·38; H, 7·25; N, 11·19%).

λ_{max} 223 mμ (ε 9000); ν_{max} 3390, 3240, 1740, 1710 cm^{-1} (same assignments as for previous product).

4-*Carbetoxy*-5-(3,5-*dimethylpyrrol*-2-*yl*)-2-*pyrrolidinone* (VII, R_1 = R_3 = H; R_2 = R_4 = CH_3). Prepared using the same conditions as for previous product, except that the refluxing was for 15 min. M.p. 197–198° (fractional crystallization from 50% EtOH and final sublimation at 170°, 0·5 mm). (Found: C, 62·03; H, 7·26; N, 11·81. $C_{13}H_{18}N_2O_3$ requires: C, 62·38; H, 7·25; N, 11·19%).

λ_{max} 222·5 mμ (ε 9500); ν_{max} 3320, 3210, 1750, 1700 cm^{-1} (same assignments as for previous products). NMR ($CDCl_3$) 5·58 δ (H—4, doublet with each line further split by Me—5, $J_{1,4}$ = 2·0 Hz); 2·18 δ ($w_{1/2}$ = 1·8 Hz, Me—5, $J_{4,Me-5}$ ~ 0·8 Hz); 2·00 δ (s, $w_{1/2}$ = 1 Hz, Me—3); 9·0 δ (broad, pyrrolic NH); 6·03 δ (NHCO); 4·18 and 1·27 δ (q, resp. t, J = 7·0 Hz, OEt); 2·5–3·5 δ (11 lines), 5·01 δ (d): 4 protons of an ABCX spectrum, approx. AA'MX, δ_X = 5·01 (H—5'), δ_A = 2·67 (CH_2—3'); δ_M = 3·24 (H—4'), $^{1/2}(J_{AM} + J_{A'M})$ = 9·0, J_{MX} = 6·5 Hz (H—5' and H—4' *trans*).

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