Tetrahedron, 1963, Vol. 19, pp. 1661 to 1673. Pergamon Press Ltd. Printed in Northern Ireland

THE FORMATION OF CYCLOLS FROM N-HYDROXYACYLLACTAMS

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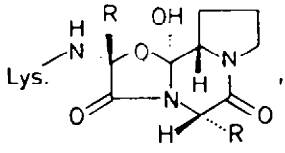
(*Received* 1 *April* 1963)

Abstract—It was shown that N-(α- or β-hydroxyacyl)-lactams can exist in an equilibrium with two tautomeric forms, the so-called cyclol and a large membered ring form. The position of the equilibrium depends on the polarity of the solvent, the p*K* of the solution, the lactam ring-size and the substituents on the side-chain. Cyclols of such structures can give rise to stable crystalline compounds.

THE peptide part of the ergot alkaloids, the structure (I) of which was first demonstrated on the basis of degradation studies[1] and recently by a total synthesis[2], contains an unusual ortho acid system which for brevity is called cyclol.[3]



I

The discovery that such a labile system can be stabilized under certain conditions was first reported for simple models,[4] and as a result made possible the realization of the ergotamine synthesis. In this paper our findings about cyclol formation in the simple model systems are described.

The formation of a cyclol system of the general structure B (Fig. 1) can theoretically be explained either through a covalent addition of the hydroxyl oxygen to the lactam carbonyl group in A or the covalent addition of the amide nitrogen to the

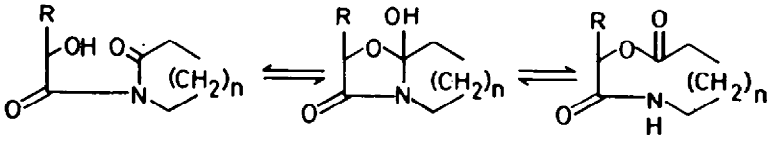


FIG. 1

[1] A. Stoll, A. Hofmann and Th. Petrzilka, *Helv. Chim. Acta* **34**, 1544 (1951).

[2] A. Hofmann, A. J. Frey and H. Ott, *Experientia* **17**, 206 (1961).

[3] Structures of this type have been assumed as intermediates in rearrangements that involved amide bond participation. For examples refer to the work on rearrangements in *The Chemistry of Amino Acids and Peptides* by L. A. Cohen and B. Witkop, *Angew. Chem.* **73**, 253 (1961) and D. Wrinch, *Chem. Aspects of the Structure of Small Peptides* Munksgaard, Copenhagen (1960).

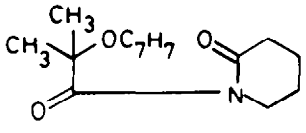
[4] First announced at the 4th *European Symposium on Peptides* Moscow August (1961) by A. Hofmann, A. J. Frey, H. Ott and J. Rutschmann, *Zh. Vsesoyuz. Khim. Obshestva Im. D. I. Mendeleeva* **7**, 466 (1962). A group of Russian scientists have carried out similar experiments: M. M. Shemyakin, V. K. Antonov, A. M. Shkrob, Yu. N. Sheinker and L. B. Senyavina, *Tetrahedron Letters* No. **16**, 701, (1962) and V. K. Antonov, A. M. Shkreb and M. M. Shemyakin, *5th Peptide Symposium* Oxford, September (1962).

ester carbonyl in the large ring compound C.[5] We first investigated the formation of cyclols starting from the N-hydroxyacyllactams A. The presence of an imide structure in A appeared to be useful in promoting cyclization since the lactam carbonyl group is activated enough to interact with the hydroxyl oxygen.[6] In addition the new hydroxyl group that forms in the cyclol system has a stronger acid character, i.e. is able to form a stable anion. On the basis of this, it was expected that the stability of the three possible tautomeric forms A, B and C would depend on the polarity and pK value of the solvent.

In addition to these electronic factors steric interactions were also assumed to be of significance. We, therefore, limited ourselves to the production of N-(α- or β-hydroxyacyl)-lactams that would result in the formation of five or six membered rings.

On the other hand it could be assumed that under certain conditions a tautomeric equilibrium exists between the three theoretically possible forms A, B, and C. The purpose of this work was, therefore, to determine what factors favorably influence the shifting of the possible equilibrium to the desired cyclol form B.[7] Since the conditions for most chemical reactions do not preclude the possibility of disturbing a tautomeric equilibrium, the structure of each tautomer was elucidated, primarily, by physical-chemical measurements. The U.V. spectra[8] proved to be a useful method for both qualitative and quantitative distinction between the cyclol B and the open chain alcohol A. The chromophore system of acylated lactams (Form A) absorbs at 217–220 mμ (ε = 8,000–13,000)[9] whereas the lactam group in the oxazolidone-cyclol ring (Form B) absorbs at 190–197 mμ ($\varepsilon \sim 7000$).[10]

The I.R. spectra could be used only for a limited distinction between the open form A and the cyclol B since the two carbonyl groups in A were not separated but usually absorbed at the same range as the oxazolidone carbonyl in B.[11] The infrared was also



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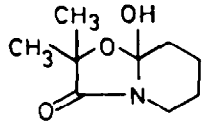


ii

[5] See L. A. Cohen and B. Witkop, *J. Amer. Chem. Soc.* **77**, 6595 (1955).

[6] Diacylamides have already been recognised as active carbonyl compounds, which under certain conditions lead to rearrangements whose transition state can be easily explained on the basis of cyclol type intermediates: T. Wieland and H. Urbach, *Liebigs Ann.* **613**, 84 (1958).

[7] The stereochemical path of cyclol formation in optically active rings connected with the ergotamine synthesis will be reported in a forthcoming paper in Tetrahedron.

[8] The U.V. determinations were carried out in a BECKMAN DK-2A instrument. All measurements were carried out in double distilled water using a Suprasil quartz cell of 0·1 mm thickness. If the apparatus was freed of oxygen by purging with high purity nitrogen, clear and reproducible measurements down to 1780 Å were obtained, cf. K. Stitch and H. G. Leemann, *Helv. Chim. Acta* **46**, 1151 (1963).

[9] For example, N-acetylpyrrolidone: 217 mμ (ε = 12,000), N-acetylpiperidone: 221 mμ (ε = 11,000), N-acetylcaprolactam: 221 mμ (ε = 10,020).

[10] For example, caprolactam: 197 mμ (ε = 7700), typical cyclol: 192 mμ (ε = 7800).

[11] The only exceptions to this rule were observed in the side-chain substituted compound of type i or ii. The open form (i) showed in the I.R. spectrum (CH_2Cl_2) a clear separation of piperidone carbonyl (1685 cm^{-1}) and acyl carbonyl (1710 cm^{-1}) whereas the I.R. of the cyclol (ii) gave only one sharp oxazolidone carbonyl at 1705 cm^{-1}.

unreliable in distinguishing between the hydroxyl group in A and the cyclol hydroxyl. The tautomer C could be detected by infrared since the secondary amide band could be clearly located.

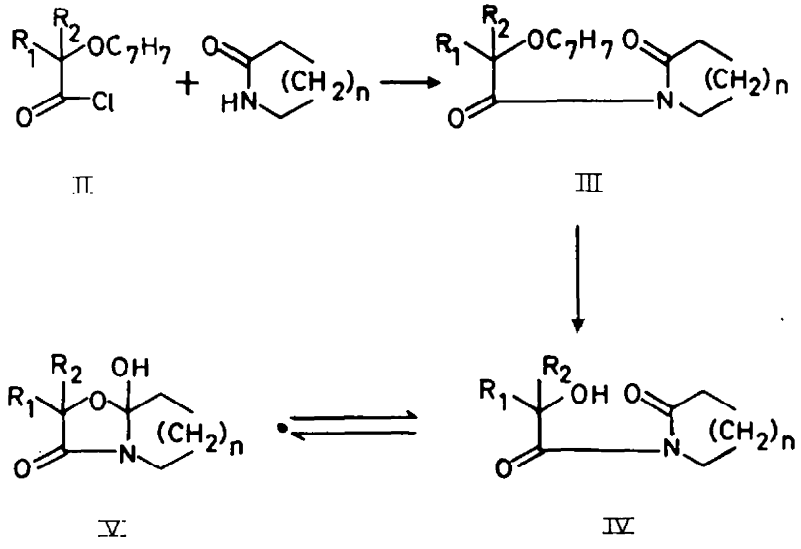
In certain cases the N.M.R. spectra gave very precise information. The isolated CH_2-group in the side chain or the alkyl substituents on this atom gave signals that showed a definite separation between the cyclol (multiplet) and the non-cyclol form (Free rotation: singlet). The —OH-proton could be identified as a sharp singlet that rapidly exchanged with D_2O.

Finally, cyclols that existed mainly in one tautomeric form could be detected by chemical means. A simple and very characteristic test for distinguishing the open form A and the cyclol B was their stability in alkaline media. While acylamides of type A are hydrolyzed very rapidly in 0·1 N sodium hydroxide the cyclols are very stable. The enhanced stability of the cyclols is probably due to the increased acidity of the hydroxyl group which can form a stable anion in the basic environment.

Another typical reaction for all cyclols determined up to now is their interaction with phenylisocyanate. Cyclols in the presence of excess phenylisocyanate at room temperature give rise to carbon dioxide and diphenylurea[12] whereas the open form A gives a quantitative yield of a phenylurethane.

Five-ring cyclols

The general synthetic approach to the five membered cyclols involved the N-acylation of the lactams with the known[13] α-benzyloxylacyl chlorides (II) in pyridine at 0°, hydrogenolytic cleavage of the benzyl group of compound (III) in 50 per cent acetic acid to the α-hydroxy-acyl imide (IV), which under certain conditions formed a five-membered cyclol (V).



II III

V IV

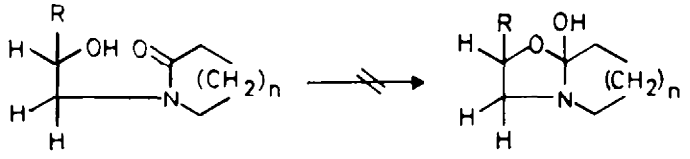
[12] This reaction is typical of oxazolidones in general and evidently holds for the cyclol type oxazolidone. Cf. J. W. Clark-Lewis, *Chem. Rev.* **58**, 86 (1958).

[13] For example, benzyloxyacetylchloride: H. O. L. Fischer and B. Gohlke, *Helv. Chim. Acta* **16**, 1130 (1933).

The conditions found necessary for five-ring cyclol formation are as follows:

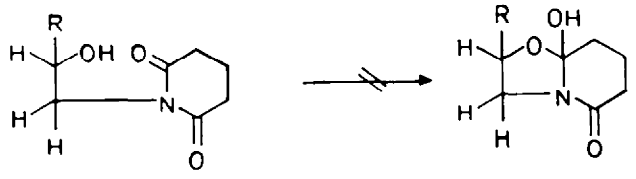
1. *Cyclol formation takes place only in α-hydroxyacyl- and not in α-hydroxyalkyl-lactams*

The β-hydroxyalkyllactams (VI) in every case failed to give any trace of cyclol (VII). All derivatives of (VI) (R = H or CH_3 and n = 1, 2 or 3) gave I.R. and U.V. spectra that contained absorption bands characteristic of N-alkyllactams (VI) and phenylurethane derivatives of the alcohol.



VI VII

The N-alkylglutarimides of type (VIII) also failed to give any cyclol formation (IX). Even though, in this system the imide structure is present, another prerequisite for cyclol formation, i.e. the presence of a carbonyl group in the five membered ring to be formed is not fulfilled.



VIII IX

2. *5-Ring cyclol formation takes place only if the acylated lactam is at least a six-membered ring*

Acylated piperidones and caprolactams (IVa) to (IVe) gave the cyclols (Va) to (Ve) in very good yield. These were always crystalline compounds that absorbed in the ultraviolet at 189–192 mμ (ε = 7,800–9,800) and did not give alcohol derivatives with phenyl isocyanate, but gave rise to carbon dioxide and diphenylurea formation. Experiments with acylated pyrrolidones (IVf) and (IVg) resulted only in the open forms. These structures were definitely confirmed by their ease of hydrolysis to starting materials, U.V. absorption at 216 mμ (ε = 11,700) and formation of phenylurethanes in good yield.

Formula	R_1	R_2	n	m.p.
V a	H	H	2	88–89°
b	CH_3	H	2	101–103°
c	CH_3	CH_3	2	121–123°
d	H	H	3	76–78°
e	CH_3	H	3	136–138°

Formula	R_1	R_2	n
IV a	H	H	2
b	CH_3	H	2
c	CH_3	CH_3	2
d	H	H	3
e	CH_3	H	3
f	H	H	1
g	CH_3	H	1

* crystallized from ethyl ether.

3. *Alkyl substituents in the oxazolidone ring increase the stability of the cyclol form*

When the cyclol compound (Va) was dissolved in chloroform an equilibrium occurs, which on the basis of N.M.R. spectra consists of the open form (IVa) and cyclol (Va). This equilibrium was very easy to determine with N.M.R. spectra. The N.M.R. spectrum in deuterochloroform showed after a short time the appearance of the open form CH_2-group at 279 c.p.s. as a singlet and an intensity decrease of the cyclol form CH_2-AB-signal centered at 258 c.p.s.[14] When equilibrium was reached at room temperature structures IVa and Va exist in a 1:2 ratio (Fig. 2).

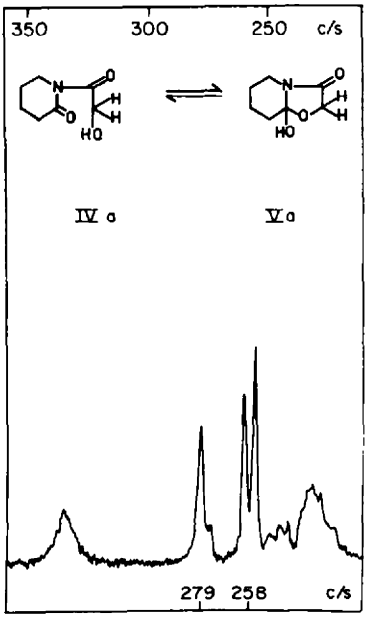


FIG. 2

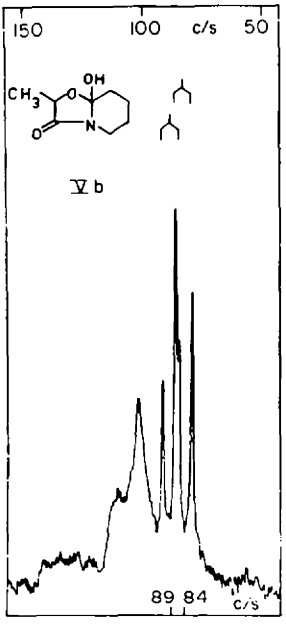


FIG. 3

In contrast, on the basis of U.V. and N.M.R. spectral data, solutions of cyclol compounds with alkyl substituents in the oxazolidone ring examined in this study do not contain any measurable amount of the open form tautomer.

The N.M.R. spectra of compounds (Vb) (Fig. 3) and (Ve) show two methyl proton doublets, one at 84 c.p.s., J = 7 c.p.s. and another at 89 c.p.s., J = 7 c.p.s. These peaks are evidently due to a *cis*:*trans* mixture (CH_3:OH) of (Vb) and (Ve).[15,16]

The fact that alkyl substituents in the pre-cyclolyzed side-chain increase the stability of the formed cyclol ring is not new. The explanation[17] that cyclization decreases the number of unfavorable rotamers apparently also holds for this system.

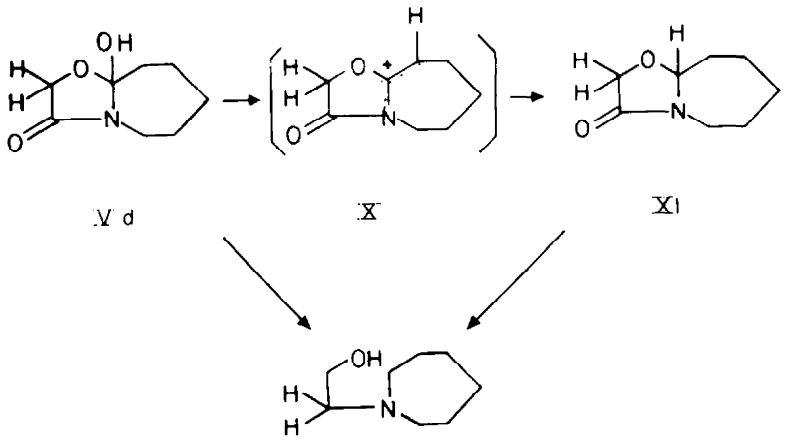
In reference to general properties of the cyclol hydroxyl group in 5-ring cyclols the following notable results were observed. A property of the cyclol-OH group and also

[14] The appearance of the isolated CH_2-group as an AB spectrum at 258 c.p.s. (J_{AB} = 14 c.p.s., $\delta_B - \delta_A$ = 10 c.p.s.), is evidence for the cyclic form.

[15] Cf. footnote 7.

[16] A simple chemical test for cyclols with a methyl substituent in the oxazolidone-ring (Vb and Ve) is based on the iodoform test. On these compounds the test is negative, while with the open form (IVg) iodoform formation occurs readily.

[17] Cf. T. C. Bruice and U. K. Pandit, *J. Amer. Chem. Soc.* **82**, 5858 (1960).



V d X XI

XII

an indirect proof of the existence of such a structure, is the case of exchanging the —OH-group in solvolyzing media.[18] In acid media compound (Vd) forms the carbonium ion (X). This change is supported by U.V. data where the cyclol (Vd) maximum at 190 mμ is bathochromically displaced to 219 mμ when acid is added (Fig. 4).

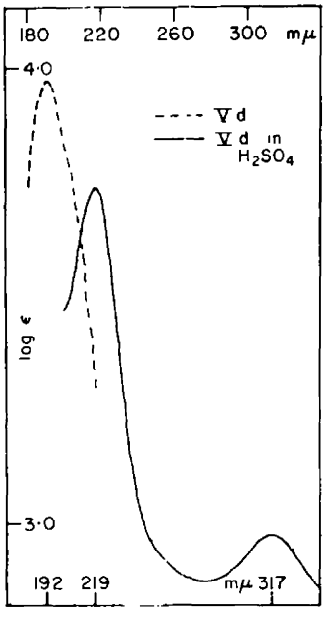


FIG. 4

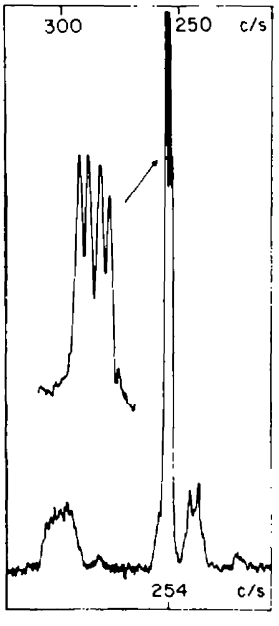
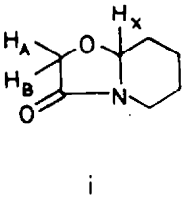


FIG. 5



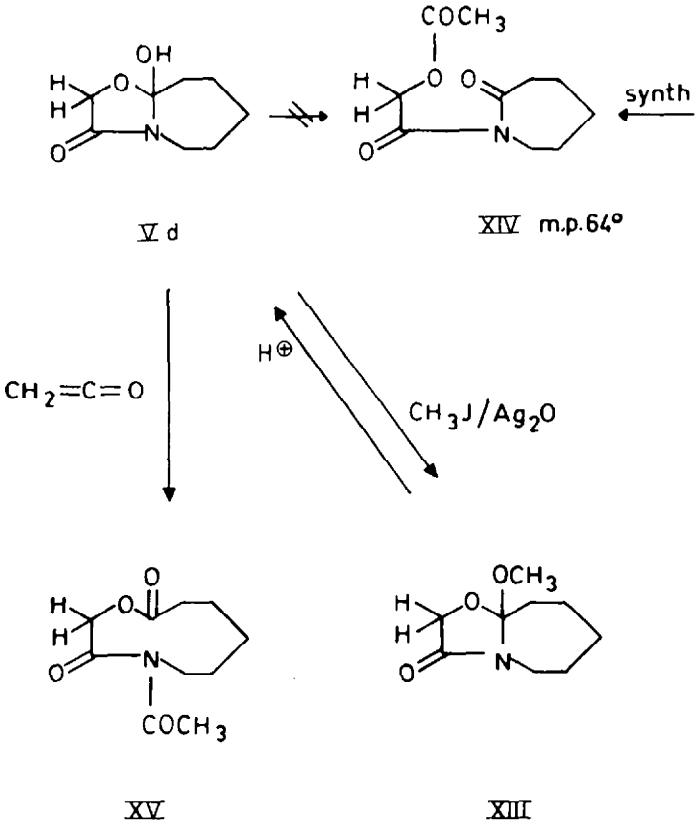
i

[18] Experimental data for this result will be furnished in the forthcoming work in *Tetrahedron*. Cf. footnote 7.

If an acid solution of (Vd) was hydrogenated in the presence of a palladium catalyst it very rapidly absorbed one mole of hydrogen and gave (XI) in over 70 per cent yield.[19]

With lithium aluminium hydride (XI) was converted to (XII) with cleavage of the oxazolidone ring. The same product was also obtained when (Va) is treated with lithium aluminium hydride.

The cyclol-hydroxyl can be methylated with methyl iodide and silver oxide. The methyl ether (XIII) derived from the cyclol (Vd) is very stable towards alkali as expected and can be converted under acidic conditions to starting material.



V d XIV m.p. 64°

XV XIII

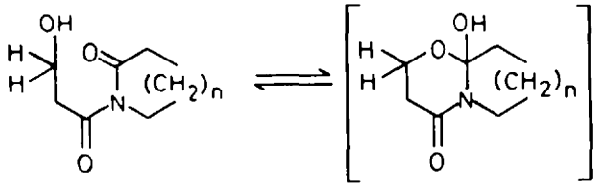
In reference to the ability to acylate the cyclol-OH group it was found, as expected, that it, like a tertiary-OH group under the usual conditions can neither be acylated nor tosylated. An acylation could be observed only when a dioxane solution of cyclol was treated with ketene. When the crystalline cyclol (Vd) was treated under these

[19] Compound i gave an N.M.R. spectrum (Fig. 5) that contained an extraordinary coupling between protones separated by an oxygen bridge. The isolated methylene group (H_A, H_B) gave a quartet of bands of almost equal intensity centered at 254 c.p.s. The appearance of this quartet has to be interpreted as follows: The two protons form a strong deformed AB-spectrum ($\delta_B - \delta_A \sim 1$ c.p.s., $J_{AB} = 12$–15 c.p.s.) whose outer lines are not recognizable. Both intensive inner lines are split into a doublet each by coupling with H_x (proton JAX = JBX = 1·8 c.p.s.). The H_x proton appears as a complex multiplet at 300 c.p.s. due to additional coupling with its adjacent methylene group.

conditions a fair yield of a free flowing oil was obtained whose thin layer chromatogram indicated it was uniform. It showed a maximum at 220 mμ only and no O-acetyl group in the infrared. That the theoretically possible compound (XIV) did not form was proven by synthesis of XIV (m.p. 64°) by an authentic route. It seems probable to us that under the above-mentioned conditions the ten membered ring compound (XV) had formed. Unlike the cyclols an acetic acid solution of this substance failed to hydrogenate in the presence of a palladium catalyst. This and the results given earlier are in agreement with the ten membered ring system C.[20]

Six-ring cyclols

As an additional part of our study the ability of the N-(β-hydroxyacyl)-lactams (A; Fig. 6) to form cyclols were investigated. It was observed that the homogeneous reaction products, isolated as crystalline materials (70 per cent yield), did not have the characteristics of the cyclol structure B but corresponded to the large ring system C (XVIa and XVIb).



Formula C	n	m.p.
XVI a	2	107–108°
XVI b	3	138–139°

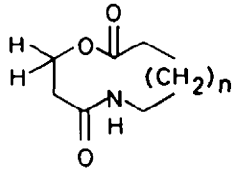


FIG. 6

Evidence for C was obtained from the following physical-chemical data: The I.R. spectra of XVIa and XVIb in methylene chloride gave in addition to the ester and amide bands at 1720 and 1670 cm^{-1} a clean secondary amide stretching band at 1525 cm^{-1} (Fig. 7) that was shifted to 1560 cm^{-1} in potassium bromide.[21] The secondary amide band disappeared when (XVIb) was acylated. The U.V. spectra of the compounds show a maximum at 192 mμ ($\varepsilon = 7200$) corresponding to a lactam group. In the

[20] See L. A. Cohen and B. Witkop, see ref. 5.

[21] A. D. Cross, *Introduction to Practical Infrared Spectroscopy* pp. 30, 66. Butterworth, London (1960); W. Brügel, *An Introduction to Infrared Spectroscopy* p. 340, Methuen, London (1962).

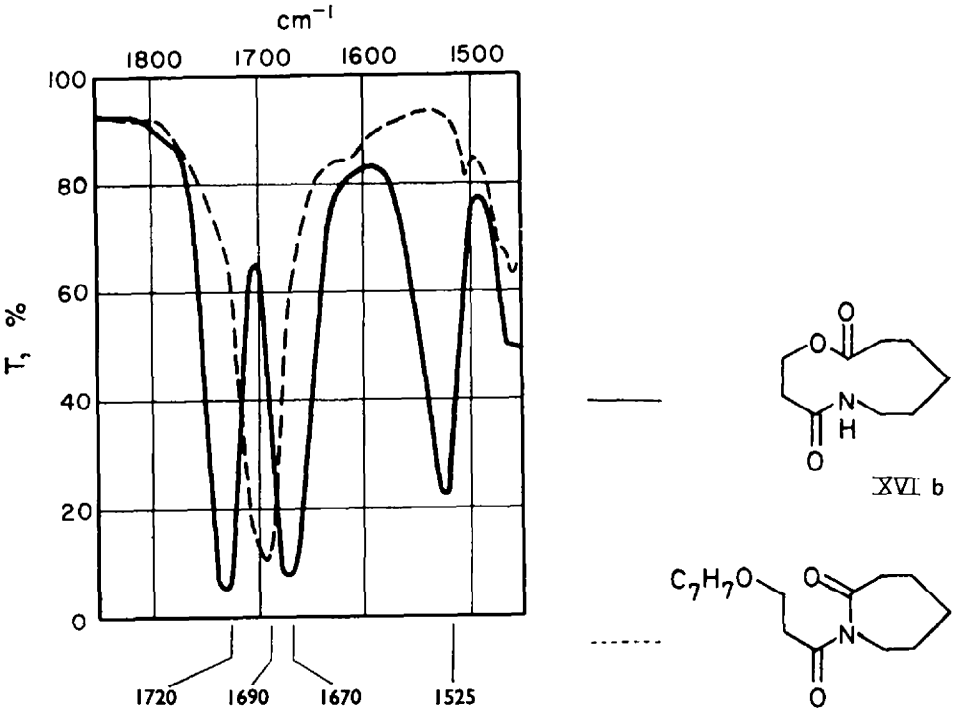


FIG. 7

N.M.R. spectra the presence of an —NH-group could be shown by the slow disappearance of the 340–370 c.p.s. signal when the compounds were treated with D_2O.

It should be apparent that the information obtained from the formation of stable cyclols demonstrated on simple models, which has already supplied the key to the synthesis of the ergot peptide, could also serve as the starting point for the explanation of important effects in other complicated substances that contain a peptide structure.[22]

EXPERIMENTAL*

General procedure for acylating lactams. A solution of 0·1 mole lactam in 0·1 mole pyridine and 20 ml benzene was frozen by means of liquid air and the solid mixture was added to 0·05 moles of the appropriate acid chloride and kept at 0° for several hr. When the reaction mixture was molten it was refluxed for 10–14 hr. After cooling to 0° the mixture was poured onto 100 ml ice-water, separated and the organic phase treated with 100 ml chilled saturated sodium hydrogen carbonate. The benzene solution was dried over magnesium chloride and the solvent was removed *in vacuo*. The residue was either distilled under high vacuum or crystallized from a suitable solvent.

N-(*Benzyloxyacetyl*)-*pyrrolidone.* This was prepared from benzyloxyacetyl chloride[18] (b.p. 124°/12 mm) and α-pyrrolidone in 86% yield as 107–108°; I.R., 1730 cm^{-1} (lactam C=O), 1700 cm^{-1} (amide C=O). (Found: C, 67·0; H, 6·4; N, 6·1; O, 20%. $C_{13}H_{15}NO_3$ requires: C, 66·9; H, 6·5; N, 6·0; O, 20·6%.)

General procedure for reductive cleavage of the benzyl-group of the benzyloxyacetyl-lactams. One part of a benzyloxyacetyl-lactam was added to 0·5 parts pre-hydrogenated palladium on alumina catalyst (5% Pd) in 10 to 20 pts. 50% acetic acid and hydrogenated on a shaking apparatus. After the

* All m.p. were taken on a Tottoli-apparatus and were corrected. I.R. spectra, unless otherwise stated, were taken in methylene chloride solution. U.V. spectra.[8]

[22] M. L. Bender, *Chem. Rev.* 60, 106 (1960).

uptake of one mole H_2 was complete the catalyst was filtered off and the solution evaporated *in vacuo*. The residue was dissolved in a suitable solvent as e.g. ether, benzene, acetone or ethylacetate and again filtered from inorganic material (from the carrier of the catalyst). The hydrogenated product was then either crystallized or distilled under high vacuum.

N-(*Hydroxyacetyl*)-*pyrrolidone*. This compound was obtained in 67% yield by the hydrogenation of the product described above; needles, m.p. 64·5–65·5°; I.R., 3500 cm^{-1} (OH), 1740 cm^{-1} (lactam C=O) 1685 cm^{-1} (amide C=O); U.V. spectrum max 216·5 mμ (ε = 11,700). The hydrogenation in glacial acetic acid resulted in the uptake of 1 mole H_2 and gave the same product. (Found: C, 50·7; H, 6·4; N, 10·0; O, 33·1. $C_6H_9NO_3$ requires: C, 50·3; H, 6·3; N, 9·8; O, 33·5%.) The *Phenylurethane* of this substance was obtained in 74% yield, m.p. 127–128°. (Found: C, 59·6; H, 5·4; N, 10·6; O, 24·0. $C_{13}H_{14}N_2O_4$ requires: C, 59·5; H, 5·4; N, 10·7; O, 24·4%).

N-(α-*Hydroxypropionyl*)-*pyrrolidone*. Pyrrolidone was acylated with 2-benzyloxyacetyl chloride and the resultant oily product was then hydrogenated in a mixture of ethanol–acetic acid (9:1) in the presence of a palladium catalyst. The yield was 74% of the title compound, m.p. 43–45°, U.V. λ_{max} 219 mμ (ε = 10,700). (Found: C, 53·8; H, 7·0; N, 9·0; O, 30·4. $C_7H_{11}NO_3$ requires: C, 53·5; H, 7·0; N 8·9; O, 30·6%). *The* p-*nitrophenylbenzoate* of this compound melted at 96°. (Found: C, 55·1; H, 4·8; N, 9·7; O, 31·2. $C_{14}H_{14}N_2O_6$ requires: C, 54·9; H, 4·6; N, 9·2; O, 31·3%).

N-(α-*Benzyloxypropionyl*)-*pyrrolidone*. This was prepared from 2-benzyloxypropionyl chloride (b.p. 88°/12 mm) and pyrrolidone. After the frozen reaction mixture it was kept for 36 hr at 20° and not refluxed subsequently. The product was an oil; b.p. 150°/0·005 mm; $n_D^{20°}$ = 1·5370; yield 33%; I.R., 1740 cm^{-1} (lactam C=O), 1690 cm^{-1} (amide C=O). (Found: C, 68·1; H, 6·9; N, 5·5; O, 20·0. $C_{14}H_{17}NO_3$ requires: C, 68·0; H, 6·9; N, 5·7; O, 19·4%).

N-(α-*Hydroxypropionyl*)-*pyrrolidone*. This was prepared in 66% yield from the above compound by hydrogenation. The product had b.p. 110°/0·005 mm, n_D^{20} = 1·5031, I.R., 3450 cm^{-1} (OH), 1735 cm^{-1} (lactam C=O), 1690 (amide C=O); U.V., λ_{max} 218 mμ (ε = 10,000). (Found: C, 53·9; H, 7·2; N, 8·8; O, 30·5. $C_7H_{11}NO_3$ requires: C, 53·5; H, 7·1; N, 8·9; O, 30·5%). 3,5-*Dinitrobenzoate*, m.p. 134°, yield: 61%. (Found: C, 48·2; H, 3·8; N, 12·2; O, 36·3. $C_{14}H_{13}N_3O_8$ requires: C, 47·9; H, 3·7; N, 12·0; O, 36·4%.)

N-(*Benzyloxyacetyl*)-*piperidone*. This was prepared from benzyloxyacetylchloride and piperidone in 71% yield; needles, m.p. 40–41°; I.R., 1700 cm^{-1} (lactam and amide C=O together). (Found: C, 68·3; H, 6·9; N, 5·7; O, 19·1. $C_{14}H_{17}NO_3$ requires: C, 68·0; H, 6·9; N, 5·7; O, 19·4%).

6-*Hydroxy*-7-*oxa*-l-*azabicyclo* [4.3.0] *nonanone*-(9), (Va). The above benzyl derivative was hydrogenated with 1 mole H_2 to give a 48% yield of the cyclol, m.p. 88–89°; I.R., 3600 and 3350 cm^{-1} (OH), 1700 cm^{-1} (lactam C=O); U.V., λ_{max} 190 mμ (ε = 8300) and shoulder at 220 mμ (ε = 1200); N.M.R., AB spectrum with center at 258/262 c.p.s.; CH_2-signal of the open form at 279 c.p.s. The ratio of the open form: cyclol was about 1:2. (Found: C, 53·4; H, 7·0; N, 8·9; O, 30·7. $C_7H_{11}NO_3$ requires: C, 53·5; H, 7·1; N, 8·9; O, 30·5%). The *Phenylurethane* of the open form IVa was obtained in 55% yield, m.p. 128° (Found: C, 61·0; H, 5·9; N, 9·9; O, 23·4. $C_{14}H_{16}N_2O_4$ requires: C, 60·9; H, 5·8; N, 10·1; O, 23·2%).

7-*Oxa*-l-*azabicyclo* [4.3.0] *nonanone*-(9). This derivative was obtained either by hydrogenation of N-(benzyloxyacetyl)-piperidone with 2 moles H_2 in glacial acetic acid (74% yield) or by hydrogenation of compound Va with 1 mole H_2 in the same solvent (84% yield). The product had b.p. 95°/0·1 mm; $n_D^{20°}$ = 1·4986; I.R.; 1700 cm^{-1} (lactam C=O); U.V.; λ_{max} 197 mμ (ε = 8300); N.M.R., *vide* footnote (19). (Found: C, 59·6; H, 7·9; N, 9·9; O, 22·7. $C_7H_{11}NO_2$ requires: C, 59·6; H, 7·9; N, 9·9; O, 22·7%).

N-(β-*Hydroxyethyl*)-*piperidine*. To a boiling suspension of 0·296 g (7·8 mmoles) of lithium aluminium hydride in 10 ml ether a solution of 0·740 g (5·2 mmoles) 7-oxa-1-azabicyclo [4.3.0] nonanone-(9) in 10 ml ether was added and the mixture refluxed for 20 hr. After isolation of the formed N-(hydroxyethyl)-piperidine in the usual way, the *picrate* of the latter was precipitated and crystallized from alcohol, m.p. 98–99·5°. (Found: C, 43·7; H, 5·1; N, 15·6; O, 35·6. Calc. for $C_7H_{15}NO \cdot C_6H_3N_3O_7$: C, 43·6; H, 5·1; N, 15·6; O, 35·7%). *Chlorohydrate*: m.p. 121° from alcohol–ether. The mixed m.p. of the two salts with authentic materials were not depressed.

N-(α-*Benzyloxypropionyl*)-*piperidone*. This compound was obtained from racemic α-benzyloxypropionyl chloride (b.p. 133°/20 mm, n_D^{20} = 1·511) and piperidone in 57% yield, b.p. 125–127°/0·01 mm; n_D^{20} = 1·5322; I.R.: 1695 cm^{-1} (lactam C=O), 1640 cm^{-1} (amide C=O). (Found: C, 69·1; H, 7·3; N, 5·4; O, 18·4. $C_{15}H_{19}NO_3$ requires: C, 69·1; H, 7·4; N, 5·4; O, 18·5%).

6-*Hydroxy*-8-*methyl*-7-*oxa*-1-*azabicyclo* [4.3.0] *nonanone*-(9), (Vb). The benzylderivative described above gave the title compound in 93% yield by hydrogenation with 1 mole H_2. Crystallization from AcOEt gave, m.p. 101–103°; I.R., 3570 and 3350 cm^{-1} (OH), 1710 cm^{-1} (lactam C=O); U.V., λ_{max} 191 mμ (ε = 9100), N.M.R., *vide* text. (Found: C, 56·4; H, 7·7; N, 8·3; O, 28·0. $C_8H_{13}NO_2$ requires: C, 56·1; H, 7·7; N, 8·2; O, 28·0%).

8-*Methyl*-7-*oxa*-1-*azabicyclo* [4.3.0] *nonanone*-(9). This substance was obtained in 70% yield from Vb as well as from its starting material, the benzyl derivative, by hydrogenation with one or two moles hydrogen in glacial acetic acid. It had b.p. 79°/0·08 mm; n_D^{20} = 1·4838; I.R., 1700 cm^{-1} (lactam C=O). (Found: C, 61·4; H, 8·4; N, 9·0; O, 20·6. $C_8H_{13}NO_2$ requires: C, 61·9; H, 8·4; N, 9·2; O, 20·9%).

N-(α-*Hydroxypropyl*)-*piperidine*. The reduction of the above heterocyclic derivative with lithium aluminium hydride carried out as described before yielded 83% of N-(2-hydroxypropyl)-piperidine, b.p. 90°/16 mm. The *picrate* of this amine proved to be identical with an authentic sample, m.p. 138°. (Found: C, 45·3; H, 5·4; N, 15·0; O, 34·6. Calc. for $C_8H_{17}NO{\cdot}C_6H_3N_3O_7$: C, 45·2; H, 5·4; N, 15·0; O, 34·4%).

N-(α-*Benzyloxyisobutyryl*)-*piperidone*. This compound was synthesized from isobutyrylchloride (b.p. 80°/0·01 mm) and piperidone in 46% yield, m.p. 64–66°; I.R., 1710 cm^{-1} (lactam C=O), 1685 cm^{-1} (amide C=O). (Found: C, 69·8; H, 7·6; N, 5·2; O, 17·2. $C_{16}H_{21}NO_3$ requires: C, 69·8; H, 7·7; N, 5·1; O, 17·4%).

8,8-*Dimethyl*-6-*hydroxy*-7-*oxa*-1-*azabicyclo* [4.3.0] *nonanone*-(9), (Vc). The benzyl derivative from above yields on hydrogenation 46% of the crystalline cyclol Vc; m.p. 121–123°; I.R., 3550 and 3350 cm^{-1} (OH), 1705 cm^{-1} (lactam C=O); U.V., λ_{max} 189 mμ (ε = 9800); N.M.R., OH at 278 c.p.s., CH_3 doublet at 92 c.p.s. (J = 6 c.p.s.). (Found: C, 58·7; H, 8·0; N, 7·6; O, 25·7. $C_9H_{15}NO_3$ requires: C, 58·4; H, 8·2; N, 7·6; O, 25·9%).

N-(β-*Benzyloxypropionyl*)-*piperidone*. This compound was synthesized from β-benzyloxypropionyl chloride and piperidone in 53% yield; b.p. 148°/0·005 mm; n_D^{20} = 1·5370; I.R., 1700 cm^{-1} (lactam and amide C=O together). (Found: C, 68·9; H, 7·2; N, 5·3; O, 18·3. $C_{15}H_{19}NO_3$ requires: C, 68·9; H, 7·3; N, 5·4; O, 18·4%).

7-*Oxa*-1-*azacyclo*-*decan*-*dion*-(6,10), (XVIa). This derivative was obtained by the hydrogenation of N-(β-benzyloxypropionyl)-piperidone in glacial acetic acid with 1 mole H_2. Crystallization from AcOEt gave a product that melted at 107–108°; I.R., 3450 cm^{-1} (NH), 1720 cm^{-1} (lactam C=O), 1675 cm^{-1} (lactam C=O), 1520 cm^{-1} (NH-stretch); U.V., λ_{max} 193·5 mμ (ε = 6750); N.M.R., NH at 340–370 c.p.s., OH at 240–255 c.p.s. (Found: C, 56·4; H, 7·9; N, 8·2; O, 28·3. $C_8H_{13}NO_3$ requires: C, 56·1; H, 7·7; N, 8·2; O, 28·0%). Reaction of phenylisocyanate (2 hr, 90°) with XVIa probably gave the *phenylurethane* of N-(β-*hydroxypropionyl*)-piperidine in 88% yield, m.p. 89–91°. (Found: C, 62·3; H, 6·1; N, 9·6; O, 22·0. $C_{15}H_{18}N_2O_4$ requires: C, 62·1; H, 6·2; N, 9·6; O, 22·0%).

N-(β-*Hydroxypropyl*)-*glutarimide*.[22] Glutaric anhydride (11·4 g, 0·10 mole) and 15 g/0·2 moles of isopropanolamine were refluxed (distilled) together. The crude product was dissolved in CH_2Cl_2 and washed subsequently with dil hydrochloric acid, water and a saturated solution of sodium hydrogen carbonate. The solution was dried over magnesium sulfate and the solvent removed *in vacuo*. The product was again distilled under high vacuum to yield 31% of an oil, b.p. 105–110°/0·05 mm; n_D^{20} = 1·5025; I.R., 3470 cm^{-1} (OH), 1725 (m) and 1670 (st) lactam C=O; glutarimide itself shows two bands at 1700 and 1675); U.V., λ_{max} 211 mμ (ε = 15,000).

N-(*Benzyloxyacetyl*)-*caprolactam*. Caprolactam (113 g, 1·0 mole) was acylated with 74 g (0·41 mole) of benzyloxyacetyl chloride. There was obtained 92 g (86%) of N-(benzyloxyacetyl)-caprolactam, b.p. 160–163°/0·01 mm; n_D^{20} = 1·5410; I.R., 1700 cm^{-1} (lactam and amide C=O together). (Found: C, 68·7; H, 7·3; N, 5·4; O, 18·8. $C_{15}H_{19}NO_3$ requires: C, 68·9; H, 7·3; N, 5·4; O, 18·4%).

7-*Hydroxy*-8-*oxa*-1-*azabicyclo* [5.3.0] *decanone*-(10), (Vd). Twenty grams (0·077 mole) of N-(benzyloxyacetyl)-caprolactam was hydrogenated according to the general procedure mentioned before. The resulting cyclol was crystallized from ether in 79% yield, m.p. 76–78°; I.R., 3300 cm^{-1} (OH), 1705 cm^{-1} (lactam C=O); U.V., λ_{max} 192 mμ (ε = 9400); N.M.R., singlet of the isolated OH-group at 288 c.p.s. (which is an exception, for all other cyclols showed a doublet for this group). (Found: C, 56·4; H, 7·5; N, 8·2; O, 27·9. $C_8H_{13}NO_3$ requires: C, 56·1; H, 7·7; N, 8·2; O, 28·0%).

[22] Cf. S. N. Usakov, V. V. Davidenkova and V. V. Luscik, *Izv. Akad. SSSR* 901 (1961).

From cyclohexane, this substance crystallized with 1/6 moles of solvent, m.p. 89–91° (Found: C, 58·3; H, 8·1; N, 7·8; O, 25·7. $C_8C_{13}NO_3 \cdot 1/6\ C_6H_{12}$ requires: C, 58·4; H, 8·2; N, 7·6; O, 25·9%). This cyclol also crystallized from carbon tetrachloride with some trapped solvent. (Found: C, 50·1; H, 6·8; Cl, 11·7; N, 7·0; O, 24·0; $C_8H_{13}NO_3 \cdot 1/6\ CCl_4$ requires: C, 49·8; H, 6·7; Cl, 11·7; N, 7·1; O, 24·4%.)

8-*Oxa*-1-*azabicyclo* [5.3.0] *decanone*-(10), (XI). This compound was obtained either from Vd or its starting material, the benzyl derivative by hydrogenation with 1 or 2 moles hydrogen in glacial acetic acid. There was obtained 89% and 66% respectively of an oil, b.p. 64–66°/0·01 mm; $n_D^{20} = 1{\cdot}4940$; I.R., 1710 cm^{-1} (lactam C=O); U.V., λ_{max} 192·5 ($\varepsilon = 7600$). (Found: C, 61·2; H, 8·2; N, 8·7; O, 21·0. $C_8H_{13}NO_3$ requires: C, 61·9; H, 8·4; N, 9·0; O, 20·6%).

N-(*β-Hydroxyethyl*)-*hexamethyleminine*, (XII). To a boiling solution of 760 mg (20 mmoles) of lithium aluminium hydride in 50 ml ether, a solution of 1·55 g (10 mmoles) of 8-oxa-1-azabicyclo [5.3.0] decanone-(10) in 20 ml ether was added. After 20 hr the reaction was stopped, the resulting amine isolated in the usual way and then precipitated as *picrate*. This was crystallized from AcOEt to give 63% of the pure salt, melting at 99–101°. The picrate thus obtained proved to be identical with an authentic sample of N-(β-hydroxyethyl)-hexamethyleminine picrate. (Found: C, 45·5; H, 5·4; N, 15·1; O, 34·1. Calc. for $C_8H_{17}NO \cdot C_6H_3N_3O_7$: C, 45·2; H, 5·4; N, 15·0; O, 34·4%).

7-*Methoxy*-8-*oxa*-1-*azabicyclo* [5.3.0] *decanone*-(10), (XIII). Compound Vd (1·85 g, 10 mmoles) (with 1/6 mole of cyclo-hexane in the crystals) was dissolved in 12 ml methyl iodide and refluxed with freshly prepared silver oxide (from 8·5 g of $AgNO_3$) for 5 hr. The methylated product was distilled in a bulb-tube and yielded 84% of an oil, b.p. 90°/0·05 mm; $n_D^{20} = 1{\cdot}4860$. I.R., 1713 cm^{-1} (lactam C=O); U.V., λ_{max} 191·5 mμ ($\varepsilon = 7600$) and shoulder at 220 mμ ($\varepsilon = 800$); N.M.R. (in D_2O): OCH_3 at 193 and 205 c.p.s., ratio cyclol: open form about 10:1 isolated OH_3-group: AB-spectrum ($\Delta_{AB} =$ 2–3, $J_{AB} = 15$), A_2-spectrum at 274 c.p.s. (ratio 10:1). (Found: C, 58·3; H, 8·1; N, 7·7; O, 25·8. $C_9H_{15}NO_3$ requires: C, 58·4; H. 8·2; N, 7·6; O, 25·9%).

rac. N-(α-*Benzyloxypropionyl*)-*caprolactam*. This compound was obtained by the reaction of racemic α-benzyloxypropionyl chloride with caprolactam in 80% yield, m.p. 78–79°; I.R., 1690 cm^{-1} (lactam and amide C=O together). (Found: C, 69·9; H, 7·5; N, 5·2; O, 17·2. $C_{16}H_{21}NO_3$ requires: C, 69·8; H, 7·7; N, 5·1; O, 17·4%).

rac. 7-*Hydroxy*-9-*methyl*-8-*oxa*-1-*azabicyclo* [5.3.0] *decanone*-(10), (Ve). This cyclol was formed by the hydrogenation of the benzyl derivative above in 60% yield, m.p. 136–138°; I.R., 3550 and 3350 cm^{-1} (OH), 1710 cm^{-1} (lactam C=O); U.V., λ_{max} 192·5 mμ ($\varepsilon = 7800$). (Found: C, 58·6; H, 8·0; N, 7·6; O, 25·9. $C_9H_{15}NO_3$ requires: C, 58·4, H, 8·2; N, 7·6; O, 25·9%).

9-*Methyl*-8-*oxa*-1-*azabicyclo* [5.3.0] *decanone*-(10). This compound was obtained either by the hydrogenation of the derivative Ve with one mole hydrogen in glacial acetic acid or by the reduction of the N-(α-benzyloxypropionyl)-caprolactam with two moles hydrogen in the same solvent. The yields were about 80%; 75–80°/0·08 mm; $n_D^{20} = 1{\cdot}4844$; U.V., λ_{max} 197 mμ ($\varepsilon = 7600$).

N-(*β-Hydroxypropyl*)-*hexamethyleminine*. This imine was obtained from the compound just mentioned by reduction with lithium aluminium hydride in an analogous way as described before. The yield was 71% of the hexamethyleminine derivative as a *picrate*, m.p. 114–115° (crystallized from alcohol). The identical picrate was synthesized in an authentic way. (Found: C, 46·7; H, 5·6; N, 14·8; O, 33·1. Calc. for $C_9H_{19}NO \cdot C_6H_3N_3O_7$: C, 46·6; H, 5·7; N, 14·5; O, 33·1%).

7-*Methoxy*-9-*methyl*-8-*oxa*-1-*azabicyclo* [5.3.0] *decanone*-(10). This ether was obtained from the cyclol Ve by methylation with methyliodide and silver oxide as described for XIII. B.p. 70°/0·001 mm; $n_D^{20} = 1{\cdot}4770$; I.R., 1705 cm^{-1} (lactam C=O); U.V., λ_{max} 192 mμ ($\varepsilon = 7950$). (Found: C, 59·9; H, 8·6; N, 7·1; O, 23·9. $C_{10}H_{17}NO_3$ requires: C, 60·3; H, 8·6; N, 7·0; O, 24·1%).

1-*Acetyl*-8-*oxa*-1-*aza*-*cyclodecanedione*-(7,10), (XV). The cyclol Vd (1·0 g) was dissolved in 10 ml dioxane, 50 mg of p-toluenesulfonic acid added and the solution was subjected for 15 minutes to a vigorous stream of ketene. The reaction mixture was evaporated *in vacuo*. The residue was taken up in ether and treated with moist potassium carbonate. The neutral etheral solution was evaporated and the crude product distilled twice. The pure compound boiled at 110–115°/0·01 mm, yield 63%; $n_D^{20} = 1{\cdot}4938$; I.R., 1745 cm^{-1} (lactone C=O), 1700 cm^{-1} (lactam C=O). U.V., λ_{max} 221 mμ ($\varepsilon = 6450$), due to hydrolysis this maximum was slowly displaced towards 192 mμ. (Found: C, 56·5; H, 7·2; N, 6·5; O, 29·9. $C_{10}H_{15}NO_4$ requires: C, 56·3; H, 7·1; N, 6·6; O, 30·0%).

N-(*Acetoxyacetyl*)-*caprolactam* (XIV). This compound was synthesized from caprolactam and acetyl glyoxylic acid chloride in order to be compared with the cyclic derivative above. The yield was

82%, b.p. 119–122°/0·1 mm, $n_D^{20} = 1{\cdot}4870$. The highly viscous oil solidified rapidly and was crystallized from AcOEt, m.p. 65–76°. U.V., λ_{max} 220 mμ ($\varepsilon = 6450$). (Found: C, 56·4; H, 6·9; N, 6·5; O, 29·7. $C_{10}H_{15}NO_4$ requires: C, 56·3; H, 7·1; N, 6·6; O, 30·0%).

N-(*β-Benzyloxypropionyl*)-*caprolactam*. This was prepared from caprolactam and β-benzyloxypropionyl chloride in 60% yield. Oil, b.p. 155–160°/0·04 mm, $n_D^{20} = 1{\cdot}5320$; I.R., *vide* text. (Found: C, 69·7; H, 7·5; N, 4·8; O, 18·1. $C_{16}H_{21}NO_3$ requires: C, 69·7; H, 7·5; N, 4·8; O, 18·1%).

8-*Oxa*-1-*aza*-*cycloundecanedione*-(7,11), (XVIb). N-(β-benzyloxypropionyl)-caprolactam (4·0 g, 0·015 mole) were hydrogenated under standard conditions. The crude product was crystallized from EtOAc to yield 61·5% of the title compound, m.p. 138–139°. U.V. spectrum, λ_{max} 192 mμ ($\varepsilon = 7200$), I.R. and N.M.R., *vide* text. A glacial acetic acid solution of the benzyl derivative could be reduced with one mole hydrogen to give the same ring compound. (Found: C, 58·2; H, 8·1; N, 7·7; O, 26·0. $C_9H_{15}NO_3$ requires: C, 58·4; H, 8·2; N, 7·6; O, 25·9%).

1-*Acetyl*-8-*oxa*-1-*aza*-*cycloundecanedione*-(7,11). This compound was prepared by the reaction of derivative XVIb with acetyl chloride and pyridine at reflux temp. The yield was 55% of an oil, b.p. 120°/0·001 mm. I.R., 1725 cm^{-1} (lactone C=O), 1695 and 1682 cm^{-1} (lactam and amide C=O); U.V., λ_{max} 227 mμ ($\varepsilon = 7100$). (Found: C, 58·2; H, 7·5; N, 6·3; O, 28·4. $C_{11}H_{17}NO_4$ requires: C, 58·1; H, 7·5; N, 6·2; O, 28·2%).

Acknowledgements—We wish to thank Dr. H. Ott for the N.M.R. interpretation and Dr. W. Houlihan for assistance in preparing the English manuscript.