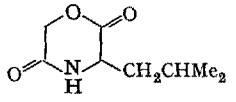
(IV), m.p. 92–97° (Found: C, 54.3; H, 7.5; N, 9.6: $C_{13}H_{22}N_2O_5$ requires C, 54.5; H, 7.75; N, 9.8%). Cyclization of (IV) to the nine-membered lactone (III) was most easily achieved by the thermal depolymerization method[6]. When the hydroxy-acid (IV) was heated at 150°/10^{-5} m.m., the monomeric lactone (III) sublimed, and after recrystallization from ether was obtained in 11.5% yield, m.p. 107–109° (Found: C, 58.4; H, 7.6; N, 10.4%; M, 246; $C_{13}H_{20}O_4N_2$ requires C, 58.2; H, 7.5; N, 10.4%; M, 268). The lactone structure of III was confirmed by its alkaline hydrolysis (Found: eq. wt. 255) which regenerated the starting hydroxy-acid (IV).

Cyclol formation was studied by infra-red spectroscopy. The spectrum of the lactone (III) in chloroform solution [ν_{max} 1762 (lactone carbonyl); 1697 (secondary amide) and 1670 cm^{-1} (inflexion, tertiary amide)] shows no evidence of transannular interaction between amide nitrogen and lactone carbonyl groups (cf. the similarly constituted δ-lactone (V), m.p. 128–129°, which has ν_{max} 1766,



V

and 1701 cm^{-1}). However, treatment of a chloroform solution of (III) with dry hydrogen chloride or *p*-toluene sulphonic acid results in the rapid disappearance of the lactone and secondary amide absorptions, and the simultaneous appearance of a new carbonyl band at 1727 cm^{-1}. The tertiary amide absorption now appears as a discrete band at 1665 cm^{-1}. The spectrum of the product supports its formulation as the cyclol (II, $R = R' = H$, $R'' = CH_2CHMe_2$) [1727 (fused γ-lactam) and 1665 cm^{-1} (tertiary amide)]. Confirmation of these assignments comes from the recent preparation of the cyclol (II, $R = R' = H$, $R'' = CH_2CHMe_2$) with identical spectrum (1730 and 1662 cm^{-1} in tetrahydrofuran solution) by SHEMYAKIN et al.[4b] by the alternative route (I→II). The cyclol is also obtained in low yield when lactonization of glycollyl-*L*-leucyl-*L*-proline (IV) is attempted in dilute solution in the presence of acid.

Zusammenfassung. Es wird die Synthese des Laktons (III) von Glykokoll-*L*-leucyl-*L*-prolin (IV) beschrieben. Spektroskopische Untersuchungen zeigen, dass das Lakton (III) eine durch Säure katalysierte transannulare Reaktion unter Bildung des Cyclol-Peptid-Derivats (II) durchläuft.

R. C. SHEPPARD

Robert Robinson Laboratories, University of Liverpool (England), September 26, 1962.

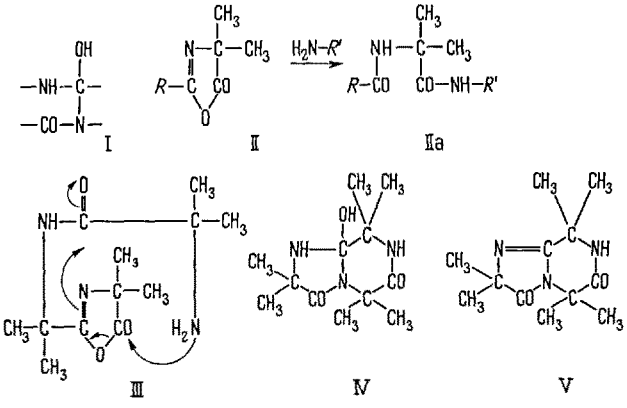
[6] E. W. SPANAGEL and W. H. CAROTHERS, J. Amer. chem. Soc. *58*, 654 (1936).

A Synthetic Cyclol Tripeptide

The cyclol hypothesis, advanced by WRINCH in 1936[1] and later extended[2], employs the idea that some of the amide groups in proteins and peptides are combined in 'ortho-amide' groups, represented in the simplest case (I). The peptide moiety of the ergot alkaloids has a similar structure[3], which in one sense may be regarded as formally derived from an ester and an amide group. This transformation has been actually demonstrated in a model system[4] and a ketonic carbonyl group can likewise form a transannular bond with an amide group[5], but an example of combination of two amide groups has been lacking. We now report[6] the preparation of a compound (IV), which contains structure (I) and might be termed a cyclol-3 in WRINCH's nomenclature.

Continuing our work[7] on the synthesis of α-methyl-alanine peptides from oxazolones (II) by the general reaction (II→IIa), we have prepared oxazolones containing an amino group in the side-chain, *R*, by hydrogenation of their benzyloxycarbonyl derivatives. The 'dipeptide oxazolone' (II: $R = NH_2 . CMe_2$), m.p. 68°, is converted, by heating in boiling toluene and then in the dry state at 160°, into a polymer, similar in molecular weight to that prepared from the N-carboxyanhydride[8], and traces of the diketopiperazine. Initially the reaction was rapid, but prolonged heating was necessary for removal of all the oxazolone residues (absorption at 1820 cm^{-1}). The analogous 'pentapeptide and hexapeptide oxazolones' were quite sluggish in polymerization and cyclic peptides were not detected in the products.

Freshly prepared 'tripeptide oxazolone' (III) had m.p. 82–85°, but after being kept ½ hr. at room temperature it no longer melted completely below 100°. Its solution in ethyl acetate gradually deposited a crystalline solid (79%), which did not melt below 300° but gradually yielded (95%) a sublimate, m.p. 255° (sealed tube). Dehydration with acetic anhydride at room temperature



[1] D. M. WRINCH, Nature *137*, 411 (1936). – D. M. WRINCH and D. JORDAN LLOYD, Nature *138*, 758 (1936). – D. M. WRINCH, Proc. R. Soc., London [A] *160*, 59 (1937).

[2] D. WRINCH, *Chemical Aspects of the Structure of Small Peptides* (Munksgaard, Copenhagen 1960).

[3] A. STOLL, Fortschr. Chem. org. Naturstoffe *9*, 114 (1952).

[4] R. C. SHEPPARD, Exper. *19*, 125 (1963).

[5] L. A. COHEN and B. WITKOP, J. Amer. chem. Soc. *77*, 6595 (1955).

[6] This work was described at the Fifth European Peptide Symposium, Oxford, 6th September 1962.

[7] M. T. LEPLAWY, D. S. JONES, G. W. KENNER, and R. C. SHEPPARD, Tetrahedron *11*, 39 (1960).

[8] We are indebted to Dr. C. H. BAMFORD, Courtaulds Ltd., for measurements of viscosity.

afforded the same compound, to which structure V is assigned on the basis of the molecular formula $C_{12}H_{19}N_3O_2$[9], infra-red spectrum (ν_{max} 1730, 1670, 1640 cm^{-1}, no amide II band) and feeble basicity comparable to that of imidazolones previously described[7]. It follows that the initial product (molecular formula $(C_4H_7NO)_n$, dimorphic ν_{max} (prisms) 1685, 1632, 1585 cm^{-1} or ν_{max} (needles) 1650, 1600 cm^{-1}) from the 'tripeptide oxazolone' must be the cyclol (IV). Inspection of molecular models shows that the concerted electronic shifts shown in (III) are stereochemically feasible. In contrast, the amino group in the 'dipeptide oxazolone' cannot reach the reactive carbonyl group in an intramolecular reaction without distortion of bond angles, and this difference accounts for the greater stability of this compound and its polymerization in preference to cyclization.

Just as structure (I) is formally derived from two amide groups, it may decompose to them. However, the cyclol (IV) is prevented from protropic change into the isomeric cyclic tripeptide by the methyl groups. (The centre of a cyclic tripeptide is too congested to contain anything but three hydrogen atoms[10]). Whether this factor is important in stabilising the structure remains to be seen. Its significance in relation to the stability of the ergot alkaloids has been made clear by EDWARD[11].

Further studies of oxazolones with regard to formation of both cyclols and polymers are in progress.

Zusammenfassung. Das dem α-Methylalanyl-α-methylalanyl-α-methylalanin entsprechende Oxazolon (III) isomerisiert leicht zum kristallisierten Cyclol (IV), dessen Struktur sich aus dem Übergang in das Imidazolon (V) unter Wasserabspaltung ergibt.

D. S. JONES, G. W. KENNER, and R. C. SHEPPARD

Robert Robinson Laboratories, University of Liverpool (England), September 26, 1962.

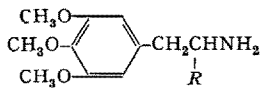
[9] Dr. R. I. REED, Glasgow, kindly determined mol. wt. 237 by mass spectrometry.

[10] G. W. KENNER and J. M. TURNER, Chem. Ind. 602 (1955). – G. W. KENNER, J. chem. Soc. *1956*, 3692.

[11] J. T. EDWARD, Research *8*, S38 (1955).

Psychotomimetic Agents Related to Mescaline

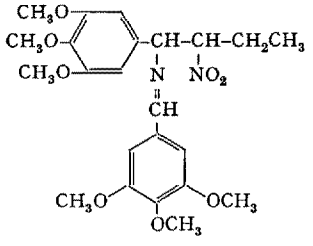
The widely studied pharmacology of mescaline (I; $R = H$)



I

and the recent descriptions of the psychotomimetic effects of *dl*-trimethoxyamphetamine[1,2] (I; $R = CH_3$) have prompted the synthesis of higher homologs (I; $R = C_2H_5$ through C_7H_{15}). All of the amines were prepared by the $LiAlH_4$ reduction[3] of the corresponding nitrostyrenes, which were in turn prepared (with the exception of the nitropropane isomer mentioned below) by the ammonia-catalyzed condensation of the appropriate nitroalkane with 3,4,5-trimethoxybenzaldehyde, in acetic acid.

With nitropropane in acetic acid, the sold product was identified as 3,4,5-trimethoxybenzonitrile[4], and substitution of isopropyl alcohol for the acidic solvent led to the unexpected formation of the Schiff base II,



II

m.p. 151.5–152 from methanol, the structure of which was established by analysis (C = 59.68, H = 6.68, N = 5.84, MW in $CHCl_3$ = 460; $C_{23}H_{30}N_2O_8$ requires C = 59.73, H = 6.54, N = 6.08, MW = 462) and its facile acid hydrolysis to trimethoxybenzaldehyde and, after neutralization, 1-(3,4,5-trimethoxylphenyl)-2-nitrobutylamine. Replacement of the ammonia catalyst with a secondary amine precluded the formation of II, and led to a proper nitrostyrene. The properties and yields of the substances studied appear in the Table.

R	Nitrostyrenes[a] mp °C	yield	Phenethylamines mp °C picrate	mp °C base-HCl	yield
-H	120 -121[b]	64%	214-216	180-181	86%[c]
$-CH_3$	93 - 94[d]	50%	171-173	208-209[e]	62%
$-CH_2CH_3$	72 - 73	29%	177-181	192-193	52%
$-(CH_2)_2CH_3$	82.5- 83.5	32%	182-184	214-218	65%
$-(CH_2)_3CH_3$	73 - 74	34%	168-170	182-184	45%
$-(CH_2)_4CH_3$	54 - 55	24%	162-163	155-158	50%
$-(CH_2)_5CH_3$	51 - 52	21%	149-151	132-134	53%
$-(CH_2)_6CH_3$	43 - 44	19%	148-149	112-116	19%
$-(CH_2)_8CH_3$	46 - 47	16%	—	—	0%

[a] All listed compounds were yellow crystalline solids, recrystallized from methanol.

[b] Literature values are reported from 118 to 121°C. It was found that if the molten material was held at this temperature for a short period, resolidification occurred yielding a new crystal form with a melting point 128–129°C.

[c] Literature value included for comparison, see [3].

[d] Literature value 95°C, see P. HEY, Quart. J. Pharm. Pharmacol. *20*, 129 (1947).

[e] Literature value 219–220°C, see above reference.

[1] D. I. PERETZ, J. R. SMYTHIES, and W. C. GIBSON, J. Mental Sci. *101*, 317 (1955).

[2] A. T. SHULGIN, S. BUNNELL, and T. SARGENT III, Nature *189*, 1011 (1961).

[3] F. A. RAMIREZ and A. BURGER, J. Amer. chem. Soc. *72*, 2781 (1950).

[4] H. M. BLATTER, H. LUKASZEWSKI, and G. DESTEVENS, J. Amer. chem. Soc. *83*, 2203 (1961).