stigmast-5-ene[13]. Conversion of, e.g., 22α to 22*S* may be visualized in the following manner. In a Fischer projection, the 22α-hydroxy group would be represented by structure III, in a tetrahedral representation by IV, and V would represent an easy model for assigning *R* or *S*. Transforming the Fischer projection by an even number of exchanges of groups provides a mnemonic[10] for easily drawing V. Inspection of structure V readily indicates that the atomic numbers of substituents attached to the asymmetric 22-carbon are decreasing counterclockwise. A choice between the two carbon-containing substituents is made on the basis of one less carbon bonded to C_{23} than to C_{20}[10]. Therefore, C_{20} acquires the higher priority and the absolute configuration at C_{22} is *S*.

Turning now to the steroidal sapogenin side-chain, the need for a more uniform and reliable system of defining absolute configuration is immediately evident, particularly in ring *F*. Substituents at positions C_{23-26}, or at asymmetric centers removed from the ring system, should be designated using *R* or *S*. Application of the *R* and *S* notation to C_{25} has already been suggested[14]. Further, adoption of *R* and *S* at C_{25} of the steroidal sapogenin side-chain would allow retaining the original IUPAC numbering system[15] for ring *F*. Use of the FIESER-PLATTNER convention would necessitate reassigning number 27, now more logically reserved for the terminal carbon, to the C_{26} ring *F* carbon[8,16]. This change would be required before the sapogenin side-chain could be numbered consistent with a Fischer projection. Although position 22 may be defined employing recent modifications[14] of current IUPAC spirostane nomenclature[15], ambiguous cases should be handled employing the *R* and *S* method. Since a substituent at C_{20} may be described using α or β, that is, below or above the general plane of rings A through E, there is no pressing requirement for *R* or *S* at this position. Partial structure VI (20β, 22*R*, 24*S*, 25*R*) illustrates these recommendations.

Extension of the *R* and *S* system to appropriate areas of steroidal alkaloid nomenclature is also recommended. A useful illustration of the *R* and *S* notation in this field was recently described by SCHREIBER[17,18].

In summary, it is proposed that the *R* and *S* system be adopted for defining absolute configuration in all non-rigid steroid side-chains.

Zusammenfassung. Ein Überblick über die angewandten Methoden zur Bestimmung der absoluten Konfiguration in Steroidseitenketten wurde gegeben. Die allgemeine Anwendung der *R*- und *S*-Regel wurde empfohlen.

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Department of Chemistry, University of Maine, Orono (Maine, U.S.A.), November 1, 1962.

[13] Since the 24-ethyl group of stigmasterol has been assigned an α*F*-configuration by K. TSUDA, R. HAYATSU, and Y. KISHIDA, J. Amer. chem. Soc. *82*, 3396 (1960), the absolute configuration of stigmastane III at C_{24} may also be α*F*. Thus, for illustrative purposes, this position has been designated *R*.

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[15] International Union of Pure and Applied Chemistry Definitive Rules for the Nomenclature of Amino Acids, Steroids, Vitamins and Carotenoids, J. Amer. chem. Soc. *82*, 5575 (1960).

[16] L. F. FIESER and M. FIESER, *Steroids* (Reinhold Publishing Corp., New York 1959), p. 819.

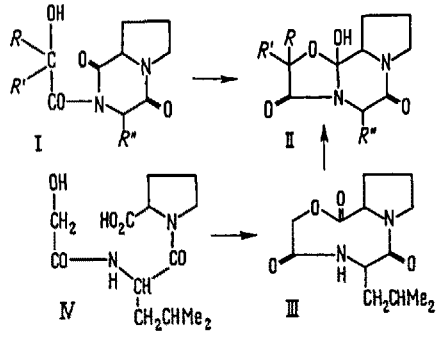
[17] K. SCHREIBER and G. ADAM, Exper. *17*, 490 (1961).

[18] During preparation of this manuscript several other applications of the *R* and *S* system to steroid side-chains were described. For example see: H. WEHRLI, M. CEREGHETTI, K. SCHAFFNER, J. URECH, and E. VISCHER, Helv. chim. Acta *44*, 1927 (1961). – G. R. PETTIT and D. M. PIATAK, J. org. Chem. *27*, 2127 (1962). – G. R. PETTIT and J. C. KNIGHT, J. org. Chem. *27*, 2696 (1962).

Transannular Reaction Between Ester and Amide Groups. Formation of a Cyclol Peptide Derivative

The researches of STOLL and his collaborators[1] have shown that the ergot alkaloids, e.g. Ergotamine (II, R = lysergylamino, R' = CH_3, R'' = $CH_2C_6H_5$) contain an unusual cyclol peptide[2] system. In principle, this ring system may be derived either by the intramolecular addition of an hydroxyl group to an amide carbonyl (I→II), or by transannular addition of amide nitrogen to ester carbonyl (III→IV). HOFMANN, FREY, and OTT[3] have used the former route successfully in their total synthesis of Ergotamine, and the reaction has since been studied in detail by SHEMYAKIN et al.[4]. This interest in the formation of cyclol peptides prompts us to report the following experiments which were made in Cambridge in 1957, and which show that the cyclol system is also attainable by transannular reaction of the macrocyclic lactone (III→II, R = R' = H, R'' = CH_2CHMe_2).

Benzyloxyacetyl-*L*-leucine, m.p. 91.5–93°, $[\alpha]_D$–13.14° (c = 1.8 in ethanol) (Found: C, 64.6; H, 7.6; N, 5.1: $C_{15}H_{21}NO_4$ requires C, 64.5; H, 7.55; N, 5.0%), prepared from benzyloxyacetyl chloride and *L*-leucine in aqueous sodium hydroxide, was condensed with *L*-proline by the sulphuric anhydride method[5]. The resulting benzyloxyacetyl-*L*-leucyl-*L*-proline, m.p. 131–133°, $[\alpha]_D$–65° (c = 3.8 in EtOH) (Found: C, 63.8; H, 7.7; N, 7.55: $C_{20}H_{28}N_2O_5$ requires C, 63.9; H, 7.45; N, 7.45%) was reduced with sodium in liquid ammonia to yield the glycollyl-dipeptide



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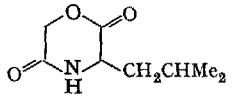
(IV), m.p. 92–97° (Found: C, 54.3; H, 7.5; N, 9.6: $C_{13}H_{22}N_2O_5$ requires C, 54.5; H, 7.75; N, 9.8%). Cyclization of (IV) to the nine-membered lactone (III) was most easily achieved by the thermal depolymerization method[6]. When the hydroxy-acid (IV) was heated at 150°/10^{-5} m.m., the monomeric 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.

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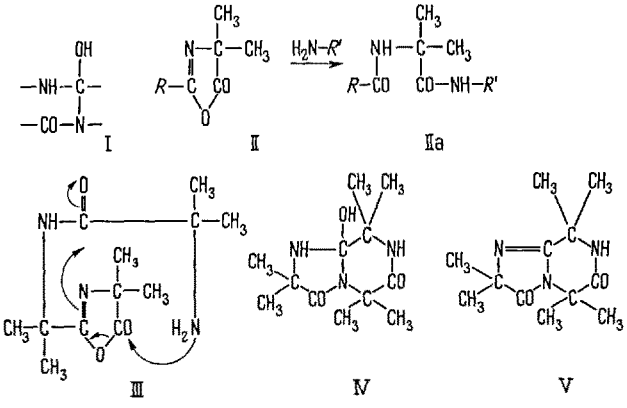
A Synthetic Cyclol Tripeptide

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



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[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.