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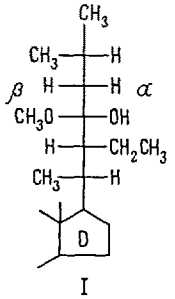
Steroid Stereochemistry[1,2]

The problems associated with designating relative and/or absolute configuration in steroid side-chains have been recognized for a number of years. In 1948, FIESER and FIESER[3] suggested that the 20-hydroxy pregnanes could be designated α or β, depending on whether the hydroxy substituent was oriented (with the 21-methyl group to the rear) to the right or left respectively. This notation was extended by PLATTNER[4] in an appendix to the 1950 steroid nomenclature rules[5] (formulated at the Ciba Foundation Conference in London) and subsequently by the FIESERS[6] to include the whole sterol side-chain. After extending the side-chain in a Fischer-type[7] projection, substituents falling to the right or left could be assigned an α- or β-configuration (e.g. I). More recently, at the suggestion of FRIED[8], the α- or β-designation was changed to α_F and β_F. The letter $_F$ now clearly distinguishes between absolute configuration based on a Fischer-type projection of the side-chain and the usual concept of α and β in the steroid nucleus.

During the period that the α- and β-notation was being developed for the steroid side-chain, the need for a more systematic method of defining absolute configuration in all branches of organic chemistry became more urgent. This situation prompted CAHN and INGOLD[9] to propose a 'sequence rule' for the specification of asymmetry based on decreasing atomic numbers of substituents attached to an asymmetric atom. Their original proposal was refined in 1956 to include, in a general manner, all types of optical isomerism encountered in organic chemistry[10]. In summary, the asymmetric atom is visualized as part of a perspective formula[11] (cf. II) in which the substituent of lowest atomic number (d) is placed away from the viewer and the other three components are projecting toward the viewer. Inspection is then made of the latter three substituents as to whether the atomic numbers decrease clockwise or counterclockwise. A right-handed pattern is designated *R* and a left-handed pattern *S*. The *R* and *S* symbols are taken respectively from the Latin words *rectus* meaning right and *sinister* referring to left. Therefore, the absolute configuration, if known in terms of a three-dimensional model, is readily converted to an *R* or *S* notation. Conversely, *R* or *S* may easily be converted to a three-dimensional model. The sequence rule may be likened to our presently accepted concept of optical isomerism based on tetrahedral carbon; that is, elegant in its simplicity.

Consequently, it now appears that the CAHN, INGOLD, PRELOG system should be used to define steroid side-chain stereochemistry with the possible exception of substitution at C_{20} where the α- and β-notation has been used frequently in the past. The *R* and *S* system presents the obvious advantages of a method which is suitable for defining absolute configuration in all branches of organic chemistry and is not subject to errors in interpretation which would most certainly be encountered in complex steroid side-chains using the α_F- and β_F-designation.

Brief application of the *R* and *S* system to several areas of steroid chemistry will, in a preliminary manner, serve to illustrate its utility. For example, the sterol isolated from *Aesculus hippocastanum* and assigned a 3α,7α,22α-trihydroxy-Δ^5-stigmastane (III)[12] structure might now be systematically named 3α,7α,22*S*-trihydroxy-24*R*-



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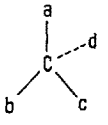

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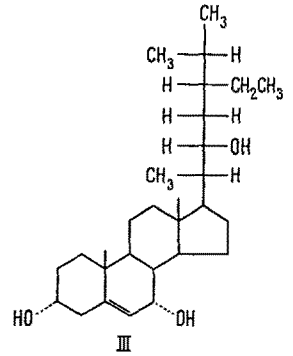

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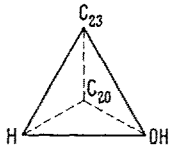

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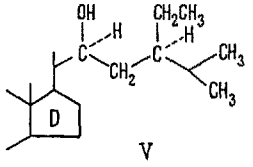

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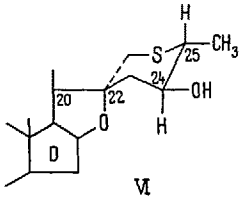


VI

[1] In part, a summary of recommendations presented by the author to a National Academy of Sciences and National Research Council *ad hoc* Committee on Steroid Nomenclature (R. C. ELDERFIELD, Chairman); October 13–15, 1961, Columbus (Ohio). The meeting of the *ad hoc* committee was made possible by a grant from the U.S. Air Force Office of Scientific Research.

[2] Part XV of a series entitled *Steroid and Related Natural Products*. Refer to G. R. PETTIT and P. HOFER, Exper. *19*, 67 (1963), for the preceding contribution.

[3] L. F. FIESER and M. FIESER, Exper. *4*, 285 (1948).

[4] PL. A. PLATTNER, Helv. chim. Acta *34*, 1693 (1951).

[5] Ciba Foundation Conference, London, Helv. chim. Acta *34*, 1680 (1951).

[6] L. F. FIESER and M. FIESER, *Steroids* (Reinhold Publishing Corp., New York 1959), p. 337.

[7] G. P. MUELLER and J. JIU, J. org. Chem. *26*, 1611 (1961).

[8] L. F. FIESER, Tetrahedron *8*, 360 (1960).

[9] R. S. CAHN and C. K. INGOLD, J. chem. Soc. *1951*, 612.

[10] R. S. CAHN, C. K. INGOLD, and V. PRELOG, Exper. *12*, 81 (1956).

[11] W. G. DAUBEN and K. Z. PITZER, *Steric Effects in Organic Chemistry* (M. S. Newman, Ed., J. Wiley and Sons, Inc., New York 1956), p. 5.

[12] F. G. FISCHER and H. MAGERLEIN, Liebigs Ann. *636*, 88 (1960).

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.

G. R. PETTIT

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*.

[14] G. P. MUELLER and G. R. PETTIT, Exper. *18*, 404 (1962).

[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.

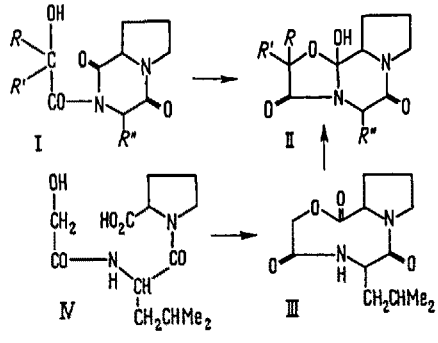
[17] K. SCHREIBER and G. ADAM, Exper. *17*, 490 (1961).

[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



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

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

[3] A. HOFMANN, A. J. FREY, and H. OTT, Exper. *17*, 206 (1961).

[4] (a) M. M. SHEMYAKIN, V. K. ANTONOV, A. M. SHKROB, YU. N. SHEINKER, and L. B. SENYAVINA, Tetrahedron Letters No. 16, 701 (1962). – (b) V. K. ANTONOV, A. M. SHKROB, and M. M. SHEMYAKIN, Vth European Peptide Symposium (Oxford 1962).

[5] D. W. CLAYTON, J. A. FARRINGTON, G. W. KENNER, and J. M. TURNER, J. chem. Soc. *1957*, 1398.