servations of Reichard,[9] and together with these, delineate the probable pathway of orotic acid synthesis in the rat: citrulline + aspartate → (arginosuccinate) → ureidosuccinate → (dihydroorotate) → orotic acid.

Neither in rat nor in pigeon liver slices (Table I) could any contribution to orotic acid from the amidine carbon of arginine be detected. The postulated intermediate arginosuccinate would therefore appear not to arise from arginine in the preparations studied.

(9) P. Reichard and U. Lagerkvist, *Acta Chem. Scand.*, **7**, 1207 (1953).

DIVISION OF NUTRITION AND PHYSIOLOGY
THE PUBLIC HEALTH RESEARCH INSTITUTE L. H. SMITH, JR.
OF THE CITY OF NEW YORK, INC. DEWITT STETTEN, JR.
NEW YORK, N. Y.

RECEIVED JUNE 15, 1954

THE STEREOCHEMISTRY OF STEROIDAL SAPOGENINS

Sir:

Despite the voluminous literature[1] dealing with the structure and chemistry of the steroidal sapogenins, the stereochemistry of the spiroketal side chain of these substances remains obscure. In light of recent discoveries this appears to have been due in large part to the failure to appreciate the importance of the asymmetry at *both* the C-22 and C-25 positions. The fact that certain of these substances can be converted[2] by rather vigorous acid treatment into isomeric substances, together with other lines of evidence,[3] has led to the assumption[3] that such naturally occurring stereoisomeric pairs of steroidal sapogenins as sarsasapogenin and smilagenin are epimeric at C-22. Recent studies[4,5] of infrared absorption have shown that the spectra of all naturally occurring steroidal sapogenins thus far examined possess bands in the vicinity of 980, 920, 900 and 860 cm.$^{-1}$, which are characteristic of the spiroketal side chain. The relative intensities of the 920 and 900 cm.$^{-1}$ bands have been correlated with the so-called "normal" and "iso" series, which were assumed to be epimeric at C-22. However, recent work[6] involving careful repetition of some earlier transformations together with degradation studies has demonstrated that sarsasapogenin and smilagenin are epimeric at C-25 and does not exclude the possibility that these substances actually have the same configuration at C-22. By means of similar degradation of diosgenin and hecogenin and by correlation of side chain degradation products with the absolute configuration of D-glyceraldehyde, James[7] has shown that diosgenin, hecogenin and smilagenin all have the D-configuration at C-25 while sarsasapogenin has the L-configuration. The configuration at C-22 (spiroketal) together with previous correlations[4,5] of infrared absorption with side-chain structure therefore comes into question.

We have converted pseudodiosgenin[8] [m.p. 165–168°, $[\alpha]^{25}D$ −39° (1% in chf.); found: C, 78.26; H, 9.91; medium band in infrared[9] at 1693 cm.$^{-1}$ (1% in chf.)] into neodiosgenin[2b] [m.p. 197–201°, $[\alpha]_D$ −122° (1% in chf.); found: C, 77.77; H, 9.84; shoulder in infrared at 982 cm.$^{-1}$, strong bands at 960, 920, 896 cm.$^{-1}$, weak bands at 856 and 973 cm.$^{-1}$ (1% in CS_2), 896 cm.$^{-1}$ band more intense than 920 cm.$^{-1}$ band. Mixture melting point with diosgenin (m.p. 208–211°), m.p. 191–192.5°] by very mild treatment with acid. Upon more vigorous acid treatment, neodiosgenin yielded diosgenin[4] [m.p. 206–211°, no depression mixed with an authentic specimen, strong bands in infrared at 982, 963, 921 and 900 cm.$^{-1}$, weak band at 860 cm.$^{-1}$; 982 cm.$^{-1}$ band more intense than 963 cm.$^{-1}$ band, 900 cm.$^{-1}$ band more intense than 921 cm.$^{-1}$ band].

Consideration of the probable mechanism of conversion of pseudodiosgenin to neodiosgenin and this to diosgenin leads to the assignment of structure II to neodiosgenin and structure III to diosgenin. These acid-catalyzed reactions are conceived to be polar in nature, with *trans* addition occurring across the C-20,C-22 double bond.[10] In the initial cyclization of pseudodiosgenin to neodiosgenin, it would appear that attack of a solvated proton at C-20 from the less hindered rear face of the molecule is kinetically favored and leads to structure II. However, on prolonged treatment with acid a process of equilibration leads to the thermodynamically more stable structure III; the driving force for the conversion of neodiosgenin (II) to diosgenin (III) is furnished by hindrance between the C-18 methyl groups and C-21 and possibly by the less stable axial conformation[11,12] of the C-27 methyl group in structure II. The initial formation of the kinetically favored but thermodynamically less stable neodiosgenin (II) and its subsequent double inversion at C-20 and C-22 to the more stable diosgenin (III) is analogous to the formation of cholesterol 5α,6β-dibromide and its isomerization to the more stable 5β,6α-dibromide.[13]

It will be noted that the relative intensities of the infrared bands near 900 cm.$^{-1}$ and 920 cm.$^{-1}$ are of

(1) See L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publ. Corp., New York, N. Y., 1949, Chapt. VIII.

(2) See, for example: (a) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 846 (1939); (b) R. E. Marker and J. Lopez, *ibid.*, **69**, 2373 (1947).

(3) See ref. 1, pp. 587, 589.

(4) C. R. Eddy, M. E. Wall and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

(5) R. N. Jones, E. Katzenellenbogen and K. Dobriner, *ibid.*, **75**, 158 (1953).

(6) I. Scheer, R. B Kostic and E. Mosettig, *ibid.*, **75**, 4871 (1953).

(7) V. H. T. James, *Chemistry and Industry*, 1388 (1953).

(8) (a) R. E. Marker, T. Tsukamoto and D. L. Turner, THIS JOURNAL, **62**, 2525 (1940). (b) D. H. Gould, H. Staeudle and E. B. Hershberg, *ibid.*, **74**, 3685 (1952).

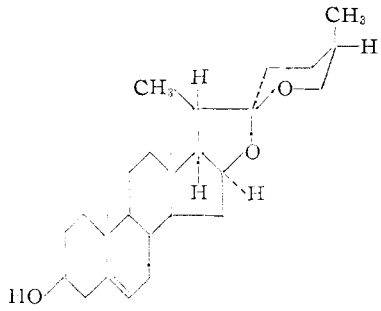
(9) A. L. Hayden, P. B. Smelzer and I. Scheer, *Anal. Chem.*, **26**, 550 (1954).

(10) The C-20,C-22 double bond of pseudodiosgenin requires the *cis* fusion of rings D and E on steric grounds, presumably in the β-configuration.

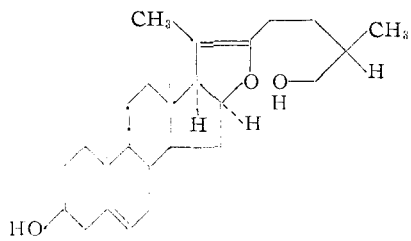
(11) The axial conformation of the C-27 methyl group coincides with hindrance between the C-18 and C-21 methyl groups *only* if the absolute configuration of the steroid nucleus is as drawn; cases II and III would then represent absolute configurations of neodiosgenin and diosgenin, respectively. If the absolute configuration of the steroid nucleus is actually the mirror image of its usual representation, neodiosgenin (II) would differ from the above structure in possessing an equatorial methyl group at C-25, and diosgenin (III) would then have the axial methyl group at C-25.

(12) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

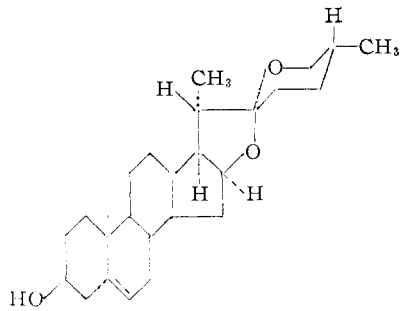
(13) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).



Neodiosgenin, II



Pseudodiosgenin, I



Diosgenin, III

the same order in both diosgenin and neodiosgenin. Since these substances are epimeric at C-22, consequent to the above considerations, then previous correlations[4,5] of the relative intensities of these bands with configuration at C-22 do not hold for all cases. To assume retention of configuration at C-22 in passing from II to III requires the further unlikely assumption either that (1) inversion has occurred at C-20 without breaking the C–O bond at C-22, or (2) *cis* addition has taken place after the initial formation of II through *trans* addition.

We intend to extend this work and to present the results in detail, together with an expanded discussion of the above considerations, in a subsequent publication. Based upon information now at hand, consistent application throughout the steroidal sapogenins of the criteria of stability toward acid and infrared absorption spectra should contribute to a clarification of the many inconsistencies and ambiguities in the literature of the side-chain stereochemistry of these substances.

RESEARCH DEPARTMENT
CIBA PHARMACEUTICAL PRODUCTS, INC.
SUMMIT, NEW JERSEY
J. B. ZIEGLER
W. E. ROSEN
A. C. SHABICA

RECEIVED APRIL 22, 1954

BOOK REVIEWS

The Alkaloids—Chemistry and Physiology, Volume III. By R. H. F. MANSKE, Dominion Rubber Research Laboratory, Guelph, Ontario, and H. L. HOLMES, The Carwin Company, North Haven, Connecticut (Editors). Academic Press, Inc., 125 East 23rd Street, New York 10, N. Y. 1953. viii + 422 pp. 16 × 23.5 cm. Price, $11.00.

The third volume of the Manske and Holmes treatise on The Alkaloids has now appeared and continues to meet the same high standards set by the earlier volumes. Again the editors have succeeded in assembling a group of reviews by especially well-qualified authors. Chapters on the cinchona alkaloids (Richard B. Turner and R. B. Woodward), quinoline alkaloids other than those of cinchona (H. T. Openshaw), quinazoline alkaloids (Openshaw), lupin alkaloids (Nelson J. Leonard), imidazole alkaloids (A. R. Battersby and H. T. Openshaw), solanum and veratrum alkaloids (V. Prelog and O. Jeger), β-phenylethylamines (L. Reti), ephedra bases (Reti) and the ipecac alkaloids (Maurice-Marie Janot) are included. The volume is highly recommended.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK
MARSHALL GATES

Elementary Introduction to Molecular Spectra. By BORGE BAK, Chemical Laboratory of the University of Copenhagen. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1954. x + 125 pp. 14.5 × 21.5 cm. Price, $2.90.

The author has compressed the most important topics and equations of modern molecular spectroscopy into one small volume of only 125 pages! He deals with the practical or experimental side of the subject and he treats the modern theory of molecular spectra as based on wave mechanics. He discusses the microwave, infrared and visible-ultraviolet regions of the spectrum. For this tremendous field he gives only 20 references to the literature. The small index contains only 125 citations. The book is written for biologists, chemists and chemical engineers. They are expected to learn enough about modern spectroscopy from both the theoretical viewpoint and to some extent from the experimental angle, so as to enable them to use modern spectroscopic investigations as a tool in the solution of their own problems. When the complexity of modern quantum theory of molecular structure and spectra is considered, it seems difficult to believe that scientists from other fields can obtain much benefit from a study of this book. The derivations are too brief to be useful as a means of teaching a neophite this complex subject matter.

On the other hand, the compact nature of this volume may well interest the expert who might use it as a quick reference book. There are a number of awkward phrases which, however, do not detract from the intended meaning. There are very few misprints. The physical appearance and the printing of the mathematical formulas are excellent.

OFFICE OF ORDNANCE RESEARCH
BOX CM, DUKE STATION
DURHAM, NORTH CAROLINA
GEORGE GLOCKLER

Radioactive Isotopes: An Introduction to their Preparation, Measurement and Use. By W. J. WHITEHOUSE and J. L. PUTMAN. Oxford University Press, 114 Fifth Avenue, New York 11, N. Y. 1953. xvi + 424 pp. 17 × 24 cm. Price, $10.00.

This book is directed primarily to those who are making practical use of radioactive isotopes. In the words of the authors, "It is intended primarily for the use of scientific