is not incompatible with C_{22} isomerism of these sapogenins.

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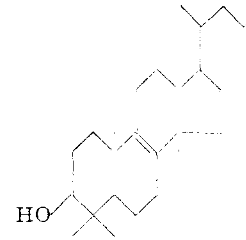
RECEIVED MARCH 13, 1954

THE SYNTHESIS OF LANOSTENOL

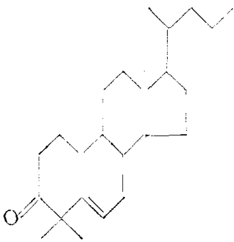
Sir:

We wish to record the conversion of cholesterol into the naturally occurring tetracyclic triterpene lanostenol (dihydrolanosterol)(I). These results constitute the first total synthesis[1] of a tetracyclic triterpene, and provide rigorous confirmation in detail of the remarkable structural and stereochemical relationships, between the lanostane group and the steroids, which have been brought to light in recent years through degradative,[2] deductive,[3] biochemical,[4] and physical[5] studies.

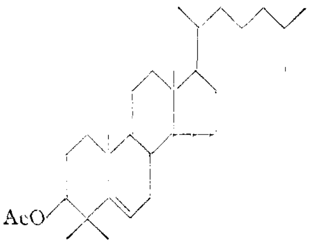


I

Direct methylation of either Δ^4- or Δ^5-cholestenone-3[6] in dry *tert*-butanol with potassium *tert*-butoxide (3 moles) and methyl iodide (6 moles) gave 4,4-dimethyl-Δ^5-cholestenone-3 (II) (63%), m.p. 176–177°, $[\alpha]_D$ +1 (c 2.07)[7] (*Anal.* Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.14; H, 11.91), which was reduced by lithium aluminum hydride to 4,4-dimethylcholesterol (75%), m.p. 150–151°, $[\alpha]_D$ − 64° (c 1.16) (*Anal.* Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.54; H, 11.98), and converted to the corresponding *acetate* (III), m.p. 136–137°, $[\alpha]_D$ −48° (c 2.15) (*Anal.* Calcd. for $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found: C, 81.21; H, 11.34). Treatment of (III) in carbon tetrachloride with N-bromosuccinimide, followed by collidine, gave 3β-acetoxy-4,4-dimethyl-$\Delta^{5,7}$-cholestadiene (IV) (56–58%), m.p. 151–152° (vac.),[8] $[\alpha]_D$ −107° (c 1.27), $\lambda\lambda_{max.}$ 273 mμ (ϵ 11,200), 282 mμ (ϵ 11,000)[9] (*Anal.* Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.86; H, 11.00), which was converted by hydrogen chloride in chloroform (−40°), followed by anhydrous ammonia in methanol (−60°), to 3β-acetoxy-4,4-dimethyl-$\Delta^{7,14}$-cholestadiene (V), m.p. 123–125° (vac.), $[\alpha]_D$ −140° (c 1.24), $\lambda_{max.}$ 244 mμ (ϵ 11,000) (*Anal.* Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.88; H, 11.05). Oxidation of (V) by perphthalic acid in ether, followed by hydrolysis with ethanolic potash, gave a *triol* (75%), very probably (VI),[10] m.p. 240–241° (vac.) (*Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28), which with hydrogen chloride in ethanol furnished 3β-hydroxy-4,4-dimethyl-15-keto-$\Delta^{8(14)}$-cholestene (VII) (30%), m.p. 161–162° (vac.), $[\alpha]_D$ +135° (c 1.44), $\lambda_{max.}$ 261 mμ (ϵ 14,700), IR (C═O, C═C) 5.89 μ, 6.15 μ (*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 80.99, H, 11.08). The *benzoate* of (VII), m.p. 154–155° (vac.), $[\alpha]_D$ +137° (c 1.56), $\lambda\lambda_{max.}$ 232 mμ (ϵ 17,000), 260 mμ (ϵ 16,600), IR (OC═O + C═O, C═C) 5.84 + 5.88 μ, 6.15 μ (*Anal.* Calcd. for $C_{36}H_{52}O_3$: C, 81.15; H, 9.84. Found: C, 80.85; H, 9.92) on direct methylation in dry *tert*-butanol with potassium *tert*-butoxide (56 moles) and methyl iodide (112 moles) gave 3β-benzoyloxy-4,4,14-trimethyl-15-keto-Δ^7-cholestene (IX) (67%), m.p. 212–213° (vac.), $[\alpha]_D$ +84° (c 1.42), $\lambda\lambda_{max.}$ 229 mμ (ϵ 15,200), 273 mμ (ϵ 1020), 281 mμ (ϵ 800), IR



II



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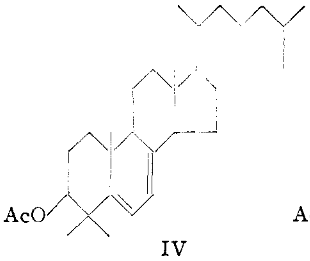

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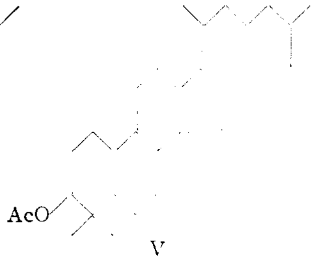

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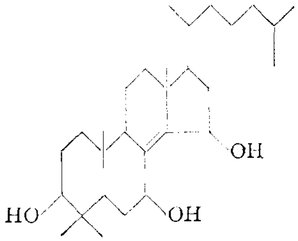

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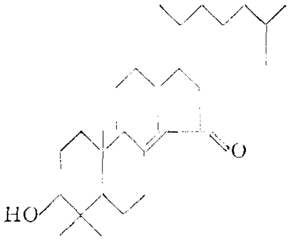

VII

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[1] For total synthesis of cholesterol, see R. B. Woodward, F. Sondheimer and D. Taub, THIS JOURNAL, **73**, 3548 (1951); R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952); H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).

[2] W. Voser, M. V. Mijovic, H. Heusser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **35**, 2414 (1952), and many earlier papers; C. S. Barnes, D. H. R. Barton, A. R. H. Cole, J. S. Fawcett, and B. R. Thomas, *J. Chem. Soc.*, 571 (1953), and earlier papers.

[3] W. Klyne, *J. Chem. Soc.*, 2916 (1952); C. S. Barnes, D. H. R. Barton, J. S. Fawcett and B. R. Thomas, *ibid.*, 576 (1953).

[4] E. Kyburz, B. Riniker, H. R. Schenk, H. Heusser and O. Jeger, *Helv. Chim. Acta*, **36**, 1891 (1953); R. B. Woodward and K. Bloch, THIS JOURNAL, **75**, 2023 (1953).

[5] R. G. Curtis, J. Fridrichsons and A. McL. Mathieson, *Nature*, **170**, 321 (1952); J. Fridrichsons and A. McL. Mathieson, *J. Chem. Soc.*, 2159 (1953).

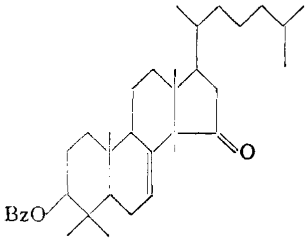
[6] For a rapid and convenient preparation of these ketones from cholesterol, see L. F. Fieser, THIS JOURNAL, **75**, 5421 (1953).

[7] All rotations were measured in chloroform.

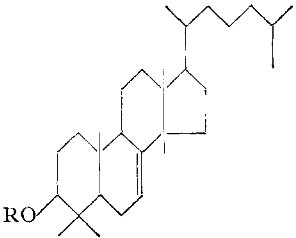
[8] Taken in a capillary sealed off at a pressure of 3 mm.

[9] All ultraviolet spectra were measured in 95% ethanol.

[10] *Cf.* C. S. Barnes, D. H. R. Barton and G. F. Laws, *Chemistry and Industry*, 616 (1953); D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954).



IX



X

(C=O, OC=O) 5.77 μ, 5.83 μ (*Anal.* Calcd. for $C_{37}H_{54}O_3$: C, 81.27; H, 9.95. Found: C, 80.94; H, 9.80), which was converted by Wolff–Kishner reduction under special conditions to Δ^7-lanostenol (β-lanostenol) (X, R = H) (70%), m.p. 162–163° (vac.) (reported,[11] 162°), $[\alpha]_D$ +10° (*c* 1.45) (*Anal.* Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.88; H, 12.15). The *acetate* prepared from synthetic Δ^7-lanostenol had m.p. 146–147°, raised after many recrystallizations to 148–149°, $[\alpha]_D$ +27° (*c* 1.27) (*Anal.* Calcd. for $C_{32}H_{54}O_2$: C, 81.64; H, 11.56. Found: C, 81.44; H, 11.72), and its identity with an authentic sample (m.p. 145–148°, $[\alpha]_D$ +28°) was established through the mixture m.p. 146–148°, and the identity of the infrared spectra of the two samples. When the *benzoate* of Δ^7-lanostenol, m.p. 207–208°, $[\alpha]_D$ +51° (*c* 1.09) (*Anal.* Calcd. for $C_{37}H_{56}O_2$: C, 83.40; H, 10.49. Found: C, 83.29; H, 10.49), was treated with hydrogen chloride in chloroform, a mixture was produced from which Δ^8-lanostenyl benzoate (23%), m.p. 193–195°, $[\alpha]_D$ +71° (*c* 1.80) [authentic sample, m.p. 194–195°, $[\alpha]_D$ +71°; m.m.p. 193–195°], could be isolated by careful chromatography. Hydrolysis of the benzoate gave lanostenol (dihydrolanosterol) (I), m.p. 139–141°, $[\alpha]_D$ +59° (*c* 1.37) [authentic sample, m.p. 193–140°; $[\alpha]_D$ +59°; m.m.p. 139–141°], further characterized as the *acetate*, m.p. 118–120°, $[\alpha]_D$ +60° (*c* 1.54) [authentic sample, m.p. 119–120°, $[\alpha]_D$ +60°; m.m.p. 118–120°].

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RECEIVED APRIL 15, 1954

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[11] Marker, Wittle and Mixon, THIS JOURNAL, 59, 1368 (1937).

BOOK REVIEWS

Physical Constants of Hydrocarbons. Vol. V. Paraffins, Olefins, Acetylenes and other Aliphatic Hydrocarbons (Revised Values). A.C.S. Monograph No. 78. By GUSTAV EGLOFF, Director of Research, Universal Oil Products Co., Chicago, Illinois. Reinhold Publishing Corporation, 330 West 42nd Street, New York 36, N. Y. 1953. ix + 524 pp. 16.5 × 23.5 cm. Price $20.00.

Volume V of "Physical Constants of Hydrocarbons" is supplementary to Volume I, bringing the literature of the paraffins, olefins and acetylenes from 1939 to approximately mid-year 1951. Melting points, boiling points, densities and refractive indices for some 950 hydrocarbons are listed. Of this number approximately 45% appear for the first time. Critical constants, including temperature, pressure and density are given where the data are available—chiefly for the lower members of the series. Hydrocarbons appearing in both volumes I and V are cross-referred by volume number and page and the corrections to previous listings are made in their proper place. The paraffins cover the range from methane to heptacontane (C_1 to C_{70}), the olefins from ethylene to methyltritetracontene (C_2 to C_{44}), and the acetylenes from ethyne to hexatricontyne (C_2 to C_{36}).

The question arises what is one to do with the multiplicity of values obtained, in the manner, for each physical constant of a hydrocarbon? Using *n*-octane as an example there are listed 16 melting points varying from −56 to −56.61°, 36 boiling points (760 mm.), 30 densities (d^{20}_4) and 29 refractive indices ($n^{20}D$), each spread over a similar range. The author recognizes this problem and has sought to resolve the difficulty by applying least squares to the data obtaining a selected "best value" for each constant. These "best values," printed in bold-faced type, are given in the present volume only where the inclusion of the new data results in a "best value" substantially different from the previous selection. "Whenever possible the values listed in the Tables of Selected Values of Properties of Hydrocarbons, compiled by the American Petroleum Institute's Project 44, were used as a guide in evaluating data."

Petroleum chemists are confronted at this point by a problem not yet shared in equal degree by investigators in other areas of organic chemistry. The above data were collected from papers published in standard scientific periodicals. These papers had been carefully reviewed and the commonly accepted criteria of validity vigorously applied. Why then these variations, which lie outside the limits of experimental error? The variations arise chiefly from two sources; (a) faulty technique in measurement of the constants and (b) impurities in the products on which the measurements were made.

The criteria of validity applied to new organic compounds by organic chemistry journals "since the days of Liebig" are ultimate analyses for carbon, hydrogen and other elements. Such analyses have only a limited value in the field of hydrocarbon chemistry. All olefins and all cycloparaffins analyze to the same percentage composition. All isomers upon analysis give the same empirical formula. Combustion analyses do have a limited application among the lower members of the paraffin and acetylene series. But for the higher members of these series the differences in percentage composition between successive members, or for the corresponding members of the different series, fall well within the limits of experimental error. The petroleum chemist must therefore turn to physical measurements for his proof of validity. Spectrograms, cooling and warming curves give unquestioned evidence of both identity and degree of purity. *Ideal* curves for physical constant values and known changes in physical constants with specific variation in the structural pattern of the molecule form valuable aids in forming a considered judgment of the validity of experimentally determined values.

At this point the five volumes of Physical Constants of Hydrocarbons become of inestimable value. Set opposite each datum is a reference number, so that the whole work becomes a bibliography or, more strictly speaking, a collection of bibliographies. By their use it is possible to trace each measured value, or each group of constants back to their source and to appraise the method of synthesis, the method of purification and the technique of measurement. In this manner one may arrive at a well considered judgment as to the degree of purity and even as to the nature of the more probable impurities.