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PHOTOCHEMICAL TRANSFORMATIONS. IX.
TOTAL STRUCTURE OF SUPRASTEROL II[1,2]

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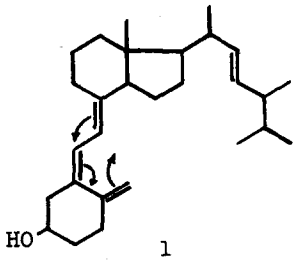
In a previous communication,[3] it was shown that the structure of suprasterol II, a photochemical transformation product of Vitamin D_2 (1), was most likely represented by formula 2. We now wish to present evidence which establishes the correctness of structure 2 and its absolute stereochemistry as depicted by structure 25.



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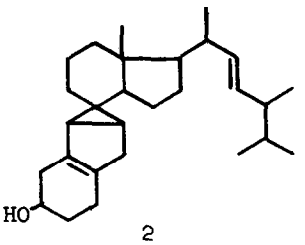

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[1] For Paper VIII, see W. G. Dauben and R. L. Cargill, Tetrahedron, in press.

[2] This work was supported, in part, by Grant No. A-709 (C8), U. S. Public Health Service.

[3] W. G. Dauben, I. Bell, T. W. Hutton, G. F. Laws, A. Rheiner, Jr. and H. Urscheler, J. Am. Chem. Soc. 80, 4116 (1958).

22-Dihydrosuprasterol II (3), upon oxidation with chromic acid in pyridine, was converted into hydroxyenone 4 (m.p. 227° $[\alpha]_D^{Chf}$ -80°, λ_{max}^{EtOH} 263 mμ (ε 13,100), ν_{max} 1670 cm $^{-1}$). The same product was obtained by epoxidation followed by oxidation under Oppenauer conditions. Lithium aluminum hydride reduction of 4 yielded the allylic diol 5 (m.p. 189°, λ_{max}^{EtOH} 211 mμ (ε 8,500)), which, upon dehydration at -15° with thionyl chloride in pyridine, gave the hydrocarbon 6 (oil, $\lambda_{max}^{cyclohexane}$ 280, 273, 259, 228, 202 mμ (ε 1,670, 1,760, 1,840, 9,000, 25,000)). The nmr spectrum of 6 showed the presence of four benzenoid protons and no vinyl protons. Upon treatment with hydrogen chloride in anhydrous chloroform, 6 rearranged to a mixture of isomeric unsaturated hydrocarbons (oil, $[\alpha]_D^{Chf}$ + 79°) in which 7 was present to an extent of greater than 80% (GLC analysis).[4] The U.V. spectrum ($\lambda_{max}^{cyclohexane}$ 273, 266, 259 mμ (ε 1,760, 1,930, 1,990) of the mixture was almost identical with that of indane, indicating that the double bond formed was not in conjugation with the benzene nucleus. The nmr spectrum of the mixture established the presence of less than 0.2 vinyl proton, showing the tetrasubstituted nature of the newly formed double bond. The mixture was osmylated and the diols were separated by alumina chromatography. The two

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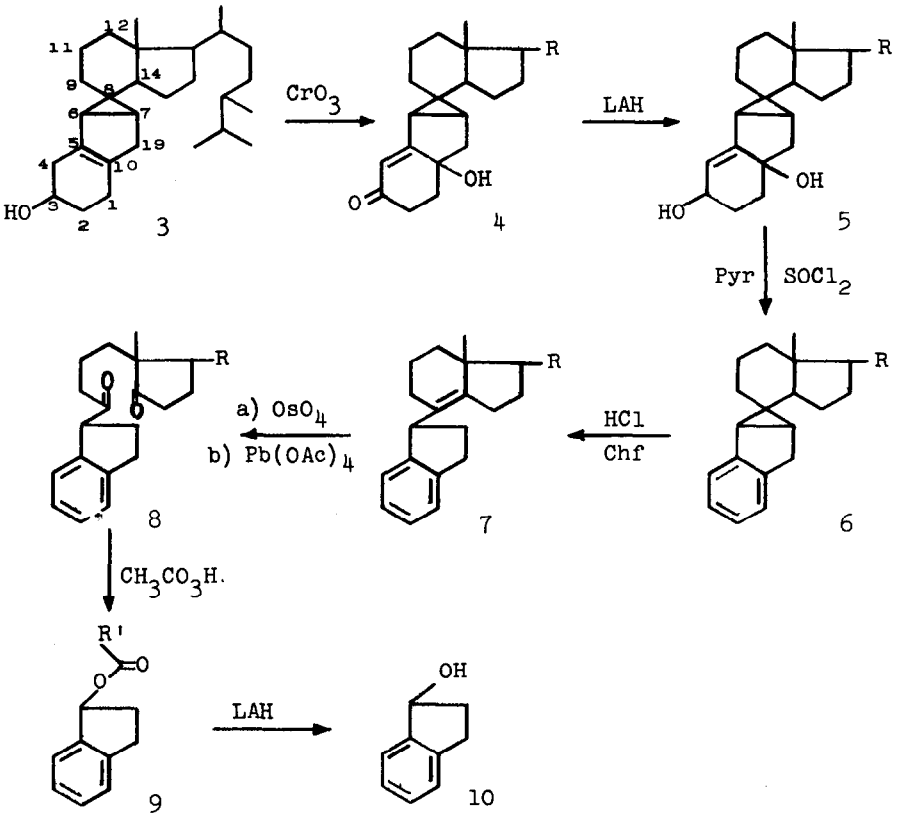
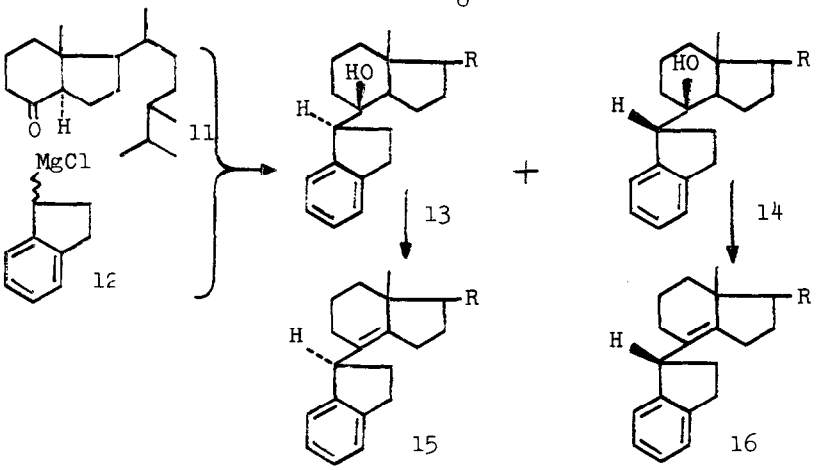
[4] W. J. A. Vanden Heuvel, C. C. Sweeley and E. C. Horning, J. Am. Chem. Soc. 82, 3481 (1960).



main products (oils, 40% and 22%, $\lambda_{max}^{cyclohexane}$ 273, 266, 260 mμ (ε 1,500, 1,400, 1,000)), upon oxidation with lead tetraacetate, gave the same oily diketone 8 ($\lambda_{max}^{cyclohexane}$ 273, 266, 260 mμ, ν_{max} 1740, 1710 cm $^{-1}$). The diketone 8 was allowed to react with peracetic acid and the ester-δ-lactone 9 was obtained (oil, ν_{max} 1740, 1710 cm $^{-1}$). Reduction of 9 with lithium aluminum hydride yielded a mixture from which 1-indanol 10 was isolated by alumina chromatography. The 1-indanol has $[\alpha]_D^{Chf}$ -10° as compared to $[\alpha]_D$ -34° for the

optically pure enantiomer,[5] indicating that the diketone 8 must have partially equilibrated at C_6.



To establish the structure of the acid catalyzed rearrangement product, hydrocarbon 7, 1-indanylmagnesium chloride 12 was allowed to react with the C_{19}-ketone 11, obtained from Vitamin D_2,[6] and the two alcohols 13 and 14, separated by alumina chromatography, were obtained in a ratio of 2.4:1. Dehydration of each alcohol yielded the related unsaturated hydrocarbon 15 ($[\alpha]_D^{Chf}$-13°) and 16 ($[\alpha]_D^{Chf}$+ 63°), respectively. The hydrocarbon 16, derived from the minor alcohol 14, was identical with the hydrocarbon 7 obtained from degradation of suprasterol II and when degraded by the

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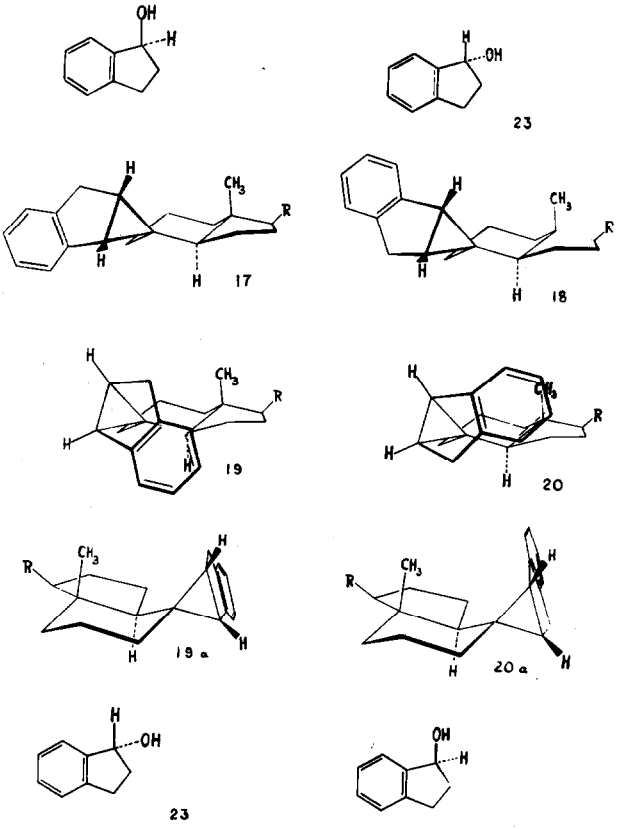
5 W. Hückel and F. Mössner, Ann. 637, 57 (1960).

6 H. H. Inhoffen, G. Quinkert, S. Schütz, G. Fredrich and E. Tober, Chem. Ber. 91, 781 (1958). A. Windaus and W. Grundmann, Ann. 524, 295 (1936).

same route as used above yielded the negatively rotating 1-indanol 10. These results establish the gross structure of suprasterol II as 2.[7]

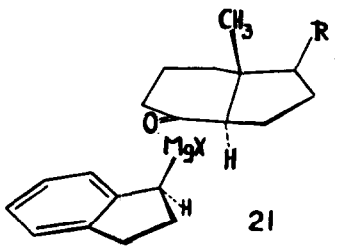
Next, the stereochemistry of suprasterol II must be considered. In the formation of this irradiation product of Vitamin D_2 only the carbon atoms in the original triene



[7] Satisfactory analytical results have been obtained for all new substances reported. The purity of the oily materials was ascertained by paper chromatography (phenyl cellosolve-hexane) and by thin layer silicic acid chromatography.

system are involved, the other centers remaining as originally present in the steroidal starting material. The transformation of suprasterol II (2) to the aromatic hydrocarbon 6 does not affect the new centers C_6, C_7 and C_8, and determination of the configuration of these latter centers in 6 leads to a complete stereochemistry of 2. With the assumption that a three membered ring can only be fused to a five membered ring in a cis fashion, there are four possible steric arrangements for 6, i.e. 17, 18, 19 and 20. If the degradation of these four isomers to optically active 1-indanol by the above described route proceeds with retention of configuration, it is seen that 17 and 20 should yield one antipode of 1-indanol and 18 and 19 the other antipode. Thus, knowledge of the absolute configuration of 1-indanol would decrease the number of possible structures to two.

The absolute configuration of 1-indanol was determined by evaluation of the steric course of the reaction between the C_{19}-ketone 11 and the 1-indanylmagnesium chloride 12. The topside of ketone 11 is shielded by the angular methyl group and the approach of the bulky Grignard reagent 12 should be limited to the bottom-side as depicted below. The racemic Grignard



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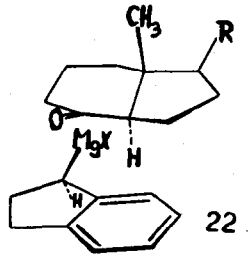

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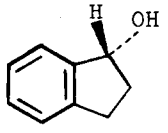
can add in two fashions, 21 and 22, to yield the two alcohols 13 and 14. Due to the lesser steric interactions of the two bulky reagents in pathway 21, the alcohol 13 should be the major product and the alcohol 14 the minor product. These latter two projections show the absolute configuration of the alcohols since the starting ketone is of known absolute stereochemistry. Recalling that the minor Grignard product 14 was the precursor of the hydrocarbon 6 which, upon degradation, yielded (-)-1-indanol, this antipode must have the absolute configuration 23.



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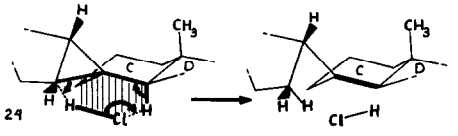
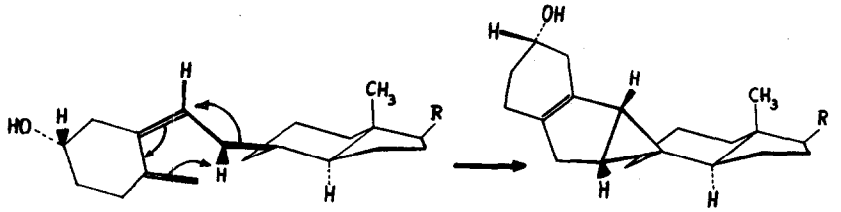
1-Indanol of this configuration is derivable only from structures 18 and 19.

Consideration of the steric aspects of the cyclopropane ring opening permits differentiation between these two remaining structures. The formation of only olefins with isolated double bonds indicates that a carbonium ion type of intermediate involving C_6 does not intervene in the ring opening reaction since such an intermediate should yield some conjugated isomer. The selectivity of the conversion of 18 to 7 can be rationalized by



postulation of a cyclic six membered transition state (24) which does not involve C_6.

Examination of 19a, a projection obtained by turning 19 by 90°, clearly shows that such a transition state is impossible for this isomer. On the basis of these mechanistic considerations, it is suggestive that the absolute stereochemistry of the hydrocarbon 6 is shown by 18. If such be the case, it follows that the total structure of suprasterol II is 25. Such a structural arrangement also suggests that the transformation of Vitamin D_2 (1) to suprasterol II (25) may proceed via the concerted process shown below.



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Hodgkin and Sanderson (see following Letter), using X-ray diffraction, have determined the structure of suprasterol II and have established the correctness of structure 25.