were eluted with water. Glycolic and lactic acids were obtained from both oxyxylan and oxydextran and identified as the 4-bromophenacyl ester in each case, m.p. and mixed m.p. 138–139° and 107–109°, respectively.

Quantitative Determinations of the Major Degradation Products. Neutral Fraction.—The neutral fractions of the degraded oxypolysaccharides were weighed directly after evaporation of the solutions resulting from deionization with Amberlite ion exchange resins, IR-120 (H) and IRA-401 (carbonate).

Total acidity and volatile acids were determined by the same methods as described for oxystarch.[4]

Major Non-volatile Acids.—Glycolic and lactic acids were first separated by the quantitative paper chromatographic method described for periodate oxystarch.[4] Calkins' method[12] was used to determine glycolic acid samples and a correction factor for recovery from paper chromatography applied as described earlier.[4] For the lactic acid eluate, the method described by Hullin and Noble[13] was used. Calibration of the recovery of authentic lactic acid from this procedure showed a considerable dependence of recovery on the loading of the paper. With loading of lactic acid comparable to that present in the mixtures, a recovery of 80% was obtained and this correction has been applied to the results in Table I. but as suggested in earlier work[4] these acid yields are approximate and may be subject to errors of the order ±10%. The higher recovery of lactic acid than of glycolic acid from the paper chromatogram in the calibration experiments is probably due to the fact that a wide band (10—15 cm.) of paper was eluted to include dimers and trimers of lactic acid, whereas a band of minimal width was cut for glycolic acid in order to exclude trace products of similar R_1 values.

(12) V. P. Calkins, *Anal. Chem.*, **15**, 762 (1943).

(13) R. P. Hullin and R. L. Noble, *Biochem. J.*, **55**, 289 (1953).

LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Structure of Photoisopyrocalciferol and Photopyrocalciferol[1—3]

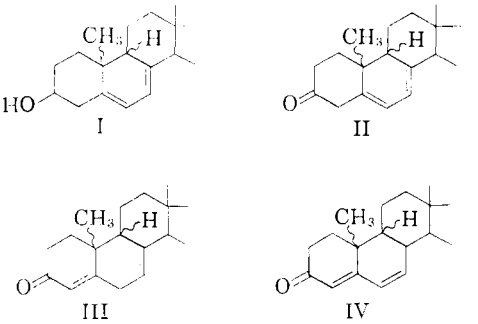
BY WILLIAM G. DAUBEN AND GERHARD J. FONKEN

RECEIVED DECEMBER 2, 1958

Windaus and Dimroth have reported the formation of "photo" compounds VIII and IX by the irradiation of the pyrocalciferols Ic and Id with ultraviolet light. On the basis of limited evidence structures XII and XIII were suggested. The present results add evidence in favor of structure XIII, a valence tautomer of Ic and Id; VIII possesses five rings, a nuclear disubstituted double bond and a Δ^{22}-unsaturated link in the sidechain. Oxidation of VIII yields the non-conjugated, unsaturated ketone X and ozonization of VIII gives a C_{22}-triacid XVI which is converted readily to a cyclic anhydride-acid XVII. Compound VIII upon hydrogenation is transformed into a 22-dihydro (XIV) and a tetrahydro derivative XV. Both XIV and XV are stable to acid; XV upon mild oxidation gives the saturated ketone XXI and upon vigorous oxidation the *seco*-diacid XXII. Perbenzoic acid oxidation of XV yields lactone XXIII which upon saponification and oxidation gives the same *seco*-diacid. Treatment of ketone X with base yields dienone IV. A similar series of transformations are found with IX. The chemistry of Ic and Id and of various valence tautomers are discussed. The mechanism of the transformation is considered.

In the course of their classical work on the mechanism of formation of vitamin D_2 from ergosterol, Windaus and his collaborators[4] prepared the four 5,7-dienes (Ia-d), isomeric at C_9 and C_{10}. Recently, the stereochemistry of the four isomers has been shown[5] to be 9α-H,10β-CH_3 in ergosterol (Ia), 9 β-H,10α-CH_3 in lumisterol (Ib), 9β-H,10β-CH_3 in isopyrocalciferol (Ic) and 9 α-H, 10α-CH_3 in pyrocalciferol (Id).[6] It is seen that the first two compounds are 9,10-*anti* isomers while the last two compounds are 9,10-*syn* isomers.

The change from *anti* to *syn* in the backbone stereochemistry reflects itself in many of the reactions shown by these two series of compounds. For example, in the *anti* series when the alcoholic group is oxidized under Oppenauer conditions, a 4,7,22-triene-3-one (IIIa or b) is obtained directly.[7] In the



a, 9α-H,10β-CH_3; b, 9β-H,10α-CH_3
c, 9β-H,10β-CH_3; d, 9α-H,10α-CH_3

syn series, similar oxidation yields the unrearranged 5,7,22-triene-3-one (IIc or d) which must be treated with base to be transformed into the isomeric 4,7,22-triene-3-one (IIIc or d). In the *anti* series, when the alcohol (Ia or b) is hydrogenated under neutral or slightly acid conditions, only a tetrahydro product ($\Delta^{8,14}$) is obtained,[8] but under strongly acid conditions a hexahydro product is formed.[9] With the *syn* series, it has been reported

(1) Presented at the 15th National Organic Chemistry Symposium of the American Chemical Society, Rochester, N. Y., June 17–20, 1957.

(2) This work was supported, in part, by Grant A-709 (C5)-Bio (5) of the U. S. Public Health Service, National Institutes of Health, Department of Health, Education and Welfare.

(3) A preliminary communication of these results appeared in THIS JOURNAL, **79**, 2972 (1957).

(4) For a summary of this work, see L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 3rd edition, 1949, p. 167.

(5) J. Castells, E. R. H. Jones and R. W. J. Williams, *Proc. Chem. Soc.*, 7 (1958); *J. Chem. Soc.*, **1159** (1959).

(6) Jones and his co-workers[5] recently suggested that isopyrocalciferol be called 9β-ergosterol and pyrocalciferol be called 9α-lumisterol. In the present discussion, the older trivial names will be used since all previous work has been based upon this nomenclature system.

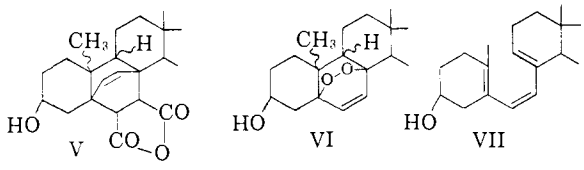
(7) R. V. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937); I. M. Heilbron, T. Kennedy, F. S. Spring and G. Swain, *J. Chem. Soc.*, 869 (1938).

(8) F. Reindel, E. Walter and H. Rauch, *Ann.*, **452**, 34 (1927); F. Reindel and E. Walter, *ibid.*, **460**, 212 (1928); M. C. Hart, J. H. Speer and F. W. Heyl, THIS JOURNAL, **52**, 2016 (1930).

(9) G. Ahrens, E. Fernholz and W. Stoll, *Ann.*, **500**, 109 (1933); I. M. Heilbron, G. L. Moffet and F. S. Spring, *J. Chem. Soc.*, 411 (1937).

that a hexahydro derivative is obtained directly when acetic acid is the solvent[10] and it has now been found that a very rapid hexahydrogenation occurs in ethanol (pyro, 150 min.; isopyro, 40 min.).

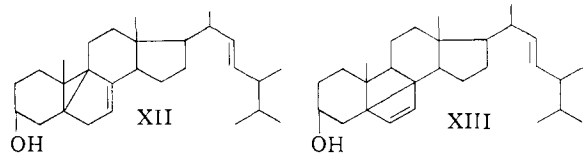
Of particular interest are the reactions which reflect the dienic structure. All four dienes react with maleic anhydride to yield the expected adduct V,[11] but in refluxing benzene where ergosterol reacts to an extent of less than 15% in 3 hours[11] *syn* isomers show complete reaction in 5 hours. The formation of 5,8-epidioxides VI also is possible in both



series, but in the *anti* series the reaction is always accompanied by dehydrogenation to a 5,7,9(11),22-tetraene[12] while in the *syn* series no such side reaction occurs. Furthermore, the rate of reaction in the ergosterol series is slower than in the isopyrocalciferol series. The foregoing reactions indicate a greater reactivity of the dienic system in the *syn* series.

The most interesting difference in these two series is the reaction induced when the materials are irradiated with ultraviolet light. It is now well established that the two *anti* isomers upon irradiation first undergo a bond cleavage reaction to give rise to a 9,10-*seco*-sterol, precalciferol (VII).[13] On the other hand, Windaus and Dimroth[14] have shown that upon similar irradiation, the two *syn* isomers undergo a bond-forming reaction to yield "photoisopyrocalciferol (VIII)" and "photopyrocalciferol (IX)." These materials show identical reactions and appear to be stereoisomers. Thus, in this irradiation process one finds the first reaction sequence in which the *syn* and *anti* series differ by more than a rate effect.

The photo compounds VIII and IX have not been investigated extensively but it has been shown that they form no precipitate with digitonin, possess no maximum in the ultraviolet above 249 mμ and are monomeric. The presence of only two double bonds was indicated by reaction with only two moles of perbenzoic acid and by tetrahydrogenation to yield materials not well characterized but which were inert toward perbenzoic acid. Since the starting materials Ic and Id contained three double bonds and the irradiation products only two such linkages, it was assumed that a new ring had been formed. To gain information regarding the relative positions of the remaining nuclear double bond (it being assumed that the side-chain double bond remained), VIII and IX were oxidized with chromic acid in acetic acid to yield the ketones photoisopyrocalciferone (X) and photopyrocalciferone (XI), respectively, which possessed no maxima in the ultraviolet above 226 mμ. Since, in general, a β,γ-unsaturated alcohol when oxidized under these conditions yields the conjugated α,β-unsaturated ketone possessing an ultraviolet maximum in the range measured above, it could be assumed that the remaining double bond either was not β,γ to the hydroxy group and/or the migration was blocked due to substitution. It also was found that the photo compounds VIII and IX upon heating to 188° were converted, in high yield, to the starting homoannular dienes Ic and Id, respectively. On the basis of these results, two alternate structures, XII and XIII, were postulated. Structure XII which possessed a cyclopropane ring seemed unlikely since the photo compounds were stable to an acetic acid–hydrogen chloride mixture.



In the present work, it was found that photoisopyrocalciferol (VIII) absorbed in the infrared at 970 cm.$^{-1}$, characteristic of a *trans*-symmetrically disubstituted olefin, and at 748 cm.$^{-1}$ (doublet), characteristic of a *cis*-symmetrically disubstituted double bond.[15] The nuclear magnetic resonance spectrum showed the presence of vinyl proton bands at 0 and −1.0 (doublet) p.p.m. (parts per million relative to ethanol). The absorption at 0 p.p.m. corresponded in area to two protons and the relative position was found to be characteristic for the Δ^{22}-double bond in ergosterol. The latter doublet at −1.0 p.p.m. thus must be assigned to the second double bond and the area of the bands again corresponded to two vinyl protons.

Further evidence of the presence of only two double bonds in VIII was gained by a hydrogenation study. Under carefully controlled conditions, one mole of hydrogen was absorbed to yield a dihydro derivative XIV whose infrared spectrum indicated the presence of only the Δ^{22}-double bond (band at 970 cm.$^{-1}$) in the side-chain. On treatment of the dihydro compound with ozone, α-methylisovaleraldehyde was isolated, a degradation product which clearly established the placement of the unsaturation at C-22.

Upon further hydrogenation of the dihydro compound XIV, or by direct hydrogenation of VIII itself, a crystalline tetrahydro derivative XV was obtained. The spectral characteristics of the material showed it to be a saturated alcohol. The magnetic resonance spectrum exhibited no vinyl proton absorption, the infrared bands at 970 and 748 cm.$^{-1}$ were missing and the ultraviolet spectrum showed only weak end absorption (ϵ_{205} 250). Also, the compound resisted further hydrogenation even in the presence of mineral acid and did not react with perbenzoic acid. Only a highly hindered and

(10) P. Busse, *Z. physiol. Chem.*, **214**, 211 (1933).

(11) A. Windaus and A. Lüttringhaus, *Ber.*, **64**, 850 (1931); M. Müller, *Z. physiol. Chem.*, **233**, 223 (1935).

(12) A. Windaus and J. Brunken, *Ann.*, **460**, 225 (1928); P. Bladon, *J. Chem. Soc.*, 2180 (1955).

(13) L. Velluz, G. Amiard and B. Goffinet, *Bull. soc. chim., France*, 882 (1957), and earlier papers; M. P. Rappoldt, J. A. Keverling Buisman and E. Havinga, *Rec. trav. chim.*, **77**, 327 (1958), and earlier papers.

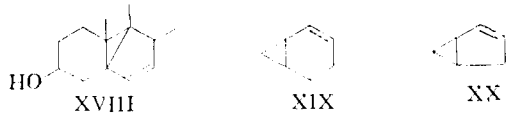
(14) K. Dimroth, *Ber.*, **70**, 1631 (1937); A. Windaus, K. Dimroth and W. Breywisch, *Ann.*, **543**, 240 (1940).

(15) H. B. Henbest, G. Meakins and G. Wood, *J. Chem. Soc.*, 800 (1954).

substituted double bond would resist reaction under these conditions, but if such groupings were present high end absorption in the ultraviolet (ϵ_{205} 4000–8000) would be expected.[16] It can be concluded that photoisopyrocalciferol possesses 5 rings and 2 disubstituted double bonds. Of these latter groupings, the *trans* bond is at Δ^{22} in the side-chain and the *cis* bond must be in a ring.

Establishment of the position of the nuclear double bond was gained by ozonization of photoisopyrocalciferyl acetate (VIII) followed by oxidation of the ozonide. The product, the acetate of a C-22 tricarboxylic acid (XVI), contained all of the carbon atoms of the precursor, other than those lost by cleavage of the Δ^{22}-double bond. The tricarboxylic acid XVI upon warming with acetic anhydride readily yielded a cyclic anhydride XVII, indicating a close spacial proximity of two of the carboxyl functions. Since ring A must be saturated as shown by the fact that photoisopyrocalciferone (X), obtained by oxidation of the parent alcohol, was a saturated ketone, only three positions remain for the placement of the nuclear double bond (assuming no gross skeletal rearrangements during photolysis), in ring B between C-6 and C-7, in ring C between C-11 and C-12 and in ring D between C-15 and C-16. A choice between these three positions is possible by consideration of the fact that the photo compound VIII upon heating at 188° is transformed into its progenitor, the $\Delta^{5,7}$-diene. The nuclear double bond in VIII must be intimately associated with this reversal since the saturated tetrahydro derivative XV is stable at this temperature. Furthermore, when this pyrolysis was performed in EtOD, no stable bonded deuterium was introduced, suggesting that no carbon–hydrogen bonds were broken in the process. To move, originally, in the irradiation a double bond to rings C or D and then to reverse this process by heat involves three successive migrations and in such a process equilibration of one or more of the intervening asymmetric centers as well as deuterium introduction might be expected. These results and considerations suggest placement of the nuclear double bond between C-6 and C-7 in ring B.

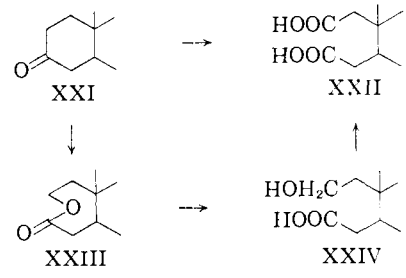
With this placement of the nuclear unsaturation, it is now possible to evaluate one of the formulas suggested by Windaus and Dimroth, that is, a modified structure such as XVIII containing a cyclopropane ring. In the ultraviolet, photoisopyrocalciferol shows only modest end absorption (ϵ_{200} 3100). Recently, the cyclopropane-ene chromophore has been studied in various natural products



XVIII XIX XX

and when it is part of a 7-membered ring (XIX) a maximum occurs at 222–224 mμ (ϵ 4000–6000).[17] When it is part of a 6-membered ring (XX) no maximum is observed down to 205 mμ but the extinction coefficient is about 5000.[18] When the absorption associated with the side-chain double bond (ϵ_{205} 1000–2000)[19] in the photo compound is subtracted from its total absorption, it is clearly evident that the residual absorption (ϵ_{200} 1000–2000) is too small to be associated with a cyclopropane–ene conjugated system. Also, the presence of an isolated cyclopropane ring is ruled out since, in addition to the earlier results with hydrogen chloride in acetic acid, it has been found that the tetrahydro derivative XV is stable to hydrogen chloride in chloroform under conditions which have been shown to isomerize such small rings to olefins.[20]

To gain information regarding the placement of the new ring, some transformations of ring A were studied. It was found that oxidation of the tetrahydro alcohol XV with chromium trioxide in acetic acid at 0° yielded tetrahydroisopyrocalciferone (XXI), which also was obtained by tetra-



XXI XXII XXIII XXIV

hydrogenation of photoisopyrocalciferone (X) The carbonyl group absorbed at 1705 cm.$^{-1}$ indicating a six or larger membered ring ketone, the former being more likely in view of the structure of the starting material. When the tetrahydro ketone XXI was oxidized at 70° with the same reagents, a di-acid XXII was obtained, thus showing the presence of at least one methylene group adjacent to the carbonyl group. Oxidation of the ketone XXI with perbenzoic acid yielded a lactone XXIII which could be hydrolyzed to a hydroxy acid XXIV. Oxidation of the latter material gave rise to di-acid XXII. If a substituent had been present α to the carbonyl group in XXI, the oxidation product of the hydroxy acid XXIV would have been a keto acid, not a di-acid, since peracid cleavage occurs between the carbonyl group and the adjacent carbon bearing the larger number of alkyl groups.[21] These results show that the original C-3 hydroxyl group is flanked by two methylene groups and that ring A is most likely unsubstituted in the photo compound.

In view of the earlier conclusion that the new ring and the nuclear double bond must be closely associated and the above demonstration of the absence of bonding into ring A, it leaves C-5, C-8, C-9 and C-10 as the only carbon atoms

(16) P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(17) A. Zürcher, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **37**, 2145 (1954); J. M. Beaton, J. D. Easton, M. M. MacAuther, F. S. Spring and R. Stevenson, *J. Chem. Soc.*, 3992 (1955); C. Djerassi, F. W. Donova, S. Burstein and R. Mauli, THIS JOURNAL, **80**, 1972 (1958).

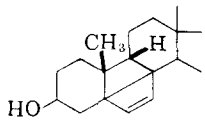
(18) The spectrum of Δ^4-thujene taken in this Laboratory shows only ϵ_{200} 5500.

(19) This value was determined in this Laboratory by a study of various ergosterol derivatives.

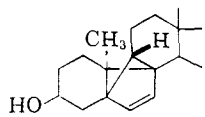
(20) D. H. R. Barton, J. E. Page and E. W. Warnhoff, *J. Chem. Soc.*, 2715(1954).

(21) W. von E. Doering and L. Speers, THIS JOURNAL, **72**, 5515 (1950).

which can be associated with the new ring. From this combination of positions, only two structures can be written, *i.e.*, bonding of C-5 to C-8 and C-9 to C-10 (XIII) or C-5 to C-9 and C-8 to C-10 (XXV). The structure XIII is one previously

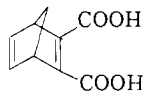


XIII

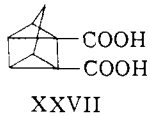


XXV

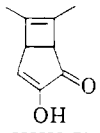
postulated by Windaus and Dimroth[14] and is a valence tautomer of the starting conjugated diene. The formation of valence tautomers recently has been observed in three irradiation reactions. First, Cristol[22] has found that bicyclo[2,2,1]2,5-diene-2,3-dicarboxylic acid (XXVI) is transformed to the quadricyclic compound XXVII; second,



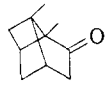
XXVI



XXVII



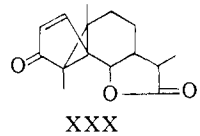
XXVIII



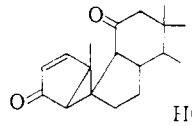
XXIX

Forbes and Gardner[23] have presented evidence supporting structure XXVIII for a modified tropolone ring in lumicolchicine; and, third, Büchi[24] has established the structure of carvonecamphor formed from carvone as XXIX.

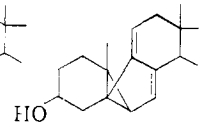
The second possible structure, XXV, of photoisopyrocalciferol is the result of a "bond switching" reaction which has been noted recently in many irradiation reactions. Some examples of this type of reaction are the formation of lumisantonin (XXX) from santonin,[25] lumiprednisone (XXXI) from prednisone,[26] and photodehydroergosterol (XXXII) from dehydroergosterol.[27]



XXX



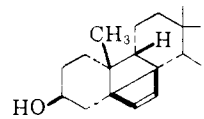
XXXI



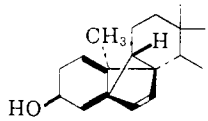
XXXII

The two structures XIII and XXV have in common the attachment of ring A to ring C *via* a cyclobutane ring, but in the former the ethylenic bridge is connected 1,2 and in the latter 1,3. Thus, in XIII there is present a cyclobutene unit and in XXV a strained cyclopentene unit. As discussed earlier, the nuclear magnetic resonance spectrum of the material displayed an absorption at very low field (−1.0 p.p.m.) and such an absorption has been found to be characteristic of cyclobutenes.[28] No spectral information is available for the type of cyclopentene present in XXV. It can be concluded, however, that the low field absorption is suggestive of a cyclobutene structure as in XIII, but this evidence cannot rule out structure XXV.

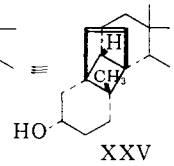
To better evaluate these two formulations, the consideration of the stereochemistry is of aid. Both systems have rings fused to cyclobutane rings and, accordingly, all ring junctures most likely possess *cis* stereochemistry. It can further be assumed that since the pyrolytic reversal reaction yields the starting 9,10-*syn* isomer which is thermodynamically unstable, the C-9 β-H is not involved in the reaction and all structural formulations must retain this feature. Following these assumptions, the stereochemical formulations are shown below and it is to be noted that in XXV, the C-10 methyl group must be inverted in order to fulfill the stereochemical requirements. Thus, the pyrolytic reversal of structure XXV required one bond migration to occur with inversion and at the present time no analogy exists for this type of stereospecific migration in a pyrolytic reaction. On the other hand, structure XIII does not require any inversions and the bonds involved in the pyrolytic reversal are not associated with any asymmetric center common to both starting material and product. The heat reversal of a valence tautomer has been observed with various systems such as in the reconversion of XXVII to XXVI reported by Cristol[22] and the reversal of cyclobutane derivatives.[29,32]



XIII

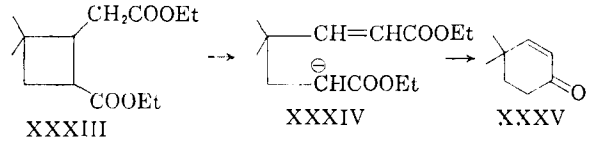


XXV



XXV

Another characteristic reaction of a properly substituted cyclobutane system is a base-catalyzed ring opening. For example, when carophyllenic acid diester (XXXIII) is treated with base, the four-membered ring is opened and the resultant product XXXIV undergoes cyclization to a six-membered ring (XXXV).[30]

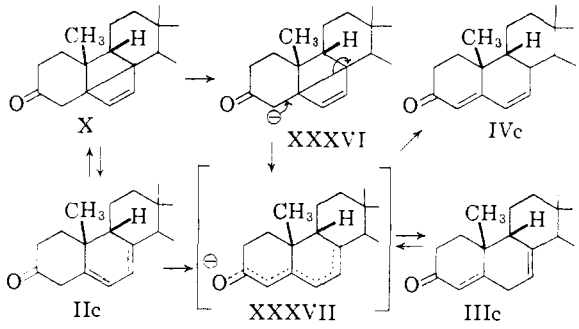


XXXIII XXXIV XXXV

One driving force of such a reaction is the stabilization of the resulting carbanion XXXIV by the carbethoxy group. It was found that when photoisopyrocalciferone (X) was allowed to react with potassium *t*-butoxide, the conjugated dienone IVc was formed. When tetrahydrophotoisopyrocalciferone (XXI) was subjected to the same reaction

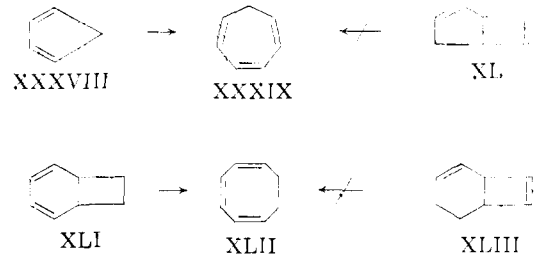
(22) S. J. Cristol and R. L. Snell, THIS JOURNAL, **80**, 1950 (1958).
(23) J. W. Forbes, *J. Chem. Soc.*, 3864 (1955); P. D. Gardner, R. L. Brandon and G. R. Haynes, THIS JOURNAL, **79**, 6334 (1957).
(24) G. Büchi and I. M. Goldman, *ibid.*, **79**, 4741 (1957).
(25) D. H. R. Barton, P. deMayo and M. Shafig, *J. Chem. Soc.*, 140 (1958); D. Arigoni, H. Bosshard, H. Bruderer, G. Büchi, O. Jeger and L. K. Krebaum, *Helv. Chim. Acta*, **40**, 1732 (1957).
(26) D. H. R. Barton and W. C. Taylor, THIS JOURNAL, **80**, 244 (1958).
(27) D. H. R. Barton and A. S. Kende, *J. Chem. Soc.*, 688 (1958).
(28) We are indebted to Professors J. D. Roberts and K. S. Wiberg for the information regarding cyclobutenes.
(29) A. C. Cope, A. C. Haven, Jr., F. L. Ramp and E. R. Trumbull, THIS JOURNAL, **74**, 4867 (1952).
(30) A. Eschenmoser and A. Fürst, *Experientia*, **7**, 290 (1951).

conditions, the material was recovered unchanged and this stability could be rationalized in terms of intermediate XXXVII which adds a driving force to the reaction of X. The direct isolation of the 4,6-diene-3-one (IVc) from the reaction was of



interest since earlier in this study, it had been found that when the 5,7-diene-3-one (IIc) was allowed to react for 20 minutes on the steam-bath with aqueous methanolic potassium hydroxide, the 4,7-diene-3-one (IIIc) was obtained. Both base-catalyzed interconversions must involve the same intermediate enolate ion XXXVII and, such being the case, should yield the same product. It was found, as could be expected, that the formation of the 4,7-diene-3-one IIIc was the result of rate controlled protonation while the formation of the 4,6-diene-3-one IVc was the result of thermodynamic control. When IIc was dissolved in aqueous methanolic potassium hydroxide, the ultraviolet spectrum showed the complete absence of the starting 274 mμ band and the presence of the 242 mμ band of IIIc. As the reaction solution was allowed to stand, the intensity of the 242 mμ band decreased and the 283 mμ band of IIIc started to appear. At the end of 100 minutes, only the 283 mμ band was present and pure IVc was isolated directly from the reaction. The stereochemistry of C-8 of IVc is not known, but the method of formation employed for the preparation of IVc directly from IIc shows that in both materials the C-9 hydrogen atom is beta and the unstable *syn* stereochemistry of the A/C juncture is present. The direct formation of this unstable *syn* isomer from the photo compound X indicates that the C-9 hydrogen is not involved in the base-catalyzed transformation. The identity of the C-9 configuration in both IIc and X, the starting materials, was established by formation of X directly from IIc by irradiation and transformation of X to IIc with heat. These same series of transformations might also be possible with structure XXV, but structure XIII is strongly favored on this basis.

One final feature of the valence tautomeric structure XIII which is of interest is the stability of the the system. In general, the saturated valence tautomer of a diene is stable,[22-27] whereas the stability of an unsaturated tautomer depends upon the number, location and type of substituent on the system. For example, in cycloheptatriene (XXXIX)[31] and cycloöctatriene (XLII),[29] the valence tautomeric forms which possess a conjugated diene, XXXVIII and XLI, respectively, either show no stability or are convertible to triene at 80°.



The valence tautomeric forms which do not possess a conjugated diene, XL and XLIII, respectively, are stable to temperature of at least 160°.[32] On the basis of these results, Vogel[32] has postulated the need for a conjugated system if the valence tautomeric forms are to be interconvertible with ease. Therefore, it is not unreasonable to expect a system such as in structure XIII to be stable.

Turning now to the structure of photopyrocalciferol (IX), the early work of Windaus and Dimroth[14] clearly suggested a structure similar to that of photoisopyrocalciferol (VIII). Sufficient additional evidence now has been obtained to justify this conclusion. The infrared spectrum of IX exhibited bands at 970 and 750 cm.$^{-1}$, characteristic of a *trans* and a *cis* symmetrically disubstituted ethylenic group, respectively. The nuclear magnetic resonance spectrum was essentially identical with that of VIII, again containing the low field absorption doublets (−1.0 p.p.m.) suggestive of a cyclobutene structure. The ultraviolet spectrum between 200 and 400 mμ showed no maximum and the end absorption at 205 mμ was only 2300. Photopyrocalciferone (XI), formed by chromic acid oxidation, showed no maximum in the ultraviolet and the carbonyl absorption was at 1707 cm.$^{-1}$. Upon reaction with perbenzoic acid, IX yielded a saturated diepoxide and upon hydrogenation yielded a tetrahydro derivative. This latter material upon oxidation was transformed into a saturated ketone. Ozonolysis of IX yielded a C-22 tricarboxylic acid which upon reaction with acetic anhydride gave rise to a cyclic anhydride.

Finally, a set of interconversions found in both series speaks again for a similarity of structure. It was found that photoisopyrocalciferol (VIII) on oxidation yielded photoisopyrocalciferone (X) which upon heating at 160° was transformed into isopyrocalciferone (IIc). This latter material upon reduction with lithium aluminum hydride gave the starting alcohol (Ic) and upon irradiation reformed the photo ketone X. A similar "round-robin" was observed in the pyrocalciferol series with one stereochemical difference. This material belonging to the 10α-methyl series requires that the naturally occurring 3β-hydroxyl group be in an axial conformation.[33] Thus, when pyrocalciferone (IId) was reduced with lithium aluminum hydride, the 3α-equatorial isomer was obtained.[34] When pho-

(31) W. von E. Doering and L. H. Knox, THIS JOURNAL, **75**, 297 (1953); E. J. Corey, H. J. Burke and W. H. Remers, *ibid.*, **77**, 4941 (1955).

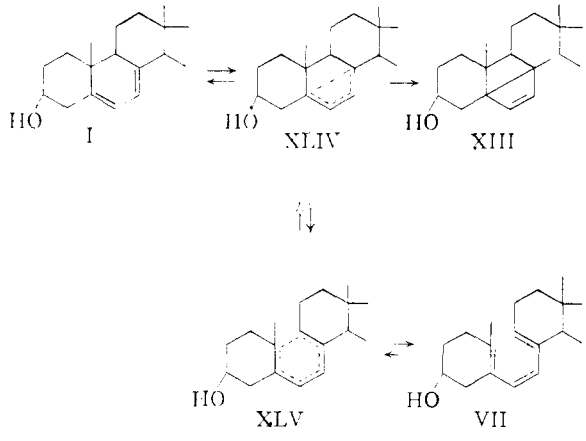
(32) E. Vogel, *Angew. Chem.*, **66**, 306, 640 (1954); *Fortschr. Chem. Forsch.*, **3**, 430 (1955).

(33) A. H. R. Cole, *J. Chem. Soc.*, 4969 (1952).

(34) D. H. R. Barton, *ibid.*, 1027 (1953); W. G. Dauben, E. J. Blanz, J. Jiu and R. A. Micheli, THIS JOURNAL, **78**, 3752 (1956).

topyrocalciferone (XI) was reduced with the same reagent the inverted alcohol was obtained, but in this case since the conformation of ring B is not known with certainty the conformation of the hydroxyl group cannot be assigned. However, in photopyrocalciferol (IX) the hydroxyl bending frequency appeared at 1000 cm.$^{-1}$ while in *epi*-photopyrocalciferol the band appeared at 1040 cm.$^{-1}$. This shift of 40 cm.$^{-1}$ is suggestive of a conformational change from axial to equatorial[35] and would indicate that ring A has a normal chair conformation.

With regard to the over-all irradiation process in which a ring B diene possessing 9,10-*anti* stereochemistry leads to ring opening while a 9,10-*syn* isomer leads to ring formation, it is of interest to examine the process in more detail. In the irradiation of a conjugated diene with ultraviolet light, the first stage of the process could lead to an excited singlet state. A reasonable diagrammatic representation of this excited state could be XLIV in which partial bonding between C-5 and C-8 would be present. Such a state could then collapse either to starting diene I or to the valence tautomeric structure XIII. Perhaps a less energetically favored collapse of the initial exited state would involve cleavage of the 9,10-bond to form the *seco*-excited state XLV which would ultimately stabilize itself as the conjugated trienic system found in precalciferol (VII). This latter sequence is similar to that



previously suggested by Havinga.[13] The controlling feature of such a sequence is the relative energies of the valence tautomeric forms derived from *syn* and *anti* isomers. As pointed out earlier, to achieve a stable valence tautomer such as suggested for photoisopyro and photopyrocalciferol, the fusion of rings A and C to the cyclobutane ring must be *cis*. Such an arrangement is possible with a *syn* isomer but not in an *anti* isomer which would have at least one juncture *trans*. This latter valence tautomeric form would be highly unstable and collapse of the excited state to such a structure would not be favored, and the irradiation process would follow the alternate course of ring opening.

(35) A. Fürst, H. H. Kuhn, R. Scotoni, Jr., and Hs. H. Günthard, *Helv. Chim. Acta*, **35**, 951 (1952); A. H. R. Cole, R. N. Jones and K. Dobriner, THIS JOURNAL, **74**, 5571 (1952); H. Rosenkrantz, A, T. Milhorat and M. Farber, *J. Biol. Chem.*, **195**, 509 (1952).

Experimental[36]

Isopyrocalciferol Series

Isopyrocalciferone ($\Delta^{5,7,22}$-9β-Ergostatrien-3-one) (IIc).—A solution made up from 1.02 g. (2.58 mmoles) of isopyrocalciferol (m.p. 115–116°),[10] 0.748 g. of aluminum isopropoxide, and 3 ml. cyclohexanone in 75 ml. of dry toluene was refluxed for one hour. The pale yellow solution was decomposed by dilution with 250 ml. of a saturated solution of Rochelle salt, the toluene phase separated and the aqueous phase extracted three times with 70 ml. of ether. The combined toluene and ether extracts were washed with water and subjected to steam distillation until the odor of cyclohexanone could not be detected in the distillate. Upon cooling, the residue solidified and was separated by suction filtration. The solid was recrystallized by 10% ether–methanol to yield 791 mg. (77%) of colorless needles, m.p. 119–122°. Two additional recrystallizations from the same solvents gave 728 mg. (71%) of isopyrocalciferone, m.p. 124.5–126.0°, $[\alpha]^{20}D$ + 545° ($CHCl_3$); λ_{max}^{EtOH} 274 mμ, ϵ 9930; 283 mμ, ϵ 9800.

Anal. Calcd. for $C_{28}H_{42}O$ (394.62): C, 85.22; H, 10.73. Found: C, 85.07; H, 10.63.

$\Delta^{4,7,22}$-9β-Ergostatrien-3-one (IIIc).—A solution of 483 mg. (1.23 mmoles) of isopyrocalciferone (IIc) in 20 ml. of 2% methanolic potassium hydroxide was warmed on a steam-bath for 20 minutes. The yellow solution was neutralized with acetic acid and concentrated to a small volume. The residue was diluted with water, extracted with ether, the ethereal extracts dried and the solvent evaporated. The remaining yellow oil was chromatographed on 15 g. of alumina (Woelm neutral activity I). Elution with 30% benzene–pentane yielded a light yellow oil which crystallized from methanol at −10°. Three recrystallization from 10% ether–pentane at −20° gave 268 mg. (55.5%) of thick rods, m.p. 116–118°, λ_{max}^{EtOH} 242 mμ, ϵ 11,600.

Anal. Calcd. for $C_{28}H_{42}O$ (394.62): C, 85.22; H, 10.73. Found: C, 85.01; H, 10.69.

$\Delta^{4,6,22}$-9β-Ergostatrien-3-one (IVc). (a) By Acid Isomerization.—A solution of 591 mg. (1.50 mmoles) of isopyrocalciferone (IIc) in 20 ml. of methanol was heated to reflux and 1 ml. of concentrated hydrochloric acid was added. The resulting red solution was refluxed for one hour, 1 g. of sodium bicarbonate was added cautiously and the solution allowed to cool. The precipitated salts were filtered, the filtrate concentrated and the yellow-brown residue chromatographed on 20 g. of alumina (Woelm, neutral, Activity I). Elution with 40% benzene–pentane yielded a light yellow oil, λ_{max}^{EtOH} 283 mμ, ϵ 20,700.

The majority of the product was allowed to stand for several weeks at which time a portion had crystallized. Upon trituration of the mixture with methanol, the entire material crystallized and was recrystallized twice from aqueous methanol, yield 101 mg. (17%), m.p. 161–162.5°, $[\alpha]^{22}D$ −15.5° ($CHCl_3$), λ_{max}^{EtOH} 283 mμ, ϵ 24,800.

Anal. Calcd. for $C_{28}H_{42}O$ (394.62): C, 85.22; H, 10.73. Found: C, 85.36; H, 10.88.

The semicarbazone was prepared in the usual manner utilizing a portion of the crude product, m.p. 221–223°, λ_{max}^{EtOH} 305 mμ, ϵ 37,400.

Anal. Calcd. for $C_{29}H_{45}ON_3$ (451.67): C, 77.11; H, 10.04; N, 9.30. Found: C, 77.31; H, 10.05; N, 9.17.

(b) By **Alkaline Isomerization.**—A solution of 300 mg. (0.76 mmole) of isopyrocalciferone (IIc) in 20 ml. of 2% methanolic potassium hydroxide was refluxed on a steam-bath and after 100 minutes the ultraviolet spectrum of the solution displayed a single absorption at 283 mμ. The brown reaction solution then was poured into water, the excess methanol evaporated and the residue dissolved in ether. The ethereal solution was washed with water, dried and the solvent evaporated to yield 230 mg. of brown oil. Upon addition of a few drops of petroleum ether, the residue crystallized and the solid was recrystallized from benzene, yield 157 mg. (52%), m.p. 161–163°, $[\alpha]^{20}D$ −12° ($CHCl_3$).

Hexahydroisopyrocalciferol.—A solution of 638 mg. (1.6 mmoles) of isopyrocalciferol in 100 ml. of 95% ethanol containing 71 mg. of pre-reduced PtO_2 catalyst was hydrogenated at atmospheric pressure and room temperature. Three

(36) Analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California. All melting points are corrected.

equivalents of hydrogen was absorbed in 40 minutes. After removal of the catalyst and evaporation of most of the solvent, the product crystallized and was recrystallized from the same solvent, yield 581 mg. (90%), m.p. 81–82°, $[\alpha]^{20}D$ −9.5° ($CHCl_3$). Busse[10] reported m.p. 68–80°, $[\alpha]^{20}D$ −6.9°.

Anal. Calcd. for $C_{28}H_{50}O$ (402.69); C, 83.51; H, 12.52 Found: C, 83.37; H, 12.68.

Isopyrocalciferyl Acetate–Maleic Anhydride Adduct (Vc).—A solution of 450 mg. (1.03 mmoles) of isopyrocalciferyl acetate (m.p. 114.5–115.5°)[10] and 400 mg. of maleic anhydride in 10 ml. of benzene was refluxed for 5 hours, the solvent removed at reduced pressure and the residue recrystallized three times from acetic anhydride, yield 375 mg. (68%), 204.0–205.5°, $[\alpha]^{22}D$ +121.5° ($CHCl_3$).

Anal. Calcd. for $C_{34}H_{48}O_5$ (536.72): C, 76.08; H, 9.01. Found: C, 75.91; H, 9.09.

Isopyrocalciferyl Acetate 5,8-Epidioxide (VIc).—A solution of 1.00 g. (2.29 mmoles) of isopyrocalciferyl acetate, 1 ml. of pyridine and 500 mg. of eosin yellow (American Dyewood Co., No. 6700) in 500 ml. of absolute ethanol was placed in a 1-l. round-bottomed flask equipped with a gas inlet tube and a reflux condenser capped with a drying tube. The flask was placed in the center of a three tier system of 40 watt G.E. daylight circular fluorescent lamps[37] and dry oxygen was introduced through the gas inlet tube at the rate of 5.0–5.5 liters per hour. The course of the reaction was followed by removing aliquots, diluting to an appropriate concentration and determining the residual ultraviolet absorption from 270 to 300 mμ (corrected for eosin absorption). The reaction was more than 90% complete in 6 hours. At this time, the irradiation was stopped, the solution evaporated to dryness at 40° under reduced pressure and the residual material chromatographed on 100 g. of alumina (Woelm, neutral, Activity I). Elution with 4% ether–benzene (fractions 8–19) yielded 873 mg. (81%) of crude isopyrocalciferyl acetate 5,8-epidioxide, m.p. 151–155°. Three recrystallization from ethanol gave 781 mg. (73%) of product, m.p. 160.2–161.8°, $[\alpha]^{20}D$ +69° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{46}O_4$ (470.67): C, 76.55; H, 9.85. Found: C, 76.88; H, 9.59.

By systematic change of solvents, a mixture of 1% methanol–ether (fractions 51–57) yielded 73 mg. (7.4%) of crystalline material, m.p. 134–139°. Two recrystallizations from aqueous ethanol gave 41 g. (4%) of isopyrocalciferol 5,8-epidioxide, m.p. 145–146°.

Anal. Calcd. for $C_{28}H_{44}O_3$ (428.63): C, 78.40; H, 10.34. Found: C, 78.59; H, 10.50.

Hydrolysis of isopyrocalciferyl acetate 5,8-epidioxide with methanolic potassium hydroxide yielded the free alcohol, m.p. 145–147°, undepressed on admixture with material isolated directly from chromatography. Acetylation of the epidioxide yielded the starting acetate.

Examination of all intermediate fractions and final washings from the chromatography for $\Delta^{9,11}$-dehydroergosterol (by ultraviolet absorption) failed to show its presence.

Photoisopyrocalciferol (VIII).—The material was prepared in 93% yield following the procedure of Dimroth,[14] m.p. 81–82°, $[\alpha]^{20}D$ −11.5° ($CHCl_3$).

Photoisopyrocalciferone (X).—A solution of 1.30 g. (3.3 mmoles) of photoisopyrocalciferol in 390 ml. of glacial acetic acid was cooled to 0–5° and 10 ml. of benzene was added to prevent crystallization. The cooled mixture was swirled slowly and a solution of 0.525 g. of chromium trioxide in 130 ml. of glacial acetic acid was added, portionwise, over a period of 15-minutes. The mixture was allowed to stand for 2 hours in an ice-bath and then 12 hours at room temperature. The excess oxidant was destroyed by addition of 10 ml. of ethanol and the solution concentrated under reduced pressure to a volume of about 20 ml. The residue was diluted with 300 ml. of water and extracted with three 100-ml. portions of ether. The combined ether extracts were washed with dilute sodium bicarbonate solution, dried and concentrated under reduced pressure. The residual oil crystallized on trituration with ethanol and the crude product was recrystallized twice from ethanol to yield 1.131 g. (87%) of photoisopyrocalciferone, m.p. 79.2–80.3°, $[\alpha]^{24}D$ −114.9° ($CHCl_3$), $\epsilon^{heptane}_{205}$ 430 (lit.[14] m.p. 79–80°, $[\alpha]^{19}D$ −116°).

The ketone also was prepared directly by irradiation of isopyrocalciferone (IIc). From 783 mg. (1.98 mmoles) of IIc, there was obtained 731 mg. (93%) of the photoketone X.

Ozonization of Photoisopyrocalciferyl Acetate (Tricarboxylic Acid XVI).—A solution of 1.12 g. (2.55 mmoles) of photoisopyrocalciferyl acetate and 1 ml. of pyridine in 50 ml. of chloroform was cooled to −15° and a stream of ozone in oxygen (0.5 mmole ozone per minute) was passed through the solution. When 2.1 equivalents of ozone had been consumed by the solution, it was allowed to warm to room temperature and concentrated at reduced pressure to a volume of 20 ml. The residual solution was diluted with a solution of 3 ml. of 30% hydrogen peroxide in 20 ml. of ethyl acetate and 20 ml. of acetic acid. After standing for 12 hours, the solution was diluted with 300 ml. of water and the chloroform layer separated. The aqueous phase was extracted twice with 100-ml. portions of ether. The combined extracts were dried, the solvent evaporated and the residual colorless oil crystallized from acetonitrile. After three recrystallizations from acetonitrile, there was obtained 403 mg. (35%) of thick needles, m.p. 272–275° dec., $[\alpha]^{21}D$ +21.5° ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{34}O_8$ (450.51): C, 63.90; H, 7.60; neut. equiv., 150. Found: C, 64.71; H, 7.51; neut. equiv., 157.

A solution of 193 mg. (0.43 mmole) of the tricarboxylic acid acetate in 40 ml. of 5% methanolic potassium hydroxide was warmed on a steam-bath for 30 minutes, cooled, acidified with acetic acid and diluted with 300 ml. of water. The precipitate was recrystallized three times from aqueous acetonitrile, yield 97 mg. (55%), m.p. 289–292° dec., $[\alpha]^{18}D$ +29° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_7$ (408.48): C, 64.68; H, 7.89. Found: C, 64.51; H, 7.81.

Tricarboxylic Acid Anhydride Acetate (XVII).—A solution of 163 mg. (0.37 mmole) of tricarboxylic acid acetate in 5 ml. of acetic anhydride was heated and the solvent allowed to distil. After removal of the solvent, the colorless crystalline residue was recrystallized three times from 50% benzene–acetonitrile, yield 92 mg. (57.5%), m.p. 243–244°, $[\alpha]^{20}D$ +17.5° ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{32}O_7$ (432.50): C, 66.64; H, 7.46. Found: C, 66.78; H, 7.62.

6,7-Dihydrophotoisopyrocalciferol (XIV).—A solution of 500 mg. (1.26 mmoles) of photoisopyrocalciferyl acetate in 20 ml. of 95% ethanol was hydrogenated at room temperature and atmospheric pressure over 95 mg. of pre-hydrogenated 5% palladium–charcoal catalyst. In 12 minutes, 1.05 equivalents of hydrogen had been absorbed and then the catalyst was filtered and washed with ethanol. The combined filtrate and washing were evaporated to yield a colorless oil which resisted crystallization. The material was hydrolyzed by heating on a steam-bath for 20 minutes with 100 ml. of 5% methanolic potassium hydroxide. Upon cooling the hydrolysis mixture and diluting with water, the product crystallized as long fibrous needles. The material was recrystallized three times from aqueous methanol to yield 419 mg. (83.5%) of 6,7-dihydrophotoisopyrocalciferol, m.p. 58–59°, $[\alpha]^{20}D$ −49° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{46}O$ (398.65); C, 84.35; H, 11.63. Found: C, 84.46; H, 11.58.

The 3,5-dinitrobenzoate ester was prepared by reaction with 3,5-dinitrobenzoyl chloride and was recrystallized from methanol, m.p. 131.5–132.5°.

Anal. Calcd. for $C_{35}H_{48}O_6N_2$ (592.75): C, 70.92; H, 8.16; N, 4.73. Found: C, 71.10; H, 8.09; N, 4.84.

6,7,22,23-Tetrahydrophotoisopyrocalciferol (XV).—Photoisopyrocalciferol (1.731 g., 4.25 mmoles) in 50 ml. of 95% ethanol was hydrogenated in the presence of 5% palladium–charcoal catalyst at atmospheric pressure. Two equivalents of hydrogen was absorbed in 25 minutes. The catalyst was filtered, the filtrate concentrated and the remaining oil was crystallized three times from methanol, yield 1.620 g. (93%), m.p. 51.0–52.5°, $[\alpha]^{20}D$ −11.5° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.07. Found: C, 84.02; H, 12.01.

The hydrogenation of 6,7-dihydrophotoisopyrocalciferol under the same conditions yielded the same tetrahydro derivative.

The 3,5-dinitrobenzoate ester was prepared by reaction with 3,5-dinitrobenzoyl chloride and was recrystallized from methanol, m.p. 127–128°.

(37) E. Mosettig and I. Scheer, *J. Org. Chem.*, **17**, 764 (1952).

Anal. Calcd. for $C_{35}H_{50}O_6N_2$ (594.77): C, 70.67; H, 8.47; N, 4.71. Found: C, 70.49; H, 8.55; N, 4.63.

6,7,22,23-Tetrahydrophotoisopyrocalciferone (XXI).—A solution of 983 mg. (2.42 mmoles) of tetrahydrophotoisopyrocalciferol in 30 ml. of glacial acetic acid and 10 ml. of benzene was cooled to 5° and a solution of 1.031 g. of chromium trioxide in 30 ml. of glacial acetic acid was added, portionwise, over a period of 30 minutes. After standing 4 hours at 5° and 12 hours at room temperature, the mixture was processed in the usual fashion. The pale yellow oily product was dissolved in petroleum ether (30–60°) and on chilling to 25° yielded 794 mg. (81%) of crystalline material, m.p. 47.0–48.5°, $[\alpha]^{20}D$ 19.5° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{46}O$ (398.65): C, 84.35; H, 11.63. Found: C, 84.51; H, 11.47.

The semicarbazone was prepared in the standard fashion, m.p. 199–201°.

Anal. Calcd. for $C_{29}H_{49}ON_3$ (455.70): C, 76.42; H, 10.84; N, 9.22. Found: C, 76.62; H, 10.73; N, 9.31.

The tetrahydro ketone also was prepared directly from photoisopyrocalciferone (X) by hydrogenation in ethanol in the presence of 5% palladium–charcoal catalyst. The yield was 78%.

Tetrahydrophotoisopyrocalciferol Ring A-*seco*-diacid (XXII).—A solution of 783 mg. (1.93 mmoles) of tetrahydrophotoisopyrocalciferol and 2.110 g. of chromium trioxide in 75 ml. of 95% acetic acid was heated at 70° for a period of 2 hours. The solution was allowed to cool to room temperature and the excess oxidant destroyed by the addition of 10 ml. of ethanol. The mixture was concentrated under reduced pressure to a small volume and diluted with 200 ml. of water. The organic material was extracted with ether, the ethereal solution washed with water and then extracted with 100 ml. of 5% aqueous sodium bicarbonate solution.

The ethereal solution containing neutral material was dried and evaporated to yield unreacted starting alcohol (121 mg.). The sodium bicarbonate extract was acidified with 5% hydrochloric acid and the organic material extracted with ether. The ethereal extracts were dried and evaporated to yield an oil which would not crystallize. This material was dissolved in 10 ml. of ether and allowed to react with an excess of diazomethane. After destroying the excess reagent, the ether was evaporated and the residual oil crystallized upon triturating with ethanol and cooling in an ice-bath, yield 421 ml. (47%), m.p. 59–62°. The diester was recrystallized twice from methanol, m.p. 65.0–66.5°, $[\alpha]^{20}D$ +81° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{50}O_4$ (464.64): C, 77.55; H 8.68; sapn. equiv., 232.3. Found: C, 77.68; H, 8.47; sapn. equiv., 229.

A solution of 201 mg. (0.432 mmole) of the dimethyl ester in 30 ml. of 5% methanolic potassium hydroxide was refluxed for one hour. The solution was diluted with 300 ml. of water, acidified with 5% hydrochloric acid and extracted three times with 70-ml. portions of ether. The combined ether extracts were washed with water, dried and the ether evaporated. The crude diacid was recrystallized three times from acetonitrile, yield 126 mg. (65%), m.p. 135.0–136.5°, $[\alpha]^{20}D$ +63.5° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{46}O_4$ (446.65): C, 75.29; H, 10.38; neut. equiv., 223.3. Found: C, 75.12; H, 10.47; neut. equiv., 219.

When 502 mg. (1.26 mmoles) of tetrahydrophotoisopyrocalciferone (XV) was oxidized at 70° with a solution of 1.873 g. of chromium trioxide in 50 ml. of acetic acid, 204 mg. (36%) of the above *seco*-diacid was obtained.

Tetrahydrophotoisopyrocalciferol Ring A-*seco*-lactone (XXIII).—To a solution of 631 mg. (1.58 mmoles) of tetrahydrophotoisopyrocalciferone in 10 ml. of chloroform, there was added 12 ml. of a chloroform solution of perbenzoic acid containing 71.5 mg. of perbenzoic acid per ml. The mixture was allowed to stand at room temperature for 27 hours and then diluted with 100 ml. of ether and extracted with a saturated solution of sodium bicarbonate. The ether phase was washed with water, the solvent evaporated and the oily residue was triturated with methanol and cooled in an ice-bath. The crystalline product was recrystallized three times from methanol, yield 418 mg. (65%), m.p. 71.5–73.0°, $[\alpha]^{20}D$ +18.5° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{46}O_2$ (414.65): C, 81.10; H, 11.18. Found: C, 81.30; H, 11.31.

Tetrahydrophotoisopyrocalciferol Ring A-*seco*-hydroxy Acid (XXIV).—A solution of 728 mg. (1.76 mmoles) of lactone XXIII in 30 ml. of 5% methanolic potassium hydroxide was refluxed for one hour, the solution cooled to room temperature and acidified with acetic acid. The mixture was diluted with 200 ml. of water, extracted with ether and the ethereal solution dried and evaporated. The crystalline residue was recrystallized three times from aqueous acetonitrile, yield 493 mg. (65%), m.p. 172–173°, $[\alpha]^{20}D$ +37.5° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{48}O_3$ (432.66): C, 77.72; H, 11.18. Found: C, 77.59; H, 11.01.

The methyl ester was prepared by allowing the hydroxy acid to react with an excess of diazomethane and was recrystallized from methanol, m.p. 57.5–59.0°, $[\alpha]^{20}D$ +29° ($CHCl_3$).

Anal. Calcd. for $C_{29}H_{50}O_3$ (446.69): C, 77.97; H, 11.28. Found: C, 77.69; H, 11.19.

A solution of 163 mg. (0.38 mmole) of hydroxy acid XXIV in 50 ml. of acetic acid was allowed to react at 5° with a solution of 211 mg. of chromium trioxide in 10 ml. of acetic acid. After 10 hours, the reaction was processed in the usual manner and there was obtained 84 mg. (50%) of ring A-*seco*-diacid XXII, m.p. 135–136°, undepressed upon admixture with authentic sample.

Base-catalyzed Isomerization of Photoisopyrocalciferone to $\Delta^{4,6,22}$-9β-Ergostatrien-3-one (IVc).—To a solution of 500 mg. of potassium in 20 ml. of *t*-butyl alcohol was added 683 mg. (1.73 mmoles) of photoisopyrocalciferone (X) and the solution allowed to stand at room temperature for 49 hours. During this period, aliquots were withdrawn and their ultraviolet spectrum in the 280–285 mμ range was measured; the final extinction coefficient was 9500. The solution then was diluted with water and extracted with ether. Evaporation of the ether yielded a yellow oil which was chromatographed on 25 g. of alumina (Woelm, neutral, activity I). Elution with 40% benzene–pentane gave an almost colorless oil which crystallized upon standing for several weeks. The material then was recrystallized from aqueous methanol, yield 178 mg. (26%), m.p. 160–162°, undepressed upon admixture with authentic sample, $[\alpha]^{22}D$ −15.5° ($CHCl_3$), λ_{max}^{EtOH} 283 mμ (ε 24,700).

The semicarbazone was prepared in the usual manner, m.p. 221–223°, λ_{max}^{EtOH} 305 mμ (ε 38,500).

Pyrolysis of Photo Compounds. (a) **Photoisopyrocalciferol (VIII).**—Photoisopyrocalciferol (281 mg., 0.71 mmole) was heated *in vacuo* at 180° in a oil-bath for a period of 3 hours. Upon cooling, the melt crystallized and after trituration with methanol and filtration there was obtained 270 mg. (96%) of isopyrocalciferol, m.p. 114–116°, undepressed upon admixture with authentic sample, $[\alpha]^{20}D$ +330° ($CHCl_3$). Pyrolysis of photoisopyrocalciferyl acetate in the same manner yielded isopyrocalciferyl acetate. (b) **Photoisopyrocalciferone (X).**—The ketone, 289 mg. (0.73 mmole), was heated as above, and upon cooling the product was recrystallized to yield 247 mg. (86%) of isopyrocalciferone, m.p. 120–123°. Two additional recrystallizations gave 226 mg. of pure ketone, m.p. 125–126°, undepressed upon admixture with an authentic sample, $[\alpha]^{20}D$ +51.5° ($CHCl_3$). (c) **Tetrahydrophotoisopyrocalciferol (XV).**—The tetrahydro alcohol (357 mg. 0.89 mmole) was heated for 10 hours at 200°. Upon cooling, the solid melt was recrystallized from methanol to yield 304 mg. (85%) of unchanged starting material, m.p. 51–52°.

Lithium Aluminum Hydride Reduction of Ketones. (a) **Isopyrocalciferone (IIc).**—A solution of 211 mg. (0.54 mmole) of isopyrocalciferone and 197 mg. of lithium aluminum hydride in 20 ml. of anhydrous ether was allowed to react for 6 hours. The excess reducing agent was destroyed with ethyl acetate and the mixture diluted with water. The ether phase was washed with water, dried and the solvent evaporated. The crystalline residue was recrystallized from 10% ether–methanol to yield 181 mg. (85%) of isopyrocalciferol, m.p. 109–112°. A further recrystallization from the same solvent yielded 164 mg. of product, m.p. 115–116°, undepressed upon admixture with an authentic sample, $[\alpha]^{20}D$ +332° ($CHCl_3$). (b) **Photoisopyrocalciferone (X).**—A solution of 327 mg. (0.83 mmole) of photoisopyrocalciferone and 294 mg. of lithium aluminum hydride in 30 ml. of anhydrous ether was allowed to react for 4 hours and then processed as above. The residue was crystallized from ether–methanol to yield 267 mg. (81%) of photoiso-

pyrocalciferol, m.p. 76–80°. Two additional recrystallizations gave 221 mg. of product, m.p. 81–82°, undepressed upon admixture with an authentic sample, $[\alpha]^{20}D$ −11.0° ($CHCl_3$).

Pyrocalciferol Series.

Pyrocalciferone ($\Delta^{5,7,22}$-9α-Lumistatrien-3-one (IId).—The Oppenauer oxidation was conducted as in the isopyro series. From 1.3 g. (3.3 mmoles) of pyrocalciferol (m.p. 95–96°)[10] there was obtained 918 mg. (71%) of pyrocalciferone after three recrystallizations from ether–pentane, m.p. 117–119°, $[\alpha]^{21}D$ +940° ($CHCl_3$); λ_{max}^{EtOH} 272 mμ (ε 9100); 285 mμ (ε 9050).

Anal. Calcd. for $C_{28}H_{42}O$ (394.62): C, 85.22; H, 10.73. Found: C, 85.37; H, 10.75.

$\Delta^{4,7,22}$-9α-Lumistatrien-3-one (IIId).—The base-catalyzed isomerization was conducted as in the isopyro series. From 187 mg. (0.47 mmole) of pyrocalciferone, there was obtained 61 mg. (32.6%) of IIId after four recrystallizations from methanol, m.p. 97–99°, λ_{max}^{EtOH} 243 mμ (ε 9850).

Anal. Calcd. for $C_{28}H_{42}O$ (394.62): C, 85.22; H, 10.73. Found: C, 85.01; H, 10.69.

Hexahydropyrocalciferol. (a) **Neutral Solution.**—A solution of 103 mg. (0.26 mmole) of pyrocalciferol in 20 ml. of 95% ethanol containing 15 mg. of pre-reduced PtO_2 catalyst was hydrogenated at atmospheric pressure and room temperature. Three equivalents of hydrogen was absorbed in 150 minutes, after removal of the catalyst and evaporation of the solvent, the product crystallized and was recrystallized three times from aqueous acetone, yield 84 mg. (81%), m.p. 131.0–132.5°, $[\alpha]^{20}D$ +36° ($CHCl_3$). Busse[10] reported m.p. 130–131°, $[\alpha]^{18}D$ +34.5°.

Anal. Calcd. for $C_{28}H_{50}O$ (402.69): C, 83.51; H, 12.52. Found: C, 83.42; H, 12.59.

(b) **Acetic Acid Solution.**—A solution of 97 mg. (0.25 mmole) of pyrocalciferol in 20 ml. of glacial acetic acid containing 16 mg. of pre-reduced PtO_2 catalyst was hydrogenated as above. After 20 minutes the reaction was complete and the material processed in the usual manner. There was obtained 71 mg. (72%) of hexahydropyrocalciferol, m.p. 131–132°, no depression when admixed with above sample, $[\alpha]^{20}D$ +35.5° ($CHCl_3$).

Pyrocalciferyl Acetate–Maleic Anhydride Adduct (Vd).—Proceeding as in the isopyro series, there was obtained from 131 mg. (0.30 mmole) of pyrocalciferyl acetate, 101 mg. (63%) of crystalline adduct after three recrystallizations from acetic anhydride, m.p. 159–161°, $[\alpha]^{23}D$ +217° ($CHCl_3$).

Anal. Calcd. for $C_{34}H_{48}O_5$ (536.72): C, 76.08; H, 9.01. Found: C, 76.13; H, 8.90.

Pyrocalciferyl Acetate 5,8-Epidioxide (VId).—A solution of 1.00 g. (2.29 mmoles) of pyrocalciferyl acetate, 1 ml. of pyridine and 500 mg. of eosin yellow in 500 ml. of absolute ethanol was irradiated in the presence of oxygen as described in the isopyro series. The reaction was more than 95% complete in 4 hours. Upon chromatography of the reaction product on alumina, 10% ether–benzene elutants yielded 784 mg. (72.5%) of crude epidioxide acetate and 1% methanol–ether elutants yielded 104 mg. (10.6%) of crude epidioxide. The acetate was recrystallized three times from methanol, yield 691 mg. (64%), m.p. 148.5–150.01, $[\alpha]^{20}D$ +295° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{44}O_4$ (470.67): C, 76.55; H, 9.85. Found: C, 76.72; H, 9.69.

The pyrocalciferol 5,8-epidioxide from the latter fractions was recrystallized from aqueous acetone, yield 81 mg. (8.3%), m.p. 175.5–177.5°, $[\alpha]^{20}D$ +206° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{44}O_3$ (428.63): C, 78.40; H, 10.34. Found: C, 78.52; H, 10.41.

Photopyrocalciferol (IX) was prepared in 93% yield following the procedure of Dimroth,[14] m.p. 104–105°, $[\alpha]^{20}D$ +52° ($CHCl_3$).

Photopyrocalciferone (XI).—The oxidation of photopyrocalciferol was conducted as described for the photoisopyro series. From 1.72 g. (4.33 mmoles) of starting alcohol, there was obtained after three crystallization from aqueous acetone, 1.12 g. (65.5%) of photopyrocalciferone, m.p. 91–92°, $[\alpha]^{22}D$ +192.5° ($CHCl_3$) (lit.[14] m.p. 91°, $[\alpha]$ +197°).

The ketone also was prepared directly by irradiation of pyrocalciferone IId. From 283 mg. (0.72 mmole) of IId, there was obtained 201 mg. (71%) of photopyrocalciferone. In addition, direct oxidation of 3-*epi*-photopyrocalciferol ($LiAlH_4$ reduction product of photo ketone XI) yielded the photopyrocalciferone in 83.5% yield.

Ozonization of Photopyrocalciferyl Acetate (Tricarboxylic Acid Preparation).—Photopyrocalciferyl acetate (513 mg., 1.17 mmoles) in 50 ml. of chloroform and 1 ml. of pyridine was ozonized and processed in the same manner as described for the photoisopyro series. The product was recrystallized three times from acetonitrile, yield 261 ml. (49.5%), m.p. 259–262°, $[\alpha]^{19}D$ −31.5° ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{34}O_8$ (450.51): C, 63.90; H, 7.60; neut. equiv., 150. Found: C, 63.82; H, 7.61; neut. equiv., 151.

The anhydride was prepared in the manner described for the photoisopyro series, m.p. 217–219°, $[\alpha]^{21}D$ −39.3° ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{32}O_7$ (432.50): C, 66.64; H, 7.46. Found: C, 66.54; H, 7.59.

Pyrolysis of Photo Compounds. (a) **Photopyrocalciferol.**—An evacuated sealed tube containing 216 mg. (0.545 mmole) of photopyrocalciferol was heated to 185° for one hour. The tube was allowed to cool and its contents recrystallized from 5% ether–methanol to yield 201 mg. (93%) of pyrocalciferol, m.p. 94.5–95.5°, $[\alpha]^{21}D$ +512° ($CHCl_3$), λ_{max}^{EtOH} 272 mμ (ε 9150), 285 mμ (ε 9000). The infrared spectrum was identical with an authentic sample. (b) **3-*epi*-Photopyrocalciferol.**—The *epi*-alcohol (109 mg., 0.275 mmole) was heated as above and product recrystallized three times from methanol, to yield 3-*epi*-pyrocalciferol, m.p. 124–125°, $[\alpha]^{21}D$ +409° ($CHCl_3$), λ_{max}^{EtOH} 272 mμ (ε 9200) 285 mμ (ε 9120).

Anal. Calcd. for $C_{28}H_{44}O$ (396.63): C, 84.78; H, 11.18. Found: C, 84.52; H, 11.27.

Lithium Aluminum Hydride Reduction of Ketones. (a) **Pyrocalciferone.**—A solution of 461 mg. (1.17 mmoles) of pyrocalciferone and 387 mg. of lithium aluminum hydride in 80 ml. of anhydrous ether was allowed to react for 2 hours. After processing the reaction mixture as in the isopyro series, the product was recrystallized three times to yield 401 mg. (86%) of 3-*epi*-pyrocalciferol, m.p. 123.5–125.0°, no depression when admixed with 3-*epi* product from pyrolysis of photo compound, $[\alpha]^{19}D$ +411° ($CHCl_3$). (b) **Photopyrocalciferone.**—A solution of 179 mg. (0.543 mmole) of photopyrocalciferone and 104 mg. of lithium aluminum hydride in 30 ml. of anhydrous ether was allowed to react for 6 hours. After processing the reaction mixture in the standard fashion, the product was recrystallized twice from methanol to yield 151 mg. (83.5%) of 3-*epi*-photopyrocalciferol, m.p. 90–91°, $[\alpha]^{23}D$ +41° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{44}O$ (396.63): C, 84.78; H, 11.18. Found: C, 84.83; H, 11.07.

When 247 mg. (0.623 mmole) of 3-*epi*-pyrocalciferol in 300 ml. of anhydrous ether was irradiated in the usual fashion and the product recrystallized twice from methanol, there was obtained 198 mg. (80%) of 3-*epi*-photoisopyrocalciferol, m.p. 90–91°, undepressed upon admixture with product from above $LiAlH_4$ reduction, $[\alpha]^{23}D$ +40.5° ($CHCl_3$).

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