The Crystal Structure of Photoisopyrocalciferyl *m*-Bromobenzoate[1]

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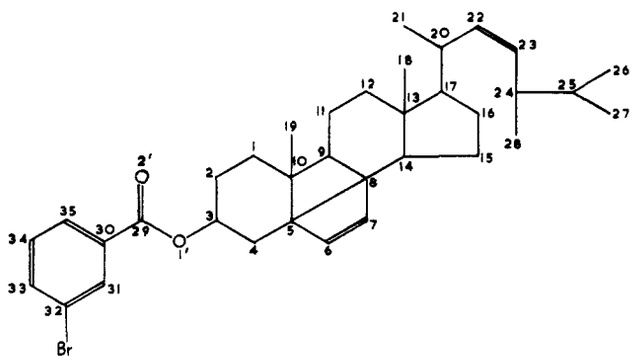
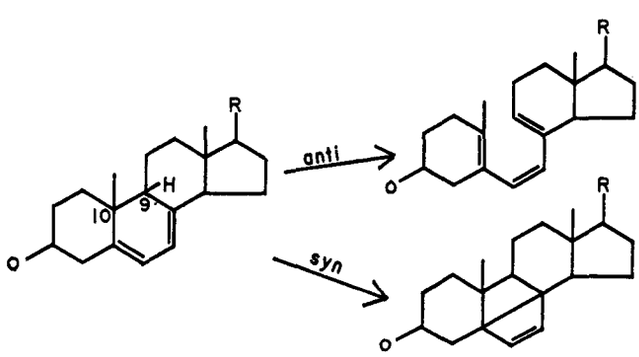
The molecular structure of photoisopyrocalciferol has been determined by a crystallographic investigation of the *m*-bromobenzoate ester. The unit cell is described by space group $P2_1$ with dimensions *a* 21.20, *b* 7.38, *c* 10.34 Å, β 92.77° containing two $C_{35}H_{47}O_2Br$ molecules. The B ring of the sterol nucleus is in the form of two fused four-membered rings, one of which contains a double bond. The cyclobutene ring is *cis* to the C-19 methyl group on one side of the cyclobutane ring, while on the opposite side the A and C rings are attached in *cis* configuration. The sterol configuration may be described as 3β-OH, 9β-H, 10β-CH_3, 13β-CH_3, and 17β-C_9H_{17}.

The structural formula of photoisopyrocalciferyl *m*-bromobenzoate was proposed by Dauben and Fonken,[2] and it has been confirmed by this analysis. Photoisopyrocalciferol is a member of the vitamin D series



of sterols derived from ergosterol.[3] If calciferol is heated at 188° in a sealed tube a 1:1 mixture of pyrocalciferol and isopyrocalciferol is produced.[4] The latter compounds contain the conjugated diene structure as does ergosterol.[5]

Ultraviolet irradiation of these pyro compounds gives, respectively, photopyrocalciferol and photoisopyrocalciferol.[6] The compounds with the conjugated diene bonds in the B ring undergo rearrangement when irradiated with ultraviolet light. The products which form depend on the configuration at C-9 and C-10.[2] When the C-9 and C-10 substituents are in the *anti* configuration, in particular 8α-H, 10β-CH_3 in ergosterol and 9β-H, 10α-CH_3 in lumisterol, irradiation induces ring opening between C-9 and C-10 to form the triene precalciferol now believed to be the precursor of calciferol in its formation from ergosterol. In the case of the two *syn* isomers, 9α-H, 10α-CH_3 in pyrocalciferol and 9β-H, 10β-CH_3 in isopyrocalciferol, the irradiation products are those formed by ring closure with a single bond across the B ring between C-5 and C-8 and with a double bond in the position between C-6 and C-7.



Dauben and Fonken have proposed the structures of the photo compounds based on chemical and spectroscopic studies.[2] The present study was undertaken to determine the stereochemistry of photoisopyrocalciferol by independent means.

Experimental Section

The crystals used in this study were kindly supplied by Dr. Dauben and Dr. Bauman. They prepared crystals of the ester of photoisopyrocalciferol and *m*-bromobenzoic acid with mp 94.0–94.5°. *Anal.* Calcd for $C_{35}H_{47}O_2Br$: C, 72.52; H, 8.17; Br, 13.79. Found: C, 72.23; H, 8.17; Br, 13.58. The crystals form flat colorless needles with the long dimension parallel to the *b* axis (Table I). The *a* axis is perpendicular to the flat sides of the crystals. Weissenberg photographs show monoclinic symmetry with systematic absences only of the type 0*k*0 for *k* odd. For assymmetric molecules the only space group possible is $P2_1$. Quartz-calibrated photographs of the *h*0*l* and *hk*0 were used to determine the cell dimensions. Multifilm equiinclination Weissenberg photographs of the layers *h*0*l* through *h*6*l* were taken with Cu Kα radiation. The intensities of the reflections were measured by visual comparison with an intensity standard. Absorption corrections were not made. The reflection intensity cut off sharply at high angles indicating large thermal motions or possible radiation damage to the crystals. A fresh crystal was chosen for each long exposure to minimize the effects of the latter.

TABLE I

a, Å	21.20 ± 0.04
b, Å	7.38 ± 0.01
c, Å	10.34 ± 0.02
β	92.77 ± 0.25°
Space group	$P2_1$
Molecules per unit cell	4
Measd *d*, g/ml	1.17
Calcd *d*, g/ml	1.19
Observed reflections	1342

Determination of the Structure.—The structure was determined by heavy-atom electron-density methods followed by nine cycles of least-squares refinement. The listing of atomic parameters, isotropic temperature factors, and observed and calculated structure factors has been deposited with the American Documentation Institute.[7] The final $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.205$.

(1) This investigation was supported by U. S. Public Health Service Grants A-5382 and GM 10941-02 and by a special postdoctoral fellowship 1-F3-GM-28,496-01.

(2) W. G. Dauben and G. J. Fonken, *J. Amer. Chem. Soc.*, **81**, 4060 (1959).

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(4) P. Busse, *Z. Physiol. Chem.*, **214**, 211 (1933).

(5) A. Windaus and J. Naggatz, *Ann.*, **542**, 204 (1939); A. Windaus and K. Bucholz, *Z. Physiol. Chem.*, **256**, 273 (1938).

(6) K. Dimroth, *Ber.*, **70**, 1631 (1937).

(7) Document NAPS-00022 from ASIS National Auxiliary Publications Service, % CCM Information Sciences, Inc., 22 West 34th Street, New York, N. Y. 10001; remit $1.00 for microfiche or $3.00 for photocopies.

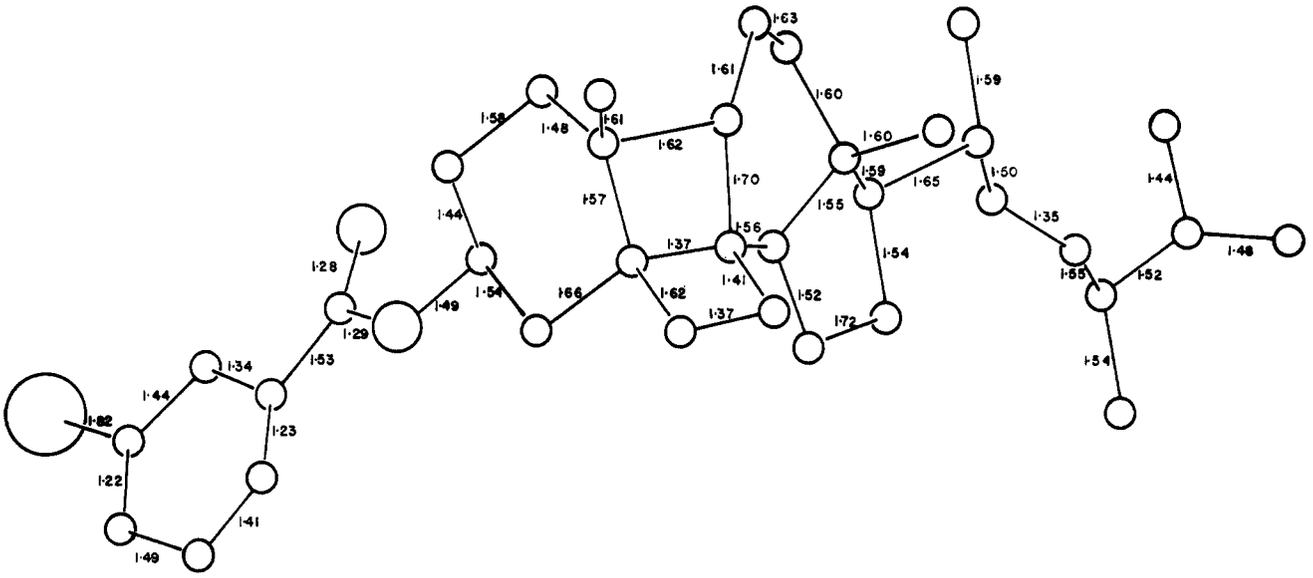

Figure 1a.—The bond distances in photoisopyrocalciferyl *m*-bromobenzoate.

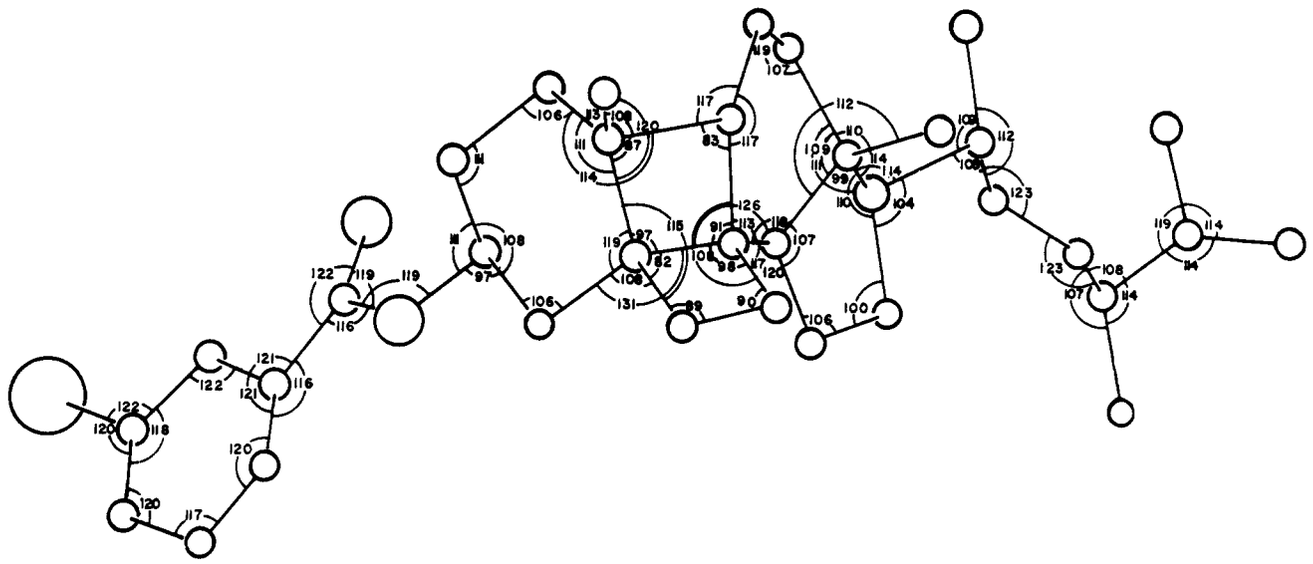

Figure 1b.—The bond angles in photoisopyrocalciferyl *m*-bromobenzoate.

The isotropic temperature factors fall in the range 2.9–11.6 with the lower values for carbon atoms in the sterol framework and the highest values for Br (11.2) and C-26 (11.6 Å^2). No dispersion corrections were applied to the Br scattering which may be an explanation for this high value. The large value for C-26 may be caused by large thermal motions of this methyl group at the end of the carbon side chain. The over-all temperature factor determine by intensity statistics is 7.2. From the determined positional standard deviations the expected average standard deviation for a carbon–carbon bond length is 0.05 Å, and the average standard deviation for a bond angle about a carbon atom is 4° (see Figures 1a and b).

Discussion

The rearrangement of atoms is in agreement with the structure proposed by Dauben and Fonken.[1] The configuration of the sterol nucleus is 3β-OH, 9β-H, 10β-CH_3, 13β-CH_3, and 17β-C_9H_{17}. The novel feature of this sterol is the system of two fused four-membered rings, one of which contains a double bond. One of these rings containing C-5, C-8, C-9, and C-10 joins ring A and ring C in *cis* configuration giving a right-angle bend in the over-all shape of the molecule. On the opposite side of the cyclobutane ring the C-19 methyl group and the cyclobutene ring are in *cis* configuration. The bromobenzoate phenyl group is planar within a maximum deviation of 0.04 Å. The plane of the carboxyl group is tilted 8° with respect to the plane of the bromobenzene ring. The A ring shows the chair configuration with the oxygen atom attached to C-3 in the equatorial position as has been found for calciferol.[8] The cyclobutane ring and the cyclobutene ring make an angle of 110°. The angles about the C-5–C-8 bond show distortions up to 20° from tetrahedral owing to the necessary bending of this bond. The four-membered rings appear to be twisted out of square shape by as much as 8°. Such a distortion places the atoms in the cyclobutene double bond more distant from the C-19 methyl group, and it allows ring A to adopt a less strained chair arrangement. Ring C which is usually in the chair form in this series of sterols is in this case flattened with C-9 lying in the plane of atoms C-8, C-11, C-12, and C-14 in order to

(8) D. C. Hodgkin, B. M. Rimmer, D. D. Dunitz, and K. N. Trueblood, *J. Chem. Soc.*, **83**, 4945 (1963).

accommodate the strained B ring system. In the D ring C-13 lies 0.66 Å out of the plane of the other four atoms. The ethylene group in the side chain is found to be planar. Examination of the intramolecular distances leads to the conclusion that the packing of molecules in the crystal is determined by the bulk and shape of the molecules, and it is not influenced by specific interactions between molecules.

Registery No.—Photoisopyrocalciferyl *m*-bromobenzoate, 17448-36-1.

Acknowledgments.—We are indebted to Dr. Dorothy C. Hodgkin who made available the facilities of the Chemical Crystallography Laboratory at Oxford and offered much encouragement and many suggestions for the completion of this work. For the earlier computational work we are indebted to the Control Data Corporation, Minneapolis, Minn., and to the Numerical Analysis Center of the University of Minnesota. The final calculations were completed through the kind offer of the facilities of the Computing Laboratory of Oxford University.

Reactions of 1,2-Dichloroperfluorocycloalkenes and Perfluorocycloalkenes with Various Trivalent Phosphines

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The reactions of trivalent phosphines with certain 1,2-dichloroperfluorocycloalkenes or perfluorocycloalkenes give the corresponding phosphobetaines in fair to excellent yields. Ample physical data are presented to substantiate the assigned structures. This includes ir, ^{19}F and ^{31}P nmr, and analytical data. Although the literature is voluminous with possible mechanistic paths of various nucleophiles with the above type olefins, there exists no proof of the suggested first intermediates involved. This paper describes the isolation and experimental results of the initial 1:1 adduct of triphenylphosphine and perfluorocyclobutene, as well as discussing a plausible mechanism for the formation of the phosphobetaine. The betaine 4,4,5,5-tetrafluoro-2-(triphenylphosphoranylidene)cyclobutane-1,3-dione undergoes several crystal structure changes and two melts before its final melting solid. This interesting and novel polymorphism is discussed.

When trialkyl phosphites and 1,2-dichlorohexafluorocyclopentene (DCHFC) are heated together, the corresponding tetraalkyl perfluoro-1-cycloalken-1,2-ylenediphosphonates are formed as the major products.[1] Owing to the extreme reactivity of trivalent phosphorus compounds towards electron-deficient olefins, we considered the possibility of preparing phosphobetaines by treating 1,2-dichloroperfluorocycloalkenes and perfluorocycloalkenes with trivalent phosphines. This was based on our previous work involving the reaction of certain tertiary amines with DCHFC, which gave nitrogen betaines under hydrolytic conditions,[2] and some unreported work involving the reaction of 1-chloro-2-methoxyhexafluorocyclopentene with triphenylphosphine. In the latter case the phosphobetaine was obtained in fair yields.

Our experimental approach was devised from a recent communication which illustrates the use of acetic acid and water for the preparation of the betaine 1-(3,3,4,4-tetrafluoro-2-hydroxy-5-oxo-1-cyclopenten-1-yl)pyridinium hydroxide, inner salt.[3] By adopting this procedure for our own work we were able to prepare various phosphobetaines in fair to excellent yields depending on the particular olefinic substrate.

Reactions Studied.—Although the reaction of several tertiary phosphines are included in this paper, only triphenylphosphine was extensively investigated with all of the halo olefins studied in this paper. These olefins include 1,2-dichlorooctafluorocyclohexene, 1,2-dichlorohexafluorocyclopentene, 1,2-dichlorotetrafluorocyclobutene, perfluorocyclohexene, perfluorocyclopentene, and perfluorocyclobutene. In the 1,2-dichloro series an interesting but not altogether unexpected trend was observed. The cyclobutene derivative was by far the most reactive, followed by the cyclopentene as depicted in Figure 1. The cyclohexene derivative does not give any phosphobetaine under these reaction conditions. Instead, only triphenylphosphine oxide and tars are found. Even under more strenuous conditions, using an auto-clave at temperatures above 125° under a slight nitrogen atmosphere, identical results were observed. In the perfluoro series a similar trend was observed, where perfluorocyclobutene and perfluorocyclopentene reacted readily, and perfluorocyclohexene remained unreacted. No effort was made to compare the reactivities of the 1,2-dichloro and perfluoro cyclic olefins.

A plausible explanation for this observed deviation can be rationalized from Table I.[4] This shows a noticeable reduction of the double-bond strain in cyclohexene. By applying this reasoning to the perhalo olefins it becomes apparent why the six-membered cyclic compounds are less reactive than the corresponding four-, five-, and seven-membered compounds. Although this

TABLE I

Ring size	Excess strain of cyclo olefin, kcal/mol
C_3	54.3
C_4	
C_5	5.9
C_6	0
C_7	5.2

(1) A. W. Frank, *J. Org. Chem.*, **30**, 3663 (1965).

(2) F. H. Megson, M. T. Beachem, and R. F. Stockel, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 11P.

(3) S. E. Ellzey, Jr., and W. A. Guece, *J. Org. Chem.*, **31**, 1300 (1966).

(4) N. S. Zefirov and V. I. Sokolov, *Russ. Chem. Rev.*, **36** (2), 90 (1967).