Anal. Calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 66.92; H, 8.31; N, 4.43.

The benzylamine salt was added to 5 ml. of 6 *N* hydrochloric acid, the mixture was extracted with five 10-ml. portions of chloroform and the extracts were dried over anhydrous magnesium sulfate. Filtration of the solution and evaporation of the solvent yielded the regenerated acid V, which distilled as a colorless liquid, b.p. 131° (0.2 mm.), $n^{25}D$ 1.4780.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.67; H, 8.44.

***p*-Phenylphenacyl Ester of V.**—A 170-mg. sample of the acid V was dissolved in 5 ml. of 50% aqueous ethanol and neutralized with 3 *N* sodium hydroxide solution. The solution was then made acid to litmus by the addition of a few additional milligrams of the acid and heated under gentle reflux for 3 hr. with *p*-phenylphenacyl bromide (300 mg.). The hot solution was diluted with water until the solution became cloudy and then cooled overnight. Filtration gave a solid (325 mg.), m.p. 100–105°, which after several crystallizations from methanol formed white glistening plates of the *p*-phenylphenacyl ester of V, m.p. 109.4–110.2°.

Anal. Calcd. for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91; CH_3CO, 0.00. Found: C, 73.42; H, 6.95; CH_3CO, 0.00.

Hydrolysis of V.—A 720-mg. sample of the acid V was added to a solution of 720 mg. of 2,4-dinitrophenylhydrazine in 5 ml. of concentrated sulfuric acid, 10 ml. of water and 25 ml. of ethanol. The mixture was boiled for 5 min. and allowed to stand at room temperature overnight. Filtration of the mixture gave 578 mg. of an orange solid, m.p. 121.5–124.5°. Two recrystallizations from a hexane–benzene mixture gave orange blades, m.p. 124–125°, and mixed m.p. with acetone 2,4-dinitrophenylhydrazone, 124.4–125.6°. The filtrate was diluted with 200 ml. of methanol and neutralized with solid potassium carbonate. The solids were removed by filtration and the filtrate was evaporated, leaving a reddish residue. A chloroform solution of the residue was dried over potassium carbonate and evaporated leaving 441 mg. of an orange oil that slowly solidified. Sublimation of the material at 60° (0.2 mm.), followed by several crystallizations from hexane, gave 201 mg. of colorless, glistening plates of *cis*-1,2-cycloheptanediol, m.p. 49.2–50.0°. A mixed melting point with an authentic sample of *cis*-1,2-cycloheptanediol of m.p. 49.2–50.8° was 49–50°.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

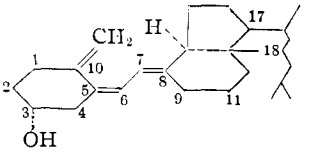
Studies in the Synthesis of the Antirachitic Vitamins. V. The Synthesis of 1-Cyclohexylidene-2-(5′-methoxy-2′-methylene-1′-cyclohexylidene)-ethane

BY NICHOLAS A. MILAS AND CHARLES P. PRIESING[1]

RECEIVED JUNE 14, 1957

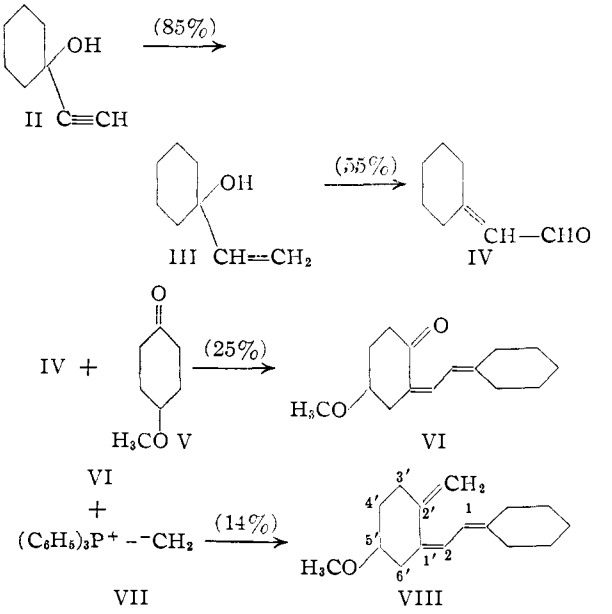
The synthesis of 1-cyclohexylidene-2-(5′-methoxy-2′-methylene-1′-cyclohexylidene)-ethane, a true homolog of vitamin D, has been described and its infrared and ultraviolet spectra compared with those of vitamin D_3. The yields of some of the intermediates have been substantially improved. A reasonable explanation has been advanced to account for the formation of the *cis* rather than the *trans* homolog of vitamin D.

It has now been fairly well established that the natural vitamin D's have the 5-*cis*-configuration (I).[2,3] The only synthetic homolog which has similar configuration was reported recently from this Laboratory.[4] Other synthetic homologs were reported to have the corresponding *trans*-configuration.[5,6] In view of these results we have reinvestigated and extended our original work and wish to report a more detailed account in the present communication. The synthesis of the homolog VIII is outlined in a sequence of reactions shown below.



Vitamin D_3 (I)

Commercially available 1-ethynylcyclohexan-1-ol (II)[7] was partially hydrogenated using palladium-on-calcium carbonate to give 85% yield of 1-ethenylcyclohexan-1-ol (III). The aldehyde IV was first obtained from compound III in small yields by Dimroth[8] using a four-step synthesis *via* the intermediates 1-bromo-2-cyclohexylidene-ethane, 1-acetoxy-2-cyclohexylidene-ethane and 2-cyclohexylidene-ethane-1-ol. In the present investigation a shorter route was found which resulted in substantially improved yields. A one-step, acid-



(1) From the Ph.D. Thesis of C. P. Priesing, M.I.T., April, 1957.

(2) D. Crowfoot and J. D. Dunitz, *Nature*, **162**, 608 (1948).

(3) E. Kodicek, *Ann. Rev. Biochem.*, **25**, 505 (1956).

(4) N. A. Milas, L. C. Chiang, C. P. Priesing, A. A. Hyatt and J. Peters, THIS JOURNAL, **77**, 4180 (1955).

(5) I. T. Harrison, B. Lythgoe and S. Frippett, *Chemistry & Industry*, 507 (1955); *J. Chem. Soc.*, 4016 (1955).

(6) H. H. Inhoffen, K. Brückner, G. F. Domagk and H. M. Erdmann, *Chem. Ber.*, **88**, 1415 (1955).

(7) A generous quantity of this substance supplied by the Air Reduction Chemical Co. is gratefully acknowledged.

(8) K. Dimroth, *Ber.*, **71**, 1333, 1346 (1938).

TABLE I

INFRARED SPECTRA OF COMPOUNDS IN THE CYCLOHEXANE SERIES (10% IN CHLOROFORM)[12,13]

Compound	Group	Infrared bands,[a] cm.$^{-1}$
2-Cyclohexylidene-ethan-1-al (IV)	—CHO	1686vs, 1895w
	R_2C=CHR	1646s, 853m
	—C_6H_{10}	960r, 933m, 907w, 867r
1-Cyclohexylidene-2-(5′-methoxy-2′-one-1′-cyclohexylidene)-ethane (VI)	>C=O	1665vs, 1415rw, 1242s
	R_2C=CHR	1610vs, 1565vs, 865m, 853m, 1292s
	—OCH_3	1316m, 1202r, 1180m, 1138s, 1114r, 1096vs, 1072r, 1039w, 1022vw,
	—C_6H_{10}	970r, 965m, 936m, 913m, 894r, 887w, 843r, 833vw
1-Cyclohexylidene-2-(5′-methoxy-2′-methylene-1′-cyclohexylidene)-ethane (VIII)	=CH_2	2980r, 1646w, 891s
	R_2C=CHR	1625m, 1595r, 1294w, 864m, 852m
	—OCH_3	1315w, 1258w, 1202vw, 1180w, 1135w, 1103r, 1090vs, 1075r, 1046w, 1040w, 1011w
	—C_6H_{10}	980m, 970r, 952w, 932m, 913w
Vitamin D_3 (I)	=CH_2	3100r, 1645m, 892m
	R_2C=CHR	1630m, 1600w, 1287vw, 860m
	—OH	1100r, 1090vs, 1080r, 1054r, 1040r, 1030vs, 1008r
	—C_6H_{10}	958m, 950r, 940w, 922vw, 905m, 880r

[a] vs = very strong; s = strong; m = medium; w = weak; vw = very weak; p = sharp; q = broad; r = shoulder.

catalyzed rearrangement–oxidation[9] of compound III gave, under optimal conditions, a 55% yield of 2-cyclohexylideneethane-1-al (IV), ϵ (237 mμ) 15000 (in ethanol).

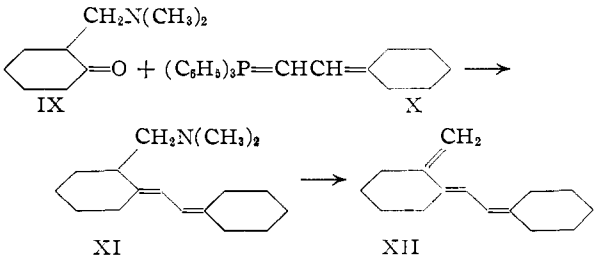
The aldol condensation between the aldehyde IV and 4-methoxycyclohexanone (V) was best carried out in an atmosphere of nitrogen by adding the aldehyde with rapid stirring at a moderate rate to a methanolic sodium hydroxide solution (0.1 *N*) of the 4-methoxycyclohexanone. After several crystallizations of the crude condensation product the pure dienone VI, ϵ (309mμ) 29,100 (in ethanol) was isolated in a yield of 25%.

When the dienone VI was allowed to react with freshly prepared triphenylphosphinemethylene (VII)[10] a product was obtained from which was isolated by chromatographic separation the *cis*-homolog VIII of vitamin D, ϵ (265 mμ) 23,200 (in petroleum ether), in 14% yield and an undetermined amount of the *trans*-homolog, λ_{max} 272 mμ.

The principal infrared bands of the aldehyde IV, dienone VI and the *cis*-homolog together with those of vitamin D_3[11] for comparison are listed in Table I.

Discussion

Since the isomerism due to the double bond 1′,2 should not be affected by the Wittig reaction on the dienone VI, the latter must exist in both *cis* and *trans* forms although we were unable to isolate two isomers in this case.[14] When the Wittig reaction was used to form a double bond which is subject to *cis–trans* isomerism both isomers were found in the final product.[10] However, when Harrison, *et al.*,[5] and Inhoffen, *et al.*,[6] applied this reaction to form the double bond 1′,2 by allowing cyclohexylidene-ethylenetriphenylphosphine (X) to react with 2-dimethylaminomethylcyclohexanone (IX) and subjecting the product formed to a Hofmann degradation, only the *trans* analog XII was formed. This result was attributed to the steric



hindrance of the dimethylamino group which prevented the formation of the *cis* isomer. In an attempt to eliminate the steric effect of the dimethylamino group Inhoffen, *et al.*, substituted 2-methylenecyclohexanone for 2-dimethylaminomethylcyclohexanone, but due to a rearrangement of the Wittig addition product only the all-*trans* analog was obtained.

In a later article Inhoffen, *et al.*,[15] applied the Wittig reaction to C_{27}-ketone XIII obtained by an aldol condensation[16] and reported the partial synthesis of 5,6-*trans*-vitamin D_2 (3-epimeric mixture) (XIV). They concluded that the *trans* compound was the only isomer expected since the dienone used had the 5,6-*trans*-configuration.

It may be seen, therefore, that since we obtained a *cis* homolog of vitamin D, our dienone must have been a mixture of *cis* and *trans* isomers. It is well known that iodine catalyzes the *cis–trans* isomeric equilibria.[17] This reaction has been utilized by Havinga and co-workers[18] to effect the conversion of precalciferol (XV), ϵ (265 mμ) 9000, to tachy-

(9) *Cf.* M. Stoll and A. Commarmont, *Helv. Chim. Acta*, **32**, 1355 (1949).

(10) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954); **88**, 1654 (1955).

(11) The authors wish to acknowledge with thanks pure samples of vitamin D_3 supplied by E. I. du Pont de Nemours and Co. and by Vitamins, Inc.

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

(13) K. Dobriner, E. R. Katzenellenbogen and R. N. Jones, "Infrared Absorption Spectra of Steroids," Interscience Publ. Inc., New York, N. Y., 1953.

(14) See Part IV, THIS JOURNAL, **79**, 3610 (1957).

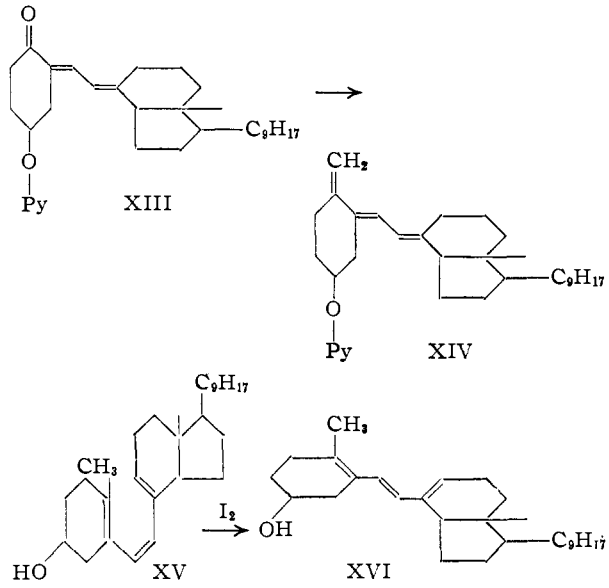
(15) H. H. Inhoffen, J. F. Kath and K. Brückner, *Angew. Chem.*, **67**, 276 (1955).

(16) H. H. Inhoffen, K. Brückner and R. Grundel, *Chem. Ber.*, **87**, 1 (1954).

(17) L. Zechmeister, *Chem. Revs.*, **34**, 267 (1944).

(18) A. L. Koevoet, Z. Verloop and E. Havinga, *Rec. trav. chim.*, **74**, 788, 1126 (1955).

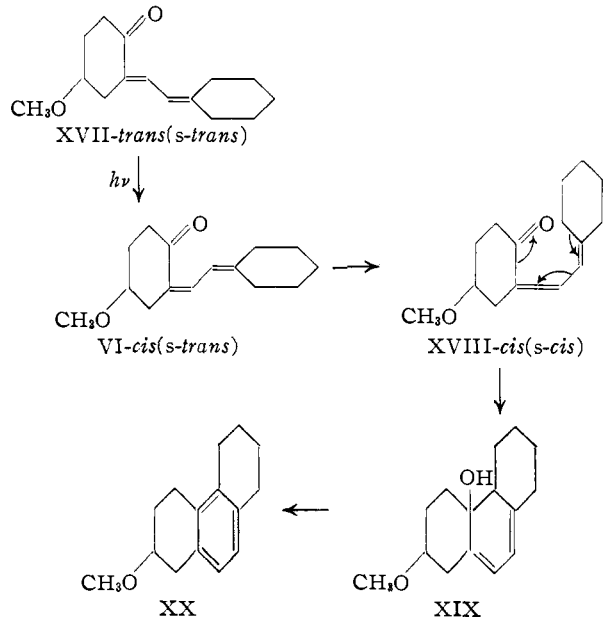
sterol (XVI), ϵ (281 mμ) 24600. When a similar reaction was attempted with the dienone VI no change was observed either in the ultraviolet absorption maximum or in the extinction coefficient. One may conclude from this experiment that either iodine fails to cause any observable change in the configuration of α,β-unsaturated carbonyl compounds or that the original dienone was already an equilibrium mixture of *cis*- and *trans* isomers.



It is equally well known that ultraviolet light causes conversion of *trans* to *cis* isomers. This is especially illustrated by the recent observation of Inhoffen[19] who was able to obtain by the ultraviolet irradiation of 5,6-*trans*-vitamin D_2 acetate a 25% yield of the 5,6-*cis*-vitamin D_2 acetate. Prior to this publication we made an attempt to convert the *trans*-dienone XVII in the equilibrium mixture into the *cis*-dienone VI by irradiating the mixture in petroleum ether with ultraviolet light. After four hours of irradiation a decrease in the extinction coefficient at 309 mμ ($\Delta E^{1\%}_{1cm.}$ 500) was observed, consistent with the assumption that either the *trans*-dienone was converted into the *cis*-dienone or the dienone was slowly destroyed. In another experiment a heptane solution of the dienone was irradiated for 24 hours whereby the K-absorption at 309 mμ had completely disappeared and an infrared analysis of the product failed to show the presence of the characteristic bands for the dienone chromophore, but instead it showed a strong band for hydroxyl at 3200 cm.$^{-1}$ and bands between 1500–1600 cm.$^{-1}$ with a strong peak at 1548 cm.$^{-1}$ suggesting strongly the presence of an aromatic ring.

The results of these experiments seem to show that, under the influence of ultraviolet light, the *trans*(s-*trans*)-dienone is presumably first converted through the *cis*(s-*trans*)-dienone to the *cis*(s-*cis*)-dienone which cyclizes to the unstable methoxycarbinol XIX which in turn loses water to give the methyl ether XX.

Since we obtained a mixture of *cis* and *trans* homologs of vitamin D, the dienone used must also have been a mixture of the *cis*- and *trans*-dienones, One may argue, however, that since the dienones are prepared by alkali-catalyzed condensation and are known to enolize in alkaline media to give the



most stable configuration, it is reasonable to assume that the only dienones formed must have the *trans* configuration. In the preparation of the various known dienones widely different conditions were employed and no attempt was made to find *cis* isomers; only the products having the highest ultraviolet absorption maxima consistent with the dienone chromophore were considered. Furthermore, it is not yet clear whether dehydration of the aldol occurs under alkali catalysis during the condensation,[20,21] or under acid catalysis upon acidification of the reaction mixture,[22,23] or whether both mechanisms may operate depending upon the conditions employed. Since the dienone obtained in the present investigation appeared to be an equilibrium mixture of *cis* and *trans* isomers, it may be concluded that the dehydration of the aldol must be acid catalyzed or that the methanolic sodium hydroxide used was of insufficient strength to bring about dehydration in that medium.

Experimental

Ethenylcyclohexan-1-ol (III).—The selective hydrogenation of ethynylcyclohexan-1-ol (100 g.) was carried out in the presence of freshly reduced palladium hydroxide (2%) on calcium carbonate (15 g.) suspended in 300 cc. of absolute ethanol. After one mole equivalent plus 10% excess of hydrogen was absorbed, the hydrogenation was discontinued and the mixture filtered through a Celite, analytical filter aid. The filtrate was then diluted with concd. sodium chloride solution and extracted with ether, dried over magnesium sulfate and the ether removed. The residue was fractionated through a 30-cm. Vigreux column and the fraction boiling at 75–76° (15 mm.) collected; yield 85%,

(19) H. H. Inhoffen, *Naturwiss.*, **44**, 11 (1957).

(20) D. Vorländer and K. Kinze, *Ber.*, **59**, 2078 (1926).

(21) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 645.

(22) E. R. Alexander, "Principles of Ionic Organic Reactions." John Wiley and Sons, Inc., New York, N. Y., 1951, p. 180.

(23) A. C. Cope, THIS JOURNAL, **59**, 2327 (1937).

$n^{24.7}D$ 1.4731; 3,5-dinitrobenzoate, m.p. 119–120°; lit. b.p. 75° (15 mm.),[24] $n^{20}D$ 1.4740.[8]

2-Cyclohexylideneethan-1-al (IV).—In a 1-liter three-necked, round-bottom flask equipped with a stirrer, dropping funnel and a nitrogen inlet was placed 34 g. of ethenylcyclohexan-1-ol, 300 cc. of thiophene-free benzene and 4 cc. of glacial acetic acid. To this was added alternately with stirring at 0° two solutions, the first containing 14 cc. of concd. sulfuric acid and 150 cc. of water and the chromic acid and 150 cc. of water, beginning with sulfuric acid in four portions each over a period of 20 min. allowing a 20-min. interim of stirring between each addition. Finally the mixture was stirred overnight (20–24 hr.) whereby a color change from orange-red to green was observed. The mixture was then rinsed with benzene into a separatory funnel, the benzene layer removed and the aqueous layer extracted thoroughly with benzene. The combined benzene extracts were washed with water, then with dilute sodium carbonate solution, then again with water and the benzene evaporated. The crude residue (32 g.) was shaken continuously for two hours with 100 cc. of saturated sodium bisulfite solution and the mixture extracted with ether from which was recovered 8.0 g. of the starting material. The bisulfite addition product was decomposed with concd. sodium hydroxide solution (100 cc.) and the mixture extracted several times with ether, the extracts washed with water, then with dil. sulfuric acid, then again with water and dried over magnesium sulfate. When the ether was distilled 18.6 (55%) of the aldehyde was recovered and fractionated under reduced pressure and the fraction boiling at 79–84° (15 mm.) collected; $n^{25}D$ 1.5061, ϵ (237 mμ) 15,000 (in ethanol); 2,4-dinitrophenylhydrazone (bright red), m.p. 195°; lit.[8] b.p. 80–85° (13.5 mm.), ϵ (232 mμ) 17,400; 2,4-dinitrophenylhydrazone, m.p. 200–200.5.[25]

4-Methoxycyclohexanone (V).[26]—Hydroquinone was converted to hydroquinone monomethyl ether with dimethyl sulfate in the presence of sodium hydroxide. The product was purified by distillation under a reduced pressure and the fraction boiling at 128° (12 mm.) collected; yield 55%.[27] Hydroquinone monomethyl ether was then reduced under pressure[28] with Raney nickel to 4-methoxycyclohexanol, b.p. 96–98° (11 mm.), yield 81%. Oxidation of 4-methoxycyclohexanol with potassium dichromate and sulfuric acid gave a 50% yield of 4-methoxycyclohexanone, b.p. 84–85° (14 mm.), $n^{20}D$ 1.4560; semicarbazone, m.p. 175–176.5°; 2,4-dinitrophenylhydrazone, m.p. 150°.[27] The product, which became yellow after standing for a period of several years, was freshly distilled before use.

1-Cyclohexylidene-2-(5'-methoxy-2'-one-cyclohexylidene)-ethane (VI).—A solution of 4 g. of sodium hydroxide in 10 cc. of water diluted with 700 cc. of methanol was placed in a 1-liter, 3-necked round-bottom flask equipped with a dropping funnel, a stirrer and an inlet for nitrogen. To this solution was added with vigorous stirring in one portion 14 g. (0.109 mole) of 4-methoxycyclohexanone dissolved in 100 cc. of methanol, followed by a dropwise addition of 6.8 g. (0.055 mole) of 2-cyclohexylideneëthan-1-al in 200 cc. of methanol over a period of one-half hour. Stirring was continued for an additional 12-hour period whereby the solution changed from pale-yellow to wine-red color. After acidification with 3 cc. of concd. sulfuric acid in 200 cc. of water, the mixture was salted out and extracted with ether; the extract washed with water, dried over magnesium sulfate and the ether removed; a highly viscous residue (13.7 g.) was secured. From this was obtained by distillation under reduced pressure 1.3 g. of the original aldehyde at 120° (6 mm.) and a highly viscous oil at 140–160° (1.2 mm.) which was crystallized from ligroin in yellow needles, m.p. 79.5–80.5°, yield 25%, ϵ (309 mμ) 29100 (in ethanol); principal infrared bands are listed in Table I.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.92; H, 9.47; mol. wt., 234. Found: C, 76.77; H, 9.45; mol. wt., 224 (in exaltone).

2,4-Dinitrophenylhydrazone (deep red), m.p. 178–179°. *Anal.* Calcd. for $C_{21}H_{26}N_4O_5$: C, 60.86; H, 6.33; N, 13.52. Found: C, 61.05; H, 6.68; N, 13.66.

Semicarbazone, m.p. 131.5–132.5°, ϵ (310 mμ) 36000; lit.[29] m.p. 84°, ϵ (306–307 mμ) 24500.

The Influence of Iodine Catalysis on the Configuration of Dienone VI.—To a petroleum ether solution (425 cc.) containing 2.5 mg. of dienone VI was added 0.05 mg. (2%) of iodine and the resulting mixture shaken under nitrogen and diffuse daylight at room temperature for 40 minutes. Before iodine treatment the dienone used had an $E^{1\%}_{1cm}$ (308 mμ) value of 1150 and after treatment 1080. This decrease in the extinction coefficient was too small to be of any significance and was therefore attributed to experimental error.

The Influence of Ultraviolet Light on Dienone VI.—In 170 cc. of petroleum ether was dissolved 53.4 mg. of dienone VI and the solution circulated through a quartz circular coil[30] by means of a slow stream of dry, prepurified nitrogen. The coil was irradiated at room temperature from a distance of about 12 inches with a General Electric Sun-Lamp for a period of four hours. Aliquot portions of 1 cc. were withdrawn and the ultraviolet absorption spectrum determined It was found that the $E^{1\%}_{1cm}$ value at 309 mμ decreased, after 4 hours of irradiation, from 1240 to 739.

Another sample of the dienone VI was dissolved in heptane and irradiated for 24 hours. At the end of this period the K-absorption at 309 mμ had completely disappeared. An infrared spectrum of the product showed a sharp band at 3200 cm.$^{-1}$, and bands between 1500–1600 cm.$^{-1}$ with an intense peak at 1548 cm.$^{-1}$, respectively. The characteristic bands for the dienone chromophore were completely absent. These data strongly suggest the presence of a tetrasubstituted aromatic compound of the structure XX.

Methyltriphenylphosphonium Bromide.—To 5 g. (0.019 mole) of triphenylphosphine (dried over phosphorus pentoxide under high vacuum for ~5 hr.) dissolved in dry benzene and cooled to −10° in a pressure bottle was added 3 g. (0.031 mole) of methyl bromide and the mixture kept at room temperature for 4 days. It was then filtered through a sintered glass funnel using dry nitrogen. The crystals were washed with benzene and dried in vacuum over phosphorus pentoxide, m.p. 227–231°, yield 88.5%.

Triphenylphosphinemethylene (VII).[31]—In a Thiele tube under nitrogen was placed 14.35 cc. of 0.3087 *N* phenyllithium solution (4.432 mmoles) in ether prepared by the action of lithium metal on bromobenzene. To this solution was then added 1.583 g. (4.432 mmoles) of methyltriphenylphosphonium bromide and the mixture diluted with 10 cc. of dry ether. The mixture was then shaken in nitrogen at room temperature for five days, then used in the next reaction.

1-Cyclohexylidene-2-(5'-methoxy-2'-methylene-1'-cyclohexylidene)-ethane (VIII).—The triphenylphosphinemethylene mixture prepared above was transferred under nitrogen to a 300-cc. pressure bottle and to it was added 0.8758 g. (3.769 mmoles) of the dienone VI, stoppered and heated in a sand-bath at 65° for three hours. The mixture was then cooled and filtered in nitrogen through a sintered glass funnel; the filtrate was washed once with water, then with saturated sodium chloride solution and dried over magnesium sulfate. The ether was removed under reduced pressure and the yellow viscous residue extracted with petroleum ether. The extract was chromatographed through a column containing 25 g. of ethyl acetate-washed alumina (Act. III) and separated into 17 fractions by elution with 20-cc. portions of each of petroleum ether, benzene, ether and methanol grading the change of solvent to the ratios, 19:1, 9:1, 4:1 and 1:1. Eluents, petroleum ether–benzene, 19:1 and 9:1, had λ_{max} 265 mμ and were combined; yield 0.274 g. (14%). This product was redissolved in petroleum ether and passed through a column containing 1 g. of alumina and eluted with a 9:1 petroleum ether–benzene mixture. The eluents were combined and the solvent removed in vacuum; the residue was subjected to a high vacuum at room tem-

(24) H. J. Backer and J. R. van der Bij, *Rec. trav. chim.*, **62**, 561 (1943).

(25) J. B. Aldersly, G. N. Burkhardt, A.E. Gillam and N. C. Hindly, *J. Chem. Soc.*, 10 (1940).

(26) This compound was synthesized by H. L. Holmes during a Research Associateship tenure 1939–1940 and was available in our Laboratory. Experimental directions were transcribed from Dr. Holmes' notes.

(27) *Cf.* L. Heifer, *Helv. Chim. Acta*, **7**, 951 (1924); R. Robinson and J. C. Smith, *J. Chem. Soc.*, 393 (1936).

(28) L. W. Covert and H. Adkins, THIS JOURNAL, **54**, 4116 (1932).

(29) K. Dimroth and H. Johnson, *Ber.*, **71**, 2658 (1938).

(30) N. A. Milas, U. S. Patent 2,115,206, April 26, 1938.

(31) This preparation and the Wittig reaction[10] were originally carried out in this Laboratory by Dr. L. C. Chiang.

perature for 20 hr. and at 40–50° for 3 hr. Attempts to crystallize this homolog were not successful; ϵ (265 mμ) 23,200 (in petroleum ether). The principal infrared bands are listed in Table I and compared with those of vitamin D_3.

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.69; H, 10.41. Found: C, 82.61; H, 10.34.

The other fractions obtained in the chromatography were isolated and purified further, but qualitative ultraviolet spectroscopic analysis indicated the presence of a *trans* isomer, λ_{max} 270–275 mμ, and unreacted dienone, λ_{max} 290–310 mμ.

Acknowledgment.—The authors are indebted to Dr. Nagy and his associates for the all analyses, to Dr. Nelson and Miss Cassie for the infrared spectra and to Research Corporation–Milas–M.I.T. Fund for financial support of this investigation.

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Reaction of *keto*-Acetates with Diazomethane[1,2]

BY M. L. WOLFROM, J. B. MILLER,[3] D. I. WEISBLAT AND A. R. HANZE

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The reaction of diazomethane with *keto*-D-fructose pentaacetate and *keto*-L-sorbose pentaacetate yields 1,2-anhydroalditol acetates branched at C2. Treatment with mineral acids opens the ring with the formation of a 1-deoxy derivative and consequent retention of (the unknown) configuration at C2.

Reaction of diazomethane with an aldehyde or ketone yields an homologous epoxide or carbonyl compound with the ratio of epoxide to carbonyl product being larger for acyclic ketones than for the corresponding aldehydes and larger when electronegative substituents are present.[4] The reported formation of epoxides on treatment of *keto*-D-fructose pentaacetate[2] and *scyllo*-inosose pentaacetate[5] with diazomethane suggests that in general the grouping, –CHOAc–CO–CHOAc–, may be expected to yield epoxides on reaction with diazomethane. The work reported herein demonstrates this to be the case for *keto*-L-sorbose pentaacetate and presents proof of structure (but not configuration) for the epoxide from *keto*-D-fructose pentaacetate previously reported in a preliminary communication.[2] Only one epoxide has as yet been characterized in each of these diazomethane reactions although an epimeric product might also be expected.

The epoxide ring opens on treatment with hydrogen chloride,[6,7] hydrogen bromide[5] or magnesium bromide[8] and the resulting halohydrins may be reconverted to the epoxide on treatment with a variety of bases.[9] The products obtained using hydrogen chloride in acetic acid and hydrogen chloride in methanol represent the same direction of ring opening in agreement with the results of Wasserman and Aubrey[6] and contrary to the experience of Jörlander[7] who obtained different chlorohydrins on opening of an epoxide ring with hydrogen chloride depending on whether the solvent was acetic acid or ethanol. The position of ring opening was established herein by periodate oxidation of the deacetylated chlorohydrin III derived from D-fructose. Had the ring opened with cleavage of the C2 oxygen bond on treatment with acid then a tertiary halide would have resulted which would have reduced three moles of periodate and liberated one mole of formaldehyde per mole of chlorohydrin. Ring opening at the C1 oxygen bond, however, would give a chlorohydrin which would reduce five moles of periodate and liberate two moles of formaldehyde per mole of chlorohydrin. The latter was found to be the case (Table I). The rapid consumption of periodate by this compound and by N-acetyltetrahydrostreptobiosamine[10] (95% complete in fifteen minutes),[11] both of which contain a primary–tertiary glycol group, infers little difference in rate of oxidation between this group and a primary–secondary glycol group, although when the tertiary carbinol is in a five-membered ring there does exist a difference in rate sufficiently large to be of preparative value.[12]

TABLE I

PERIODATE OXIDATION OF COMPOUND III

Time, min.	Moles of oxidant consumed per mole of III at 0°[a]	Moles of HCHO produced per mole of III at 25°[b]
17	5.0	
27	5.2	
56	5.2	
60		2.0
91	5.2	
148	5.3	

[a] Arsenite method, E. L. Jackson, *Org. Reactions*, **2**, 361 (1944). [b] Chromotropic acid method, J. C. Speck, Jr., and A. A. Forist, *Anal. Chem.*, **26**, 1942 (1954). Analysis by Dr. D. S. Miyada.

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(5) T. Posternak, *Helv. Chim. Acta*, **27**, 457 (1944).

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