solved in 150 ml. of ether and chromatographed on 250 g. of activity III alumina.

Fraction	Volume, ml.	Solvent, ether–methanol	Weight, g.
9–17	630	99:1 to 98:2	0.096
24–32	630	195:5 to 193:7	0.536
33–44	840	193:7 to 90:10	1.330

Fractions 9–17 were oils that were not examined further and probably contained 1,2-cycloheptanediols which were not completely removed in the treatment with cupric sulfate and acetone. A portion of fractions 24–32 was crystallized from ethyl acetate; m.p. 46.8–48.3°. Similar material from another chromatogram was crystallized five times from ethyl acetate, after which it had m.p. 48.5–49.5° (this 1,3-cycloheptanediol of unknown configuration is designated as the α-form).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.39; H, 10.91.

A bis-phenylurethan was prepared from the above glycol in the fashion described earlier (it was rather insoluble in carbon tetrachloride) and was crystallized three times from aqueous methanol, m.p. 169.2–170.6°.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57. Found: C, 68.48; H, 6.80.

Fractions 37–44 formed a glass when sublimed onto a cold finger and solidified when allowed to stand at room temperature. A portion of this material was crystallized as a solid mass from ethyl acetate; fine, white crystals were obtained when the glycol was crystallized from a mixture of ether and ethyl acetate, m.p. 53.6–54.6° (this is designated as the β-isomer of 1,3-cycloheptanediol).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.87; H, 10.61.

A mixture of this glycol with the other 1,3-cycloheptanediol described above (m.p. 48.5–49.5°) had a melting range of 33–53° immediately after being formed and became liquid on standing at room temperature.

A bis-phenylurethan of the β-1,3-cycloheptanediol, m.p. 53.6–54.6°, had m.p. 134.8–136.2° after three crystallizations from aqueous methanol.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.61. Found: C, 68.64; H, 6.60; N, 7.71.

Hydrolysis of the 1,2-Cycloheptanediol Isopropylidene Ketals and Chromatography of the Glycols.—A mixture of 0.508 g. of the 1,2-cycloheptanediol isopropylidene ketals prepared from the mixture of glycols obtained by lithium aluminum hydride reduction of VII and 15 ml. of 88% formic acid was stirred at 100° for 2 hr. To this mixture was added at room temperature with stirring about 30 ml. of 20% sodium hydroxide solution (until basic); stirring was continued at room temperature for 30 min., after which the solution was extracted continuously with chloroform overnight. The residue from these extracts was dissolved in 100 ml. of dry benzene and chromatographed on 45 g. of activity III alumina (50-ml. fractions were collected). Fractions 24–32 (0.161 g.) were eluted with ether–methanol (97:3). A portion of this material that was crystallized twice from ethyl acetate, m.p. 46–47°, had an infrared spectrum identical with the spectrum of authentic *cis*-1,2-cycloheptanediol. Its bis-phenylurethan, m.p. 173.2–174.4°, did not depress the melting point of authentic *cis*-1,2-cycloheptanediol bis-phenylurethan, and the spectra of the two samples were identical. Fractions 33–49 (0.115 g.) were eluted with ether–methanol (97:3 to 70:30) and could not be crystallized. However, the bis-phenylurethan that was prepared from a portion of the corresponding fractions in a similar chromatogram had m.p. 215.0–216.4°, and its infrared spectrum was identical with the spectrum of *trans*-1,2-cycloheptanediol bis-phenylurethan.

CAMBRIDGE, MASSACHUSETTS

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

Proximity Effects. XI. Reaction of *trans*-1,2-Dibromocycloheptane with Silver Acetate[1]

BY ARTHUR C. COPE, EDWARD M. ACTON,[2a] HERBERT E. JOHNSON[2b] AND GEOFFREY W. WOOD

RECEIVED JULY 15, 1957

The reaction of *trans*-1,2-dibromocycloheptane with silver acetate in acetic acid has been shown to form 2-cyclohepten-1-yl acetate, *trans*-1,2-cycloheptanediol diacetate and a product which is the cyclic ketal of *trans*-2-acetoxycycloheptyl acetoacetate with *cis*-1,2-cycloheptanediol.

It became of interest to study the reaction of *trans*-1,2-dibromocycloheptane with silver acetate in glacial acetic acid when the solvolysis of cycloheptene oxide with dilute hydrochloric acid[3] was shown to form *cis*-1,4-cycloheptanediol in 2.4% yield. The normal product, *trans*-1,2-cycloheptanediol, and some 2,2′-dihydroxydicycloheptyl ether were obtained in that reaction in addition to the non-vicinal glycol, which can have arisen only from a "transannular reaction." In the cycloöctane series it had been found that the reaction between *trans*-1,2-dibromocycloöctane and silver acetate in acetic acid gave rise to a larger proportion of abnormal products than did the solvolysis of *cis*-cycloöctene oxide with dilute hydrochloric acid.[4] By analogy, it seemed likely that transannular effects might also be more prominent in the reaction of *trans*-1,2-dibromocycloheptane with silver acetate than in the solvolysis of cycloheptene oxide.

trans-1,2-Dibromocycloheptane was treated with silver acetate in hot anhydrous acetic acid, and it was found that the product separated into three distinct fractions on distillation: an unsaturated monoacetate fraction (I), a diacetate fraction (II) and a high-boiling residue (III). Fraction I was saponified and treated with phenyl isocyanate. Chromatography of the resulting mixture of phenylurethans separated the monophenylurethan (70%) from some *trans*-1,2-cycloheptanediol bis-phenylurethan (24%) that also was present. The monophenylurethan fraction on further chromatography yielded 2-cyclohepten-1-yl phenylurethan as the only identifiable component. Comparison of the infrared spectrum of I with the spectrum of an authentic sample of 2-cyclohepten-1-yl acetate[3] showed that fraction I was composed principally of this allylic acetate.

(1) Supported by a research grant (NSF-G990) of the National Science Foundation.

(2a) National Science Foundation Fellow, 1954–1955; National Institutes of Health Fellow, 1955–1956. (2b) National Institutes of Health Postdoctoral Fellow, 1955–1956.

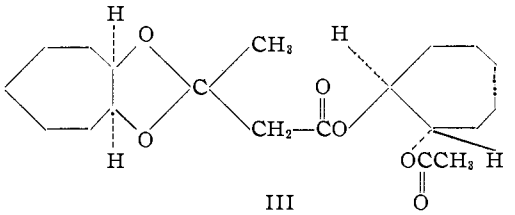
(3) A. C. Cope, T. A. Liss and G. W. Wood, THIS JOURNAL, **79**, 6287 (1957).

(4) A. C. Cope and G. W. Wood, *ibid.*, **79**, 3885 (1957).

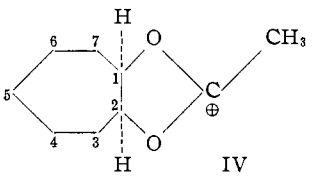
Fraction II was saponified and the glycols were separated by a procedure described previously.[3] The crude glycols were stirred with acetone and anhydrous copper sulfate, giving almost entirely the isopropylidene ketal of *trans*-1,2-cycloheptanediol, most of which was separated by distillation. Chromatography of the distillation residue removed the remaining isopropylidene ketal, which was not absorbed when the mixture was added to a column of alumina. Elution of the chromatogram afforded a sirup (1% from II, 0.7% over-all) which would have contained abnormal glycols that were present. This material was re-chromatographed and separated into seventy fractions. About half of it (0.5% from II, 0.35% over-all) was recovered in fractions (some of which partially crystallized) eluted with ether containing methanol in concentrations increasing from 3 to 20%. After recrystallization and sublimation, only *trans*-1,2-cycloheptanediol could be obtained from these fractions. No other products could be isolated from the mother liquors or the remaining fractions, which could not be crystallized. Since the total amount of material that failed to form an isopropylidene ketal, which could have contained abnormal products, represented only 0.7% over-all yield, and chromatography showed about half of that to be *trans*-1,2-cycloheptanediol, it is apparent that if any other glycols were formed in the reaction, they could have been formed in no more than 0.35% over-all yield.

It was possible to distil fraction III at 182–184° and 0.2 mm. pressure. The distillate corresponded in analysis to the formula $C_{20}H_{32}O_6$ and contained one acetate group. Saponification formed *trans*-1,2-cycloheptanediol and an acid, $C_{11}H_{18}O_4$, that formed a benzylamine salt and a *p*-phenylphenacyl ester as crystalline derivatives. The acid was hydrolyzed with dilute acid in the presence of 2,4-dinitrophenylhydrazine to *cis*-1,2-cycloheptanediol and acetone-2,4-dinitrophenylhydrazone. Since the acetone formed in this reaction could have arisen from acetoacetic acid by loss of carbon dioxide, it was possible on the basis of this evidence to formulate the acid as *cis*-3a,5,6,7,8-*cis*-8a-hexahydro-2-methyl-4*H*-cyclohepta-1,3-dioxole-2-acetic acid (V). This structure corresponds to the cyclic ketal of acetoacetic acid with *cis*-1,2-cycloheptanediol. The parent compound III accordingly is the ester of this acid with *trans*-1,2-cycloheptanediol monoacetate or *trans*-2-acetoxycycloheptyl *cis*-3a,5,6,7,8,*cis*-8a-hexahydro-2-methyl-4*H*-cyclohepta-1,3-dioxole-2-acetate.

A possible reaction path leading to III proceeds through an intermediate acetoxonium ion IV, analogous to the ion postulated[5] as an intermediate in the reaction of *trans*-1,2-dibromocyclohexane with silver acetate in glacial acetic acid. Condensation of the normal product, *trans*-1,2-cycloheptanediol diacetate (through a methyl group), with such an intermediate would lead to III. Formation of I and II from the intermediate acetoxonium ion IV can be explained by loss of a proton from C_3 and attack by acetate ion at C_2 with Walden inversion, respectively. Thus the products of the reaction of *trans*-1,2-dibromocycloheptane with silver acetate in acetic acid can be explained without recourse to transannular effects, and it has been shown that if any abnormal glycol is formed, its yield must be less than 0.35%. These results are to be contrasted with the reaction of *trans*-1,2-dibromocycloöctane with silver acetate in anhydrous acetic acid leading almost exclusively to transannular products.[4]



III



IV

Experimental[6]

***trans*-1,2-Dibromocycloheptane.**—A solution of bromine (80 g.) in carbon tetrachloride (200 ml.) was added dropwise to a solution of cycloheptene (48 g.) in carbon tetrachloride (100 ml.). The temperature of the reaction mixture was not allowed to rise above 8° during the course of the addition. After the solution was stirred at room temperature for 30 min., the solvent was removed under reduced pressure below 50°, giving a yellow residue. This on distillation yielded almost pure *trans*-1,2-dibromocycloheptane (100 g., 79%), b.p. 52–55° (0.3 mm.), $n^{25}D$ 1.5524–1.5535. A small sample redistilled for analysis had b.p. 53° (0.3 mm.), $n^{25}D$ 1.5530.

Anal. Calcd. for $C_7H_{12}Br_2$: C, 32.84; H, 4.73. Found: C, 32.91; H, 4.80.

The bulk of the material was stored in a refrigerator, where it solidified to a white crystalline mass, which did not discolor on standing for several months.

The preparation of *trans*-1,2-dibromocycloheptane has been described previously,[7] but the material was reported as an unstable liquid and was not obtained in a state of purity. No physical constants were reported.

Reaction of *trans*-1,2-Dibromocycloheptane with Silver Acetate in Acetic Acid.—A suspension of silver acetate (176 g.) in glacial acetic acid (1200 ml.) containing acetic anhydride (32 ml.) was stirred at 110° with exclusion of atmospheric moisture for 6 hr. *trans*-1,2-Dibromocycloheptane (75 g.) was added dropwise with stirring during 20 min. Stirring and heating at 110° were then continued for 14 hr. The reaction mixture was cooled to room temperature, diluted with ethyl ether (700 ml.) and filtered; the solids were washed with several 200-ml. portions of ether. The filtrate was diluted with water until two phases were formed. (The total volume of the two-phase mixture was 3–4 l.) The aqueous layer was separated, partially neutralized with sodium bicarbonate (2 lb.) and extracted twice with 200-ml. portions of ether. The extraction was repeated after a further neutralization of the aqueous phase with sodium bicarbonate (1 lb.). The ether solutions were combined and washed with water and then with saturated sodium bicarbonate solution until free from acid. After drying over magnesium sulfate, the solution was filtered and concentrated to remove the solvent. The oily residue (60 g.) afforded three distinct fractions upon fractional distillation:

(5) S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2780 (1942).

(6) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses. Infrared spectra were determined with a Baird double beam recording spectrometer, model B, fitted with a sodium chloride prism. For details concerning the alumina used in chromatography and crystallization techniques, see ref. 3, footnote 13.

(7) E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, THIS JOURNAL, **61**, 1057 (1939).

	Wt., g.	B.p. °C.	Mm.	$n^{25}D$	Yield, %
I	2.1	39–40	0.45	1.4603	4.6
II	46.0	80–85	.45	1.4517	73
III	4.6	165–170	.16	1.4809	8.5

Hydrolysis of I.—Eight grams of sodium hydroxide in 15 ml. of water was added to 100 ml. of methanol containing I (1.5 g.), and the solution was heated under gentle reflux for 1 hr. The reaction mixture was diluted with water and extracted with five 25-ml. portions of ether. The combined extracts were dried over magnesium sulfate, filtered and concentrated to an oily residue (350 mg.). This was treated with phenyl isocyanate (for the procedure see ref. 3), giving a phenylurethan (710 mg.), which was dissolved in benzene and passed onto a column of alumina (100 g., Peter Spence and Sons, grade "H"). Elution with benzene afforded a monophenylurethan fraction (500 mg.). Elution with benzene–ether (1:1) gave *trans*-1,2-cycloheptanediol bis-phenylurethan (170 mg.), m.p. 218–219°, which showed no depression on admixture with an authentic specimen.[3] The monophenylurethan fraction was rechromatographed, giving 2-cyclohepten-1-yl phenylurethan (160 mg.) as the only identifiable product, m.p. after several crystallizations from aqueous methanol 104.5–105.0°, which was undepressed on admixture with an authentic specimen.[3]

Hydrolysis of II.—A solution of II (46 g.) in 750 ml. of methanol was added to 75 g. of sodium hydroxide in 80 ml. of water and heated under gentle reflux for 1.5 hr. Most of the methanol was removed by warming under reduced pressure. The residue was diluted with 500 ml. of water and extracted five times with 25-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate, filtered and concentrated, leaving crude *trans*-1,2-cycloheptanediol as a moist solid.

The crude glycol was dissolved in 900 ml. of acetone, 90 g. of anhydrous cupric sulfate was added, and the mixture was stirred for 20 hr. The cupric sulfate was removed by centrifugation. After removal of the acetone by concentration under reduced pressure, most of the *trans*-1,2-cycloheptanediol isopropylidene ketal, b.p. 102–103° (30 mm.), $n^{25}D$ 1.4512, was separated by distillation. (Hydrolysis of the ketal regenerated the glycol, as described below.)

The liquid residue (3.0 g.) was dissolved in 5 ml. of ethyl ether and passed onto a column (50 × 2.5-cm.) containing 100 g. of alumina (grade II) in ethyl ether. *trans*-1,2-Cycloheptanediol isopropylidene ketal (2.70 g.), having the physical constants noted above, was not absorbed but was recovered directly upon elution with ethyl ether. Elution with 10% and then with 50% methanol in ether yielded 0.22 g. (over-all yield 0.7%; 1% from II) of partly solid material after evaporation of the effluent.

This material was dissolved in 0.5 ml. of ethyl ether and passed onto a column (40 × 1.2-cm.) containing 12 g. of alumina (grade II) in ether. The chromatogram was developed as shown in the Table.

Fraction	Volume, ml.	Solvent	Weight, mg.
1–8	100	Ether	33
9–13	60	Ether–methanol (98:1)	5
14–22	100	Ether–methanol (98:2)	22
23–25	35	Ether–methanol (97:3)	15
26–34	110	Ether–methanol (97:3)	50
35–40	70	Ether–methanol (97:3)	
41–47	85	Ether–methanol (96:4)	45
48–53	70	Ether–methanol (95:5)	
54–59	70	Ether–methanol (92:8)	
60–63	50	Ether–methanol (5:1)	13
64–67	50	Ether–methanol (5:1)	
68–70	35	Ether–methanol (1:1)	7

Fractions 1–13 were discarded. Fractions 26–34 and 54–63 partially crystallized upon evaporation of the solvent. After sublimation and recrystallization from an ether–pentane mixture (about 1:3), fractions 26–34 gave 15 mg. of a white crystalline solid, m.p. 52–58°. Further recrystallization afforded 5 mg., m.p. 58.5–61.0°. Similarly, fractions 54–63 gave 3 mg., m.p. 56–58.5°. The infrared spectra of the solids were identical with each other and with the spectrum of an authentic sample of *trans*-1,2-cycloheptanediol. Mixed melting points with authentic samples gave no depression. Sublimation of the intermediate fractions 35–53 yielded 30 mg. of a partly crystalline oil which could not be crystallized further. However, this material was identified as mainly *trans*-1,2-cycloheptanediol by its infrared spectrum. No product could be obtained from the mother liquors or from the preliminary and final fractions.

***trans*-1,2-Cycloheptanediol Diacetate.**—Acetic anhydride (25 ml.) was added to a solution of *trans*-1,2-cycloheptanediol (4.5 g.) in dry pyridine (25 ml.), and the mixture was kept at room temperature overnight. The mixture was then poured into water and extracted with ether. After removal of the ether the residue was distilled, yielding the diacetate as a mobile liquid (7.6 g., 86%), b.p. 78–79° (0.1 mm.), $n^{25}D$ 1.4512. The distillate solidified on scratching. Crystallization from aqueous methanol afforded the diacetate as plates, m.p. 42–44°.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.64; H, 8.46. Found: C, 61.66; H, 8.51.

***trans*-1,2-Cycloheptanediol Di-*p*-nitrobenzoate.**—A 10% excess of *p*-nitrobenzoyl chloride was added to a solution of the glycol in pyridine (60 ml./g.), and the mixture was kept at room temperature overnight. The reaction mixture was then poured into water and extracted with benzene. The benzene extract, after being washed successively with water, 10% hydrochloric acid and water, was concentrated to a small volume and passed onto a short column of alumina (grade II–III). Elution with benzene and evaporation of the effluent gave the pure ester, free from *p*-nitrobenzoic acid and small amounts of colored impurities, in almost quantitative yield. After recrystallization from a mixture of methanol and ethyl acetate, the *trans*-1,2-cycloheptanediol di-*p*-nitrobenzoate had m.p. 139.6–141.2°.

Anal. Calcd. for $C_{21}H_{20}O_8N_2$: C, 58.88; H, 4.71; N, 6.54. Found: C, 58.85; H, 4.94; N, 6.51.

Hydrolysis of *trans*-1,2-Cycloheptanediol Isopropylidene Ketal.—A solution of *trans*-1,2-cycloheptanediol isopropylidene ketal ($n^{25}D$ 1.4512, 2.19 g.) in 15 ml. of 88% formic acid was heated on a steam-bath for 2 hr. Most of the formic acid was removed by concentration under reduced pressure, and the residue was diluted with 20 ml. of methanol. Sodium hydroxide (4 g.) in 10 ml. of water was added, and the solution was heated on a steam-bath for 30 min. The cooled solution was extracted five times with 10-ml. portions of chloroform. The extracts were dried over magnesium sulfate, filtered and concentrated to a viscous oil (1.3 g., 76%) that crystallized on cooling. After three recrystallizations from a carbon tetrachloride–hexane mixture (about 1:2), 0.85 g. (51%) of *trans*-1,2-cycloheptanediol was obtained, m.p. 62.0–63.2°, undepressed on admixture with an authentic sample.

Hydrolysis of III.—Fraction III was analyzed.

Anal. Calcd. for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75; 1 CH_3CO, 11.68; mol. wt., 368. Found: C, 64.99; H, 8.91; CH_3CO, 11.54; mol. wt. (Rast method in camphor), 331.

A solution of 5.30 g. of fraction III in 100 ml. of methanol was saponified with 10 g. of sodium hydroxide in 20 ml. of water by refluxing for 1.5 hr. The methanol was removed by warming under reduced pressure, and the residue was dissolved in 100 ml. of water. This solution was extracted five times with 25-ml. portions of chloroform. The extracts were dried over anhydrous magnesium sulfate and evaporated, giving 1.85 g. of an oil that solidified slowly. Several crystallizations from ethyl acetate gave pure *trans*-1,2-cycloheptanediol, m.p. and mixed m.p. with an authentic sample, 61.5–62.5°.

The aqueous solution remaining after chloroform extraction was acidified with dilute hydrochloric acid to *p*H 5 and extracted five times with 20-ml. portions of chloroform. After drying over anhydrous magnesium sulfate, the extracts were evaporated, leaving 2.83 g. of a viscous yellow liquid.

***cis*-3a,5,6,7,8,*cis*-8a-Hexahydro-2-methyl-4*H*-cyclohepta-1,3-dioxole-2-acetic Acid (V).**—A 215-mg. sample of the above oil was dissolved in hexane, and benzylamine was added until precipitation was complete. On cooling to 5° the product completely solidified, and filtration yielded 267 mg., m.p. 88–91°. After several crystallizations from hexane, the benzylamine salt of V was obtained (215 mg.) as feathery, colorless needles, m.p. 92–93°.

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]

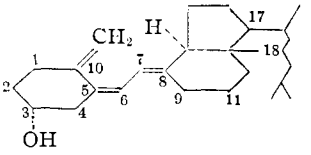
Studies in the Synthesis of the Antirachitic Vitamins. V. The Synthesis of 1-Cyclohexylidene-2-(5′-methoxy-2′-methylene-1′-cyclohexylidene)-ethane

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

RECEIVED JUNE 14, 1957

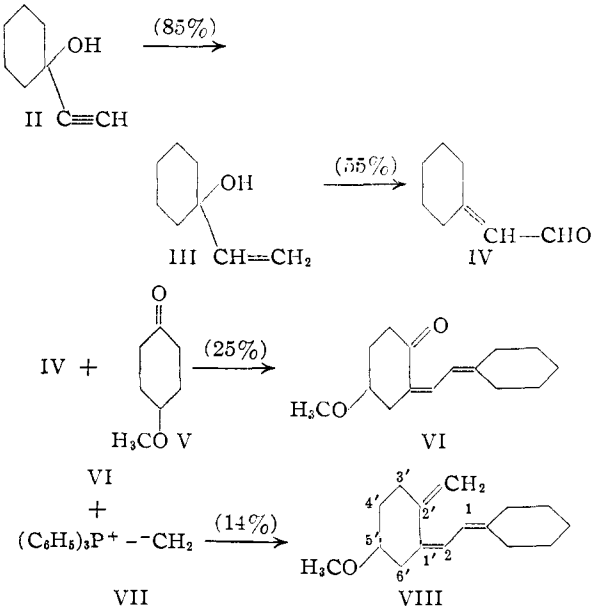
The synthesis of 1-cyclohexylidene-2-(5′-methoxy-2′-methylene-1′-cyclohexylidene)-ethane, a true homolog of vitamin D, has been described and its infrared and ultraviolet spectra compared with those of vitamin D_3. The yields of some of the intermediates have been substantially improved. A reasonable 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).

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