Still further evidence for the validity of periodate oxidation measurements by the Fleury–Lange procedure at 4° is provided by infrared analysis, which shows "Type II" absorption[27] by dextrans proportionate to their content of 1,3-like linked units.[3] Infrared analysis indicates the presence of approximately 5% and 3% 1,3-like linked units in dextrans B-512 and B-1146, respectively, none in the dextran fractions B-742 (L) L-R and B-1254 C-3, and approximately 9% in B-1299 S-R. Thus, there is agreement between the results of infrared analysis and periodate oxidation measurements at 4° for all these representative dextran products except B-1299 S-R, which appears to be unusually susceptible to over-oxidation. Results comparable with these for B-1299 have been obtained for other dextrans (B-1298, B-1399, B-1402, B-1424) which have less than 75%, 1,6-linked units and no more than about 10% 1,3-like linked units.[3] The unusually sensitive structure in these dextrans might be 1,2-linked units.

By comparison with preliminary methylation data for B-512 dextran, our results for non-1,6-links by 4° titration may still be off by 2–3% (runs 2, A-4 and 3, A-4, Table I). This appears to be the limiting error of the method and is believed to be due partly to over-reduction of periodate by B-512 as well as by many other dextrans, and partly to accumulation of errors in calculating by difference the content of 1,3-like linked units. The over-reduction of periodate can be diminished somewhat by decreasing the amount of excess periodate used in oxidations, especially for dextrans having low proportions of units linked 1,6.

Acknowledgments.—We should like to acknowledge our indebtedness to C. H. VanEtten for assistance with standardization of barium hydroxide, to Dr. E. H. Melvin for the infrared analyses, and to J. W. Sloan for the dialdehyde dextrans.

PEORIA, ILLINOIS

(27) S. C. Burket and E. H. Melvin, *Science*, **115**, 516 (1952).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES OF SCHERING CORPORATION]

Simple Analogs of the Antiarthritic Steroids[1]

BY DOMENICK PAPA, HELEN F. GINSBERG AND FRANK J. VILLANI

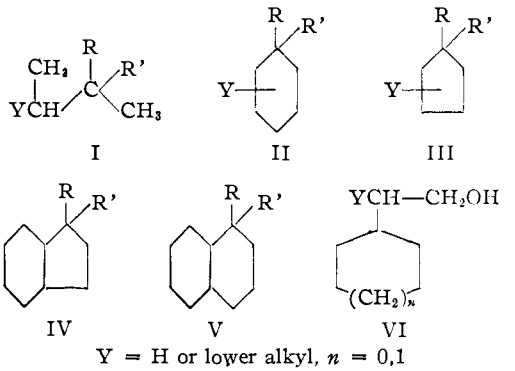
RECEIVED MARCH 11, 1954

Five series of compounds representing fragments of the steroids proposed for and/or in clinical use as antiarthritic agents have been prepared. These simple analogs are for the most part aliphatic (comparable to the steroid carbons 11–17 inclusive) and alicyclic (rings C and D and ring CD) substances with substituents characteristic of the C_{17} moieties of the steroids.

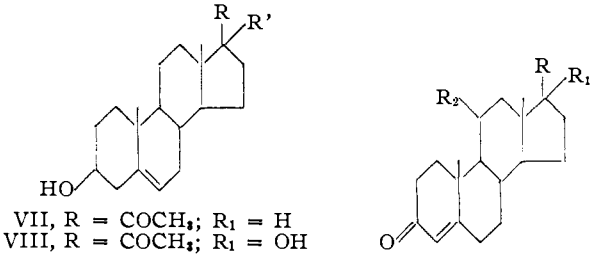
Shortly after the initial clinical successes with compound E and the investigations of related steroids as antiarthritic agents, we undertook the synthesis and the pharmacological evaluation of simple analogs of these compounds. The object of this investigation was to determine whether the dissection of the cyclopentanophenanthrene nucleus with the retention of the C-17 substituents of these steroids, as shown in formulas I–VI would yield relatively simple compounds retaining even to a small degree the pharmacodynamic action of the parent steroids. This approach in the case of other complex natural medicinal agents has indeed been fruitful in recent years.

At the time this study was initiated, the steroids which were proposed or in clinical study as antiarthritic agents were pregnenolone (VII), 17α-hydroxypregnenolone (VIII), desoxycorticosterone (IX), compound E (X) and the polyhydric adrenal cortical hormones of types XI and XII. The structures I–V denote the D and CD rings of these steroids as well as fragments thereof and the next higher cyclic homologs of these rings, the quantities R and R_1 representing the C-17 substituents of the steroids. Along with these five types, several representative glycols of formula VI were prepared in view of their relationship to XI and XII.

In the course of the preparation of compounds of type I–V, several syntheses were explored and in a



Y = H or lower alkyl, n = 0,1



VII, R = $COCH_3$; R_1 = H
VIII, R = $COCH_3$; R_1 = OH

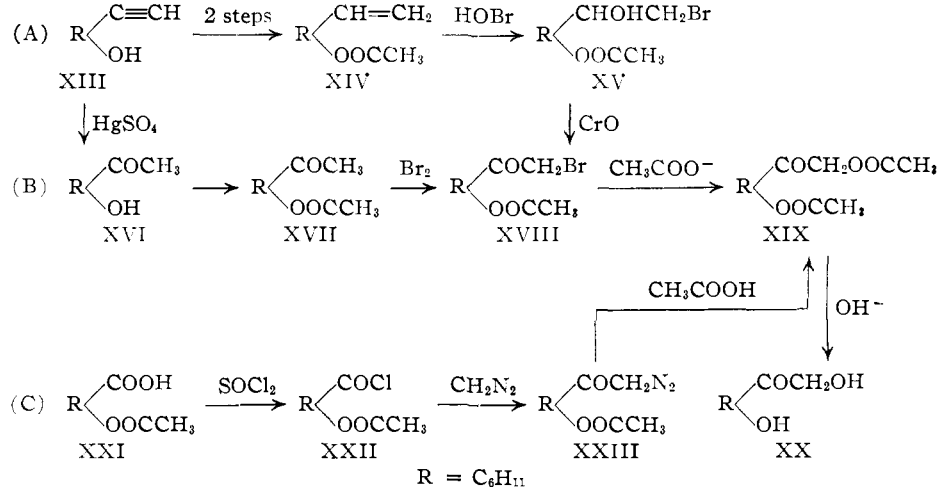
IX, R = $COCH_2OH$; R_1 and R_2 = H
X, R = $COCH_2OH$; R_1 = OH; R_2 = O
XI, R = $CHOHCH_2OH$; R_1 = OH; R_2 = O
XII, R = $CHOHCH_3$; R_1 = OH; R_2 = O

number of instances the intermediates in these syntheses, on pharmacological examination, were shown to possess sedative-hypnotic and anticon-

(1) Presented in abstract before The Division of Medicinal Chemistry, American Chemical Society Meeting, Atlantic City, N. J., September 15, 1952.

vulsant activity.[2] These unexpected findings materially enlarged the scope of the original study and has resulted in delay of publication of this work. In the interim, other investigators[3] have reported the synthesis and in certain instances preliminary pharmacological data for several compounds of types II, III and IV.

The simple acetyl derivatives of general formulas I–V (R = $COCH_3$, R_1 = H) were prepared for the most part by oxidation of the corresponding carbinols and in the case of the cyclopentyl derivatives by the reaction of cyclohexane or substituted cyclohexanes with acetyl chloride and subsequent ring contraction.[4] The acetyl carbinols (R = $COCH_3$, R_1 = OH) were secured readily by the hydration of the hydroxy ethinyl compounds, which in turn were formed by ethination of the appropriately substituted ketones.[2b] The hydration catalysts comprised yellow mercuric oxide with either sulfuric acid (method A) or boron trifluoride etherate and methanol (method B). In the case of the solid and liquid (*cis* and *trans*) isomers of 1-ethinyl-2-methyl-1-cyclohexanol only the acetyl carbinol from the solid ethinyl isomer was obtained irrespective of the method of hydration. This acetylcarbinol was obtained as a viscous liquid, which solidified to a low-melting white crystalline solid. Using hydration method A, the liquid isomer gave *o*-methylcyclohexanone, whereas method B with the mixed isomers gave *o*-methylcyclohexanol and 1-acetyl-2-methylcyclohexanol identical with that obtained from the solid ethinyl isomer.[5]



Several ketols of formulas II and III (R = $COCH_2OH$ or $COCH_2OCOCH_3$ and R_1 = H) were prepared from cyclopentyl-, Δ^1-cyclopentenyl-, cyclohexyl- and Δ^1-cyclohexenylcarboxylic acids. The acids were converted to the acid chlorides, the latter treated with diazomethane and the diazoketones decomposed with either sulfuric or acetic acid giving the hydroxy and acetoxy ketones, respectively.

Several approaches were investigated for the preparation of the simple substituted dihydroxyacetone analogs of X. The following three methods were successfully employed for the synthesis of the cyclohexyl compound. The corresponding cyclopentyl analog was obtained by method A. The series of transformation shown in method A parallels that employed by Salamon and Reichstein in the steroid field.[6] All the intermediates in the synthesis of XX by method A were obtained in good yields (74–92%) and were isolated and characterized. In the cyclopentyl series the bromoketone XVIII could not be purified and was converted to the acetoxy ketone directly. The alternate syntheses B and C comprise conventional reactions, which, since the completion of this work, have been described by others.[3] Hydrolysis of the acetoxy compounds XIX was carried out with either dilute aqueous sodium hydroxide or with potassium bicarbonate in methanol. The latter method not only gave a higher yield of the dihydroxy compound XX but also a purer product easily recrystallizable from ether–petroleum ether.

Two triols containing the C-17 substituents of XI were prepared by hydrolysis of the corresponding bromomethylcarbinols (XV) with potassium hydroxide in aqueous dioxane.[6] The triols prepared were derived from the bromomethylcarbinols of cyclopentane and cyclohexane.

The glycols of type VI were secured from the appropriately substituted ketones and the α-bromo aliphatic acids by the Reformatsky reaction followed by lithium aluminum hydride reduction of the esters or the free acids. In most cases it was desirable to isolate the free acids prior to reduction in order to eliminate dehydration products which usually contaminated the tertiary alcohols.

Pharmacology.—As already indicated, the tertiary acetylenic alcohols show hypnotic and anticonvulsant activity.[2] The test methods and the relative potency of these compounds are described

(2) (a) D. Papa, F. J. Villani and H. F. Ginsberg, *Arch. Biochem. and Biophys.*, **33**, 482 (1951); (b) D. Papa, F. J. Villani and H. F. Ginsberg, THIS JOURNAL, **76**, 4446 (1954); (c) S. Margolin, P. Perlman, F. Villani and T. H. McGavack, *Science*, **114**, 384 (1951); (d) R. W. Schaffarzick and B. J. Brown, *ibid.*, **116**, 663 (1952), and others.

(3) (a) W. H. Linnell, D. W. Mathieson and G. Williams, *Nature*, **167**, 237 (1951); (b) J. D. Billimoria and N. F. Maclagan, *ibid.*, **167**, 81 (1951), and *J. Chem. Soc.*, 3067 (1951); (c) J. A. Alexander, E. Cocker, W. Cooker and C. Lipman, *Chemistry and Industry*, 112 (1951); (d) G. W. Stacy and C. A. Hainley, THIS JOURNAL, **73**, 5911 (1951); (e) J. D. Billimoria, *Nature*, **170**, 248 (1952); (f) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 467 (1952); and others.

(4) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, p. 746.

(5) J. D. Billimoria, *J. Chem. Soc.*, 2626 (1953), has described the hydration of both isomers using mercuric sulfate in aqueous sulfuric acid. The acetyl ketone from the solid isomer after purification through the semicarbazone was obtained as a white crystalline solid. The acetyl ketone from the liquid isomer is a liquid also purified through the semicarbazone.

(6) I. Salamon and T. Reichstein, *Helv. Chim. Acta*, **30**, 1616 (1947).

in other publications.[2b-d] The simple acetyl derivatives of general formulas I to V (R = $COCH_3$, R_1 = H) are relatively weak anticonvulsants and show no hypnotic effect. The acetyl carbinols (R = $COCH_3$, R_1 = OH) have anticonvulsant activity against electrically induced seizures with little or no activity against metrazol seizures, the monocyclic acetylcarbinols showing the highest order of anticonvulsant activity. The ketols (R = $COCH_2$-OH and R_1 = H), the dihydroxyacetone analogs of X and the triols were screened for "cortisone-like" activity by liver glycogen deposition test and the Selye formalin test. None of these compounds were sufficiently active to warrant further study.

Acknowledgment.—The authors wish to express their sincere appreciation to Dr. S. Margolin for permission to publish preliminary pharmacological data on the compounds, to Dr. P. Perlman for the glycogen studies, and to Miss Margaret Sherlock, Mrs. Rosemarie Fircano, Mrs. Florence Villani and Mrs. Virginia DeCamp for the preparation of many of the compounds reported herein. We are also indebted to Mr. Edwin Conner of our microanalytical laboratories for the analyses.

Experimental

Ethinyl Compounds.—The procedure used and the physical properties of the products obtained have been described.[2b]

Acetylcarbinols. Procedure A.—The hydrating reagent was prepared by dissolving 6.8 g. of yellow mercuric oxide in 46 cc. of concentrated sulfuric acid and diluting the solution with water to a volume of 225 cc. To this solution 0.3 mole of the ethinyl compound was added with caution and the mixture refluxed for 3 hours. After diluting with ice-water, the ketone was steam distilled.[7]

Procedure B.—The hydrating catalyst was prepared from 2 g. of yellow mercuric oxide, 1 cc. of boron trifluoride etherate and 1 cc. of absolute methanol.[8] To the catalyst was added 10 cc. of absolute methanol, the mixture warmed to 35° and 0.25 mole of ethinyl compound in 10 cc. of absolute methanol added with stirring at a rate to keep the temperature at 35–40°. The reaction mixture was stirred for an additional 1.5 hours, 10 cc. of water added and the mixture stirred for one hour then neutralized with potassium carbonate. The ketone was isolated by ether extraction and after washing, was distilled.

1-Acetyl-1-cyclohexanol, method B, yield 73%, b.p. 85–87° (10 mm.), $n^{22}D$ 1.4670, literature b.p. 91° (11 mm.), $n^{11}D$ 1.4726[9]; semicarbazone, recrystallized from alcohol m.p. 214° dec. *Anal.* Calcd. for $C_9H_{17}O_2N_3$: C, 54.25; H, 8.59. Found: C, 54.10; H, 7.98.

The oxime was recrystallized from ligroin, m.p. 106–107°, literature m.p. 94–95° 106–107°.[3d]

1-Acetyl-1-cyclopentanol, method B, yield 40%, b.p. 92–94° (28 mm.), $n^{21}D$ 1.4638. *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.67; H, 9.08.

1-Acetyl-2-methyl-1-cyclohexanol, method A, yield 62%, b.p. 115–118° (25 mm.), $n^{21}D$ 1.4717, m.p. 35.5–36.5° after recrystallization from petroleum ether. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.28; H, 10.83.

This ketone was obtained from the solid isomer of 1-ethinyl-2-methyl-1-cyclohexanol. The liquid isomer did not give any ketonic product by either method. With the sulfuric acid method 25 g. of the liquid isomer gave 13 g. of ketonic product, b.p. 89–90° (20 mm.), $n^{23}D$ 1.4727, identified as *o*-methylcyclohexanone. *Anal.* Calcd. for $C_7H_{12}O$: C, 75.00; H, 10.71. Found: C, 75.07; H, 10.98.

With the mixture of isomers (35 g.), hydration by the boron trifluoride method gave two fractions: (a) yield 21.4 g., b.p. 72–74° (15 mm.) and (b) yield 6.3 g., b.p. 99–101° (15 mm.). Fraction (a) was identified as *o*-methylcyclohexanol; α-naphthylurethan, m.p. 154–155°, literature m.p. 155°.[10] Fraction (b) was 1-acetyl-2-methyl-1-cyclohexanol,[11] m.p. 35.5–36.5°. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.80; H, 10.30.

The semicarbazone of fraction (b), melted at 208–208.5° after recrystallization from aqueous ethanol, literature m.p. 229–230°.[5] *Anal.* Calcd. for $C_{10}H_{19}O_2N_3$: C, 56.31; H, 8.98. Found: C, 56.93; H, 9.03.

1-Acetyl-3-methyl-1-cyclohexanol, method A, yield 85%, b.p. 100–104° (10 mm.), $n^{28}D$ 1.4616. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.18; H, 10.33. Found: C, 68.89; H, 10.19.

1-Acetyl-4-methyl-1-cyclohexanol, method A, yield 65%, b.p. 95–98° (9 mm.), 115–116° (19 mm.), $n^{28}D$ 1.4641. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.18; H, 10.33. Found: C, 69.60; H, 10.37.

1-Acetyl-4-methoxy-1-cyclohexanol, method B, yield 34%, b.p. 110–113° (7 mm.), $n^{21}D$ 1.4714. *Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.42. Found: C, 63.13; H, 9.49.

1-Acetyl-3,3,5-trimethyl-1-cyclohexanol, method A, yield 81%, b.p. 101–102° (11 mm.), $n^{30}D$ 1.4587. *Anal.* Calcd. for $C_{11}H_{20}O_3$: C, 71.69; H, 10.94. Found: C, 71.15; H, 10.97.

3-Methyl-3-hydroxy-4-pentanone, method A, yield 40%, b.p. 64–66° (25 mm.), literature b.p. 154°.[12] *Anal.* Calcd. for $C_6H_{12}O_2$: C, 62.10; H, 10.35. Found: C, 62.13; H, 10.41.

2,3-Dimethyl-3-hydroxy-4-pentanone, method A, yield 64%, b.p. 60–62° (15 mm.), $n^{24}D$ 1.4265, literature b.p. 58° (16 mm.).[13] *Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.57; H, 10.86. Found: C, 64.32; H, 11.05.

2,4-Dimethyl-4-hydroxy-5-hexanone, method A, yield 58%, b.p. 68–70° (12 mm.), $n^{23}D$ 1.4300, literature[13] b.p. 69–70° (12 mm.).

2,2,3-Trimethyl-3-hydroxy-4-pentanone, method A, yield 54%, b.p. 76–78° (16 mm.), $n^{29}D$ 1.4379, literature[9] b.p. 70–72° (14 mm.). *Anal.* Calcd. for $C_8H_{16}O_2$: C, 67.30; H, 11.20. Found: C, 67.31; H, 11.39.

1-Acetyl-1-decalol, method A, yield 68%, b.p. 88.5–89° (1 mm.), $n^{29}D$ 1.4918. *Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.47; H, 10.27. Found: C, 73.84; H, 10.48.

Acetoxy and Hydroxymethyl Ketones.—To a cold methylene chloride solution (−40°) containing 3 molar equivalents of diazomethane, prepared in the usual way, there was added 1 mole of the appropriate acid chloride with stirring (all-glass stirrer) maintaining the temperature at −35 to −50°. The mixture was stirred for 4 hours at −40°, the cooling bath removed and the mixture kept overnight. The solvent was removed under reduced pressure and the crude diazoketone decomposed with an excess of acetic acid. The mixture was poured into water, neutralized with sodium hydroxide and extracted with ether. The ether extracts were washed with saturated salt, dried and distilled, to yield the acetoxymethyl ketones. For the hydroxymethyl ketones 2 *N* sulfuric acid was used to decompose the diazoketones.

Hydroxymethyl 2,3-dimethylcyclopentyl ketone, yield 36%, b.p. 132–135° (13 mm.), $n^{25}D$ 1.4512. *Anal.* Calcd. for $C_{11}H_{18}O_2$: C, 66.62; H, 9.17. Found: C, 66.52; H, 9.37.

Acetoxymethyl Δ^1-cyclohexenyl ketone, yield 32%, b.p. 133–135° (8 mm.), $n^{24}D$ 1.4924. *Anal.* Calcd. for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 65.76; H, 8.00.

Hydroxymethyl Δ^1-cyclohexenyl ketone, yield 46%, b.p. 120–122° (15 mm.), $n^{26}D$ 1.4956. *Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.56; H, 8.56. Found: C, 68.73; H, 8.35.

Acetoxymethyl 2-methyl Δ^1-cyclopentenyl ketone, yield 45%, b.p. 133–135° (8 mm.), $n^{25}D$ 1.4939. *Anal.* Calcd. for $C_{10}H_{14}O_3$: C, 65.90; H, 7.76. Found: C, 65.32; H, 7.82.

Hydroxymethyl 2-methylcyclopentyl ketone, yield 29%,

(7) H. Rupe and E. Kambli, *Ann.*, **459**, 215 (1927).

(8) G. F. Hennion, D. B. Killian, T. H. Vaughn and J. A. Nieuwland, THIS JOURNAL, **56**, 1130 (1934).

(9) R. Locquin and W. Sung, *Compt. rend.*, **176**, 516 (1923).

(10) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 185.

(11) The referee has suggested the possibility of the presence of *o*-methylcyclohexanone and *o*-methylcyclohexanol in the 1-ethinyl-2-methyl-1-cyclohexanol prior to the hydration reaction. We wish to report that the ethinylcarbinol was purified by careful fractionation through a 30-plate packed column. In our experiences impure 1-ethinyl-2-methyl-1-cyclohexanol cannot be separated into the liquid and solid isomers.

(12) O. Diels and J. M. Johlin, *Ber.*, **44**, 406 (1911).

(13) L. Leers, *Bull. soc. chim.*, [4] **39**, 423 (1926).

b.p. 108–110° (22 mm.), $n^{25}D$ 1.4616. *Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.70; H, 9.86. Found: C, 67.74; H, 9.30.

Acetoxymethyl cyclohexyl ketone, yield 61%, b.p. 133–137° (14 mm.), $n^{25}D$ 1.4609. *Anal.* Calcd for $C_{10}H_{16}O_3$: C, 65.21; H, 8.68. Found: C, 65.15; H, 9.23.

Acetoxymethyl 2-methylcyclohexyl ketone, yield 35%, b.p. 130–137° (10 mm.), $n^{22}D$ 1.4594. *Anal.* Calcd. for $C_{11}H_{18}O_3$: C, 66.62; H, 9.17. Found: C, 65.94; H, 9.31.

1-Acetoxyacetyl-1-acetoxycyclohexane. 1-Acetoxy-1-vinylcyclohexane.—A mixture of 124 g. (1 mole) of 1-ethinyl-1-cyclohexanol and 408 g. (4 moles) of acetic anhydride was refluxed for two hours. The excess acetic anhydride was removed under reduced pressure, the residue decomposed with water and neutralized with sodium bicarbonate. The resulting mixture was extracted with ether, the ether extracts washed with salt solution and dried. After removal of the ether, the residue was distilled, yield 131 g. (80%), b.p. 90–92° (12 mm.), $n^{25}D$ 1.4635; literature[14] for 1-acetoxy-1-ethinylcyclohexane, b.p. 87° (10 mm.). Fifty grams of acetoxy compound was dissolved in 100 g. of anhydrous pyridine and 2.5 g. of 5% palladium–calcium carbonate catalyst added. The mixture was reduced at low pressure in a Parr apparatus and after one mole of hydrogen was absorbed, the reduction was stopped, the catalyst filtered off and the pyridine removed under reduced pressure. The 1-acetoxy-1-vinylcyclohexane was obtained in a yield of 74%, b.p. 94–95° (25 mm.), $n^{24}D$ 1.4555.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.95; H, 9.71.

Bromomethyl-1-acetoxycyclohexylcarbinol.—To a mixture of 33 g. of 1-acetoxy-1-vinylcyclohexane, 500 cc. of *t*-butyl alcohol, 30 g. of N-bromoacetamide and 32 g. of sodium acetate, in 165 cc. of water, there was added 82 cc. of acetic acid. The reaction mixture was kept at 15° for 3.5 hours and the solvent then removed under reduced pressure. The residue was extracted with ether, the extract washed with sodium carbonate solution, with water and then dried. On evaporating the ether solution to a small volume, crystals of bromomethyl-1-acetoxycyclohexylcarbinol separated, yield 48 g. (92%), m.p. 96–97° after recrystallization from ether. In other runs, yields varied from 78–90%.

Anal. Calcd. for $C_{10}H_{17}O_3Br$: C, 45.30; H, 6.46. Found: C, 45.66; H, 6.64.

Bromomethyl 1-Acetoxycyclohexyl Ketone.—To 13.3 g. of the carbinol dissolved in 50 cc. of glacial acetic acid, there was added a solution of 20 g. of chromium trioxide in 100 cc. of acetic acid and 10 cc. of water. The mixture was kept overnight at room temperature and after decomposing the excess chromic acid with methanol, the solvent was removed under reduced pressure. The residue was extracted with ether, the extract washed with dilute sulfuric acid, with sodium carbonate solution and finally with water. After removal of the ether, the residue was triturated with petroleum ether and, on cooling in a Dry Ice–acetone-bath, crystallized. Recrystallized from a mixture of ether–petroleum ether, the bromomethyl 1-acetoxycyclohexyl ketone melted at 34–35°, yield 11 g. (83%).

Anal. Calcd. for $C_{10}H_{15}O_3Br$: C, 45.64; H, 5.75. Found: C, 45.69; H, 5.94.

Treatment of the bromoketone (2 g.) with zinc dust (1 g.) in acetic acid (35 cc.) and sodium acetate (1 g.) for 10 minutes at 80° gave 1-acetylcyclohexanol, identified as the oxime, m.p. 106–107°; mixed m.p. with an authentic sample, m.p. 106–107°.

The bromoketone was also prepared as follows: To a solution of 52 g. of 1-acetyl-1-acetoxycyclohexane in 600 cc. of acetic acid, there was added dropwise a solution of 45 g. of bromine in 50 cc. of acetic acid. During the bromination the temperature increased to 45°. The solution was poured on ice, extracted with ether, the extracts washed three times with water, then with sodium bicarbonate solution and finally with water. After removing the ether, the residue was dissolved in 250 cc. of petroleum ether and on cooling in a Dry Ice–acetone mixture, crystals of the bromoketone separated. Recrystallized from petroleum ether, yield 26 g., m.p. 34–35°; mixed m.p. with bromoketone obtained by oxidation of the carbinol, 34–35°.

1-Acetoxyacetyl-1-acetoxycyclohexane.—To a solution of 15 g. of potassium acetate in 500 cc. of absolute ethanol and 50 cc. of acetic acid, there was added 30 g. of the bromoketone. The mixture was refluxed with stirring for 12 hours, filtered and evaporated *in vacuo*. Water was added to the residue, the yellow oil extracted with ether and, after washing, the ether extract was evaporated. The residue on distillation gave 25 g. of a yellow oil, b.p. 130–142° (3 mm.), $n^{24}D$ 1.4768. The distillate gave a positive Fehling test and a positive test for bromine. Treatment with zinc dust (50 g.) in acetic acid (150 cc.) gave the bromine-free 1-acetoxyacetyl-1-acetoxycyclohexane, yield 16 g., b.p. 140–142° (3 mm.), $n^{24}D$ 1.4621.

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.50; H, 7.59. Found: C, 59.82; H, 7.70.

Alternate Synthesis of 1-Acetoxyacetyl-1-acetoxycyclohexane. 1-Acetoxycyclohexylcarboxylic Acid.—The requisite intermediate, 1-hydroxycyclohexylcarboxylic acid, m.p. 105–106°[15] was prepared from the cyanohydrin of cyclohexanone.[16] To 134 g. of 1-hydroxycyclohexylcarboxylic acid, there was added slowly 300 cc. of acetyl chloride at room temperature. The mixture was then warmed gently on the steam-bath for one hour, the solution poured into ice-water and carefully neutralized with sodium carbonate solution. The product was filtered, air-dried and recrystallized from benzene–petroleum ether, m.p. 99–100°, yield 145 g. (84%). The analytical sample, after two recrystallizations, melted at 101–102°, mixed m.p. with the hydroxy acid 75–84°.

Anal. Calcd. for $C_9H_{14}O_4$: C, 57.44; H, 7.44. Found: C, 57.71; H, 7.60.

The 1-acetoxycyclohexylcarboxylic acid was also prepared as follows; To 30 g. of the hydroxy acid suspended in 60 cc. of acetic anhydride cooled in an ice-bath there was added 8 drops of boron trifluoride etherate. After one hour, the mixture was poured into ice-water and extracted with ether. The extracts were washed with water, the acidic fraction removed by extraction with sodium bicarbonate solution and, after acidification of the bicarbonate solution, it was extracted with ether. This ether solution yielded 12 g. (25%) of the acetoxy acid, m.p. 99–100°. From the initial ether extract a neutral fraction was obtained in a yield of 12 g., b.p. 108–111° (3 mm.), $n^{25}D$ 1.4523. The analysis indicates that this product is the 1-acetoxycyclohexyl-1-carboxylic acetic anhydride.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.01. Found: C, 57.90; H, 6.93.

1-Acetoxyacetyl-1-acetoxycyclohexane.—To a cold (10°) mixture of 14 g. of 1-acetoxycyclohexyl-1-carboxylic acid, 50 cc. of anhydrous benzene and 10 cc. of anhydrous pyridine, there was added slowly 10 cc. of freshly distilled thionyl chloride (distilled over quinoline and linseed oil). The mixture was kept at 10° for two hours and at room temperature for three hours with occasional shaking. The precipitated pyridine hydrochloride was filtered off, washed with anhydrous benzene and the filtrates evaporated under reduced pressure. The acid chloride was distilled, yield 10 g., b.p. 109–115° (12 mm.), and was used without further purification. The reaction of the acid chloride with diazomethane was carried out as described, using acetic acid to decompose the diazoketone; yield of 1-acetoxyacetyl-1-acetoxycyclohexane 44%, b.p. 133–135° (2 mm.), $n^{25}D$ 1.4635.

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.50; H, 7.49. Found: C, 59.70; H, 7.46.

1-Hydroxyacetyl-1-cyclohexanol.—To a solution of 24 g. of 1-acetoxyacetyl-1-acetoxycyclohexane in 375 ml. of methanol there was added 72 g. of finely powdered potassium bicarbonate and the mixture stirred under nitrogen for 2 days. After dilution with water, the solution was saturated with salt and extracted thoroughly with ether. The dried ethereal extracts were evaporated under reduced pressure and the residue recrystallized from ether–petroleum ether; yield 12.5 g., m.p. 87–88°, literature 87–89°,[3f] 89–90°.[3b]

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.73; H, 8.92. Found: C, 60.98; H, 9.14.

Hydrolysis of the diacetyl compound with 10% sodium hydroxide solution at room temperature afforded the dihydroxy compound in 15% yield, m.p. 86–88°.

(14) H. Rupe, W. Messner and E. Kambli, *Helv. Chim. Acta*, **11**, 453 (1928).

(15) H. Bucherer, *Ber.*, **27**, 1230 (1894), reports m.p. 106–107°.

(16) K. v. Auwers and F. Krollpfeiffer, *ibid.*, **48**, 1389 (1915).

1-Acetoxyacetyl-1-acetoxycyclopentane.—The requisite intermediates were prepared by the procedures for the cyclohexyl compound. 1-Acetoxy-1-ethinylcyclopentane, yield 61%, b.p. 85–87° (19 mm.), 95–96° (29 mm.), $n^{24}D$ 1.4568.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.99; H, 8.21.

1-Acetoxy-1-vinylcyclopentane, yield 75%, b.p. 83–85° (26 mm.), $n^{24}D$ 1.4510. This compound was not analyzed but was used in the next operation. Bromomethyl-1-acetoxycyclopentylcarbinol, yield 37%, m.p. 55–56° after recrystallization from ether–petroleum ether.

Anal. Calcd. for $C_9H_{15}O_3Br$: C, 43.04; H, 6.06. Found: C, 43.17; H, 6.55.

The bromomethyl-1-acetoxycyclopentyl ketone was not isolated, but converted to the 1-acetoxyacetyl-1-acetoxycyclopentane, yield 22% from the carbinol, b.p. 124–126° (2 mm.).

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.62; H, 7.06.

Hydroxymethyl-1-hydroxycyclohexylcarbinol.—To 53.2 g. of bromomethyl-1-acetoxycyclohexylcarbinol dissolved in one liter of dioxane (distilled over sodium), there was added a solution of 67.2 g. of potassium hydroxide in 800 cc. of water. The solution was refluxed for one hour, neutralized with carbon dioxide and evaporated under reduced pressure. The residue was extracted with ether in a continuous extractor for several days. The ether extract yielded 27 g. of trihydroxy compound (84%), m.p. 112–113°; recrystallized for analysis from chloroform–petroleum ether, m.p. 112–112.5°.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.66; H, 10.13.

Hydroxymethyl 1-hydroxycyclopentylcarbinol was prepared as described for the cyclohexyl compound, yield 57%, m.p. 54–55° after recrystallization from chloroform–petroleum ether.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.51; H, 9.93.

β-Glycols.—The hydroxy esters were obtained by the conventional Reformatsky reaction on the appropriate ketones.[17] Hydrolysis of the hydroxy esters with 2 equivalents of potassium hydroxide in 50% ethanol at reflux temperature gave the hydroxy acids. In the extraction of the hydroxy acids from the acidified hydrolysis mixture, after removal of the alcohol, the aqueous solution was saturated with sodium chloride and ether extracted.

To a solution of 8.36 g. (0.22 mole) of lithium aluminum hydride in 600 cc. of absolute ether was added dropwise, with vigorous stirring, 31.6 g. (0.2 mole) of the hydroxy acid in 200 cc. of ether. After the final addition of the acid, the reaction mixture was refluxed with stirring for 2 hr., and then kept at room temperature overnight. The mixture was cooled, decomposed with water and 10% sodium carbonate and the layers separated. The aqueous layer was extracted with ether, the combined extracts dried over sodium sulfate and the ether removed. The residue was distilled *in vacuo* at pressures below 5 mm. For the reduction of the esters a ratio of 2 moles of lithium aluminum hydride to one mole of ester was used.

1-(β-Hydroxyethyl)-1-cyclohexanol, from cyclohexanol-1-acetic acid; yield 46%, b.p. 112–114° (2 mm.), $n^{26}D$ 1.4850. *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.19. Found: C, 67.13; H, 11.15.

1-(β-Hydroxyethyl)-1-cyclopentanol, from cyclopentanol-1-acetic acid; yield 63%, b.p. 103–105° (1 mm.), $n^{25}D$ 1.4815. *Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.56; H, 10.85. Found: C, 64.82; H, 11.19.

1-(β-Hydroxyethyl)-2-methyl-1-cyclohexanol from 2-methylcyclohexanol-1-acetic acid; yield 84%, b.p. 108–110° (1.5 mm.), $n^{25}D$ 1.4850. *Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 67.95; H, 11.59.

2-(1-Hydroxycyclohexyl)-1-butanol from α-(1-hydroxycyclohexyl)-butyric acid (b.p. 144–146° (2 mm.), m.p. 80–81° after recrystallization from petroleum ether. *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 64.47; H, 9.74. Found: C, 64.72; H, 9.45); yield 59%, b.p. 112–113° (1 mm.), $n^{28}D$ 1.4815.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.73; H, 11.71. Found: C, 69.76; H, 11.26.

2-(1-Hydroxycyclohexyl)-1-propanol from α-(1-hydroxycyclohexyl)-propionic acid; yield 67%, b.p. 110–112° (1 mm.), $n^{25}D$ 1.4860. *Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.02; H, 11.33.

1-(β-Hydroxyethyl)-3,3,5-trimethyl-1-cyclohexanol from α-(1-hydroxy-3,3,5-trimethylcyclohexyl)-acetic acid (m.p. 115.5–116.5° after recrystallization from water. *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 65.95; H, 10.08. Found: C, 66.11; H, 11.62); yield 61%, m.p. 110.5–111.5° after recrystallization from ether.

Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.89; H, 11.90. Found: C, 70.30; H, 12.16.

2-Cyclohexylbutane-2,4-diol, from ethyl β-cyclohexyl-β-hydroxybutyrate (prepared from acetylcyclohexane and ethyl bromoacetate *via* the Reformatsky reaction; yield 66%, b.p. 108–110° (2 mm.), $n^{26}D$ 1.4617. *Anal.* Calcd. for $C_{12}H_{22}O_3$: C, 67.23; H, 10.35. Found: C, 67.79; H, 10.61); yield 76%, b.p. 125–127° (2 mm.), $n^{26}D$ 1.4865.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.73; H, 11.71. Found: C, 69.84; H, 11.51.

2-Phenylbutanediol-2,4 from ethyl-β-phenyl-β-hydroxybutyrate; yield 67%, b.p. 134–136° (1 mm.), $n^{26}D$ 1.5320. *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found: C, 72.87; H, 8.75.

3-Methylpentane-1,3-diol from 3-methyl-3-hydroxyvaleric acid; yield 66%, b.p. 112–115° (11 mm.), $n^{25}D$ 1.4493. This compound also has been obtained by the reduction of ethyl 2,3-epoxy-3-methylvalerate by sodium and alcohol[18]; b.p. 115° (10 mm.), $n^{20}D$ 1.4522. The 3-methyl-3-hydroxyvaleric acid was obtained from ethyl 3-methyl-3-hydroxyvalerate[19] as a colorless liquid, b.p. 142–144° (19 mm.), $n^{30}D$ 1.4432; the literature[20] describes the compound as a sirupy liquid.

1-Hydroxy-1-hydrindanylacetic Acid.—The intermediate, 1-hydrindanone, was prepared as follows: *o*-Carboxycinnamic acid, m.p. 208–209°, was prepared by peracetic acid oxidation of β-naphthol[21] reduced with platinum oxide in acetic acid to β-(2-carboxycyclohexyl)-propionic acid, m.p. 102–103°,[23] and the latter cyclized by pyrolysis with barium oxide[22]; b.p. 88–90° (16 mm.), $n^{24}D$ 1.4814; semicarbazone m.p. 216–217°, literature[23] m.p. 214–215°. The 1-hydroxy-1-hydrindanylacetic acid was prepared as follows: 1-hydrindanone with ethyl bromoacetate gave ethyl 1-hydroxy-1-hydrindanylacetate, b.p. 117–125° (2–3 mm.), $n^{25}D$ 1.4782, which on saponification with potassium hydroxide in 50% ethanol gave the acid as a white crystalline solid, m.p. 100–101° after recrystallization from ether–petroleum ether; yield based on 1-hydrindanone, 32%.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.65; H, 9.15. Found: C, 66.53; H, 9.18.

Reduction of the acetic acid gave the diol in 78% yield, b.p. 125–128° (1 mm.), m.p. 60–61°. *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.72; H, 10.94. Found: C, 71.58; H, 11.07.

BLOOMFIELD, N. J.

(17) "The Reformatsky Reaction," in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942.

(18) A. St. Pfau and Pl. Plattner, *Helv. Chim. Acta*, **15**, 1250 (1932).

(19) H. Bohnsack, *Ber.*, **74B**, 1575 (1941).

(20) A. Pokrovsky *J. Russ. Phys. Chem. Soc.*, **32**, 65 (1900); *Brit. Chem. Abstr.*, **78**, 328 (1900).

(21) F. P. Greenspan, *Ind. Eng. Chem.*, **39**, 847 (1947).

(22) Wm. S. Johnson, THIS JOURNAL, **66**, 215 (1944).

(23) A. Windaus, W. Hückel and G. Reverey, *Ber.*, **56**, 91 (1923).