crystallized from an alcohol–water mixture, colorless plates, micro m.p. 154–154.5°.

Anal.[18] Calcd. for $C_{16}H_{21}O_4Br$: C, 53.79; H, 5.93. Found: C, 53.78; H, 6.17.

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[18] Microanalysis by Galbraith Laboratories, Knoxville, Tennessee.

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DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. XXXV. Cyclic Ketene Acetals and Orthoesters from 2,2-Dimethoxy-2,3-dihydropyran

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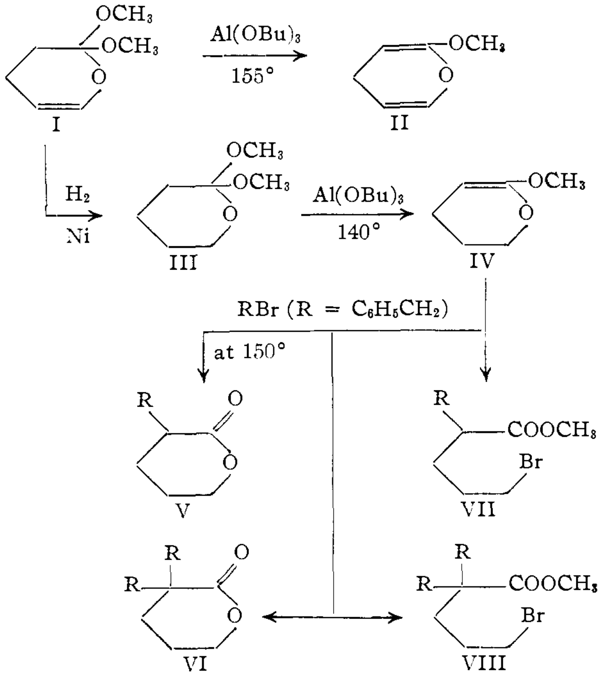
2,2-Dimethoxy-2,3-dihydropyran (I) has been dealcoholated to the unstable 2-methoxypyran (II) and also converted to 2-methoxy-5,6-dihydropyran (IV). Some reactions of the latter of these ketene acetals are described; of particular interest is the addition of acrolein to produce a bicyclic orthoester IX, which is converted *via* hydrogenation and dealcoholation to the bicyclic ketene acetal XI. This ketene acetal readily adds acrolein to yield, after hydrogenation, the tricyclic orthoester XVIII. This orthoester and the corresponding normal ester, the dihydroxylactone XIX, are readily interconvertible.

The preparation of 2,2-dimethoxy-2,3-dihydropyran (I) from the addition of acrolein to ketene dimethylacetal was described in a recent paper[2] of this series. The present paper describes the conversion of this dihydropyran to cyclic ketene acetals and the addition of acrolein to these compounds to produce some novel bicyclic and tricyclic orthoesters.

The dealcoholation of the cyclic enol orthoester I with sublimed aluminum *t*-butoxide[3] gave a quantitative yield of *t*-butyl alcohol but only a 20% yield of 2-methoxypyran (II). This colorless liquid rapidly changed to an amber gum on contact with air. The yield of II was raised only slightly (to 25%) when the dealcoholation of I was carried out under nitrogen. The structure of II was indicated by the presence of two bands at 5.90 μ (ketene acetal)[3] and at 6.07 μ (enol ether) in the infrared, and its hydrolysis to methyl γ-formylbutyrate.

The hydrogenation of I to the tetrahydropyran III was accomplished in 95% yield with W-7 Raney nickel.[4] The saturated orthoester III, whose spectrum was completely devoid of the enol ether band at 6.06 μ, was dealcoholated to 2-methoxy-5,6-dihydropyran (IV) in 85% yield with sublimed aluminum *t*-butoxide. This dealcoholation, which begins at approximately 140°, appears more facile than any previously observed with other orthoesters.[3,5]

The ketene acetal IV, which shows a monosubstituted ketene acetal band at 5.99 μ in the infrared,[3] readily absorbed bromine and was hydrolyzed to a mixture of δ-valerolactone and methyl δ-hydroxyvalerate, which was converted to δ-hydroxyvalerohydrazide. When heated with benzyl bromide at 150° for two hours, IV was converted mainly into α,α-dibenzyl-δ-valerolactone (VI) (51%) and smaller amounts of α-benzyl-δ-valerolactone (V) (6%), methyl α-benzyl-δ-bromovalerate (VII) (11%) and methyl α,α-dibenzyl-δ-bromovalerate (VIII) (11%). It is of interest to note that while the single methyl substituent of methylketene diethylacetal prevented the dibenzylation of this acyclic ketene acetal, the monosubstituted cyclic ketene acetal IV gives greater amounts of dibenzylated products (VI and VIII) than did the unsubstituted ketene diethylacetal.[6]



The ketene acetal IV condensed with acrolein at 100° to yield the bicyclic enol orthoester IX, which was hydrogenated to 1-methoxy-2,10-dioxabicyclo[4.4.0]decane (X). When this orthoester was distilled at 87° (8 mm.) its infrared spectrum had a noticeable absorption band at 5.91 μ, indicating the presence of a ketene acetal. However, when X was distilled at 38° (0.1 mm.) a product with no absorption at this wave length was ob-

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[1] Wisconsin Alumni Research Foundation Research Assistant 1954–1955.

[2] S. M. McElvain, E. R. Degginger and J. D. Behun, THIS JOURNAL, **76**, 5736 (1954).

[3] S. M. McElvain and R. E. Starn, Jr., *ibid.*, **77**, 4571 (1955).

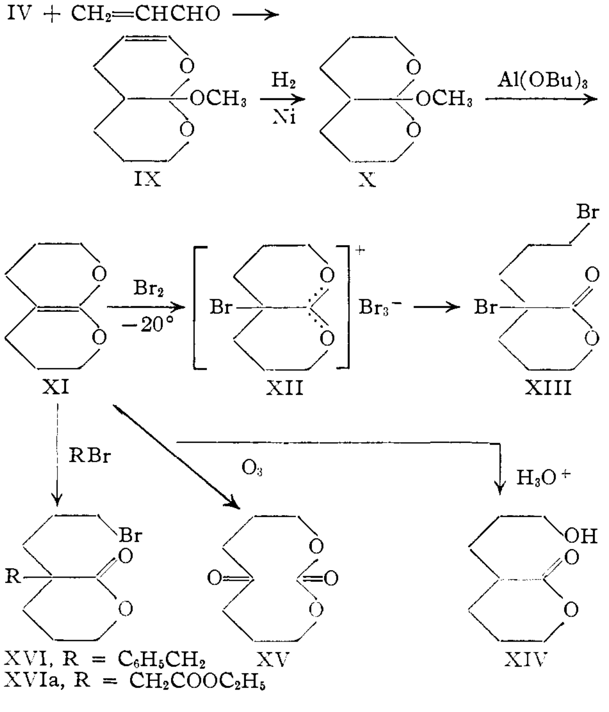
[4] H. Adkins and H. R. Billica, *ibid.*, **70**, 695 (1948).

[5] A temperature range of 160–190° has been required for the dealcoholation of a variety of cyclic and acyclic orthoesters, *cf.* S. M. McElvain, *et al.*, *ibid.*, **72**, 1661 (1950); **73**, 1400 (1951).

[6] S. M. McElvain and H. F. McShane, *ibid.*, **74**, 2662 (1952).

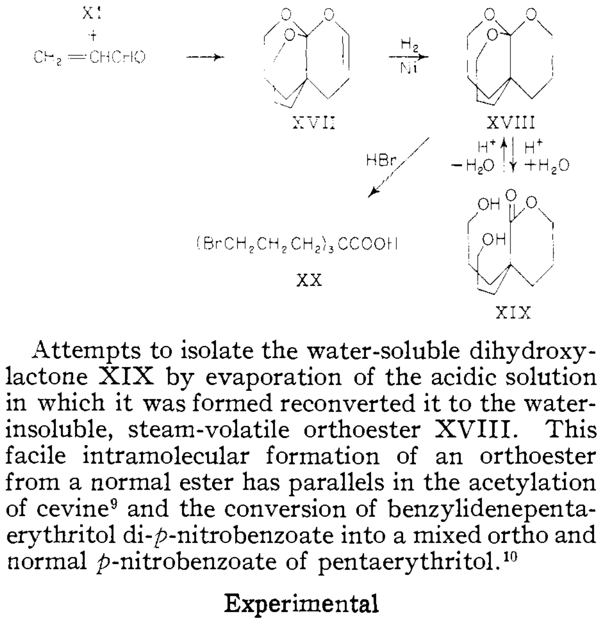
tained. It would appear, therefore, that the orthoester X undergoes partial dealcoholation to XI at the higher distillation temperature. The orthoester X shows the characteristic bands of an α,α-disubstituted orthoester[3] at 8.07, 8.69, 9.25 and 10.04 μ.

The orthoester X was dealcoholated in 85% yield to the ketene acetal XI with aluminum *t*-butoxide at 145°. This ketene acetal absorbed 97% of an equivalent of bromine to form the dibromolactone XIII; if this bromination were carried out at −20°, the orange-yellow tribromide salt[7] XII could be isolated. Hydrolysis converted XI to the hydroxylactone XIV. Ozonolysis of XI at −70° produced the cyclic keto carbonate XV, which yielded a 2,4-dinitrophenylhydrazone. Benzyl bromide and XI reacted at 110° to give α-benzyl-α-(γ-bromopropyl)-δ-valerolactone (XVI) in 86% yield. This benzylation of XI occurs more readily than that of dimethylketene dimethylacetal.[8] Similarly, ethyl bromoacetate converted XI to the bromolactone XVIa.



Methanol adds exothermically to the ketene acetal XI to yield an orthoester with significantly different properties and spectrum than X. This product, which appears to be a mixture of *cis* and *trans* forms of X, gives XI in high yield on dealcoholation with aluminum *t*-butoxide. With these isomers it has been possible to show that X is at least 97% one isomer, which, considering its formation from IV *via* IX, appears to be the *cis* form.

The condensation of the bicyclic ketene acetal XI with acrolein produced the unsaturated tricyclic orthoester XVII, m.p. 83–84°, in 79% yield. This enol orthoester showed an absorption band in the infrared at 6.01 μ. Hydrogenation of XVII yielded the saturated orthoester XVIII, m.p. 116–117°. This orthoester remained insoluble in refluxing dilute sodium hydroxide solution, but dissolved in dilute acid, slowly on standing or rapidly when heated, with formation of the dihydroxylactone XIX. Hydrogen bromide in ether converted XVIII into the tribromo acid XX, m.p. 93–94°.



Attempts to isolate the water-soluble dihydroxylactone XIX by evaporation of the acidic solution in which it was formed reconverted it to the water-insoluble, steam-volatile orthoester XVIII. This facile intramolecular formation of an orthoester from a normal ester has parallels in the acetylation of cevine[9] and the conversion of benzylidenepentaerythritol di-*p*-nitrobenzoate into a mixed ortho and normal *p*-nitrobenzoate of pentaerythritol.[10]

Experimental

Ketene Dimethylacetal.—In a three-necked, 5-l. round-bottom flask, fitted with a reflux condenser and mechanical stirrer, 138 g. (6 g. atoms) of sodium was slowly added to 3 l. of dimethylphenylcarbinol[11] held at 140°. At this temperature the reaction proceeded rapidly and was maintained by its own heat. The sodium melted as it was added and was whipped into fine particles by the stirrer. As the reaction subsided, the temperature of the solution was raised to 180° to ensure complete reaction of the sodium. A Claisen still-head, connected by a spiral condenser and adapter to a 1-l. receiver, then was attached to the reaction vessel and a Pyrex tube (7 mm.) which led to the bottom of the reaction flask was inserted in place of the reflux condenser. The tube was curved in such way that it did not interfere with the action of the stirrer. From a dropping funnel connected to the tube leading beneath the surface, 616 g. (5 moles) of chlorodimethylacetal was added *dropwise* as rapidly as possible while the alcohol solution was maintained at 175–185°. After a few minutes the ketene acetal began to be evolved from the reaction mixture and was collected in the receiver. This material was recycled through the dropping funnel into the reaction mixture, after which the condensed material was distilled through a 25-cm. Podbielniak column and the fraction boiling at 85–95° collected. Redistillation of this fraction gain 231 g. (52.5%) of ketene dimethylacetal: b.p. 89–91°, n^{25}D 1.4045 (reported[6] b.p. 89–89.5°, n^{25}D 1.4050). The yield was not increased by an additional recyclization of the product.

The next run was made by adding another 138 g. of sodium to the carbinol and repeating the procedure. A yield of 49.2% of the ketene acetal was obtained. A third run was not feasible as the reaction mixture became so viscous with the suspended and dissolved sodium chloride that stirring was inefficient.

The material which remained in the reaction flask was washed with water, dried over sodium sulfate and distilled.

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[7] *Cf.* S. M. McElvain and W. L. McLeish, This Journal, **77**, 3786 (1955).

[8] S. M. McElvain and C. L. Aldridge, *ibid.*, **75**, 3987 (1953).

[9] D. H. R. Barton, *et al.*, *J. Chem. Soc.*, 2138 (1954).

[10] E. D. Bergman, *et al.*, This Journal, **73**, 2352 (1951).

[11] Kindly supplied by Hercules Powder Company, Wilmington, Delaware. This material was approximately 85% pure, with acetophenone as the principal impurity. The alcohol was purified by recrystallization from petroleum ether cooled with Dry Ice.

A considerable amount of isopropylbenzene, from the hydrogenolysis of the phenyldimethylcarbinol, was collected as forerun: b.p. 50–51° (35 mm.), 150° (737 mm.), $n^{25}\text{D}$ 1.4887. The product contained 89.52% C and 10.00% H (calcd. 89.94 and 10.07). An authentic sample possessed identical physical properties and both materials displayed the same infrared absorption spectrum.

After distillation of the main fraction of dimethylphenylcarbinol, b.p. 65–80° (32 mm.), a higher boiling product, b.p. 86–87° (0.6 mm.), $n^{25}\text{D}$ 1.4857, was collected. This material did not give a positive Fehling test until it had been treated with dilute hydrochloric acid. The infrared spectrum showed absorption at 6.25 and 6.67 μ characteristic of a phenyl group and also twin peaks, 7.24 and 7.33 μ, which have been assigned to a *gem*-dimethyl grouping.[12] When treated with Brady's 2,4-dinitrophenylhydrazine reagent,[13] an 85% yield of glyoxal bis-2,4-dinitrophenylhydrazone, m.p. 315–316° from pyridine, was obtained. The derivative contained 40.49% C and 2.45% H (calcd. 40.20 and 2.41) and showed no depression of melting point when mixed with an authentic sample. This behavior indicates that the product is dimethylphenylcarbinyloxy dimethylacetal,[14] $C_6H_5C(CH_3)_2OCH_2CH(OCH_3)_2$.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.44; H, 8.84.

2-Methoxypyran (II).—A mixture of 28.8 g. (0.20 mole) of 2,2-dimethoxy-2,3-dihydropyran[2] (I) and 49.2 g. (0.20 mole) of sublimed aluminum *t*-butoxide[3] was magnetically stirred in a 200-ml. round-bottom flask that carried a 10 cm. Vigreux column and a stillhead and was protected by a calcium chloride drying tube. The mixture was heated under an atmosphere of nitrogen. At 155° *t*-butyl alcohol began to be evolved at a moderate rate. In 1 hour the temperature had reached 185° and a quantitative yield of alcohol had been collected. As the reaction mixture was cooled to 100°, the pressure was slowly reduced to 25 mm., whereupon 5.6 g. (25%) of 2-methoxypyran (II), b.p. 63–64° (25 mm.), $n^{25}\text{D}$ 1.4619, was collected. Without the nitrogen atmosphere the dealcoholation gave a 20% yield. The product was extremely sensitive to air. Although II was colorless when freshly distilled, it became amber within a few seconds and turned to a tacky mass after several minutes of contact with air. A pure sample could not be obtained for analysis even when the material was collected under nitrogen. The infrared spectrum of II showed absorption characteristic of an enol ether at 6.07 μ[15] and of a ketene acetal at 5.90 μ.[3] There was an extremely vigorous reaction when II was treated with dilute hydrochloric acid. A yellow 2,4-dinitrophenylhydrazone was obtained by treatment of the hydrolysis mixture with methanolic Brady's reagent.[13] The derivative after recrystallization from 95% ethyl alcohol melted at 107–108.5° and showed no depression of melting point when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone (m.p. 107.5–108.5°) of methyl γ-formylbutyrate[2] obtained from the hydrolysis of I.

2,2-Dimethoxytetrahydropyran (III).—In a 500-ml. glass bottle 253 g. (1.75 moles) of 2,2-dimethoxy-2,3-dihydropyran (I) was shaken with 6 teaspoonsful of Raney nickel (W-7)[4] which had been washed free of ethanol with anhydrous ether. A pressure of one to three atmospheres of hydrogen was maintained in the bottle and the reduction proceeded smoothly to 90% completion in 10 hours. The reaction was completed in another 24 hours with the theoretical amount of hydrogen absorbed.

The catalyst was removed by centrifugation and washed with anhydrous diethyl ether. The washings and product were distilled through a 25-cm. Podbielniak column. After removal of the diethyl ether at reduced pressure, 243 g. (94.8%) of 2,2-dimethoxytetrahydropyran (III) was collected: b.p. 69–70° (20 mm.), 164.5–165° (739 mm.), $n^{25}\text{D}$ 1.4298, d^{25}_4 1.029.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65; *M*R*D*, 37.26. Found: C, 57.65; H, 9.22; *M*R*D*, 36.69.

The product absorbed only an insignificant amount of bromine in carbon tetrachloride and the infrared spectrum showed only a slight indication of the enol ether band at 6.06 μ which was so prominent in the starting material I.

The enol ether group of I is extremely sensitive to hydrogenolysis. When 10% palladium-on-carbon was used as catalyst in methanol as solvent, none of the saturated cyclic orthoester III was obtained; with dry dioxane as solvent the yield of III was 40%. The reduction seemed erratic and caused some hydrogenolysis of the orthoester to yield a mixture of products. The hydrogenolysis portion of the reaction mixture seemed to be a pure compound, b.p. 112–113° (34 mm.); however, elemental analysis did not correspond to any expected product. The product does not give a test with Fehling solution until it is hydrolyzed with acid. A solution of 0.311 g. of this product in methanol yielded 0.522 g. of a yellow 2,4-dinitrophenylhydrazone, m.p. 94–98°; after several recrystallizations from absolute methanol the melting point was raised to 109.5–110.5°. This product contained 47.17% C and 4.76% H; calcd. for the 2,4-dinitrophenylhydrazone of δ-hydroxyvaleraldehyde,[16] m.p. 109°; 46.81 and 5.00. These data indicate the hydrogenolysis product of I to be the dimethylacetal of δ-hydroxyvaleraldehyde.

2-Methoxy-5,6-dihydropyran (IV).—A mixture of 29.2 g. (0.200 mole) of III and 49.2 g. (0.200 mole) of sublimed aluminum *t*-butoxide was placed in a 250-ml. round-bottom flask surmounted by a heated 10-cm. Vigreux column connected to a partial take-off total reflux stillhead. The magnetically stirred reaction mixture began to evolve *t*-butyl alcohol vigorously at 140–145° and continued for 1 hour, during which time the temperature of the reaction mixture was raised to 185°. The yield of *t*-butyl alcohol, b.p. 82–83°, $n^{25}\text{D}$ 1.3857, was quantitative.

The reaction mixture was cooled to 100° and the pressure slowly reduced to 30 mm. with an aspirator. In this manner 20.4 g. (89.5%) of the ketene acetal IV was collected. After fractionation through a 25-cm. Podbielniak column, 19.3 g. (84.8%) of product was obtained: b.p. 70–70.5° (34 mm.), 153.5–154.5° (741 mm.), $n^{25}\text{D}$ 1.4555, d^{25}_4 1.023.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83; OCH_3, 27.2; *M*R*D* 30.53. Found: C, 63.47; H, 8.61; OCH_3, 25.6; *M*R*D*, 30.29.

The dealcoholation of 2.5 moles of orthoester III with unsublimed aluminum *t*-butoxide produced only a 54.5% yield of IV. However, a quantitative yield of *t*-butyl alcohol was evolved during this dealcoholation.

The product, 2-methoxy-5,6-dihydropyran (IV), reacted vigorously with dilute hydrochloric acid and bromine in carbon tetrachloride. The infrared spectrum showed strong absorption at 5.99 μ, characteristic of monosubstituted ketene acetals.[3]

When a few drops of dilute hydrochloric acid was added to a mixture of 7.1 g. of ketene acetal III and 0.5 ml. of water, a vigorous reaction occurred. The product was distilled through a 25-cm. Podbielniak column to yield 5.2 g. (84%) of δ-valerolactone,[17] b.p. 108–109.5° (13–14 mm.), 224–226° (740 mm.), $n^{20}\text{D}$ 1.4557 (reported b.p. 219–222°, $n^{20}\text{D}$ 1.4568).

The hydrolysis of the orthoester III gave a similar yield of this lactone product on hydrolysis. The infrared spectrum of the valerolactone obtained from the hydrolysis of both III and IV showed a strong carbonyl group absorption band at 5.83 μ, and a weak hydroxyl absorption at 2.90 μ. It seemed likely that this latter band was due to the presence of a small amount of methyl δ-hydroxyvalerate. This conclusion was substantiated by the presence of 2.2% methoxyl in the hydrolysis product; this value would indicate that 7.8 mole per cent. of the hydroxy ester is formed in the hydrolysis of III and IV.

δ-Hydroxyvalerohydrazide was prepared by the method of Coffman[17] from the ester mixture obtained from the hydrolysis of both III and IV. It melted at 107–108° (reported[17] 105°) and contained 45.54% C and 8.94% H (calcd. 45.43 and 9.15).

Reaction of IV. (a) **With Benzyl Bromide.**—A mixture of 6.3 g. (0.055 mole) of ketene acetal IV and 9.4 g. (0.055 mole) of benzyl bromide was placed in a 25-ml. round-bottom flask attached to a stillhead. A pipet capped with a rubber nipple was fitted in the side of the flask for the re-

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[12] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 23.

[13] O. L. Brady, *J. Chem. Soc.*, 756 (1931).

[14] *Cf.* Properties of Ethoxyacetal, S. M. McElvain and C. H. Stammer, THIS JOURNAL, **73**, 915 (1951).

[15] W. H. T. Davison and G. R. Gates, *J. Chem. Soc.*, 2607 (1953).

[16] G. F. Woods and H. Sanders, THIS JOURNAL, **68**, 2111 (1946).

[17] *Cf.* D. D. Coffman, *ibid.*, **57**, 1984 (1935); R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 583 (1933).

moval of samples. The system was connected through a cold-trap to a calcium chloride drying tube. The reaction mixture was heated at 150° while magnetically stirred. The progress of the reaction was followed periodically by titration of a two-drop aliquot with dilute bromine in carbon tetrachloride. After 1 hr. the reaction was 90% complete and showed no further progress after 2 hr. Distillation of the mixture from the reaction flask gave the following fractions: (a) 3.9 g., b.p. 82–90° (13 mm.), n^{25}_{D} 1.4860; (b) 1.0 g., b.p. 90–130° (13 mm.), n^{25}_{D} 1.4654; (c) 2.35 g., b.p. 145–149° (1 mm.), n^{25}_{D} 1.5253; (d) 5.05 g., b.p. 196–198° (1.3 mm.), which solidified. In addition, 2.2 g. (39%) of methyl bromide was found in the cold-trap.

Recrystallization of fraction (d) from ethanol yielded 3.25 g. (42.3%) of α,α-dibenzyl-δ-valerolactone (VI), m.p. 106.5–107°.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19; sapon. equiv., 280. Found: C, 81.46; H, 6.84; sapon. equiv., 271.

The mother liquors were evaporated at reduced pressure to leave an oil which was evaporatively distilled and found to contain 13.4% bromine. If the oil were a mixture of VI and methyl α,α-dibenzyl-δ-bromovalerate (VIII) the bromine content would indicate 56 mole per cent. of VIII and 44 mole per cent. of VI. Thus about 1.15 g. (11%) of VIII and 0.65 g. (9%) of VI would be in the oil remaining from fraction (d).

Analysis of fraction (c) showed 60.30% C and 20.6% Br. If the material were a mixture of α-benzyl-δ-valerolactone (V) and methyl α-benzyl-δ-bromovalerate (VII), both carbon and bromine content would indicate 66 mole per cent. of VII and 34 mole per cent. of V. Thus about 1.7 g. (11%) of VII and 0.65 g. (6%) of V are the estimated constituents of fraction (c).

1-Methoxy-2,10-dioxabicyclo[4.4.0]-3-decene (IX).—The condensation of 57.0 g. (0.500 mole) of IV and 30.0 g. (0.530 mole) of freshly distilled acrolein was carried out in a manner similar to the condensation of ketene dimethylacetal and acrolein to form I, except that the reaction mixture was heated at 100° for 15 hours. The reactants liberated considerable heat when mixed.

The pale yellow reaction mixture was fractionated through a 1.5 × 24 cm. Heli-pak column. A forerun of acrolein weighing 4.7 g. preceded the 54.4 g. (64%) yield of 1-methoxy-2,10-dioxabicyclo[4.4.0]-3-decene (IX). The pot residue that was not distilled amounted to 26.5 g.

An analytical sample had the following physical properties: b.p. 99° (20 mm.), 111–112° (36 mm.), n^{25}_{D} 1.4727, d^{25}_{4} 1.106.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29; OCH_3, 18.2; Mr_D, 43.83; sapon. equiv., 170. Found: C, 63.54; H, 8.14; OCH_3, 16.8; Mr_D, 43.14; sapon. equiv., 169.[18]

IX showed a strong absorption band at 6.05 μ in the infrared. This band was identical with that of unsaturated orthoester I and, as stated previously, corresponded to that of an enol ether. IX reacted readily with bromine in carbon tetrachloride. It dissolved with liberation of considerable heat in dilute hydrochloric acid.

The condensation of ketene acetal IV and acrolein in 2.5 mole quantities was carried out in a 1700-ml. steel bomb to yield 65.5% of IX. Even though the reactants were ice-cold when mixed, they caused the bomb to become too hot to handle without protection in 20 minutes. The reactants were subsequently heated for 15 hours at 150°.

1-Methoxy-2,10-dioxabicyclo[4.4.0]decane (X).—In a 900-ml. glass bottle 275 g. of 1-methoxy-2,10-dioxabicyclo-[4.4.0]-3-decene (IX) was shaken with 2 tablespoonsful of W-7 Raney nickel[4] which had been washed free of ethanol with anhydrous diethyl ether. A pressure of one to three atmospheres of hydrogen was maintained in the bottle and the reduction proceeded smoothly to 90% completion in 12 hours. The hydrogenation was continued another 24 hours to permit absorption of the theoretical amount of hydrogen.

The catalyst was removed by centrifugation and washed with anhydrous diethyl ether. The ether solution was distilled through a short-path modified Claisen distillation system to yield 268 g. (96.3%) of the orthoester X, b.p. 38° (0.1 mm.), n^{25}_{D} 1.4653, d^{25}_{4} 1.087.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.37; Mr_D, 44.30. Found: C, 62.53; H, 9.23; Mr_D 43.77.

The orthoester, which was distilled at 38° (0.1 mm.), absorbed no bromine in carbon tetrachloride and the infrared spectrum showed the absence of any carbon-to-carbon double bond in the molecule. When distilled at 87° (8 mm.), the sample of X absorbed some bromine and its infrared spectrum displayed a moderate absorption band at 5.91 μ, characteristic of disubstituted ketene acetals.[3] This band occurs at the same position as the strong band appearing in the infrared spectrum of ketene acetal XI described below. X, which is insoluble in water, dissolved exothermically in dilute hydrochloric acid.

2,10-Dioxabicyclo[4.4.0]-1-decene (XI).—In a 100-ml. round-bottom flask surmounted by a heated 10 cm. Vigreux column and stillhead, 13.3 g. (0.0774 mole) of the orthoester X and 25.0 g. (0.101 mole) of unsublimed aluminum *t*-butoxide were heated with magnetic stirring. At 145° *t*-butyl alcohol was vigorously evolved; during the next hour the temperature was gradually raised to 185°; a total of 5.60 g. (98%) of the alcohol was collected. The reaction mixture was cooled at 150° and the pressure slowly reduced until 9.60 g. (88.7%) of ketene acetal XI had been collected. Upon fractionation through a 25-cm. Podbielniak column, there was obtained 9.20 g. (85%) of XI, b.p. 108–109° (22 mm.), 90–91° (8 mm.), n^{25}_{D} 1.4913, d^{25}_{4} 1.091.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63; Mr_D 37.57. Found: C, 68.29; H, 8.45; Mr_D 37.25.

The use of sublimed aluminum *t*-butoxide in the above dealcoholation did not improve the yield of XI. This ketene acetal reacted with bromine in carbon tetrachloride and became water soluble with vigorous evolution of heat when treated with dilute hydrochloric acid. The infrared spectrum contained a strong absorption peak, characteristic of disubstituted ketene acetals,[3] at 5.91 μ.

A small sample of XI was hydrolyzed with a few drops of dilute acid and the product XVI obtained by evaporative distillation, 140° (0.1 mm.). The infrared spectrum displayed strong hydroxyl absorption at 2.95 μ and strong carbonyl absorption at 5.82 μ. When treated with *p*-nitrobenzoyl chloride in pyridine, the solid α-(γ-*p*-nitrobenzoyloxypropyl)-δ-valerolactone, was obtained and recrystallized from petroleum ether (b.p. 90–100°), m.p. 108–109.5°.

Anal. Calcd. for $C_{15}H_{17}NO_6$: C, 58.62; H, 5.58. Found: C, 58.55; H, 5.40.

Reactions of XI. (a) With Benzyl Bromide.—A mixture of 7.0 g. (0.05 mole) of XI and 8.55 g. (0.05 mole) of benzyl bromide was placed in a 25-ml. round-bottom flask attached to a stillhead. A pipet with a rubber nipple was fitted in the side of the flask for the removal of samples and the system was protected with a calcium chloride tube. The progress of the reaction was periodically followed by titration of a two-drop aliquot of the magnetically stirred reaction mixture with dilute bromine in carbon tetrachloride. The bromine titer indicated 60% completion of reaction at 110° after 2.5 hr. and 98% after 10 hr.; no reaction was indicated after 1.5 hr. at 100°.

Distillation of the viscous, yellow reaction mixture yielded: (a) 1.0 g. forerun, b.p. 50–80° (13 mm.); (b) 13.3 g. (85%) of α-benzyl-α-(γ-bromopropyl)-δ-valerolactone (XVI), b.p. 159–160° (0.03 mm.), n^{25}_{D} 1.5561.

Anal. Calcd. for $C_{15}H_{19}O_2Br$: C, 57.88; H, 6.15. Found: C, 58.03; H, 6.01.

(b) With Ethyl Bromoacetate.—A mixture of 7.0 g. (0.05 mole) of ketene acetal XI and 8.3 g. (0.05 mole) of ethyl bromoacetate was placed in the apparatus described in (a). The reaction was 90% complete after 16.5 hr. at 140°. The viscous reaction mixture was distilled to yield: (a) 2.3 g. forerun, b.p. 55–60° (13 mm.); (b) 10.3 g. (67%) of α-carboethoxymethyl-α-(γ-bromopropyl)-δ-valerolactone (XVIa), b.p. 153–154° (0.05 mm.), n^{25}_{D} 1.4990.

Anal. Calcd. for $C_{12}H_{19}O_4Br$: C, 46.91; H, 6.23. Found: C, 47.17; H, 6.08.

(c) With Ozone.—In a 230-ml. glass bottle a solution of 2.33 g. of the ketene acetal XI in 50 ml. of absolute ethyl acetate was cooled to −70° in a Dry Ice–acetone mixture. A stream of oxygen containing ozone was first passed through a cold trap and then through the ketene acetal solution until the appearance of a blue color. To the cold reaction mixture was added 2.5 g. of 6% palladium-on-strontium carbonate

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[18] This sapon. equiv. was determined by first hydrolyzing the orthoester with standard acid and then neutralizing this acid and saponifying the resulting lactone with standard base.

and the ozonide decomposed by shaking the solution with hydrogen at 40 p.s.i. The reduction was continued until the absence of peroxides was demonstrated with starch-iodide paper. The catalyst was removed by centrifugation and the reaction mixture distilled. After removal of solvent, 0.94 g. (33%) of the carbonate of 4-keto-1,7-heptanediol (XV), was collected, b.p. 94.5–95.5° (0.06 mm.), n^{25}D 1.4755.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 56.16; H, 6.79.

There was higher boiling material which was not identified. When treated with 2,4-dinitrophenylhydrazine reagent, XV gave an orange 2,4-dinitrophenylhydrazone, which after recrystallization from ethyl acetate melted at 253–254°.

Anal. Calcd. for $C_{14}H_{16}N_4O_7$: C, 47.73; H, 4.58. Found: C, 48.01; H, 4.51

The infrared spectrum of keto carbonate XV displayed ketonic carbonyl absorption at 5.86 μ and an ester carbonyl absorption at 5.72 μ. The hydrazone derivative (in chloroform solution) absorbed at 5.72 μ but not at 5.86 μ.

(d) **With Methanol.**—To a solution of 18.0 g. of ketene acetal XI in 10 ml. of absolute methanol was added a drop of concentrated hydrochloric acid on the bulb of a thermometer. The temperature of the mixture rose to 90° in ten seconds. After removal of the excess methanol, 19.7 g. (89.2%) of an orthoester was collected, b.p. 41.5° (0.1 mm.), n^{25}D 1.4663, $d^{25}{}_4$ 1.091.

The physical properties of this orthoester differed from those of X. Their infrared spectra differed in that the orthoester obtained from the addition of methanol to XI displayed absorption at four wave lengths at which X did not absorb; *viz.*, 10.15, 10.59, 11.25 and 11.83 μ. When X was fractionated through a 10-cm. Vigreux column, all fractions were found to have identical infrared spectra; however, when 3% of the product formed by the addition of methanol to XI was added to X, the characteristic infrared bands of the former were detectable. Thus X appeared to be at least 97% of one isomer, probably the *cis* form of 1-methoxy-2,10-dioxabicyclo[4.4.0]decane. Since all the infrared absorption bands of X were also present in the product formed from the addition of methanol to XI, and since the spectra of the various distillation fractions of the latter material were not identical, it seemed likely that this material was a mixture of *cis* and *trans* isomers. Both this product and X were dealcoholated with aluminum *t*-butoxide to the ketene acetal XI in good yield (*ca.* 85%).

(e) **With Bromine.**—To a magnetically stirred solution of 5.80 g. of the ketene acetal XI in 40 ml. of dry carbon tetrachloride, maintained at room temperature, was added dropwise a solution of 6.97 g. of bromine in 32.0 g. of dry carbon tetrachloride. A permanent, faint yellow color was caused by the addition of sufficient of this solution to represent 6.42 g. (97%) of bromine. When the addition of the reactants was reversed, 94% bromine was absorbed.

After removal of the solvent at reduced pressure, α-bromo-α-(γ-bromopropyl)-δ-valerolactone (XIII) was distilled with decomposition, b.p. 160–162° (0.2 mm.). The product contained 52.2% bromine (calcd. 53.3%) and was collected as a light-brown liquid. Most of the material resinified in the distillation flask. The infrared spectrum of a sample which contained 49.1% bromine showed the presence of some unsaturation with weak absorption at 6.12 μ in the infrared.

When a solution of 1.40 g. (0.01 mole) of XI in 5 ml. of carbon tetrachloride was added slowly to stirred solution of 3.20 g. (0.02 mole) of bromine in 60 ml. of carbon tetrachloride at −20°, a yellow-orange precipitate XII separated. After filtration through a sintered glass filter stick, the carbon tetrachloride filtrate and the solid XII were treated separately with 25 ml. of cold water (the solid liquefied), then with 20 g. of potassium iodide in 30 ml. of water and the liberated iodine titrated with standard sodium thiosulfate solution. In this manner it was found that XII contained 0.0094 mole (47% of the original bromine) of titratable bromine and the carbon tetrachloride filtrate contained 0.001 mole (5%) of unreacted bromine.

In another bromination at −20°, the stirred slurry of XII in carbon tetrachloride was treated with a second equivalent of ketene acetal XI. As XI was added, XII and the bromine color disappeared and the dibromolactone (XIII) was isolated.

2,10,11-Trioxatricyclo[4.4.4.0^{1,6}]-3-tetradecene (XVI).—Condensation of 8.70 g. (0.062 mole) of the disubstituted ketene acetal XI and 3.92 g. (0.070 mole) of freshly distilled acrolein was conducted according to the procedure described in the condensations of ketene dimethylacetal and ketene acetal IV with acrolein, except that the reactants were heated at 150° for 15 hours.

The pale-yellow reaction mixture solidified when poured into a flask for distillation. Upon distillation through a modified Claisen flask, a forerun of less than 1 g. was collected before the main body of 9.65 g. (79.2%) of unsaturated orthoester XVI was collected, b.p. 90–91° (0.2 mm.). The undistilled pot residue amounted to 2.1 g. Heating was necessary to keep the product from solidifying in the distillation system. An analytical sample melted at 82.5–84°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.23. Found: C, 67.16; H, 7.85.

The enol orthoester XVI added bromine in carbon tetrachloride to form a solid dibromide, which decomposed to a brown oil on attempted isolation. The infrared spectrum contained the expected enol ether band; however, it had shifted from a position near 6.06 μ, which it occupies in the spectra of enol orthoesters I and IV, to 6.01 μ.

The product was water insoluble; however, upon long standing or when heated in the presence of dilute hydrochloric acid it became water soluble.

2,10,11-Trioxatricyclo[4.4.4.0^{1,6}]tetradecane (XVIII).—A solution of 16.9 g. (0.0863 mole) of the unsaturated orthoester XVII in 50 ml. of anhydrous diethyl ether was shaken with one teaspoonful of Raney nickel (W-7) in a 230-ml. glass bottle under a pressure of 1–3 atmospheres of hydrogen. The reduction proceeded smoothly to 75% completion in 9 hr. The hydrogenation was continued another 24 hr. to permit absorption of the theoretical amount of hydrogen.

The catalyst was removed by centrifugation and washed with diethyl ether. After removal of the solvent, 16.3 g. (96%) of XVIII (m.p. 111–113°), was collected. This material was recrystallized from petroleum ether (b.p. 60–68°) and sublimed at 100° (0.1 mm.) to yield 15.2 g. (89%) of XVII, m.p. 116–117°.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; sapon. equiv., 198. Found: C, 66.92; H, 9.09; sapon. equiv., 198.[17]

XVIII remained unchanged after several hours in refluxing dilute sodium hydroxide solution. The compound was steam volatile, insoluble in water at room temperature, but slightly soluble in boiling water. A sample subjected to steam distillation indicated that at least 0.025 g. of XVIII was volatilized with each 10 ml. of distillate because this amount of product could be recovered by evaporation of the homogeneous distillate at room temperature and atmospheric pressure.

The orthoester XVIII became water soluble after long standing, but quite rapidly on heating in dilute acid. The hydrolysis product XIX was obtained by evaporative distillation after removal of the water by azeotropic distillation with benzene. The infrared spectrum of this product displayed strong absorption at 3.00 and 5.80–5.90 μ; the former band is characteristic of an associated hydroxyl group,[19] and the latter to an associated ester carbonyl group.[20]

All distilled samples of XIX showed crystals of the orthoester XVIII and consequently were never obtained in sufficient purity for analyses. This apparent reconversion of XIX into XVIII prompted the following experiment.

A 0.501-g. sample of XVIII was added to 40 ml. of water which had been acidified by a trace (amount retained on the tip of a stirring rod dipped into the acid) of concentrated sulfuric acid and the mixture was refluxed for 24 hr. The homogeneous solution was subjected to steam distillation until 300 ml. of distillate had been collected and only 10 ml. of residual solution remained. This quantity of distillate was sufficient to have volatilized 0.75 g. of XVIII. This solution was transferred to a sublimation tube, the remaining water removed by azeotropic distillation with benzene. The residual viscous liquid XIX

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[19] A. E. Martin and J. J. Fox, *Proc. Roy. Soc.* (*London*), **A162**, 419 (1937).

[20] F. A. Miller in H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 146.

was heated at 100° (0.1 mm.) whereupon 0.336 g. (67.2%) of XVIII was collected as sublimate. Evaporation at room temperature and atmospheric pressure of the 300 ml. of distillate from the steam distillation left no trace of XVIII. A non-distillable residue of 0.080 g. remained in the sublimation tube.

α,α,α-**Tri-(γ-bromopropyl)-acetic Acid (XX).**—To a solution of 0.500 g. of XVIII in 30 ml. of anhydrous ether was added 70 ml. of a saturated solution of hydrogen bromide in anhydrous ether. After standing overnight at room temperature, the ether and hydrobromic acid were evaporated in a stream of air to approximately 30 ml., which was shaken with water until the washings were no longer acidic. After removal of the ether at reduced pressure, the remaining oil was dissolved in hot petroleum ether (b.p. 60–68°). Upon cooling, 0.561 g. (52.5%) of colorless crystals, m.p. 90.5–92°, precipitated; after two recrystallizations the m.p. was 93–94°.

Anal. Calcd. for $C_{11}H_{19}O_2Br_3$: C, 31.23; H, 4.53. Found: C, 31.73; H, 4.44.

MADISON, WISCONSIN

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Chemistry of Fumagillin. II[1]

BY J. R. SCHENCK, M. P. HARGIE AND A. ISARASENA

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The alcohol portion ($C_{16}H_{26}O_4$) of fumagillin ($C_{26}H_{34}O_7$) can be ozonized to yield a crystalline α,β-unsaturated aldehyde ($C_{13}H_{20}O_5$) and acetone. The dihydroalcohol reacts with dinitrobenzoyl chloride to yield a crystalline chlorine-containing dinitrobenzoate ($C_{23}H_{31}N_2O_9Cl$). The hexahydroalcohol reacts with dinitrobenzoyl chloride to form a bis-dinitrobenzoate ($C_{30}H_{36}N_4O_{14}$). Dehydrogenation of the hexahydroalcohol yields ethyl isoamyl ketone and aromatic products. Oxidation of the dihydroalcohol yields succinic acid.

Fumagillin[1-3] has the empirical formula $C_{26}H_{34}O_7$ and is a mono-ester of decatetraenedioic acid and a neutral substance $C_{16}H_{26}O_4$, which we have called alcohol I. Analyses of fumagillin itself as well as alcohol I indicate that the alcohol must contain one methoxyl, one hydroxyl, two C-methyl groups and two non-carbonyl oxygen atoms.

Ozonolysis.—When alcohol I[4] is ozonized, it is split into acetone and a crystalline α,β-unsaturated aldehyde $C_{13}H_{20}O_5$. The reaction of this ozonolysis product with Tollens reagent, its ultraviolet spectrum and the spectrum of its thiosemicarbazone are all in agreement with its formulation as an α,β-unsaturated aldehyde. Since alcohol I shows no evidence of a conjugated system, the carbon–carbon double bond must have arisen by opening of an oxygen bridge or by migration of another double bond. The first hypothesis explains the appearance of both the double bond and an extra hydroxyl group. Further ozonolysis yields glyoxal.

CHART I

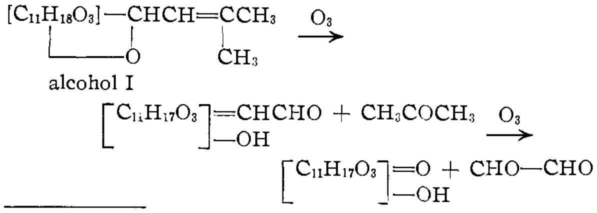

Chart I indicates one possible course of this reaction.

Hydrogenation.—The alcohol portion of fumagillin forms a series of hydrogenation products in which one, two and three moles of hydrogen are added. It is believed that only one double bond is involved and that the other two moles of hydrogen enter by hydrogenolysis of oxygen bridges. The elementary composition of alcohol I is in agreement with the presence of three rings and one double bond. A dihydroalcohol may be prepared by hydrogenation of fumagillin, followed by saponification. A crystalline tetrahydroalcohol[5] has been obtained by hydrogenation of alcohol I. A hexahydroalcohol has been prepared by hydrogenation of the tetrahydroalcohol in glacial acetic acid or by hydrogenation of fumagillin in glacial acetic acid, followed by saponification.

The preparations of the dihydroalcohol made either by hydrogenation of fumagillin followed by saponification or by saponification of fumagillin followed by hydrogenation usually contained a considerable amount of hydrated material as shown by low carbon and high oxygen analyses. A crystalline derivative was obtained by reaction with dinitrobenzoyl chloride. Analyses disclosed that this compound was not a normal dinitrobenzoate but contained chlorine and had the composition ($C_{23}H_{31}N_2O_9Cl$) corresponding to addition of one mole of dinitrobenzoyl chloride to one mole of the dihydroalcohol. Active hydrogen determinations indicated that two hydroxyl groups remained. The presence of chlorine indicates that the reaction involves addition, probably by cleavage of an oxygen bridge. The chlorine atom is inert; it does not react with silver nitrate.

The hexahydroalcohol reacts with dinitrobenzoyl chloride forming a crystalline bis-dinitrobenzoate ($C_{30}H_{36}N_4O_{14}$) which contains no chlorine, and the infrared spectrum indicates absence of hydroxyl groups.

The three hydrogenation products, according to our hypothesis of hydrogenation of one double

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[1] Previous publication, J. R. Schenck, M. P. Hargie, D. S. Tarbell and P. Hoffman, THIS JOURNAL, **75**, 2274 (1953). Part of this material was presented before the Division of Medicinal Chemistry at the American Chemical Society Meeting in New York, September, 1954; D. S. Tarbell, H. R. Al-Kazimi, P. Hoffman, G. A. Page, H. R. Vogt, J. R. Schenck, M. P. Hargie and A. Isarasena, Abstracts of New York Meeting, 1954, p. 17 N.

[2] T. E. Eble and F. R. Hanson, *Antibiotics and Chemotherapy*, **1**, 54 (1951).

[3] C. J. Brown and J. K. Landquist, *Chemistry & Industry*, 973 (1953).

[4] Our preparations of alcohol I were probably not as pure as those of Tarbell,[5] *et al.*, and we have generally used the crude neutral fraction from saponification of fumagillin for ozonolysis.

[5] Paper III of this series: D. S. Tarbell, P. Hoffman, H. R. Al-Kazimi, G. A. Page, J. M. Ross, H. R. Vogt and B. Wargotz, THIS JOURNAL, **77**, 5610 (1955).