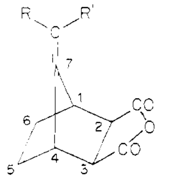
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

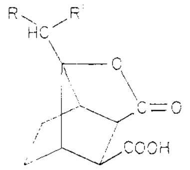
An Infrared Investigation of the Stereochemistry of Some Tricyclic Lactones[1]

BY PELHAM WILDER, JR., AND ANTHONY WINSTON[2]

RECEIVED APRIL 21, 1955

Seven new compounds derived from *exo*-adducts of fulvenes and maleic anhydride have been prepared. An analysis of the infrared spectra of these compounds determined in Nujol mull and in carbon tetrachloride solution has shown that lactones V–XI are correctly represented as six-membered (δ-)lactones. It has also been shown that these lactones are readily susceptible to hydrogen bonding and that care must be exercised in assigning a ring size on the basis of spectral data where intermolecular associations may give rise to frequencies not characteristic of the free lactonic carbonyl stretching.


I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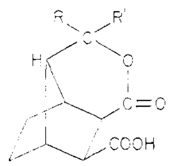
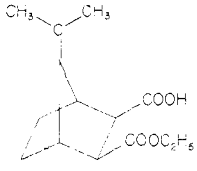
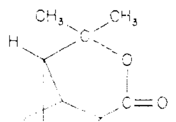
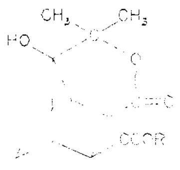

III

The formation of a lactone has long been used to determine the steric course of addition in the Diels–Alder reaction. In the case of an adduct of a fulvene and maleic anhydride, the resulting diene can be selectively reduced by catalytic methods to a 7-alkylidenebicyclo[2.2.1]heptane derivative (I), the configuration of which may be proved *exo* or *endo* by successful or unsuccessful lactonization, respectively. In the case of the *exo* configuration, two isomeric lactones are possible, the five-membered (II) and six-membered lactone (III). Woodward and Baer preferred to represent the lactone derived from the *exo*-pentamethylenefulvene–maleic anhydride adduct as a five-membered ring, although it was noted at the time that this assignment was arbitrary.[3] Alder and Rühmann, on the other hand, suggested that the lactone derived from the *exo*-dimethylfulvene–maleic anhydride adduct was six-membered because of the ease of addition of phenyl azide to the Δ^5-double bond of the adduct after lactonization.[4] On the basis of chemical evidence, it is difficult, if not virtually impossible, to distinguish between these isomeric forms. It is the purpose of this paper to elucidate by means of infrared spectroscopic methods the stereochemistry of a series of lactones derived from *exo-cis*-7-isopropylidenebicyclo[2.2.1]heptane-2,3-dicarboxylic acid anhydride (I, R = R′ = CH_3), which was prepared by the catalytic reduction of the *exo*-adduct of dimethylfulvene and maleic anhydride. Alcoholysis of the parent compound yielded the acidic ester IV.

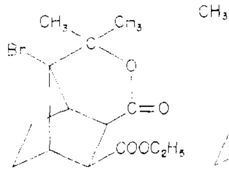

IV

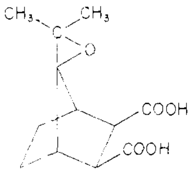

V, R = C_2H_5
VI, R = H

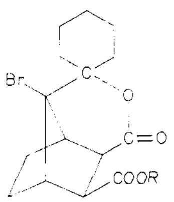

VII, R = C_2H_5
VIII, R = H

When the acidic ester IV was treated in an aqueous sulfuric acid solution for four hours at room temperature, lactonic ester V was isolated. When the reaction was repeated under the same experimental conditions, but for a period of 18 hours, the product was an acidic compound which was shown to be acidic lactone VI, the hydrolysis product of V. On peracetic acid oxidation of IV in acetone solution, hydroxy lactonic ester VII was isolated. Alkaline hydrolysis of lactone VII afforded hydroxy lactonic acid VIII, which had previously been prepared by Alder and Rühmann by oxidation of the parent anhydride (I, R = R′ = CH_3) with hydrogen peroxide in acetic acid solution.

Reaction of the silver salt of acidic ester IV in bromoform solution with an equimolar amount of bromine afforded the bromolactonic ester IX, which on hydrolysis in hot, aqueous sodium hydroxide solution yielded an epoxy dibasic acid IXA.


IX


IXA


X, R = H
XI, R = CH_3

For comparison the bromolactonic acid (X) of Woodward and Baer[3] was prepared as well as its methyl ester XI.

Discussion

To distinguish between derivatives of the five-membered (γ)-lactone (II) and the six-membered (δ-)lactone (III), an analysis of the carbonyl stretching frequencies of the lactones was made. It is well known these frequencies are, other things being equal, a function of the size of the lactone ring.[5–8] The carbonyl absorption band associated with simple five-membered lactones has been reported to occur near 5.65 μ and the same band associated with six-membered lactones near 5.74 μ. In this connection Berson has recently reported that a number of tricyclic γ-lactones derived from cyclopentadiene–maleic acid and furan–maleic acid

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(1) (a) Presented in part at the Southeastern Regional Meeting of the American Chemical Society in Birmingham, Alabama, October 21, 1954. (b) Taken from a thesis submitted by Anthony Winston to the Graduate School of Duke University in partial fulfillment of the requirements for the Ph.D. degree, October, 1954.

(2) Du Pont Pre-doctoral Fellow, 1953–1954.

(3) R. B. Woodward and H. Baer, THIS JOURNAL, **66**, 645 (1944).

(4) K. Alder and R. Rühmann, *Ann.*, **566**, 1 (1950).

(5) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

(6) R. N. Jones, P. Humphries and K. Dobriner, *ibid.*, **72**, 956 (1950).

(7) S. Searles, M. Tamres and G. M. Barrow, *ibid.*, **75**, 71 (1953).

(8) G. N. Walker, *ibid.*, **75**, 3393 (1953).

Diels–Alder addition products absorb at 5.65 ± 0.03 μ.[9]

The infrared maxima associated with carbonyl absorptions for compounds V-XI are recorded in Table I. The mean value for lactone absorption in Nujol mull for these compounds was found, with one exception, to be 5.74 μ with a maximum deviation from the mean of 0.07 μ. From this value lactones V-XI might be predicted directly to be six-membered were it not for the fact that the maximum deviation in this case is the difference usually observed between simple five- and six-membered lactones.

TABLE I

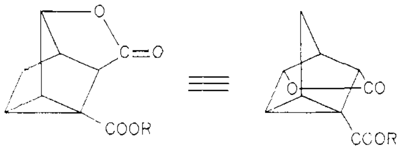
WAVE LENGTHS IN MICRONS OF CARBONYL ABSORPTIONS OF SUBSTITUTED LACTONES IN NUJOL MULL AND CARBON TETRACHLORIDE SOLUTION

Compd.	Acid (A) or ester (E) absorption Nujol	CCl$_4$	Lactone absorption Nujol	CCl$_4$	Δμ
V	5.73 (E)	5.74 (E)	5.67	5.70	0.03
VI	5.91 (A)	5.83 (A)	5.76	5.68	.08
VII	5.78 (E)	5.74 (E)	5.85	5.67	.18
VIII	5.84 (A)	..	5.80	..	..
IX	5.75, 5.79 (E)	5.72 (E)	5.67	5.64	.03
X	5.85 (A)	5.82 (A)	5.74	5.65	.09
XI	5.75 (E)	5.72 (E)	5.70	5.65	.05
XII	5.80 (A)	..	5.58	..	..
XIII	..	5.76 (E)	..	5.53	..

It should be recalled that the spectrum of a compound dispersed in Nujol mull is very nearly equivalent to the spectrum recorded for the material in the solid state. Under these conditions both the crystalline forces of the solid and the forces of intermolecular hydrogen bonding combine to create a pronounced effect upon the carbonyl absorption. It is significant that for those compounds which contain either hydroxyl groups or carboxyl groups (VI, VII, VIII, X) the lactone carbonyl bands occur consistently at longer wave lengths than the lactone bands for compounds which do not contain these groups (V, IX, XI). For lactones V, IX and XI, which are incapable of association, absorption occurs at 5.68 ± 0.02 μ; for lactones VI, VII, VIII and X, which may undergo hydrogen bonding, the absorption values range from 5.74 to 5.85 μ. Carbonyl shifts of this type are not unusual. An examination of Berson's data[9] reveals that the absorption for γ-lactones incapable of association is 5.61 μ and the value for the other lactones is 5.67 ± 0.03 μ. Searles, Tamres and Barrow have found that the carbonyl bands of some simple lactones and esters are displaced toward longer wave length upon association with methanol in carbon tetrachloride solution and furthermore that this shift is more pronounced for lactones than for esters.[7]

To show that hydrogen bonding is responsible, at least to some extent, for the range in the observed carbonyl frequencies, the spectra of the same lactones were determined in carbon tetrachloride solution at a dilution sufficient to eliminate the effects of intermolecular hydrogen bonding.[10] These values are recorded in Table I. The mean value for lactones V–XI in dilute carbon tetrachloride solution was found to be 5.67 μ with a maximum deviation of 0.03 μ. This value is in excellent agreement with the value of 5.68 ± 0.03 μ found for lactones V, IX, and XI in Nujol mull.

For comparison the infrared spectra of the nortricyclenic acidic lactone XII and its methyl ester XIII, both of which had been prepared in a previous investigation[11] in this Laboratory, were recorded (*cf.* Table I). These compounds are of immediate interest in the present investigation since they contain a ring system closely analogous to γ-lactone II. It would be reasonable to expect, then, that, were the lactones under investigation to be γ-lactones, the lactone carbonyl absorption of compounds V–XI would lie close to the lactone absorptions of the nortricyclenic lactones. On the contrary, the γ-lactones XII and XIII lie considerably below 5.67 μ. The absorption at 5.58 μ for XII in Nujol mull and at 5.53 μ for XIII in solution (instead of the 5.61 μ band[9]) may reflect the existence of some strain in these compounds resulting from the attachment of the lactone ring to the fused tricyclo[2.2.1.0^{2,6}]heptane system.



XII, R = H
XIII, R = CH$_3$

Based on the evidence above, the assignment, first, of a single ring size to lactone V-XI and, second, of the six-membered (δ-)lactone structure to these compounds seems completely justified. The 5.67 μ band is clearly at shorter wave length than the band at 5.74 μ reported for δ-valerolactone in carbon tetrachloride solution, but again this deviation may be a direct consequence of the rigidity of the bicyclic system of which the lactone is a part.[12]

A word of support for the facile formation of six-membered lactone rings in preference to the five-membered variety seems in order, especially since Brown and his co-workers have recently pointed out that five-membered lactones are generally less strained than the corresponding δ-lactones.[13] It should be recalled that Brown's observations in the relative stabilities of the γ- and δ-lactones were made upon simple molecules and that these generalizations do not apply to lactones which are parts of rigid molecules. Additional evidence favoring the formation in this instance of six-membered lactones is provided by Linstead and Rydon who found that allylacetic acid on treatment with heat or mineral acid yielded γ-valerolactone, free of the δ-isomeride, while under identical

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[9] J. A. Berson, THIS JOURNAL, **76**, 4975 (1954).

[10] All samples were measured at approximately the same concentration as lactone VII for which a sharp band at 2.76 μ clearly indicates an unassociated hydroxyl group.

[11] A. Winston and P. Wilder, Jr., THIS JOURNAL, **76**, 3045 (1954).

[12] Consideration of a molecule of this type suggests that carbon atoms 2, 1 and 7 which are rigidly fixed in the bicyclic ring system prevent the lactone ring from becoming planar and introduce a permanent "puckering" into the molecule.

[13] H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954).

experimental conditions, Δ^γ-isoheptanoic acid afforded the δ-lactone, exclusively.[14]

Once the size of the lactone ring is established, the stereochemistry of the entire series of compounds is determined. If the hydrogen atom, the bromine atom or the hydroxyl group at C_7 should assume the opposite configuration, then the isopropyl group also attached to C_7 would be forced beyond bond forming distance and lactonization would be impossible.

Experimental[15]

Infrared spectra were determined with the Perkin–Elmer, Model 21, double beam spectrophotometer, NaCl prism, 1 cm. cell for solution spectra. Reagent grade carbon tetrachloride, dried over calcium chloride, was distilled and the center fraction was collected for use in the spectral analysis. In most cases a saturated solution of the lactone in carbon tetrachloride was employed. The spectrum of hydroxy lactonic acid (VIII) could not be determined in carbon tetrachloride solution because of its limited solubility in this solvent.

Dimethylfulvene.—This compound was prepared according to the method of Kohler and Kable[16] with one exception. Ethyl ether rather than chloroform was used in the extraction of the fulvene from the reaction mixture; yield 80%, b.p. 54–57° (12 mm.).

***exo*-7-Isopropylidenebicyclo[2.2.1]heptane-2,3-dicarboxylic Acid Anhydride** (I, R = R′ = CH_3).—The addition product of dimethylfulvene and maleic anhydride was prepared in boiling benzene by the method of Alder and Rühmann.[4] Hydrogenation of the adduct was effected in ethyl acetate solution over Adams catalyst until one molecular equivalent of hydrogen had been absorbed. The dihydro adduct was crystallized from ligroin (60–90°), micro m.p. 132.5–134° (reported 138°).[4]

Acidic Ester IV.—A solution of 33.6 g. (0.163 mole) of the anhydride (I, R = R′ = CH_3) in 350 ml. of absolute ethyl alcohol was heated under reflux for 24 hours. Upon evaporation of the solvent under reduced pressure 39.5 g. (96%) of the crystalline acidic ester was obtained, micro m.p. 150–152°.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99; neut. equiv., 252. Found: C, 66.75; H, 8.13; neut. equiv., 258.

Lactonic Ester V.—Two grams of the acidic ester IV was suspended in 35 ml. of 70% sulfuric acid solution by constant stirring at room temperature. Dissolution was complete after 2 hours, but stirring was continued for two additional hours. The acid solution was added dropwise to 100 ml. of cooled 5% sodium carbonate solution whereupon a solid separated. The solid was collected and crystallized from ligroin to give 0.8 g. of colorless crystals, micro m.p. 64–66°.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.96; H, 8.01.

Lactonic Acid VI.—Three grams of the acidic ester IV was suspended in 100 ml. of 70% sulfuric acid solution and stirred at room temperature. Solution was complete within three hours. The solution was stirred for four additional hours and then was allowed to stand overnight, the total time in contact with the sulfuric acid being 18 hours. The sulfuric acid solution was added gradually with cooling to a 5% sodium carbonate solution. The carbonate solution was acidified and extracted 3 times with ether. The ether solution was dried over sodium sulfate and was then evaporated to dryness. The solid residue was crystallized from water to yield 1.0 g. of product, micro m.p. 176–177.2° (reported 176°)[4]; neut. equiv. calcd. 224, found 234.

7-Hydroxylactonic Ester VII.—Five grams of the acidic ester IV was dissolved in 75 ml. of acetone. To this solution was added 15 ml. of a 25% solution of peracetic acid in acetone. Soon after this addition enough heat was evolved to raise the temperature of the reaction mixture from 25 to 32° where it remained for 20 minutes. The solution was stirred for 6 hours and was then allowed to stand overnight. The solution was evaporated to a very small volume. Addition of a small amount of water to the viscous residue caused the separation of a solid which was collected and crystallized from water. The yield was 2.8 g. of colorless crystals, micro m.p. 125–128°.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.70; H, 7.45.

7-Hydroxylactonic Acid VIII.—A solution of 1.3 g. of the hydroxy lactonic ester VII, in 20 ml. of 10% aqueous sodium hydroxide solution, was heated under reflux for 3 hours. The solution was cooled, acidified with sulfuric acid, and extracted continuously with ether for 24 hours. The ether solution was dried over sodium sulfate and evaporated almost to dryness, whereupon a solid separated. The product which was crystallized from water gave 0.85 g. of colorless crystals, micro m.p. 244–246° (reported 252°)[4]; neut. equiv. calcd. 240, found 240.

Silver Salt of Acidic Ester IV.—Twelve grams (0.0476 mole) of the acidic ester IV was dissolved in 200 ml. of water containing 5 ml. of 28% ammonia water. To this solution was added gradually with stirring 8.10 g. (0.0476 mole) of silver nitrate dissolved in 100 ml. of water. The silver salt, which was precipitated immediately, was removed by filtration. It was washed with alcohol, then with ether, and was dried under reduced pressure at 70° over phosphorus pentoxide. The yield was 13.6 g. (80%).

Anal.[17] Calcd. for $C_{14}H_{19}O_4Ag$: Ag, 30.0. Found: Ag, 29.1, 29.2.

Bromination of the Silver Salt of the Acidic Ester IV.—Bromoform was dried over calcium chloride and distilled under reduced pressure. Bromine was dried over phosphorus pentoxide. The silver salt was dried for two days under reduced pressure at 70° over phosphorus pentoxide.

In a 200-ml. three neck flask fitted with a mechanical stirrer and a reflux condenser were placed 6.0 g. (0.016 mole) of the silver salt and 30 ml. of bromoform. To the silver salt suspension at room temperature was added dropwise, with stirring, 2.68 g. (0.017 mole) of bromine dissolved in 5 ml. of bromoform. After the addition was complete ($^1/_2$ hour) the temperature of the mixture was raised to 80° whereupon silver bromide precipitated. The temperature was maintained at this point and the mixture was stirred for an additional hour.

After removal of silver bromide, the solution was washed first with bicarbonate and then with bisulfite solution and was dried over sodium sulfate. Acidification of the bicarbonate solution yielded only 0.1 g. of acidic material. Bromoform was removed by distillation under reduced pressure and the residue, a viscous oil, solidified upon standing. The solid was crystallized from ligroin (60–90°) to give the 7-bromolactonic ester IX, micro m.p. 95–97°.

Anal. Calcd. for $C_{14}H_{19}O_4Br$: C, 50.77; H, 5.78. Found: C, 51.09; H, 5.49.

Epoxydicarboxylic Acid IXA.—Fourteen grams of 7-bromolactonic ester IX was suspended in 200 ml. of 50% (by volume) ethanol–water mixture in which had been dissolved 20 g. of sodium hydroxide. The mixture was heated for 3 hours under reflux. The solution was cooled and extracted three times with ether. Upon acidification with hydrochloric acid a crystalline solid appeared and was collected. The mother liquor was subjected to continuous ether extraction for 24 hours. Evaporation of the ether yielded a colorless solid which was identical with the solid which had separated upon acidification of the reaction mixture. Crystallization from water yielded 8.0 g. (79%) of colorless crystals, micro m.p. 180–186° (with dehydration).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71; neut. equiv., 129. Found: C, 59.83; H, 6.92; neut. equiv., 124, 128.

Bromolactonic Acid X.—This compound was prepared according to the method of Woodward and Baer,[3] m.p. 150–151° dec.

Bromolactonic Ester XI.—About 100 mg. of the bromolactonic acid X was treated with an excess of diazomethane in ethyl ether solution. Upon evaporation of the solvent there was obtained 100 mg. of a crystalline solid which was

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[14] R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933).

[15] Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois, unless otherwise specified.

[16] E. P. Kohler and J. Kable, THIS JOURNAL, **57**, 917 (1935).

[17] Analysis carried out in this Laboratory by the Volhard method.

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.

Acknowledgment.—This work was supported in part by a grant from the Duke University Research Council.

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

BY S. M. MCELVAIN AND G. ROBERT MCKAY, JR.[1]

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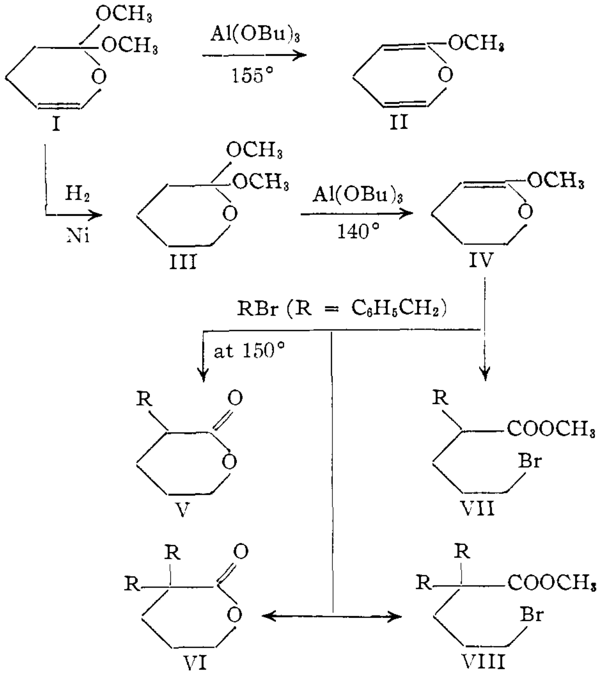
2,2-Dimethoxy-2,3-dihydropyran (I) has been dealcoholated to the unstable 2-methoxypyran (II) and also converted to 2-methoxy-5,6-dihydropyran (IV). Some reactions of the latter of these ketene acetals are described; of particular interest is the addition of acrolein to produce a bicyclic orthoester 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).