was filtered and recrystallized from toluene to give 0.16 g, mp 147–148°. It was homogenous on tlc and had physical constants and an ir spectrum identical with those of compound XVI.

Further precipitation from the filtrate from the above reaction gave mixtures of XVI and XIV as shown by tlc.

Registry No.—VIII, 24718-05-6; IX, 39533-58-9; X, 10512-69-3; XI, 39533-60-3; XII, 39533-61-4; XIII, 39599-19-4; XIV, 39533-62-5; XV, 39533-63-6; XVI, 39533-64-7; XVII, 39533-65-8; *p*-toluenesulfonyl chloride, 98-59-9.

A Condensed Methyl Reductic Acid from Hydrolysis of Amino-hexose-reductones

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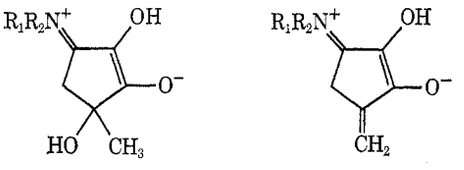
Dilute mineral acid hydrolyzes the amino group of hexose-reductones to yield 26% of a new yellow reductone, 2-hydroxy-2-(2′,3′-dihydroxy-5′-methyl-2′-cyclopentenon-5′-yl)-4-methyl-4-cyclopentene-1,3-dione. The structure is assigned from ultraviolet, infrared, mass spectral, and proton magnetic resonance data. Chemical evidence supporting the condensed methyl reductic acid structure was obtained from periodate and hydrogen peroxide oxidations; 2-methyl-(*Z*)-butenedioic acid and 2-carboxy-2-methylbutanedioic acids were identified. Reduction of the yellow reductone and acetylation of the mixture produce the diacetate of methyl reductic acid, the di- and triacetates of unreacted yellow reductone, and the mixed acetates of the partially reduced parent material. These products were also identified by spectral techniques and confirmed by comparisons with data from authentic compounds whenever possible.

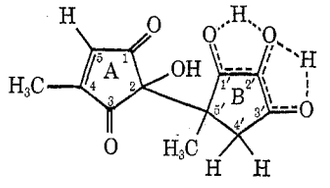
The hydroxy- and amino-substituted methyl reductic acids (**1**), trivially named amino-hexose-reductones, have been prepared from aldo- and ketohexoses in reactions with various secondary amine salts.[2–5] Dehydration of **1** by dehydrohalogenation yields **2**.[3,4] The mechanism of formation of piperidino-hexose-reductone has been determined.[6,7] Although both **1** and **2** are excellent antioxidants in animal fats and vegetable oils,[8] most of the different amino derivatives of **1** and **2** are toxic to small animals.[9,10]

To eliminate the toxicity and retain the antioxidant properties, removal of the amino group by acid hydrolysis was tried; however, no simple hexose-reductone was isolated. Instead, hydrolysis condensed the C_6 methyl reductic acid radicals to C_{12}, C_{22}, and higher compounds. The major product after hydrolysis of either **1** or **2** (R_1, R_2 = C_5H_{10} or $C_2H_4OC_2H_4$; $R_1 = R_2 = C_6H_5CH_2$) in 2 or 4 *N* hydrochloric acid at 25° was a new, yellow, crystalline, nonnitrogenous reductone, 2-hydroxy-2-(2′,3′-dihydroxy-5′-methyl-2′-cyclopentenon-5′-yl)-4-methyl-4-cyclopentene-1,3-dione (**3**). This reductone did not induce the neurological effects that were observed for various amino derivatives of **1**, and lethal dosages were much higher than those of amino derivatives of **2**.[11]

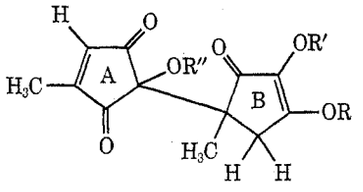
Elemental analysis of **3** furnished the formula $C_{12}H_{12}O_6 \cdot H_2O$, and this composition was confirmed by mass spectrometry (*m/e* 252.0660, M·+). Ir analysis



1 **2**



3

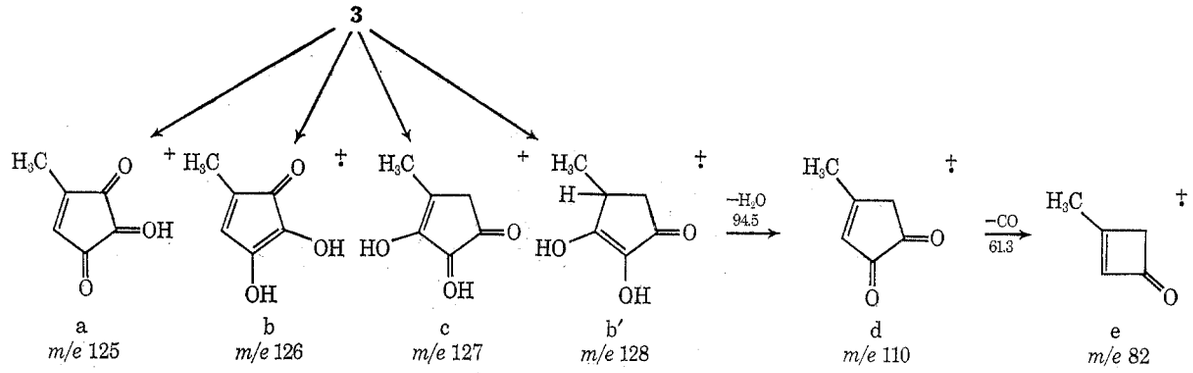


4a, R = OAc; R′ = R″ = H
b, R = R′ = OAc; R″ = H
c, R, R′, R″ = OAc
5, R = CH_3; R′ = R″ = H

(KBr disk) of **3** indicated several H-bonded hydroxyl groups (3500–3250 cm^{-1}). The yellow reductone **3** forms a monoacetate **4a** and, since the diacetate **4b** still exhibited a broad absorption at 3410 cm^{-1}, a third hydroxyl group was evident. Isolation of the triacetate **4c** confirmed the number of free hydroxyls. The important absorptions at 1748, 1706, and 1607 cm^{-1} were difficult to assign with certainty. The weaker 1748-cm^{-1} absorption is not congruent with an ene-1,3-dione, other reductone systems, an overtone, or a Fermi resonance assignment. Hesse, *et al.*,[12,13] presented solid-state ir spectra for methyl reductic acid and a tetramethyl, six-membered ring reductone, which

(1) Agricultural Research Service, U. S. Department of Agriculture.
(2) J. E. Hodge and C. E. Rist, *J. Amer. Chem. Soc.*, **75**, 316 (1953).
(3) J. E. Hodge, U. S. Patent 2,936,308 (1960).
(4) F. Weygand, H. Simon, W. Bitterlich, J. E. Hodge, and E. E. Fisher, *Tetrahedron*, **6**, 123 (1959).
(5) H. Simon and G. Heubach, *Chem. Ber.*, **98**, 3703 (1965).
(6) H. Simon, *ibid.*, **95**, 1003 (1962).
(7) J. E. Hodge, B. E. Fisher, and E. C. Nelson, *Amer. Soc. Brew. Chem., Proc.*, 84 (1963).
(8) C. D. Evans, H. A. Moser, P. M. Cooney, and J. E. Hodge, *J. Amer. Oil Chem. Soc.*, **35**, 84 (1958).
(9) A. M. Ambrose, D. J. Robbins, and F. DeEds, *Proc. Soc. Exp. Biol. Med.*, **106**, 656 (1961).
(10) W. Cutting, A. Furst, D. Read, G. Read, and H. Parkman, *ibid.*, **104**, 381 (1960).
(11) K. Nishie and A. C. Keyl, unpublished results of the Pharmacology Laboratory, Western Regional Research Laboratory, Albany, Calif., 1970.
(12) G. Hesse, H. Broll, and W. Rupp, *Justus Liebigs Ann. Chem.*, **697**, 62 (1966).
(13) G. Hesse and P. Beyer, *ibid.*, **747**, 84 (1971).

SCHEME I



revealed weak absorptions at 1710 and 1730–1745 cm^{-1}, respectively, and left those frequencies unassigned. The 1710–1745- and the 1748-cm^{-1} absorptions may indicate that the reductones and crystalline **3** contain, in small amounts, an unenolized ane-1,3-dione B ring structural contributor.[14] The strong, broad absorption at 1706 cm^{-1} was assigned to both carbonyls of the five-membered, ene-1,3-dione ring,[15-17] and the one of the reductone moiety.[12,14,18] The strongest absorption at 1607 cm^{-1}, also broadened, was assigned to the carbonyl-conjugated double bonds of both rings.[12,14,16-18]

Further evidence for the 2,3-dihydroxy-2-enone reductone moiety was indicated by the strong reducing action of **3** with 2,6-dichloroindophenol (Tillmans' reagent) and methylene blue in acid solution. Ferric chloride produced a temporarily blue solution indicative of the enolic hydroxyl function. In our earlier study with disubstituted enones,[19] absorptions in the 1800–1600-cm^{-1} region were similar. Monomethylation of **3** with diazomethane or methanol–hydrogen chloride yields **5**, and **5** fails to reduce Tillmans' reagent. Preferential alkylation would occur at the more acidic 3′-hydroxy group in agreement with the alkylation results of methyl reductic acid[12] and the methylation of 2,3-dihydroxy-4,4,6 6-tetramethyl-2-cyclohexenone.[13] A change in the ir absorptions in the 3500–3200- and 2750–2510-cm^{-1} regions indicated that chelation was greatly disrupted.

The uv spectrum of **3** in 95% ethanol provided two maxima at 234 nm (ϵ 12,600) and 268 (7068) which represent two separate conjugated systems. These maxima are consistent with reported literature values for the proposed chromophores.[12,20-22]

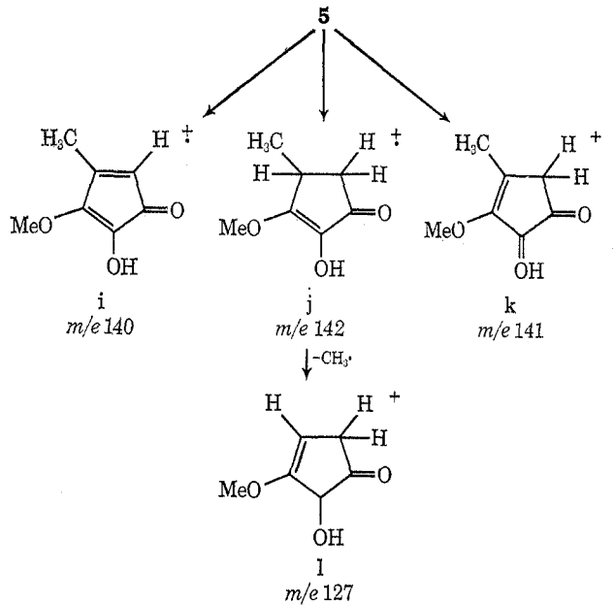
Examination of **3** by pmr in dimethyl sulfoxide-d_6 (DMSO-d_6) provided evidence for an uncoupled, aliphatic methyl group (singlet, δ 1.16), one vinyl methyl group (δ 1.98) coupled to a vinyl proton (δ 6.94), and a geminal methylene quartet (δ_A 3.15, δ_B 1.84, J_{AB} = −18 Hz). The negative AB coupling constant agrees with the values reported for methylene protons α to carbonyl groups.[23,24] Irradiation of each doublet of the AB quartet allows the individual frequency assignments. Three hydroxyl protons were present as broad resonances at δ 8.10, 6.10, and 3.39. The vinyl proton resonance collapsed to a singlet when the methyl protons at δ 1.98 were irradiated. Acetyl or methyl substitution, **4a** and **5**, produces no change in the basic pmr spectral pattern of **3**. The acetyl group (δ 2.01 in $CDCl_3$) is assigned to the 3′ position because this derivative failed to reduce Tillmans' reagent, and previously examined α-acetoxy methyl groups in α,β-unsaturated cyclopentanes and cyclohexanes in chloroform-*d* were shielded more and displaced to a lower field near δ 2.2.[25]

Low- and high-resolution mass spectra were analyzed for **3**, its monomethyl ether (**5**), and the monoacetyl derivative (**4a**). The composition of each fragment from **3** shown in Scheme I is verified by high-resolution analysis. The intensity of the fragments at *m/e* 125–128 indicates the relative ease of cleavage of the 2–5′ bond, and the splitting results in two fundamental ions each representing one ring of the proposed structure. The formation of fragment b, *m/e* 126, arises *via* a hydrogen transfer, most likely through a McLafferty rearrangement,[26] and may involve both the 5′-methyl and 4′-methylene protons on the methyl reductic acid moiety. Fragment d, *m/e* 110, was shown to be produced from b′ (formed with a proton transfer) by a metastable ion, and then d expels CO to form e, *m/e* 82. The pattern of *m/e* 128 → 110 → 82 is also observed in the fragmentation of the mono- and diacetates of methyl reductic acid after the loss of one and two molecules of ketene. This ketene expulsion process agrees with results by Biemann, *et al.*[27] Fragments at *m/e* 237 (f), 224 (g), and 234 (h) arise, respectively, from loss of a methyl radical (C-5′ most likely), carbon monoxide, and water.

The fragmentation of **5** (Scheme II) produces high-intensity peaks at *m/e* 140, 141, and 142 that represent fragments i, j, and k. As in the fragmentation pattern

(14) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., and Nankodo Co., Tokyo, 1964, Chapter 2.
(15) K. Hiraga, *Chem. Pharm. Bull.*, **13**, 1300 (1965); *Chem. Abstr.*, **64**, 49086 (1965).
(16) M. Nilsson, *Acta Chem. Scand.*, **18**, 441 (1964).
(17) C. H. DePuy, R. D. Thurn, and M. Isaks, *J. Org. Chem.*, **27**, 744 (1962).
(18) R. Müller and H. Plieninger, *Chem. Ber.*, **92**, 3016 (1959).
(19) F. D. Mills, B. G. Baker, and J. E. Hodge, *Carbohyd. Res.*, **15**, 205 (1970).
(20) C. H. DePuy and E. F. Zaweski, *J. Amer. Chem. Soc.*, **79**, 3923 (1957).
(21) A. A. Kiang, H. H. Lee, and K. Y. Sim, *J. Chem. Soc.*, 4328 (1962).
(22) A. J. Birch and R. J. English, *ibid.*, 3805 (1957).
(23) T. Takahashi, *Tetrahedron Lett.*, **No. 11**, 565 (1964).
(24) C. H. DePuy, C. E. Lyons, and L. B. Rodewald, *J. Chem. Eng. Data*, **11**, 102 (1966).
(25) α-Acetyl methyl proton resonances in α,α'-diacetoxydihydro-γ-pyrone, methyl cyclopentenolone acetate, dihydromaltol acetate, and maltol acetate are 2.20, 2.22, 2.21, and 2.30.
(26) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectroscopy of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 155.
(27) K. Biemann, D. C. DeJongh, and H. K. Schones, *J. Amer. Chem. Soc.*, **85**, 2289 (1963).

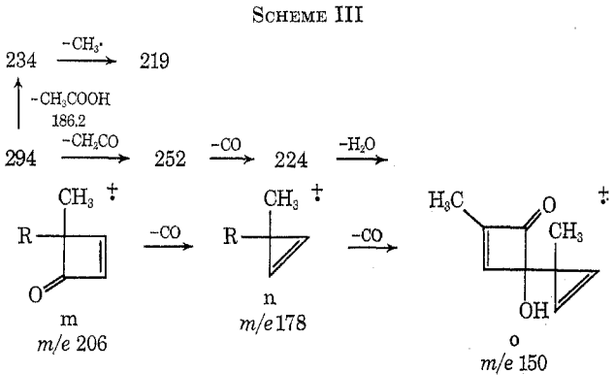
SCHEME II



of **3**, the loss of a methyl radical, *m/e* 251, and CO, *m/e* 238, are present in the mass spectrum of **5**; however, since no $M \cdot^+ - 18$ ion is observed, water expulsion during ionization of **3** evidently arises from the dihydroxyenone portion of the molecule. Ions at *m/e* 125 (a), 126 (b), and 127 (c) are still present at reduced intensities. All are assumed to originate by loss of $CH_3 \cdot$ from ions i, j, and k since l, *m/e* 127, originates from k as shown by the metastable peak at 113.5.

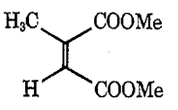
The mass spectral pattern of the monoacetate **4a** is somewhat more complicated owing to this modifying group; new decomposition paths became available. The new fragments, *m/e* 219, 206, 178, and 150, are rationalized in Scheme III, which brings all the more

SCHEME III

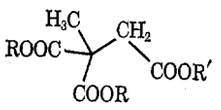


significant mass spectral data for the parent compound and its two derivatives into agreement.

Further information to support the assigned structure came from oxidation and reduction of **3**. Periodate treatment of **3** furnishes chemical evidence for the 1,3-enedione structural unit in the A ring. A dibasic acid, isolated after periodate treatment of **3** as its methyl ester, is identified as **6** (81% yield of free acid) by comparative glc and mass spectral analyses with authentic dimethyl citraconate. The mass spectrum is straightforward, does not contain any skeletal rearrangements, and is in agreement with the work of Bowie, *et al.*,[28] on malates.



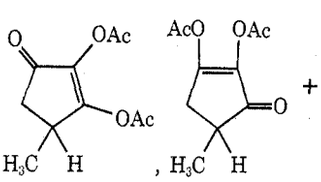
6



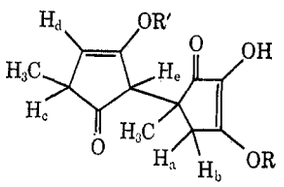
7, R, R′ = H
8, R, R′ = CH_3

A second polybasic acid, **7**, was isolated in 43% yield (50% overall) after hydrogen peroxide treatment of **3** and arises from ring B plus C-2 of ring A. Pmr of compound **8**, the trimethyl ester of **7**, reveals the *C*-methyl protons at δ 1.53, two equivalent methyl ester groups (R, δ 3.76), and a third group (R′) displaced further upfield (δ 3.65); a 3:2 ratio of methyl-methylene protons is also demonstrated. No molecular ion is observed in the mass spectrum of **8**; the highest mass is at *m/e* 187. The structure of compound **8** was confirmed by comparison with an authentic sample.

Partial hydrogenation of **3**, with isolation of the reduced products as their acetate derivatives, also supports the assigned structure. Three products, **9** (37.7%), **10** (5.7%), and **11** (6.6%), are assigned structures based on spectral data; **9** is identical with a synthetic product. Analyses of **9** by glc and tlc indicate this material to be homogeneous, but pmr shows **9** to be a mixture of the two isomers **9a** and **9b**.

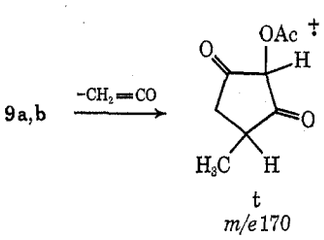


9a,b



10, R = R′ = OAc
11, R = H; R′ = OAc

Analogous isomers are indicated for the mono-*O*-methyl ethers of methyl reductic acid.[12] Mass spectrometry of the mixture **9** shows that the first fragmentation of each isomer, **a** and **b**, produces a common ion t, *m/e* 170, which is responsible for the remaining fragmentation pattern; *viz.* below.



The ir, pmr, and mass spectral data from the isolated product agree with spectral information obtained from an authentic sample of **9**. Structure **10** is assigned primarily from pmr and mass spectral information. Mass spectrometry establishes a formula of $C_{16}H_{18}O_7$ ($M \cdot^+$ 322), a diacetate by pmr; the loss of two ketene units ($m \cdot^+ - 42 - 42$) in the fragmentation of **10** supports the diacetate assignment and also shows these functional groups to be attached to double bonds. The pmr spectrum of **10** indicates that the

(28) J. H. Bowie, D. H. Williams, P. Madsen, G. Schroll, and S.-C. Lawesson, *Tetrahedron*, **23**, 305 (1967).

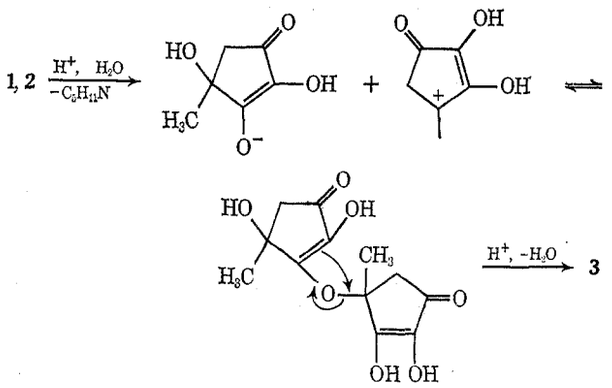
ring A methyl group is involved in a six-spin system (shown by decoupling experiments) including the methyl group (δ 1.18, J_{CH_3,H_c} = 6.7 Hz), H_c (δ 2.85, multiplet,) and H_d (δ 4.70, J_{H_c,H_d} = 4.8 Hz, finely split quartet). Two resonances at δ 2.15 and 2.27 (one-half proton each) are assigned to proton H_e; irradiation indicates long-range coupling between H_c and H_e protons, as should occur in the planar, modified A ring.[29] The chemical shifts of H_e (at 2.15 and 2.27) on the diastereotopic muclei arising from the C-2 chiral carbon atom,[30] along with the lack of optical activity, indicate that **10** (also **11**) exists as a racemic modification. Homoallylic coupling of H_e, H_c supports structure **10**.[31] Further irradiation at δ 2.85 converts the finely split doublet of the vinyl proton into a broadened singlet and produces a broadened, methyl group singlet at δ 1.18. The complicated six-spin interaction lends itself to only a partial solution by first-order analysis, and the parameters indicate a $CH_3CHRCH{=}CROAc$ relationship. The geminal protons (H_A, H_B) are still present at δ 2.86 and 3.15 (J_{H_A,H_B} = −18 Hz) along with two acetyl methyl groups at δ 2.10 and 2.22.

The ir spectrum of **10** supports the five-membered ketone, vinyl acetate, bonded hydroxyl, and a substituted α,β-enone assignment. Other spectral information (pmr, mass spectrum) shows product **11** to be similar to **10**, except that this derivative has only a single acetate group. The pmr data are in concert with that of **10**: acetyl methyl δ 2.22; aliphatic methyl δ 1.36; aliphatic methyl δ 1.16 (J_{CH_3,H_c} = 6.4 Hz), a broadened singlet upon irradiation of H_c; geminal methylene protons, δ 2.52 and 2.96 (J_{H_A,H_B} = −18.7 Hz); vinyl proton at δ 4.63; methine proton at δ 2.02 and 2.12 (one proton); methine proton at δ 2.87 (multiplet). Three different irradiations show C-2, C-4, and C-5 protons plus methyl protons to be involved in a six-spin interaction. High-resolution mass spectrometry fixes the formula at $C_{14}H_{16}O_6$ and shows the material to contain a vinyl acetate moiety ($M\cdot^+ - 42$). A positive reduction test with Tillmans' reagent supports the placement of the acetate group in the modified A ring.

In effect, reduction of the double bond in the A ring of the yellow reductone occurs along with either one of the carbonyl groups and yields a product which should be easily dehydrated (loss of the tertiary hydroxyl group) during the anhydrous acetylation. Finally, enolization and acetylation gives compounds **10** and **11**. The reduction sequence agrees with early information on the reduction of 4-cyclopentene-1,3-dione[20] and its 2,2-dimethyl derivative.[32] Also, products **4b** (23.8%) and **4c** (11.6%) are isolated from the reduced, acetylated mixture by fractional crystallization of the solid that initially crystallizes from the reaction mixture.

Initially, a vinyl–allyl ether linkage between the two rings in **3** was proposed because of the *m/e* fragments a and b. This assignment was discarded because vinyl ethers are readily hydrolyzed in acidic media.[33–35] Nevertheless, the vinyl ether is involved in a logical explanation for formation of the yellow reductone (Scheme IV). After hydrolysis and carbonium ion formation in the strongly acidic medium, a labile and reversible ether bond forms. The vinyl–allyl ether is short lived and the methyl reductic acid double bond enhances (anchiomeric assistance) rearrangement to the final product in a 1,3-intramolecular shift. This phenomenon of the reductone double bond assistance probably promotes the σ bond (C-2–C-5′) cleavage that takes place during the hydrogenation of **3**. The lack of optical activity in compound **3**, which contains two chiral centers, indicates a racemic modification and nonstereospecificity in the overall reaction (Scheme IV). Also, hydrolysis of **2** results in **3**, and it is likely that both reactions proceed *via* the same intermediate.

SCHEME IV



Experimental Section

General.—Melting points were recorded on a Thomas-Hoover Unimelt[36] apparatus and are uncorrected. Ir spectra were obtained with a Perkin-Elmer Model 612 spectrophotometer from potassium bromide disks or solutions in chloroform. The mass spectra were determined with a Nuclide 12-90-DF double-focusing spectrometer at 70 eV and either a direct or heated inlet (approximately 160°) was used. The pmr spectra were recorded with a Varian HA-100 instrument, and various sweep widths (50, 100, 500 Hz) were employed in coupling constant evaluations. Me_4Si served as an internal standard. The uv spectrum was measured on a Cary Model 60 recording photometer from 95% ethanol solutions. Optical rotations were measured on a Beckman automatic recording polarimeter Model 1169 from absolute ethanol solutions. Tillmans' reagent is a slightly basic, dilute solution of 2,6-dichloroindophenol.

Yellow Reductone (3), 2-Hydroxy-2-(2′,3′-dihydroxy-5′-methyl-2′-cyclopentenon-5′-yl)-4-methyl-4-cyclopentene-1,3-dione.—Piperidino-hexose-reductone (1, 143.5 g)[2-5] was added to 273 ml of 4 *N* hydrochloric acid. Upon dissolution, the mixture turned orange-red. The head space was filled with nitrogen and the stoppered flask was stored in the dark for 12 days. At the end of this period, the yellow, crystalline precipitate was removed and recrystallized from hot water (cooling to room temperature). After 24 hr, 48.4 g precipitated (26.3%) and had mp 153–156° (drying over calcium chloride at 26° for 12 hr at 0.1 Torr); $[\alpha]^{26}D$ −0.01 (0.7 g/100 ml ethanol). Compound **3** may

(29) M. Barfield and D. M. Grant, *Advan. Magn. Resonance*, **1**, 189 (1965).

(30) J. F. Stoddart, "Stereochemistry of Carbohydrates," Wiley-Interscience, New York, N. Y., 1971, Chapter 2.

(31) C. M. Cimarusti and J. Wolinsky, *J. Org. Chem.*, **31**, 4118 (1966), and references cited therein.

(32) W. C. Agosta and A. B. Smith, III, *ibid.*, **35**, 3856 (1970).

(33) P. Paul, *Bull. Soc. Chim. Fr.*, **1**, 971 (1934).

(34) A. Skrabel and R. Skrabel, *Z. Phys. Chem.*, **A181**, 449 (1938).

(35) T. Okuyama, T. Fueno, H. Nakatsuji, and J. Furukawa, *J. Amer. Chem. Soc.*, **89**, 5826 (1967).

(36) Mention of companies or products by name does not imply their endorsement by the U. S. Department of Agriculture over others not cited.

also be prepared from morpholino- (in similar yields) and *N,N*-dibenzylamino- (in 10% yield) hexose-reductones.

Anal. Calcd for $C_{12}H_{12}O_6 \cdot H_2O$: C, 53.33; H, 5.22; neut equiv, 270. Found: C, 53.41; H, 5.45; neut equiv, 279.

Ir (KBr disk) 3560 (br), 3470 (br), 3350 (br), 3250 (br), 2990, 2750–2510 (v br), 1748 (m), 1706 (vs), 1607 (br, vs), 1418, 1379, 980, 898 cm^{-1}.

Pmr (DMSO-d_6) δ 1.16 (3 H) aliphatic methyl; 1.98 (3 H) vinyl methyl; 3.15 (1 H_A) and 1.84 (1 H_B), $J_{H_AH_B} = -18$ Hz; 8.10 (1 OH), 6.10 (1 OH), and 3.39 (1 OH), broad, hydroxyl protons; 6.94 (1 H) vinyl proton, $J_{CH_3,H} = 1.3$ Hz.

Mass spectrum *m/e* (rel intensity) 252 (50), 237 (2), 234 (1), 224 (17), 167 (6), 128 (98), 127 (84), 126 (100), 125 (29), 110 (76), 82 (16), 68 (37).

Uv $\lambda_{max}^{95\% EtOH}$ 234 nm (ϵ 12,600), 268 (7068).

Acetylation of 3 (4a).—One gram of **3** was dissolved with warming in 6 ml of acetic anhydride. Acetyl chloride (6 drops) and pyridine (6 drops) were added and the solution was refluxed for 2 hr. After cooling, the solution was concentrated *in vacuo* and the resulting residue was crystallized from methanol–water (90 mg). After two crystallizations the melting point was 194–196° dec.

Ir (KBr disk) 3430, 3080, 1780 (w), 1760, 1665, 1650, 1610 cm^{-1}.

Pmr (acetone-d_6) δ 1.30 (3 H), aliphatic methyl; 2.01 (3 H), vinyl methyl; 2.03 (3 H), acetyl methyl; 3.16 (1 H_A), 2.06 (1 H_B), $J_{H_A,H_B} = -18$ Hz); 6.84 (1 H), vinyl proton, $J_{CH_3,H} = 1.6$ Hz.

Mass spectrum *m/e* (rel intensity) 294 (64), 252 (19), 234 (18), 224 (3), 206 (28), 192 (11), 178 (15), 177 (13), 128 (64), 127 (64), 126 (83), 125 (18), 110 (26), 69 (17), 43 (100).

Acetylation of 3 (4b).—Yellow reductone **3** (100 mg) was dissolved with warming in 10 ml of acetic anhydride containing 40 mg of anhydrous sodium acetate. The mixture was heated on a steam bath for 2 hr. After cooling, the mixture was poured onto 100 ml of ice and the solution was then neutralized with sodium bicarbonate. After standing for 30 min, a white precipitate formed, 20 mg, mp 258°. Extraction of the aqueous phase with chloroform and the subsequent work-up yielded, after recrystallization from ethanol–water, an additional 50 mg of product.

Ir (KBr disk) 3430, 3080, 2990, 2830, 1775, 1760, 1735, 1708, 1650, 1610 cm^{-1}.

Pmr (DMSO-d_6) δ 1.31 (3 H), aliphatic methyl protons; 2.02 (3 H), vinyl methyl protons, doublet; 2.16 and 2.17 (6 H), acetyl methyl protons; 2.47 and 3.34 (2 H), geminal protons, $J_{H_A,H_B} = -18$ Hz; 6.55 (1 H) vinyl proton, quartet, $J_{CH_3,H} = 1.6$ Hz.

Mass spectrum *m/e* (rel intensity) 336 (65), 318 (4), 308 (4), 300 (12), 294 (22), 276 (26), 266 (10), 252 (2), 248 (24), 234 (100), 224 (42), 219 (40), 216 (24), 206 (76), 201 (7), 178 (27), 165 (6), 150 (8), 149 (10), 128 (5), 127 (27), 126 (23), 125 (6), 110 (13), 69 (3).

Monomethyl Ether 5. A. Prepared with Diazomethane.—An ethereal solution of 9 mmol of diazomethane was added in three portions to 0.840 g (3 mmol) of **3** in 10 ml of methanol. The resulting solution was allowed to stand at room temperature for 24 hr (after 1.5 hr a slight precipitate formed), the solvent was removed with a stream of nitrogen, and the residue was taken up in 4 ml of methanol. Ether (50 ml) was added and the solution was cooled; 400 mg of product was obtained, mp 198–200°. Tlc on silica gel (Brinkmann, precoated silica gel F-254, 0.25 mm) using benzene–acetone–methanol (20:10:5) showed this material to be a mixture. The mixture was chromatographed on a 70-g silica gel column (Baker, chromatographic grade). The column was developed with the same solvent system. Those fractions that contained only the fastest moving component were combined, and the product was isolated by solvent evaporation. The residues were combined and crystallized from methanol–ether, 200 mg, mp 229–230°. Tlc showed this product to be homogeneous.

Ir (KBr disk) 3410, 3230, 3060, 3000, 2982, 1738, 1695, 1610, 1580, 1468, 1400, 915, 905 cm^{-1}.

Pmr (DMSO-d_6) δ 1.17 (3 H), aliphatic methyl protons; 1.95 (3 H), vinyl methyl protons; 2.10 and 3.33 (2 H), geminal protons, $J_{H_A,H_B} = -18$ Hz; 3.25 and 3.27 (2 H), hydroxyl protons; 3.90 (3 H), *O*-methyl protons; 6.98 (1 H) vinyl proton, $J_{CH_3,H} = 1.5$ Hz.

Mass spectrum *m/e* (rel intensity) 266 (74), 251 (6), 238 (17), 234 (18), 224 (3), 206 (2), 178 (2), 142 (100), 141 (44), 140 (33), 127 (62), 126 (11), 125 (9), 124 (19), 114 (17), 110 (19), 69 (36).

B. Prepared with Methanol–Hydrogen Chloride.—To 20 ml of a solution of anhydrous HCl in methanol (prepared from acetyl chloride–methanol) **3** (0.4 g) was added. The solution stood at room temperature for 18 hr, and then the solvent was removed *in vacuo*. The residue was crystallized twice from methanol–ether, 380 mg, mp 227–229°. Tlc on silica gel with either the above solvent system or ethyl acetate indicated the product to be homogeneous. A mixture melting point determination, with the previously prepared *O*-methyl ether, gave no depression. Pmr data in DMSO-d_6 were identical with that of the above monomethyl ether.

Oxidation of 3 with Sodium Periodate (6, 8).[37]—Yellow reductone **3** (2.52 g in 50 ml of water) was treated with three portions of sodium periodate (12.83 g in 100 ml of water). The first 30-ml addition changed the solution to a light yellow; some free iodine was liberated. Hydrochloric acid (0.1 *N*) was added to bring the pH of the solution to 3. The stoppered flask was protected from light, and the mixture was stirred overnight. The colorless reaction mixture was continuously extracted with ether for 5 hr and the resulting extract was dried with sodium sulfate. After filtration and solvent removal, 1.49 g of residue was isolated.

A portion of this residue was methylated with excess diazomethane in methanol–ether; glc analysis (6 ft × 0.25 in., 15% SE-30 on 80–100 UPh) indicated that the sample contained **6** (85%) and a lesser quantity of **8** (10%). Another portion was treated for 1 hr on a steam bath with 25 ml of water containing 2 ml of 30% hydrogen peroxide. The products were isolated by solvent extraction in the usual manner and methylated with diazomethane. Glc analysis showed this mixture to consist of **6**:**8**:unknown in a 65:22:13 ratio [diethyl 2-methylmalonate (DEMM) was used as an internal standard]. Total yields of free acids: citraconic, 81%; **7**, 6%.

A further portion of the methylated mixture was separated by preparative glc on a 6 ft × 0.25 in., 15% SE-30 on 80–100 UPh column. The material corresponding to **6** was isolated and subjected to ir and mass spectral analyses.

Ir ($CHCl_3$) 3010, 2955, 2850, 1665, 1445, 1435, 1372, 1360, 1280, 1168, 1125, 1040 cm^{-1}.

Mass spectrum *m/e* (rel intensity) 158 (4), 144 (2), 129 (2), 128 (8), 127 (100), 100 (2), 99 (20), 64 (5), 63 (6), 59 (22).

Hydrogen Peroxide Oxidation of 3 (6, 7, and 8).—Yellow reductone (5.0 g) was dissolved in 100 ml of water, and three 8-ml portions of 30% hydrogen peroxide were added to the stirred, heated (90°) solution. After 1.5 hr, the solution was cooled and 40 g of lead acetate trihydrate was added. This turbid mixture was allowed to stand for 24 hr, and the precipitate was isolated, dried, ground into a fine powder, and suspended in 75 ml of water. Excess hydrogen sulfide was passed into the solution for 30 min; after the lead sulfide was removed, the filtrate was concentrated to a thick syrup *in vacuo*. When the oil (3.0 g) was treated with ethyl acetate, 1.5 g (43%) of crystalline **7** was produced.

The ethyl acetate mother liquor was concentrated and a portion of the residue was treated with diazomethane. This mixture was analyzed by glc with DEMM as an internal standard. The mixture contained 19% **8** (dimethyl 2-carboxymethyl-2-methylbutanedioate) and 2% **6** [dimethyl 2-methyl-(*Z*)-butenedioate].

A portion of compound **7** dissolved in ether–methanol was treated with excess diazomethane. The solvent was removed with a stream of nitrogen and a portion of the methylated product was examined on the 15% SE-30 column that was programmed at 80°, 4°/min to 200°. The ester **8** was homogeneous, retention time 11 min (relative to DEMM).

Ir ($CHCl_3$) 2962, 2850, 1731, 1458, 1439, 1370, 1169, 1115 cm^{-1}.

Pmr (CDCl) δ 1.53 (3 H), aliphatic methyl protons; 2.92 (2 H), methylene protons; 3.65 (3 H) and 3.76 (6 H), *O*-methyl protons.

Mass spectrum *m/e* (rel intensity) no parent ion, 187 (53), 159 (28), 145 (11), 131 (9), 127 (100), 115 (67), 99 (27), 69 (41), 59 (49).

Hydrogenation of 3 (4a, 4b, 9a, 9b, 10, and 11).—After the yellow reductone **3** (3 g) was dissolved in 40 ml of 95% ethanol, 0.2 g of 10% Pd/C in 40 ml of ethanol was added, and the final volume was brought to 100 ml with ethanol. The mixture was hydrogenated at 3.1 atm and room temperature for 2 hr. The

(37) M. L. Wolfrom and J. M. Bobbitt, *J. Amer. Chem. Soc.*, **78**, 2489 (1956).

solution was filtered through Celite and concentrated. The resulting thin syrup (3.0 g) was added to 50 ml of chloroform containing 16 ml of acetic anhydride and 80 mg of anhydrous sodium acetate. The mixture was refluxed for 3 hr and, after cooling, poured into 200 ml of ice. The aqueous mixture was stirred for 1.5 hr and was then extracted three times with 25 ml of chloroform. The combined organic phase was dried over calcium chloride. Filtration and solvent removal produced a light oil (3.10 g). The oil was distilled at 0.1 Torr: fraction 1, 140–160°, 1.0 g; fraction 2, 160–180°, 2.0 g.

Fraction 1 (1.0 g) was examined by glc on the SE-30 column and shown to be 95% pure; retention time 26.8 min, programmed from 80° at 4°/min and a flow rate of 56 ml He/min. A portion of this material was purified by preparative glc (50 mg of **9**).

Ir ($CHCl_3$) 2970, 2925, 2870, 1778, 1717, 1660, 1450, 1425, 1408, 1369, 1330, 1172, 1155 cm^{-1}.

Pmr ($CDCl_3$) δ 1.18 and 1.27 (3 H), doublet of doublets representing two different methyl group protons; 3.02–4.00 (3 H), methylene protons, multiplet; 2.21, 2.24, 2.26, and 2.28 (6 H), representing two acetyl methyl groups per isomer of the two diacetates present.

Mass spectrum *m/e* (rel intensity) 212 (6), 170 (22), 128 (68), 113 (7), 110 (3), 100 (4), 85 (4), 69 (3), 43 (100).

A 1.0-g portion of fraction 2 was dissolved in ethyl acetate–methanol and stirred at −15°. After 3 days, a white, crystalline precipitate formed, 0.174 g, mp 246–250° dec (**4c**).

Ir (KBr disk) 2810–2740 (br), 1782, 1778, 1740, 1655, 1615, 1425, 1370, 1235, 1190, 1170, 1145, 1098 cm^{-1}.

Pmr (DMSO-d_6) δ 1.27 (3 H), aliphatic methyl protons; 1.90 (3 H), aliphatic acetyl methyl protons; 2.09 (3 H), vinyl acetyl methyl protons; 2.11 (3 H), vinyl acetyl methyl protons; 1.98 (3 H), vinyl methyl protons; 2.15 and 2.28 (2 H), $J_{AB} = -18$ Hz, geminal, methylene protons; 7.02 (1 H), vinyl proton (quartet).

Mass spectrum *m/e* (rel intensity) 378 (11), 336 (59), 294 (49), 276 (6), 266 (10), 252 (54), 234 (85), 224 (32), 206 (28), 192 (7), 178 (9), 170 (13), 169 (14), 150 (8), 129 (8), 128 (61), 127 (44), 126 (63), 125 (10), 110 (10), 69 (16), 43 (100).

Compound **4b** was isolated by careful concentration of the mother liquors resulting from the retreatment of the difficulty soluble residue (0.475 g). The mass and ir spectra were superimposable on those from previously prepared **4b**.

The remainder of the residue soluble in the original supernatant (over **4c**) was applied to a small amount of silica gel (<2.0 g). The mixture, after solvent removal, was placed on a silica gel dry-packed column (42 g of Baker chromatographic grade containing 10% water by weight). The column was developed and eluted with chloroform; 5-ml samples were taken. Fractions 25–37 contained 200 mg of **10**, $[\alpha]^{25}D$ −0.02° (*c* 1.0, ethanol), and fractions 50–70 yielded 250 mg of **10** and **11**. Fractions 50–70 were combined and the resulting residue was applied to a 2-mm silica gel preparative plate (Brinkmann) which was then developed three times with benzene–ethyl acetate (3:1). Each zone corresponding to **10** and **11** was removed and extracted with ethyl acetate: 20 mg **10**, 220 mg **11**.

Spectra of 10.—Ir ($CHCl_3$) 3400 (v br), 2975, 2930, 2878, 1772 (br), 1695, 1668, 1445, 1372, 1368, 975, 955 cm^{-1}.

Pmr ($CDCl_3$) δ 1.18 (3 H), aliphatic methyl protons, doublet $J_{Me,H_c} = 6.7$ Hz; 1.30 (3 H), aliphatic methyl protons; 2.10 and 2.22 (6 H), acetyl methyl groups; 2.27 and 2.15 (1 H), methine proton H_c; 2.86 and 3.15 (2 H), geminal protons, $J_{H_A,H_B} = -18$ Hz; 4.70 (1 H), vinyl proton (H_d) finely split doublet; 2.85 (1 H_c), multiplet, $J_{H_c,H_d} = 4.8$ Hz.

Mass spectrum *m/e* (rel intensity) 322 (3), 280 (83), 238 (5), 220 (22), 192 (32), 172 (100), 164 (21), 161 (23), 148 (32), 133 (10), 110 (5), 86 (5), 69 (6), 43 (100).

Spectra of 11.—Ir ($CHCl_3$) 2980, 2940, 2918, 2860, 1750 (br), 1602 (br), 1489, 1440, 1390, 1372, 1300, 942, 905 cm^{-1}.

Pmr ($CDCl_3$) δ 1.16 (3 H), aliphatic methyl, $J_{CH_3,H_c} = 6.4$ Hz; 1.36 (3 H), aliphatic methyl group; 2.22 (3 H), acetyl methyl protons; 2.52 and 2.96 (2 H), geminal methylene protons, $J_{H_A,H_B} = -18.6$ Hz; 2.02 and 2.12 (1 H), methine proton H_c; 2.87 (1 H_c), methine proton, multiplet; 4.63 (1 H_d), vinyl proton, finely split doublet, $J_{H_c,H_d} = 4.4$ Hz.

Mass spectrum *m/e* (rel intensity) 280 (18), 238 (53), 220 (18), 192 (6), 164 (3), 148 (2), 124 (8), 123 (8), 43 (100).

2-Carboxy-2-methylbutanedioic Acid.—This compound was prepared according to a modified, previously established procedure.[38] Sodium (2.3 g) was dissolved in absolute ethanol, and diethyl 2-methylmalonate (17.4 g) was added to the solution over 30 min. Ethyl chloroacetate (12.62 g) was added to the sodium salt over a 40-min period, and the final mixture was refluxed for 4 hr. The reaction was cooled and most of the alcohol was removed *in vacuo;* the residue was added to water and the new mixture was extracted with ether. The combined ether extract was dried over calcium sulfate, filtered, and then reduced to a light oil by solvent evaporation; distillation at 150° and 18 Torr produced 10 g of ester (38%).

The ethyl ester (5 g) was saponified with 10% potassium hydroxide (100 ml). Extraction of the cooled, acidified solution with ether produced (after the usual work-up) 4.5 g of tricarboxylic acid, mp 174° (lit. mp 176°).

Dimethyl 2-Carbomethoxybutanedioate.—The free acid (1.0 g) was dissolved in a small amount of methanol, and an excess of diazomethane (in ether) was added in two portions. The solvent was removed after 1 hr with a stream of nitrogen and the product was distilled at 15 Torr. The product was homogeneous (glc on 15% SE-30 column), and the spectral data of this ester were identical with those of **8**.

Dimethyl 2-Methyl-(*Z*)-butenedioate (Dimethyl Citraconate).—An authentic sample of acid (1.0 g) was methylated with an excess of diazomethane in methanol–ether. Solvent removal produced the desired product, 1.20 g. The ir, pmr, and mass spectral analyses of this compound were identical with those of **6**.

2,3-Diacetoxy-4-methyl-2-cyclopentenone and 2,3-Diacetoxy-5-methyl-2-cyclopentenone.—An attempt to prepare methyl reductic acid by the procedure of Hesse and Breig[39] met with limited success. A slight modification allowed isolation of the diacetate derivative of methyl reductic acid. The residue from the hydrolysis of the monohalocyclopentenolone was distilled and the fraction of bp 160–170° (0.1 mm) was isolated. This material was added to 25 ml of chloroform, 4 ml of acetic anhydride, and 60 mg of sodium acetate. The mixture was refluxed for 4 hr and, after cooling, poured into ice water. After stirring for 2 hr, the organic phase was removed and the aqueous portion was extracted with chloroform three times. Combination of all organic phases yielded 8% of the diacetate after drying and filtration. The isolate did not crystallize on standing in the cold. Glc (SE-30 column) and tlc (silica gel, benzene–ethyl acetate solvent systems) showed this material to be homogeneous. However, pmr information indicated this product to be a mixture of 2,3-diacetoxy-4-methyl-2-cyclopentenone and 2,3-diacetoxy-5-methyl-2-cyclopentenone. The two isomer isolates agreed with the work of Hesse, *et al.*,[12] on the monoalkyl ether derivatives of methyl reductic acid.

Ir ($CHCl_3$) 2970, 1785, 1722, 1665, 1372, 1335, 1190, 1165, 1000 cm^{-1}.

Pmr ($CDCl_3$) δ 1.24 (3 H), doublet, superimposition of two methyl group protons; 2.21, 2.22, 2.24, and 2.26 (6 H), acetyl methyl protons; 3.00–4.30 (3 H), multiplet, methine and methylene protons.

Mass spectrum *m/e* (rel intensity) 212 (2), 170 (22), 128 (68), 113 (8), 110 (2), 100 (4), 85 (4), 69 (3), 43 (100).

Registry No.—**1** (R_1R_2N = piperidino), 39994-32-6; **1** (R_1R_2N = morpholino), 39994-33-7; **1** ($R_1 = R_2$ = benzyl), 39994-34-8; **3**, 39994-35-9; **4a**, 39994-36-0; **4b**, 39994-37-1; **4c**, 40081-61-6; **5**, 39994-38-2; **6**, 617-54-9; **7**, 39994-39-3; **8**, 39994-40-6; **9a**, 39994-41-7; **9b**, 39994-42-8; **10**, 39994-43-9; **11**, 39994-44-0; diethyl 2-carboethoxy-2-methylbutanedioate, 39994-45-1.

(38) A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957).

(39) G. Hesse and K. Breig, *Justus Liebigs Ann. Chem.*, **592**, 120 (1955).