[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY, ATLANTA 13, GA.]

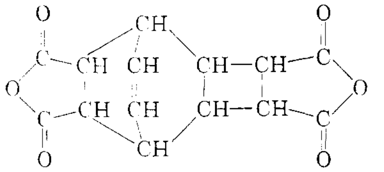
The Structure and Stereochemistry of the Photochemical Adduct of Benzene with Maleic Anhydride[1]

BY ERLING GROVENSTEIN, JR., DURVASULA V. RAO AND JAMES W. TAYLOR

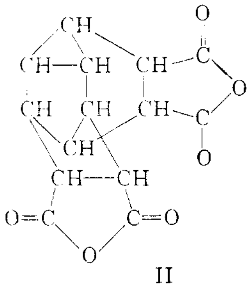
RECEIVED NOVEMBER 28, 1960

Benzene combines with two molecules of maleic anhydride under the influence of ultraviolet light to give an adduct which is assigned the structural and stereochemical formula XIV. This structural assignment rests in part upon oxidation of the adduct with lead tetraacetate in pyridine to give a product which is identical with the known maleic anhydride addition product of cycloöctatetraene. The maleic anhydride adduct of cycloöctatetraene is assigned the stereochemical formula XIII. The photochemical adduct XIV of benzene is unusual in that it contains a highly hindered double bond which fails to react with either bromine or potassium permanganate under ordinary conditions of tests for unsaturation.

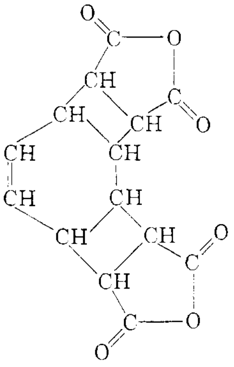
Angus and Bryce-Smith in a recent communication[2] have described the addition of maleic anhydride to benzene at 60° under the influence of ultraviolet radiation to give a product of m.p. 356° which they provisionally suggest has the structure I. We have independently discovered this[3] same adduct and wish to report experiments which provide proof for the structure I proposed by Angus and Bryce-Smith and which moreover establish the likely stereochemical structure of the adduct.



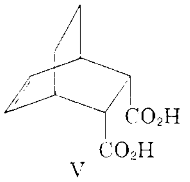
I



II



III



V

We have prepared the adduct in 13% yield (based on maleic anhydride) by irradiating for 16 hours with ultraviolet light a nearly saturated solution of maleic anhydride in benzene in a quartz apparatus at room temperature. Larger scale preparations of the adduct in the same apparatus were made in a mixed solvent of acetone and benzene in which maleic anhydride is some ten times more soluble than in benzene alone; acetone seems to have no adverse effect on the yield of product. The adduct is a white crystalline solid of m.p. 355–357° dec. It is somewhat soluble in acetone but is essentially insoluble in common organic solvents such as benzene and ether.

The adduct gave correct carbon–hydrogen analyses for $C_{14}H_{10}O_6$ and a saponification equivalent of 68.4 as expected for an adduct from one molecule of benzene combined with two molecules of maleic anhydride. Molecular weight determinations by the melting-point depression technique were unsuccessful in camphor, triphenylethane, β-naphthol, biphenyl or 2,4,6-tribromophenol apparently because the adduct is too insoluble in the melts from these compounds. However the adduct cannot likely have a molecular weight which is twofold or more that of $C_{14}H_{10}O_6$ because the adduct can be sublimed with only slight decomposition at 240° and 0.02 mm. pressure. Moreover the adduct gives, upon refluxing with 0.08 M methanolic hydrogen chloride, a tetramethyl ester, m.p. 134.5–135.0°, which has correct carbon–hydrogen analyses and molecular weight (in camphor) for $C_{18}H_{22}O_8$.

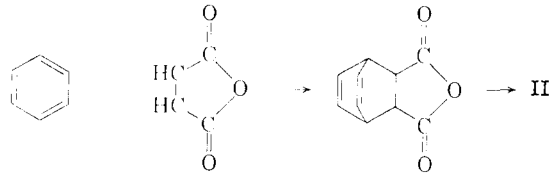
The tetracarboxylic acid obtained from saponification of the adduct had satisfactory carbon–hydrogen analyses for $C_{14}H_{14}O_8$ and decomposed at 125–200°, evidently with loss of water, and finally melted at 355–357° dec., which is the same as the melting point observed for the adduct anhydride. The acid upon hydrogenation in glacial acetic acid over a 5% platinum-on-carbon catalyst at room temperature and atmospheric pressure slowly absorbed over a 24-hour period one mole of hydrogen per mole of acid. The anhydride did not decolorize $KMnO_4$ in acetone and showed no reaction with bromine in boiling acetic acid under otherwise the usual conditions for these tests. Similarly, the methyl ester did not decolorize $KMnO_4$ in ethanol nor show any reaction with bromine in methanol in the dark, the latter even after six days. We were led on the basis of these tests for unsaturation to postulate[3] the presence of a cyclopropane ring in our adduct rather than a double bond. A simple structure for the adduct which contains a cyclopropane ring is structure II. This structure could be formed by 1,4-addition of one molecule of maleic anhydride to benzene to give IV and then 1,5-addition of a second molecule of the anhydride to give II.

---

[1] This research was supported in part by the Office of Ordnance Research, U. S. Army.

[2] H. J. F. Angus and D. Bryce-Smith, *Proc. Chem. Soc.* (*London*), 326 (1959).

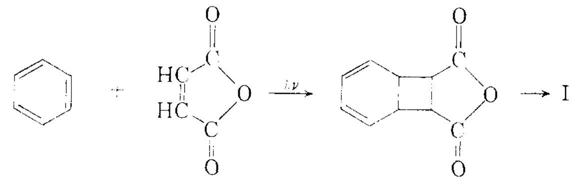
[3] Our discovery of the 2:1 adduct of maleic anhydride with benzene is contained in the M.S. thesis of J. W. Taylor, Georgia Institute of Technology, June, 1958, and was announced by E. G. at the Seventh Reaction Mechanisms Conference, University of Chicago, September 5, 1958, during the discussion of the paper of Prof. G. Büchi on light-catalyzed organic reactions.



IV

As an analogy for the reaction of IV with maleic anhydride to give II, the thermal addition of maleic anhydride to bicyclo[2.2.1]heptadiene[4] may be cited.

In agreement with a structure such as II, the sodium salt of the tetracarboxylic acid shows no ultraviolet absorption maxima down to 210 mμ but does show "end-absorption" ($\epsilon_{220\ m\mu} \simeq 530$) much like that of the sodium salt of *endo-cis*-bicyclo-[2.2.2]-5-octene-2,3-dicarboxylic acid[5] (V) ($\epsilon_{220\ m\mu}$ 390). Angus and Bryce-Smith[2] report for the tetracarboxylic acid a weak absorption maximum at 265 mμ (ϵ 55). These workers observed that peracid titration of the tetramethyl ester indicated the presence of one ethylenic bond per molecule and, on the basis of this information and data rather similar to those given previously, suggested provisionally structure I for the adduct. They noted that structure I could reasonably be formed by 1,2-addition of one molecule of maleic anhydride to benzene to give VI followed by 1,4-addition of a second molecule of the anhydride to give I.



VI

We would note that VI could conceivably add a second molecule of maleic anhydride by 1,2-addition, rather than by 1,4-addition, to give III rather than I. Furthermore structures I, II and III can exist in many different stereochemical forms. Finally in view of the known complexity of some photochemical reactions, there is no certainty that the principle of minimum chemical change is not violated in the photochemical reactions leading to the benzene–maleic anhydride adduct. Obviously more detailed studies are necessary to decide between the many possibilities.

The nuclear magnetic resonance spectrum of the tetramethyl ester of the benzene adduct in deuteriochloroform shows the proton chemical shifts,[6] $\delta = 10^5 (H_r - H_c)/H_r$, measured relative to water at the relative intensities given in parentheses (expressed as number of hydrogen atoms): +0.16 (1.8); doublet at −0.13 (12.1); −0.195, −0.202, −0.24 (8.1). The first band is attributable to two ethylenic hydrogen atoms, though the absorption is nearer the value recorded[6] for tiglaldehyde or benzene than for cyclohexene. The band at −0.13 is in the region expected[6] for CH_3O and is of the correct intensity for four methoxyl groups; that this band is split into two bands of essentially equal intensity must mean that two of the methoxyl groups are in one type of environment and two are in an appreciably different environment (this cannot be ordinary spin–spin splitting because of the isolation of the hydrogen atoms of the carbomethoxyl groups from nearest neighboring hydrogen atoms by five or more intervening bonds). The last group of bands are not well resolved and appear near the region expected[7] for hydrogen on a carbon atom adjacent to a carbonyl or ethylenic group. It is significant that no absorption was found in the region expected for hydrogen on a cyclopropane ring.[4,8] The infrared spectrum of the adduct as the anhydride, the acid or the methyl ester contains no absorption in the 6.73–6.92 μ region (frequency of CH_2 deformations[9]), while a band appears at 6.80 μ in the hydrogenated acid.

Since the nuclear magnetic resonance absorption spectrum of the tetramethyl ester of the benzene adduct strongly indicates the presence of an olefinic bond and the absence of a cyclopropane ring, the chemical evidence was examined in greater detail. While the sodium salt of the tetracarboxylic acid does not decolorize $KMnO_4$ in 5 minutes at room temperature, some decolorization occurs within a half-hour. Similarly the tetracarboxylic acid in dilute hydrochloric acid solution slowly decolorizes bromine–water over a period of several hours. In sharp contrast, the sodium salt of the tetracarboxylic acid in aqueous solution reacts almost instantaneously with bromine to give, after acidification, a bromolactonic acid which after reaction with excess diazomethane was isolated as a methyl ester VII, m.p. 215–216°. This compound had a satisfactory analysis for carbon, hydrogen and bromine as calculated for the formula $C_{17}H_{19}BrO_8$ and therefore appears to be a trimethyl ester-bromolactone. This ester has infrared absorption at 5.63 and 5.80 μ near that expected,[10] respectively, for the carbonyl group of a γ-lactone and of a carbomethoxyl group. Moreover the sodium salt of the tetracarboxylic acid with aqueous I_2–KI solution absorbs in 72 hours at room temperature 9.7% or at 50° 70% of one mole of iodine per mole of acid. In comparative runs under similar conditions the sodium salt of *endo-cis*-bicyclo[2.2.2]5-octene-2,3-dicarboxylic acid[5] (V) immediately decolorizes aqueous $KMnO_4$ and absorbs 97% of one molar equivalent of iodine in 23 seconds at room temperature (*i.e.*, iodination occurs about a million times faster with the salt of V than with the salt of the benzene–maleic anhydride adduct). In conclusion, the chemical evidence shows that the benzene–maleic anhydride adduct has one rather highly hindered double bond. Structure II for the adduct therefore can be discarded on the basis of

---

[4] E. F. Ullman, *Chemistry & Industry*, 1173 (1958).

[5] K. Alder and G. Stein, *Ann.*, **514**, 15 (1934).

[6] L. H. Meyer, A. Saika and H. S. Gutowsky, *J. Am. Chem. Soc.*, **75**, 4567 (1953).

[7] K. L. Rinehart, Jr., W. A. Nilsson and H. A. Whaley, *ibid.*, **80**, 503 (1958).

[8] J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 236.

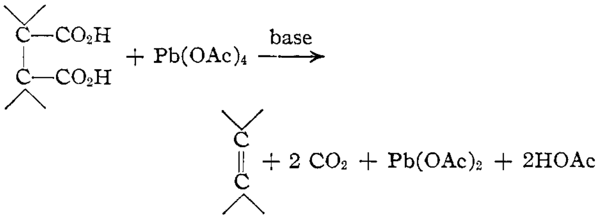
[9] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed., Methuen & Co., Ltd., London, 1958, p. 13.

[10] Reference 9, p. 179.

both the chemical data and the nuclear magnetic resonance absorption spectrum.

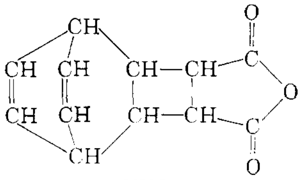
The tetramethyl ester of the adduct when heated at reflux in methanol containing a large excess of hydrazine gave a 85% yield of a product, m.p. 218–219° dec., which gave a fair analysis for a dihydrazide, $C_{16}H_{22}O_6N_4$. The dihydrazide when distilled at 0.01 mm. lost hydrazine and gave a cyclic hydrazide, m.p. 204.7–205.7°, which gave a good analysis for $C_{16}H_{18}O_6N_2$. The cyclic hydrazide when heated at reflux in methanol containing a large excess of hydrazine deposited crystals (87% yield) of the starting dihydrazide. As judged by the behavior of the tetramethyl ester with hydrazine, two of the carbomethoxyl groups are considerably more readily attacked by hydrazine than the other two, and these reactive carbomethoxyl groups must be part of the same maleic acid radical since the dihydrazide may be pyrolyzed to a cyclic hydrazide. The chemical evidence, therefore, supports the nuclear magnetic resonance absorption data in indicating that two of the carbomethoxyl groups of the tetramethyl ester are in an appreciably different environment from the other two carbomethoxyl groups. These data render structure III improbable in any of its likely stereochemical forms either because its double bond should be readily attacked by $KMnO_4$ or because it has two maleic anhydride radicals in equivalent positions. Of the structures for the benzene–maleic anhydride adduct which are in accord with the principle of minimum structural change, we are left with structure I as the most probable structure.

Much more conclusive evidence for the structure of the adduct has been provided by oxidation[11] of a pyridine solution of the tetracarboxylic acid or better the adduct anhydride itself with lead tetraacetate. Grob[12] and co-workers have reported that oxidation of several *cis*-1,2-dicarboxylic acids in the presence of one to two molar equivalents of a base such as pyridine in benzene or acetonitrile as solvent gave 50–70% yield of olefin in accord with the process

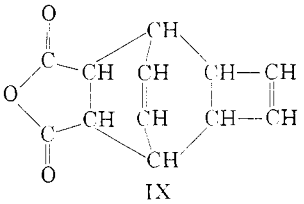


$$>C(CO_2H)-C(CO_2H)< + Pb(OAc)_4 \xrightarrow{\text{base}} >C{=}C< + 2\,CO_2 + Pb(OAc)_2 + 2HOAc$$

From oxidation of the benzene–maleic anhydride adduct with lead tetraacetate in pyridine at 50 to 62°, 56% yield was obtained of a product of m.p. 167–168.7° which had satisfactory analysis for $C_{12}H_{10}O_3$. The same product, but in lower yield, was obtained by oxidation of the tetracarboxylic acid. During the lead tetraacetate oxidation, therefore, only one of the two maleic anhydride radicals of the adduct was oxidized. On the basis of structure I for the adduct, the lead tetraacetate oxidation could give either VIII or IX for the product of composition $C_{12}H_{10}O_3$. Structure IX can exist in four stereochemical forms (involving *cis* fusion of the four- and five-membered rings to the [2.2.2]bicyclooöctene system); one of these forms corresponds to the known[13] maleic anhydride adduct of cyclooctatetraene. It is remarkable, therefore, that the product $C_{12}H_{10}O_3$ from lead tetraacetate oxidation of the benzene–maleic anhydride adduct was found to be identical (mixed m.p. and infrared spectral comparisons) with the maleic anhydride adduct of cyclooctatetraene. This evidence conclusively establishes the structure of the benzene–maleic anhydride adduct as I in agreement with the brilliant provisional suggestions of Angus and Bryce-Smith.[2] There remains unanswered the question of the stereochemical structure of the photochemical adduct.

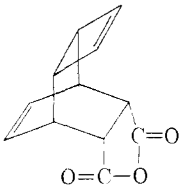


VIII

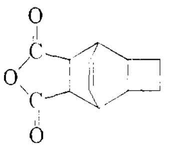


IX

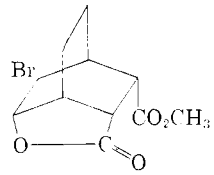
Structure I can exist in eight possible stereoisomeric forms with *cis* fusion of the maleic anhydride groups. A key to the stereochemical form of the benzene–maleic anhydride adduct is found in the stereochemistry of the cyclooctatetraene–maleic anhydride adduct IX. Reppe[13a] and co-workers reported that this adduct gives a bromolactonic acid; therefore, the carboxyl groups of the adduct must be located in close proximity to one of the double bonds of the adduct. These workers have proposed that the cyclooctatetraene–maleic anhydride adduct has the stereochemical formula X and, therefore, that bromolactone formation involves attack of bromine on the double bond in the six-membered ring to give a γ-lactone. Cope[14] and co-workers have proved that hydrogenation of the cyclooctatetraene–maleic anhydride adduct under mild conditions adds a mole of hydrogen to the double bond of the four-membered ring to give XI rather than to the double bond of the six-membered ring as previously supposed.[13a] Hence



X



XI



XII

---

[11] We are indebted to Mr. Gary G. Hammer and Dr. Leon H. Zalkow for pointing out to us the method of Grob and co-workers and to Dr. Jack Hine for suggesting the use of pyridine as a solvent for this reaction.

[12] C. A. Grob, M. Ohta and A. Weiss, *Angew. Chem.*, **70**, 343 (1958).

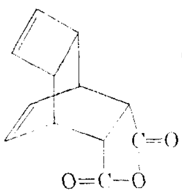
[13] (a) W. Reppe, O. Schlichting, K. Klager and T. Toeppel, *Ann.*, **560**, 1 (1948); (b) A. C. Cope and C. G. Overberger, *J. Am. Chem. Soc.*, **70**, 1433 (1948).

[14] A. C. Cope, A. C. Haven, Jr., F. L. Ramp and E. R. Trumbull, *ibid.*, **74**, 4867 (1952).

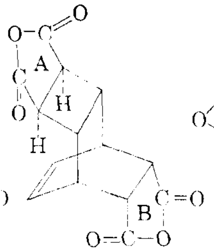
Cope, *et al.*, have pointed out that bromolactone formation may involve addition of bromine to the double bond of the four-membered ring; if this is the case, the bromolactone of IX is a δ-lactone. To distinguish between these possibilities we have examined the infrared absorption spectrum of the monomethyl ester[13a] of the bromolactone of IX. This compound has carbonyl absorption at 5.69 and 5.76 μ. The first value agrees somewhat more closely with the absorption expected[10] for a γ-lactone (5.62–5.68 μ) than that for a δ-lactone (5.71–5.76 μ), while the second value corresponds to the value expected for the carbonyl groups of an ester. We find that the bromolactonic ester XII of *endo-cis*-bicyclo[2.2.2]-5-octene-2,3-dicarboxylic acid[5] (V) has carbonyl absorption at 5.69 and 5.79 μ; hence γ-lactones in polycyclic systems may give carbonyl absorption at 5.69 μ as found for the cycloöctatetraene adduct.

To provide more conclusive proof of the stereochemistry of IX, the reaction of the dihydro derivative XI with bromine has been investigated. Of the four possible stereoisomers of IX with *cis* orientation of the carbonyl groups, it may be seen that the carbonyl groups of the corresponding acid may be oriented near one or the other or none of the double bonds but cannot be oriented for a particular isomer such that bromolactone formation can take place with either double bond. Hence one method for determining which double bond is oriented near to the carbonyl groups is to remove one double bond by hydrogenation and see if the corresponding dihydro derivative can form a bromolactone. Cope and co-workers evidently had this strategy in mind when they reported[14] that dihydro derivative XI "does not react readily with bromine," but did not specify the conditions tried. Because of our previous experience in bromination of the benzene–maleic anhydride adduct (see earlier discussion), we were led to reinvestigate the bromination of XI. While XI did not decolorize a solution of bromine in CCl_4 or acetic acid in 3 hours the potassium salt of XI in water reacted almost instantaneously with one molar equivalent of bromine to give a good yield of a crystalline product of m.p. 243–244° dec., which had the expected composition for a bromolactonic acid, $C_{12}H_{13}O_4Br$. The corresponding crystalline monomethyl ester, $C_{13}H_{15}O_4Br$, had carbonyl absorption at 5.65 and 5.77 μ as expected for the methyl ester of a γ-lactone. Hence the carbonyl groups of IX are oriented near the double bond in the six-membered ring rather than near the double bond of the four-membered ring. Thus structure X of Reppe, *et al.*,[13a] is correct in so far as this particular structural detail is concerned.

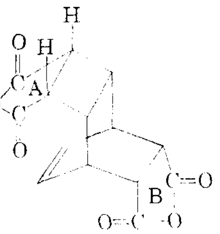
There was never, however, any compelling evidence for the steric orientation of the four-membered ring of X relative to the cyclohexene ring. Structure XIII would appear to be equally probable and has been written by Abel, Bennett and Wilkinson.[15] These workers have found that the cycloöctatetraene–maleic anhydride adduct forms a crystalline rhodium(I) chloride complex which is believed to involve chelation by the diolefin group to one rhodium atom. The two double bonds in the cycloöctatetraene–maleic anhydride adduct are, therefore, almost certainly oriented as in XIII especially since bicyclo[2.2.1]heptadiene (norbornadiene) forms a similar rhodium(I) chloride complex.[15]



XIII



XIV



XV

If no changes in steric orientation of groups occur during the oxidation of the benzene–maleic anhydride adduct I by lead tetraacetate to give XIII, then only structures XIV and XV need be considered for the photochemical adduct. No changes in stereochemistry are expected to occur during the lead tetraacetate oxidation because of the mild conditions of the reaction and the speed of the oxidative decarboxylation. These expectations appear to be confirmed since the tetracarboxylic acid of I gave XIII as the only insoluble acidic product while at least some of the *trans*-acid[13a] would have been expected if any isomerization had occurred at the centers bearing the carboxyl groups. Furthermore the photochemical adduct I gave a bromo-γ-lactone and hence one acid anhydride group in I must be oriented as in XIII. Of the two structures XIV and XV, structure XIV appears much more probable than XV. The location of anhydride group A as in XIV rather than as XV is implied from the observations: (1) hydrazine readily attacks only two adjacent carbomethoxyl groups of the corresponding tetramethyl ester, (2) lead tetraacetate oxidation removes the two carbonyl groups of anhydride group A and hence these are implicated as the less hindered carbonyl groups, (3) the alternative location of the carbonyl groups A as in XX would place these groups very close to the double bonds and models indicate that the carbonyl groups A would then be more hindered than the carbonyl groups B, (4) bromolactone formation gives a γ-lactone as expected from XIV while a δ-lactone might be expected from XV.

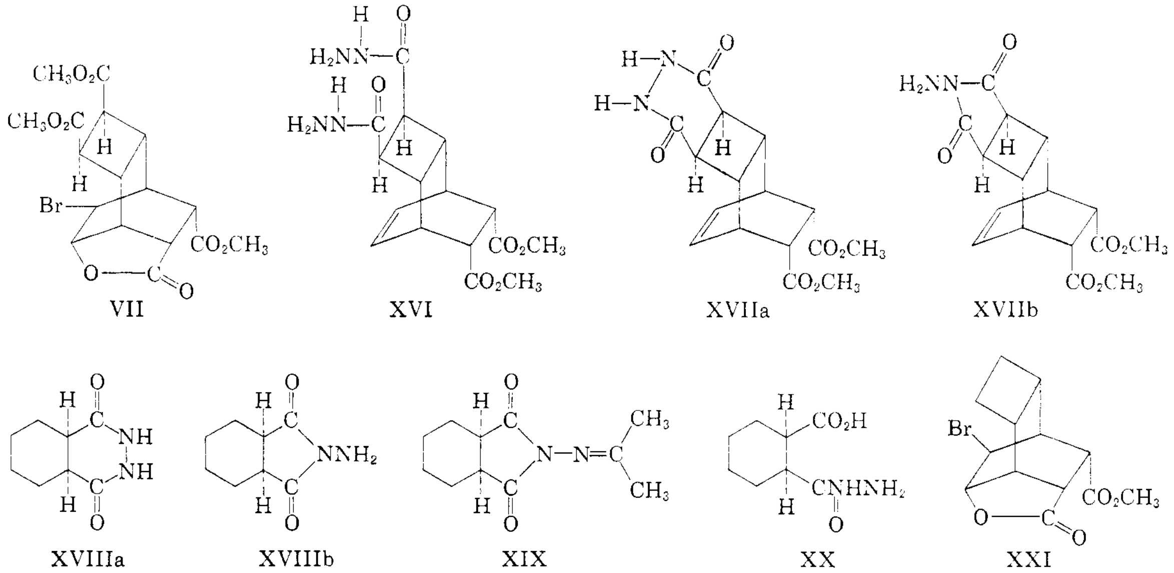
In conclusion, structure XIV is assigned as the probable stereochemical structure of the photochemical adduct of benzene with maleic anhydride. This structure contains a double bond which is hindered on either side from the approach of external reagents. Structure XIV, therefore, accounts for the remarkable unreactivity of the double bond toward permanganate and halogens. The structures of some of the other compounds prepared in the present work are summarized in Chart 1 and certain of these structural assignments are discussed in the Experimental Details.

NOTE ADDED IN PROOF.—The details of the work of Angus and Bryce-Smith have now appeared [*J. Chem. Soc.*, 4791 (1960)]. These authors have suggested stereochemical structure XV for the benzene-maleic anhydride adduct on the basis of the usual stereochemistry of Diels–

---

[15] E. W. Abel, M. A. Bennett and G. Wilkinson, *J. Chem. Soc.*, 3178 (1959).

CHART I



VII XVI XVIIa XVIIb

XVIIIa XVIIIb XIX XX XXI

Alder reactions and in order to account for the ultraviolet absorption which they observed. We, however, have been unable to observe absorption of highly purified samples of the tetracarboxylic acid of the benzene–maleic anhydride adduct at the position and intensity reported (λ_{max} 265 mμ, $\epsilon = 55$); at this wave length we find for the acid in water $\epsilon < 5$.

Confirmation of stereochemical structure XIII for the cycloöctatetraene–maleic anhydride adduct is supplied by the report that *both* double bonds of the adduct participate in electrophilic additions such as bromolactone formation [R. C. Cookson, J. Hudec and J. Marsden, *Chemistry & Industry*, **23** (1961)]. While we did not consider the possibility of participation of both double bonds in bromolactone formation, our basic arguments for the stereochemistry of the cycloöctatetraene–maleic anhydride adduct remain unchanged. We wish to thank Dr. Bryce-Smith for calling this reference to our attention.

Experimental Details[16]

Benzene–Maleic Anhydride Adduct (XIV).—Maleic anhydride (10.0 g., 0.102 mole) was dissolved in 300 ml. of thiophene-free benzene. The solution was placed in a water-cooled quartz cell which encircled a 1000-watt Hanovia mercury-arc lamp.[17] The solution was irradiated for 16 hours. During this time white crystals precipitated on the walls of the cell. The precipitate of XIV was separated by filtration and washed with three 25-ml. portions of boiling benzene. The yield of XIV was 1.90 g. or 13.6% of product, m.p. 355–357° dec.

For larger scale preparations 118 g. (1.20 moles) of freshly distilled maleic anhydride was dissolved in 100 ml. of acetone (which had been purified by distillation from $KMnO_4$) and 125 ml. (1.4 moles) of thiophene-free benzene was added. The solution after irradiation in the apparatus described above for 25 hours deposited 10.5 g. of adduct which was separated by filtration. Another 6.5 g. of adduct was recovered by evaporation of the solvent, boiling the residue with about 200 ml. of acetone to dissolve unreacted maleic anhydride, and separation of the adduct by filtration. The yield of product (17.0 g.) was 10.3%. In similar runs with 120 g. of maleic anhydride and an irradiation time of 48 hours, 16.0 to 18.0 g. of adduct deposited in the cell but only some 1.5 g. of additional adduct was recoverable from the reaction solution.

The adduct when thoroughly washed with hot benzene or acetone did not decolorize dilute solutions of $KMnO_4$ in acetone; however, maleic anhydride readily decolorizes such $KMnO_4$ solutions and thus the permanganate test is a convenient test for the purity of the adduct from the present preparations. The adduct sublimed slowly at 0.015 mm. and a bath temperature of 240–250° to give a product of m.p. 355–357° dec., while at higher temperatures a brown product was obtained.

Anal. Found: C, 61.24, 61.37; H, 3.64, 3.74; sapon. equiv., 68.4. Calcd. for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68; sapon. equiv. for tetrabasic acid anhydride, 68.55.

Tetramethyl Ester of XIV.—The benzene–maleic anhydride adduct (1.80 g.) was esterified by boiling under reflux with anhydrous methanol (100 ml.), which was 0.078 *M* in anhydrous hydrogen chloride, for 6 hours. The solution was concentrated to 20 ml. and, on cooling, 1.58 g. of white crystals, m.p. 130–132°, precipitated. Recrystallization three times from anhydrous methanol gave methyl ester, m.p. 134.5–135.0°. This product sublimed readily at a bath temperature of 200° and a pressure of 0.015 mm.

Anal. Found: C, 58.82, 58.91; H, 5.88, 5.89; mol. wt., 366 (det. in camphor, with triphenylmethane used to determine the melting-point depression constant). Calcd. for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05; mol. wt., 366.4.

The tetracarboxylic acid of XIV (see below) upon esterification with methanolic hydrogen chloride by a rather similar procedure gave a methyl ester of m.p. 133.0–133.4° which showed no m.p. depression with the methyl ester prepared from the anhydride and, moreover, had an identical infrared absorption spectrum.

Tetracarboxylic Acid of XIV.—The benzene–maleic anhydride adduct (25.5 g., 0.0929 mole) was heated at reflux with 254 ml. of 1.46 *M* aqueous KOH (0.372 mole) with occasional shaking for 5 hours. The solution was cooled and filtered to remove a small amount of suspended solid. The solution upon acidification with hydrochloric acid yielded a fine crystalline precipitate. The precipitate was separated and recrystallized from water to give 20.0 g. of crystals. After two additional crystallizations from water, the product showed decomposition at 125–200° ($-H_2O$) and finally melted at 350–353° dec. The analytical sample was recrystallized two more times from water and had m.p. 356–357° dec. with previous loss of water near 120°.

Anal. Found: C, 54.46, 54.69; H, 4.16, 4.21. Calcd. for $C_{14}H_{14}O_8$: C, 54.20; H, 4.55.

The tetracarboxylic acid (0.553 g.) in 80 ml. of glacial acetic acid was hydrogenated at room temperature over 0.49 g. of a 5% Pt-on-charcoal catalyst. After 24 hours the sample had absorbed 36.9 ml. (S.T.P.) of hydrogen or 0.925 mole of hydrogen per mole of acid taken. No more hydrogen was absorbed in an additional 72 hours. An analysis of the particular sample of tetracarboxylic acid taken gave: C, 49.99; H, 4.38; ash, 7.4. After correction for ash, the analytical data became: C, 53.98; H, 4.73; 1.00 mole of hydrogen absorbed per mole of acid.

---

[16] All melting points are corrected. Analyses are by Clark and Galbraith Microchemical Laboratories.

[17] For a more detailed description of the apparatus see E. Grovenstein, Jr., and S. P. Theophilou, *J. Am. Chem. Soc.*, **77**, 3795 (1955).

From the hydrogenation mixture an acid of m.p. 295–297° dec. was isolated; this dihydro acid was considerably more soluble in acetic acid than the starting acid and was converted into an acid anhydride upon heating with acetic anhydride.

Bromolactone Trimethyl Ester (VII) of XIV.—The tetracarboxylic acid of XIV, 1.52 g. or 4.9 mmoles, was dissolved in about 20 ml. of aqueous sodium hydroxide and the excess of base was neutralized with hydrochloric acid to *p*H 9. Bromine was added slowly with shaking until a pale yellow color of bromine remained (0.24 ± 0.02 ml. of bromine added or some 4.7 mmoles). The bromine color was almost instantaneously discharged at first, but near the end of the addition the color remained a short while. The solution was acidified with 10 ml. of concentrated hydrochloric acid and evaporated to dryness in the steam-bath. The residue was ground up and extracted several times with, in all, 55 ml. of tetrahydrofuran. A solution of diazomethane in ether was added to the tetrahydrofuran solution until a yellow color persisted. Evaporation of the solvents gave white crystals which were partially dissolved by 125 ml. of hot methanol. Filtration of the cooled solution gave 1.07 g. of white crystals, m.p. 211–215°. After two crystallizations from benzene the product had m.p. 215.0–216.3.

Anal. Found: C, 47.11, 47.19; H, 4.35, 4.41; Br, 18.52, 18.59. Calcd. for $C_{17}H_{19}BrO_8$: C, 47.34; H, 4.44; Br, 18.53.

Iodolactone Formation by XIV and V.—The sodium salts of the anhydrides of XIV and V were prepared by heating the anhydride with some 30% excess sodium hydroxide solution and back-titration with hydrochloric acid almost to the disappearance of the color of phenolphthalein. For iodolactone formation one volume of the sodium salt of XIV or V was mixed with an equal volume of iodine-potassium iodide solution to give an initial solution which was 0.018 *M* in the salt of XIV or V, 0.025 *M* in iodine and 0.137 *M* in sodium iodide. For measurement of the consumption of iodine, slow iodinations were acidified with acetic acid and titrated with thiosulfate to a starch end-point, while fast reactions were made strongly acidic with hydrochloric acid before titration of unreacted iodine.

Reaction of Tetramethyl Ester of XIV with Hydrazine.—The tetramethyl ester of XIV (2.00 g.) was heated at reflux with 5.0 ml. of 98% hydrazine in 25 ml. of methanol for 2 hours. A white precipitate separated during the reaction and after separation by filtration from the cold reaction mixture amounted to 1.70 g. (85% yield) of compound, m.p. 218–219° dec. This compound XVI appears to be a dihydrazide dimethyl ester of XIV and was found to be identical (mixed m.p. and infrared spectral comparisons) with the compound of similar m.p. prepared below by reaction of hydrazine with the cyclic hydrazide XVII. Compound XVI was soluble in water and acetic acid but was essentially insoluble in solvents such as benzene and methyl alcohol. Since attempts to recrystallize XVI from common solvents were unsuccessful, a 1.3-g. sample of XVI was subjected to vacuum sublimation at 0.01 mm. and a bath temperature of 270°. Sublimation was complete in 0.5 hr. The sublimate was taken up in 25 ml. of hot methanol. The solution was filtered to remove a small amount of insoluble material and on cooling deposited white crystals. After two recrystallizations from methanol the product amounted to 1.0 g. of material, m.p. 202.7–203.7°. The analytical sample was recrystallized two more times from methanol and sublimed four times (at 240° and 0.01 mm.) to give cyclic hydrazide XVII (structure XVIIa or XVIIb), m.p. 204.7–205.7°.

Anal. Found: C, 57.65; H, 5.55; N, 8.32. Calcd. for $C_{16}H_{18}O_6N_2$: C, 57.48; H, 5.43; N, 8.38.

Compound XVII (0.50 g.) was dissolved in 25 ml. of methanol. To the solution was added 2.0 ml. of 98% hydrazine and the mixture was heated at reflux for 1.5 hr. during which time a white precipitate appeared. Filtration of the cooled solution gave 0.48 g. (87% yield) of white crystals of XVI, m.p. 218–219° dec.[18]

Anal. Found: C, 51.80; H, 6.01; N, 15.36. Calcd. for $C_{16}H_{22}O_6N_4$: C, 52.45; H, 6.05; N, 15.29.

The tetramethyl ester of XIV (2.0 g.) was heated at reflux with 5.0 ml. of 98% hydrazine for 15 min. Methanol (20 ml.) was added and the reaction mixture was heated at reflux for 3 hr. The dull white solid which separated amounted to 1.6 g. The product was boiled with 10 ml. of absolute methanol and on separation by filtration was a pure white solid, m.p. 211–213° dec. The material did not sublime or distil at temperatures up to 300° at 0.015 mm. and may therefore be a polymer. The product had almost as much nitrogen as expected for the tetrahydrazide of XIV.

Anal. Found: N, 28.30. Calcd. for $C_{15}H_{22}O_5N_6$: N, 22.94. Calcd. for $C_{14}H_{22}O_4N_8$: N, 30.59.

The reaction of the dimethyl ester of *cis*-hexahydrophthalic acid with hydrazine was studied as a model to aid in understanding the reactions of the tetramethyl ester of XIV with hydrazine.

Cyclic Hydrazide XVIII of *cis*-Cyclohexane-1,2-dicarboxylic Acid.—Dimethyl *cis*-cyclohexane-1,2-dicarboxylate (5.0 g.) was heated with 5.0 ml. of 98% hydrazine at reflux for 15 min. Just enough methanol was added to give a homogeneous solution and the mixture was heated at reflux for 1 hour. Concentration of the solution gave a crystalline product which, after one recrystallization from 85% methanol, amounted to 4.8 g. of dihydrazide, m.p. 229–230° dec. (recorded: *trans*,[18a] 229–231°; *cis*,[18a] 123–124.5° and then 228.5–229.5°; unspecified isomer,[18b] 245°). The dihydrazide (45 g.) from a similar large-scale preparation was pyrolyzed at a bath temperature of 280–290° and a pressure of 20 mm. to give distillate of b.p. 220–230° at 20 mm. The distillate (30 g.) solidified on cooling and had m.p. 55–60°. A second distillation gave a colorless product, b.p. 152–160° at 0.5 mm., m.p. 60–63°. Redistillation through a short fractionating column gave cyclic hydrazide XVIII, m.p. 60.4–62.9°.

Anal. Found: C, 57.42; H, 7.02; N, 16.42. Calcd. for $C_8H_{12}O_2N_2$: C, 57.13; H, 7.19; N, 16.66.

The cyclic hydrazide XVIII (3.0 g.) was dissolved in 30 ml. of concentrated hydrochloric acid and the mixture heated at reflux for 15 minutes. The solid which precipitated was separated by filtration of the cool solution and was washed with water. The product (2.6 g.) had m.p. 187.3–188.7° as expected for *cis*-cyclohexanedicarboxylic acid (recorded[18a] m.p. 189.5–190.5°). Similar treatment of our starting dihydrazide of cyclohexane-1,2-dicarboxylic acid (3.0 g.) with 30 ml. of concentrated hydrochloric at reflux for 30 minutes gave 1.3 g. of product, m.p. 182–204°. This product upon sodium fusion gave a negative test for nitrogen and halogen and thus appears to be a mixture of *cis*- and *trans*-cyclohexane-1,2-dicarboxylic acids.

For an attempted purification by recrystallization, XVIII was dissolved in a minimum amount of acetone and two volumes of *n*-hexane was added. The mixture was heated on a steam-bath and the supernatant hexane layer was separated. Two similar hexane extractions were made and from the combined hexane extracts crystals in the form of needles were obtained on cooling. These after another similar crystallization from acetone–*n*-hexane had m.p. 124.0–125.5° (with previous sintering at 120°).

Anal. Found: C, 63.89; H, 7.98; N, 13.12. Calcd. for $C_{11}H_{16}O_2N_2$: C, 63.44; H, 7.74; N, 13.45.

This product has an analysis corresponding to that of an isopropylidene derivative of XVIII. The only likely structure for the isopropylidene derivative appears to be XIX. The ready formation of XIX from XVIII suggests that XVIII has structure XVIIIb rather than the isomeric structure XVIIIa. However, since Drew and Hatt[19] have shown that the more stable phthalhydrazide gives the same benzylidine derivative as the less stable N-aminophthalimide though under more vigorous conditions, the reaction of XVIII with acetone cannot be regarded as affording proof of structure XVIIIb.

The potentiometric titration of succinhydrazide as a monobasic acid has been cited[20] as evidence in favor of the

---

(18) (a) V. G. Iashunskii, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*), **28**, 1420 (1958); (b) H. Wieland, O. Schlichting, W. v. Langsdorff, *Z. physiol. Chem., Hoppe-Seyler's*, **161**, 78 (1926). The m.p. of our dihydrazide of cyclohexane-1,2-dicarboxylic acid was variable with the rate of heating. At a fast rate of heating the m.p. was some 15° higher than the value reported above. Similar observations were made with respect to the m.p. of dihydrazide XVI.

(19) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).

(20) H. Feuer, G. B. Bachman and E. H. White, *J. Am. Chem. Soc.*, **73**, 4716 (1951).

hydrazide structure as opposed to the N-aminosuccinimide structure. We find that XVIII, when dissolved in excess sodium hydroxide and back-titrated potentiometrically with hydrochloric acid, gives a neutralization equivalent of 172 (theory for monobasic acid $C_8H_{12}O_2N_2$, 168). The direct titration of XVIII with sodium hydroxide is difficult since XVIII combines rather slowly with the base and our titrimetric data indicate that XVIII undergoes hydrolysis to give the salt of XX under the conditions of the titration. Since either XVIIIa or XVIIIb might be expected to undergo ready hydrolysis to XX, the titration is also unable to distinguish between the two likely structures for XVIII.

Oxidation of XIV with Lead Tetraacetate.—The anhydride XIV (5.0 g., 0.0182 mole) was dissolved in 200 ml. of hot pyridine (which had been dried over KOH pellets and freshly distilled). Lead tetraacetate (9.0 g., 0.020 mole) was added and the pyridine solution was maintained at 70–80° for 1 hour. During the first 5 minutes of reaction there was a vigorous evolution of carbon dioxide. The solvent was removed *in vacuo* with aid of a steam-bath. The dark brown residue was acidified with hydrochloric acid and extracted with ether three times. The ethereal extracts were combined, washed with water twice and dried over anhydrous $MgSO_4$. After removal of the ether, 1.5 g. of crystalline product was obtained. This was sublimed at 0.025 mm. at a bath temperature of 170° to give 1.45 g. (39.5% yield) of crystalline sublimate. After two recrystallizations from chlorobenzene the product XIII had m.p. 166.9–168.7°.

Anal. Found: C, 70.89, 70.92; H, 4.80, 4.95. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98.

A sample of the maleic anhydride addition product of cycloöctatetraene was prepared[13] by heating maleic anhydride with cycloöctatetraene under a nitrogen atmosphere at a bath temperature of 180° for 30 min. The product after sublimation *in vacuo* and recrystallization from chlorobenzene had m.p. 167.3–168.7° and gave no depression of m.p. when mixed with the product from the lead tetraacetate oxidation. Likewise the two products had identical infrared spectra.

A higher yield was obtained from reaction of 2.40 g. (0.00875 mole) of the anhydride XIV with 5.8 g. (0.013 mole) of lead tetraacetate in 85 ml. of pyridine maintained at 50–60° for 1 hour. The reaction mixture after standing overnight was worked up as previously. After one sublimation *in vacuo*, the product amounted to 1.00 g. (56% yield) of material, m.p. 166.6–168.3°. A similar oxidation with lead tetraacetate in which 2 moles of lead tetraacetate was used per mole of anhydride gave only 34% yield of XIII.

Oxidation of the tetracarboxylic acid of XIV with lead tetraacetate was hindered, at least in part, by the low solubility of the acid in pyridine. Tetracarboxylic acid (5.0 g., 0.0161 mole) did not dissolve very completely in 150 ml. of boiling pyridine. To the mixture at 95–100° was added 10.0 g. (0.023 mole) of lead tetraacetate and the reaction mixture was kept at this temperature for 1 hour. The reaction was worked up as with the anhydride. From the ether extracts 0.50 g. of crude product was obtained. After one recrystallization from methanol the product amounted to 0.35 g. of material, m.p. 160–161.5°. Another recrystallization from methanol gave a product XIII of m.p. 167.1–167.9° which was identical with the maleic anhydride adduct of cyclooctatetraene (mixed m.p. and infrared spectral comparisons).

Bromolactone of XI.—The dihydro derivative[14] of the maleic anhydride adduct of cycloöctatetraene (XI) (2.00 g., 0.0098 mole, m.p. 142.5–143.5°) was dissolved in a warm solution of 3 g. of KOH in 50 ml. of water and the solution was filtered to remove a trace of suspended material. The solution was neutralized to a phenolphthalein end-point with hydrochloric acid and bromine was added dropwise with shaking. The color of bromine disappeared rapidly during addition of 0.45 ml. (8.8 mmoles), but a permanent yellow color remained after addition of 0.05 ml. (1.0 mmole) more bromine. Acidification gave a precipitate which after separation by filtration and recrystallization from 95% ethanol amounted to 2.50 g. (85% yield) of bromolactonic acid, m.p. 243.3–243.8° dec.

Anal. Found: C, 47.73, 47.81; H, 4.52, 4.40; Br, 26.61. Calcd. for $C_{12}H_{13}O_4Br$: C, 47.86; H, 4.35; Br, 26.54.

The bromolactonic acid was dissolved in tetrahydrofuran and a solution of diazomethane in ethyl ether was added until a pale yellow color persisted. The solvents were removed by evaporation and the resulting crystalline residue was recrystallized twice from methanol to give methyl ester XXI, m.p. 166.9–167.9°.

Anal. Found: C, 49.45, 49.63; H, 4.80, 4.96; Br, 25.25. Calcd. for $C_{13}H_{15}O_4Br$: C, 49.54; H, 4.80; Br, 25.35.

Spectra.—Infrared spectra were run with samples in potassium bromide disks on a Perkin–Elmer model 21 infrared spectrometer with rock-salt prisms. Ultraviolet spectra were determined on a Beckman model DK-1 quartz spectrophotometer. The nuclear magnetic resonance absorption spectrum was determined on a Varian frequency R-F unit model V4310C with frequency of 40 megacycles and a field of 10,000 gauss. The tetramethyl ester of XIV (0.1 g.) was dissolved in 0.3 ml. of $DCCl_3$ and the chemical shifts were determined relative to $HCCl_3$ which was contained within an inner concentric tube. For calculations of chemical shifts relative to water, chloroform was taken to have a chemical shift of 96 cycles/sec. at 40 Mc.

Acknowledgment.—We are indebted to Dr. Leon Mandell for the nuclear magnetic resonance spectrum.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, THE UNIVERSITY OF CALIFORNIA, BERKELEY, CALIFORNIA]

The Synthesis and Properties of D-*glycero*-Tetrulose 1-Phosphate and 4-Phosphate (D-Erythrulose 1-Phosphate and 4-Phosphate)

BY NING-JO CHÜ AND CLINTON E. BALLOU

RECEIVED NOVEMBER 4, 1960

The synthesis of two phosphate monoesters of a keto-tetrose is described. These are D-*glycero*-tetrulose 1-phosphate and D-*glycero*-tetrulose 4-phosphate, the common names being D-erythrulose 1-phosphate and D-erythrulose 4-phosphate. The compounds were obtained as stable dimethyl ketals, which by mild acid hydrolysis yield the free ketoses. The degradation of the tetrulose phosphates by acid and alkali followed the pattern previously observed for the triose phosphates. D-*glycero*-Tetrulose 1-phosphate acts as a substrate for the enzyme *glycerol phosphate dehydrogenase* and is reduced to D-erythritol 1-phosphate. This product is consistent with the specificity of the action of the enzyme on its normal substrate dihydroxyacetone phosphate.

At present, information concerning the possible metabolic role of keto-tetroses is meager. L-Glycero-tetrulose (L-erythrulose) has been shown to be formed and cleaved in systems involving the enzyme transketolase,[1] and it is also metabolized by rat-liver slices.[2] Glycero-tetrulose 1-phosphate has been obtained by the action of a

---

[1] B. L. Horecker, P. Z. Smyrniotis and H. Klenow, *J. Biol. Chem.*, **205**, 661 (1953); J. Hickman and G. Ashwell, *ibid.*, **234**, 758 (1959); F. Dickens and D. H. Williams, *Nature*, **178**, 1349 (1956); A. G. Datta and E. Racker, *Arch. Biochem. Biophys.*, **82**, 489 (1959).

[2] R. D. Batt, F. Dickens and D. H. Williams, *Biochem. J.*, **74**, 10P (1960).