calculated ΔF of alcohol stability of 0.25 kcal./mole.[26] In view of the errors inherent in the estimations of ΔF and the neglect of any special factors like variable inductive effects, this is a surprisingly good fit and it supports the idea of relating alcohol stability to oxidation rate.

To the extent that relations like Fig. 1 are general for epimeric alcohols it is possible to estimate the composition of equilibrated epimeric alcohol mixtures from the oxidation rates of the pure alcohols.[27] Thus, if the oxidation rates of the four bicyclic alcohols are converted into alcohol stability ratios, it is calculated, using 0.74 as the factor for approach to energetic equivalence, that *at 30°* equilibrated norborneol mixtures would contain 22% *endo*-norborneol (20% observed at 100°) and equilibrated borneol mixtures would contain 71% borneol (71% observed at 100°).

Experimental

***d,l*-Borneol.**—*d,l*-Borneol (Aldrich) was crystallized twice from pentane [m.p. (sealed tube) 194–195.5°]. Gas chromatographic analyses indicated that it was a mixture of 79% borneol and 21% isoborneol.

***d,l*-Isoborneol.**—A solution of 25 g. (0.165 mole) of camphor in 85 ml. of anhydrous ether was added over a period of 1 hr. to a stirred, refluxing suspension of 7.5 g. (0.198 mole) of lithium aluminum hydride in 330 ml. of ether. The mixture was heated under reflux for 16 hr., then dilute hydrochloric acid was added until all of the solid dissolved. The ether layer was separated, dried over anhydrous magnesium sulfate, and evaporated. The resulting solid was crystallized twice from pentane to give 20 g. (80%) [m.p. (sealed tube) 192–194°] of a mixture of borneol and isoborneol. Gas chromatographic analysis indicated that the mixture was 11% borneol and 89% isoborneol.

***endo*-Norborneol.**—*endo*-Norborneol was prepared by lithium aluminum hydride reduction at −5 to 0° of norcamphor (Aldrich). The product was purified by sublimation and analysis by gas chromatography indicated that it contained 91% *endo*-norborneol and 9% *exo*-norborneol, m.p. (sealed capillary) 145–146°.

***exo*-Norborneol.**—The procedure of Schmerling[28] was followed to obtain *exo*-norborneol formate in 85% yield. To 30 g. (0.53 mole) of potassium hydroxide dissolved in 100 ml. of ethanol (95%) was added 38 g. (0.25 mole) of *exo*-norbornyl formate. The mixture was heated under reflux for 3 hr., cooled, and water added. The resulting oily layer was separated, diluted with ether and the ether solution concentrated until a solid separated. The solid was recrystallized at 0° from pentane and then sublimed to give 19 g. (67%) [m.p. (sealed capillary) 126–126.5°] of a solid that contained by gas chromatographic analysis 96% *exo*-norborneol and 4% *endo*-norborneol.

Gas Chromatographic Analysis.[3]—A 10-ft. column of 18% UCON H-B 2000 (a water-soluble monoalkyl ether of a mixed polyoxyethylene-oxy-propylene) on a support of Celite (30–60 mesh) was used to resolve the norborneols. Although this column did not give complete resolution, excellent agreement was obtained for a synthetic mixture of *exo*- and *endo*-norborneol. A mixture consisting of 0.0482 g. of 4% *endo*-norborneol and 96% *exo*-norborneol and 0.0458 g. of 91% *endo*-norborneol and 9% *exo*-norborneol analyzed for 54% *exo*-norborneol and 46% *endo*-norborneol, which is identical to the theoretical composition.

A 10-ft. commercial column of 20% LAC-446 (the adipate polyester of diethylene glycol partially cross-linked with pentaerythritol) on a support of Sil-o-cel C-22 diatomaceous earth firebrick (30–60 mesh) gave good resolution of the borneols.

Equilibration Experiments.[3]—Sealed test tubes were prepared that contained 0.3 g. (0.0015 mole) of aluminum isopropoxide, 0.005 ml. of acetone, 2 ml. of isopropyl alcohol, and 0.1 g. of the compound to be equilibrated. After the compound had been equilibrated for the indicated time the tube was chilled, and the contents dissolved in the minimum amount of cold 3 *M* hydrochloric acid. This solution was extracted three times with 5 ml. of ethyl ether. The ether layers were washed with a saturated sodium bicarbonate solution, water, and dried over anhydrous magnesium sulfate. The ether layer was condensed and used directly for the analysis. Control experiments on the known mixtures showed no change in composition after they were put through this treatment. The experiments did indicate the importance of using several extractions.

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[26] Also shown in Fig. 1 but not included in the calculation of the slope are the points for the 7α- and 7β-cholestanols and the 11α- and 11β-hydroxyallopregnanediones (3, 20).[17] The relative stabilities of the 7-epimers were estimated by taking the interactions with the C-17 CH_2 group to be one half of what they would have been if the D-ring had been six-membered. The 11-hydroxyallopreganediones were calculated as with the other epimers. The 11α-isomers deviate markedly (*ca.* 4 × the average deviation).

[27] One obvious restriction is that the epimers must react by the same mechanism. Most of the epimeric 1,2-diols discussed by Kwart[16] would fail.

[28] L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Am. Chem. Soc.*, **78**, 2819 (1956).

Rearrangement Accompanying the Permanganate Oxidation of Ethyl *cis*-2,2,4,4-Tetracarbethoxycyclobutane-1,3-dimalonate[1,2]

George C. Buzby, Jr.,[3a] Albert J. Castro,[3b,4] and Evans B. Reid[3c]

Department of Chemistry, The Johns Hopkins University, Baltimore 18, Maryland

Received February 5, 1962

Potassium permanganate oxidation of the compound reported in the literature to be ethyl *cis*-2,2,4,4-tetracarbethoxycyclobutane-1,3-dimalonate (I) in acetic acid yields ethyl 1,5-hexadiene-1,1,3,3,4,4,6,6-octacarboxylate (II). A possible pathway for the transformation is suggested. Because of the different literature reports concerning the oxidation product its constitution was reinvestigated and established as correct.

During the course of an investigation aimed at the synthesis of cyclobutane-1,2,3,4-tetracarboxylic acid[5,6] the potassium permanganate oxidation of ethyl *cis*-2,2,4,4 - tetracarbethoxycyclobutane - 1,3 - dimalonate (I) (*vide infra*) in acetic acid was undertaken as one step in a sequence. From the reaction, a compound, $C_{30}H_{42}O_{16}$, was obtained in a good yield. An attempt to distil this substance resulted in its conversion to ethyl 6-ethoxy-α-pyrone-3,5-dicarboxylate (IV). From the ozonolysis of $C_{30}H_{42}O_{16}$, ethyl ethane-1,1,2,2-tetracar-

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[1] Taken for the most part from the dissertation of G. C. Buzby, Jr. submitted in partial fulfillment of the requirements for the Ph.D. degree.

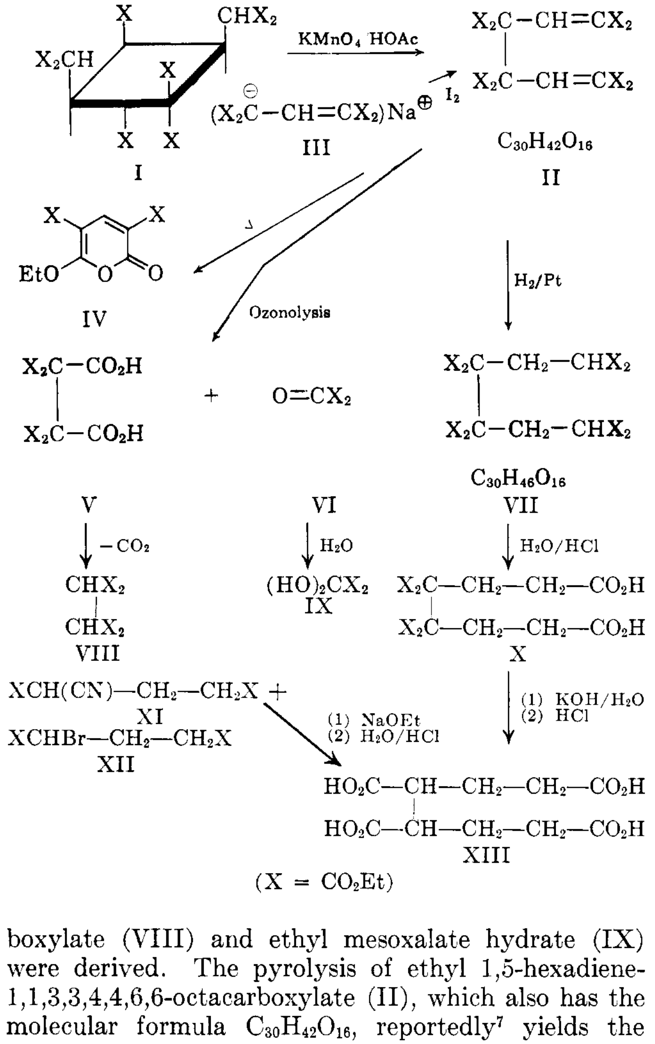
[2] Presented in part as Paper 125 before the Organic Division at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 14, 1960, Abstracts, p. 83-O.

[3] Present address: (a) Wyeth Laboratories Inc., Philadelphia 1, Pa.; (b) Department of Chemistry, San Jose State College, San Jose 14, Calif.; (c) Department of Chemistry, Colby College, Waterville, Me.

[4] To whom requests for reprints should be sent.

[5] R. Criegee and W. Funke, *Chem. Ber.*, **94**, 2358 (1961).

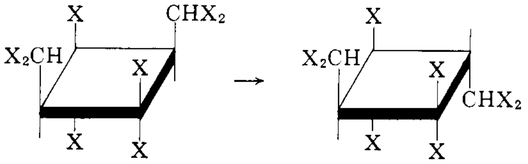
[6] G. W. Griffin, J. E. Basinski, and L. I. Peterson, *J. Am. Chem. Soc.*, **84**, 1012 (1962).



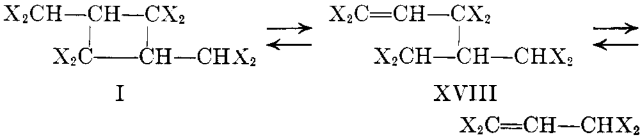
(X = CO$_2$Et)

boxylate (VIII) and ethyl mesoxalate hydrate (IX) were derived. The pyrolysis of ethyl 1,5-hexadiene-1,1,3,3,4,4,6,6-octacarboxylate (II), which also has the molecular formula $C_{30}H_{42}O_{16}$, reportedly[7] yields the aforementioned pyrone (IV) and the ozonolysis products are consistent with the hexadiene ester constitution (II) for the permanganate oxidation product. Ethyl mesoxalate hydrate (IX) arises from ethyl mesoxalate (VI), initially isolated, and the tetraester (VIII) is considered as resulting from 1,1,2,2-tetracarbethoxyethane-1,2-dicarboxylic acid (V), which would be expected[8] to decarboxylate with ease. Final proof of the identity of the permanganate oxidation product was furnished by a direct comparison (infrared spectra, mixture melting points) with the hexadiene octaester (II) synthesized from the reaction of the sodium salt of ethyl propene-1,1,3,3-tetracarboxylate (III) and iodine as described by Guthzeit and Hartmann.[9] In view of the unsaturated nature of II, it should be mentioned that the inertness and low reactivity of alkene linkages to attack by permanganate has been noted in other examples.[10–12]

The cyclobutane ester (I) employed in our work was synthesized as described by Guthzeit, Weiss, and Schaefer,[13] who obtained it as a solid, m.p. 103°, having the proper elemental analysis and molecular weight from the piperidine-catalyzed dimerization of ethyl propene-1,1,3,3-tetracarboxylate (XIV) in ether. Its comparative resistance to attack by alkaline permanganate and bromine in contrast with the ready susceptibility to such attack by XIV was noted by these workers. The saturated character of I is further shown in a comparison of its ultraviolet absorption spectrum with those of XIV, ethyl 1-pentene-1,1,3,3-tetracarboxylate (XV) and the compound we establish herein as definitely ethyl 1,5-hexadiene-1,1,3,3,4,4,6,6-octacarboxylate (II). All of the last three show strong absorption at around 205–210 mμ, which is described as typical of the $C{=}C{-}CO_2R$ chromophore, while I shows only weak absorption.[14] Treatment of the *cis*-cyclobutane ester I with piperidine in benzene at room temperature reportedly[13] converts it to the *trans* isomer (XVI), m.p. 87–88°. There are five isomeric 2,4-dicarboxycyclobutane-1,3-diacetic acids theoretically possible. Three could be derived from I and two are possible from XVI. Neither of the latter should be interconvertible with the former, aside from some comparatively drastic reaction. Experimental evidence in support of the existence of the five isomeric acids, actually obtained from I, XVI, and ethyl 1,1,3,3-tetracarbethoxycyclobutane-2,4-diacetate (XVII), is not so convincing as might be desired. Nevertheless three isomeric acids have been reported as derived from I and a fourth isomer, different from these, from XVI.[15] A cyclobutane ester such as I is a logical product from successive inter- and intramolecular Michael reactions starting with a compound like XIV. The reversal of the reaction then would not be surprising and indeed reportedly occurs when I is in the fused state or in solution. The equilibrium composition is *ca.* 80% cyclobutane ester (I), upwards to 10% of the unsaturated acyclic isomer, ethyl 1,1,3,3,5,5-hexacarbethoxy-1-pentene-4-malonate (XVIII), plus a small amount of XIV.[15] Bateman and Jeffrey[11] have concluded from an X-ray examination that the space group for I (triclinic) is probably P1,[16,17] with a centrosymmetric molecule; for XVI (monoclinic), A2/a. However, molecular centrosymmetry would be impossible for a compound with the formula shown for I, which has a C_{2v} molecular point group sym-



I (X = CO$_2$Et) XVI



I XVIII XIV

(*cis*) (X = CO$_2$Et)

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(7) C. K. Ingold and C. W. Shoppee, *J. Chem. Soc.*, 1619 (1930).

(8) C. E. Dalgliesh, A. W. Johnson, A. G. Long, and G. J. Tyler, "Chemistry of Carbon Compounds," Vol. 1^b, E. H. Rodd, ed., Elsevier Publishing Co., New York, N. Y., 1952, p. 1146.

(9) M. Guthzeit and E. Hartmann, *J. prakt. Chem.*, **81**, 329 (1910).

(10) H. Koch and F. Hilberath, *Ber.*, **73**, 1171 (1940).

(11) L. Bateman and G. L. Jeffrey, *J. Chem. Soc.*, 211 (1945).

(12) P. D. Bartlett and M. Stiles, *J. Am. Chem. Soc.*, **77**, 2806 (1955).

(13) M. Guthzeit, A. Weiss, and W. Schaefer, *J. prakt Chem.*, **80**, 393 (1909).

(14) L. Bateman and H. P. Koch, *J. Chem. Soc.*, 216 (1945).

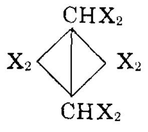
(15) C. K. Ingold, E. A. Perren, and J. F. Thorpe, *ibid.*, **121**, 1765 (1922).

(16) M. J. Buerger, "X-Ray Crystallography," J. Wiley and Sons, Inc., New York, N. Y., 1942, p. 84, *et seq.*

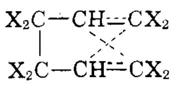
(17) P. J. Wheatley, "The Determination of Molecular Structure," Oxford University Press, London, 1959, p. 100 *et seq.*, p. 128.

metry[18] corresponding to any one of twenty-two space groupings,[19] none of which is P$\bar{1}$. A triclinic system can only possess P1 or P$\bar{1}$ space group symmetry[17] and these cannot be distinguished by an X-ray study alone.[18] The first allows any molecular point group symmetry, except centrosymmetry, and C_{2v} is one of these. P$\bar{1}$ only permits centrosymmetric molecular point groups. A compound having the formula written for XVI has C_{2h} molecular point group summetry and A2/a is one of six space groups corresponding thereto, but the presence of eight molecules in the unit cell for XVI[11] militates against a conclusion as far as molecular geometry is concerned. In summary, the X-ray data concerning I and XVI is inconclusive. All other available experimental results are in agreement with the stated constitution and configuration of I, none is incongruous therewith.

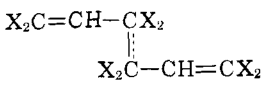
Interestingly, three proposals have been made for the constitution of the hexadiene octaester (II). These include: ethyl 2,2,4,4-tetracarbethoxybicyclo[1.1.0]-butane-1,3-dimalonate (XIX) suggested by Guthzeit and Hartmann and shown to be incorrect by Ingold, Parekh, and Shoppee[20]; the ring–chain mesomeric formula (XX) of the latter, wherein the carbon double bonds shown in II are replaced and represented as involved in a mesomeric state as indicated by the dotted bonds in XX in order to explain the different reactions of this type of compound; the hyperconjugation structure (XXI) of Bateman,[11,14] Jeffrey, and Koch in which the vertical carbon to carbon bond of formula II is represented as a bond having some double bond character. In view of this, the anomalous properties[20] and conflicting claims[9,20] recorded for such compounds it seemed desirable to investigate the constitution of the supposed hexadiene octaester (II) further. In contrast with the earlier described[20] inability to catalytically hydrogenate the methyl analog (XXII), which is reported[20] to yield methyl 2,2,3,3,5,5-hexacarbomethoxycyclopentane-1-malonate (XXIII) upon electrolytic reduction, hydrogenation of the compound considered as being the hexadiene ester (II) in glacial acetic acid with a platinum catalyst gave a new substance, $C_{30}H_{46}O_{16}$. An attempt to synthesize the expected product, ethyl hexane-1,1,3,3,4,4,6,6-octacarboxylate (VII), from the reaction of ethyl propane-1,1,3,3-tetracarboxylate (XXIV) with lithium followed by reaction of the resulting product with iodine resulted in the formation of ethyl cyclohexane - 1,1,2,2,4,4,5,5 - octacarboxylate (XXV), a consequence expected from the lithium replacement of the hydrogens at both the α and α′ carbons of the propane ester (XXIV) rather than at one as was sought. However, the acid-catalyzed hydrolysis of the hydrogenation product, $C_{30}H_{46}O_{16}$, yielded a compound which upon analysis gave the correct values for a hexane tetraethyl ester dicarboxylic acid. From the saponification of this compound, hexane 1,3,4,6-tetracarboxylic acid (XIII) was obtained. From a steric standpoint[21] the terminal carbethoxy groups of the expected product (VII) from hydrogenation of the supposed hexadiene octaester (II) would be anticipated to hydrolyze more readily than those in the 3,4-positions and *gem*-dicarboxyl groups are well known to decarboxylate readily. Accordingly, the acid-catalyzed hydrolysis product is 3,3,4,4-tetracarbethoxyhexane-1,3-dicarboxylic acid (X) and the hydrogenation product, $C_{30}H_{46}O_{16}$, must be ethyl hexane-1,1,3,3,4,4,6,6-octacarboxylate (VIII). In the light of these results and the nature of the ozonolysis products, the formula shown (II) for the hexadiene octaester is correct.[22]



XIX

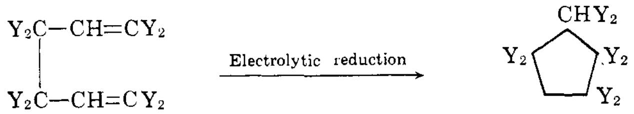


XX



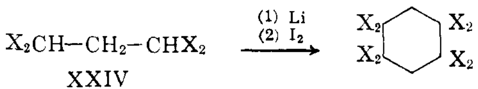
XXI

($X = CO_2Et$)



XXII XXIII

($Y = CO_2Me$)



XXIV XXV

($X = CO_2Et$)

The main steps in a plausible mechanism, following Levitt's general theory,[27] for the conversion of ethyl 2,2,4,4-tetracarbethoxycyclobutane-1,3-dimalonate (I) to ethyl 1,5-hexadiene-1,1,3,3,4,4,6,6-octacarboxylate (II) are as shown on p. 1085.

Variations can be imagined. For example, the formation of II from B could conceivably occur in one step without the intervention of C. The possible complexities[27–29] involved in permanganate oxidations are recognized and $MnO_3^{\oplus}$ is considered a provisional choice. However, since ethyl 1,1,3,3,5,5-hexacarbethoxy-1-pentene-4-malonate (XVIII) has been shown[15] to be

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(18) G. Herzberg, "Molecular Spectra and Molecular Structure, Vol. II, Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., Inc., New York, N. Y., 1945, p. 1, *et seq.*

(19) P. J. Wheatley, *ibid.*, p. 133.

(20) C. K. Ingold, M. M. Parekh, and C. W. Shoppee, *J. Chem. Soc.*, 142 (1936).

(21) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 776.

(22) As has already been pointed out by Bateman and Jeffrey,[11] their X-ray study establishing that the solid methyl ester analog (XXII) is centrosymmetric makes the *cis* configuration required for the ring-chain mesomeric formula analogous to (XX) impossible for the crystalline methyl ester. Experimental evidence for the solid ethyl ester is considered non-definitive, although a similar situation is indicated. Data in support of the non-existence of ring-chain mesomerism for the esters in solution has been presented.[14] The alternate possible explanation of chain hyperconjugation (XXI) to account for the unique properties of the hexadiene esters was suggested by comparison with geranylamine hydrochloride, a 2,6-diene which was thought to have an abnormally short central C—C distance (1.43 Å.).[23] A recalculation,[24,25] taking into account individual atomic temperature factors, shows the central interatomic distance is normal (1.537 ± 0.045 Å.). A *trans* arrangement as required for a centrosymmetric structure would be predicted from a conformational analysis.[26] The same type of conformation would likewise be expected for geranylamine hydrochloride and this is indeed the case.[23] An explanation for the peculiar properties of the hexadiene octaesters is simply a neighboring group effect with no interaction involving the carbon to carbon double bonds in the ground state implied.

(23) L. Bateman and G. A. Jeffrey, *Nature*, **152**, 446 (1943).

(24) D. W. J. Cruickshank and G. A. Jeffrey, *Acta Cryst.*, **7**, 646 (1954).

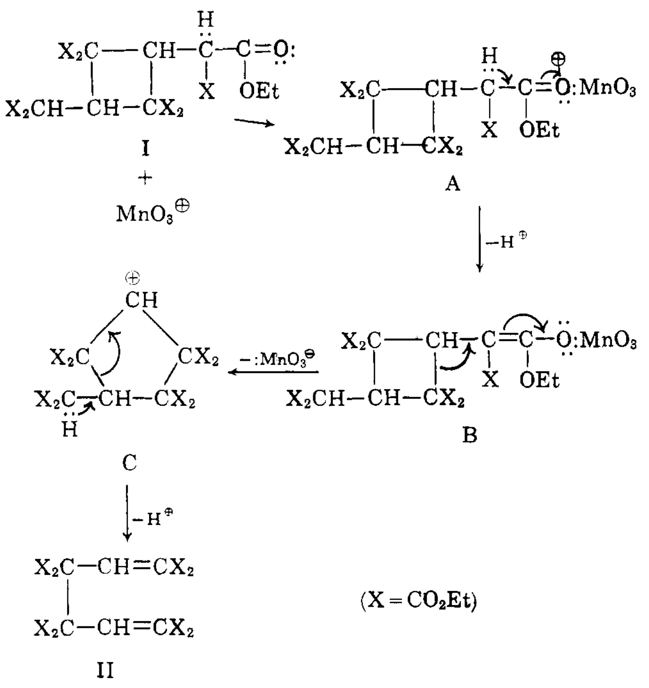
(25) D. W. J. Cruickshank and G. A. Jeffrey, *Ann. Rept. Progr. Chem.* (*Chem. Soc. London*), **LI**, 388 (1954).

(26) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **X**, 44 (1956).

(27) L. S. Levitt, *J. Org. Chem.*, **20**, 1297 (1955).

(28) J. W. Ladbury and C. F. Cullis, *Chem. Rev.*, **58**, 403 (1958).

(29) W. A. Waters, *Quart. Rev.* (London), **XII**, 277 (1958).



formed from the cyclobutane octaester in the fused state, or in solution, as has been mentioned, this presents the possibility of an alternate route for the formation of ethyl 1,5-hexadiene-1,1,3,3,4,4,6,6-octacarboxylate (II). Although this cannot be completely eliminated at the present, upon refluxing an acetic acid solution of the cyclane ester for fifteen hours the starting ester was recovered in almost a quantitative yield.

Experimental[30]

Ethyl *cis*-2,2,4,4-Tetracarbethoxycyclobutane-1,3-dimalonate (I).—The ester, m.p. 103°, was prepared according to the method of Guthzeit, *et al.*,[13] from the piperidine in ether-catalyzed dimerization of ethyl propene-1,1,3,3-tetracarboxylate.[31]

Permanganate Oxidation of Ethyl *cis*-2,2,4,4-Tetracarbethoxycyclobutane-1,3-dimalonate.—Two grams of potassium permanganate was added to a solution of 13.2 g. of ethyl *cis*-2,2,4,4-tetracarbethoxy-1,3-cyclobutanedimalonate (I) in 100 ml. of glacial acetic acid. The mixture was refluxed for 1 hr., at which time the permanganate color had disappeared. An additional 2.0 g. of potassium permanganate was added and the mixture was refluxed for three more hours. The solvent was removed under reduced pressure and a brown oil remained. This was boiled with ether, the ethereal solution was washed with water, the ether was evaporated, and the oily residue was crystallized from 95% ethyl alcohol. Nine grams (68%) of white crystals (II), m.p. 83–84°, was obtained. A recrystallized sample melted at 86°.

Anal. Calcd. for $C_{30}H_{42}O_{16}$: C, 54.71; H, 6.43; mol. wt., 659. Found: C, 54.63; H, 6.50; mol. wt., 647, 656, 658.

Pyrolysis of Permanganate Oxidation Product from Ethyl *cis*-2,2,4,4-Tetracarbethoxycyclobutane-1,3-dimalonate.—An attempt to distill the oxidation product (II) yielded a yellow oil, b.p. 192–220°(*ca.* 20 mm.). The oil crystallized when ether was added and the wall of the container was scratched. Upon recrystallization from a mixture of ether and petroleum ether, crystals of ethyl 6-ethoxy-α-pyrone-3,4-dicarboxylate (IV), m.p. 92–93°, were obtained. When admixed with a sample of the pyrone, m.p. 93°, prepared similarly by the pyrolysis[7] of ethyl 1,5-hexadiene-1,1,3,3,4,4,6,6-octacarboxylate no depression of the melting point was observed.

Ozonolysis of Permanganate Oxidation Product from Ethyl *cis*-2,2,4,4-Tetracarbethoxycyclobutane-1,3-dimalonate.—Twenty grams of $C_{30}H_{42}O_{16}$ (II) was ozonized in 150 ml. of chloroform at 0°. The chloroform was removed at reduced pressure and the viscous residue was treated with four 50-ml. portions of 3% hydrogen peroxide while heating gently during a period of 1 hr. The water was filtered off and the residue extracted with ether. The resulting ether solution was dried over magnesium sulfate, the ether was evaporated, and the residue was distilled. Three liquid fractions were collected: (a) b.p. 50–60° (5 mm.), (b) b.p. 118–135° (5 mm.), and (c) b.p. 160–185° (5 mm.).

Fraction a (VI) crystallized slowly upon exposure to the atmosphere and immediately upon the addition of a small amount of water. After recrystallization from a mixture of benzene and petroleum ether, the product (IX) melted at 57°.

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.29. Found: C, 43.60; H, 6.20.

A mixture melting point with a sample of ethyl mesoxalate hydrate synthesized by the method of Curtiss[32] showed no depression.

Fraction b (VIII) solidified upon standing and after recrystallization from a mixture of ether and petroleum ether melted at 75–76°.

Anal. Calcd. for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97. Found: C, 52.80; H, 7.09.

A mixture melting point with authentic ethyl ethane-1,1,2,2-tetracarboxylate showed no depression.

No conclusive results were obtained from an investigation of fraction c.

Ethyl 1,5-Hexadiene-1,1,3,3,4,4,6,6-octacarboxylate (II).—The ester, m.p. 86°, was synthesized by the method of Guthzeit and Hartmann[9] from the reaction of the sodium derivative of ethyl propene-1,1,3,3-tetracarboxylate (III) with iodine.

Hydrogenation of Ethyl 1,5-Hexadiene-1,1,3,3,4,4,6,6-octacarboxylate.—Three grams of the ester in 100 ml. of glacial acetic acid with 1 g. of platinum oxide was shaken under hydrogen in a Burgess–Paar hydrogenator until hydrogenation ceased. After removal of the catalyst and distillation of the solvent at reduced pressure, the product was crystallized from benzene followed by recrystallization from a mixture of ether and petroleum ether. The resulting flat, white crystals (VII) melted at 54°.

Anal. Calcd. for $C_{30}H_{46}O_{16}$: C, 54.37; H, 7.00. Found: C, 54.33; H, 6.97.

Attempted Synthesis of Ethyl Hexane-1,1,3,3,4,4,6,6-octacarboxylate.—A mixture of 8 g. of ethyl propane-1,1,3,3-tetracarboxylate (XXIV), derived from the reaction of the sodium derivative of ethyl malonate and methylene iodide,[33] in 8 ml. of benzene and 0.17 g. of lithium was refluxed for 24 hr. To the mixture, 3.1 g. of iodine was then added and the mixture was refluxed for 8 hr. The solution was separated, washed with water, dried over magnesium sulfate, and distilled. The liquid collected at 160–180° (2 mm.) crystallized from hexane yielding white crystals (XXV), m.p. 45°. The literature[34] melting point for ethyl cyclohexane-1,1,2,2,4,4,5,5-octacarboxylate is 46°.

Anal. Calcd. for $C_{30}H_{44}O_{16}$: C, 54.54; H, 6.71. Found: C, 54.50; H, 6.67.

Hydrolysis of Hydrogenation Product from Ethyl 1,5-Hexadiene-1,1,3,3,4,4,6,6-octacarboxylate.—A mixture of 4 g. of the hydrogenation product and 60 ml. of 6 *N* hydrochloric acid was refluxed for 15 hr. Upon cooling, 2.1 g. of a white solid deposited from the solution. After recrystallization from water, the shiny, white plates (X) obtained melted at 137.5°.

Anal. Calcd. for $(C_{10}H_{15}O_6)_2$: C, 51.94; H, 6.54; neut. equiv., 231. Found: C, 52.08; H, 6.56; neut. equiv., 230.

A mixture of 2.0 g. of the acid (X) from the preceding hydrolysis, 20 ml. of 10% potassium hydroxide in ethyl alcohol and enough water to effect solution of the acid was refluxed for 30 hr. The solution was evaporated to dryness on a steam bath at reduced pressure, the residue was acidified with hydrochloric acid, and the resulting mixture was evaporated to dryness. Extraction of the remainder with hot acetone followed by cooling of the extract yielded a solid. After decolorizing with charcoal in water and crystallization from the same solvent, a white solid (XIII), m.p. 215–216° (rapid heating), was obtained.

Anal. Calcd. for $(C_5H_7O_4)_2$: C, 45.80; H, 5.38; neut. equiv., 65.5. Found: C, 45.59; H, 5.35; neut. equiv., 65.3.

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[30] Melting points and boiling points are uncorrected. Analyses are by Drs. G. Weiler and F. B. Strauss, 164 Banbury Road, Oxford, England, and Mr. J. Walter.

[31] C. K. Ingold and E. A. Perren, *J. Chem. Soc.*, **119**, 1582 (1921).

[32] R. S. Curtiss, *Am. Chem. J.*, **35**, 477 (1906).

[33] M. Guthzeit and O. Dressel, *Ber.*, **21**, 2233 (1888).

[34] T. W. D. Gregory and W. H. Perkin, Jr., *J. Chem. Soc.*, **83**, 782 (1903).

A solution of 2.0 g. of the acid from the last hydrolysis in 10 ml. of methanol was saturated with dry hydrogen chloride. The mixture was allowed to stand in the laboratory for 48 hr. Upon concentrating the reaction mixture followed by the addition of a small amount of water, shiny white crystals, m.p. 68.5°, were obtained.

Anal. Calcd. for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97. Found: C, 52.60; H, 6.91.

A mixture melting point of the acid, m.p. 215–216°, with authentic hexane-1,3,4,6-tetracarboxylic acid and of the methyl esters from each showed no depressions.

Hexane-1,3,4,6-tetracarboxylic Acid (XIII).—The acid, m.p. 215°, was synthesized according to the direction of Ruzicka and co-workers[35] by the hydrolysis of the cyano ester resulting from the reaction of ethyl α-cyanoglutarate (XI) and ethyl α-bromoglutarate (XII) in the presence of sodium ethoxide. Esterification of the acid with methanol, as described above, gave the methyl ester, m.p. 68.5°.

Acknowledgment.—We are indebted to Professor A. H. Corwin for his initial proposal of a mechanism from which ours is derived, to Dr. R. F. Curtis for his assistance with early phases of the investigation, and to R. W. Richardson for the discussion concerning X-ray results and symmetry. We are also grateful to Dr. J. H. Wotiz for kindly communicating the results of his independent study, in collaboration with Dr. D. E. Mancuso, concerned with the nature of the hexadiene octaester, as well as to Dr. J. Ogilvie and the Microanalytical Department of the Wyeth Laboratories, Inc., for molecular weight determinations.

[35] L. Ruzicka, A. Borges de Almeida, and A. Brack, *Helv. Chim. Acta*, **17**, 183 (1934).

The Stereoisomeric Farnesols[1]

R. B. BATES, D. M. GALE, AND B. J. GRUNER

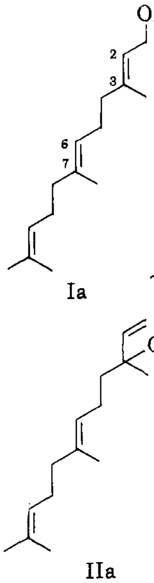
Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

Received October 5, 1962

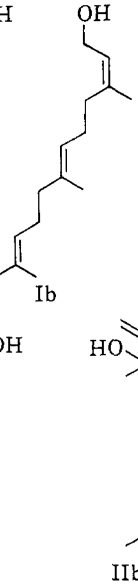
The preparation and characterization of the four stereoisomeric farnesols (Ia–d) is described. Farnesol from *Hibiscus abelmoschus* and farnesic acid prepared *via* the S-benzylthiuronium salt, m.p. 130–131°, were shown to be the *trans–trans* isomers.

Because of its pleasing odor, farnesol (I) has long been used in perfumery.[2] Although it has been reported to occur in many plants, it is always a minor constituent, and is prepared commercially by isomerizing the much more abundant natural substance *trans*-nerolidol (IIa).[3] Farnesol has recently taken on new importance, since it has become increasingly clear that a farnesol derivative (or derivatives) is a key intermediate in the biosynthesis of many substances: almost all other sesquiterpenoids, almost all diterpenoids and triterpenoids, and all steroids and carotenoids.[4] In particular, farnesyl pyrophosphate has been demonstrated to be a biological precursor of squalene,[5] which is then converted into other triterpenoids and into steroids. It has been reported recently that farnesol and farnesal exhibit juvenile hormone action in insects.[6]

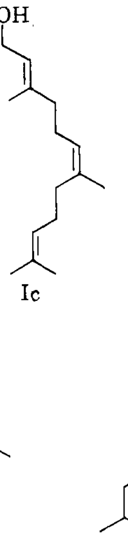
Although farnesol was first isolated over fifty years ago, was (appropriately, in view of the position of its esters in biogenetic schemes) the first sesquiterpenoid of known constitution, and has been synthesized many times,[3,5b,7] little is known regarding its stereochemistry. The stereochemistry of farnesol derivatives is undoubtedly of biological importance, since only a *trans–trans* derivative can give squalene, whereas a *cis–trans*[8] or *cis–cis* derivative is needed to give bisabolyl carbonium ion (III), a probable intermediate in the formation of many sesquiterpenoids.[4]



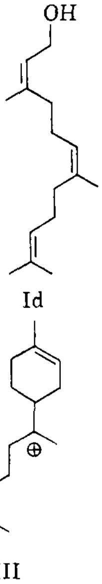
Ia



Ib



Ic



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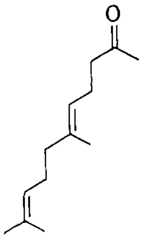
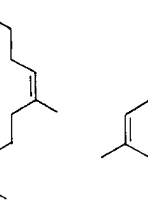
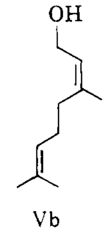


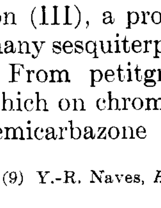
IIa



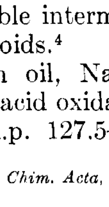
IIb



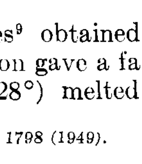
III



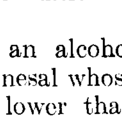
IVa



IVb



Va



Vb

From petitgrain oil, Naves[9] obtained an alcohol which on chromic acid oxidation gave a farnesal whose semicarbazone (m.p. 127.5–128°) melted lower than

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[1] Terpenoids, Part VII.

[2] E. Guenther, "The Essential Oils," Vol. II, D. Van Nostrand Company, Inc., New York, N. Y., 1949, p. 258.

[3] *e.g.*, L. Ruzicka and G. Firmenich, *Helv. Chim. Acta*, **22**, 392 (1939).

[4] L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 362 (1953); P. Crabbe and G. Ourisson, *Ind. chim. Belge*, **22**, 1309 (1957); J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

[5] (a) F. Lynen, H. Eggerer, U. Henning, and I. Kessel, *Angew. Chem.*, **70**, 738 (1958); (b) G. Popjak, J. W. Cornforth, R. H. Cornforth, R. Ryhage, and D. S. Goodman, *J. Biol. Chem.*, **237**, 56 (1962).

[6] P. Schmialek, *Z. Naturforsch.*, **16b**, 461 (1961).

[7] *e.g.*, (a) L. Ruzicka, *Helv. Chim. Acta*, **6**, 492 (1923); (b) I. N. Nazarov, B. P. Gusev, and V. I. Gunar, *Zh. Obshch. Khim.*, **28**, 1444 (1958); (c) E. Y. Shvarts and A. A. Petrov, *ibid.*, **30**, 3598 (1960).

[8] The first configurational designation refers to the 2,3 double bond, the second to the 6,7 double bond.

[9] Y.-R. Naves, *Helv. Chim. Acta*, **32**, 1798 (1949).