[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL]

Syntheses in the Terpene Series. XI.[1] Model Experiments with *sym*-Dicyclohexylethane Derivatives[2]

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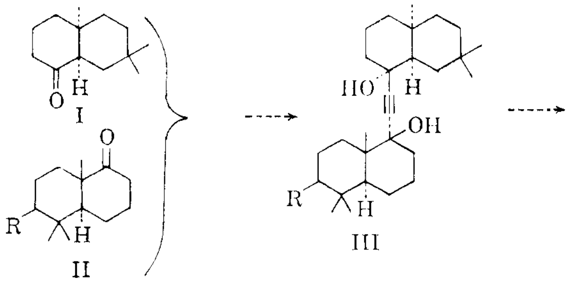
The conversion of bis-(1-hydroxycyclohexyl)-acetylene (VI) to 1,2-bis-(2-ketocyclohexyl)-ethane (XI) by two different routes is described, a transformation which serves as a model for a projected synthesis of triterpenes related to β-amyrin. In addition, related experiments with *sym*-dicyclohexylethane derivatives are reported.

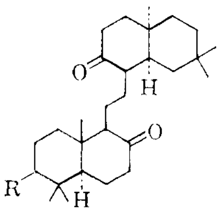
Syntheses of the bicyclic ketones I[4] and II (R = H or OH)[5] have been described in previous parts of this Series. It was our intention to utilize these substances for the total synthesis of triterpenes related to β-amyrin (V), *e.g.*, through conversion to the "mixed" acetylenic 1,4-diol III, followed by successive transformation to the diketone IV, treatment with methylmagnesium bromide and acid cyclization. As a model for the conversion of III to IV, it was decided first to study methods for the analogous transformation of bis-(1-hydroxycyclohexyl)-acetylene (VI) to 1,2-bis-(2-ketocyclohexyl)-ethane (XI), since the acetylenic diol in this series can be obtained readily in quantity. In this paper we describe two methods of synthesis of the diketone XI from the acetylenic diol VI, as well as the results of related experiments designed to bring about this transformation. One of these methods was subsequently applied successfully to the synthesis of diketones of type IV, as will be reported in a later paper of this series.



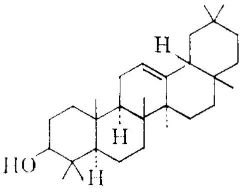
I

II

III



IV



V

The acetylenic diol VI was dehydrated smoothly to dicyclohexenylacetylene (VII) by means of potassium bisulfate at 200°, essentially as described previously.[6] It has been shown that peracids attack double bonds much more rapidly than triple bonds.[7a] As expected, oxidation of the dienyne VII with 2.3 molar equivalents of perbenzoic acid readily yielded 60% of the acetylenic diepoxide VIII, the structure of which is based on the elemental composition and the absence of appreciable absorption in the ultraviolet. The compound proved to be a liquid, and most probably consists of a mixture of *meso* and racemic forms.[8]

The diepoxide VIII in ethanol was hydrogenated first over a Lindlar lead-poisoned palladium–calcium carbonate catalyst,[9] and then (when uptake of hydrogen had become very slow) over a palladium–charcoal catalyst. Chromatography of the resulting mixture on alumina yielded *ca.* 25% of the di-*sec*-diol IX as a mixture of two stereoisomers, which could be separated into the pure components, m.p. 98–99° (isomer A) and 115–116° (isomer B).[10] In addition, the liquid secondary mono-ol X was isolated in *ca.* 30% yield. The structures of these hydrogenation products follow from their behavior on oxidation. The fact that secondary alcohols rather than saturated oxides or tertiary alcohols are formed is presumably due to the fact that cleavage of the weak propargylic (or allylic) carbon–oxygen bond occurs readily and prior to complete saturation of the acetylenic linkage. The loss of oxygen leading to the mono-ol X was unexpected, but finds some analogy in the literature.[12]

Oxidation of either isomer of the di-*sec*-diol IX (or of the mixture of isomers) with chromium

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[1] For Part X, see, N. Danieli, Y. Mazur and F. Sondheimer, *Tetrahedron Letters*, 310 (1961).

[2] This work was supported in part by a grant from Mr. Arthur B. Krim, New York.

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[4] F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).

[5] F. Sondheimer and D. Elad, *J. Am. Chem. Soc.*, **79**, 5542 (1957); **80**, 1967 (1958).

[6] (a) P. S. Pinkney, G. A. Nesty, D. E. Pearson and C. S. Marvel, *ibid.*, **59**, 2666 (1937); (b) H. H. Inhoffen and G. Quinkert, *Ber.*, **87**, 1418 (1954).

[7] See R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworths Scientific Publications, London, 1955; (a) pp. 33–34 and references cited there; (b) p. 35.

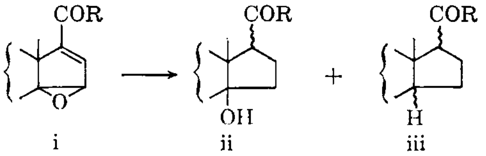
[8] No stereochemical assignments are implied in formulas VIII *et seq.*

[9] H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

[10] Neither of these isomers appears to be identical with the isomer of IX (m.p. 139°) reported to be formed by hydrogenation of 2,2'-dihydroxybibenzyl.[11]

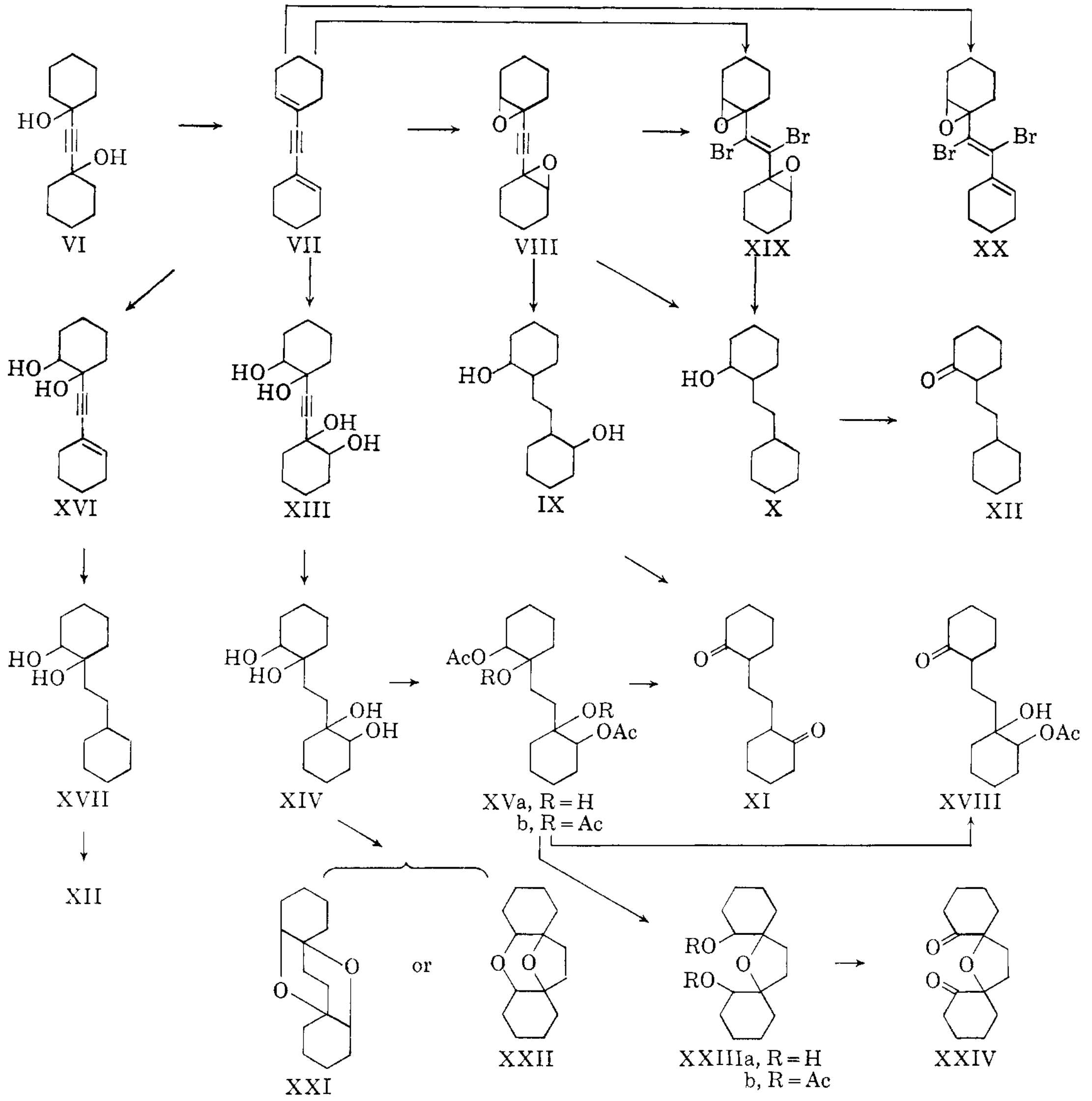
[11] S. C. Bhattacharyya, *J. Indian Chem. Soc.*, **33**, 545 (1956).

[12] *Cf.* the catalytic hydrogenation of steroidal 14β,15β-epoxy-Δ^{16}-etienic acid esters (i, R = OCH_3) and pregnen-20-ones (i, R = CH_3) to the desoxy compounds iii in addition to the 14β-alcohols ii.[13]



i ii iii

[13] P. A. Plattner, L. Ruzicka, H. Heusser, J. Pataki and K. Meier, *Helv. Chim. Acta*, **29**, 942 (1946); P. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *ibid.*, **30**, 385 (1947); H. Heusser, N. Frick, E. V. Jensen and P. A. Plattner, *ibid.*, **32**, 1334 (1949).



trioxide in pyridine[14] yielded *ca.* 35% of the diketone XI as a mixture of the *meso* and racemic forms, m.p. in the range 55–70°. Very similar results were obtained when the oxidations were carried out with chromium trioxide in acetone–dilute sulfuric acid.[15] Crystallization led to one pure isomer of XI, m.p. 83–84°, showing an infrared spectrum (carbonyl band at 5.86 μ, no hydroxyl bands) essentially identical to that of the mixture of isomers. Subjecting the pure isomer to the chromium trioxide–pyridine oxidation conditions (involving subsequent shaking with sodium sulfite solution[16]), or to treatment with alkaline alumina, regenerated the mixture of stereoisomers. The m.p. of the pure isomer of XI agreed well with that (84°) reported for XI derived by oxidation of the diol IX from 2,2'-dihydroxybibenzyl,[11] and our substance proved to be identical (by direct comparison) with the diketone XI prepared by Stork and Meisels through electrolysis of the sodium salt of 2-ketocyclohexylacetic acid.[17]

Oxidation of the secondary mono-ol X with chromium trioxide in pyridine led to the liquid monoketone XII, characterized as the 2,4-dinitrophenylhydrazone, m.p. 120–121°. The structure of the ketone XII follows from its infrared spectrum (carbonyl band at 5.84 μ, no hydroxyl bands), the elemental composition of the dinitrophenylhydrazone, and the fact that the same ketone was obtained by two other routes described below.

The method described above for converting the acetylenic diol VI to the diketone XI failed when applied in the tetracyclic series, since the dienyne obtained by dehydration of the tetracyclic acetylenic diol III (R = H) could not be transformed to the corresponding diepoxide by peracid oxidation. Other routes leading from VI to XI were therefore

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(14) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(15) *Inter al.*, K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, *ibid.*, 2402 (1951); R. G. Curtis, I. M. Heilbron, E. R. H. Jones and G. F. Woods, *ibid.*, 457 (1953).

(16) See S. Bernstein and R. Littell, *J. Am. Chem. Soc.*, **82**, 1235 (1960).

(17) G. Stork and A. Meisels, private communication. We are indebted to Dr. Meisels for a sample of XI prepared by the electrolytic route.

investigated. After considerable experimentation, the main results of which are reported later in this paper, the following satisfactory method was found which subsequently was applied successfully in the tetracyclic series.

Hydroxylation of dicyclohexenylacetylene VII with a considerable excess of osmium tetroxide in pyridine again affected only the ethylenic bonds, and yielded the acetylenic tetrol XIII, containing *cis*-1,2-diol groupings, as a mixture of *meso* and racemic forms (isomers A and B). The osmate esters of the two stereoisomers were found to be cleaved at different rates by means of boiling sodium sulfite solution. This fact was utilized for the separation of the two substances, since cleavage conditions could be found whereby essentially only one of the two tetrol isomers was generated. It was difficult to purify the acetylenic tetrols efficiently, and purification was best effected at the next stage.

Hydrogenation of each isomer of the acetylenic tetrol XIII in methanol over a platinum catalyst separately led to the corresponding saturated tetrol XIV (isomer A, m.p. 205–207°; isomer B, m.p. 165–166°), which could be converted to the 2,2'-diacetates XVa (isomer A, m.p. 151–152°; isomer B, m.p. 130–131°) by treatment with acetic anhydride and pyridine, and to the tetraacetates XVb (isomer A, m.p. 120–122°; isomer B, m.p. 134–135°) by treatment with acetic acid, acetic anhydride and *p*-toluenesulfonic acid. The over-all yield in the conversion VII→XIV (both isomers) was *ca.* 50%. The hydrogenation of the acetylenic tetrols XIII was carried out under a number of different conditions with the intention of obtaining diols of type IX by hydrogenolysis of the tertiary hydroxyl groups, but this objective could not be realized in practice.

Hydroxylation of dicyclohexenylacetylene VII with 2 molar equivalents of osmium tetroxide gave a mixture of the acetylenic tetrols XIII and the vinyl-acetylenic *cis*-diol XVI, whereas only the last-mentioned substance could be isolated (in 58% yield) when *ca.* 1 molar equivalent of the tetroxide was used. The liquid diol XVI, which showed ultraviolet spectral properties [λ_{max}^{EtOH} 227 mμ (ε 15,400)] compatible with the assigned structure,[18] on hydrogenation in ethyl acetate over a platinum catalyst smoothly gave the corresponding saturated *cis*-diol XVII, m.p. 105–106°.

After several methods to remove the tertiary hydroxyl groupings from the saturated tetrols XIV met with no success (see below), it was found that the required transformation could be brought about by application of the Serini reaction to the tetrol diacetates XVa. This reaction, first carried out with cafestol[20] and used repeatedly in the steroid series,[21] involves the treatment of a 1,2-diol monoacetate [>C(OH)CH(OAc)–] with zinc, whereby the ketone or aldehyde [>CHCO–] is formed by loss of acetic acid.

Treatment of either isomer of the saturated tetrol diacetate XVa (or of the mixture of isomers) with zinc powder in boiling toluene yielded *ca.* 40% of the diketone XI, again as a mixture of *meso* and racemic forms, m.p. in the range 50–65°. As previously, crystallization produced one pure isomer, m.p. 82–83°, which proved to be identical with that prepared by the first route. The presently observed formation of a mixture of stereoisomers in the Serini reaction is in contrast to the previous reports[21] that the conversion of the acetates of pregnane-17,20-diols to pregnan-20-ones proceeds with complete inversion at C-17, even when the configuration of the product thereby is the unstable one. This difference is probably due to the fact that the diketone XI is more readily enolized toward the asymmetric centers than the pregnan-20-ones, resulting in equilibration under the reaction conditions employed.

When the saturated tetrol diacetate XVa (isomer B) was subjected to treatment with zinc in boiling toluene under less vigorous conditions than those used previously, the hydroxy-acetoxy-ketone XVIII (m.p. 67–68°) was obtained in 38% yield besides only 14% of the diketone XI. The structure of the new substance, derived from XVa by reaction of only one-half of the molecule, follows from the elemental composition and the infrared spectrum (presence of hydroxyl, acetoxyl and saturated ketone groupings).

The remainder of the present paper is concerned with other experiments designed to bring about the conversion of VI to XI. These experiments are of interest *per se*, despite the fact that they did not result in the achievement of the prime objective.

The conversion of the dienyne VII to the acetylenic diepoxide VIII by a method not involving peracid oxidation was studied, in view of the abovementioned failure to bring about the analogous transformation in the tetracyclic series by means of peracids. It has been shown that epoxides may be prepared from ethylenes through reaction with hypobromous acid and subsequent treatment of the resulting *trans*-bromohydrins with base, the products generally being stereoisomeric with the epoxides obtained by direct peracid oxidation.[22] Consequently, dicyclohexenylacetylene (VII) was treated with a considerable excess (*ca.* 5 molar

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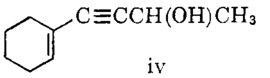
(18) *Cf.* 4-(1-cyclohexenyl)-3-butyn-2-ol (iv), containing the same chromophoric system as XVI, which shows λ_{max}^{EtOH} 227 mμ (ε 12,500–14,500).[19]



iv

(19) I. M. Heilbron, E. R. H. Jones, D. G. Lewis, R. W. Richardson and B. C. L. Weedon, *J. Chem. Soc.*, 742 (1949); J. D. Chanley and H. Sobotka, *J. Am. Chem. Soc.*, **71**, 4140 (1949).

(20) K. H. Slotta and K. Neisser, *Ber.*, **71**, 2342 (1938); H. Hauptmann and J. Franca, *Z. physiol. Chem.*, **259**, 245 (1939).

(21) A. Serini, W. Logemann and W. Hildebrand, *Ber.*, **72**, 391 (1939); A. Butenandt, J. Schmidt-Thomé and H. Paul, *ibid.*, **72**, 1112 (1939); C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **23**, 729 (1940); C. W. Shoppee, *ibid.*, **23**, 925 (1940); C. W. Shoppee, *Experientia*, **4**, 418 (1948); C. W. Shoppee, *J. Chem. Soc.*, 1671 (1949); L. F. Fieser and Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 1840 (1949); C. Djerassi and C. R. Scholz, *ibid.*,**71**, 3962 (1949); A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, **77**, 148 (1955); N. L. Wendler, *Proc. Chem. Soc.*, 422 (1960); T. Goto and L. F. Fieser, *J. Am. Chem. Soc.*, **83**, 251 (1961).

(22) *Inter al.*, see S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939); G. H. Ott and T. Reichstein, *Helv. Chim. Acta*, **26**, 1799 (1943); B. Löken, S. Kaufmann, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 1738 (1956); J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

equivalents) of hypobromous acid, generated from N-bromoacetamide in aqueous acetone, and the product was dehydrobrominated by means of potassium acetate in boiling ethanol. This procedure yielded 12% of the ethylenic dibromo-diepoxide XIX, apparently as a mixture of *meso* and racemic forms, from which one pure isomer (m.p. 163–164°) was obtained by crystallization. The structure of XIX (pure isomer) is based on the elemental composition and the fact that the identical substance was obtained by addition of bromine to the above-described acetylenic diepoxide VIII. This independent synthesis of XIX from VIII points to the *trans* configuration of the bromo groupings in the dibromoethylene XIX.[7b]

Treatment of the dienyne VII with only *ca.* 2 molar equivalents of N-bromoacetamide in aqueous acetone, followed by dehydrobromination with potassium acetate in boiling ethanol as before, gave 18% of a new substance, m.p. 72–73°, as sole crystalline product. This substance, which was not investigated further, is tentatively assigned the dibromo-monoepoxide structure XX, since the elemental analysis showed it to be derived from VII by addition of only one oxygen as well as two bromine atoms, and the infrared spectrum (unlike that of the dibromo-diepoxide XIX) indicated the presence still of a trisubstituted double bond.

The presently observed addition of bromine (as well as the elements of hypobromous acid) by means of N-bromoacetamide in aqueous acetone is not without precedent. Thus, Δ^{11}-steroids on treatment with N-bromoacetamide in aqueous acetone or *t*-butyl alcohol have been shown to give the 11,12-dibromo compounds in addition to the bromohydrins,[23] while the action of N-bromoacetamide under anhydrous conditions on a number of ethylenes has likewise been found to result in the addition of bromine.[24] Related reactions are the addition of the elements of bromine to ethylenes[25] and to the acetylenic bond of ethyl tetrolate[26] by means of N-bromosuccinimide under anhydrous conditions.

Hydrogenation of the dibromo-diepoxide XIX in ethanol–ethyl acetate over a palladium–charcoal catalyst did not lead to the expected di-*sec*-diol IX, but mainly, by loss of oxygen, to the secondary mono-ol X.[12] This conclusion follows from the fact that oxidation of the total hydrogenation product with chromium trioxide in pyridine[14] gave the monoketone XII (characterized as the 2,4-dinitrophenylhydrazone, identical with that described above), but no detectable amount of the diketone XI.

We now turn to the methods for removing the tertiary hydroxyl groupings from the saturated tetrols XIV which were investigated before the successful Serini method was developed.

The direct dehydration of *cis*-1,2-diols to the corresponding ketones under acid conditions usually proceeds smoothly, in view of the *trans*-relationship of the hydroxyl and hydrogen groups which are eliminated.[27] In fact, the saturated *cis*-diol XVII underwent the expected dehydration on being boiled with sulfuric acid in ethanol, yielding the same ketone XII (identified as the 2,4-dinitrophenylhydrazone) as had been obtained from the diepoxides VIII and XIX. The saturated tetrols XIV did not, however, undergo a similar dehydration to the required diketone XI. On being boiled with sulfuric acid in ethanol, the tetrol XIV (isomer A) was transformed to a liquid substance, derived from XIV by loss of two molecules of water. The new substance was saturated toward tetranitromethane, was only weakly adsorbed on an alumina chromatography column, and showed ether (but no hydroxyl or carbonyl) bands in the infrared. The compound under discussion is evidently either the di-ether XXI or the di-ether XXII, although at present it is not possible to distinguish between these two structures. The other isomer of XIV (isomer B) on treatment with sulfuric acid in boiling ethanol underwent an analogous dehydration, yielding a liquid di-ether (XXI or XXII) with an infrared spectrum almost identical with that of the first-described, presumably stereoisomeric, di-ether.

The formation of the di-ethers XXI or XXII could be avoided by subjecting the saturated tetrol diacetates XVa to dehydration. Treatment of XVa (isomer A) with sulfuric acid in acetic acid (no methanol was used to avoid ester interchange) at *ca.* 40° smoothly yielded a crystalline substance (m.p. 101–102°) which must be the diacetoxy-ether XXIIIb in view of the elemental composition, the infrared spectrum (presence of acetate and ether, but no hydroxyl bands) and its saturated nature toward tetranitromethane. Saponification with boiling methanolic potassium hydroxide led to the corresponding diol XXIIIa (m.p. 91–92°), which was oxidized with chromium trioxide in pyridine,[14] or alternatively with chromium trioxide in acetone–dilute sulfuric acid.[15] The liquid diketo-ether XXIV which resulted from either method of oxidation showed a carbonyl band at 5.82 μ in the infrared, and was characterized as the dioxime (m.p. 216–217°). The diketo-ether XXIV possesses the carbonyl groups in the required positions, but several attempts to cleave the ether bridge reductively (*e.g.*, by means of lithium in liquid ammonia or sodium in *n*-propyl alcohol[28]) failed and this approach was not pursued further.

The acetylenic tetrols XIII were subjected to a number of different dehydration conditions (*e.g.*, *p*-toluenesulfonic acid in benzene, potassium bisulfate, sulfuric acid in ethanol, phosphorus oxychloride in pyridine, *etc.*), since the presence of the acetylenic bond makes impossible the formation of the above-described types of ethers. Only the use of *p*-toluenesulfonic acid in boiling benzene resulted in the production of material containing carbonyl groups. The infrared spectrum of the product obtained under these conditions showed a weak band at 3.68 μ in addition to a strong band at 5.84 μ, suggestive of the presence of an aldehyde

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[23] T. Reichstein, *et al.*, *Helv. Chim. Acta*, **26**, 562, 586, 598, 705, 721, 1799 (1943).

[24] R. E. Buckles, *J. Am. Chem. Soc.*, **71**, 1157 (1949).

[25] E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 1116 (1952), and references given there.

[26] J. English and J. D. Gregory, *J. Am. Chem. Soc.*, **71**, 1115 (1949).

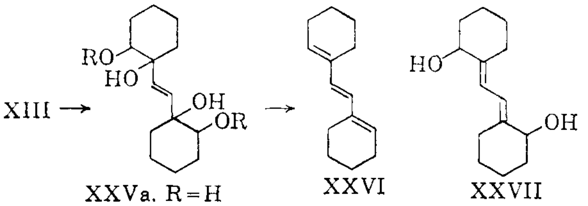
[27] *Inter al.*, see G. D. Meakins and J. S. Stephenson, *J. Chem. Soc.*, 526 (1958).

[28] See E. Romann, A. J. Frey, P. A. Stadler and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1900 (1957).

grouping.[29a] We believe that ring contraction has most probably taken place resulting in the formation of the cyclopentanealdehyde system, although this reaction was not further investigated.

The direct oxidation of the saturated tetrols XIV was also studied, in order to convert the secondary hydroxyl groups to ketones and then remove the excess tertiary hydroxyl groups. The results of these oxidation experiments proved to be more complex than anticipated, and will be reported in detail in a subsequent paper.

Finally, some experiments involving the reduction of the acetylenic tetrols XIII are described. Treatment of XIII (isomer A) with lithium aluminum hydride in boiling ether–tetrahydrofuran led to the *trans*-ethylenic tetrol XXVa (isomer A, m.p. 197–199°) which could be acetylated to the corresponding 2,2'-diacetate XXVb (m.p. 189–191°). Similar lithium aluminum hydride reduction of XIII (isomer B) yielded the corresponding *trans*-ethylene XXVa (isomer B, m.p. 135–136°) and then by acetylation the corresponding 2,2'-diacetate XXVb (m.p. 186–187°). The *trans* configuration of the double bond in the reduction products was anticipated from the previous observation that treatment of α-hydroxyacetylenes with lithium aluminum hydride produces the α-hydroxy-*trans*-ethylenes,[30] and confirmation was provided by the fact that both isomers of XXVa as well as of XXVb showed infrared bands at *ca.* 10.50 μ, indicative of *trans* disubstituted double bonds.[29b] Each isomer of the ethylenic tetrol diacetate XXVb was hydrogenated smoothly to the corresponding saturated tetrol diacetate XVa, obtained previously by direct hydrogenation of the acetylenic tetrols XIII and subsequent acetylation.



XXVa. R = H
b. R = Ac

XXVI

XXVII

It was hoped that reduction of the ethylenic tetrols XXVa or of the diacetates XXVb with phosphorus diiodide might result in the removal of the tertiary hydroxyl groups and lead to the diene-diols XXVII, in view of similar 1,4-reductions which have previously been carried out by means of this reagent.[31] The desired reaction could not, however, be effected in practice, since each isomer of XXVa or of XXVb on treatment with phosphorus diiodide under several different conditions was either recovered unchanged or else (through 1,2- rather than 1,4-reduction) was transformed to the known conjugated triene XXVI.[6b] The last-mentioned compound was identified by the characteristic triple maxima at 259, 269 and 280 mμ in the ultraviolet.[6b]

Acknowledgment.—We are indebted to Miss Nurit Shoef for her skillful technical assistance.

Experimental[32]

Dicyclohexenylacetylene (VII) was prepared by dehydration of bis-(1-hydroxycyclohexyl)-acetylene (VI) with potassium bisulfate at *ca.* 200° essentially as described by Pinkney, *et al.*,[6a] except that equal weights of the diol VI and the salt were employed as described by Inhoffen and Quinkert[6b] (see also footnote 13 in ref. 33).

Bis-(1,2-epoxycyclohexyl)-acetylene (VIII).—An experiment in which 10 mg. of the dienyne VII was allowed to stand with an excess of perbenzoic acid in benzene solution at room temperature (aliquots being withdrawn at intervals and titrated against a standard sodium thiosulfate solution) showed that almost exactly 2 molar equivalents of the peracid had been used up in 50 minutes and the amount of peracid present then remained constant.

For preparative purposes, 48 cc. of a 0.78 *N* solution of perbenzoic acid (0.037 mole) in benzene was added gradually during 10 minutes to 3 g. (0.016 mole) of the dienyne VII dissolved in 50 cc. of benzene. After being allowed to stand at room temperature for a further 50 minutes, the solution was diluted with ether, and washed well with sodium bicarbonate solution and then with water. The extract was dried, evaporated, and the residue, dissolved in pentane, was chromatographed on 200 g. of alumina. Pentane–benzene (4:1) eluted 2.05 g. (59%) of the diepoxide VIII as a colorless oil, n^{21}_{D} 1.5301; no appreciable absorption in the ultraviolet; infrared bands at 10.72 and 10.93 μ (epoxide ?).[29c]

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.93; H, 8.23.

1,2-Bis-(2-hydroxycyclohexyl)-ethane (IX) (Isomers A and B) and 1-Cyclohexyl-2-(2-hydroxycyclohexyl)-ethane (X) by Hydrogenation of the Diepoxide VIII.—A solution of 1 g. of the diepoxide VIII in 25 cc. of ethanol was shaken in hydrogen over 400 mg. of a Lindlar palladium catalyst[9] at 23° and 764 mm. After *ca.* 3 hr., 212 cc. (1.91 molar equivalents) of gas had been absorbed and uptake had become very slow. The catalyst was removed by filtration, 300 mg. of a 10% palladium–charcoal catalyst was added, and the hydrogenation was allowed to continue. After a further 4 hr. an additional 245 cc. (2.21 molar equivalents) of hydrogen had been absorbed and uptake had stopped. The catalyst was removed, the solvent was evaporated and the oily residue, dissolved in pentane, was chromatographed on 40 g. of alumina. Investigation of various fractions showed that a complex mixture of substances had been formed. Only the major products were investigated further, as described.

The oily fractions (295 mg., 31%), eluted with pentane–ether (9:1), consisted of the *sec*-mono-ol X; the infrared spectrum showed hydroxyl bands at 2.75 and 2.89 μ. The compounds, without further characterization, was oxidized directly to the ketone XII (see below).

The crystalline fractions (265 mg., 26%), eluted with pentane–ether (1:1), consisted of a mixture of two stereoisomers of the di-*sec*- diol IX. The separation between the two isomers in succeeding fractions was incomplete and no quantitative method of separation was found. One isomer of IX (isomer A) was obtained from the less polar fractions by crystallization from hexane as regular prisms, m.p. 98–99°; the infrared spectrum showed hydroxyl bands at 2.77 and 2.91 μ with considerably greater intensity than those of the mono-ol X.

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[29] See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1958; (a) Chapter 9; (b) Chapter 3; (c) Chapter 7.

[30] *Inter al.*, see J. D. Chanley and H. Sobotka, *J. Am. Chem. Soc.*, **71**, 4140 (1949); R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 3185 (1950); K. R. Bharucha and B. C. L. Weedon, *ibid.*, 1584 (1953); E. B. Bates, E. R. H. Jones and M. C. Whiting, *ibid.*, 1854 (1954).

[31] R. Kuhn and K. Wallenfels, *Ber.*, **71**, 1889 (1938); H. H. Inhoffen and K. Weissermel, *ibid.*, **87**, 187 (1954).

[32] Melting points are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina. Ultraviolet spectra were measured on a Unicam model S.P. 500 spectrophotometer. Infrared spectra were determined in chloroform solution (unless indicated otherwise) by means of a Perkin–Elmer Infracord recording spectrophotometer with sodium chloride optics. Analyses were carried out in our microanalytical department under the direction first of Mr. Erich Meier and then of Mr. Raoul Heller.

[33] F. Sondheimer and D. Elad, *J. Am. Chem. Soc.*, **81**, 4429 (1959).

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.11; H, 11.28.

The second isomer of IX (isomer B) was obtained from the more polar fractions by crystallization from hexane as fine needles, m.p. 115–116°; the infrared spectrum was very similar to that of isomer A, showing hydroxyl bands at 2.76 and 2.90 μ.

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.26; H, 11.34.

1,2-Bis-(2-ketocyclohexyl)-ethane (XI) by Oxidation of the Diols IX (Isomers A and B). (a) With Chromium Trioxide in Pyridine.—A solution of 100 mg. of the diols IX (mixture of both isomers, as obtained by chromatography) in 3 cc. of pyridine was added to a mixture of 400 mg. of chromium trioxide and 6 cc. of pyridine, and the mixture was then shaken at room temperature for 48 hr. A saturated sodium sulfite solution (15 cc.) was added and shaking was continued for a further 4 hr. Isolation with methylene chloride furnished 54 mg. of material, which was chromatographed on 4 g. of alumina. Elution with pentane–ether (7:3) then produced 32 mg. (33%) of the diketone XI as a mixture of the *meso* and racemic forms, m.p. 56–71°. Repeated crystallization from pentane (with cooling to −10°) resulted in a gradual raising of the m.p. until one pure isomer, with constant m.p. 83–84°, was obtained (reported[11] m.p. 84°). The pure isomer showed an infrared spectrum (strong carbonyl band at 5.86 μ, no hydroxyl bands) almost identical with that of the mixture of isomers. It was identified with a specimen (m.p. 80–82°), provided by Dr. A. Meisels,[17] through infrared spectral comparison and non-depression of the m.p. on admixture.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.55; H, 9.86.

Oxidation separately of the two pure isomers of IX with chromium trioxide in pyridine, as described above, in each case after chromatography yielded a stereoisomeric mixture of the diketone XI (m.p. 57–72° from isomer A; m.p. 54–68° from isomer B). In each case several crystallizations from pentane gave essentially one pure isomer of XI (m.p. 79–82° from isomer A; m.p. 77–79° from isomer B), undepressed in m.p. on admixture with the pure diketone described above or with each other.

The pure isomer of the diketone XI (m.p. 83–84°) suffered only a few degrees lowering in m.p. on being chromatographed on alumina (Merck, acid-washed). However an ethereal solution on being absorbed on alkaline alumina (Aluminum Co. of America, Pittsburgh, Pa.; grade F-20) for 16 hr. yielded material which after trituration with a little pentane showed m.p. 45–55° (infrared spectrum almost unchanged). Very similar results were obtained when the pure isomer was subjected to the chromium trioxide–pyridine oxidation conditions and work-up (m.p. 52–56° after chromatography).

(b) With Chromium Trioxide in Acetone–Sulfuric Acid.—Three drops of an 8 *N* chromium trioxide solution (prepared by dissolving 26.67 g. of the trioxide in 40 cc. of water and 23 cc. of concd. sulfuric acid, followed by dilution to 100 cc. with water)[15] was added to a solution of 40 mg. of the diols IX (mixture of isomers) in 4 cc. of acetone. After being shaken at room temperature for 4 minutes, the mixture was diluted with water and extracted with methylene chloride. The resulting material (38 mg.) after chromatography on 4 g. of alumina and elution with pentane–ether (4:1) furnished 16 mg. (41%) of the diketone XI as a mixture of stereoisomers, m.p. 54–74°. Recrystallization from pentane again yielded one isomer, m.p. 79–81°, undepressed on admixture with the material obtained by oxidation with chromium trioxide in pyridine.

1-Cyclohexyl-2-(2-ketocyclohexyl)-ethane (XII) by Oxidation of the Alcohol X.—A solution of 280 mg. of the alcohol X (obtained by hydrogenation of the diepoxide VIII) in 5 cc. of pyridine was added to a mixture containing 1 g. of chromium trioxide and 10 cc. of pyridine. After being stirred at room temperature for 48 hr., the mixture was concentrated to small volume under reduced pressure and the product (165 mg.) was isolated with benzene. Chromatography on 10 g. of alumina and elution with pentane–benzene (17:3) yielded 97 mg. of the ketone XII as a colorless oil, showing a strong carbonyl band at 5.84 μ but no hydroxyl bands in the infrared. The 2,4-dinitrophenylhydrazone crystallized from ethanol as yellow needles, m.p. 120–121°.

Anal. Calcd. for $C_{20}H_{28}N_4O_4$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.73; H, 7.19; N, 14.66.

Bis-[1,2-(*cis*)-dihydroxycyclohexyl]-acetylene (XIII) (Isomers A and B).—A solution of 4 g. (0.016 mole) of osmium tetroxide in 45 cc. of dry pyridine was added to a solution of 0.9 g. (0.0048 mole) of dicyclohexenylacetylene (VII) in 30 cc. of pyridine. After being allowed to stand in the dark for 3 days, the mixture was evaporated almost to dryness under reduced pressure, and the black residue was then boiled under reflux for 2.5 hr. with 40 cc. of ethanol and a solution of 10 g. of sodium sulfite in 50 cc. of water. The cooled mixture was diluted with water and extracted well with *n*-butyl alcohol.

The *n*-butyl alcohol extract was washed with water, dried and evaporated under reduced pressure. The residue was treated with a little chloroform, the mixture was filtered, and the filtrate was chromatographed on 30 g. of alumina after being diluted with an equal volume of ether. The column was washed with ether–chloroform (1:1) and then with pure chloroform. When no more material was eluted, chloroform–methanol (9:1) was used for washing, whereby 0.49 g. (40%) of what appears to be mainly one isomer (isomer A) of the acetylenic tetrol XIII was eluted. This substance, without crystallization, showed m.p. 124–132°, no appreciable absorption in the ultraviolet, very strong hydroxyl band at 2.91 μ in the infrared.

The aqueous alcoholic sodium sulfite layer remaining after the extraction with *n*-butyl alcohol was diluted with 25 cc. of a 20% aqueous sodium sulfite solution and was then boiled under reflux for a further 4 hr. Extraction with *t*-butyl alcohol and subsequent chromatography on alumina, exactly as described directly above, gave 0.32 g. (26%) of material [also eluted with chloroform–methanol (9:1)] which appears to be mainly the other isomer (isomer B) of the acetylenic tetrol XIII. This material, without crystallization, showed m.p. 150–160° (depressed on admixture with isomer A), no appreciable absorption in the ultraviolet The infrared spectrum (very strong hydroxyl band at 2.92 μ) was almost identical to that of isomer A. Neither of the isomers of XIII was purified further at this stage, since purification was found to be effected most efficiently at the next stage.

1,2-Bis-[1,2-(*cis*)-dihydroxycyclohexyl]-ethane (XIV) (Isomers A and B) and the 2,2′-Diacetate XVa (Isomers A and B).—A solution of 0.49 g. of the acetylenic tetrol XIII (isomer A) in 20 cc. of methanol was shaken in hydrogen over 0.15 g. of a prereduced platinum catalyst at room temperature and atmospheric pressure. Almost exactly 2 molar equivalents of hydrogen had been absorbed after 3 hr. and uptake stopped.[34] The catalyst was removed, the filtrate was evaporated to dryness and the residue, dissolved in chloroform–ether (1:1), was chromatographed on 20 g. of alumina. The material eluted with chloroform–methanol (9:1), consisting of the saturated tetrol XIV (isomer A), weighed 0.36 g. (72%) and showed m.p. 192–200°. Crystallization from ethyl acetate–methanol gave the analytical sample as plates, m.p. 205–207°. The infrared spectrum (KBr disk) exhibited a very strong hydroxyl band at 2.91 μ.

Anal. Calcd. for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 65.38; H, 10.07.

The corresponding 2,2′-diacetate XVa (isomer A), prepared by treatment of the tetrol XIV (isomer A) with acetic anhydride in pyridine for 16 hr. at room temperature, after crystallization from hexane–ethyl acetate formed prisms, m.p. 151–152°. The infrared spectrum showed hydroxyl bands at 2.78 and 2.89 μ and acetate bands at 5.78 and 8.02 μ.

Anal. Calcd. for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 63.23; H, 8.56.

A solution of 0.32 g. of the acetylenic tetrol XIII (isomer B) in 15 cc. of methanol was hydrogenated over platinum and the product was purified by chromatography, exactly as described above for isomer A. The resulting saturated tetrol XIV (isomer B), eluted with chloroform–methanol (9:1), weighed 0.27 g. (83%) and showed m.p. 158–162°. Crystallization from ethyl acetate–methanol led to the

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(34) In some experiments the hydrogenation became very slow before the theoretical amount of hydrogen had been taken up. A second lot of platinum catalyst was added in this event, whereby the reaction proceeded to completion.

analytical sample as needles, m.p. 165–166° (depressed on admixture with isomer A). The infrared spectrum (KBr disk) (very strong hydroxyl band at 2.92 μ) was similar to that of isomer A, although definite differences were apparent.

Anal. Calcd. for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 65.40; H, 9.95.

The corresponding 2,2′-diacetate XVa (isomer B), prepared in the same way as isomer A, after crystallization from hexane–ethyl acetate, formed needles, m.p. 130–131° (depressed on admixture with isomer A). The infrared spectrum, which showed hydroxyl bands at 2.79 and 2.90 μ as well as acetate bands at 5.78 and 8.03 μ, was very similar to that of isomer A.

Anal. Calcd. for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 63.34; H, 8.66.

In some larger scale experiments it was found that the separation between the two isomers of the acetylenic tetrol XIII by the above-described preferential osmate ester cleavage was incomplete. In these cases the mixture of isomers was fully hydrogenated and then acetylated. The resulting mixture of saturated tetrol 2,2′-diacetates XVa could then be separated either by fractional crystallization from hexane–ethyl acetate (isomer B being less soluble and crystallizing first) or by chromatography on alumina (isomer A being eluted first).

1,2-Bis-[1,2-(*cis*)-dihydroxycyclohexyl]-ethane Tetraacetate (XVb) (Isomers A and B).—A solution containing 200 mg. of the tetrol XIV (isomer A) and 150 mg. of *p*-toluenesulfonic acid in 30 cc. of glacial acetic acid and 10 cc. of acetic anhydride was allowed to stand for 16 hr. at room temperature. Addition of methylene chloride, followed by washing with 5% sodium hydroxide solution and water, gave a solution which was dried and evaporated. Trituration with pentane yielded 230 mg. (70%) of the tetraacetate XVb (isomer A), m.p. 102–108°. Two crystallizations from hexane led to the analytical sample as prisms, m.p. 120–122°. The infrared spectrum showed acetate bands at 5.78 and 8.02 μ, no hydroxyl bands.

Anal. Calcd. for $C_{22}H_{34}O_8$: C, 61.95; H, 8.04; acetyl (4), 40.38. Found: C, 61.78; H, 7.96; acetyl, 40.78.

In the same way, 100 mg. of the tetrol XIV (isomer B) was converted to 110 mg. (66%) of the tetraacetate XVb (isomer B), m.p. 128–132°. Crystallization from hexane yielded a pure sample as prisms, m.p. 134–135° (depressed on admixture with isomer A). The infrared spectrum, which showed acetate bands at 5.79 and 8.02 μ but no hydroxyl bands, was very similar to that of isomer A.

Anal. Calcd. for $C_{22}H_{34}O_8$: C, 61.95; H, 8.04. Found: C, 62.19; H, 7.91.

A number of partial saponification experiments were carried out with both isomers of the tetraacetate XVb (treatment with sodium hydroxide, sodium carbonate or sodium methoxide in methanol, tetrahydrofuran, etc.) in order to obtain the corresponding ditertiary diacetate. In no case, however, could any of this diacetate be isolated.

1-Cyclohexenyl-[1,2-(*cis*)-dihydroxycyclohexyl]-acetylene (XVI) and 1-Cyclohexyl-2-[1,2-(*cis*)-dihydroxycyclohexyl]-ethane (XVII).—A solution containing 270 mg. (1.5 mmoles) of dicyclohexenylacetylene (VII) and 400 mg. (1.6 mmoles) of osmium tetroxide in 25 cc. of dry pyridine was allowed to stand in the dark for 4 days. The complex was then cleaved (boiling in ethanol with aqueous sodium sulfite for 2 hr.) and the product was isolated with chloroform. Chromatography on 10 g. of alumina and elution with benzene–chloroform (1:1) yielded 185 mg. (58%) of the vinyl-acetylenic *cis*-diol XVI as a colorless oil, $\lambda_{\max}^{\mathrm{EtOH}}$ 227 mμ (ε 15,400).

The unsaturated diol XVI (150 mg.) in 20 cc. of ethyl acetate was shaken in hydrogen over 50 mg. of a prereduced platinum catalyst. When absorption of gas had ceased (*ca.* 1 hr.), the catalyst was removed, the solvent was evaporated and the solid residue was crystallized from hexane. The resulting saturated diol XVII (105 mg., 68%) formed needles, m.p. 105–106°, possessing a pleasant odor. The infrared spectrum showed hydroxyl bands at 2.80 and 2.89 μ.

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.38; H, 11.62.

1-Cyclohexyl-2-(2-ketocyclohexyl)-ethane (XII) from the Diol XVII.—A solution containing 130 mg. of the diol XVII, 2 cc. of concd. sulfuric acid and 20 cc. of ethanol was boiled under reflux for 2.5 hr. Addition of water and isolation with ether furnished 120 mg. of product, which was chromatographed on 6 g. of alumina. Elution with pentane–benzene (4:1) yielded 64 mg. (53%) of the ketone XII as a colorless oil, the infrared spectrum of which (carbonyl band at 5.84 μ, no hydroxyl bands) was identical with that of the above-described ketone XII obtained by oxidation of X. The 2,4-dinitrophenylhydrazone after crystallization from ethanol formed yellow needles, m.p. 120–121°, undepressed on admixture with the previously described sample.

1,2-Bis-(2-ketocyclohexyl)-ethane (XI) from the Tetrol Diacetates XVa (Isomers A and B).—A mixture of 100 mg. of the tetrol diacetate XVa (isomer A), 2 g. of zinc powder and 6 cc. of dry toluene was boiled under reflux for 18 hr. by means of an oil-bath kept at 140–143°, moisture being excluded. The product was isolated with ether and chromatographed on 10 g. of alumina. Elution with pentane–ether (7:3) yielded 25 mg. (38%) of a mixture of the *meso* and racemic forms of the diketone XI, m.p. 49–66°. Three crystallizations from pentane led to a pure isomer, m.p. 82–83°, identified with the sample (m.p. 83–84°) described above, as well as with the sample (m.p. 80–82°) provided by Dr. A. Meisels,[17] through comparison of the infrared spectra and non-depression of the melting points on admixture. The combined mother liquors slowly solidified to a mass, m.p. 29–37°, showing an infrared spectrum almost identical with that of the pure isomer.

Essentially identical results were obtained when the Serini reaction was carried out with isomer B of the tetrol diacetate XVa or with the mixture of the two isomers as obtained from VII by osmium tetroxide hydroxylation, followed by hydrogenation of the resulting mixture of tetrols and subsequent acetylation. In repeated experiments, a certain variation in yield was observed, the range being 25–40%.

1-(1-Hydroxy-2-acetoxycyclohexyl)-2-(2-ketocyclohexyl)-ethane (XVIII) from the Tetrol Diacetate XVa (Isomer B).—The Serini reaction was carried out with 100 mg. of the tetrol diacetate XVa (isomer B) as described in the preceding experiment, except that the reaction time was only 10 hr. and the bath temperature was maintained at 125°. Isolation as before, followed by chromatography on 10 g. of alumina and elution with pentane–ether (7:3) gave only 9 mg. (14%) of the diketone XI, m.p. 52–65°. Further elution with pentane–ether (1:1) yielded 31 mg. (38%) of the hydroxy-acetoxy-ketone XVIII, m.p. 51–59° (possibly a mixture of stereoisomers), which after two crystallizations from hexane formed prisms, m.p. 67–68°. The infrared spectrum showed bands at 2.77 and 2.87 μ (hydroxyl), 5.79 and 8.02 μ (acetate), as well as at 5.85 μ (saturated ketone).

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 67.66; H, 8.95.

Reaction of Dicyclohexenylacetylene (VII) with N-Bromoacetamide. (a) To Give 1,2-(*trans*)-Dibromo-1,2-bis-(1,2-epoxycyclohexyl)-ethylene (XIX).—Powdered N-bromoacetamide (5 g., 0.036 mole) was added to a solution of 1.4 g. (0.0075 mole) of the dienyne VII in 36 cc. of acetone (previously distilled over potassium permanganate) and 4 cc. of water. After being allowed to stand at room temperature in the dark under nitrogen for 14 hr., the solution was poured into ice and water. The mixture was extracted with methylene chloride, the organic extract was washed with sodium thiosulfate solution and water, and was then dried and evaporated under reduced pressure in a bath kept at *ca.* 50°. The resulting material (5.2 g.)[35] was dissolved in 10 cc. of absolute ethanol and boiled under reflux for 40 minutes with a solution of 3 g. of fused potassium acetate in 30 cc. of ethanol, moisture being excluded. Addition of water and extraction with ether yielded 2.95 g. of product, which was chromatographed on 100 g. of alumina. Elution with pentane–benzene (3:2) yielded 0.37 g. (12%) of the dibromo-diepoxide XIX (probably as a mixture of the *meso* and racemic forms), m.p. 141–150°. No other crystalline substance could be isolated. Several crystallizations of XIX from hexane gave what appears to be one pure isomer as plates, m.p. 163–164°. The infrared spectrum showed bands at 10.75 and 10.89 μ (epoxide?),[29c] but no hydroxyl or carbonyl bands.

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[35] No crystalline product could be obtained when this material was chromatographed on alumina.

Anal. Calcd. for $C_{14}H_{18}Br_2O_2$: C, 44.47; H, 4.80; Br, 42.27. Found: C, 44.43; H, 4.60; Br, 42.80.

(b) **To Give 1,2-(*trans*)-Dibromo-1-(1-cyclohexenyl)-2-(1,2-epoxycyclohexyl)-ethylene (XX).**—N-Bromoacetamide (460 mg., 3.3 mmoles) was added to a solution of 313 mg. (1.7 mmoles) of the dienyne VII in 8.5 cc. of acetone and 1.5 cc. of water. The reaction, isolation of the product and subsequent potassium acetate treatment was then carried out exactly as described under (a). Chromatography on 20 g. of alumina yielded as sole crystalline material 116 mg. (18%) of the dibromo-monoepoxide XX, m.p. 65–69° (eluted with pentane–benzene (4:1)). Crystallization from aqueous methanol led to the analytical sample as prisms, m.p. 72–73°, $\lambda_{\max}^{\text{EtOH}}$ 209 mμ (ϵ 9,900). The infrared spectrum showed bands at 6.02 and 12.22 μ (trisubstituted ethylene?),[29b] 10.90 μ (epoxide?),[29c] but no hydroxyl or carbonyl bands.

Anal. Calcd. for $C_{14}H_{18}Br_2O$: C, 46.41; H, 5.01; Br, 44.20. Found: C, 46.61; H, 4.72; Br, 44.12.

1,2-(*trans*)-Dibromo-1,2-bis-(1,2-epoxycyclohexyl)-ethylene (XIX) by Addition of Bromine to the Acetylenic Diepoxide VIII.—A solution of 100 mg. (0.46 mmole) of the acetylenic diepoxide VIII in 10 cc. of carbon tetrachloride was cooled in an ice-salt-bath, and a solution of 75 mg. (0.47 mmole) of bromine in 5 cc. of carbon tetrachloride was then added dropwise with stirring and continued cooling. The solution was allowed to reach room temperature, whereby decolorization took place. The solvent was evaporated under reduced pressure and the residual crude dibromo-diepoxide isomer mixture XIX (152 mg., m.p. 138–146°) was chromatographed on 10 g. of alumina. Elution with pentane–benzene (3:2) yielded fractions, which on crystallization from hexane gave one pure isomer of XIX, m.p. 162–164°. The m.p. was undepressed on admixture with XIX (m.p. 163–164°) obtained as described above, and the infrared spectra were identical.

1-Cyclohexyl-2-(2-ketocyclohexyl)-ethane (XII) from the Dibromo-diepoxide XIX.—A solution of 235 mg. of the dibromo-diepoxide XIX (m.p. 163–164°) in 10 cc. of ethanol and 10 cc. of ethyl acetate was shaken in hydrogen over 100 mg. of a 5% palladium–charcoal catalyst at 25° and 766 mm. After *ca.* 2 hr., 86 cc. (5.7 molar equivalents) of gas had been absorbed and uptake had ceased. The catalyst was removed, the filtrate, diluted with ether, was then washed with sodium bicarbonate solution and water. The solution was dried and evaporated, yielding 145 mg. of a liquid bromine-free product containing the saturated alcohol X. This material, dissolved in 3 cc. of pyridine, was added to a mixture of 450 mg. of chromium trioxide and 5 cc. of pyridine, and the mixture was allowed to stand at room temperature for 24 hr. Isolation with benzene then yielded 82 mg. of an oil which was chromatographed on 5 g. of alumina. The only pure compound obtained was the monoketone XII (35 mg., 24%), eluted with pentane–benzene (4:1). The infrared spectrum of this substance was identical with those of the above described samples. The 2,4-dinitrophenylhydrazone formed yellow needles, m.p. 120–121°, undepressed on admixture with the previously described samples.

1,2′:2,1′-Diepoxy-*sym*-dicyclohexylethane (XXI) or 1,1′:2,2′-Diepoxy-*sym*-dicyclohexylethane (XXII) (Isomers A and B) from the Tetrols XIV (Isomers A and B).—A solution containing 40 mg. of the saturated tetrol XIV (isomer A), 0.6 cc. of concd. sulfuric acid and 6 cc. of ethanol was boiled under reflux for 2.5 hr. Isolation with ether yielded 35 mg. of material which was chromatographed on 4 g. of alumina. Pentane–benzene (9:1) eluted 21 mg. (62%) of the di-ether XXI or XXII (isomer A) as a colorless oil, which gave no yellow color with tetranitromethane. The infrared spectrum showed bands at 8.93 and 9.19 μ (ether?),[29c] but no carbonyl or hydroxyl bands.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.42; H, 9.90.

Treating the tetrol XIV (isomer B) under the same conditions produced an analogous di-ether (XXI or XXII, isomer B), also eluted with pentane–benzene (9:1). The infrared spectrum was almost identical with that of isomer A, showing ether bands at 8.93 and 9.18 μ.

1,1′-Epoxy-2,2′-dihydroxy-*sym*-dicyclohexylethane Diacetate (XXIIIb) and the Free Diol XXIIIa from the Tetrol Diacetate XVa (Isomer A).—A solution containing 200 mg. of the saturated tetrol diacetate XVa (isomer A), 2 cc. of concd. sulfuric acid and 20 cc. of glacial acetic acid was kept at 40–45° for 1 hr. Isolation with methylene chloride gave 180 mg. of material which was chromatographed on 10 g. of alumina. Elution with pentane–ether (9:1) then yielded 122 mg. (65%) of the diacetoxy-ether XXXIIIb, m.p. 96–99°. Crystallization from hexane yielded the analytical sample as plates, m.p. 101–102°. The infrared spectrum showed bands at 5.79 and 8.00 μ (acetate), but no hydroxyl bands.

Anal. Calcd. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.81; H, 8.74.

The corresponding dihydroxy-ether XXIIIa, obtained by boiling XXIIIb with a 2% solution of potassium hydroxide in methanol for 1 hr., crystallized from hexane as plates, m.p. 91–92°. The infrared spectrum showed bands at 2.80 and 2.88 μ (hydroxyl) and 9.01 μ (ether ?),[29c] but no carbonyl bands in the 5.7–6.0 μ region.

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.03; H, 10.09.

1,1′-Epoxy-2,2′-diketo-*sym*-dicyclohexylethane (XXIV) by Oxidation of the Dihydroxy-ether XXIIIa. (a) With Chromium Trioxide in Pyridine.—A solution of 70 mg. of the dihydroxy-ether XXIIIa in 2 cc. of pyridine was added to a mixture of 200 mg. of chromium trioxide and 2 cc. of pyridine, and the mixture was then shaken at room temperature for 48 hr. Isolation with benzene led to 48 mg. of material which was chromatographed on 4 g. of alumina. Elution with pentane–ether (9:1) yielded 22 mg. (32%) of the diketo-ether XXIV as a colorless oil, showing infrared bands at 5.82 μ (ketone) as well as at 8.90 and 9.16 μ (ether ?),[29c] but no hydroxyl bands. The substance was characterized as the dioxime (formed in over 90% yield), which after crystallization from acetone showed m.p. 216–217°.

Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.35; H, 8.30; N, 10.79.

(b) **With Chromium Trioxide in Acetone–Sulfuric Acid.**—Five drops of an 8 *N* chromium trioxide solution (prepared as described above for the oxidation of IX, method (b)) was added to a solution of 70 mg. of the dihydroxy-ether XXIIIa in 5 cc. of acetone. After being shaken at room temperature for 5 minutes, the mixture was diluted with water and extracted with ether. The resulting material (68 mg.) yielded by chromatography on 4 g. of alumina and elution with pentane–ether (9:1) 17 mg. (25%) of the diketo-ether XXIV as an oil with an infrared spectrum identical with that of the substance obtained by method (a). The dioxime showed m.p. 215–216°, undepressed on admixture with the sample described above.

1,2-Bis-[1,2-(*cis*)-dihydroxycyclohexyl]-(*trans*)-ethylene (XXVa) (Isomers A and B) and the 2,2′-Diacetate XXVb (Isomers A and B).—A solution of 400 mg. of the acetylenic tetrol XIII (isomer A) in 20 cc. of tetrahydrofuran was added to 250 mg. of lithium aluminum hydride in 10 cc. of ether, and the mixture was boiled under reflux for 3 hr. A saturated solution of sodium sulfate was then added, followed by solid sodium sulfate. Filtration, followed by washing with tetrahydrofuran and evaporation of the filtrate to dryness, yielded material which crystallized on addition of pentane and ether (4:1). Decantation furnished 205 mg. (51%) of the *trans*-ethylenic tetrol XXVa (isomer A), m.p. 184–190°. Crystallization from ethyl acetate-chloroform led to the analytical sample as plates, m.p. 197–199°. The infrared spectrum (KBr disk) showed strong hydroxyl bands at 2.80 and 2.90 μ as well as a band at 10.51 μ (*trans*-disubstituted double bond).[29b]

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.61; H, 9.34.

The corresponding 2,2′-diacetate XXVb (isomer A), prepared by means of acetic anhydride and pyridine (16 hr. at room temperature), after crystallization from hexane–ethyl acetate formed needles, m.p. 189–191°; infrared bands at 2.76 μ (hydroxyl), 5.79 and 8.05 μ (acetate) as well as at 10.49 μ (*trans*-disubstituted double bond).[29b]

Anal. Calcd. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.10; H, 8.24.

Full hydrogenation of the 2,2′-diacetate XXVb (isomer A) in methanol over a 5% palladium–charcoal catalyst smoothly yielded the saturated tetrol diacetate XVa (isomer A), m.p. 151–152°, undepressed on admixture with the above-described compound.

The acetylenic tetrol XIII (isomer B, 400 mg.) was reduced with lithium aluminum hydride as described for isomer A, except that the reflux time was 5 hr. (boiling under reflux for only 3 hr. gave less satisfactory results than those described). The product did not crystallize well directly, and was therefore chromatographed on 20 g. of alumina. Elution with chloroform–methanol (49:1) yielded 175 mg. (43%) of the *trans*-ethylenic tetrol XXVa (isomer B), m.p. 132–135°. Crystallization from ethyl acetate gave a pure sample as needles, m.p. 135–136°. The infrared spectrum (KBr disk), which showed definite differences from that of isomer A, exhibited bands at 2.80 and 2.91 μ (hydroxyl) as well as at 10.47 μ (*trans*-disubstituted double bond).[29b]

The corresponding 2,2′-diacetate XXVb (isomer B) crystallized from ethyl acetate–hexane as a monohydrate, m.p. 186–187° (depressed on admixture with isomer A); infrared bands at 2.78 μ (hydroxyl), 5.79 and 8.06 μ (acetate) as well as at 10.50 μ (*trans*-disubstituted double bond).[29b]

Anal. Calcd. for $C_{18}H_{28}O_6.H_2O$: C, 60.31; H, 8.44. Found: C, 60.67; H, 8.20.

Full hydrogenation of the 2,2′-diacetate XXVb (isomer B) in methanol over a 5% palladium–charcoal catalyst readily yielded the saturated tetrol diacetate XVa (isomer B), m.p. 129–130°, undepressed on admixture with the previously described sample.

1,2-Dicyclohexenyl-(*trans*)-ethylene (XXVI) from the (*trans*)-Ethylenic Tetrol Diacetates XXVb (Isomers A and B).—The reduction of the ethylenic tetrols XXVa and the corresponding diacetates XXVb with phosphorus diiodide was carried out under several different conditions, whereby either unchanged starting material or the conjugated triene XXVI was obtained. The following experiment to give XXVI is typical.

Phosphorus diiodide[31] (70 mg.) was added in portions during 15 minutes to a stirred solution of 60 mg. of the diacetate XXVb (isomer A) in 3 cc. of tetrahydrofuran, under purified nitrogen, and the dark brown-black reaction mixture was then stirred at room temperature for a further 20 minutes. After addition of ether, the mixture was washed successively with sodium hydroxide solution, sodium thiosulfate solution and water. The dried extract on evaporation yielded a residue (26 mg.) showing $\lambda_{\max}^{\text{EtOH}}$ 259, 269 and 280 mμ (ε 22,100, 25,100 and 21,800), indicating it to be mainly the triene XXVI [reported[6b]: $\lambda_{\max}^{\text{MeOH}}$ 260, 269 and 281 mμ (ε 23,960, 26,160 and 23,060)].

The diacetate XXVb (isomer B) on analogous treatment with phosphorus diiodide gave an essentially identical result.

[Contribution from the Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Md.]

Conformational Mobility of (−)-α-Phellandrene, Deduced from its Optical Rotatory Dispersion

By Herman Ziffer, Elliot Charney and Ulrich Weiss

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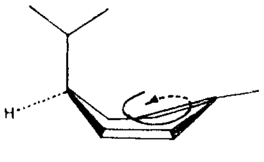
The optical rotations of (−)-α-phellandrene (I) and 3,5-cholestadiene (III) have been measured at 11, 23, and 82°. The observed temperature-dependence of the rotation of I, but not of III, is interpreted as indicating the existence of a mobile equilibrium between two conformations of I. The populations and relative stabilities of these conformers are discussed. It is concluded that one of these conformers Ia has the larger rotational strength, but it is present in smaller concentrations than Ib, at least at room temperature.

In a recent communication from this Laboratory[1] it was deduced from the rotatory dispersion curve of (−)-α-phellandrene that the preferred conformation of this molecule is that in which the isopropyl group is quasi-axial (IA). This conclusion was based on the "skewed diene" rule[2] which allows the sign of the optical rotation of a molecule containing a non-planar cisoid diene to be predicted from the skew sense or helicity of the diene: if the four carbon atoms of the conjugated system form a left-handed helix, its contribution on the long-wave length side of the diene absorption band produces levorotation, whereas a right-handed helix produces dextrorotation. Furthermore, the contribution to the optical activity produced by the skewed diene is much greater than that associated with, *e.g.*, an asymmetric carbon atom. Consequently, the rotatory dispersion in the vicinity of the diene absorption will largely reflect the relative orientation of the double bonds of the chromophore. By this reasoning, in the case of (−)-α-phellandrene of known absolute configuration, the observed *negative* rotation suggested that the predominant conformer at room temperature was the quasi-axial (IA) rather than the quasi-equatorial (IB) one, since in the former the diene system has left-handed skew sense.

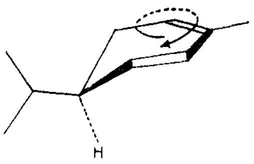
As Table I shows, the molar rotation, [M], of (−)-α-phellandrene at the first extremum is much lower than that of (+)-*trans*-9-methyl-1,4,9,10-tetrahydronaphthalene[2] (II), although the $\lambda_{\max}$ and $\epsilon_{\max}$ of the two compounds are almost identical. Similarly, 2,4-cholestadiene (III), with only twice the value of $\epsilon_{\max}$, has an [M] about ten times that of (−)-α-phellandrene. These facts suggested the

IA



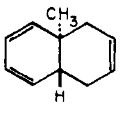
Levorotatory

IB

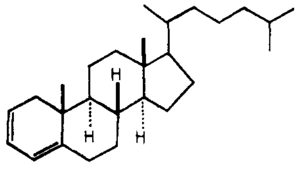


Dextrorotatory

II



III



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[1] A. W. Burgstahler, H. Ziffer and U. Weiss, *J. Am. Chem. Soc.*, **83**, 4660 (1961).

[2] A. Moscowitz, E. Charney, U. Weiss and H. Ziffer, *ibid.*, **83**, 4661 (1961).