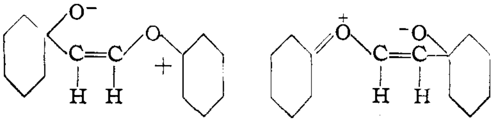
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

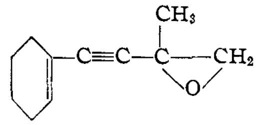
Synthesis and Properties of Spiranes Containing Oxygen Heterocycles

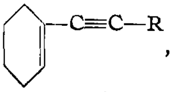
BY J. D. CHANLEY

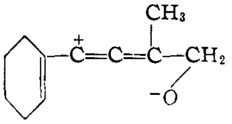
This investigation[1e] concerns itself with the preparation and properties of the *dl*-bis-epoxide of symmetric dicyclohexylethane (IV). This compound contains a new and interesting dispirane system. Numerous investigations of the ultraviolet absorption spectra of compounds containing a cyclopropyl group[1d] or epoxy group,[1c,2] adjacent to an unsaturated grouping, such as an ethylenic linkage, a carbonyl, phenyl, or pyridyl group, have shown that such compounds exhibit a shift of absorption to the longer wave lengths. This phenomenon as well as chemical evidence[3] indicates that three-membered rings resemble in many respects the ethylenic linkage. In these systems, the observed shift in the spectrum is commonly attributed to the participation of the three-membered ring in some of the excited (ionic) states of the molecule.[1a–d] It was of interest to investigate whether an epoxy-group, adjacent to a second one or to an acetylenic linkage, would display similar spectral properties. The *dl*-bis-epoxide of *sym*-dicyclohexylethane (IV) was prepared and proved to be completely transparent down to λ = 214 mμ. A possible explanation is that such excited states as



which presumably would favor a shift in the spectrum toward the longer wave lengths, are extremely improbable. In this connection, it is of interest to know that the maximum of the 3,4-epoxide of 1-cyclohexenyl-3-methyl-1-butyne is



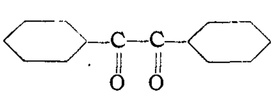
as low as 230 mμ.[4] The max. values[4] for systems of the type , with R denoting a saturated group, lie in the range 227–229 mμ. The epoxy group in this instance does not appear to possess double bond character. It is extremely unlikely that hypothetical excited states as



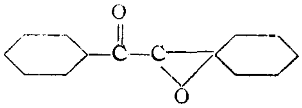
which would produce a shift of absorption to longer wave lengths, occur.

The synthesis and proof of structure of the bis-epoxide (IV) are outlined in the Scheme. The assigned *cis* configuration for 1,1′-vinylene-bis-cyclohexanol (II) is based on the general experience that mild catalytic hydrogenation of an acetylenic linkage produces the *cis* ethylenic derivative.[5] The α,β-(1,1′-dihydroxycyclohexyl)-α,β-dibromoethane (III), obtained by bromination of the ethylenic compound (II), is a racemate since bromine adds *trans* to ethylenic linkages.[6] The assigned structure for compound III was further confirmed by catalytic reduction of the dibromide to the *sym*-1,1′-ethylene bis-cyclohexanol (XII), identical with the product resulting from the complete catalytic reduction of 1,1′-ethynylene-bis-cyclohexanol (I), or of 1,1′-vinylene-bis-cyclohexanol (II).

Dehydrohalogenation of the double bromohydrin III yielded the *dl*-bis-epoxide of *sym*-dicyclohexylethane (IV). Since it is generally accepted that, both in the opening and in the formation of epoxy rings, an inversion at one of the carbon atoms ensues,[7a–h] it is therefore postulated that the racemic form only of the bis-epoxide IV may be expected from the racemic double bromohydrin III, since inversion would occur at each of the carbon atoms,[7d,g,h] bearing bromine atoms in III. Other conceivable structures for the new compound with the correct empirical elementary composition such as



(A)



(B) and VII

were considered at the time, but eliminated for the following reasons: (a) Compound IV gave no ketonic derivatives; (b) Compound A has been

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(1) (a) Carr and Burt, THIS JOURNAL, **40**, 1590 (1918); (b) Klotz, *ibid.*, **66**, 88 (1944); (c) Rogers, *ibid.*, **69**, 2544 (1947); (d) Mariella, Peterson and Ferris, *ibid.*, **70**, 1494 (1948); (e) the results of this investigation were presented before the Section of Organic Chemistry at the Semi-Annual Meeting of the American Chemical Society, August 30, 1948, in Washington, D. C.

(2) Heilbron, Johnson, Jones and Spinks, *J. Chem. Soc.*, 727 (1942).

(3) Kohler and Conant, THIS JOURNAL, **39**, 1404 (1917).

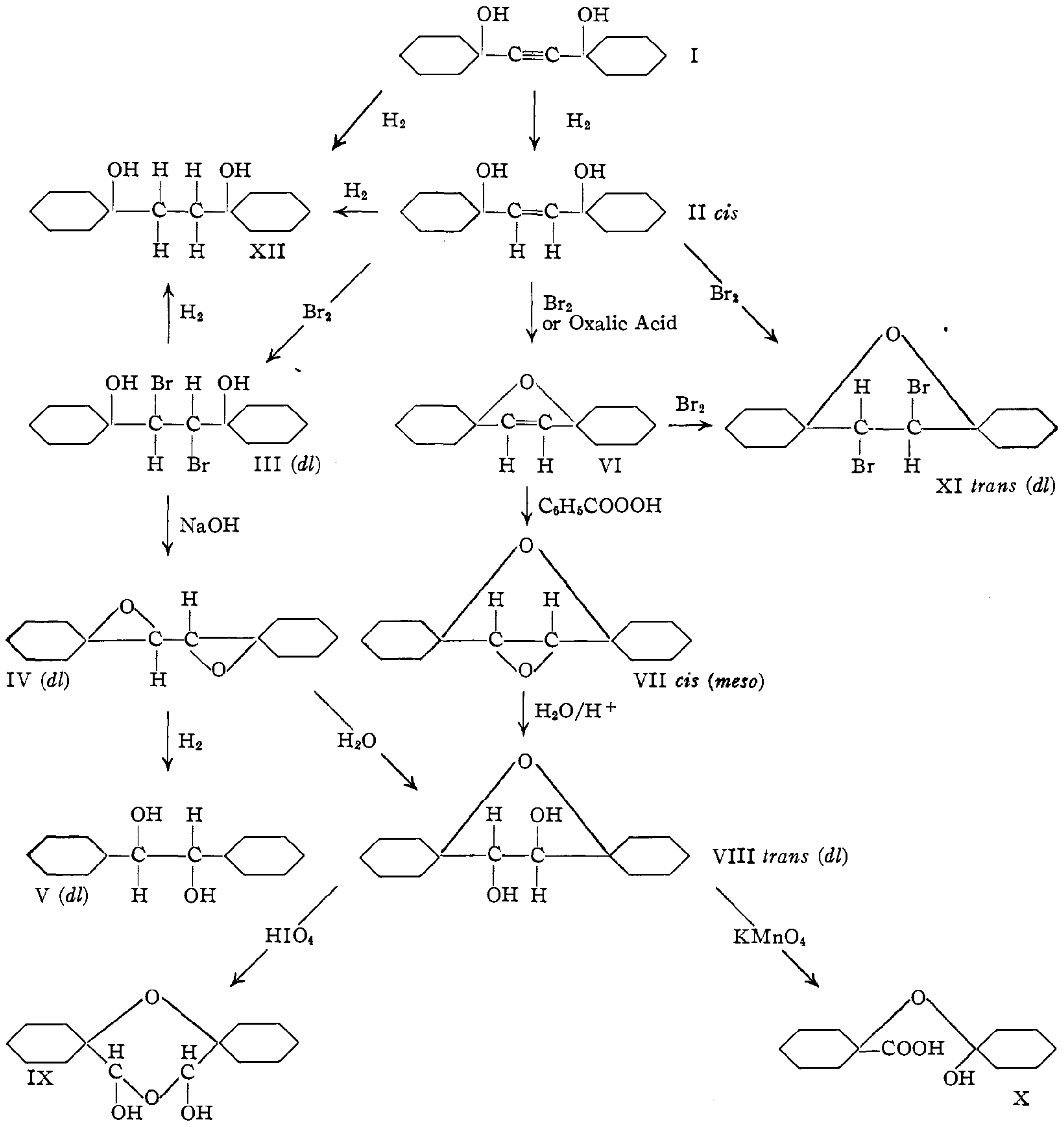
(4) Sobotka and Chanley, *ibid.*, **70**, 3914 (1948); *cf.* Milas, *et al.*, *ibid.*, **70**, 1584 (1948).

(5) Bourguel, *Bull. soc. chim.*, [4] **45**, 1067 (1929); Campbell and O'Connor, THIS JOURNAL, **61**, 2897 (1939).

(6) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 147.

(7) (a) Kuhn and Ebel, *Ber.*, **58**, 919 (1925); (b) Böeseken, *Rec. trav. chim.*, **47**, 683 (1928); (c) Wilson and Lucas, THIS JOURNAL, **58**, 2396 (1936); (d) Winstein and Lucas, *ibid.*, **61**, 1576, 1581 (1939); (e) Lucas, Schlatter and Jones, *ibid.*, **63**, 22 (1941); (f) Lucas and Gould, *ibid.*, **63**, 2541 (1941); (g) Winstein and Grunwald, *ibid.*, **70**, 828 (1948); (h) Swern, *ibid.*, **70**, 1235 (1948).

Scheme



synthesized[8] and its properties bear no resemblance to those of compound IV; (c) compound VII was prepared in the course of the present investigation and proved to be different from compound IV. Confirmatory evidence for the assigned structure was obtained when the bis-epoxide yielded, on catalytic hydrogenation, the *dl*-α,β-dicyclohexylethylene glycol (V). Since the oxygen atoms remain attached to the same carbon atom after hydrogenolysis of the racemic bis-epoxide, the glycol of m. p. 154° must necessarily be a racemate. This compound is identical with the so-called "iso-α,β-dicyclohexylethylene-glycol" of m. p. 153°, prepared by Buck and Ide[9] by condensation of glyoxal and cyclohexylmagnesium bromide. Thus, the *meso* configuration should be assigned to the isomeric α,β-dicyclohexylethylene glycol, m. p. 194°, obtained by the catalytic reduction of benzoin.[10]

Treatment of the bis-epoxide IV with water in a sealed tube did not give the tetrahydroxy compound, but rather the 3,4-dihydroxy-dispiro[dicyclohexane-tetrahydrofuran] (VIII).[11,12] This was confirmed by the following synthesis; di-

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[8] Pinkney, Nesty, Wiley and Marvel, *ibid.*, **58**, 972 (1936); Fisher and Stoffers, *Ann.*, **500**, 253 (1933).

[9] Buck and Ide, This Journal, **54**, 820 (1932).

[10] Buck and Ide, *ibid.*, **53**, 3510 (1931).

[11] *Cf.* Przybytek, *Ber.*, **18**, 1352 (1885).

[12] This designation follows rule 23 for nomenclature of spiro systems, Patterson and Capell, "Ring Index," Reinhold Publ. Corp., New York, N. Y., 1940, p. 27. Under rule 22 this compound would be named 7,8-dihydroxy-15-oxa-trispiro[5,2,5,1]-pentadecane,

spiro[dicyclohexane-2,5-dihydrofuran] (VI), was prepared from compound II according to Burkhardt and Hindley.[13] This compound, when treated with perbenzoic acid, yielded the 3,4-epoxide (VII). This epoxide, on hydrolysis with a trace of acid, gave the expected *trans*-glycol, 3,4-dihydroxy-dispiro[dicyclohexane-2,5-tetrahydrofuran] (VIII). The *trans* position of the hydroxy groups with reference to the plane of the furan ring is anticipated since oxide rings open with inversion.[7]

This compound (VIII), on treatment with an equivalent amount of periodic acid, gave a quantitative yield of a new compound of elementary composition and molecular weight $C_{14}H_{24}O_4$. It gave no fuchsin test for aldehyde nor is it soluble in strong base, thus excluding a lactone formulation; therefore it is tentatively formulated as an internal acetal of a dialdehyde with a *p*-dioxane structure (IX). On oxidation of compound VIII with potassium permanganate in water or pyridine, a new acid $C_{13}H_{22}O_4$ was formed which has been tentatively assigned the structure X.

The bromination of 1,1′-vinylene-dicyclohexanol (II) yielded, in addition to the main product (III), relatively minor quantities of two by-products. One of them was free of bromine and proved to be identical with the dihydrofuran derivative VI. Evidently, the hydrobromic acid, whose evolution was observed during the bromination and must be ascribed to some minor side-reaction, is responsible for the furan formation from the 1,4-glycol (II). This is in analogy to the cyclizing effect of oxalic acid, leading to the same product.[13]

As the second by-product in the bromination, we have found *dl*-3,4-*trans*-dibromo-dispiro[cyclohexane-2,5-tetrahydrofuran] (XI). This substance was also obtained by bromination of the dihydrofuran (VI), which as stated in the preceding paragraph, was obtained in two ways: by the procedure of Burkhardt and Hindley and as the first by product in the above reaction. The transformation of compound III into compound XI by boiling with oxalic acid could not be effected.

Experimental

1,1′-Ethynylene-bis-cyclohexanol (I).—This was prepared from acetylenedimagnesium bromide[14] and cyclohexanone according to the procedure of Du Pont[15] and Marvel[8] m. p. 108–109°; reported[8] m. p. 108–110°.

1,1′-Vinylene-bis-cyclohexanol (II).—Forty grams of compound I was dissolved in 100 cc. of absolute ethanol and hydrogenated at 2–3 atm. pressure in the presence of 0.5 g. of platinum oxide as catalyst. Hydrogenation was interrupted after 1 mole of hydrogen had been absorbed after twenty to thirty minutes, hydrogen uptake then slackened perceptibly and the product precipitated in the hydrogenation flask. The mixture was boiled down to 35 cc., filtered, cooled and the product recrystallized from ethanol; yield, 60–70%, m. p. 150–151°; reported 153–154[16]; 152°.[17] The same product was obtained when hydrogenation was carried out in the presence of a 5% palladium on barium sulfate catalyst at atmospheric pressure.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.79. Found: C, 75.00; H, 10.88.[18]

***dl*-α,β-(1,1′-Dihydroxycyclohexyl)-α,β-dibromoethane** (III).—**Dispiro[dicyclohexane - 2,5 - dihydrofuran]** (VI). **3,4-*trans*-Dibromo-dispiro[dicyclohexane-2,5-tetrahydrofuran]** (XI).—A solution of 64.8 g. (0.4 mole) of bromine in 600 cc. of dry carbon tetrachloride was added over a period of three hours to a vigorously stirred, ice cooled, illuminated (light bulb or sunlight) suspension of 90 g. (0.4 mole) compound II in 600 cc. of dry carbon tetrachloride. The reaction was allowed to continue for an additional forty-five minutes at the end of which time the evolution of hydrogen bromide became particularly evident. The precipitated product, after filtration and washing with small portions of cold carbon tetrachloride (the filtrates and washings were combined and will henceforth be referred to as filtrate A), was immediately refluxed for sixteen hours with 1000 cc. of carbontetrachloride, at the end of this refluxing period the evolution of hydrogen bromide ceased and formation of water droplets in the condenser was noted. The refluxing is necessary because attempts to purify the product by recrystallization alone gave material contaminated with an impurity which turned purple on standing. The carbon tetrachloride solution was decanted from precipitated tar, evaporated to 450 cc., cooled and the dibromohydrin collected. (The filtrate will henceforth be referred to as B.) Recrystallization from carbon tetrachloride gave product III m. p. 128–130° (decomposition) in 50% yield.

Anal. Calcd. for $C_{14}H_{24}O_2Br_2$: C, 43.74; H, 6.30; Br, 41.61. Found: C, 43.54; H, 6.19; Br, 40.78.

Filtrate A after refluxing for sixteen hours, during which time a copious evolution of hydrogen bromide and formation of water was noted, was then combined with filtrate B and the burgundy-colored solution was evaporated to dryness. The residue was treated with 500 cc. of petroleum ether (40–60° b. p.), cooled in ice and filtered from a dark violet solid (unidentified) (5–7 g.). The petroleum ether solution after two successive passages through a column (16 cm. length and 1.5 cm. internal diam.) of activated aluminum oxide (−80 mesh ALCOA) was evaporated to dryness. The partially crystalline residue (30 g.) was triturated with 100 cc. of cold 95% ethanol and filtered. Four grams of compound VI was obtained on recrystallization from ethanol m. p. 95–96°; it showed no depression of m. p. on admixture with an authentic sample of m. p. 95–96°.[13]

Distillation of the alcohol soluble portion gave 3 g. of the pure dihydrofuran VI b. p. 117–118° (9.5 mm.); $n^{25}D$ 1.4915. Reported 116–118° (10 mm.).[13] The identity of this fraction was confirmed by the preparation of its dibromo derivative which melted at 95–96° and showed no depression of melting point on admixture with the authentic sample. Four grams of unidentified high boiling material was present in the alcohol soluble portion.

Hydrogenation of *dl*-α,β-(1,1′-Dihydroxycyclohexyl)-α,β-dibromoethane (III) **to 1,1′-Ethylene-bis-cyclohexanol** (XII).—One hundred and ninety-eight mg. of compound XII in 25 cc. of ethanol was hydrogenated at atmospheric pressure employing 200 mg. of 5% palladium on calcium carbonate as catalyst. Hydrogenation ceased after the theoretical quantity (2 mole) of hydrogen was absorbed. The saturated glycol, obtained in quantitative yield, was recrystallized from petroleum ether (40–60°). It melted at 128–129° and showed no depression in m. p. on admixture with an authentic sample m. p. 128–129°

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[13] Burkhardt and Hindley, *J. Chem. Soc.*, 987 (1938).

[14] Jozitch, *Bull. soc. chim.*, [3] **32**, 552 (1904); *cf.* Werner and Reynolds, THIS JOURNAL, **69**, 633 (1947).

[15] Du Pont, *Ann. chim.*, [8] **30**, 485 (1913).

[16] Pinkney, Nesty, Pearson and Marvel, THIS JOURNAL, **59**, 2662 (1937).

[17] Zal'kind, *J. Gen. Chem.* (*USSR*), **5**, 1723 (1935); *C. A.*, **30**, 3407 (1936).

[18] We are indebted for the microanalyses to the late Dr. Gertrude Oppenheimer, Microchemical Laboratory, California Institute of Technology, Pasadena, Calif.

prepared by the hydrogenation of 1,1′-vinylenebiscyclohexanol (II) in glacial acetic acid at atmospheric pressure in the presence of PtO_2 as catalyst. Reported 128–129°.[16]

***dl*-Bis-epoxide of *sym*-Dicyclohexylethane (IV).**—A solution of 17.2 g. (0.45 mole) of sodium hydroxide in 600 cc. of ethanol was added over a period of five minutes to a solution of 68 g. (0.177 mole) of the double bromohydrin (III) and set aside to stand for one to two days. After removal of the precipitated sodium bromide, the alcohol solution was evaporated almost to dryness *in vacuo* and the residue was treated with 400 cc. of ice water. The solid product was collected by filtration and recrystallized from petroleum ether (40–60°); colorless crystals, m. p. 58–58.7°; yield, 35–36 g. (90%).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.91; H, 10.02.

***dl*-α,β-Dicyclohexylethylene Glycol (V).**—Two and three-tenths grams of the bis-epoxide IV dissolved in 30 cc. of purified glacial acetic acid was hydrogenated at atmospheric pressure in the presence of 200 mg. of platinum oxide as catalyst. It was necessary to add an additional 200 mg. of catalyst to bring the hydrogenation to completion (2 mole of hydrogen were absorbed). Evaporation of the solvent and recrystallization of the residue from Skellysolve L (b. p. 93–129°) gave crystals of m. p. 153–154°; reported 153°.[9]

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.30; H, 11.58. Found: C, 74.18; H, 11.49.

3,4-Expoxide of Dispiro[dicyclohexane-2,5-tetrahydrofuran] (VII).—Compound VI (b. p. 116–118° (10 mm.) $n^{25}D$ 1.4900) was prepared according to the method of Burkhardt and Hindley[13] by boiling compound II with oxalic acid. It gave the authentic dibromide, m. p. 95–96°, on bromination according to the procedure of the same authors.

A solution of 16 g. (0.077 mole) compound (VI) was allowed to stand for one week at room temperature with 275 cc. of perbenzoic acid solution in carbon tetrachloride which contained 1.58 g. (0.1 mole) of active oxygen. At the end of this time the theoretical amount of oxygen had been absorbed. The carbon tetrachloride solution was washed thoroughly with 10% sodium hydroxide, water and dried over anhydrous sodium sulfate. Distillation gave a slight forerun of starting material and 10 g. of pure compound (VII) b. p. 143° (10 mm.) $n^{25}D$ 1.4930.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.58; H, 10.06.

***dl*-3,4-Dihydroxy-dispiro[dicyclohexane-2,5-tetrahydrofuran] (VIII). (a) From Compound (IV).**—A sealed tube containing 25 g. of the bis-epoxide (IV) and 75 cc. of water was heated at 120° for two to three days. After separating the water by decantation the residual viscous oil was mixed with 300 cc. of petroleum ether (40–60°) and cooled in ice; the product crystallized in felt-like needles. Recrystallization from Skellysolve L, b. p. 93–129° gave 7 g. of pure material m. p. 145–146°.

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 70.07; H, 10.00. Found: C, 70.18; H, 9.67.

The residue after evaporation of the original petroleum ether was evaporatively distilled at 0.1 mm. and the fraction collected at 50–60° was redistilled to yield 4 g. of starting material boiling at 118–119° (0.5 mm.) $n^{25}D$ 1.4940 which solidified on standing. After recrystallization from petroleum ether (40–60°) it melted at 57–58° and showed no depression in melting point on admixture with the bis-epoxide (IV). The remainder of the petroleum ether solution were intractable polymers; yield, 30–35% based on recovered starting material.

(b) From Compound (VII).—One gram of compound (VII) was mixed with 10 cc. of water, containing three drops of dilute hydrochloric acid (hydrolysis did not occur with water alone) and heated in a sealed tube for two days at 120°. The reaction mixture was worked up as described above. Three-tenths of a gram of product, m. p. 145–146°, was obtained which showed no depression in m. p. when mixed with the glycol (VIII) as obtained above.

Compound $C_{14}H_{24}O_4$ (IX).—A suspension of 1.23 g. (0.005 mole) of the glycol (VIII) in 35 cc. of the solution of periodic acid containing 0.0054 equivalent of oxidizing agent was shaken mechanically for sixteen hours. The product was collected by filtration and recrystallized from 35% aqueous ethanol; yield 90% m. p. 133° (dec.). Molecular weight determination by Rast: 243 (camphor); average of four determinations (pinene dibromide): 260, calcd. 256.

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.45. Found: 65.76; H, 9.46.

Compound $C_{13}H_{22}O_4$ (X).—A mixture of 700 mg. (0.0029 mole) of compound (VIII), 1.05 g. (0.006 equivalent) of potassium permanganate in 30 cc. of 3.3% sodium hydroxide solution was heated on steam-bath with occasional shaking for fifteen to twenty minutes. The mixture was cooled and filtered. Acidification with dilute hydrochloric acid of the filtrate yielded the acid which after recrystallization from Skellysolve C (86–100°) melted with decomposition at 132–134°. The same product was obtained by oxidation of compound (VIII) by potassium permanganate in dried pyridine.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.42; H, 9.15. Found: C, 63.96; H, 9.02.

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Summary

The preparation and properties of the *dl*-bis-epoxide of symmetric dicyclohexylethane and of the isomeric 3,4-epoxide of dispiro[dicyclohexane-2,5-tetrahydrofuran] are described and discussed.

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