ring structures. The increase in J_{H_5,H_6} from 2.5 cps for type IV materials to 9 cps for type VI indicates a large change in environment for these protons.

Registry No.—I, 10562-19-3; III, 10562-21-7; IVa, 10562-22-8; IVb, 10562-23-9; IVc, 10562-24-0; IVd, 10562-25-1; VIa, 10562-20-6; VIb, 10562-26-2; VIc, 10562-27-3; VId, 10562-28-4; VIe, 10562-29-5; VIf, 10562-30-8.

Acknowledgment.—The author wishes to express his gratitude to Dr. E. E. Gilbert and Professor J. Meinwald for helpful discussions, to Dr. J. O. Peterson for obtaining and interpreting the nmr data, and to Mr. Stephen Horensky for performing much of the experimental work.

Synthesis of *cis,cis*-4,8-Dimethyl-*cis*-2-oxa-6-ketodecahydroazulene. A Precursor in an Attempted Synthesis of β-Vetivone

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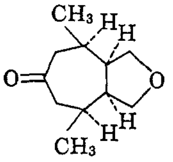
The synthesis of *cis,cis*-4,8-dimethyl-*cis*-2-oxa-6-ketodecahydroazulene (**1**) was undertaken to develop a stereospecific route to a seven-membered ring from the readily accessible unsaturated ether **2**. Through conversion of the tetrahydrofuran ring to the corresponding carbocyclic ring system, the intermediate **1** was envisioned as a precursor in a synthetic route to **3**.



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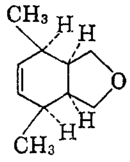

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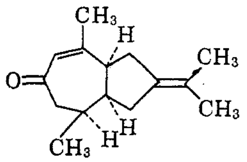


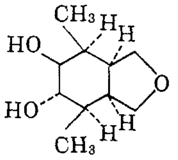
3

Structure **3** has been proposed for the sesquiterpene, β-vetivone.[2] The remarkably similar chemistry and physical properties of α- and β-vetivone led Naves and Perrotet to conclude that they differed only in the asymmetric center bearing the methyl group. However, a new structural formulation has been proposed for α-vetivone.[3]

The experimental facts do not rule out the structure of β-vetivone as being epimeric with **3** in having the methyl group and the ring-fusion hydrogens *cis*, that is, the structure originally assigned to α-vetivone.[2] It is possible that **1** may or may not be related to β-vetivone. The configuration of the methyl group in β-vetivone could be unambiguously established by a stereospecific conversion of **1** to **3** and a comparison of the latter compound to natural β-vetivone.

Results and Discussion

The reaction of **2** with performic acid has previously been reported by us as yielding the diol **4**.[4] The reaction of **4** with aqueous sodium periodate at 0° yielded the crude dialdehyde **5** in nearly a quantitative yield. The reduction of **5** to the diol **6** (R = H) was effected using sodium borohydride in methanol at 0°. This diol **6** (R = H) had previously been prepared by us *via* the sodium bismuthate oxidation of **4** and reduction of **5** to **6** (R = H) by use of lithium aluminum hydride.[4] The sodium periodate–sodium borohydride route is operationally simpler and also results in higher over-all yields.



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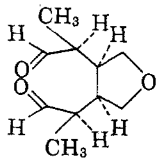

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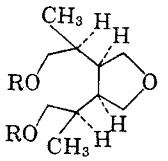

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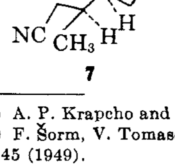
In order to obtain experimental data as to whether enolization of **5** under the oxidation conditions might effect the stereochemistry of the methyl groups, the sodium periodate oxidation was performed in deuterium oxide at 0°. Infrared analysis of the crude dialdehyde **5** showed no detectable incorporation of deuterium. The nmr [deuteriochloroform solution with values reported in parts per million (ppm) with TMS as an internal standard] exhibited a sharp doublet centered at 1.30 which can be assigned to the methyl groups ($J \sim 6$ cps with the adjacent hydrogen). A complex multiplet centered at 2.5 can be attributed to the tertiary hydrogens. A multiplet centered at 3.8 can be assigned to the hydrogens adjacent to the oxygen function, while a sharp doublet centered at 9.62 can be attributed to the protons of the aldehyde groups. Integration is in accord with the formulation of the structure as **5**. It seems reasonable to assume that no isomerization of the methyl groups occurred under the oxidation conditions utilized.

The formation of the ditosylate **6** (R = Ts) was readily effected by reaction of **6** (R = H) with excess *p*-toluenesulfonyl chloride in pyridine solution. The dinitrile **7** was obtained by reaction of the ditosylate with sodium cyanide using dimethyl sulfoxide as the reaction medium. The dinitrile **7** was quantitatively hydrolyzed to the diacid **8** by refluxing with aqueous sodium hydroxide followed by acidification. Pyrolysis of this diacid from a barium hydroxide–iron powder mixture[5] produced the ketone **1** in a 25% yield.

The structure of the ketone **1** was established by nmr spectroscopy. The spectrum (carbon tetrachloride solution with values reported in parts per million using TMS as an external standard) exhibited a doublet



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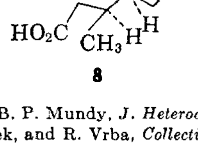

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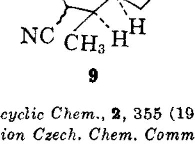

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[1] (a) National Defense Education Act Fellow, 1962–1965. (b) Abstracted in part from a thesis presented to the Graduate College of the University of Vermont, Sept 1965, in partial fulfillment of the requirements for the Ph.D. degree.

[2] (a) Y. R. Naves and E. Perrotet, *Helv. Chim. Acta*, **24**, 3 (1941). (b) For a summary of the experimental data, see J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, London, 1952, pp 224–232.

[3] K. Endo and P. de Mayo, *Chem. Commun.*, **2**, 89 (1967).

[4] A. P. Krapcho and B. P. Mundy, *J. Heterocyclic Chem.*, **2**, 355 (1965).

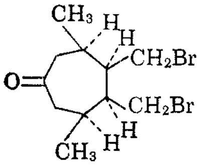
[5] F. Šorm, V. Tomasek, and R. Vrba, *Collection Czech. Chem. Commun.*, **14**, 345 (1949).

centered at 1.00 which can be assigned to the methyl groups. An unresolved multiplet centered at 3.72 can be attributed to the four hydrogens adjacent to the oxygen function. A complex multiplet centered at 2.33 can be assigned to the remaining eight hydrogens. Integration is in accord with this interpretation.

In an alternate route to **1**, the dinitrile **7** was cyclized using potassium *t*-butoxide in refluxing benzene. Hydrolysis of the crude reaction mixture with dilute hydrochloric acid yielded the ketonitrile **9**. The infrared spectrum (potassium bromide pellet) showed weak cyanide absorption at 4.46 and strong carbonyl absorption at 5.87 μ. Several attempts to convert **9** to **1** under acid hydrolysis were not very promising as only trace amounts of **1** could be isolated. The crude hydrolysis products exhibited strong hydroxyl absorption in the infrared suggestive of ring opening of the ether linkage.

The conversion of **1** to **10** was attempted in order to obtain a possible precursor to the corresponding carbocyclic skeleton. It was expected that **10** might be converted into **11** by way of the displacement reaction with diethyl malonate. Intermediate **11** could then be converted into **3** in a series of steps.

Several methods are available for the conversion of ethers to the corresponding dihalo compounds. Anderson[6] has recently utilized triphenyldibromophosphorane as a mild reagent for ether opening. In a model run, the reaction of **12** with triphenyldibromophosphorane in acetonitrile at room temperature yielded **13** in a fair yield. All attempts to convert **1** to **10** *via* this reaction have been unsuccessful as oils were obtained from which no pure **10** could be isolated. At this stage further work was abandoned on this approach to **3**.



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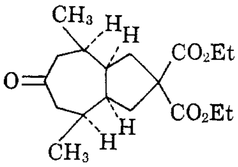

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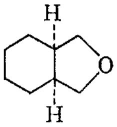

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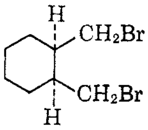

13

Experimental Section

***cis*-3,4-Di(1-hydroxy-2-propyl)tetrahydrofuran (6, R = H).**—The glycol **4**[4] (2.0 g, 0.011 mole) was placed in 20 ml of distilled water in a two-necked, 100-ml flask. In an addition funnel was placed 3.0 g (0.014 mole) of sodium periodate dissolved in 30 ml of water. The diol solution was cooled in an ice bath and the sodium periodate solution was added dropwise over a period of 0.5 hr. The mixture was allowed to stir in the ice bath for 1 additional hr after completion of the addition. The mixture was extracted with four 10-ml portions of methylene chloride and the extracts were dried over sodium sulfate. Removal of the solvent under water aspirator pressure, then vacuum pump pressure, yielded 1.8 g (95%) of the crude dialdehyde **5**. This was spectrally identical with the oxidation product previously obtained using sodium bismuthate.[4]

The crude dialdehyde was dissolved in 20 ml of anhydrous methanol. This solution was added over a period of a few minutes to 0.5 g of sodium borohydride in 10 ml of methanol which was cooled in an ice bath. After a few minutes, 0.2 g of additional sodium borohydride was added to the mixture. The mixture was allowed to stir for 15 min. The solvent was removed under water aspiration and then 3 ml of water was added. The diol was extracted with methylene chloride and the extracts were dried over sodium sulfate. The solvent was removed by water aspiration and then finally under vacuum pump pressure. This yielded 1.8 g (96%) of solid **6**. This material was identical with the diol previously prepared by lithium aluminum hydride reduction.[4]

The oxidation in deuterium oxide was performed as above. The nmr of the crude dialdehyde was reported in the Discussion.

The Di-*p*-toluenesulfonate of *cis*-3,4-Di(1-hydroxy-2-propyl)tetrahydrofuran (6, R = Ts).—The *p*-toluenesulfonyl chloride (22.9 g, 0.12 mole) was dissolved in 60 ml of dry pyridine and the solution was cooled in an ice bath. To this stirred solution was added, dropwise over a period of 3 hr, the diol **6** (R = H, 10.0 g, 0.053 mole) in 40 ml of pyridine. After the addition had been completed, the reaction mixture was stoppered and placed in the freezer overnight.

The mixture was poured into ice water, and after a few minutes the heavy oil solidified. The solid was filtered and washed thoroughly with water. After air drying there was obtained 21 g (83% yield) of the ditosylate with a melting point of 94–95°. Recrystallization could be effected from absolute ethanol with no change in the melting point.

The infrared spectrum (potassium bromide pellet) showed a peak for the aromatic ring at 6.25 μ (1600 cm^{-1}) and two strong peaks characteristic of SO_2 stretches at 7.38 (1352 cm^{-1}) and 8.50 μ (1176 cm^{-1}).

Anal. Calcd for $C_{24}H_{32}O_7S_2$: S, 12.91. Found: S, 13.14.

***cis*-3,4-Di(1-cyano-2-propyl)tetrahydrofuran (7).**—The ditosylate **6** (R = Ts, 10.0 g, 0.02 mole) and 7.0 g (0.14 mole) of sodium cyanide were placed in 100 ml of dry dimethyl sulfoxide. The suspension was heated in an oil bath at 135° for about 1 hr. The mixture was cooled slightly and the bulk of the solvent was distilled off under the reduced pressure of the water aspirator. The residual solvent was then removed under vacuum pump pressure of about 1 mm with heating. Water was added to the residue and the solid which separated was filtered and washed thoroughly with water. To obtain more product the aqueous filtrate was extracted three times with 25-ml portions of methylene chloride. The solvent was removed under reduced pressure and water was added to the remaining oil. The material solidified and was filtered and combined with the first crop dicyanide. The yield of the crude dicyanide was 3.3 g (81% yield), 76–79°. Recrystallization from ether at low temperature gave white needles, mp 84.5–85.0°.

The infrared spectrum (potassium bromide pellet) showed absorption for C≡N at 4.44 μ (2250 cm^{-1}).

Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.62; H, 8.85; N, 13.54.

***cis*-3,4-Di(1-carboxy-2-propyl)tetrahydrofuran (8).**—The dinitrile (1.0 g, 0.0048 mole) was added to a solution of sodium hydroxide prepared by dissolving 1.0 g (0.025 mole) of sodium hydroxide in 5 ml of water. The suspension was warmed and the dinitrile formed an oily layer on the surface of the water. The mixture was refluxed for 12 hr until the ammonia ceased to be evolved and a solution had resulted.

While the reaction mixture was still warm, it was acidified with 10% hydrochloric acid. A precipitate formed and the diacid was filtered to give 1.2 g (quantitative yield) of a light-colored product with a melting range of 194–197°. The diacid could be recrystallized from acetonitrile to give a white, crystalline acid with a melting point of 198–199°.

The infrared spectrum (potassium bromide pellet) showed the characteristic broad OH of the carboxyl group at 3.48 (2870 cm^{-1}) and the carboxyl carbonyl group at 5.87 μ (1701 cm^{-1}).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.95; H, 8.17.

***cis,cis*-4,8-Dimethyl-*cis*-2-oxa-6-ketodecahydroazulene (1).**—An intimate mixture of 5.0 g of the diacid **8**, 5.0 g of iron powder, an 6.0 g of barium hydroxide was placed in a 25-ml distilling flask with the side arm leading into a test tube cooled in an ice bath. The flask was stoppered and held with the neck parallel to the desk top. The mixture was then heated with a free flame in an air bath. Water distilled and a brown oil also came over. The distillate was taken up in 10 ml of methylene chloride, washed once with a dilute potassium hydroxide solution and once with

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[6] A. C. Anderson, Jr., and F. J. Freenor, *J. Am. Chem. Soc.*, **86**, 5037 (1964).

water, and then dried over potassium carbonate. When the mixture was filtered from the drying agent and then concentrated, a brown-yellow oil remained (1.6 g). The oil was distilled and a fraction boiling at 85–95° (0.4 mm) weighing 1.2 g was collected. This material was taken up in pentane, and on cooling in the freezer white crystals, weighing 0.9 g (24% yield), separated and were collected.

The infrared spectrum of the ketone (melt) showed a strong carbonyl peak at 5.92 μ (1690 cm^{-1}). The nmr was listed in the Discussion.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.31; H, 10.10.

Preparation of 13.—Bromine (4.2 g, 0.025 mole) in 5 ml of acetonitrile was added dropwise to a stirred, cooled suspension of triphenylphosphine (6.8 g, 0.025 mole) in 25 ml of acetonitrile. When the ice bath had warmed to 20°, the ether 12[7] (3.0 g, 0.025 mole) was added to the triphenyldibromophosphorane. After the reaction had stood at room temperature for 1 hr, solution occurred. The reaction mixture was placed in the freezer overnight.

The mixture was poured into ice–water and the oil was extracted with pentane. The pentane extracts were dried over sodium sulfate and then concentrated. Distillation yielded 2.0 g (30%) of material boiling at 86–89° (0.3 mm) [lit.[8] bp 103–106° (2 mm)].

An nmr spectrum (neat, values in parts per million from an external TMS standard) exhibited a doublet centered at 3.76 (4 H on the carbons bearing the bromine atom), an undefined multiplet at 2.54 (2 H), and a broad singlet at 1.84 (8 H).

Reaction of 1 with Triphenyldibromophosphorane.—In an addition funnel was placed 0.43 g (0.00236 mole) of 1 dissolved in 2 ml of acetonitrile. In a flask was placed 0.62 g (0.00236 mole) of triphenylphosphine in 2 ml of acetonitrile. The suspension was cooled in an ice bath and 9.38 g (0.00236 mole) of bromine in 3 ml of acetonitrile was added dropwise from another addition funnel. After completion of the bromine addition, the solution of 1 was added over a period of 6 min. The color of the mixture gradually changed to yellow-brown with the suspended solid still present. The mixture was stirred overnight from which a black solution resulted. The acetonitrile was removed under vacuum. Water was added to the residue and the mixture was extracted with pentane. The pentane extracts were dried over sodium sulfate and the pentane was removed under vacuum. A small amount of yellow oil was obtained. The nmr spectrum (neat, parts per million from external TMS standard) indicated that some elimination had occurred as resonances appeared at 4.7 and 5.2. A complex methyl pattern (about ten peaks) was centered at 1.0. Attempts at purification led only to the recovery of a small amount of starting material.

Registry No.—**1,** 13019-24-4; **3,** 4895-34-5; **6** (R = Ts), 13019-26-6; **7,** 13019-27-7; **8,** 13019-28-8; **9,** 13019-29-9; **13,** 13019-30-2.

Acknowledgment.—This study was supported by Research Grant GM-08241 from the U. S. Public Health Service.

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[7] G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1959).

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The Reduction of Free Aldonolactones by Disiamylborane

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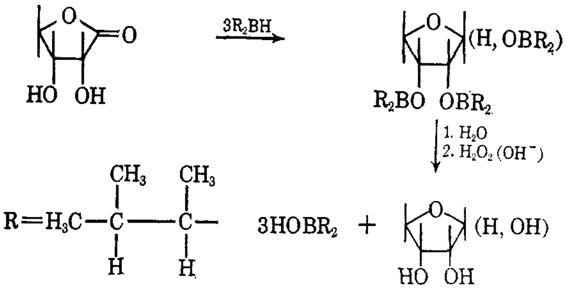
Los Angeles, California 90007

Received January 12, 1967

The most difficult step in the cyanohydrin synthesis of carbohydrates is the reduction of the aldonolactones to the aldose. The reagents commonly used for the reduction of lactones are sodium amalgam[1] and buffered sodium borohydride;[2] in both cases the reactions are difficult to control and unless extreme care is exercised will give poor yields.[3] In the case of erythronolactone, neither of these methods give the desired aldose.[4,5] Recently a procedure for the reduction of fully acylated lactones of aldonic acids was reported.[6] It utilized bis-3-methyl-2-butylborane (disiamylborane), a reagent developed by Brown for selective hydroboration.[7,8]

Disiamylborane is known to react with free hydroxyl groups to form the dialkylalkoxyborane derivative with the evolution of hydrogen; therefore, if a nonacylated lactone is treated with sufficient reducing agent to react with all of the hydroxyl groups as well as the carbonyl group, the reduction to the aldose should be possible. The alcoholic hydroxyls would be regenerated during the hydrolytic step giving the free sugar as a direct product (Scheme I).

Scheme I



We would like to report the successful use of disiamylborane for the direct reduction of aldonic acid γ- and δ-lactones. The success of this reaction in the presence of free hydroxyl groups renders unnecessary the acylation and subsequent saponification to remove the blocking groups during a synthetic sequence.

D-Erythronolactone was reduced to D-erythrose by this method; to our knowledge this is the first time this lactone has been successfully reduced to the aldehyde. The reagent was also shown to reduce unacylated D-galactono-γ-lactone and D-glucono-δ-lactone to the respective aldohexoses in good yield.

Results and Discussion

The reaction conditions for the disiamylborane reductions of the unblocked lactones were investigated using D-erythronolactone, since this compound is the most difficult to reduce by other techniques and since our principal interest is with tetrose chemistry. The extent of lactone reduction to aldose was determined spectrophotometrically, using the phenol–sulfuric acid assay.[9] D-Erythronolactone was rapidly reduced to yield about 60% of theoretical tetrose which then remained unchanged over an extended period of time.

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