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Synthesis of *Cis,cis*-4,8-Dimethyl-*cis*-2,6-dioxadecahydroazulene

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In the course of investigating the preparation of a *cis*-decahydroazulene (bicyclo-[5.3.0]decane) ring system, a dioxo analog was synthesized as a model compound. This paper describes the preparation of the hitherto unknown heterocyclic system *cis,cis*-4,8-dimethyl-*cis*-2,6-dioxadecahydroazulene (IX).

Occasionally an oxygen-containing compound is used to study the chemistry of its carbon analog. Thus, in a study reported by Eliel (2) *cis*-2-oxa-3a,4,7,7a-tetrahydroindan (I), which quite closely resembles *cis*- Δ^5 -tetrahydroindan (II) in its conformational aspects, was substituted for the less accessible carbon counterpart. In the present study, we report the synthesis of the dioxo heterocyclic ring system which geometrically approximates the *cis*-decahydroazulene ring system. The pharmacological properties of this system will be investigated.

The Diels-Alder reaction of *trans-trans*-2,4-hexadiene with maleic anhydride gave the well characterized adduct (III). The stereochemistry of this adduct has been elucidated by Alder (3). Reduction of the anhydride (III) with lithium aluminum hydride yielded the diol (IV).

The addition of *p*-toluenesulfonyl chloride to a refluxing solution of the diol (IV) in pyridine following the method of Eliel (2) gave the tetrahydrofuran derivative (V). This compound was also prepared by heating the diol (IV) in dimethylsulfoxide (4).

The *trans*-glycol (VI) could be obtained in good yield by basic hydrolysis of the formate ester formed in the reaction of V with performic acid. Cleavage of the *trans*-glycol (VI) by the Rigby oxidation (5) (sodium bismuthate) afforded the dialdehyde (VII) in excellent yield. Because of the known thermal sensitivity of 1,6-dialdehydes, the crude dialdehyde was reduced directly to the diol (VIII) with lithium aluminum hydride.

The formation of the oxepane (oxacycloheptane) ring was effected by the addition of *p*-toluenesulfonyl chloride to a refluxing pyridine solution of the diol (VIII). The structure of the resulting dioxo analog of the *cis,cis*-4,8-dimethyl-*cis*-decahydroazulene system was established by nuclear magnetic resonance spectroscopy. The nuclear magnetic resonance spectrum of IX (in carbon tetrachloride solution with values reported as parts per million using tetramethylsilane as an external standard) exhibited a multiplet at 3.4 (hydrogens at C-a), a multiplet at 3.9 (hydrogens at C-e), a multiplet at 1.9 (hydrogens at C-b and C-c), and a sharp doublet at 1.0 (methyl hydrogens at C-d). Integration of the

spectrum showed the hydrogens C-a: C-b and C-c: C-d: C-e in the ratios 4:4:6:4 which corresponded to the assigned structure.

EXPERIMENTAL

Cis,cis-3,6-Dimethyl-4-cyclohexene-*cis,cis*-1,2-dicarboxylic Anhydride (III).

The *trans,trans*-2,4-hexadiene, commercially available from Columbia Organic Chemicals (25.3 g., 0.3 mole), was mixed with 50 ml. of dry benzene and three crystals of iodine. The mixture was allowed to stir at reflux for 1 hour, after which a solution of maleic anhydride (23.5 g., 0.24 mole) in 100 ml. of benzene was added dropwise. The reaction was exothermic and refluxing continued without external heating. When the addition was complete, the reaction mixture was refluxed for an additional 2 hours.

On cooling the reaction mixture in the refrigerator the mixture crystallized. The solid was filtered and the filtrate was concentrated by distillation. Additional product was obtained by the addition of petroleum ether (30-60°) to the remaining benzene solution.

The crystals were filtered and combined with the solid initially obtained. Recrystallization of the crude product from ethyl acetate yielded 39 g. (90% yield based on maleic anhydride) of III with a melting point of 92.0-93.0°, lit. m.p. 94° (2).

Cis,cis-3,6-Dimethyl-*cis,cis*-1,2-dihydroxymethyl-4-cyclohexene (IV).

The lithium aluminum hydride (3.2 g., 0.085 mole) was pulverized and added to 150 ml. of anhydrous ether. This slurry was allowed to stir and heat at reflux while the anhydride (III) (9.5 g., 0.050 mole) in 300 ml. of dry ether was added dropwise. The addition was completed in 3.5 hours, after which the reaction mixture was allowed to reflux for an additional 16 hours.

Ice water was added to destroy the excess lithium aluminum hydride and to hydrolyze the complex. When the salts became white, the reaction mixture was subjected to aspirator filtration. The residue was washed several times with ether, and the combined filtrates were dried over sodium carbonate. The ethereal solution was filtered, and the filtrate was reduced in volume by distillation. After most of the solvent had been removed, the reaction mixture was taken to dryness on a rotary evaporator. The product (8.3 g.) was obtained in 98% yield, and could be recrystallized from ethyl acetate-petroleum ether (30-60°) to give a pure product with a melting range of 78.0-78.2°.

The infrared spectrum (potassium bromide pellet) showed an -OH stretch at 2.99 μ (3345 cm^{-1}), -CH₃ at 7.25 μ (1378 cm^{-1}) and a C-O stretch for primary alcohols with α -branching at 9.67 μ (1034 cm^{-1}).

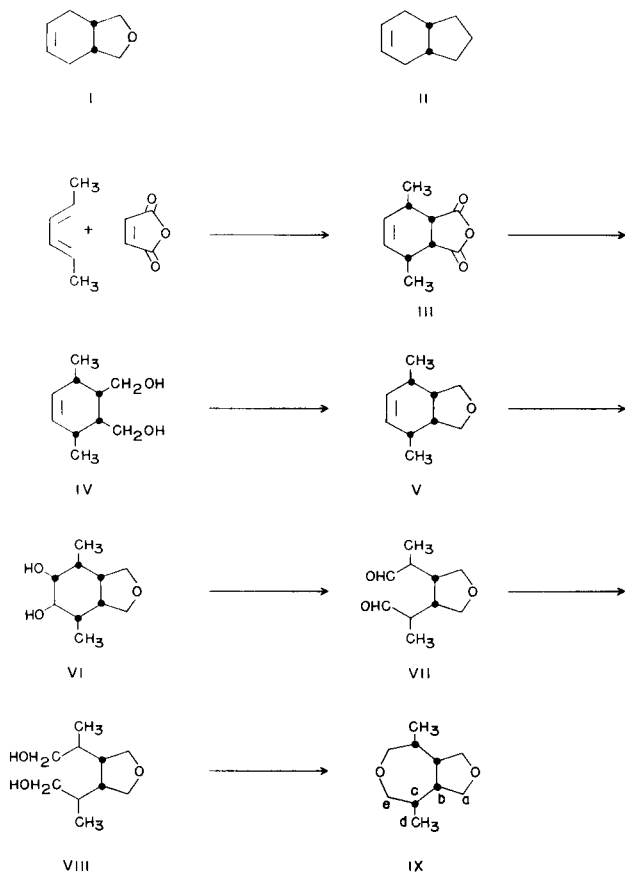
Anal. Calcd. for C₁₀H₁₈O₂: C, 70.55; H, 10.66. Found: C, 70.33; H, 10.46.

Cis,cis-4,7-Dimethyl-*cis*-2-oxa-3a,4,7,7a-tetrahydroindan (V).

The diol (IV) (10.0 g., 0.059 mole) was dissolved in 15 ml. of pyridine and heated to reflux. To this refluxing solution was added, dropwise, a solution of *p*-toluenesulfonyl chloride (12.0 g., 0.063 mole) in 20 ml. of pyridine. When the addition had been completed, the reaction mixture was allowed to stir at reflux for an additional hour.

The reaction mixture was cooled, and poured into an ice-sulfuric acid slurry. An oily layer formed, and was separated. The aqueous

SYNTHETIC SEQUENCE



portion was extracted (4 x 50 ml.) with petroleum ether (30-60°). The combined extracts were dried over calcium sulfate.

The petroleum ether solution was filtered, and the filtrate was distilled. The product (8.7 g., 95% yield) distilled at 46-47° (1.0 mm.).

The infrared spectrum (neat on sodium chloride plates) showed a peak at 9.1 μ (1098 cm^{-1}) which has been shown to be characteristic for tetrahydrofuran derivatives (4).

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}$: C, 78.89; H, 10.59. Found: C, 78.25; H, 10.58.

Cis, cis-4,7-Dimethyl-*cis*-2-oxa-3a,4,5,6,7,7a-hexahydroindan-*trans*-5,6-diol (VI).

The ether (V) (15.2 g., 0.1 mole) was added dropwise to a stirred and cooled solution of performic acid (prepared from 13 g. of 31% hydrogen peroxide and 55 ml. of 85% formic acid). The temperature was kept at about 40° during the addition.

After stirring at room temperature for 17 hours, the excess reactants were removed by vacuum distillation (about 55 ml.). When most of the liquid had been removed, there remained in the reaction flask a heavy, viscous oil. An aqueous solution of potassium hydroxide, prepared from 12 g. of sodium hydroxide in 25 ml. of water, was slowly added to the oil while maintaining the temperature about 30° by an ice-water bath. When all of the base had been added, the reaction mixture was stirred for an additional hour at room temperature.

The crude reaction mixture was filtered, washed with cold water and dried (weight, 11.2 g., m.p. 116-118°, 60% yield). Additional product was obtained by continuous extraction of the aqueous phase with methylene chloride. The crude product was pure enough for the next step. The crude product could be crystallized from chloroform-petroleum ether. The pure *trans*-glycol melted at 123-124°.

The infrared spectrum (potassium bromide pellet) showed a strong -OH stretch at 2.92 μ (3425 cm^{-1}).

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_3$: C, 64.48; H, 9.74. Found: C, 64.17; H, 9.66.

Cis-3,4-Di(1-hydroxy-2-propyl)tetrahydrofuran (VIII).

The glycol (VI) (7.0 g., 0.038 mole) was mixed with 12.6 g. (0.045 mole) of sodium bismuthate, 16 ml. of water, 30 ml. of 33% phosphoric acid, and 50 ml. of ether. This reaction mixture was allowed to stir at room temperature, and after 0.5 hour, the bismuthate-phosphate salts were gray-colored. The stirring was continued at room temperature for an additional hour, after which the reaction mixture was subjected to vacuum filtration.

The residue was washed thoroughly with methylene chloride, and the combined methylene chloride layers were dried over anhydrous calcium sulfate. Filtration, followed by evaporation of the methylene chloride, resulted in a clear oil. This was subjected to high vacuum aspiration to remove any trace amounts of solvent, leaving 7.0 g. of product. Due to the known thermal instability of this type of compound, no attempt was made to purify the aldehyde further.

The infrared spectrum (sodium chloride plates, neat) showed the characteristic C-H stretch of the aldehyde group at 3.64 μ (2740 cm^{-1}) and the aldehyde carbonyl at 5.78 μ (1725 cm^{-1}).

The unpurified aldehyde (7.0 g., 0.038 mole) was mixed with 50 ml. of anhydrous ether, and the ethereal solution was added dropwise to lithium aluminum hydride (1.0 g., 0.026 mole) in 100 ml. of dry tetrahydrofuran. When the addition was complete, the reaction mixture was gray-white in color. This mixture was allowed to stir and heat at reflux for 1 hour. After this time, a few drops of water were added. The reaction mixture became very white and was filtered immediately. The salts obtained as the residue were washed with tetrahydrofuran and then mixed with a dilute solution of hydrochloric acid in tetrahydrofuran. After boiling the acidic solution for about 0.5 hour, the solution was filtered. The tetrahydrofuran filtrates and washings were combined and distilled. The product (5.05 g., 70% yield from VI) was distilled from the crude reaction mixture in the range 162-164° (1 mm.). Upon standing at room temperature, the alcohol crystallized to give a white solid of m.p. 72-74°. Recrystallization could be accomplished from the solvent system ether-petroleum ether (30-60°) to give a product with m.p. 75.0-75.5°.

The infrared spectrum (potassium bromide pellet) showed strong -OH stretch at 3.15 μ (3165 cm^{-1}) and -CH₃ stretch at 7.26 μ (1378 cm^{-1}). The characteristic peak for the tetrahydrofuran group could not be separated from the alcoholic C-O stretch at 9.23 μ (1082 cm^{-1}).

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{O}_3$: C, 63.80; H, 10.71. Found: C, 63.62; H, 10.48.

Cis, cis-4,8-Dimethyl-*cis*-2,6-dioxadecahydroazulene (IX).

The diol (VIII) (0.9 g., 0.0048 mole) was dissolved in 6 ml. of pyridine and was heated to reflux. To this refluxing solution was added dropwise a pyridine solution of *p*-toluenesulfonyl chloride (1.0 g. in 5 ml. of pyridine). The reaction mixture was allowed to heat at reflux for about 1 hour after the addition had been completed.

The reaction mixture was cooled and poured into an ice-sulfuric acid slurry. Four extractions of the acidic aqueous solution with 15 ml. portions of petroleum ether (30-60°) were considered sufficient to remove the bulk of the product. The extracts were combined and dried over anhydrous calcium sulfate. Filtration of the dried petroleum ether extracts, followed by distillation of the filtrate, resulted in 0.45 g. (50% yield) of a pleasant smelling liquid. The sample was further purified by distillation, b.p. 105-108° (3.5 mm.).

The infrared spectrum (neat on sodium chloride plates) showed a strong, sharp C-H region centered at 3.44 μ (2910 cm^{-1}) and 3.52 μ (2840 cm^{-1}). A moderately strong absorption at 6.87 μ (1455 cm^{-1}) can be attributed to absorption of the methylene groups. The methyl groups show a sharp peak at 7.24 μ (1383 cm^{-1}), characteristic for a C-CH₃ stretch. Two peaks at 9.18 μ (1088 cm^{-1}) and 9.46 μ (1057 cm^{-1}) correspond to the tetrahydrofuran, and oxepane moieties, respectively.

Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_2$: C, 70.55; H, 10.66. Found: C, 70.35; H, 10.67.

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