hydrous ether. The mixture was boiled under reflux for 19 hr. under an atmosphere of nitrogen. The mixture was cooled and 100 ml. of water was carefully added. The resulting mixture was treated with 300 ml. of a 10% aqueous solution of sulfuric acid. The ether layer was separated and the aqueous phase was extracted with three 500-ml. portions of ether. The combined ether extract was dried over magnesium sulfate and concentrated. The residual oil was distilled, affording as the main fraction 101 g. of a colorless oil which solidified in the receiver, b.p. 99–110° (0.35 mm.). The crude diol was recrystallized from benzene to give 49.7 g. (40% based on total diester) of the pure diol as colorless needles, m.p. 76–77.5°.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.58; H, 9.44. Found: C, 65.80; H, 9.56.

The infrared spectrum (6% chloroform) shows a sharp band at 3610 cm.$^{-1}$ and a broad band centered at 3380 cm.$^{-1}$ attributed to free and associated O–H, respectively. The n.m.r. spectrum was determined as a 10% solution in chloroform containing tetramethylsilane.

1,1-Dimethylol-d_4-3-cyclopentene.—Difficulties were encountered in trying to separate the desired deuterated diol from side products in small-scale reductions of the diester mixture.[9] A sample of pure 1,1-dicarbethoxy-3-cyclopentene[10] was obtained in 55% yield by the action of thionyl chloride on pure 3-cyclopentene-1,1-dicarboxylic acid[8] followed by treatment of the diacid chloride with ethanol. The most notable difference between the properties of this pure diester and the mixture[9] previously reported is seen in the infrared spectra. The infrared spectrum[11] of the mixture of diesters shows a strong band at 918 and a shoulder at 993 cm.$^{-1}$ attributed to C–H deformation modes of a monosubstituted ethylene present in the contaminating 1,1-dicarbethoxy-2-vinylcyclopropane. The infrared spectrum[11] of pure 1,1-dicarbethoxy-3-cyclopentene shows a slight sharpening of the ester carbonyl band at 1740 and the bands at 918 and 993 cm.$^{-1}$ are removed. The pure diester (2.53 g., 0.0119 mole) was reduced with 0.500 g. (0.0119 mole) of lithium aluminum deuteride as described for the reduction using lithium aluminum hydride. The crude product was distilled and then recrystallized from benzene affording 0.505 g. (32%) of colorless needles, m.p. 74–75°. A mixture melting point with the undeuterated diol showed no depression below 74°. The infrared spectrum (7% in chloroform) is very similar to that of the undeuterated diol (identical in the 3-μ region) and shows two bands at 2105 and 2200 cm.$^{-1}$ attributed to the methylene C–D symmetric and antisymmetric stretching modes. The n.m.r. spectrum was determined as a 4% solution in chloroform containing tetramethylsilane.

1,1-Dimethylol-3-cyclopentene Sulfite.—A solution of 35.1 g. (0.274 mole) of the diol in 150 ml. of dry ether and 44 ml. of anhydrous pyridine was cooled by means of an ice bath. The cooled solution was stirred as 98.0 g. (0.823 mole) of thionyl chloride was added, dropwise, over a period of 30 min. The mixture was stirred for 1 hr. and, after allowing it to warm to room temperature, it was stirred an additional 4 hr. It was then carefully poured onto ice and extracted with three 30-ml. portions of ether. The ether extract was washed with aqueous sodium bicarbonate and then with water, dried over magnesium sulfate, and concentrated. The crude sulfite was distilled affording 28.3 g. (59%) of a colorless oil which solidified in the receiver, b.p. 117–119° (8 mm.), m.p. 47.5–49.0°. One recrystallization from anhydrous ether raised the melting point to 49–50°.

Anal. Calcd. for $C_7H_{10}O_3S$: C, 48.26; H, 5.78; S, 18.40. Found: C, 48.00; H,5.86; S, 17.90.

The infrared spectrum (10% in carbon disulfide) showed a strong band at 1190 cm.$^{-1}$ (S=O). The n.m.r. spectrum was determined as a 9% solution in benzene containing tetramethylsilane.

1,1-Dimethylol-d_4-3-cyclopentene Sulfite.—The deuterated diol (0.200 g., 0.00152) was converted to the corresponding cyclic sulfite by the procedure described for the undeuterated compound. The product was distilled through a Hickman still followed by crystallization from ether to yield 0.037 g. (14%) of colorless crystals, m.p. 47–48.5°. A mixture melting point determination with undeuterated sulfite showed no depression below 47°. The infrared spectrum (5% in chloroform) shows bands at 2120 and 2240 with a shoulder at 2160 cm.$^{-1}$ (C–D stretch). The spectrum in carbon disulfide is similar to that for the undeuterated sulfite. The n.m.r. spectrum was determined as a 6% solution in benzene containing tetramethylsilane.

Acknowledgment.—The authors wish to thank Dr. G. E. Maciel for the determination of preliminary n.m.r. spectra and to acknowledge the support of this work by Research Corporation (Frederick Gardner Cottrell Grant).

(10) J. Meinwold, P. G. Gassman, and J. K. Crandall [*J. Org. Chem.*, **27**, 3366 (1962)] report the preparation of the pure diester by cycloalkylation of malonic ester with *cis*-1,4-dibromobutene-2.

(11) Determined as a pure liquid with a Perkin-Elmer Infracord spectrophotometer.

Proton Magnetic Resonance and Stereochemistry of 2-*o*-Tolyl-3-(2-hydroxyethyl)cyclohexanol and Related Compounds[1]

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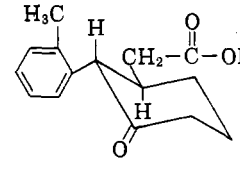
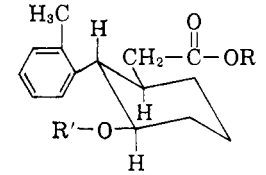
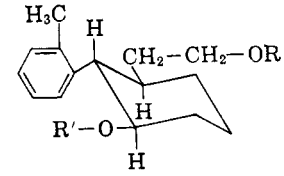
As part of an investigation dealing with the stereospecificity on biological activity of certain aryl-substituted cyclohexanols, several compounds of known stereochemistry were required. In a previous publication[3] we have reported and discussed the n.m.r. spectra and stereochemistry 1-(2-hydroxyethyl)-2-*o*-tolylcyclohexanols and related compounds. The present report treats the n.m.r. spectra of *trans*-2-*o*-tolyl-*cis*-3-(2-hydroxyethyl)cyclohexanol (VII), related intermediates, and derivatives (compounds I through VIII).



I, R = H
II, R = CH_3
III, R = CH_2–CH_3



IV, R = R′ = H
V, R = CH_3; R′ = H
VI, R = CH_3; R′ = $COCH_3$



VII, R = R′ = H
VIII, R = R′ = $COCH_3$

The diol VII was obtained from lithium aluminum hydride reduction of the hydroxy acid IV, the acetoxy methyl ester VI, and the keto ester II. No change in stereochemistry will result in the reduction of IV and VI, but the reduction of the keto ester II could yield diastereoisomeric diols. Only the all-equatorial compound VII was isolated from lithium aluminum hydride re-

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(2) Fellow of the American Foundation for Pharmaceutical Education, 1962–1963.

(3) D. C. Staiff and A. C. Huitric, *J. Org. Chem.*, **28**, 3531 (1963).

duction of II. Sodium borohydride reduction of I yielded an all-equatorial compound, hydroxy acid IV.

The all-equatorial conformation and configuration are established for compounds IV through VIII from the n.m.r. spectra of VI and VIII (Fig. 1). The assignment of signals to the pertinent protons was made by comparison of chemical shifts with those of reference compounds.[3,4] Of special importance in the assignment of configuration and conformation in six-membered ring compounds is the fact that in the chair conformation the spin–spin coupling between axial hydrogens on neighboring carbons is three to four times greater than between neighboring hydrogens in other orientations,[5] $J_{aa} \simeq 11.5$ c.p.s. and $J_{ae} = J_{ee} \simeq 3$–4 c.p.s. The triplet at τ 7.24, with spacings of 10.5 c.p.s., for the signal of H-2 in VI is consistent with H-2 being axial and coupled with two axial protons. This establishes the configuration at C-1, C-2, and C-3. Furthermore, the configuration at C-3 is substantiated by the signal of H-3. The broad multiplet at τ 5.12, of half-width of about 20 c.p.s. for the signal of H-3 in VI is consistent with H-3 being axial and coupled with two adjacent axial protons and one equatorial proton. The resulting pattern should be a sextuplet, but virtual coupling with protons on C-5 probably adds to the multiplicity of the signal. The half-width of the signal, however, establishes that H-3 has the axial orientation. Only the configuration and conformation shown for VI can give the observed patterns for signals of H-2 and H-3. In a similar manner the all-equatorial structure is established for VIII from the triplet of H-2 with spacing of 10.5 c.p.s. at τ 7.33, and the multiplet of half-width of about 20 c.p.s. for the signal of H-1 at τ 5.16.

In the spectrum of the hydroxy ester V the triplet of H-2 was partially overlapped by the signal of the aromatic methyl protons and the multiplet of H-3 was partially masked by the signal of the methyl protons of the ester function. An analogous situation resulted in the spectrum of the diol VII, where the triplet of H-2 was partially overlapped by the signal of the aromatic methyl protons and the multiplet of H-1 was overlapped by the triplet of the methylene protons B. These difficulties were nicely circumvented by acetylation, as is evident from the spectra of VI and VIII.

The difference in the chemical shifts of the methyl protons of the two acetoxy groups in VIII is attributed to a long-range shielding of group F resulting from the magnetic anisotropy of the aromatic ring. The same shielding effect is operative on the methyl protons of the acetoxy group in VI. The observed shielding effect is as expected, assuming restriction of rotation of the aromatic ring in such a way as to cause the planes of the two rings to be more closely perpendicular to each other on a time average. The results are analogous to what was observed in *trans*- and *cis*-2-*o*-tolylacetoxycyclohexane,[4] where the signal of the methyl protons of the acetoxy group has a chemical shift of τ 8.37 in the *trans* isomer and τ 8.22 in the *cis*.

(4) (a) A. C. Huitric and J. B. Carr, *J. Org. Chem.*, **26**, 2648 (1961); (b) A. C Huitric, W. G. Clarke, Jr., K. Leigh, and D. C. Staiff, *ibid.*, **27**, 715 (1962).

(5) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963), and references cited therein.

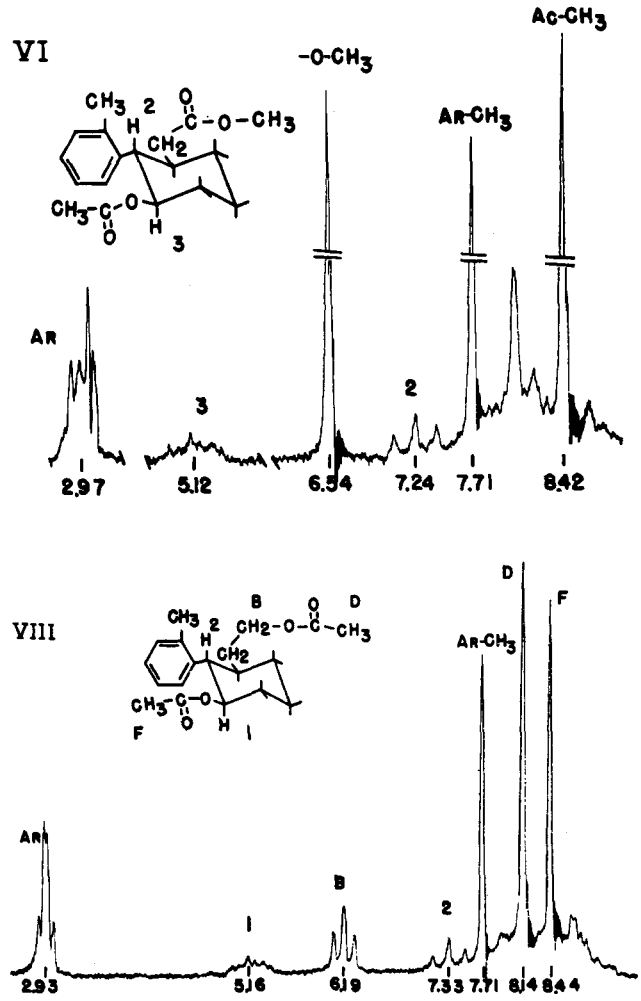

Fig. 1.—N.m.r. spectra of methyl *cis*-3-acetoxy-*trans*-2-*o*-tolylcyclohexylacetate (VI) and *trans*-2-*o*-tolyl-*cis*-3-(2-acetoxyethyl)-acetoxycyclohexane (VIII): 60 Mc., about 1 *M* in carbon tetrachloride at 23°, tetramethylsilane used as internal reference.

The n.m.r. spectra of the keto acid, 3-keto-2-*o*-tolylcyclohexylacetic acid (I), and the keto ester III are of special interest because they constitute additional[5] examples of six-membered ring compounds which yield axial–axial coupling constants directly from a simple AX system. The spectrum of I was determined in deuterated acetone and those of II and III in carbon tetrachloride. Tetramethylsilane was used as internal reference in both solvents. The spectrum of II was not very useful because the signal of H-2 is overlapped by the signal of the methyl protons of the ester function. The signal of H-2 appears as a symmetrical doublet with spacing of 12.0 c.p.s. at τ 6.18 in I and at τ 6.44 in III. In both cases the doublet of H-2 arises from spin–spin coupling with H-1, and the coupling constant of 12.0 c.p.s. establishes the diaxial orientation of H-1 and H-2. This establishes the *trans* configuration for I and III, but since isomerization can occur in these compounds through enolization no deduction should be made regarding the stereospecificity of the Michael addition of dibenzyl malonate with 3-keto-2-*o*-tolylcyclohexene in the synthesis of the keto acid I by the method of Klibansky and Ginsburg.[6] The axial–axial coupling of 12.0 c.p.s. indicates that in the solvents used the cyclo-

(6) Y. Klibansky and D. Ginsburg, *J. Chem. Soc.*, 1293 (1957).

hexanone ring in I and III is present in a chair conformation essentially free of bond-angle distortion.

Experimental

3-Keto-*trans*-2-*o*-tolylcyclohexylacetic Acid (I).—The synthesis of this compound has been reported by Klibansky and Ginsburg[6] through a Michael addition of potassium dibenzyl malonate with 3-keto-2-*o*-tolylcyclohexene. The method used in the present work varies from the method of Klibansky and Ginsburg only in using catalytic hydrogenation in the debenzylation step, a method described[7] for the synthesis of the phenyl analog. The keto acid was obtained in 51% yield starting with 10 g. of 3-keto-2-*o*-tolylcyclohexene. It was found to crystallize in polymorphic forms. Crystallization from benzene gave a crystalline material, m.p. 62–65°, while crystallization from isopropyl alcohol gave m.p. 101–102° (m.p. 102–103° was reported from heptane[6]). There were considerable differences in the finger-print region of the infrared spectra of the two polymorphs when determined in the solid state in potassium bromide pellets, but their infrared spectra were identical when measured in carbon tetrachloride solution, 0.3 *M* in 0.1-mm. pathway cell. The low-melting form gave a neutralization equivalent of 246.8. The calculated value is 246.29.

Anal. Calcd. for $C_{15}H_{18}O_3$ (m.p. 101–102°): C, 73.14; H, 7.37. Found: C, 73.16; H, 7.43.

The methyl and ethyl esters, II and III, were prepared by direct esterification catalyzed by sulfuric acid: II, m.p. 84–85°, crystallized from benzene (lit.[6] m.p. 77–78° from ethanol); III, m.p. 38–39°, crystallized from hexane.

Anal. Calcd. for $C_{16}H_{20}O_3$ (II): C, 73.82; H, 7.74. Found: C, 74.14; H, 7.56.

Anal. Calcd. for $C_{17}H_{22}O_3$ (III): C, 74.42; H, 8.08. Found: C, 74.84; H, 8.28.

***cis*-3-Hydroxy-*trans*-2-*o*-tolylcyclohexylacetic Acid (IV).**—A solution of 3.0 g. (0.012 mole) of 3-keto-*trans*-2-*o*-tolylcyclohexylacetic acid (I) in 10 ml. of 5% sodium hydroxide was added, with stirring, to 0.45 g. (0.012 mole) of sodium borohydride in 10 ml. of a saturated sodium carbonate solution. After stirring for several minutes, the resulting milky mixture cleared up. The reaction was stirred for 24 hr. at room temperature. Dilute sulfuric acid was then added dropwise to destroy the excess sodium borohydride. The mixture was then extracted with ether and the ether phase was extracted with 10% sodium bicarbonate solution. The basic aqueous solution was then acidified and extracted repeatedly with ether. The ether phase was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent yielded 2.1 g. of solid material and a small amount of oily substance. Recrystallization of the solid material from a boiling solution of benzene with enough isopropyl alcohol to clarify the solution gave 1.9 g. (63.5%) of a white crystalline material, m.p. 146–147°. The neutralization equivalent of the hydroxy acid IV was found to be 248.5 (calculated 248.31).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.46; H, 8.08.

The infrared spectrum of the hydroxy acid had two bands in the carbonyl region, 1720 and 1690 cm.$^{-1}$, when determined in the solid state in potassium bromide pellet, but when measured in carbon tetrachloride solution a single carbonyl band was present at 1720 cm.$^{-1}$. This implies that in the crystalline state all carbonyl oxygen atoms of the carboxyl groups are not associated through identical hydrogen bonds.

Methyl *cis*-3-Acetoxy-*trans*-2-*o*-tolylcyclohexylacetate (VI).—The methyl ester V was prepared by direct esterification of IV with methanol. The ester was a viscous liquid, b.p. 136–140° at 1.25 mm., which did not crystallize. Gas chromatography analysis on a 5-ft. Dow silicone QF-1 column showed only one component. The hydroxy methyl ester V was acetylated by refluxing with acetic anhydride in pyridine for 1 hr. A solution of 0.75 g. (0.003 mole) of V in 5 ml. of pyridine and 2 ml. of acetic anhydride yielded 0.6 g., 69%, of colorless crystalline product after recrystallization from hexane with m.p. 101.5–102.5°.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.94. Found: C, 71.00; H, 7.86.

***trans*-2-*o*-Tolyl-*cis*-3-(2-hydroxyethyl)cyclohexanol (VII) and *trans*-2-*o*-Tolyl-*cis*-3-(2-acetoxyethyl)acetoxycyclohexane (VIII).**—The diol VII was prepared by lithium aluminum hydride reduction of the keto ester II, the hydroxy acid IV, and the acetoxy methyl ester VI. The reactions were carried out in anhydrous ether by adding an ether solution of the compound to the lithium aluminum hydride–ether mixture at such a rate as to cause gentle refluxing of the ether. The mixture was then stirred at room temperature: 2 hr. for II, 24 hr. for IV, and 16 hr. for VI. The excess lithium aluminum hydride was destroyed by addition of ethyl acetate followed by water. The mixture was poured into water, acidified to dissolve the aluminum hydroxide, and extracted with ether. The ether solution was washed successively with sodium bicarbonate solution and water, then dried over anhydrous sodium sulfate. Removal of the solvent gave a very viscous material which could not be induced to crystallize. No elementary analysis was determined on the diol since the same crystalline diacetoxy derivative was readily obtained from the diol produced from the reduction of II, IV, and VI.

The diacetoxy derivative (VIII) was obtained by heating the diol VII at reflux temperature with an excess of acetic anhydride in pyridine. The product, m.p. 85–86.5°, was recrystallized from petroleum ether. The infrared spectrum of the solid in potassium bromide pellet had a sharp carbonyl stretching band at 1725 cm.$^{-1}$ and showed no hydroxyl stretching band.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.89; H, 8.29.

All melting points were determined with a Kofler micro hot stage. The n.m.r. spectra were obtained with a Varian HR-60 spectrometer.

(7) E. D. Bergman, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

The Synthesis of a Model Perhydroazulene Derivative

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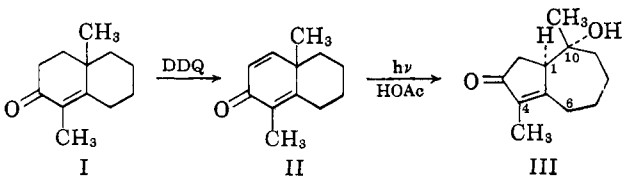
The photochemical rearrangement of 4-methyl-substituted (steroid numbering), cross-conjugated cyclohexadienones in aqueous acidic media to give perhydroazulene derivatives is well known.[1] We wish to report the synthesis of the model 5–7-fused ring system III in *ca.* 80% yield by irradiation of the cross-conjugated cyclohexadienone II,[2] related to santonin, in 45% aqueous acetic acid.

The cyclohexadienone II was obtained by treatment of the octalone I[3] with 2,3-dicyano-5,6-dichlorobenzoquinone in benzene according to the general procedure of Burn, Kirk, and Petrow.[4] On irradiation of II in 45% aqueous acetic acid at room temperature, chromatography of the product on silica gel, and evaporation of the elution solvents, III was obtained as an oil which crystallized on standing. This material showed absorption at 243 mμ and at 2.90, 5.95, and 6.17 μ. These



I II III

(1) P. de Mayo and S. T. Reid, *Quart. Rev.* (London), **15**, 393 (1961).

(2) *Cf.* L. Mandell, D. Caine, and G. E. Kilpatrick, *J. Am. Chem. Soc.*, **83**, 4457 (1961), and references therein.

(3) The authors are grateful to Dr. M. R. Willcott, III, and Mr. G. H. Beasley for providing us with a method they developed for the synthesis of I. For other published methods for the synthesis of I, see M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956), and references therein.

(4) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).