p.p.m. for cycloheximide. Material from the P spot gave no inhibition at 100 p.p.m. whereas material from the CY spot inhibited at 60 p.p.m.

Acknowledgment.—We are indebted to Dr. Francis Johnson of the Dow Chemical Company, Dr. Gerald A. Boyack of the Upjohn Company, Dr. Bernard C. Lawes of Mead Johnson and Company, Dr. Tomoharu Okuda of the Tokyo Research Laboratories, Tanabe Seiyaku Company, Ltd., and Dr. Howard J. Schaeffer of the State University of New York at Buffalo for their kindness in providing compounds for comparison and evaluation. In addition, the comments and information of Drs. Francis Johnson and T. Okuda should be expressly acknowledged. The n.m.r. information was obtained by Dr. Johnson, the O.R.D. by Dr. Okuda, and the biological activities by Dr. M. R. Siegel of the University of Maryland. The technical assistance of Mr. John Toomey is most appreciated.

Stereochemical Course of the Robinson Annelation Reaction. *cis*-9-Hydroxy-10-methyldecalin-2,5-dione

THOMAS A. SPENCER,[1] HARTLEY S. NEEL, DAVID C. WARD,

Department of Chemistry, Dartmouth College, Hanover, New Hampshire

AND KENNETH L. WILLIAMSON

Department of Chemistry, Mount Holyoke College, South Hadley, Massachusetts

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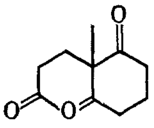
cis-9-Hydroxy-10-methyldecalin-2,5-dione (III) has been prepared by careful pyrrolidine-catalyzed cyclization of 2-methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (I). Piperidine-catalyzed cyclization of I afforded a mixture of III and bridged ketol IV. Conversion of the known β-epoxide VI to III defined the stereochemistry of the ketol, which is *cis*, as expected.

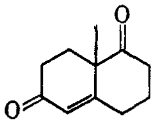
Our interest in the details of the intramolecular aldol condensation which constitutes the second step of the Robinson annelation sequence[2] led us to explore further the well-known[3] cyclization of 2-methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (I) to 10-methyl-$\Delta^{1,9}$-octalin-2,5-dione (II). Isolation of a crystalline ketol by careful amine-catalyzed cyclization of the oily Michael adduct I was the primary objective. It was found that, when I was treated briefly with pyrrolidine at 0°,[4] followed by chromatography, a trace of crystalline material other than II could be isolated. Numerous experiments to raise the yield of this substance indicated the importance of very rapid chromatography at low temperatures. Thus, when I was treated with 1 equiv. of pyrrolidine in ether at 0° for 12 min., followed by chromatography on Florisil at −30°, a 10% yield of solid, m.p. 141–142°, was obtained. With 1 equiv. of pyrrolidine, 0.3 equiv. of acetic acid, a reaction time of 6 min. at 0°, and similar chromatography, the yield was 20%. On the basis of evidence presented in this and the following paper,[5] this 141–142° compound has been shown to be *cis*-9-hydroxy-10-methyldecalin-2,5-dione (III).

When the less effective cyclization catalyst[6] piperidine was used for a 5-hr. period at room temperature, a 33% yield of a nicely crystalline product, m.p. 99–100°, was obtained. This material was shown to be a mixture of III and a bridged ketol IV, m.p. 115–116°. This bridged ketol could be isolated by treating the 99–100° material with pyrrolidine, which rapidly effected dehydration of II, while leaving IV unchanged. Recrystallization of a 1:1 mixture of III and IV produced the 99–100° material.

The n.m.r. spectra of III and IV served to establish their respective carbon skeletons: III exhibited one methyl resonance (δ = 1.32 p.p.m.); IV exhibited two (δ = 1.15 and 1.40 p.p.m.). The configuration of IV at the carbon atom bearing the methyl and hydroxyl groups has not been determined. However, in view of our interest in the stereochemical course of the Robinson annelation reaction, we undertook to establish unequivocally whether the stereochemistry of the 141–142° hydronaphthalenic ketol was *cis*, as in III, or *trans*, as in V.



I



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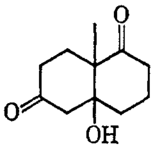
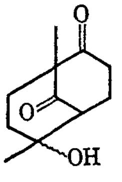
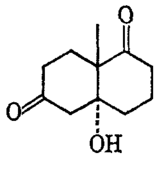


III



IV



V

Westen[7] has separated and carefully characterized the two stereoisomeric epoxides, VI (originally prepared by Wharton,[8] m.p. 158–158.5°) and VII, derived from the benzoate VIII. We prepared the crystalline β-

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[1] To whom correspondence should be addressed.

[2] T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 3785 (1963).

[3] S. Ramachandran and M. S. Newman, *Org. Syn.*, **41**, 38 (1961), and references cited therein.

[4] The amine-catalyzed cyclization of I is much faster than that of 2-acetoxy-2-(3-oxobutyl)cyclohexane-1,3-dione (XII).[2]

[5] K. L. Williamson, L. R. Sloan, T. Howell, and T. A. Spencer, *J. Org. Chem.*, **31**, 436 (1966).

[6] A preliminary account of a study of the relative effectiveness of a variety of amines as catalysts for the conversions I → II, I → III, and III → II has been published: T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Letters*, 3889 (1965).

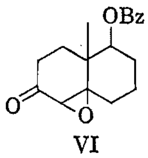
[7] H. H. Westen, *Helv. Chim. Acta*, **47**, 575 (1964).

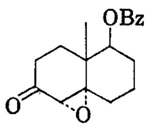
[8] P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961).

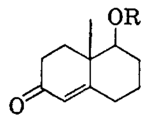
epoxide VI, m.p. 156–158°, by Westen's procedures from II, *via* IX and VIII. Lithium aluminum hydride reduction of VI afforded an oily product lacking carbonyl absorption in the infrared, presumably largely triol of structure X. Titration of this material with Jones reagent,[9] followed directly by chromatography on Florisil, afforded the 141–142° ketol (*ca.* 30% crude from VI) identical in all respects with the material obtained by cyclization of I. This proof of the stereochemistry of the ketol was confirmed by an n.m.r. study which is delineated in the following paper.[5]

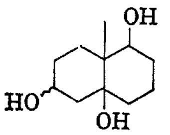
Formation of III rather than V in the cyclization of I is predicted by our hypothesis[2] that the stereochemistry of cyclization is governed by the size of the incipient angular substituent. To date, cyclizations of I and XI[10] (angular methyl) and of XII[2] (angular acetoxyl) have been shown to yield *cis*-decalin derivatives, while cyclization of XIII (angular hydrogen) affords exclusively *trans*-fused ketol.[10]

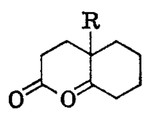
Formation of *cis*-fused ketol can occur by ring closure from either of the two chair conformations XIV (four-carbon side-chain equatorial) or XV (four-carbon side-chain axial).[11] In the former case, the carbon–carbon bond formed is axial to the initially present ring; in the latter, the bond formed is equatorial. Some insight into possible differences in the energy requirements for these two pathways may be gained from a study, now in progress, of the cyclization of the steroidal dione XVI,[12] which cannot adopt a conformation corresponding to XV.

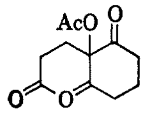

VI

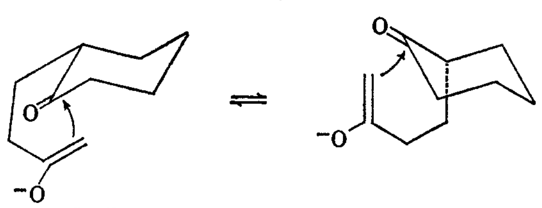

VII

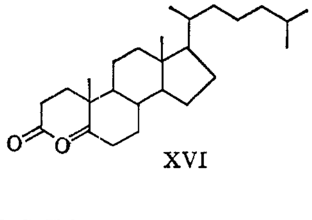

VIII, R = Bz
IX, R = H


X


XI, R = CH₃
XIII, R = H


XII


XIV XV


XVI

Experimental Section[13]

***cis*-9-Hydroxy-10-methyldecalin-2,5-dione (III).**—The Michael adduct I, b.p. 116–117° (0.1 mm.) [lit.[14] b.p. 114–116° (0.1 mm.)], was prepared in 93% yield by the method of Newman.[8] To a magnetically stirred solution of 0.97 g. (4.95×10^{-3} mole) of I in 25 ml. of technical grade ether at 0° was added by syringe 0.45 ml. (5.4×10^{-3} mole) of pyrrolidine (Matheson Coleman and Bell, reagent grade) and 0.10 ml. (1.7×10^{-3} mole) of acetic acid. After 6 min. the reaction mixture was poured directly into a jacketed column which contained 30 g. of Florisil and which was cooled to −30° by circulation of a water–ethylene glycol mixture through a Dry Ice–acetone bath and the column jacket. The column was rapidly eluted with an acetone–hexane solvent pair, and fractions were evaporated under a stream of nitrogen without heating. With 1:1 acetone–hexane there was obtained 0.75 g. of material which crystallized upon the addition of ether to afford 0.278 g. (29%) of crude ketol III, m.p. 99–120°. Two recrystallizations from ether–acetone afforded 0.193 g. (20%) of III: m.p. 141–142°; λ_{max}^{KBr} 2.95 and 5.85–5.90 μ; $\delta_{TMS}^{CS_2}$ = 1.27 p.p.m.; $\delta_{TMS}^{CDCl_3}$ = 1.32 p.p.m.[5]

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.15; H, 8.19.

The material other than III eluted from the column (mostly before III, with *ca.* 1:2 acetone–hexane) had spectra consistent with mixtures of I and II.

Preparation of the 99–100° Mixture of III and IV.—To a magnetically stirred solution of 6.02 g. (3.07×10^{-2} mole) of Michael adduct I in 100 ml. of technical grade ether at room temperature was added 3.0 ml. (3.6×10^{-2} mole) of piperidine (Matheson Coleman and Bell, reagent grade). After 5 hr. the reaction mixture was poured into a column containing 180 g. of Florisil. Elution with 1:1 acetone–hexane yielded material which crystallized from ether to afford 2.00 g. (33%) of the mixture of III and IV, m.p. 98–100°. The melting point of this material was not always this sharp. Particularly, if the melting point was taken on a hot stage, a small amount of solid might remain to *ca.* 110°. Recrystallization from ether–acetone afforded large clear crystals: m.p. 99–100°; λ_{max}^{KBr} 2.9–2.95, 5.75 (sh), 5.8–5.9 μ; $\delta_{TMS}^{CDCl_3}$ = 1.16, 1.30, and 1.38 p.p.m.[15]

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.46; H, 8.28.

Isolation of 1,6-Dimethyl-6-hydroxybicyclo[3.3.1]nonane-2,9-dione (IV) from the 99–100° Mixture of III and IV.—To a magnetically stirred solution of 0.84 g. (4.3×10^{-3} mole) of the mixture of III and IV, m.p. 99–100°, in 25 ml. of technical grade ether at room temperature was added 0.45 ml. (5.4×10^{-3} mole) of pyrrolidine. After 2 hr. the reaction mixture was poured into a column containing 30 g. of Florisil. Elution with 1:1 acetone–hexane afforded a solid which was recrystallized from ether–acetone to yield 0.18 g. of material with m.p. 115–117°. The analytical sample[16] had m.p. 115–116°; λ_{max}^{KBr} 2.90, 5.75 (sh), 5.8–5.9 μ; $\delta_{TMS}^{CDCl_3}$ = 1.15 ($CH_3\text{–}C\!<$), 1.40 ($CH_3\text{–}\overset{|}{\underset{|}{C}}\text{–}OH$), and 2.80 (–O$H$) p.p.m.[17]

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.28; H, 8.13.

Recrystallization of a 1:1 mixture of pure III and pure IV from ether–acetone afforded material with m.p. 98–100° which had an infrared spectrum identical with that of the 99–100° material prepared from I. Successive fractional sublimations of the 99–100° material afforded sublimates with infrared spectra slightly different from the starting material and each other, but with essentially unchanged melting point.

5β-Benzoyloxy-10β-methyl-1,9β-oxidodecalone-2 (VI).—The enedione II was reduced with 1 equiv. of sodium borohydride to the alcohol IX.[18] Benzoylation of IX, by either Westen's

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[9] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

[10] J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).

[11] Reference to only the two chair conformations is made to contrast an axial *vs.* an equatorial four-carbon side chain and is not intended to exclude from consideration the flexible or the other intermediate conformations.

[12] R. D. H. Heard and P. Ziegler, *J. Am. Chem. Soc.*, **73**, 4036 (1951).

[13] Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were taken either in an open capillary or on a micro hot stage; those of analytical samples are corrected. Boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer.

[14] S. Swaminathan and M. S. Newman, *Tetrahedron*, **2**, 88 (1958).

[15] The authors thank Professor Paul R. Shafer for determining this spectrum.

[16] This analytical sample was prepared by Thomas W. Flechtner, who originally isolated IV as an impurity in 4% yield from I by careful chromatography.

[17] The authors thank Dr. Lois J. Durham and Mr. Don McMillen for determining this spectrum.

procedure[7] or several others, failed to afford crystalline VII, which has been reported to have m.p. 89–90°[7] and m.p. 96–97°.[19] Chromatographically purified oil (3.3 g.) from a benzoylation [$\lambda_{\max}^{\text{film}}$ 5.83, 5.99, 6.20 (w), and 6.28 (w) μ] was epoxidized with 30% hydrogen peroxide according to Westen's procedure,[7] and the product solidified to afford, after recrystallization from ether, 1.2 g. of VI, m.p. 154–156°. Further recrystallization produced material with m.p. 156–158° (lit. m.p. 158°,[7] 158–158.5°[8]); $\lambda_{\max}^{\text{KBr}}$ 5.79 (sh), 5.83, 6.22 (w), and 6.31 μ (w).

Reduction of VI to X with Lithium Aluminum Hydride.—The crude triol X was prepared by a procedure based on that of Plattner.[20] To a magnetically stirred suspension of 0.59 g. (1.6×10^{-2} mole) of lithium aluminum hydride in 25 ml. of anhydrous ether was added dropwise a solution of 0.361 g. (1.20×10^{-3} mole) of VI, m.p. 156–158°, in 30 ml. of ether. The mixture was refluxed for 30 min. and cooled to room temperature. Excess lithium aluminum hydride was decomposed by dropwise addition of 2 ml. of wet ether and 1 ml. of 10% sodium hydroxide solution. The mixture was stirred for 10 min. more and 20 ml. of ether was added. The ether layer was carefully decanted and evaporated to yield 0.310 g. of oily residue (theoretical yield of X plus benzyl alcohol = 0.370 g.): $\lambda_{\max}^{\text{film}}$ 2.9–3.0 (vs) and 6.05 (vw) μ.

Conversion of X to III.—The crude triol product (0.310 g.) was dissolved in 50 ml. of acetone, which had been purified by distillation from potassium permanganate, and placed in an ice bath. Jones reagent[9] was added dropwise to the magnetically stirred solution until the red-orange color of the reagent persisted; this required 0.8 ml. of oxidant. After an additional 2 min. of stirring the reaction mixture was poured into 300 ml. of 5% aqueous potassium carbonate solution, which was then extracted with four 50-ml. portions of ether. The combined ether extracts were washed with four 20-ml. portions of water and two 20-ml. portions of saturated sodium chloride solution and were dried over magnesium sulfate. Evaporation of the ether gave a light yellow oil which was quickly dissolved in 20 ml. of acetone and poured through a column of Florisil. Failure to filter products from earlier runs through an adsorbent resulted in their turning dark, and no III was obtained upon subsequent chromatography. Evaporation of the eluted acetone afforded 0.079 g. (33% of III from VI) of an oil which solidified upon trituration with ether and had m.p. 138–141°. Further elution of the column gave only 0.024 g. of unidentified oil. Recrystallization of the solid from ether afforded pure III, m.p. 141–142°, which was compared with the compound prepared by cyclization of I and found to have an identical infrared spectrum and an undepressed mixture melting point.

Acknowledgment.—This investigation was supported by Public Health Service Research Grant AM-05014.

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(18) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960). We have found the rather tedious purification of the sodium borohydride used for this selective reduction by Boyce and Whitehurst to be unnecessary with the sodium borohydride we had in hand (Metal Hydrides, Inc., 98+%, as supplied). We recommend that other investigators try unpurified reagent on a small scale when attempting a selective reduction of this type.

(19) F. Sondheimer and D. Elad, *J. Am. Chem. Soc.*, **79**, 5542 (1957).

(20) A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

Additivity of Chemical Shifts in the Decalin Ring System. Determination of Configuration of *cis*-9-Hydroxy-10-methyldecalin-2,5-dione

KENNETH L. WILLIAMSON, LORETTA R. SLOAN,[1] THELMA HOWELL,

Department of Chemistry, Mount Holyoke College, South Hadley, Massachusetts

AND THOMAS A. SPENCER

Department of Chemistry, Dartmouth College, Hanover, New Hampshire

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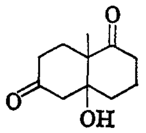
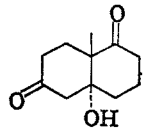
The principle of additivity of substituent effects on the n.m.r. chemical shift of the angular methyl group applies to the relatively flexible decalin ring system just as it does to steroids. This additivity principle has been used to determine as *cis* the configuration of the 9-hydroxy-10-methyldecalin-2,5-dione prepared by the cyclization of the adduct of methyldihydroresorcinol with methyl vinyl ketone, by consideration of the contributions of the hydroxyl and the two carbonyl substituents and the presence of a *cis* or *trans* ring juncture to the angular methyl resonance.

In their classical study of the n.m.r. spectra of steroids, Shoolery and Rogers[2] showed that the chemical shift of angular methyl protons is dependent on the nature and location of the various functional groups on the steroid skeleton and that the effects of these substituents are additive. These initial proposals have been extended by a number of workers, notably Zürcher.[3] He showed, in an extremely thorough analysis of the chemical shifts of some 260 steroids, that, with few exceptions, it is possible to calculate the chemical shifts for C-18 and C-19 protons to within 1 or 2 c.p.s. in a polysubstituted steroid, taking advantage of the additivity effect of each substituent on the angular methyl resonance.

Recently we have shown[4] that the additivity principle is applicable to angularly methylated decalins, by a consideration of chemical shift data for some *cis*-10-methyl-2-decalones published by Elliott, Robinson, and Riddell.[5] In the present work we sought to establish the generality of this additivity principle by an analysis of carefully measured chemical shifts for the angular methyl groups of *cis*- and *trans*-10-methyldecalin and certain of their derivatives. In particular we wished to use the additivity principle to determine whether the 9-hydroxy-10-methyldecalin-2,5-dione,[6] m.p. 141–142°, prepared by cyclization of the Michael adduct of methyldihydroresorcinol with methyl vinyl ketone,[7] had a *cis* (Ia) or *trans* (Ib) ring juncture.


Ia


Ib

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(1) Petroleum Research Fund Scholar, summer 1964.

(2) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(3) (a) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); (b) *ibid.*, **46**, 2054 (1963).

(4) K. L. Williamson and T. A. Spencer, *Tetrahedron Letters*, 3267 (1965).

(5) D. R. Elliott, M. J. T. Robinson, and F. G. Riddell, *ibid.*, 1693 (1965).

(6) All decalins in this paper are numbered as shown in structure I, Table I.

(7) T. A. Spencer, H. S. Neel, D. C. Ward, and K. L. Williamson, *J. Org. Chem.*, **31**, 434 (1966).