= 124.4 Hz), 5.20 (dd, 1 H, J = 10, 3 Hz, CHOH), 5.52 (dt, 1 H, J = 10, 7 Hz, $CH_2CH{=}CH$), 5.80 (t, 1 H, J = 10 Hz, $CH{=}CHCHOH$), 7.1–7.5 (m, 5 H).

(−)-[1α,4α,5α,7*R(*E*)]-5-Bromo-7-(benzyloxy)spiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolan]-7-yl-3(*S**)-acetoxy-1-octene (4).** To a solution of 220 mg (0.473 mmol) of alcohol **6** (R = H) in 5.0 mL of dry methylene chloride containing 1.0 mL of acetic anhydride and 0.5 mL of pyridine was added a catalytic amount of 4-(dimethylamino)pyridine. After 24 h, the reaction mixture was diluted with 50 mL of ether and was washed successively with copper sulfate solution, water, sodium bicarbonate solution, and brine. The organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo left 210 mg of residue, which was purified on 40 g of silica gel. Elution with hexane–ethyl acetate (15:1) gave 196 mg (82%) of pure acetate **6** (R = Ac) as a colorless oil: $[\alpha]^{25}_{D}$ +2.60 (*c* 3.38, $CHCl_3$); IR ($CHCl_3$) 2990, 2950, 2920, 2870, 1735, 1490, 1460, 1450, 1430, 1365, 1320, 1310, 1235, 1204, 1130, 1090, 1050, 1012, 1000, 995, 940, 910, 890, 860, 690 cm^{-1}; NMR (220 MHz) CCl_4 δ 0.91 (br t, 3 H, J = 7 Hz), 1.36 (m, 6 H), 1.55 (d, 1 H, J = 14 Hz), 1.91 (br s, 1 H), 2.00 (m, 2 H), 2.03 (s, 3 H), 2.32 (dd, 1 H, J = 14, 5 Hz), 2.41 (m, 1 H), 2.70 (dd, 1 H, J = 15, 9 Hz), 2.90 (m, 1 H), 3.6–4.0 (m, 4 H), 4.09 (dd, 1 H, J = 9, 4 Hz, CHBr), 4.78 (ABq, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 106.3 Hz), 5.57 (m, 2 H, $CH{=}CH$), 6.04 (d, 1 H, 8 Hz, CHOAc), 7.1–7.5 (m, 5 H).

To a solution of 190 mg (0.375 mmol) of bromo acetate **6** (R = Ac) in 5.0 mL of tetrahydrofuran was added 4.0 mg of bis(acetonitrile)palladium(II) chloride. After 24 h the reaction was diluted with 20 mL of ether and was washed with brine. The organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo left 200 mg of a residue, which was chromatographed on 40 g of silica gel. Elution with hexane–ethyl acetate (30:1) gave 146 mg (77%) of rearranged acetate **4** as a pure crystalline compound: mp 83.5–84.5 °C; $[\alpha]^{25}_{D}$ −80.7° (*c* 2.14, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2925, 2870, 2855, 1728, 1605, 1495, 1465, 1450, 1440, 1430, 1370, 1330, 1240, 1205, 1140, 1115, 1095, 1055, 1015, 975, 945, 925, 890, 865, 835, 692 cm^{-1}; NMR (220 MHz) CCl_4 δ 0.87 (t, 3 H, J = 7 Hz), 1.30 (m, 6 H), 1.50 (d, 1 H, J = 14 Hz), 1.64 (m, 2 H), 1.93 (s, 3 H), 2.08 (dt, 1 H, J = 14, 5 Hz), 2.33 (d, 1 H, J = 5 Hz), 2.44 (d, 1 H, J = 5 Hz), 2.64 (m, 2 H), 3.7–4.0 (m, 5 H, OCH_2CH_2O, CHBr), 4.30 (ABq, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 25.3 Hz), 5.23 (q, 1 H, J = 7 Hz, CHOAc), 5.70 (dd, 1 H, J = 16, 7 Hz, $CH(OAc)CH{=}CH$), 6.01 (d, 1 H, J = 16 Hz, $CH(OAc)CH{=}CH$), 7.24 (m, 5 H).

Anal. Calcd for $C_{26}H_{35}BrO_5$: C, 61.54; H, 6.95. Found: C, 61.65; H, 7.04.

Acknowledgment. Generous support for this work from the National Institute of Child Health and Human Development, National Institutes of Health (Grant HD 14646), and G. D. Searle and Co. is gratefully acknowledged.

Registry No. **3** (R = H), 79120-26-6; **3** (R = $OCH_2C_6H_5$), 79069-64-0; **4**, 79069-65-1; **5**, 79069-66-2; **6** (R = H), 79069-67-3; **6** (R = Ac), 79069-68-4; (−)-(1α,4α,5α,7*R**)-5-bromo-7-(benzyloxy)spiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-methanol, 79069-69-5; 1-iodo-1-*cis*-heptene, 63318-29-6; $PdCl_2(CH_3CN)_2$, 14592-56-4.

Isomeric Bicyclo[3.2.1]octane-6,8-diones: Nuclear Magnetic Resonance as a Probe for Stereochemical Distinction

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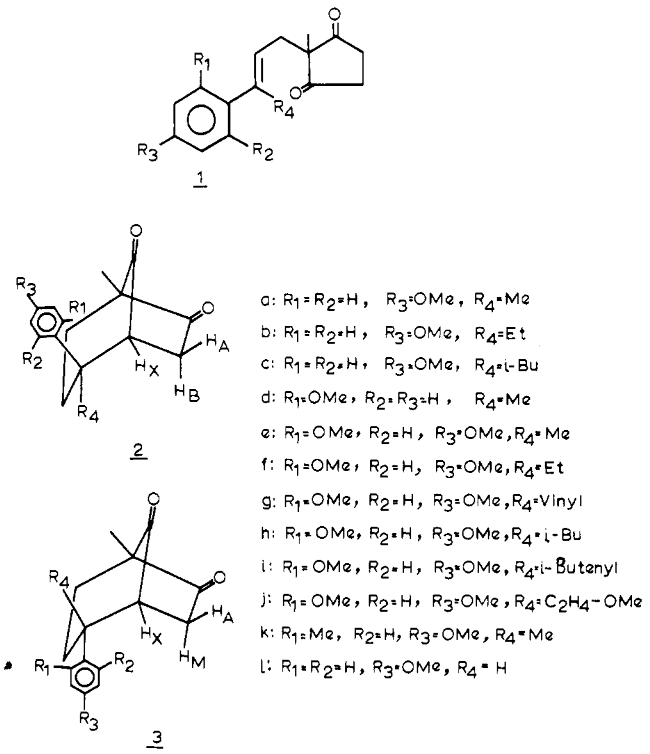
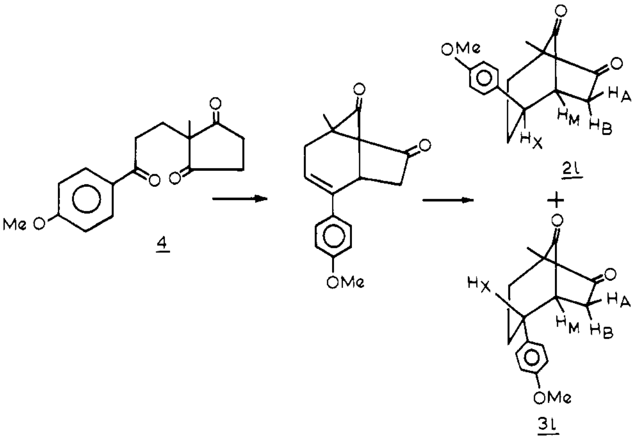
Received May 22, 1981

We have shown[1] earlier that the cyclization of diketones of the type **1** using hydrogen chloride in methanol gives isomeric bicyclo[3.2.1]octane-6,8-diones **2** and **3** (Chart I). These isomeric diones exhibit characteristic line patterns for the oxomethylene and the bridgehead protons in their ^1H NMR spectra (see Table I): pattern A (ABX),[2] δ_A, δ_B 2.3–2.8 (m), δ_X 3.1–4.0 (m); pattern B (AMX), δ_A 2.4–2.7 (q, $J_{AX} \approx 8.0$ Hz, $J_{AM} \approx 20.0$ Hz), δ_M 2.8–3.0 (d, $J_{AM} \approx 20.0$ Hz), δ_X 3.3–4.1 (d, $J_{AX} \approx 8.0$ Hz). The isomers which exhibited pattern A were assigned the *exo*-2-aryl-*endo*-2-alkyl configuration (**2**) and those isomers which exhibited pattern B were assigned the *endo*-2-aryl-*exo*-2-alkyl configuration (**3**). These assignments were based on the expectation that the aryl group in the endo position (as in **3**) would deshield the *endo*-oxomethylene proton and thus lead to a larger chemical shift difference between *exo*- and *endo*-oxomethylene protons in this isomer. Similar de-

Chart I



Scheme I



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(1) T. R. Kasturi, S. Madhava Reddy, R. Ramachandra, and E. M. Abraham, *Indian J. Chem., Sect. B.*, **19B**, 433 (1980); T. R. Kasturi and S. Madhava Reddy, *ibid.*, **20B**, 64 (1981).

(2) Spectral analysis was carried out by using the LAOCN3 computer program (A. A. Bothner-By and S. Castelleno in "Computer Programs in Chemistry", Vol. 1, D. F. Detar, Ed., W. A. Benjamin, New York, 1968, p 10).

0022-3263/81/1946-5007$01.25/0

Table I. Selected 270-MHz ^{1}H NMR Data (δ) for Isomeric Bicyclo[3.2.1]octane-6,8-diones

	2			3				2			3		
compd	H_A	H_B	H_X	H_A	H_M	H_X	compd	H_A	H_B	H_X	H_A	H_M	H_X
a	2.43	2.45	3.12	2.68	2.95	3.31	g	2.43^a	2.43^a	3.85	2.58	2.86	4.05
b	2.44	2.48	3.24	2.65	2.97	3.34	h	2.28^a	2.28^a	3.80^b	2.56	2.96	3.94
c	2.40	2.42	3.17	2.65	2.99	3.32	i	2.40^a	2.40^a	3.70^b	2.60	2.98	4.03
d	2.38	2.41	3.81	2.61	2.93	4.05	j	2.35^a	2.35^a	3.77	2.59	2.95	4.04
e	2.39^a	2.39^a	3.75	2.59	2.91	3.97	k	2.38	2.40	3.81	2.60	2.92	4.04
f	2.40^a	2.40^a	3.80	2.57	2.95	3.97	l	2.80^c	2.80^c	3.20^d	2.40	2.60	2.80^d

^{a} Deceptively simple ABX. $\Delta\delta_{AB} < 4.0$ Hz. ^{b} Overlaid with methoxyl signal. ^{c} Approximate values are given since they form a part of a complex spin system. ^{d} Refers to H_M in structures **2l** and **3l**.

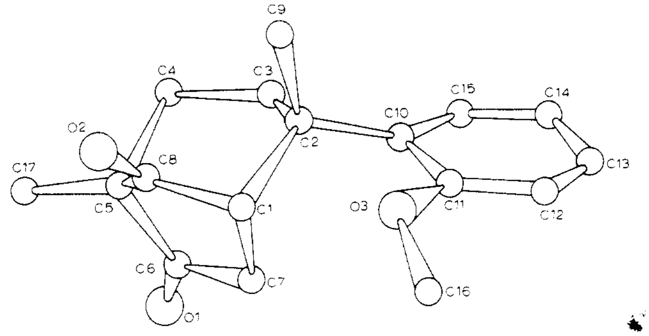

Figure 1. Perspective view (down the *a* axis) of the molecule **3d**.

shielding of the *endo*-oxomethylene proton by the *endo*-hydroxyl group in 2-hydroxy-2,5-dimethylbicyclo[3.2.1]-octane-6,8-dione has been reported[3] earlier.

The ^{1}H NMR spectra of compounds[4] **2l** and **3l** (Scheme I) were studied with the view of obtaining the coupling constants between the benzylic and the bridgehead protons which would throw more light on the orientation of the benzylic proton and hence on the configuration at C-2. The spectral features of the bridgehead and the oxomethylene proton signals are indicated in Table I. The benzylic proton in the exo isomer appeared at δ 3.6 with $J_{MX} \approx 3.3$ Hz. This value is certainly of the order of J_{ae} of cyclohexane in contrast to the expected J_{ee} (**2l**). Also, in the endo isomer, this proton signal appeared at δ 3.5 with $J_{MX} \approx 1.8$ Hz, which is of the order of J_{ee} instead of the expected J_{ae} (**3l**), and thus necessitated a reinvestigation of the previous assignments. To this end, we carried out[5] the single-crystal X-ray structural analysis of the easily crystallaizable isomer of 2-(2-methoxyphenyl)-2,5-dimethylbicyclo[3.2.1]octane-6,8-dione, which was previously assigned structure **2d**. Figure 1 shows the final X-ray model less the hydrogens. Clearly, the methyl group at C-2 and the bridge oxo group are cis with respect to each other, indicating a *exo*-2-methyl-*endo*-2-(2-methoxyphenyl) configuration (**3d**), contrary to the assigned structure **2d**.

Consequently, all the previous assignments had to be revised: the isomers which exhibit pattern A are now assigned the *endo*-2-aryl-*exo*-2-alkyl configuration and vice versa. As can be seen from Table I, the bridgehead proton signal, in both isomers, shifts downfield when an ortho substituent is introduced to the aromatic ring. From a study of the Dreiding models of the exo and the endo isomers, it is found that the ortho substituent on the aromatic ring offers steric hindrance to free rotation of the ring, the most stable conformation[6] being the one where the aromatic ring and the cyclohexane ring are mutually perpendicular.[7] Also, in this conformation, the bridgehead proton is coplanar with the aromatic ring and could become deshielded by the magnetic anisotropy of the ring. There are several examples in the literature[8] reporting the deshielding of the C-2 and C-6 protons by the 1-aryl group in substituted 1-arylcyclohexanes.

Although nothing specific can be said about the exact influence of the endo substituent at C-2 on the *endo*-oxomethylene proton, the typical line patterns exhibited by the bridgehead and the oxomethylene proton signals in these isomers can be unambigously used for their stereochemical differentiation.

Experimental Section

^{1}H NMR spectra of $CDCl_3$ solutions were recorded at 270 MHz on a Bruker WH-270 (FT) spectrometer, and the values are given as parts per million downfield from Me_4Si.

X-ray Analysis. Needle-shaped crystals of **3d** [optically active, $[\alpha]_D$ (EtOH) $-100°$] were obtained by slow evaporation from a benzene–hexane solution of its racemate. Crystal data: $a = 6.280$ (2) Å, $b = 10.069$ (2) Å, $c = 22.056$ (3) Å, $V = 1395.02$ Å^3, molecular formula $C_{17}H_{20}O_3$; $Z = 4$; measured density (flotation in aqueous KI) 1.29 g/cm^3; calculated density 1.295 g/cm^3; space group $P2_12_12_1$. Intensity data were collected on a Nonius CAD-4 diffractometer using monochromated Mo K_α radiation and in the $\omega/2\theta$ scan mode for a crystal of dimensions 0.4 × 0.7 × 1.8 mm. A total of 1470 reflections were collected out of which 1055 were significant $[|F_0| \geq 2\sigma(|F_0|)]$. The structure was solved by direct methods (MULTAN80).[9] Positions for the rigid hydrogen atoms were calculated from the molecular skeleton, and those for the methyl hydrogen atoms were assigned from the difference map. After several cycles, the full-matrix least-squares refinement of the positional and anisotropic thermal parameters of the 20 nonhydrogen atoms and the positional and isotropic thermal parameters of the 20 hydrogen atoms, with the weighting scheme $w = \sigma^2(|F_0|) + 0.0012|F_0|^2$ has led to a final R index of 0.062 for significant reflections and 0.083 for all reflections.

Acknowledgment. P.S.M., S.M.R., and M.M.B. thank the Indian Institute of Science, Bangalore, UGC, New Delhi, and CSIR, New Delhi, respectively, for research fellowships.

Registry No. 2a, 78349-14-1; **2b**, 78349-18-5; **2c**, 78349-20-9; **2d**, 78349-16-3; **2e**, 78349-15-2; **2f**, 78349-19-6; **2g**, 75778-75-5; **2h**, 75778-80-2; **2i**, 79135-46-9; **2j**, 79152-60-6; **2k**, 78349-17-4; **2l**, 79135-47-0; **3a**, 78349-21-0; **3b**, 78349-25-4; **3c**, 78349-27-6; **3d**, 78349-23-2; **3e**, 78349-22-1; **3f**, 78349-26-5; **3g**, 79135-48-1; **3h**, 79135-49-2; **3i**, 79135-50-5; **3j**, 79152-61-7; **3k**, 78349-24-3; **3l**, 79135-51-6.

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[3] Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **39**, 1612 (1974).

[4] Compounds **2l** and **3l** were prepared by *p*-tosic acid catalyzed cyclization of the triketone **4** [H. Zajac, *Chem. Abstr.*, **90**, 168827, 121226 (1979)] followed by hydrogenation and thin-layer chromatography over silica gel to separate the isomers. The assignment of configuration to these isomers was based on the earlier generalization.

[5] The details of this analysis will be published elsewhere.

[6] N. L. Allinger, J. Allinger, M. A. Darooge, and S. Greenberg, *J. Org. Chem.*, **27**, 4603 (1962).

[7] The X-ray analysis for the compound **3d** also indicated a nearly perpendicular disposition of these two rings.

[8] A. C. Huitric and J. B. Carr, *J. Org. Chem.*, **26**, 2648 (1961); A. C. Huitric, W. G. Clarke, Jr., K. Leigh, and D. C. Staiff, *ibid.*, **27**, 715 (1962); E. W. Garbisch and D. B. Patterson, *J. Am. Chem. Soc.*, **85**, 3228 (1963); A. Segre, *Tetrahedron Lett.*, 1001 (1964).

[9] P. Main, "MULTAN 80, a System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray diffraction Data", Department of Physics, University of York, York, England, 1980.