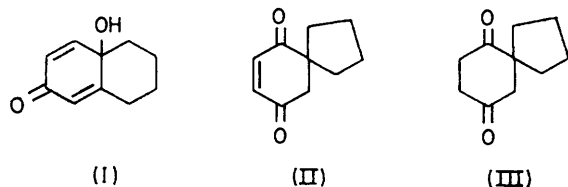


The Dienone-Phenol Rearrangement. Synthesis of Spiro[4.5]dec-7-ene-6,9-dione

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Spiro[4.5]dec-7-ene-6,9-dione (II) has been synthesized and identified as one component of the mixture formed on rearrangement of 6-hydroxybicyclo[4.4.0]deca-1,4-dien-3-one catalysed by boron trifluoride-ether complex.

PREVIOUS work¹ on the rearrangement of 6-hydroxybicyclo[4.4.0]deca-1,4-dien-3-one (I) catalysed by boron trifluoride-ether complex resulted in the identification



of a neutral product as spiro[4.5]dec-7-ene-6,9-dione (II), this being the first reported isolation of a spiran intermediate from a dienone-phenol type rearrangement.² The structural assignment was based on the i.r., ¹H n.m.r., and mass spectra of (II) and its dihydro-derivative, spiro[4.5]decane-6,9-dione (III). However, since (II) was not isolated in a pure state and was an unknown compound, we undertook its unambiguous synthesis to confirm our identification.

The synthesis involved spiroannulation of cyclohexanone to produce spiro[4.5]decan-6-one (IV), introduction of the 7,8-double bond by sequential bromination and dehydrobromination, functionalization of the allylic C-9 position, and subsequent manipulation to produce the desired oxidation level.

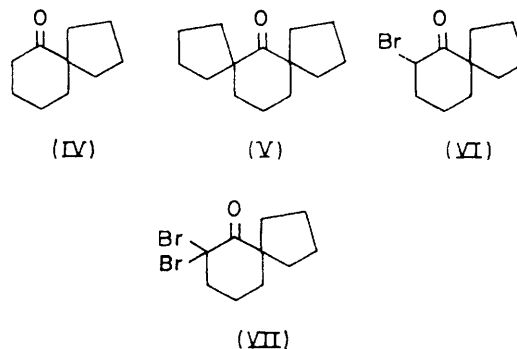
The parent spiro-compound (IV) was synthesized³ by reaction of the enolate of cyclohexanone with 1,4-

¹ G. F. Burkinshaw, B. R. Davis, E. G. Hutchinson, P. D. Woodgate, and R. Hodges, *J. Chem. Soc. (C)*, 1971, 3002.

² For reviews see A. J. Waring, *Adv. Alicyclic Chem.*, 1966, **1** (3); B. Miller in 'Mechanisms of Molecular Migration,' ed. B. S. Thyagaragan, Interscience, New York, 1968, p. 247.

dibromobutane, and was isolated in 49% yield by spinning-band distillation. Preparative t.l.c. of the distillation residue give the bis-annulation product, dispiro[4.1.4.3]tetradecan-6-one (V) in 2.4% yield.

Bromination of (IV) was initially attempted with pyridinium hydrobromide perbromide. This reagent has been used successfully to produce mono- α -bromo-ketones⁴ as it can be readily weighed out to liberate a



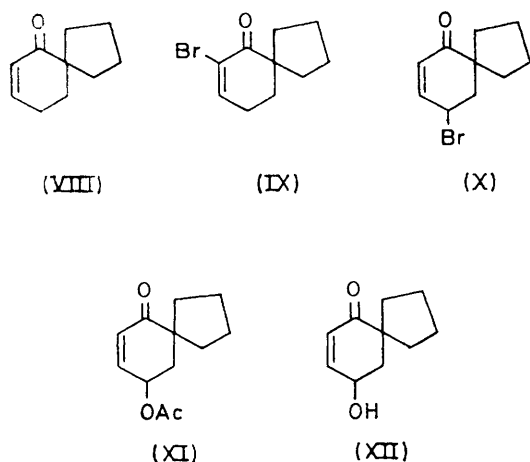
precise (equimolar) amount of bromine, thereby preventing formation of the $\alpha\alpha$ -dibromo-derivative. In the event, however, both 7-bromospiro[4.5]decan-6-one⁵ (VI) and 7,7-dibromospiro[4.5]decan-6-one (VII) were formed. Treatment of the crude bromination product with lithium bromide-lithium carbonate in dimethyl-

³ M. Mousseron, R. Jacquier, and H. Cristol, *Bull. Soc. chim. France*, 1957, 346.

⁴ C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, 1948, **70**, 417.

⁵ E. J. Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301.

formamide at 120–140° followed by preparative t.l.c. afforded pure spiro[4.5]dec-7-en-6-one (VIII) in 50% yield, and 7-bromospiro[4.5]dec-7-en-6-one (IX) in 7% yield. The 2,4-dinitrophenylhydrazone of (VIII) gave acceptable combustion data, and the enone itself



exhibited characteristic $\alpha\beta$ -unsaturated carbonyl absorptions at 1665 cm^{-1} in the i.r. spectrum and at 227 nm ($\log \epsilon$ 3.79) in the u.v. spectrum. The i.r. spectrum of the bromo-enone (IX) showed a characteristic α -halogeno- $\alpha\beta$ -unsaturated carbonyl peak at 1685 cm^{-1} , and the 8-proton signal appeared in the ^1H n.m.r. spectrum as a triplet (J 4 Hz) at δ 7.15.

The co-production of the bromo-enone (IX) was subsequently avoided by treating a solution of the spiro-ketone (IV) in tetrahydrofuran with bromine in dichloromethane;⁶ under these (non-basic) conditions the desired bromo-ketone (VI) was formed in quantitative yield. Its i.r. spectrum displayed carbonyl absorptions at 1727.5 and 1704.5 cm^{-1} , corresponding to the equatorial and axial bromine conformers, respectively. Dehydrobromination of crude 7-bromospiro[4.5]decan-6-one was best achieved by treatment with magnesium oxide in dimethylformamide under nitrogen at 120–140°.⁶ Spinning-band distillation of the total product gave pure spiro[4.5]dec-7-en-6-one (VIII) in 58% yield. The use of 1,5-diazabicyclo[4.3.0]non-5-ene in refluxing benzene or in dimethylformamide at 100–110° also afforded (VIII) but in lower yields (27 and 39%, respectively).

Attempted direct allylic oxidation of the enone (VIII) to the enedione (II) with either sodium chromate in acetic anhydride-acetic acid⁷ or cerium(IV) ammonium nitrate in acetic acid-water⁸ gave a complex mixture (t.l.c.) which was not further investigated, and after treatment of (VIII) with selenium dioxide in dimethyl sulphoxide⁹ for 40 h more than 90% of the starting material was recovered. It was therefore necessary to employ a longer route to the desired compound. Reaction of unrecrystallized *N*-bromosuccinimide with the

enone (VIII) in dry carbon tetrachloride afforded 9-bromospiro[4.5]dec-7-en-6-one (X) in 57% yield after preparative t.l.c. Spectral absorptions at 1680 cm^{-1} in the i.r. and at 221 nm ($\log \epsilon$ 3.77) in the u.v. were in the expected regions. In the ^1H n.m.r. spectrum virtual coupling between the C-8 vinyl proton and the C-10 methylene protons was demonstrated by irradiation of the C-9 proton signal, which caused the C-8 proton pattern to collapse to a clean doublet ($J_{8,7}$ 10.4 Hz). If the C-10 methylene protons and the C-9 methine proton are considered as an isolated ABX system, the near equality of the observed $J_{9,10}$ values (7.6 and 7.0 Hz) in conjunction with the appearance of two sharp signals integrating for two protons at δ 2.40 and 2.50 indicates that the observed pattern represents a deceptively simple spectrum due to ($\nu_A - \nu_B$) tending to 0. Hence the real J values cannot be extracted by a simple first-order analysis. Nevertheless, the fact that the C-7 proton signal is split by coupling through to the C-9 proton allows the conclusion that this allylic torsion angle must be close to 90°. Consequently, the molecule must assume a dominant conformation such that the bromine atom is equatorial, as would be anticipated from steric considerations (space-filling model).

Attempted displacement of the bromine atom in (X) with lithium carbonate in either dioxan-water⁹ or dimethyl sulphoxide-water afforded a seven-component mixture. However, the bromo-enone was converted into 9-acetoxyspiro[4.5]dec-7-en-6-one (XI) by treatment with silver acetate in acetone at room temperature. The i.r. and u.v. spectra showed the expected features, and in the ^1H n.m.r. spectrum a broad ($W_{1/2}$ 20 Hz) signal centred at δ 5.72 attested to the predominantly axial orientation of the C-9 proton. The allylic acetate (XI) was hydrolysed by heating under reflux in methanol-water with a catalytic amount of sodium carbonate, preparative t.l.c. then yielding pure 9-hydroxyspiro[4.5]dec-7-en-6-one (XII). Finally, spiro[4.5]dec-7-ene-6,9-dione (II) was obtained in 58% yield by oxidation of the allylic alcohol (XII) with manganese dioxide. Attempted oxidation of (XII) with silver carbonate-Celite¹⁰ returned starting material after heating under reflux for 7 h. The synthetic compound (II) was identical (i.r. and ^1H n.m.r. spectra; t.l.c.) with a sample previously obtained¹ from rearrangement of the *p*-quinol (I). Moreover, reduction of synthetic (II) with zinc-acetic acid afforded spiro[4.5]decane-6,9-dione (III), which showed identical spectral properties and no depression of m.p. with a sample obtained from the rearrangement product. This synthesis therefore confirms our previous assignment and provides unambiguous evidence for the existence of a spiran intermediate in the rearrangement of the *p*-quinol (I).

The 70 eV mass spectra of all the spiro-compounds reported above contained an intense peak, often the

⁶ M. Miyano and C. R. Dorn, *J. Org. Chem.*, 1972, **37**, 268.

⁷ J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, 1971, **36**, 877.

⁸ W. S. Trahanovsky and L. B. Young, *J. Chem. Soc.*, 1965, 5777.

⁹ A. N. Singh, A. B. Upadhye, M. S. Wadia, V. V. Mhaskar, and S. Dev, *Tetrahedron*, 1969, **25**, 3855.

¹⁰ M. Fetizon, M. Golfier, and J. Louis, *Chem. Comm.*, 1969, 1102.

base peak, whose formation can be rationalized by a McLafferty rearrangement of a γ -hydrogen atom from the cyclopentane ring, followed by allylic cleavage.

Conformational Analysis of the Bromo-ketone (VI).—The carbonyl absorptions at 1727.5 and 1704.5 cm^{-1} arise from the bromine-equatorial and bromine-axial conformers, respectively. By studying the variation with temperature of the relative areas of these peaks (Table)

TABLE ^{a, b}

T/K	258	273	288	303	318	333	348
A_h^c	77	70	65	64	60	57	54
A_1^d	23	22	22	23.5	24	23	23.5

^a These data were measured with CCl_4 as solvent by Dr. G. D. Meakins, University of Oxford, using an analogue computer method of curve resolution. ^b A = area; expressed so that $A_h + A_1 = 100\%$ at 258 K. ^c A_h = area of 1727.5 cm^{-1} peak. ^d A_1 = area of 1704.5 cm^{-1} peak.

it is possible¹¹ to obtain an accurate value for the enthalpy difference ($\Delta H = H_{ax} - H_{eq}$) between the two conformers, a value of 2.90 kJ mol^{-1} being found for the bromo-ketone (VI). Furthermore,¹¹ $\Delta S^\circ = 17.7 \text{ J K}^{-1} \text{ mol}^{-1}$, $\Delta G^\circ = -2.51 \text{ kJ mol}^{-1}$, and $K = 2.71 = 73/27$ in favour of the bromine-equatorial conformer at 303 K. This conformer ratio agrees with a value previously obtained from i.r. optical density data.¹²

Relative conformer populations may also be estimated from ^1H n.m.r. parameters by the method of Garbisch,¹³ the conformationally rigid model compounds being 2 β -bromo-6 β -t-butylcyclohexanone ($J^I = J_{AX} + J_{BX} = 17.8 \text{ Hz}$) and 2 α -bromo-6 β -t-butylcyclohexanone ($J^{II} = 5.6 \text{ Hz}$).¹⁴ The value of J° , the frequency separation between the strong terminal lines of the X resonances centred at δ 4.62, was 16.0 Hz, leading to a ratio of 85:15 in favour of the equatorial conformer (CCl_4 solution). No variation in J° was observed down to a probe temperature of 203 K, reflecting the mobile conformational equilibrium indicated by the small ΔH value. Similarly, J° was unchanged when the concentration was varied from 271.5 to 34 mg ml^{-1} . In C_6D_6 as solvent the X resonances sharpened and J° increased slightly to 17.0 Hz, indicating 93% equatorial conformer present. The discrepancy between the conformer ratios obtained from the i.r. and the ^1H n.m.r. data (CCl_4 solutions) presumably represents the uncertainty in the respective values imposed by the assumptions^{11, 13} implicit in each method.

EXPERIMENTAL

Analyses were performed by Professor A. D. Campbell, University of Otago, New Zealand. I.r. spectra were measured for thin films on a Perkin-Elmer 237 spectrometer. ^1H n.m.r. spectra were measured for solutions in CDCl_3 or CCl_4 on a Varian T60 spectrometer: J (apparent) values are reported for non first-order signals. Assignments were confirmed by double resonance where practicable.

Spiro[4.5]decan-6-one (IV).³—A mixture of cyclohexanone (9.6 g) and 1,4-dibromobutane (21.6 g) was added to a stirred suspension of potassium t-butoxide (21.9 g) in

benzene (150 ml). The mixture was heated under reflux for 4.5 h and the product was extracted into ether; usual work-up followed by spinning-band distillation gave pure spiro[4.5]decan-6-one (8.6 g, 57%), b.p. 96° at 20 mmHg (lit.,³ 104° at 18 mmHg), ν_{max} 1709 cm^{-1} , δ 1.24–2.75.

The distillation residue was subjected to column chromatography on silica gel (200 ml) with n-hexane-ether (99:1) as eluant. The eluates were further purified by preparative t.l.c. (n-hexane-ether, 99:1; two passes) to give *dispiro*[4.1.4.3]*tetradecan-6-one* (V) (0.5 g, 2.4%), m.p. 32–34° (Found: C, 81.3; H, 10.7. $\text{C}_{14}\text{H}_{22}\text{O}$ requires C, 81.5; H, 10.7%), ν_{max} (CCl_4) 1693 cm^{-1} , δ 1.20–2.20.

Spiro[4.5]dec-7-en-6-one (VIII).—(a) A solution of bromine (21.1 g) in dichloromethane (25 ml) was added dropwise to a cooled (ice-bath), stirred, solution of spiro[4.5]decan-6-one (20 g) in tetrahydrofuran (180 ml). Stirring was continued for 10 min after addition was complete (1 h). Aqueous NaHCO_3 solution was then added and the mixture was stirred until effervescence ceased. Work-up then afforded crude 7-bromospiro[4.5]decan-6-one, a small portion of which was purified by column chromatography (10% deactivated silica gel) and then repeated crystallization from n-pentane to give flakes, m.p. 48–51° (lit.,⁵ 51–55°), ν_{max} 1727.5 and 1704.5 cm^{-1} , δ 1.18–2.59 (14H, m, 7 \times CH_2) and 4.62 (1H, X part of ABX, $J_{AX} + J_{BX} = 16 \text{ Hz}$, C-7 proton).

The crude bromo-ketone dissolved in dimethylformamide (25 ml) was added under nitrogen to a stirred suspension of magnesium oxide (6.9 g) in dimethylformamide (250 ml) which had been pre-heated to 120–140°, and the mixture was stirred at this temperature for 1 h. After cooling, water (80 ml) and aqueous HCl (10%; 200 ml) were added, and the solution was extracted with ether. Spinning-band distillation of the crude product obtained after work-up gave pure (g.l.c.) spiro[4.5]dec-7-en-6-one (11.4 g, 58%), b.p. 119° at 22 mmHg, ν_{max} 1665 and 1620 cm^{-1} , λ_{max} 227 (log ϵ 3.79) and 324 nm (log ϵ 1.56), δ 1.18–1.98 (10H, m, 5 \times CH_2), 2.02–2.54 (2H, m, C-9 protons), 5.85 (1H, 2t, $J_{7,8}$ 10, $J_{7,9}$ 2 Hz, C-7 proton), and 6.75 (1H, 2t, $J_{8,7}$ 10, $J_{8,9}$ 4, $J_{8,9}$ 4 Hz, C-8 proton). The 2,4-dinitrophenylhydrazone had m.p. 133–134.5° (from methanol) (Found: C, 58.1; H, 5.4; N, 16.75. $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_4$ requires C, 58.2; H, 5.5; N, 16.95%).

(b) Pyridinium hydrobromide perbromide (10 g) was added during 20 min to a solution of spiro[4.5]decan-6-one (4.75 g) in acetic acid (50 ml). Work-up as usual followed by chromatography on silica gel (120 ml; 10% deactivated) with n-hexane-ether (49:1) as eluant afforded pure 7-bromospiro[4.5]decan-6-one (5.8 g, 78%).

Dehydrobromination of the crude product with lithium bromide (11.4 g) and lithium carbonate (9 g) in dimethylformamide (90 ml) followed by preparative t.l.c. (benzene) yielded spiro[4.5]dec-7-en-6-one (2.34 g, 50%) and 7-bromospiro[4.5]dec-7-en-6-one (0.5 g, 7%), ν_{max} 1685 and 1605 cm^{-1} , δ 1.13–2.55 (12H, m, 6 \times CH_2) and 7.15 (1H, t, $J_{8,9}$ 4 and 4 Hz, C-8 proton).

9-Bromospiro[4.5]dec-7-en-6-one (X).—N-Bromosuccinimide (1.45 g; not recrystallized) was added to a solution of spiro[4.5]dec-7-en-6-one (1.02 g) in dry carbon tetrachloride (50 ml) and the mixture was heated under reflux for 7 h. Work-up gave a yellow oil which was purified by

¹² E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Amer. Chem. Soc.*, 1955, **77**, 5415.

¹³ E. W. Garbisch, *J. Amer. Chem. Soc.*, 1964, **86**, 1780.

¹⁴ E. W. Garbisch, *J. Org. Chem.*, 1965, **30**, 2109.

¹¹ D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin II*, 1972, 1959.

preparative t.l.c. (benzene) to give pure 9-bromospiro[4.5]dec-7-en-6-one (0.88 g, 57%) as an oil (Found: C, 52.5; H, 5.6; Br, 34.4. $C_{10}H_{13}BrO$ requires C, 52.4; H, 5.7; Br, 34.8%), ν_{\max} 1680 cm^{-1} , λ_{\max} 221 nm ($\log \epsilon$ 4.02), δ 1.10—2.35 (8H, m, $4 \times CH_2$), 2.40 and 2.50 (2H, 2's', C-10 protons), 4.90 (1H, 4q, $J_{9,10}$ 7.6 and 7.0, $J_{9,8}$ 2.8, $J_{9,7}$ 1.9 Hz, C-9 proton), 5.82 (1H, 2d, $J_{7,8}$ 10.4, $J_{7,9}$ 1.9 Hz, C-7 proton), and 6.85 (1H, 4t, $J_{8,7}$ 10, $J_{8,9}$ 2.8, $J_{8,10}$ 0.6 and 0.6 Hz, C-8 proton).

9-AcetoxySpiro[4.5]dec-7-en-6-one (XI).—Silver acetate (0.29 g) was added to a solution of 9-bromospiro[4.5]dec-7-en-6-one (0.20 g) in acetone (10 ml) and the mixture was stirred at room temperature for 64 h. Filtration and evaporation of the filtrate at ambient temperature *in vacuo* gave a yellow oil. Preparative t.l.c. (benzene-acetone, 9:1) afforded pure 9-acetoxySpiro[4.5]dec-7-en-6-one (0.09 g, 50%) as an oil (Found: C, 69.35; H, 7.5. $C_{12}H_{16}O_3$ requires C, 69.25; H, 7.7%), ν_{\max} 1745, 1678, and 1629 cm^{-1} , λ_{\max} 221 nm ($\log \epsilon$ 3.90), δ 1.05—2.02 (8H, m, $4 \times CH_2$), 2.10 (3H, s, acetate), 2.18—2.59 (2H, m, C-10 protons), 5.72 (1H, 4t, $J_{9,10}$ 9, $J_{9,10}$ 6, $J_{9,8}$ 2.5, $J_{9,7}$ 2.2 Hz, C-9 proton), 6.02 (1H, 2d, $J_{7,8}$ 10.4, $J_{7,9}$ 2.2 Hz, C-7 proton), and 6.77 (1H, 2q, $J_{8,7}$ 10.4, $J_{8,9}$ 2.5, $J_{8,10}$ 1.3 Hz, C-8 proton).

9-HydroxySpiro[4.5]dec-7-en-6-one (XII).—Sodium carbonate (3 mg) was added to a solution of 9-acetoxySpiro[4.5]dec-7-en-6-one (40 mg) in 50% aqueous methanol (10 ml) and the solution was heated under reflux for 40 min. After removal of the solvent *in vacuo* the residue was

salted (NaCl) and extracted with ether. Preparative t.l.c. (benzene-acetone, 9:1) yielded pure 9-hydroxySpiro[4.5]dec-7-en-6-one (10 mg, 35%) as an oil, M^+ 166, ν_{\max} 3440, 1670, and 1622 cm^{-1} , λ_{\max} 220 nm ($\log \epsilon$ 3.72), δ 1.24—2.54 (11H, m, $5 \times CH_2$ and OH), 4.62 (1H, 4t, $J_{9,10}$ 10, $J_{9,10}$ 6, $J_{9,8}$ 2, $J_{9,7}$ 2.2 Hz, C-9 proton), 5.92 (1H, 2d, $J_{7,8}$ 10.3, $J_{7,9}$ 2.2 Hz, C-7 proton), and 6.85 (1H, 2t, $J_{8,7}$ 10.3, $J_{8,9}$ 2, $J_{8,10}$ 2 Hz, C-8 proton).

Spiro[4.5]dec-7-ene-6,9-dione (II).—Treatment of a solution of 9-hydroxySpiro[4.5]dec-7-en-6-one (50 mg) in benzene (50 ml) with manganese dioxide (40 mg) at room temperature for 10 min gave, after purification by preparative t.l.c. (benzene-acetone, 9:1), Spiro[4.5]dec-7-ene-6,9-dione (30 mg, 56%), m.p. 38—41° (Found: C, 73.0; H, 7.55. $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.4%), ν_{\max} 1682 and 1608 cm^{-1} , λ_{\max} 226 nm ($\log \epsilon$ 3.99), δ 1.0—2.4 (8H, m, $4 \times CH_2$), 2.80 (2H, s, C-10 protons), and 6.71 (2H, s, C-7 and C-8 protons).

Spiro[4.5]decane-6,9-dione.—Reaction of Spiro[4.5]dec-7-ene-6,9-dione (30 mg) with zinc (0.1 g) in acetic acid (4 ml) at room temperature afforded, after work-up, Spiro[4.5]decane-6,9-dione (20 mg, 86%), m.p. 89—91° (from n-pentane-ether) (lit.,¹ 88.5—89.5°), undepressed on admixture with the sample previously obtained;¹ ν_{\max} 1710 cm^{-1} , δ 1.18—2.30 (8H, m, C-1, C-2, C-3, and C-4 methylene protons) and 2.65—2.76 (6H, m, C-7, C-8, and C-10 methylene protons).

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