Bicyclo[2.2.2]octane-2-spirocyclohexanes, Part 4 [1]

Birch Reduction of Spirodiisophor-6-ones
Frederick Kurzer* and Zakir Kapadia
Royal Free Hospital School of Medicine, University of London, London NW 3, England
Bicyclo[2.2.2]octane-2-spirocyclohexanes, Spirodiisophoranes, Birch Reduction

Birch reduction of spirodiisophorones by sodium in liquid ammonia—t-butanol reduces their normally inert 6-keto-group, producing the corresponding secondary alcohols, the 6-hydroxy-group of which assumes the endo- or exo-configuration. 3′-Oximinospirodiisophor-6-one is converted predominantly into the 6-endohydroxy-compound, from which the 3′,6-endo-ketol is obtainable by the action of sodium bisulphite. 3′-eq(and ax)-Hydroxydiisophor-6-one each yield a pair of stereoisomeric 3′,6-diols, distinguished by their spectral characteristics and derivatives. Spirodiisophora-3′,6-dione yields a mixture of the same four diols, three of which are isolable in low yield. The structure of selected compounds is correlated with their assigned 13C NMR spectra.

Introduction

Spirodiisophora-3′,6-dione (I) is the product of the controlled dimerisation of isophorone (3,5,5-trimethylcyclohex-2-enone). Its ready synthesis form this source [2–4], together with its subsequent transformations [1–5] provide a convenient entry to the study of the bicyclo[2.2.2]octane-2-spirocyclohexane ring system.

The 3′- and 6-keto functions of the spiro structure 1, located in its respective alicyclic rings, differ in their reactivity: The 6-keto group of the trimethylated bicyclo[2.2.2]octane moiety is unusually inert, so that reactions expected to affect both ketonic centres, occur exclusively at C-3′ of the cyclohexanone ring. Thus, the 6-keto group of I fails to react with ketonic reagents [4], does not promote α-bromination [1] and is unaffected by several reducing agents [5]; all these reactions occur normally in the isolated parent bicyclo[2.2.2]octanone [6]. Our aim to modify this keto group of the extended spiro structure I has been realised in the Birch reaction, which has been found to reduce the 6-ketones to 6-secondary alcohols.

Results and Discussion

The Birch reaction [7], involving the action of alkali metals in liquid ammonia, usually in conjunction with a proton donor such as ammonium chloride or an alcohol, is a versatile method of reducing a variety of structures. Its scope extends from the controlled hydrogenation of unsaturated molecules including aromatic compounds, monon-and polyolefins, to the reductive fission of ethers, and the hydrogenolysis of groups attached to oxygen, sulphur and nitrogen [7, 8]. In addition, the successful reduction of steroid ketones (incorporating 3, 11, 12, 16 or 17α-carbonyl functions) to the corresponding secondary alcohols [9] suggested its potential applicability to the present structural pattern. Our results show that the Birch reduction is in fact capable of attacking, in the spirodiisophorane structure, the 6-keto function which is resistant to the action of several other reducing agents, including lithium aluminium hydride, boron trifluoride etherate, as well as the Huang-Minlon reduction and catalytic hydrogenation [5].

The 6-hydroxy-group arising in the Birch reduction may assume two spatial positions, which, though equivalent relative to the bicyclo[2.2.2]octane ring-system, are distinct in relation to the extended carbon framework, illustrated for example, by their differing distances from the spiro centre C-2 (ca. 2.8 and 3.8Å, respectively). They are here designated as the endo- and exo-configurations, the former referring to the substituent situated more closely, and the latter more distantly from C-2 and C-6. There is a tendency for one of the stereoisomers to be formed preferentially as the predominating, or indeed the sole isolable product: these are regarded as the endo-isomers, for reasons given below.
In model experiments, the action of sodium in liquid ammonia—$t$-butanol on 3'-oximinospirodiosphor-6-one $2$ [4] gave exclusively the 3'-oximino-6-endo-hydroxy compound $3$. Its reoxidation with Kiliani's chromic acid [10] proceeded directly to the 3',6-dione stage $1$, with simultaneous regeneration of the 3'-keto from the 3'-oximino group. The 6-hydroxy-3'-oxime $3$ was of chief interest as a potential precursor of 6-hydroxydiosphor-3'-one $4$, i.e. the position isomer of the 6,3'-ketols $5$ and $6$. In the present instance, however, the usual methods of converting the oximino into the parent keto group failed, the oxime $3$ being unaffected by conventional acid hydrolysis [11], and largely decomposed in the pyruvic acid procedure [12]. The attempted use of seleninic anhydride, known to regenerate ketones from their nitrogenous derivatives in difficult cases [13], left the 3'-oximino group intact, but reoxidised the 6-hydroxy function, affording good yields of the known [4] 3',6-dione-3'-monoxime $2$. The desired reaction (3 → 4) was finally accomplished by the use of sodium bisulphite in aqueous ethanol [14], which provided the 3',6'-ketol $4$ in good yield. Its IR spectrum resembles closely those of its position isomers $5$, $6$, except for insignificant displacements.
towards lower wave numbers of its intense hydroxy and keto absorptions (3420 and 1690 cm\(^{-1}\)) and the C-OH-stretching bands (1040, 1050 cm\(^{-1}\)). The ketol 4 was reconvertible into its 3'-oxime 3 and was further characterised as ketonic derivatives (4a, 4b) and as the 6-(3,5-dinitrobenzoate) ester (4c). Kiliani oxidation regenerated the parent 3',6-diketone 1.

The model structure most relevant for examining the Birch reaction in the present context is spirodiisophor-6-one (11), with its unreactive 6-keto group as the only function. This is unaffected by the drastic action of hydrazine and sodium of the Huang-Millon reduction (by which 11 is produced from 1 [5]), but responded readily to the Birch reaction, which afforded good yields of 6-endo-hydroxySpirodiisophorane (11→12). The product is a viscous liquid, having the correct composition and appropriate IR spectral properties, but is advantageously isolated as its crystalline 6-(3,5-dinitrobenzoate) ester.

Preliminary experiments indicated that Birch reduction of the parent 3',6-diketone 1 gave a mixture of all four possible 3',6-diols (7–10), that proved difficult to separate on the preparative scale. The reduction of the individual 3'-ax- and 3'-eq-hydroxySpirodiisophor-6-ones (5, 6) was therefore first examined, with the aim of isolating the individual stereoisomeric products. Each of the ketols (5, 6) gave one pair of 3',6-diols (7, 8 and 9, 10), which were separable by fractional crystallisation and were characterised by their spectral properties and as derivatives. In each case, the stereoisomer arising as the major product is regarded as the 6-endo-form of the respective structure (see mechanism, below). The main IR spectral feature of the diols are their intense and broad hydroxyl peaks centred, for each stereoisomer, at slightly different but constant positions (between 3300 and 3400 cm\(^{-1}\)); the spectra of the isomer pair 7 and 8 are readily distinguishable, but those of 9 and 10 resemble one another closely, except for the presence of additional sharp peaks (at 1150 and 850 cm\(^{-1}\)) in that of the latter. Each of the diols (7–10) gave a distinct 3',6-bis(3,5-dinitrobenzoate) ester; the most readily accessible isomer 9 was further characterised as the 3',6-bis-p-nitrobenzoate (9b), and a monotoluene-p-sulphonate (9c). Oxidation by chromic acid reconverted each of the four diols into the parent dione 1.

The reduction by lithium aluminium hydride of the 3’,6-diketone 1, being confined to its 3’-keto group, yields the 6,3’-eq-ketol 6 [5]. Applied to the position isomer 4, which retains the active 3’-keto group, LAH reduction gave the 3’-eq-6-endodiol 9, thus confirming the identical configuration of the 6-hydroxy group in compounds 3, 4 and 9.

The data established for the 3’,6-diols 7–10 helped in elucidating the Birch reduction of the parent 3’,6-dione 1. This gave a product, liquid at ordinary temperatures, of a mixture of presumably all four diols (7–10); it showed the expected intense broad hydroxyl absorption in the IR range (3300–3400 cm\(^{-1}\)) and was reoxidised quantitatively to the starting material 1. It was separable into the two 3’-ax-diols 7 and 8 (isolated as the free alcohols) and the 3’-eq-6-endodiol 9 (as the dinitrobenzoate), but the fourth isomer 10 was apparently retained in a substantial uncrystallisable residual fraction. The Birch reaction thus effectively reduces the 3’-keto group of the cyclohexanone ring, but the process is not stereoselective as are the LAH reduction and catalytic hydrogenation [5].

**Mechanism and Stereoisomerism**

The mechanism and stereochemical course of the Birch reaction has been interpreted by Barton [15] and by House [8, c, 16, 17] and further elaborated by Huffman [18]. Application of the accepted scheme in its simplest form to the present case suggests that reduction is initiated by a one-electron transfer from the metal, by which the ketone (i) is converted into the radical anion (ii). This is protonated to the alkoxy free radical (iii), which after
further metal reduction to the alkoxide ion (iv) and final protonation from the least hindered side gives the individual stereoisomers of the product (v).

The stereochemical aspects of this mechanism are founded on extensive classical data on the steric course of reactions in the comparable bicyclo[2.2.1]heptane (norbornane) ring system [19, 20], especially the analogous reduction of ketones: Thus, nor-camphor A, the exo-side of which is more accessible to reagent attack [19], is reduced to endo-norborneol B [21], while camphor C, with its exo-face screened by the 7-dimethyl group, yields by endo-approach predominantly exoborneol D [19, 22].

In the present spiro structure, the 6-keto group is screened from both faces (of the C-1,4,5,6-plane). Molecular models suggest that the approach of reagent is, on balance, hindered less by the proximate 10-methyl group than by the larger 5'-gem-dimethylcyclohexane moiety on the opposite side. Accordingly, the major (or sole isolable) isomers are regarded to arise by protonation from the former direction, and formulated as the 6-endo-alcohols. The concept also accounts for the formation of both configurations side by side.

$^{13}$C NMR Spectra

The $^{13}$C NMR spectra of the spirodiisophoranes now described are displayed in the usual manner (Table I) in accordance with their proposed assignments. These are ultimately based on the unequivocal identification by the INADEQUATE technique [4] of the signals of the parent 3',6-diketone 1 and the 3'-ax-ketol 5, and on further correlations within this ring system, involving groups of compounds varying in the structure of their cyclohexa­none moiety [1, 5].

$^{13}$C NMR spectral data are also available [23] for ketones, alcohols and monoolefins (including methylated examples) of the isolated bicyclo[2.2.2]octane ring-system. They provide limited guidance in identifying the doublet of the hydroxylated C-6 centre in the spirodiisophoranes (see below), but being otherwise not comparable, are not helpful in the allocation of the signals of the bicy­clo-octane moiety once this forms part of the extended spirane structure. However, the obvious close correspondence of the present numerical data with those of the mapped spectra of the model ketols 5, 6 and the diketone 1 [1, 4, 5] and its 3'-monoxime [4] provide an acceptable basis for the assignment and correlation of the new spectra.

The interpretation of the $^{13}$C NMR spectra is exemplified by reference to the two diols 7 and 8 derived from the model 3'-ax-ketol 5 [4, 5]. The near-constancy of the signals of their skeletal carbon atoms except those in the immediate proximity of the structural change is evident, and resonances are particularly close for the centres more remote from C-6 (i.e. C-3,4,8 and C-2',5',6'). The replacement of the strongly electron-attracting 6-keto by the hydroxyl group results in the expected shielding of the adjacent carbon atoms (C-1,5), with consequent upfield displacement of their signals. The same tendencies are apparent in the 3'-eq-set of compounds (6 vs 9 and 10).

In assigning the three doublets of the diols (7–10), the signal of the 3'-hydroxy-group is first identified by comparison with the reliably established resonances of the 3'-ax- and 3'-eq-hydroxy groups in the reference compounds 5 and 6 (63.5 and 68 ppm respectively), the structural environment of which is identical with that in the present examples (7–10). This leaves, in each case, a doublet in the 65–70 ppm and one in the 48–55 ppm range. Since the corresponding signals in bicyclo[2.2.2]octan-2-ols [23] and (nor)borneols [24, 25] appear consistently in the higher of these two ranges (viz. 65–80 ppm), we assign these doublets (at 65–69 ppm) to the C-6 centre of the bicyclo[2.2.2]octane moiety; their resonances differ only slightly for the endo- and exo-configuration of the 6-hydroxy group (in 7 and 8 vs 9 and 10).
Table I. $^{13}$C-NMR Spectra of bicyclo[2.2.2]octane-2-spirocyclohexanes and their assignment.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
<th>C-8</th>
<th>C-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>5°</td>
<td>60.2 d</td>
<td>36.9 s</td>
<td>50.4 t</td>
<td>33.5 s</td>
<td>46.9 t</td>
<td>215.8 s</td>
<td>32.0 s</td>
<td>50.3 t</td>
<td>26.8 q</td>
</tr>
<tr>
<td>7</td>
<td>55.1 d</td>
<td>39.6 s</td>
<td>50.4 t</td>
<td>33.6 s</td>
<td>43.1 t</td>
<td>69.0 d</td>
<td>33.1 s</td>
<td>50.1 t</td>
<td>28.0 q</td>
</tr>
<tr>
<td>8</td>
<td>47.3 d</td>
<td>38.8 s</td>
<td>50.6 t</td>
<td>34.3 s</td>
<td>41.8 t</td>
<td>69.4 d</td>
<td>33.1 s</td>
<td>49.7 t</td>
<td>27.9 q</td>
</tr>
<tr>
<td>6°</td>
<td>64.3 d</td>
<td>37.5 s</td>
<td>*49.5 t</td>
<td>33.9 s</td>
<td>*46.7 t</td>
<td>215.8 s</td>
<td>31.8 s</td>
<td>*49.2 t</td>
<td>26.9 q</td>
</tr>
<tr>
<td>9</td>
<td>55.3 d</td>
<td>39.2 s</td>
<td>*49.6 t</td>
<td>34.3 s</td>
<td>42.0 t</td>
<td>65.8 d</td>
<td>32.8 s</td>
<td>*49.3 t</td>
<td>28.1 q</td>
</tr>
<tr>
<td>1°</td>
<td>67.6 d</td>
<td>40.5 s</td>
<td>*46.0 t</td>
<td>33.5 s</td>
<td>*46.2 t</td>
<td>212.6 s</td>
<td>31.5 s</td>
<td>49.0 t</td>
<td>26.5 q</td>
</tr>
<tr>
<td>4°</td>
<td>54.0 d</td>
<td>41.2 s</td>
<td>45.9 r</td>
<td>*34.3 s</td>
<td>41.6 t</td>
<td>69.1 d</td>
<td>32.6 s</td>
<td>49.5 t</td>
<td>27.9 q</td>
</tr>
<tr>
<td>3°</td>
<td>54.6 d</td>
<td>42.8 s</td>
<td>44.5 t</td>
<td>34.0 s</td>
<td>41.7 t</td>
<td>68.9 d</td>
<td>32.5 s</td>
<td>49.4 t</td>
<td>27.7 q</td>
</tr>
</tbody>
</table>

In contrast, the chemical shifts of the remaining higher-field doublets, allotted by exclusion to C-1, are influenced significantly by the spatial position of the adjacent 6-hydroxy group (ca. 55 and 47 ppm for endo- and exo-, respectively). Attention is drawn, however, to the fact, that the same configurational differences in the detached bicyclo[2.2.2]octane structure (E, F) are conversely associated with signal shifts at the hydroxy-bearing carbon (C-2) rather than the adjacent bridgehead position (C-1). The necessity of an interchange of the C-1 and C-6 doublets (of compounds 3, 4, 7–10) is therefore not entirely discounted.

In the interpretation of the spectra of the 6-hydroxy-3'-ketone 4 and its 3'-oxime 3, the 3',6-dione 1 (and its 3'-monoxime) [4] serve as models for identifying the signals of their cyclohexanone carbons, and the present diols for those of their bicyclo[2.2.2]octane-moiety. Corresponding chemical shifts match closely and require little further comment. The resonances of the high-field C-1 doublets (at ca. 54 ppm) correspond to the endo-configuration of the 6-hydroxy group, in accord with the favoured steric course of this reduction. The apparently deviating chemical shifts of C-2', 3' and 4' of 3 are in fact characteristic of oximes and nearly coincident with those of the model 3'-oxime 2 [4].

Conclusion

The keto function of bicyclo[2.2.2]octanes undergoes the normal reactions of alicyclic ketones [6], but is remarkably unreactive, once the bicyclooctane framework forms part of the extended methylated spirodisophorane structure (e.g. 1, 2,
This inertness may possibly be ascribed to obstruction to the approach of reagents by the proximate 7-dimethyl group as well as the screening cyclohexane-moiety, especially its 3′-ax-methyl substituent. The Birch reduction now described provides the first general method of modifying this otherwise inert 6-keto function: the readiness with which it responds to this reaction may therefore be traceable to the smaller steric requirement of the one-electron transfer that initiates the reduction process (see mechanism, above). The significance of steric factors in this context could be assessed by parallel experiments involving “nor”-spirodiisophorones (e.g. G, the dimer of 3-methylcyclohex-2-enone [2]); the fact that in contrast to the 3’,6-diketone 1 [4], this yields a 3’,6-bis-hydrazone [2], holds out some promise for the utility of such an approach.

Experimental

The equipment used in determining the spectral characteristics of the compounds is specified in Part 1 [4]. This also gives details concerning solvents, reagents and general procedures, and lists abbreviations that continue to be used.

The reductions requiring the use of liquid ammonia were performed in a three-neck flask fitted with a solid carbon dioxide condenser. When reaction was complete and the deep-blue colour of the mixture had faded and permanently disappeared, the ammonia was allowed to volatilise spontaneously from the stirred reaction mixture at room temperature.

6-endo-Hydroxy-3′-oximinopirodiisophorone [6-endo-Hydroxy-4,5′,5′,7,7-pentamethyl-3′-oximinobicyclo[2.2.2]octane-2-spirocholohexane] (3)

(a) Preparation: To a stirred solution of 3′-oximinopirodiisophor-6-one (2) [4], 11.64 g, 40 mmol) in t-butanol (100 ml) was added liquid ammonia (250 ml), followed by sodium (6.9 g, 0.3 g.atom), introduced in small pieces over a period of 6 h. Initially the deep-blue colour of the liquid faded and disappeared rapidly, but later persisted and was finally discharged within 4–6 h. On spontaneous evaporation of the ammonia, there remained a suspension of a granular white material. This was extracted with ether, the extracts washed with M hydrochloric acid, then water, to neutrality, and the solvent removed under reduced pressure. The residue gave on crystallisation from light petroleum, microprisms (4.4 g, 38%) of 3, m. p. 210–212 °C.

IR (KBr): 3300 vs br (OH), 2960-2880 vs br, 1460 s, 1435-1425 ms (CH₃,CH-), 1655 ms (C=O), 1390 ms, 1370 s (CMe₂), 1290 ms, 1040 s, 990 s, 970 s, 940 m, 865 m cm⁻¹.

C₁₈H₃₁N₂O₂ (293.45)
Calcd C 73.7 H 10.65 N 4.8,
Found C 73.8 H 10.8 N 4.8.

(b) Reoxidation to 3′-oximinopirodiisophor-6-one (2): A solution of 3 (0.9 g, 3 mmol) in anhydrous tetrahydrofuran (100 ml) was treated with benzeneseleninic anhydride [13] (1.09 g, 3 mmol), and the pale-yellow liquid boiled under reflux for 2.5 h. After the removal of most of the solvent under reduced pressure, the residual liquid was stirred into ice-water (100 ml). The resulting yellow gum which failed to solidify was isolated by ether extraction, and the extracts washed with 25% lead acetate solution, then water, to neutrality. The nearly colourless oil remaining on removal of the solvent was dissolved in light petroleum (8 ml); the solution slowly deposited prisms (0.43 g, 48%) of 2, identified by mixed m.p. 177–179 °C and IR spectrum [4].

(c) Reoxidation to spirodiisophora-3′,6-dione (1): A solution of 3 (0.29 g, 1 mmol) in glacial acetic acid (10 ml) was treated dropwise with Kiliani’s 10% chromic acid [10] (3 ml, 2.5 mmol), and stirring at room temperature continued for 1 h. The reddish-brown liquid was treated with water (50 ml) and 10% aqueous sodium sulphite (10 ml), and the resulting dark-green liquid extracted with ether. The washed neutral extracts gave, on removal of the solvent, a pale-yellow oil: its solution in light petroleum deposited prisms (70%) of 1, identified by mixed m.p. 114–115 °C, and IR spectrum [4].

6-endo-Hydroxy-spirodiisophor-3′-one (4)
A stirred solution of 3 (2.1 g, 7 mmol) in ethanol (35 ml), treated with aqueous sodium bisulphite
(40% w/v, 10 ml) was boiled under reflux for 5 h, the precipitated solid (sodium bisulphite) filtered off and rinsed with a little ethanol; the combined filtrate was evaporated under reduced pressure to small volume, and stirred into ice-water (300 ml). The precipitated white gum (which solidified imperfectly) was collected, rinsed with water, air-dried and dissolved in light petroleum (15 ml). The separating product (m.p. 95–105 °C, 1.33 g, 67%) gave, on further crystallisation from methanol-light petroleum (5 ml each, recovery 70%), massive plates of 4, m.p. 115–119 °C.

IR: 3420 vs (OH), 2950–2910 vs, 2860 s sh, 1460 ms (CH₃,CH₂), 1690 vs (CO), 1390 m, 1370 ms (CMe₂), 1050, 1040 s d (C–O of OH), 1350 ms, 1295 s, 1250 m, 1140 m, 980 m, 940 m cm⁻¹.

C₁₈H₃₀O₂ (278.4)
Calcd C 77.6 H 10.9,
Found C 77.2 H 10.9.

Reconversion into spirodiisophora-3',6-dione (1): The 3',6-ketol 4 (0.28 g, 1 mmol) gave on chromic acid oxidation [10] by the procedure specified for the oxime 3 (see above), prisms of 1 (0.18 g, 64%), identified by mixed m.p. 114–115 °C and IR spectrum [4].

Reconversion into the oximino-alcohol 3: A solution of 4 (0.28 g, 1 mmol) in pyridine (10 ml), treated with hydroxylamine hydrochloride (0.21 g, 3 mmol) gave, by the standard procedure [4], prisms (72%) of 3, m.p. 210–212 °C (from light petroleum).

6-endo-Hydroxyspirodiisophor-3'-one (4): derivatives

(a) Semicarbazone (4a): A solution of 4 (0.28 g, 1 mmol) and semicarbazide hydrochloride (0.35 g, 3 mmol) in ethanol (10 ml) – pyridine (2 ml) was refluxed for 3 h, distilled to half volume under reduced pressure, and added to ice-water (80 ml) – concentrated hydrochloric acid (2 ml). The resulting precipitate gave microprisms (0.25 g, 72%) of 4a, m.p. 215 °C (decomp.) (from ethanol – light petroleum).

C₁₉H₃₅N₂O₇ (335.5)
Calcd C 68.0 H 9.9 N 12.5,
Found C 67.8 H 9.9 N 12.1.

(b) 2,4-Dinitrophenyldrazone (4b): A solution of 4 (1 mmol) and 2,4-dinitrophenyldrazine (0.20 g, 1 mmol) in ethanol (15 ml) – concentrated hydrochloric acid (1 ml) was boiled under reflux for 30 min, then distilled to half-volume. The separated derivative 4b (0.41 g, 89%) formed deep-orange prisms, m.p. 208–211 °C (from ethanol).

6-(3,5-Dinitrobenzoyl)ester (4c): A solution of 4 (1 mmol) in pyridine (10 ml), treated with 3,5-dinitrobenzoyl chloride (0.35 g, 1.5 mmol) gave, by the procedure described for the 3',6-diols (see below), a buff solid (0.5 g), which gave on crystallisation from acetone (15 ml), yellow platelets (0.36 g, 77%) of 4c, m.p. 206–208 °C.

IR: 3100 m (Ar), 2950–2910 s, 2860 ms sh, 1465 s (CH₃,CH₂), 1720 vs, 1710 vs (CO, ring and acyl), 1630 s (C=C), 1550 vs, 1350 vs (N=O), 1275 vs (C=O, ester), 1165 s (C=N), 730, 720 s (1,3,5-trisub. Ar) cm⁻¹.

C₂₁H₃₂N₂O₇ (472.55)
Calcd C 63.5 H 6.8 N 5.9,
Found C 63.7 H 6.9 N 5.9.

Spirdiisophora-3',6-diols (7–10)

Birch reduction of 3'-ax (and eq)-hydroxyspirodiisophor-6-ones (5, 6 [5])

3'-ax-6-endo (and exo)-Dihydroxyspirodiisophoranes (7, 8)

To a stirred solution of 3'-ax-hydroxydiisophor-6-one (5 [5]) (8.34 g, 30 mmol) in t-butanol (50 ml) was added successively liquid ammonia (250 ml) and sodium (5 g, 0.22 g-atom), introduced in small pieces over a period of 3 h. The deep-blue colour of the liquid faded and disappeared within 1 h. On spontaneous evaporation of the ammonia, a suspension of a white gelatinous material remained. This was extracted with ether, the extracts washed with M hydrochloric acid and water to neutrality, and the solvent removed under reduced pressure. The residual pale yellow oil was dissolved in light petroleum (25 ml); the successive crops of solid gave, on further recrystallisation, the following products:

(i) The initial less soluble fractions gave, on crystallisation from ethanol, rhombic prisms of 3'-ax-6-endo-dihydroxyspirodiisophorane 7, m.p. 156–159 °C (3.82 g, 45%).

IR: 3380 vs vbr (OH), 2965–2850 vs, 1470 s br (CH₃,CH₂), 1390 ms, 1365 s (CMe₂), 1055 vs (C=O of OH), 1030 vs, 985 vs, 900 w, 840 w cm⁻¹.

C₁₈H₃₂O₂ (280.45)
Calcd C 77.1 H 11.5,
Found C 76.8 H 11.4 M 280.
(ii) The more soluble later and final fractions gave the 6-exo-isomer 8, forming needles, m.p. 171–174 °C (from light petroleum) (1.89 g, 23%).

IR: 3350 vs vbr (OH), 2980–2860 vs, 1475–1460 vs (C=H), 1385 ms, 1365 s (CMe), 1050 vs (C=O of OH), 1320 s, 1290 s, 1245 s, 1225 m, 1175 s, 1140 ms, 1080 s, 1040–1020 vs, 990 vs, 950 m, 840 m, 680 mw cm⁻¹.

Found C 76.7 H 11.4 M 280.

Spirodiisophora-3',6-diols (7–10): 3',6-Bis(3,5-dinitrobenzoate) esters

A solution of the respective 3',6-diol (7–10) (0.28 g, 1 mmol) in pyridine (10 ml), treated with 3,5-dinitrobenzoyl chloride (0.58 g, 2.5 mmol), was kept at 100 °C for 30 min, then stirred into ice-water (100 ml) containing concentrated hydrochloric acid (10 ml). The precipitate was crystallised from acetone-light petroleum, giving pale-buff to yellow microprisms of the derivative (of 7–10). The data for that of 9 are as follows: m.p. 153–155 °C (decomp., sintering from 125 °C); yield 64%.

IR (identical for all four derivatives): 3100 m (Ar), 2960–2870 s, 1470 m (C=H), 1350 vs (N-O), 1170 vs (C-N), 1075 m, 960 m, 925 m, 775 w cm⁻¹.

C₁₂H₃₆N₄O₁₂ (668.67)
Calcd C 57.5 H 5.4 N 8.4
Found C 57.7 H 5.5 N 8.3.

The data for the other three derivatives are as follows:

<table>
<thead>
<tr>
<th>Deriv.of</th>
<th>m.p.</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>234–237 °C</td>
<td>C 57.4 H 5.5 N 8.2</td>
</tr>
<tr>
<td>8</td>
<td>243–244 °C</td>
<td>C 57.7 H 5.4 N 8.3</td>
</tr>
</tbody>
</table>

3'-eq-6-endo-Dihydroxyspirodiisophorane (9): Further derivatives

3',6-Bis(p-nitrobenzoate) ester. The use, in the foregoing procedure, of 9 (0.28 g, 1 mmol) and p-nitrobenzoyl chloride (0.56 g, 3 mmol), gave a crude product (0.73 g), which formed lemon-yellow prisms (0.48 g, 83%) of the derivative, m.p. 185–186 °C (from acetone – light petroleum).

IR: 2950–2870 vs, 1470 ms (CH₃,CH₂), 1720 vs (C=O, acyl), 1610 ms (C=O), 1535 vs, 1360–1350 s br (N=O), 1285 vs br (C-O, ester), 1120–1100 vs d (C=N), 720 vs (1,4-disub.Ar) cm⁻¹.

C₁₂H₃₆N₄O₈ (578.67)
Calcd C 66.4 H 6.6 N 4.8
Found C 66.2 H 6.6 N 4.8.

Monotoluene-p-sulphonate ester: A solution of 9 (0.21 g, 0.75 mmol) in pyridine (8 ml), treated with toluene-p-sulphonyl chloride (0.48 g, 2.5 mmol) was kept at room temperature for 12 h, then stirred into ice-water (80 ml) containing concentrated hydrochloric acid (8 ml). The precipitated white gum, which failed to solidify, was isolated by
ether-extraction and crystallised from light petroleum. On storage at 0 °C, the solution slowly deposited massive prisms (0.24 g, 73%) of the derivative, m.p. 128 – 130 °C.

IR: 3620 s (OH), 2970–2870 vs, 1465 s (CH₃, CH₂), 1600 ms (C=O), 1365 vs, 1190 vs, 1175 vs (RSO₂), 855 s, 840 s, 815 vs (1,4-disub.Ar) cm⁻¹.

C₂₅H₃₈O₄S (434.65)  
Calcd C 69.1 H 9.0,  
Found C 68.9 H 9.0.

3'-eq-6-endo-Dihydroxyspirodiisophorane (9).  
Alternative synthesis by LAH reduction of 4

A solution of 4 (0.70 g, 2.5 mmol) in anhydrous ether (75 ml) was added to a stirred suspension of lithium aluminium hydride (0.38 g, 10 mmol) in the same solvent at such a rate that the reaction mixture effervesced gently. It was boiled under reflux for 2.5 h, the excess of the reducing agent destroyed by the slow addition of water and 3 M hydrochloric acid. The product was isolated by ether extraction, and crystallised from ethanol-light petroleum, giving elongated prisms (75%) of 9, identified by mixed m.p. 140–143 °C, IR spectrum, and its bis(3,5-dinitrobenzoate) ester.

Birch Reduction of Spirodiisophor-6-one 11 [5]

To a solution of the parent diketone 11 ([5] 2.62 g, 10 mmol) was subjected, by the standard procedure, to the action of sodium (2.3 g, 0.1 g.atom) in liquid ammonia (250 ml) – t-butanol (10 ml). The crude product was a yellow oil that failed to solidify, or crystallise from the usual solvents, even at 0 °C. Its solution in light petroleum (b.p. 40–60 °C) was filtered through alumina (2.5 x 30 cm) and the eluate collected in three fractions. Removal of the solvent from each gave 6-endo-hydroxyspirodiisophorane 12, again as uncrystallisable faintly yellow liquids, identical in their IR spectra (total, 2.4 g, 90%).

IR (NaCl plates): 3450 vs br (OH), 2960–2860 vs, 1465, 1455 s d (CH₃,CH₂), 1720, 1710 w d (vegetal CO₂), 1370 m, 1370 ms (CMe₂), 1040–1020 s cm⁻¹.

C₁₈H₃₂O₂ (264.45)  
Calcd C 81.75 H 12.2,  
Found C 81.5 H 12.6.

The 6-hydroxyspirane was reoxidised by the standard procedure using Kiliani’s 10% chromic acid [10] to the 6-ketone 11 (65%), identified by mixed m.p. 62–63 °C and IR spectrum [5].

The crude product of an identical experiment (10 mmol), dissolved in anhydrous pyridine (40 ml) and treated with 3,5-dinitrobenzoyl chloride (2.8 g, 12 mmol), was kept at 100 °C for 1 h, then stirred into ice-water containing concentrated hydrochloric acid (40 ml). The soft precipitate (which failed to solidify) was isolated by ether extraction. Crystallisation from acetone – light petroleum gave colourless platelets (3.7 g, 80%) of the 6-(3,5-dinitrobenzoate) ester of 12, m.p. 154–155 °C.

IR: 3100 m (Ar), 2970–2890 vs, 1645 s br (CH₃,CH₂), 1720 vs, 1280 vs (CO–O ester), 1630 ms (C=O), 1555, 1540 vs d, 1345 vs (N–O), 1170 vs (C–N), 730, 720 vs d (1,3,5-trisub. Ar), 1075 m, 975 m, 925 m cm⁻¹.

C₁₈H₂₄N₂O₈ (458.56)  
Calcd C 65.5 H 7.5 N 6.1,  
Found C 65.5 H 7.5 N 6.2.

Recovery of the 3',6-dione 1 from its 3'-mono-oxime 2 (model experiment for reaction 3 – 4)

To a stirred solution of the oxime 2 (1.45 g, 5 mmol) in ethanol (50 ml), 40% aqueous sodium bisulphite (50 ml) was gradually added at room temperature. The reaction mixture, containing separated white solid, was boiled under reflux for 3 h, cooled, and the inorganic solid filtered off. The filtrate was evaporated to ca. half-volume and the residual turbid liquid added to water. The re-
sulting resinous precipitate solidified at 0 °C and gave, on crystallisation from ethanol—light petroleum, prisms (1.15 g, 85%) of the 3',6-dione 1, identified by mixed m.p. 112—113 °C and IR spectrum [4].

We are again indebted to Mrs. J. E. Hawkes and Mr. J. Cobb, of the University of London NMR Spectroscopy Service at King’s College, London, for the production of the 13C NMR spectra.