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

Reduction Products of Spirodiisophora-3',6-dione

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Bicyclo[2.2.2]octane-2-spirocyclohexanes, Spirodiisophoranes, Isophorone, 13C NMR Spectra

The reduction of spirodiisophora-3',6-dione under various conditions occurs exclusively at its 3'-keto-function in the cyclohexane ring. The action of lithium aluminium hydride yields the 3'-eq-hydroxyketone, while catalytic hydrogenation, hydroboration and the action of metal borohydride produces the 3'-ax-epimer. The conformers give rise to pairs of distinct epimeric functional derivatives. Anhydrous hydrazine removes the 3'-oxygen function of the 3'-dione entirely, with formation of spirodiisophor-6-one. Catalytic hydrogenation of the 3'-oximo-6-ketone yields the corresponding 3'-amine. The 13C NMR spectra of the individual products are assigned and correlated with their structures.

Introduction

Spirodiisophora-3',6-dione (1), readily accessible as the product of the self-condensation of isophorone under controlled conditions [1] is a versatile starting material for studying the bicyclo[2.2.2]octane-2-spirocyclohexane ring system. Since this diketone consists of identically substituted bicyclo[2.2.2]octane and cyclohexane moieties, the experimental observations provide direct comparisons of reactivities within these two ring systems. The sum of our results so far available reveals a superior reactivity of the cyclohexane none part of the molecule, which is affected preferentially by such reactions as reduction, halogenation, and the action of Grignard reagents. The present account deals with the products formed in the selective action of several reducing agents on the 3'-keto-function (of 1).

Results and Discussion

Reductions leading to ketols

Spirodiisophora-3',6-dione (1) was attacked selectively at its 3'-keto-function by various reducing agents to yield either or both epimers of 3'-hydroxySpirodiisophor-6-one (2, 3), the configuration depending on the reagents employed. The action of lithium aluminium hydride [2, 3a] in diethyl ether gave good yields of a product m.p. 158–160 °C formulated as the 3'-eq-epimer 2. Catalytic hydrogenation (of 1) over platinum in glacial acetic acid [3b], on the other hand, gave almost exclusively the 3'-ax-isomer 3, m.p. 147–149 °C, also obtained by the action of diborane generated from boron trifluoride etherate and lithium aluminium hydride [4], or by the use of sodium borohydride [5]; in the latter reduction, both isomers were formed side by side, the 3'-ax form predominating. The epimeric hydroxyspiroketones (2, 3) differ in their physical and spectral characteristics, and give rise to two distinct series of derivatives. Their formulation is based on the following observations:

The preservation of the ring skeleton in the reductions was shown by the reconversion of both 3'-hydroxy-isomers (2, 3) into the parent diketone (1) by chromic acid oxidation. This proof is material, because the bicyclo[2.2.2]octane structure tends to undergo rearrangement or partial ring fission under a variety of conditions, especially to the more stable bicyclo[1.2.3]octane system [6], as for example in the Clemmensen reduction of bicyclo[2.2.2]octa-2,6-dione (A) to bicyclo[1.2.3]octan-1-ol-7-one (B) [7]. The possibility of the two hydroxyketones being position isomers was excluded.

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by the failure of either compound to undergo further reduction by the procedures that yield the opposite isomer, and by the inability of both to form ketonic derivatives. This inertness to reduction of the remaining keto-group is in accord with its inability in the dione 1 to react with ketonic reagents [1]. The reductions are therefore restricted to the 3'-carbonyl group, a fact that is verified independently by the two-dimensional $^{13}$C NMR spectra of 1 and 3 [1]. For the ketol 3 (in contrast to the di-ketone 1), full connectivities are established for the complete cyclohexane ring (showing the absence of a keto-group in it), while the sequence for the bicyclo[2.2.2]octane-moiety is interrupted in both 1 and 3 by the inaccessibility of the 6-keto-signal.

The proposed orientation of the 3'-hydroxyl group in the epimer-pair 2 and 3 is based on the following considerations.

Carbon $^{13}$C NMR studies of cyclohexanols reveal a consistent correlation between the conformation of their hydroxyl-group and the resonance of the carbiny1 carbon bearing it, the axial hydroxyl generally exerting a shielding of approximately 5 ppm relative to its equatorial counterpart [8–10]. In the present epimer pair (2, 3), the 3'-carbiny1 doublet of the LAH-reduction product, m.p. 160 °C, appears at lower field (δ, 68.3 ppm) than that of the epimeric hydrogenation product, m.p. 149 °C (δ, 63.5 ppm), suggesting the eq-hydroxyl conformation in the former.
The IR spectra of the isomeric acetyl-derivatives 4 and 9 support this conclusion. Thus, the C–O band in the 1200 cm\(^{-1}\) region of the spectrum of the acetate m.p. 120 °C, derived from the LAH eq-reduction product, is less complex than the broader multiple absorption of its ax-epimer, m.p. 90 °C, in agreement with such characteristic differences established for comparable epimeric steroid acetates [11, 12]. The frequency of the C–O stretching band of unsubstituted hydroxy-groups is an additional potential criterion for distinguishing their configuration (viz. eq: 1040; ax: 1000 cm\(^{-1}\)) [11, 12]. Since the IR data of the present epimers (2, 3) deviate somewhat from these figures, a decisive choice on this basis is not possible, but the adopted assignments do conform to the observed relative positions of the peaks (LAH product 2: \(\nu 1030, 1050\); hydrogenation product 3: \(\nu 1020, 1040\) cm\(^{-1}\)).

Chemical evidence supporting the assignments was provided by the results of the solvolysis of the toluene-p-sulphonate 8. Only ax-arylsulphonyl esters lose the elements of arylsulphonic acid readily in this reaction, resulting in a net dehydration [13]; this facile 1,2-elimination is contingent upon the coplanarity of the leaving groups, necessitating their \textit{trans}-axial configuration [14]. Although the action on 8 of potassium acetate in acetic acid [15] effected some dehydration (to 13), it did so slowly in low yield, incompatible with a 3'-ax-configuration of the ester 8. Part of the reactant was either unchanged or had undergone substitution (to 4), as was separately shown by subjecting the total crude acetolysis product to alkaline hydrolysis, when the ketol 2 was isolated side by side with the olefin 13, both in low yield. Such limited dehydration as did occur may be the consequence of the generation of small amounts of a 3'-ax-configuration of 8 by conformational isomerization ("flipping") of the cyclohexane ring.

The keto-olefin 13 was also accessible, again in moderate yield, by the action of sodium ethylene glycolate on the benzenesulphonylhydrazone 15 [1] at high temperatures (Bamford-Stevens reaction [16]).

The existing knowledge of the stereoselective control of the reduction of alicyclic ketones is extensive [3] but not entirely consistent, so that the prediction of the steric outcome of individual examples may at times be uncertain [17, 3]. The steric course of the present group of reductions is broadly compatible with the available background information. The LAH reduction of unhindered ketones tends to yield the equatorial hydroxy-compounds, while sterically hindered examples produce the axial isomers [18]; the generalization is rationalized by a mechanism involving the approach of the hydride ion from the less hindered side of the ketone, and a competition between "steric approach" control and "product development" control [11, 19]. In the present case (1 \(\rightarrow\) 2), the production of the eq-epimer is compatible with the relatively exposed location of the 3'-keto-group in the spirane structure (see Fig. Part 1 [1]), resulting in the thermodynamically more stable equatorial conformer 2. The more bulky sodium borohydride [17] is expected to yield a product richer in the unstable isomer [19]: this is indeed observed, the reduction giving a mixture of both epimers, with the axial form now predominating. In the catalytic hydrogenation, the observed exclusive production of the axial epimer 3 agrees with the general experience that axial alcohols are formed from both hindered and unhindered ketones in acid media, steric hindrance becoming significant under neutral conditions [20, 21] (for mechanism, see [3, 11, 22]).

\textit{Wolff-Kishner reduction}

The more drastic reduction of keto to methylene in the present ring system was effected by the Wolff-Kishner reaction and occurred again exclusively in the cyclohexane ring. In the modified procedure due to Huang Millon [23], the diketone 1 reacted with anhydrous hydrazine in boiling diethylene glycol containing dissolved sodium to give high yields of spirodiosphor-6-one 14. Its composition, molecular weight, and single narrow IR absorption peak in the ketone range (\(\nu, 1720\) cm\(^{-1}\)) are those of a monoketone. Of the two keto-carbon NMR signals of the diketone 1, it is the higher field 3'-CO singlet that is replaced by a methylene triplet; the preserved 6-keto-function fails to react with 2,4-dinitrophenylhydrazine as expected [1]. Further structural confirmation is provided by the alternative synthesis [3c] from the 3'-sulphonylhydrazone 15, which reacts with sodium borohydride in dioxan to afford near-quantitative yields of 14. Attempts to force the Wolff-Kishner reaction beyond the mono-reduction...
stage were unsuccessful, neither the diketone 1 nor the isolated monoketone 14 being further attacked under the most severe conditions; the ultimate hydrocarbon of this ring system was therefore not obtainable by this route.

The present reduction is thought to involve, in accord with the generally accepted mechanism [3d, 24], the initial production of the hydrazone, followed by prototropic rearrangement to the diimide; subsequent deprotonation and loss of nitrogen yields the carbanion from which the final product arises by rapid reprotonation by the solvent. In view of the small spatial requirement of each of these stages, the inertness of the 6-keto-group in this reaction is particularly noteworthy.

\[ \text{I} \rightarrow \text{C}=\text{NNH}_2 \rightarrow \text{CH}–\text{N}=\text{NH} \rightarrow \text{CH}–\text{N}=\text{NH} \rightarrow \text{CH}2 (14) \]

The postulated formation of the initial stage in this sequence is supported by the course of the reaction under mild conditions; condensation involving both amino-entities of the reagent results in the azine 18. Its formulation agrees with its composition, molecular weight, and the presence of the \(-\text{C}=\text{N}–\text{N}=\text{C–}\) chromophore, to which is ascribed its yellow colour and absorption in the UV (\(\lambda_{\text{max}} 265 \text{ nm}\)) and IR range (v 1640 cm\(^{-1}\)). Trans-hydrazination by pyruvic acid [25] or Clemmensen reduction reconverted the azine to the parent diketone 1.

In conclusion, the production of the 3'-amine 17 of the present ring system is briefly reported. Cyclohexylamines are accessible from alicyclic ketones by the reduction of their oximes, a reaction that has proved widely applicable to both mono- and multi-ring systems [26]. 3'-Oximinospirodiisophor-6-one (16), though resistant to lithium aluminium hydride normally effective in this reaction, gave the 3'-amine 17 on catalytic hydrogenation; it was isolated as the toluene-p-sulphonate and further characterized as the picrate. According to the rule that the stereochemical course of the hydrogenation of oximes follows that of their parent ketones [11], the amino-group is likely to assume the axial configuration, but direct proof is lacking.

\(^13\text{C} \text{NMR spectra} \]

The mapped \(^13\text{C} \) NMR spectra of the parent diketone 1 and the 3'-ax-ketol 3, that are reliably assigned [1] by the results of the INADEQUATE technique, provide the basis for interpreting with confidence the spectra of the related spirodiisophorane derivatives now described. They are displayed in the usual manner in accordance with their assignments (Table I), forming a self-consistent set of data that contributes significantly to the structural evidence.

Their general characteristics, especially the magnitude of the individual shieldings, have been discussed in the case of the key-compounds 1 and 3 [1]. The wider range of spectra now presented demonstrates the remarkable constancy of the chemical shifts of all the carbon atoms of the bicyclo[2.2.2]octane moiety throughout the series, confirming the absence of structural changes in this region. This observation extends also to the monoketone 14; the disappearance of the electron-attracting 3'-keto-group removes the higher-field keto-singlet (209.6 ppm of 1) and simultaneously increases the electron density at the adjacent 2'- and 4'-carbons, causing the upfield displacement of their triplets (by ca. 14 ppm) as expected [1]. The correlation of chemical shifts and conformation of hydroxy-groups used in determining the configuration of the epimeric 3'-ax- and eq-ketols (2, 3) has already been indicated in the appropriate context (see above). The extended results suggest that this relationship persists in the functional derivatives (4, 5, 7 and 9, 10, 12) of the respective sec. alcohols, the axial C-3' carbons being shielded by the usual [8-10] amount (ca. 5 ppm). The signals of the exocyclic aromatic residues (in 5, 7, 8, 10, 12) were identifiable by comparison with assigned reference spectra of comparable structures [27].

**Conclusion**

The ready accessibility of spirodiisophorone and the interconversions within this ring system now described offer a profitable approach to the study of this multicyclic structure. The most noteworthy single observation so far appears to be the inertness of the 6-keto-group of the bicyclo[2.2.2]-octane moiety within the present extended ring-system towards ketonic reagents and several reducing agents, that are effective in the case of bicyclo[2.2.2]octane itself [28]. According to molecular models, the 6-keto-group is subject to steric hindrance by a 5'-ax methyl substituent; whether
Table I. \(^{13}\)C NMR Spectra of bicyclo[2.2.2]octane-2-spirocyclohexanes and their assignment.

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* ° Signals may be interchanged horizontally.

Supplement to Table I. Aromatic and additional signals.

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a The figures refer to the proton noise decoupled chemical shifts and first order multiplicities of the individual signals. Chemical shifts are given in \( \delta \) (ppm) downfield from \( \text{SiMe}_4 \) as internal standard. The solvent was deuteriochloroform; b the numbering of the carbon atoms is shown in 1 (see also Part 1 [1], structure A). In the supplementary table, C-9' refers to the extranuclear carbonyl carbon of the acyl derivatives 4, 9, 5, 10 and 7, 12; C-10' to the extranuclear methyl carbons of 4, 9 and 8. The carbon atoms C-1" to C-4" of the benzene rings are numbered from the end nearest the cyclohexane residue; c the spectra of 1 and 3 are assigned by the INADEQUATE technique [1]; d the spectrum of the parent 3',6-diketone 1 is included to facilitate direct comparisons; e signal of double intensity.
this is the only inhibiting factor might be revealed by the behaviour of the lower homologue (of 1), lacking the gem-dimethyl groupings, and further work in this connection is in progress.

Experimental

The equipment used in the determination of the spectral characteristics of the compounds is specified in Part 1 [1], which also provides general information applicable to the present experiments. Certain IR spectra are given in greater than usual detail in order to define the spectral differences between pairs of epimers.

Boron trifluoride diethyl etherate was the “Laboratory Chemical” grade (British Drug Houses) containing approximately 45% BF₃.

3'-eq-Hydroxyspirodiisophor-6-one (2)

A solution of spirodiisophora-3',6-dione (1, 11.04 g, 40 mmol) in anhydrous ether (100 ml) was added dropwise during ca. 5 min to a stirred suspension of lithium aluminium hydride (2.0 g, 52 mmol) in the same solvent (50 ml) at such a rate that the reaction mixture effervesced gently; hydrogen was evolved. Boiling under reflux was continued for 3 h and the excess of the reducing agent destroyed by the slow addition of water and 3 M hydrochloric acid. The product was extracted with ether, and the extracts washed with water to neutrality. After the removal of the solvent, the residual pale yellow oil was dissolved in light petroleum (15 ml). The separating opaque solid (m.p. 159-160 °C, 9.1—9.8 g, 82-88%) gave, on crystallization from ethanol (2 ml per g, recovery 90%), massive plates of the 3'-eq-hydroxy-6-ketone 2, m.p. 158-160 °C.

IR (KBr): 3430 vs br (OH), 2960-2895 vs, 1480 ms, 1460, 1450 s d, 1435 s (CH₃, CH₂), 1720, 1715 vs d (CO), 1420 ms (CH₂ adj. to CO), 1395 ms, 1375 s (CMe₂), 1065 vs (C—O of OH), 1370, 1345 ms d, 1265 s, 1255 s, 1140 ms, 1120 mw, 1050 vs, 1030 s, 985 ms, 960 w, 915 w cm⁻¹.

C₁₈H₃₀O₂ (278.4)
Calcld C 77.65 H 10.9,
Found C 77.7 H 11.0 M 278.

The compound was substantially recovered after being subjected to further reduction by procedures a) and c), below.

3'-ax-Hydroxyspirodiisophor-6-one (3)

a) By catalytic hydrogenation: A solution of spirodiisophora-3’,6-dione (1, 2.76 g, 10 mmol) in glacial acetic acid (20 ml) was hydrogenated over Adams’ catalyst [29] (0.15 g), when hydrogen uptake was complete after 1 h (observed: 300 cc; theoretical: 27 + 224 cc at NTP). The platinum was filtered off and most of the solvent was removed under reduced pressure. The residual viscous liquid was stirred into ice-water (150 ml) containing 3 M sodium hydroxide (10 ml), when the oily globules coagulated to a white solid. Crystallization from ethanol (5 ml) gave plates (2.3 g, 83%) of the 3'-ax-hydroxy-6-ketone (3), m.p. 147—149 °C.

IR: 3460, 3450 vs d (OH), 2950 vs-2865 vs br, 1470 vs, 1410 s (CH₃, CH₂), 1710 vs br (CO), 1395 ms, 1370 s (CMe₂), 1080, 1070 vs d (C—O of OH), 1390 s, 1355 s, 1345 s, 1325 s, 1270 s, 1255 s, 1190 s, 1150 ms, 1040 vs, 1020 ms, 980 w, 905 m, 885 w cm⁻¹.

C₁₈H₃₀O₂ (278.4)
Calcld C 77.65 H 10.9,
Found C 77.7 H 11.0 M 278.

The compound was substantially unaffected when subjected to the action of lithium aluminium hydride (procedure, see above).

b) By the action of boron trifluoride diethyl etherate: A stirred solution of 1 (8.28 g, 30 mmol) in anhydrous ether (200 ml) was treated at room temperature with boron trifluoride diethyl etherate (4.26 g, 3.75 ml, 30 mmol) within ca. 2 min, followed by lithium aluminium hydride (0.77 g, 20 mmol) at such a rate that the reaction mixture effervesced gently. It was stirred at room temperature for 5 h, and the excess of the reducing agent destroyed by the slow addition of cold water and 3 M hydrochloric acid. The product was extracted with ether, the extracts washed with water to neutrality and the solvent removed. The residual pale-yellow liquid was dissolved in light petroleum (15 ml) and gave 3 as opaque prisms, m.p. 142—143 °C (ca. 7 g, 84%), or lustrous plates, m.p. 147—149 °C (from ethanol). Fractional crystallization from ethanol (3 ml per g) showed that the entire material was the 3-ax-epimer 3.

c) By the action of sodium borohydride: A solution of 1 (5.52 g, 20 mmol) in ethanol (100 ml) was treated with sodium borohydride (6.1 g, 160 mmol), most of which dissolved with gentle effervescence during the first few mins, and the mixture set aside at room temperature for 24 h. The turbid liquid was diluted with water (600 ml) and acidified with 3 M hydrochloric acid. The resulting
precipitate (4.7–5.3 g, 85–95%) gave, on crystallization from ethanol, platelets of the 3-\(\alpha\)-hydroxy-6-ketone \(3\), m.p. 146–148 °C (yield ca. 50%). The filtrate contained a mixture of the 3-\(\alpha\)- and 3-\(\epsilon\)-epimers, the former predominating. They were separated by fractional crystallization from ethanol, affording more of the less soluble 3'-\(\alpha\)-epimer \(3\) (ca. 60% of the mixture). Evaporation of the combined filtrates resulted in material of wide melting range (130–165 °C), comprising both epimers.

The hydroxyketone \(3\) (2 mmol), treated with hydroxylamine hydrochloride (5 mmol) in pyridine (6 ml) under the usual conditions (24 h at room temperature) was recovered (75%).

Reoxidation of 2 and 3 to spirodiisophora-3',6-dione (1)

A stirred solution of the 3'-\(\epsilon\)- or 3'-\(\alpha\)-hydroxyketone (2 or 3) (0.56 g, 2 mmol) in glacial acetic acid (8 ml) was treated dropwise with Kiliani’s 10% chromic acid [30] (5 ml, 4 mmol) and stirring at room temperature continued for 1 h. The dark liquid was diluted with water and treated with 10% aqueous sodium sulphite. The crystalline precipitate (m.p. 110 °C, 75%) gave platelets (0.31–0.39 g, 55–70%) (from acetone-light petroleum) of 1, identified by mixed m.p. 113–115 °C and IR spectrum [1].

3'-\(\epsilon\)- and 3'-\(\alpha\)-Hydroxyspirodiisophor-6-ones: attempted epimerization by acid and alkali

The epimers 2 and 3 (0.42 g, 1.5 mmol) were each separately recovered (70–75% after crystallization) a) after their solution in ethanol (10 ml) – concentrated hydrochloric acid (3 ml) was boiled for 1.5 h; and b) after their solution in ethanol (10 ml) – 3 M sodium hydroxide (3 ml) was boiled for 1.5 h.

3'-\(\epsilon\)-Hydroxyspirodiisophor-6-one: derivatives

3'-\(\epsilon\)-Acetyl derivative (4)

A solution of 2 (0.42 g, 1.5 mmol) in acetic anhydride (6 ml) was boiled under reflux for 30 min, then stirred into warm water (30 ml). The oily globules solidified on storage at 0 °C, and gave platelets (0.34 g, 71%) of 4, m.p. 119–120 °C (from light petroleum).

IR: 2985–2880 vs, 1465 s (CH\(_3\), CH\(_2\)), 1750–1720 vs br (CO), 1410 s (OH), 1265–1225 vs br mult (C–O ester), 3020 m, 1370–1360 vs mult, 1350 s, 1150 m, 1030–1020 vs br, 960 m, 875 w, 650 w cm\(^{-1}\).

C\(_{29}\)H\(_{31}\)O\(_3\) (320.5)
Calcd C 75.0 H 10.1,
Found C 75.3 H 10.0 M 320.

3'-\(\epsilon\)-Benzyol derivative (5)

A solution of 2 (0.56 g, 2 mmol) in pyridine (15 ml), treated with benzyol chloride (0.62 g, 4.4 mmol), was kept at 100 °C for 15 min, then stirred into ice water (100 ml) containing concentrated hydrochloric acid (15 ml). The precipitate gave lustrous platelets (0.55 g, 71%) of 5, m.p. 129–130 °C (from light petroleum).

IR: 2980–2900 vs, 1455 s (CH\(_3\), CH\(_2\)), 1725–1715 vs br (CO), 1605 w (C=C), 1415 m (CH\(_2\) adj. to CO), 1395 mw, 1370 ms (CMe\(_2\)), 1275 vs br (C–O ester), 720 vs, 710 vs (Ar), 2875 ms, 1315 s, 1115 vs, 1070 s, 1025 s, 970 s cm\(^{-1}\).

C\(_{25}\)H\(_{14}\)O\(_3\) (382.55)
Calcd C 78.5 H 9.0,
Found C 78.4 H 9.1.

3'-\(\epsilon\)-(3,5-Dinitrobenzoyl) derivative (6)

A solution of 2 (0.28 g, 1 mmol) in pyridine (10 ml), treated with 3,5-dinitrobenzoyl chloride (0.25 g, 1 mmol), was set aside at room temperature for 5 h, then stirred into ice water (100 ml) containing concentrated hydrochloric acid (10 ml). The precipitate (m.p. 151–152 °C, 0.39 g, 81%) gave ivory prisms (0.30 g, 63%) of 6, m.p. 154–155 °C (from acetone–ethanol).

IR: 3140 w (Ar), 2995–2920 vs, 1465 s (CH\(_3\), CH\(_2\)), 1725 vs (CO), 1635 m (C=C), 1555 vs, 1345 vs (N–O), 1410 w (CH\(_3\) adj. to CO), 1395 mw, 1370 ms (CMe\(_2\)), 1285 vs br (C–O ester), 1170 s (C–N), 735 vs, 720 vs (1,3,5-trisub. Ar), 1075 m, 965 s, 925 m, 835 w, 775 w cm\(^{-1}\).

C\(_{23}\)H\(_{13}\)N\(_2\)O\(_7\) (472.55)
Calcd C 63.5 H 6.8 N 5.9,
Found C 63.6 H 6.8 N 6.0.

3'-\(\epsilon\)-Pheny lurane derivative (7)

A solution of 2 (0.56 g, 2 mmol) in anhydrous benzene (10 ml), treated with triethylamine (0.15 ml) and phenyl isocyanate (0.29 g, 2.5 mmol), was boiled under reflux for 1 h, the solvent removed under reduced pressure, and the residual oil dissolved in light petroleum (8 ml). The separating product gave on crystallization from acetone (10 ml) – light petroleum (3 ml), microprisms (0.58 g, 73%) of 7, m.p. 224–225 °C.
IR: 3320 vs, 1550 vs (NH), 3150 w, 3090 w (Ph), 2960 vs–2860 s, 1445 s (CH3, CH2), 1710 vs (CO), 1690 vs (CO amide), 1605 s, 1505 ms (C=C), 1395 w, 1365 m (CMe2), 1250, 1240, 1230 vs t (C–N–C=O of urethane), 740 ms (Ph), 1410 w, 1320 vs, 1190, 1175, 1150, 1125 w q, 1070 s, 1055 s, 1035 ms, 765 cm$^{-1}$.

C$_{25}$H$_{35}$N$_{2}$O$_{3}$ (397.6)

Calcd C 75.5 H 8.9 N 3.5
Found C 75.3 H 8.9 N 3.8.

3'-eq-Toluene-p-sulphonyl ester (8)

A solution of 2 (0.56 g, 2 mmol) in pyridine (10 ml) was treated with toluene-p-sulphonyl chloride (0.42 g, 2.2 mmol), set aside at room temperature for 12 h, then stirred into ice water (100 ml) containing concentrated hydrochloric acid (10 ml). The pink precipitate gave, on crystallization from acetone–ethanol (3:5), opaque prisms (0.50 g, 57%) of 8, m.p. 171–172 °C.

IR: 2940–2850 vs, 1470, 1455 s d (CH3, CH–), 1720 vs (CO), 1600 m (C=C), 1390 ms, 1385’s, 1360 vs, 1180 vs br (SO$_2$–O), 860 s, 825 s (p-disub. Ar), 1410 m, 1315 ms, 1255 ms, 1095 s, 1040 s, 940 vs br, 760 vs, 665 vs cm$^{-1}$.

C$_{25}$H$_{36}$O$_{4}$S (432.6)

Calcd C 69.4 H 8.4
Found C 69.1 H 8.6.

The 3-ax-epimer 3 was recovered (70%) under the foregoing conditions, or after 5 h heating at 100 °C.

**Spirodiisophor-2'(or 3')-en-6-one (13)**

a) By action of potassium acetate–acetic acid on 8: A solution of the 3'-eq-toluene-p-sulphonate 8 (1.08 g, 2.5 mmol) in glacial acetic acid (25 ml) – acetic anhydride (8 ml) was treated with anhydrous potassium acetate (7.35 g, 75 mmol) and boiled under reflux for 3 h, then stirred into ice water (300 ml). The pale-yellow crude resinous product (ca. 0.8 g) gave platelets (0.13 g, 20%) of the keto-olefin 13, m.p. 95–98 °C (from light petroleum). If the crude product failed to solidify, it was isolated by ether extraction.

IR: 2980–2860 vs mult, 1475, 1465 s d (CH$_3$, CH$_2$), 1730 vs (CO), 1390 ms, 1370 s (CMc$_2$), 3020 ms, 1690 m, 1410 ms, 1265 s, 1240 s, 1225 s, 995 s, 725 vs cm$^{-1}$.

C$_{18}$H$_{12}$O (260.4)

Calcd C 83.0 H 10.8
Found C 82.6 H 10.8.

In a variant procedure, the acetate-solvolyzed total crude product was refluxed in 5 M methanolic potassium hydroxide solution (10 ml) for 3 h, the product isolated by ether extraction and separated by fractional crystallization or chromatographically (in light petroleum over alumina) into the eq-hydroxyketone 2 (identified by IR, 0.25 g, 36%) and the keto-olefin 13 (28%), identical with the foregoing material.

b) From 3'-benzenesulphonylhydrazonospirodiisophor-6-one (15): A solution of 15 [1] (0.89 g, 2 mmol) in ethylene glycol (40 ml) containing dissolved sodium (0.7 g, 30 mmol) was kept at 160 °C under nitrogen for 15–20 min, after which effervescence ceased. The cooled liquid was stirred into water, and the product extracted with ether. Evaporation of the (washed) extracts gave an oil, which yielded microcrystalline 13, m.p. 95–97 °C (from light petroleum) (total, 0.13–0.18 g, 25–35%). Reaction did not occur appreciably at 100 °C.

3'-ax-HydroxySpirodiisophor-6-one (3): derivatives

The 3'-ax-epimer 3 gave by the foregoing procedures the following derivatives:

3'-ax-Acetyl derivative (9)

The crude product (80%) gave lustrous platelets (65%) of 9, m.p. 90–91 °C (from light petroleum).

IR: 2960–2870 vs, 1465 m (CH$_3$, CH$_2$), 1725 vs (CO), 1415 ms (CH$_2$ adj. to CO), 1395 m, 1380 ms (CMc$_2$), 1260, 1240 vs d (C=O ester), 1360 s, 1345 m, 1200 s, 1035, 1015, 1005 m t, 955, 945 ms d cm$^{-1}$.

C$_{25}$H$_{34}$O$_{3}$ (382.6)

Calcd C 78.5 H 9.0
Found C 78.5 H 8.9.

3'-ax-Benzoyl derivative (10)

The crude product was a white gum which failed to solidify; it was dissolved in ether, the solution washed neutral, and the oil remaining on removal of the solvent dissolved in ethanol (3 ml). On storage at 0 °C, there appeared prisms of 10, m.p. 114–117 °C (0.49 g, 64%).

IR: 2980–2890 vs, 1460 s br (CH$_3$, CH$_2$), 1710 vs br (CO), 1605 w, 1585 w (C=C), 1415 m (CH$_3$ adj. to CO), 1395 m, 1370 ms (CMc$_2$), 1280 vs br (C=O ester), 720 vs (Ph), 1320 s, 1180 ms, 1115 vs, 1075 s, 1030 ms, 965 s cm$^{-1}$.

C$_{25}$H$_{34}$O$_{3}$ (382.6)

Calcd C 78.5 H 9.0
Found C 78.5 H 8.9.
3'-ax-(3,5-Dinitrobenzoyl) derivative (11)

The crude solid (m.p. 140 °C, 85%) gave lustrous pale-yellow prisms (65%) of the derivative 11, m.p. 142–143 °C (from ethanol).

IR: Identical with spectrum of 3'-eq-epimer 6 between 3140 and 1075 cm⁻¹, then 1000 s, 960 s, 945 s, 925 s, 820 s, 780, 770 s d, 730, 720 vs d cm⁻¹.

C₂₅H₃₂N₇O₇ (472.55)
Calcd C 63.5 H 6.8 N 5.9,
Found C 63.5 H 6.8 N 5.8.

3'-ax-Phenyldurethane derivative (12)

The crude product (m.p. 159–162 °C, 83%) gave, on crystallization from ethanol (with addition of a few drops of water) prisms (58%) of 12, m.p. 162–164 °C.

IR: Identical with spectrum of 3'-eq-epimer 7 between 3320 and 1320 cm⁻¹, then 1300 ms, 1250, 1240, 1230 vs t, 1190, 1170, 1150, 1125 mw q, 1080 m, 1070 ms, 1055 s, 1030 ms, 765 ms, 740 ms, 700 ms br cm⁻¹.

C₂₅H₃₅N₃O₃ (397.6)
Calcd C 75.5 H 8.9 N 3.5,
Found C 75.1 H 8.6 N 4.0.

Spirodiisophor-6-one (14)

a) By Wolff-Kishner reduction of 1: Sodium (2.3 g, 0.1 g-atom) was dissolved in anhydrous boiling diethylene glycol (50 ml); to the solution, freshly distilled anhydrous hydrazine (9.6 g, 300 mmol) was added and the yellow liquid boiled under reflux (ca. 170 °C) for 15 min. It was cooled to 100 °C, the 3',6-diketone (1, 11.0 g, 40 mmol) added and the solution refluxed for 45 h, then stirred into ice water (150 ml). The resulting precipitate (m.p. 60 °C, 10.1 g, 96%) gave on crystallization from light petroleum (10 ml, b.p. 40–60 °C), prisms (8.7 g, 83%) of spirodiisophor-6-one (14), m.p. 62–63 °C.

IR: 2950-2870 vs, 1470, 1460 s d, 1415 s (CH₃, CH₂), 1720 vs br (CO), 1390 m, 1375 s (CMe₂), 1345 s, 1305 s, 1245 s, 1220 s, 1175 m cm⁻¹.

C₁₈H₃₀O (262.2)
Calcd C 82.45 H 11.45,
Found C 82.5 H 11.8 M 262.

The monoketone 14 failed to yield a 2,4-dinitrophenylhydrazone under the standard conditions.

b) By the action of sodium borohydride on 3'-benzenesulphonylhydrazone of spirodiisophor-6-one (15): A solution of the reactant (15 [I], 1.72 g, 4 mmol) in dioxan (40 ml) was slowly treated with sodium borohydride (3.8 g, 100 mmol) and boiled under reflux for 24 h. A little undissolved solid was filtered off, the filtrate evaporated to small volume under reduced pressure and acidified at room temperature with dilute sulphuric acid to destroy the remaining reagent. The product was extracted with chloroform; the washed (water), dried (Na₂SO₄) neutral extract gave, on removal of the solvent, a pale-yellow oil which produced on crystallization as above, prisms (0.94 g, 90%) of 14, identical with material obtained in a).

Dimeric azine (18)

Preparation: A solution of the 3',6-dione (1, 4.14 g, 15 mmol) in ethanol (25 ml) – hydrazine hydrate (7.5 g, 150 mmol) was boiled under reflux for 30 min. Most of the solvent was removed under reduced pressure and the residual colourless liquid stirred into ice water (150 ml) containing concentrated hydrochloric acid (8 ml). The precipitated pale-yellow solid (m.p. 182 °C, 3.7 g) gave, on crystallization from acetone–light petroleum (1:2) pale-yellow microprisms (1.39 g, 34%) of the azine 18, m.p. 214–215 °C.

UV: λmax 265 nm (logd 4.3). - IR: 2960-2800 vs br, 1465 s, 1455 s, 1430 ms (CH₃, CH₂), 1720 vs br (CO), 1645 vs (C=N), 1395 ms, 1365 s (CMe₂), 1345 s, 1300 s, 1245 s, 1220 s, 1175 m cm⁻¹.

C₃₆H₅₆N₂O₂ (548.9)
Calcd C 78.8 H 10.3 N 5.1,
Found C 78.7 H 10.4 N 5.1 M 548.

Reconversion into the 3',6-dione (1)

a) By the action of pyruvic acid: A solution of 18 (0.55 g, 1 mmol) in glacial acetic acid (15 ml) and pyruvic acid (0.88 g, 10 mmol in 1.3 ml water) was boiled under reflux for 1 h. Most of the solvent was removed under reduced pressure and the residual red oil treated with M sodium hydroxide until neutral. The resulting solidified product (0.53 g) gave, on crystallization from ethanol–light petroleum (1:1), plates (0.39 g, 71%) of 1, identified by mixed m.p. 114–115 °C, and IR spectrum.

b) By metal reduction: A solution of the azine (18, 1.1 g, 2 mmol) in glacial acetic acid (20 ml) containing amalgamated zinc (3 g) was boiled under reflux for 3 h. The decanted liquid was stirred into ice water (100 ml) and neutralized with 3 M sodium hydroxide. The resulting light-brown gum failed to solidify and was extracted with ether; the washed dried neutral solution gave, on removal of the solvent and dissolution of the residue in light petroleum (8 ml), platelets (0.40 g, 36%) of 1, identified as above.
3'-Aminospirodiisophor-6-one (17)

A solution of 3'-oximinospirodiisophor-6-one (16 [1], 2.91 g, 10 mmol) in glacial acetic acid (65 ml) was hydrogenated at room temperature over Adams’ catalyst [29] (from platinum oxide monohydrate, 0.30 g, 1.2 mmol). Hydrogen was taken up rapidly by the catalyst but slowly by the oxime, and was complete after 5–6 h (observed uptake: 570 cc, theoretical: 55 + 450 cc at NTP). The platinum was filtered off, the filtrate added to water, basified with 3 M sodium hydroxide (0.5 mmol each) in ethanol (10 ml) and the resulting water was used to dissolve the lustrous flat prisms which separated slowly (m.p. 254–256 °C, 1.9–2.5 g, 42–56%) gave 17, toluene-p-sulphonate, m.p. 256–257 °C (decomp.) (from ethanol). We are indebted to Mrs. J. E. Hawkes and Mrs. F. B. Gallwey, for the production of the 13C NMR spectra.

IR: 3460 m br, 1640 s br, 1535 ms (NH3+), 2980–2870 vs, 1475 s (CH3, CH2), 1695 vs (CO), 1395 m (CMe3), 1245 vs, 1160 vs, 1125 vs, 1035 vs (R5O–), 820 vs (p-disub. Ar), 2720 ms, 2630 mw, 685 vs cm–1.

C18H31NO·C6H3N3O7 (506.6)
Calcd C 66.8 H 8.7 N 3.1 S 7.1,
Found C 66.7 H 8.8 N 3.2 S 7.0.

C18H31NO·C7H8O3S (506.6)
Calcd C 56.9 H 6.8 N 11.1,
Found C 56.5 H 7.1 N 10.9.

[7] K. Mori, Y. Nakahara, and M. Matsu, Tetrahe­
dron 28, 3217 (1972).