

Bicyclo[2.2.2]octane-2-spirocyclohexanes, Part 3 [1]

Synthesis and Reactions of Mono- and Dibromospirodiisophoranes

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Bicyclo[2.2.2]octane-2-spirocyclohexanes, Bicyclo[2.2.2]octane-2-spirocyclopentanes,
Spirodiisophoranes, Bromospirodiisophorones, Favorski Reaction

Halogenation by the appropriate amounts of bromine or N-bromosuccinimide converts spirodiisophora-3',6-dione (**1**), a compound based on the bicyclo[2.2.2]octane-2-spirocyclohexane ring-system (**B**), into the 4'-ax mono- and 2',4'-diax-dibromo-3',6-dione. The latter is reduced by lithium aluminium hydride to the corresponding 6,3'-ketol, with retention of one or both bromo-substituents, depending on conditions. The bromoketones undergo the Favorski ring-contraction under the influence of alkalis to compounds of the bicyclo[2.2.2]octane-2-spirocyclopentane ring-system. The ¹³C NMR spectra of the individual products are assigned and correlated with their structures.

Introduction

Spirodiisophora-3',6-dione (**1**), a compound based on the bicyclo[2.2.2]octane-2-spirocyclohexane ring-system (**B**), is readily accessible by the self-condensation of isophorone (**A**; R, R' = Me) under specified alkaline conditions [2], as are its lower homologues (e.g. **C**) from the appropriate 3-methylcyclohex-2-enones (**A**; R, R' = H; R = H, R' = Me) [3, 4]. The structure of their carbon skeleton has recently been established by two-dimen-

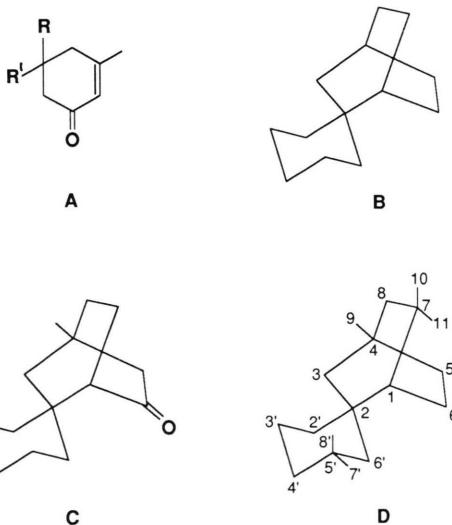
sional ¹³C NMR measurements by the INADEQUATE technique [2], thus confirming the formulation of **C** originally proposed on chemical evidence, that had been contingent on certain assumptions [3].

The two keto-groups of the 3',6-dione **1**, though situated in comparable structural environments, differ conspicuously in their reactivities: that of the bicyclo[2.2.2]octane moiety is unexpectedly inert towards both ketonic reagents [2] and several reducing agents [1], all of which react readily at the cyclohexanone function of the extended structure. In the mono- and dibromination of the 3',6-diketone **1** now described, this contrasting behaviour is maintained.

In order to avoid the excessively long official names of the present structures, we continue to use the proposed [2] simplified nomenclature based on the term “spirodiisophorane” for the parent hydrocarbon, 4,5',5',7,7-pentamethylbicyclo[2.2.2]octane-2-spirocyclohexane (**D**, showing the adopted numbering). The full name of compound **2** is exemplified in the Experimental part.

Results and Discussion

The halogenation of cyclohexanone occurs in the positions adjacent to the activating keto-group, producing sequentially the 2-mono- and 2,6-dihalogenated derivatives [5, 6]. The bromination of spirodiisophora-3',6-dione **1**, being confined to the cyclohexanone moiety, was similarly found to yield successively a mono- and dibromo-substitution product; beyond this stage, halogenation



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tion proceeded only slowly, with formation of complex mixtures.

Bromination

Thus, monobromination of the diketone **1** by molecular bromine [5], or bromine radicals derived from N-bromosuccinimide [6] gave high yields of a product formulated as 4'-ax-bromospirodiisophora-3',6-dione **2** on the following grounds: The introduction of the bromine substituent has no significant effect on the chemical shift of the 6-keto-carbon (**1**, δ , 212.6; **2**, 211.2 ppm), but causes a shielding (by 5.5 ppm) of the 3'-keto-carbon: bromination has therefore occurred at C-2' or C-4'. Since, according to molecular models, the former position appears to be subject to greater steric hindrance by the bicyclo[2.2.2]octane framework than the 4'-position by its adjacent 5'-gem-dimethyl group, the more accessible 4'-methylene is regarded as the preferred site of the attack.

The axial conformation of the 4-bromo-substituent (in **2**) is assigned tentatively in conformity with the available information on the steric course of the halogenation of alicyclic ketones [7, 8]. In α -haloketones, electrostatic repulsion between the two polar substituents exceeds the effect of their steric interaction, thus favouring the axial conformation of the halogen. This trend is reversed by the effect of steric 1,3-diaxial interaction due to the presence of additional substituents, as for example, by 4-ax-methyl in the formation of 2-eq-bromo-4,4-dimethylcyclohexanone **E** [7]. A possible assessment of such conformations (though requiring caution in its application [8]) is based on the use of IR data. An upward shift in frequency of the carbonyl-peak (by *ca.* 20 cm^{-1}) is observed for each α -C-Br bond which is codirectional-coplanar with the carbon-oxygen bond (*i.e.* C-Br eq), but is absent when these bonds are located in different planes (*i.e.* C-Br ax) [7, 9]. In the present example **2**, the proposed 4'-ax-conformation is in accord with the absence of an interfering axial substituent (in β -position, *i.e.* at C-6'), and the unchanged frequency of the broad IR keto-peak upon bromination (Table I); however, the validity of the latter observation may possibly be impaired by the effect, in each case, of the contribution of the 6-carbonyl group.

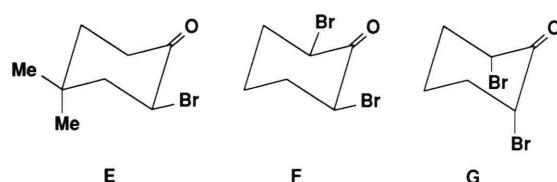
The dibromination of cyclohexanone is reported [5, 10] to produce mixtures of halogenated prod-

Compound	ν_{CO} cm^{-1}
1	1720 vs vbr ^a
2	1720 vs br
3	1725 vs br
15 [1]	1720 vs

Table I. Carbonyl frequencies of spirodiisophorones.

^a Given as 1700–1740 cm^{-1} multi in [1].

ucts from which only modest yields (15–20%) of the 2,6-dibromo-derivative are isolable. In contrast, reaction occurred smoothly in the cyclohexanone moiety of spirodiisophora-3',6-dione, affording high yields of the dibromo-compound **3**, from both the parent diketone **1** and the monobromo-derivative **2**, by di- and mono-halogenation, respectively. Its 2',4'-dibromo-structure is in accord with the constancy, upon halogenation, of the chemical shift of the C-6 carbonyl singlet, but substantially enhanced shielding (by 9 ppm) of that of the 3'-carbonyl signal. The appearance of a new doublet (replacing the C-2' triplet) excludes the possible 4',4'-dibromo-structure. The following reasoning supports the proposed 2',4'-diaxial disposition of the substituents: The axial conformation of the 4'-bromo-substituent in **2** is presumed to persist during further bromination. The 2'-equatorial position is obstructed by the 7-gem-dimethyl group, especially its proximate C-10 component. No significant displacement occurs in the frequency of the broad carbonyl IR peak upon dibromination (Table I), indicating that the C-Br bonds do not share an approximate plane with the C=O bond, and are therefore axial. This *cis*-diaxial assignment differs from that of the parent 2,6-dibromocyclohexanone, the *cis*-diequatorial conformation **F** of which has been demonstrated by Corey [10]. In this model, the energy due to the electrostatic and steric repulsion between its 2- and 6-bromine atoms exceeds that due to dipole repulsion involving the carbonyl group and two codirectional-coplanar C-Br dipoles (thus disfavouring **G**). In the extended molecule **3**, the reversal of this effect may be due to steric restraints exerted within the structure as a whole.



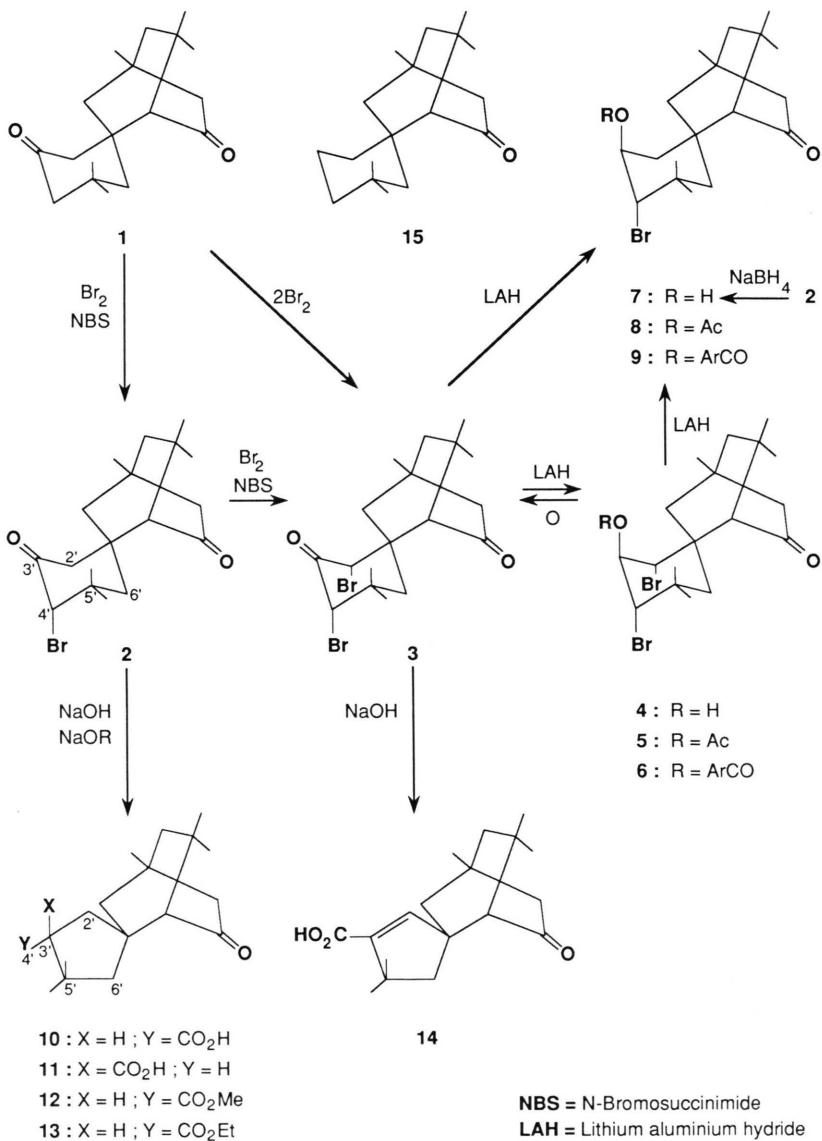
It is significant that spirodiisophor-6-one **15** [1], lacking the cyclohexanone function, failed to undergo bromination under the standard conditions, emphasising once again the essential activating role of the 3'-keto-group, and the inertness of its 6-counterpart in the bicyclo[2.2.2]octane part of the molecule.

Reduction

The reduction of the bromospirodiisophorones to the corresponding alcohols by lithium alumin-

um hydride [1, 11] occurred with or without simultaneous loss of halogen, depending on the experimental conditions. The reagent does not readily attack halocycloalkanes, affording for example only low yields (10%) of cyclohexane from the bromo-derivative even when used in excess [11, 12], but is more effective when the halogen of the substrate is activated by conjugation [11, 13], as in the present examples.

The action of 1 mole of lithium aluminium hydride on the 2',4'-dibromo-compound **3**, confined to the active 3'-keto-group as usual [1], gave good



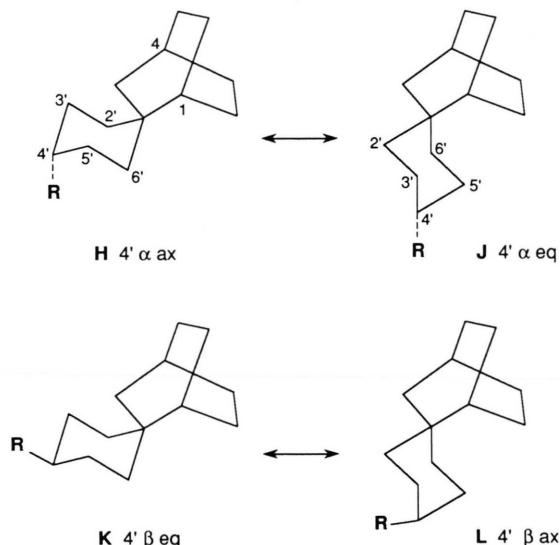
yields of 2',4'-dibromo-3'-hydroxyspirodiisophorone **4**. In the parent diketone **1**, LAH-reduction of its unhindered 3'-keto-group yields the 3'-equatorial alcohol [1]. In the dibromo-derivative **3**, however, the electrostatic effect of the two flanking axial bromo-substituents is likely to direct the emerging 3'-hydroxyl-group (of **4**) into the position furthest from them, *i.e.* into the axial conformation. The structural change is reflected in the replacement, in the ^{13}C NMR spectrum, of the 3'-carbonyl singlet by a doublet of an alicyclic secondary alcohol, and by the intense hydroxyl-absorption in the IR range (3460 cm^{-1}). The near-quantitative reconversion of the reduction product into the parent ketone (**4** \rightarrow **3**) by chromic acid oxidation confirmed the absence of skeletal rearrangement during these reactions.

The action of an excess of lithium aluminium hydride on either **3** or **4** removed additionally one of the bromo-substituents by hydrogenolysis. Assuming that the less readily introduced 2'-halogen is also the one that is preferentially given up, the product, obtained in excellent yield, is formulated as **7**. This structure was confirmed unequivocally by the direct production of **7** in good yield from the 4'-monobromo-3',6-dione **2** by reduction with sodium borohydride. Both the mono- (**4**) and dibromohydrin (**7**) were characterized by appropriate acyl-derivatives (**5**, **6**, **8**, **9**).

Steric aspects

In the context of the configurational assignment to the 2',3'- and 4'-substituents in the foregoing compounds, attention is drawn to a remaining steric complication inherent in their spirane structures. Their cyclohexane ring, retaining the capacity of conformational isomerization ("flipping", involving the C3'-4' and C5'-6' bonds, *via* the flexible intermediate) may assume two chair conformations, interconvertible into one another, but differently disposed with respect to the bicyclo[2.2.2]octane component. They may be specified by the spatial relation of the C2'-3' (and C5'-6') bond and the central C1-4 axis, being parallel in one isomer, but subtending approximately half the tetrahedral angle (of $109^\circ 28'$) in the other. As a consequence, any one axial or equatorial substituent may be situated on opposite faces of the cyclohexane ring in either of its conforma-

tions, giving potentially rise to four stereoisomers. These are represented, though inadequately, by structures **H**–**L**, which are drawn from models to emphasize the position of the substituent relative to the plane of the 6-membered ring: Conformational isomerization occurs between horizontal pairs of structures, but vertical pairs are distinct non-interconvertible individuals.



Stereoisomers of 4'-monosubstituted spirodiisophorones (peripheral methyls omitted). The "upper" face of the cyclohexane ring is the one on the same side as the 1-bridgehead position. The notation α - and β -refers to the space *below* and *above* this ring (as used in steroid nomenclature).

These considerations do not invalidate the arguments that seek to attribute axial and equatorial configurations, but mean that a substituent so assigned may appear on one or other side of the cyclohexane ring, depending on the conformation of the latter. The structure involving the least intramolecular steric hindrance is presumably the preferred alternative. In the case of the diaxial dibromodiketone **4**, for example, the 2',4'- α,α -diaxial form (based on **H**) is thought to be favoured, because the 10-methyl group obstructs the 2'- α -axial bromo-substituent less than the 2'- β -axial bromine in the alternative 2',4'- β,β -diaxial conformer (based on **L**).

Favorski reaction

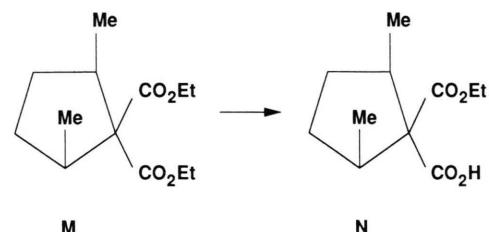
In their interaction with alkalis and alkoxides, the bromoketones **2**, **3** underwent the Favorski ring-contraction characteristic of α -haloketones [14] to yield carboxylic acids (or esters) of the bicyclo[2.2.2]octane-2-spirocyclopentane ring system (**10–14**). Since the simplified nomenclature (see above) is not applicable to this modified ring-system, its members are named according to the official IUPAC rules [15], except for the numbering of their cyclopentane ring; this is chosen (see **10**) to facilitate direct comparisons of the two spirane ring-systems, especially of corresponding ^{13}C NMR signals.

The 4-monobromodiketone **2** was converted by sodium hydroxide, on brief or more prolonged treatment, successively into two isomeric carboxylic acids, formulated as **10** and **11**. The former was separately convertible into the latter on continued treatment with alkali. The prolonged action of sodium carbonate in aqueous dioxan gave mixtures of **10** and **11**, the former predominating. The reaction, though involving a net exchange of one bromine for a hydroxy-group, is a Favorski ring-contraction rather than a simple substitution. The resulting carboxylic acids are soluble in alkali and reprecipitated by acid; one example was converted nearly quantitatively by diazomethane [16] into its methyl ester (**10** \rightarrow **12**). Their IR spectra lack hydroxyl absorption, but include strong carboxyl keto-peaks. In their ^{13}C NMR spectra, the 3'-ketosinglet is replaced by one (δ , 174–179 ppm) within the established range for alicyclic carboxylic acids [17, 18]. The distinctness of the isomeric acids (**10**, **11**) was confirmed by consistent, if small, differences in their spectral characteristics, and the individuality of their *p*-nitrobenzyl esters.

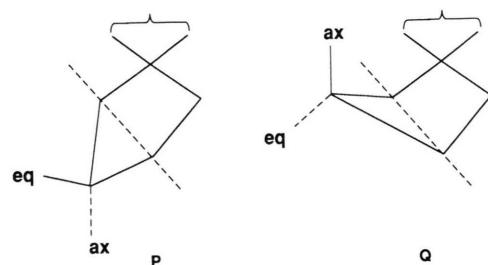
The proposed attachment of the carboxyl at the C-3' in preference to the theoretically possible C-2'-position (see mechanism, below) is justified by the greater steric hindrance exerted on the latter by the bicyclo[2.2.2]octane carbon skeleton, especially its proximate 7-methyl substituent. This argues, at the same time, against the representation of the products as position isomers, as does the facile transformation of one into the other (**10** \rightarrow **11**).

Brief treatment of the α -bromoketone **2** with sodium alkoxide in the appropriate alcohol gave

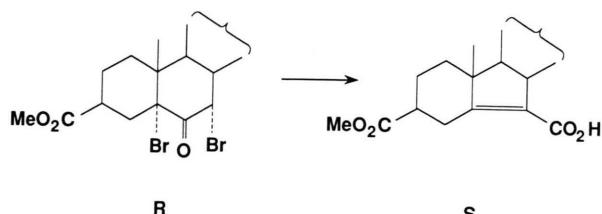
moderate yields of the methyl and ethyl esters (**12**, **13**). Their configuration is that of the carboxylic acid **10**, as was shown by the conversion of the latter into the identical methyl ester **12** by the action of diazomethane (**2** \rightarrow **12** \leftarrow **10**). The esters resisted hydrolytic attack by both acids and alkalis, attributable [19] to obstruction of the ester group by the adjacent 5'-gem-dimethyl substituents. A relevant precedent is the hydrolysis of the diethyl- (**M**) into the monoethyl ester (**N**), which occurs exclusively at the *trans*-carboxyl of **M**, its *cis*-counterpart flanked by methyl groups being unaffected [20].



Because of the flexibility of the cyclopentane ring [21], a 3'-substituent in the extended spiro-structure (e.g. **10**) may assume four steric positions relative to the molecule as a whole: a given pseudo-axial (or equatorial) group may subtend one or the opposite face of the approximate plane of the cyclopentane ring, depending on the conformation of the latter (**P**, **Q**). The precise configurations of the 3'-carboxyl groups in **10** and **11** are therefore as yet not attributable with certainty. The preferred structure selected (but not proved), involving the least intramolecular steric interference, is the one in which the C3'- ϕ -ax-carboxyl bond is approximately parallel to the C1–C4-axis. In this model, the 3'- ϕ -eq-position appears to be less hindered than its 3'- ϕ -ax-counterpart, leading to the tentative formulation of the more readily formed isomer **10** as the 3'- ϕ -eq-compounds.



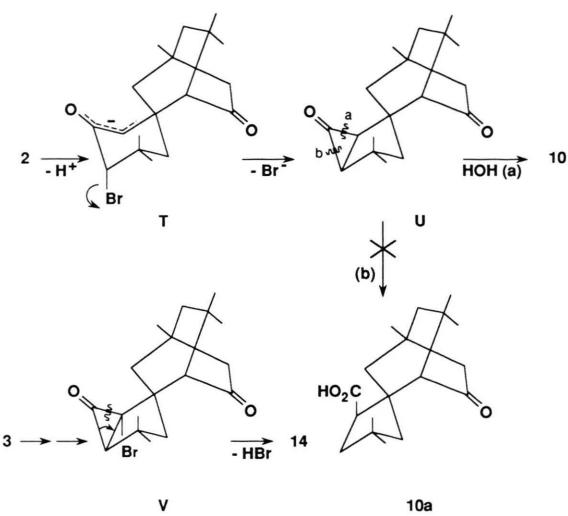
The 2',4'-dibromodiketone **3** underwent the Favorski ring contraction to afford excellent yields of the expected [14] unsaturated carboxylic acid **14**. The reaction was effected by ethanolic sodium hydroxide, sodium methoxide or ethoxide, sodium carbonate in aqueous dioxan, and by boiling pyridine. The conversion of the steroid dibromoketone **R** into the unsaturated carboxylic acid **S** by pyridine described by Woodward [22] provides a closely comparable precedent.



Mechanism. No single mechanism is universally applicable to all Favorski reactions, interpretations varying according to the structure of the reacting species [14]. The present reactions are explicable in terms of Loftfield's mechanism [23] applicable to α -haloketones incorporating at least one α -hydrogen in their structure, a condition which the present examples fulfil. Accordingly, the initial step of the reaction sequence involves the removal of a 2'-proton (from **2**), with formation of the enolate ion **T**. Concerted or subsequent ejection of halide results in the intermediate cyclopropanone **U**, which is rapidly cleaved at C-2'-3' to the 3'-carboxylic acid **10** (but not to **10 a** by cleavage **b**). The scheme is readily extended to the Favorski reaction of **3**: Here, the intermediate **V** retains one halogen substituent; loss of hydrogen bromide therefrom introduces the 2',3'-olefinic bond.

^{13}C NMR spectra

The unequivocal assignment by the INADEQUATE technique of the ^{13}C NMR signals of the parent 3',6-diketone **1**, and of the corresponding 3'-ax-hydroxy-6-monoketone [2] provides the basis for interpreting the spectra of the present derivatives. They are presented in Table II in the usual manner [1] in accordance with their proposed assignments. The spectral evidence shows that the structural changes involved in the present reac-



tions occur exclusively in the cyclohexane-moiety of the molecule.

Thus, the carbon atoms of the bicyclo[2.2.2]-octane framework (C-1 to C-11) of the spirodiisoporphone derivatives **2–8** produce signals of remarkably constant chemical shifts, almost identical with those of the parent diketone **1**. The spiro-carbon C-2, though shared with the reactive cyclohexane ring, retains its resonance unchanged on α -mono- or α,α' -dibromination of the 3'-hydroxy- (or acetoxy)-6-ketone (to **4–8**, $\delta_{\text{C-2}}$ all at *ca.* 37 ppm), but does undergo minor deshielding in the parallel changes involving the parent diketone (**1**, $\delta_{\text{C-2}}$ 40.5 to **2, 3**, $\delta_{\text{C-2}}$ *ca.* 43 ppm). Other minor fluctuations occur in the bridgehead carbon C-1, which is thought to respond by non-bonded interaction to structural changes in the proximate cyclohexane ring.

In the ring-contracted compounds (**10–14**), the bicyclo[2.2.2]octane skeleton displays the same constancy of its spectral characteristics except for minor deviations: The exchange of the cyclohexane for a cyclopentane ring shields the C-1 bridgehead position (by *ca.* 3 ppm), and, due to the altered geometry of the spirane junction, displaces the C-2 singlet to lower field.

A comparison of the spectra of the ultimate parent hydrocarbon **W** [24, 25], the 2-ketone **X** [25, 26] and its homologue **Y** [25] reveals the distinct deshielding effect of a carbonyl- and gem-dimethyl-group on adjacent carbon atoms, displacing their

Table II. ^{13}C NMR spectra of bicyclo[2.2.2]octane-2-spirocyclohexanes (and pentanes)^a.

Compound ^b	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
1^c	67.6 d	40.5 s	*46.0 t	33.5 s	*46.2 t	212.6 s	31.5 s	49.0 t	26.5 q
2	63.0 d	42.9 s	47.4 t	33.9 s	46.7 t	211.2 s	31.7 s	49.2 t	26.5 q
3	*63.4 d	+42.7 s	45.8 t	33.9 s	46.7 t	210.7 s	31.8 s	49.2 t	26.4 q
7	66.6 d	*36.9 s	+47.1 t	33.7 s	+46.9 t	214.7 s	32.0 s	49.8 t	26.8 q
8^d	*65.4 d	37.1 s	48.2 t	33.8 s	47.0 t	214.6 s	32.1 s	+49.3 t	27.0 q
4	63.9 d	36.8 s	*47.3 t	33.8 s	*46.4 t	213.2 s	32.0 s	49.3 t	○26.7 q
5^e	65.2 d	36.9 s	*47.3 t	33.8 s	*46.2 t	211.8 s	32.0 s	48.9 t	27.0 q
10	60.5 d	47.0 s	42.7 t	33.7 s	47.1 t	215.8 s	31.8 s	49.5 t	26.9 q
13^f	60.7 d	47.3 s	42.7 t	33.8 s	47.2 t	214.0 s	31.8 s	49.6 t	27.0 q
11	60.7 d	*43.5 s	+47.4 t	33.4 s	+48.6 t	215.7 s	32.3 s	49.7 t	26.7 q
14	64.5 d	*46.7 s	+47.6 t	33.3 s	+48.6 t	214.3 s	32.3 s	49.6 t	26.5 q

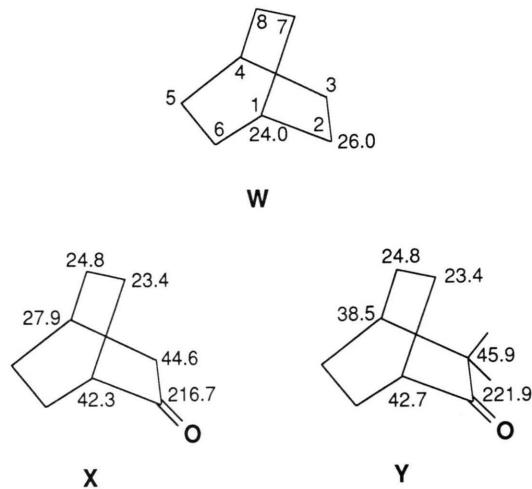
Compound ^b	C-10	C-11	C-2'	C-3'	C-4'	C-5'	C-6'	C-7' eq	C-8' ax
1^c	+33.4 q	+34.1 q	54.0 t	209.6 s	53.5 t	36.7 s	50.9 t	32.8 q	28.0 q
2	+33.3 q	+34.5 q	*44.4 t	204.0 s	61.9 d	36.2 s	*44.0 t	+34.3 q	29.7 q
3	○33.2 q	○34.3 q	*62.7 d	195.1 s	*61.6 d	+42.1 s	43.7 t	○32.7 q	25.0 q
7	○33.0 q	○34.5 q	50.7 t	72.7 d	70.6 d	*35.9 s	44.8 t	○32.0 q	27.2 q
8^d	○33.0 q	○34.6 q	+49.7 t	71.0 d	*65.1 d	36.0 s	42.9 t	32.0 q	27.9 q
4	33.3 q	34.6 q	+65.4 d	78.2 d	+65.5 d	40.8 s	44.5 t	34.0 q	○26.1 q
5^e	○33.4 q	○34.5 q	58.3 d	77.1 d	61.0 d	40.7 s	45.3 t	○34.0 q	25.5 q
10	○33.5 q	○33.4 q	55.3 t	58.2 d	178.0 s	38.8 s	50.3 t	*31.9 q	*31.8 q
13^f	33.4 q	33.4 q	55.6 t	58.4 d	174.4 s	38.7 s	50.4 t	31.8 q	31.8 q
11	36.4 q	33.4 q	53.4 t	66.4 d	179.4 s	*40.6 s	51.8 t	29.4 q	24.1 q
14	○32.0 q	○33.1 q	151.7 d	140.1 s	170.1 s	*45.3 s	59.2 t	+28.4 q	+28.3 q

* + ○ Signals may be interchanged horizontally.

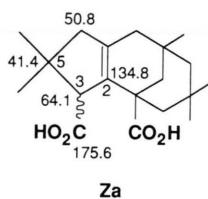
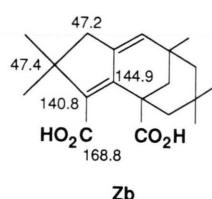
^a The figures refer to the proton noise – decoupled chemical shifts and first order multiplicities of the individual signals. Shieldings are given in δ (ppm) downfield from SiMe_4 . The solvent was deuteriochloroform; ^b the numbering of the carbon atoms is given in structure **D**. In the ring-contracted structures (**10–14**), the cyclopentane ring is numbered (see **10**) so that its carbon atoms C-2',3',5',6' occupy comparable positions relative to the spiro-link with those in spirodiisophorones (**1–8**); ^c the spectrum of the parent 3',6-diketone **1**, assigned [2] by the INADEQUATE technique, is included for comparison; ^d additional signals of the acetyl group: 169.7 s (CO); 21.1 q (CH_3); ^e additional signals of the acetyl group: 169.0 s (CO); 21.0 q (CH_3); ^f additional signals of the ester ethyl group: 60.0 t (CH_2); 14.1 q (CH_3).

signals towards lower field. The same influences are even more apparent in the comparable sequence norbornane (bicyclo[2.2.1]heptane), norcamphor and camphor (for details, see [27]). On this basis, the numerical values of the chemical shifts (of C-1 to C-11) now established are found within acceptable limits in the high-field range. The resonances of the 6-carbonyl-singlet closely match those in alicyclic rings [28], including bridged ones [25, 26], and the closeness of those of the two quartets (δ ca. 33 ppm) expresses the spatial near-equivalence of the methyl carbons of the 7-dimethyl-group.

Structural alterations in the cyclohexane ring produce appropriate spectral changes, some al-



ready alluded to (see above). On mono- and dibromination of the ketone **1**, the α -carbon atoms (C-4', C-2'), notwithstanding their different environment, produce new doublets of very similar chemical shift. The 3'-keto-carbon is progressively shielded (by 5.6 and 8.9 ppm), as has also been observed [29] upon α -bromination of norcamphor and camphor, and indeed in simple aliphatic examples [30]. This shielding is attributable [31] to decreased polarization of the π -bond, the electron-withdrawing effect of the α -halogen atoms decreasing the contribution of the polarized form in the equilibrium $\text{C=O} \leftrightarrow \text{C}-\text{O}^-$. In contrast, the introduction of α -bromo-substituents into both the 3'-ax-hydroxy- (and acetoxy-)spiro-6-ketones (resulting in **4**, **5**, **7**, **8**), progressively deshields the 3'-carbon, and to a somewhat lesser extent, the adjacent C-5'-carbon, presumably by the dominating inductive effect of the electron-attracting halogen atoms.

**Za****Zb**

Although no immediately relevant precedents are available for comparison with the cyclopentane moiety of the ring-contracted products (**10**–**13**), its signals may be assigned with some confidence as follows: The carbon atoms C-2' and C-6' adjacent to the spiro-junction do not differ materially in their spatial positions from those in the spirodiisophorones (**1**–**8**), and thus give rise to triplets of the usual chemical shifts (δ , 53 and 51 ppm). The ring-carbon C-5' bearing the gem-dimethyl group is associated with the high field singlet (remaining by exclusion after the bicyclonane singlets have been allotted). The exocyclic carboxyl carbon C-4' produces a low-field singlet in the expected [17, 18] range. The consistency of all the signals of the carboxylic acid **10** and its ethyl ester **13** is noteworthy. Variations in the numerical values of the shieldings in the saturated (**10**, **11**) and olefinic carboxylic acid (**14**) correspond closely to available data for the comparable structural regions in neodiisophorones (C-3,4,5 in **Za** and **Zb** [32]).

Experimental

The equipment used in the determination of the spectral characteristics of the compounds is specified in Part 1 [2], which also provides information concerning reagents, solvents and general techniques that continue to be applicable.

4'-ax-Bromospirodiisophora-3',6-dione (**2**) [4'-ax-Bromo-4,5',5',7,7-pentamethylbicyclo[2.2.2]-octane-2-spirocyclohexane-3',6-dione]

a) By the action of bromine

A stirred solution of spirodiisophora-3',6-dione (**1**) (5.52 g, 20 mmol) in glacial acetic acid (50 ml) containing 60% hydrobromic acid (0.5 ml) was treated dropwise during 30 min at room temperature with 0.5 M bromine in glacial acetic acid (40 ml, 20 mmol), which was immediately decolorized. The liquid was stirred into ice-water (300 ml) and the precipitated pale-yellow solid (crude: m.p. 140 °C, 5.80–6.0 g, 82–85%) collected, washed neutral with water, air-dried and crystallized from ethanol (3 ml per g, recovery 80–90%), giving prisms of **2**, m.p. 158–159 °C. Slow addition of the dilute bromine solution is essential to avoid partial dibromination (to **3**).

IR (KBr): 2960–2890 vs, 1465 s (CH_3 , CH_2), 1720 vs br (CO), 1425 ms (CH_2 adj. to CO), 1395 m, 1370 ms (CMe_2), 1405 ms, 1285 s, 1230 vs, 1215 vs, 1180 s, 915 ms, 715 m cm^{-1} .

$\text{C}_{18}\text{H}_{27}\text{BrO}_2$ (355.33)

Calcd	C 60.8	H 7.7	Br 22.4,
Found	C 60.9	H 7.65	Br 23.1 M 355.

b) By the action of *N*-bromosuccinimide

A solution of **1** (1.38 g, 5 mmol) in anhydrous chloroform (10 ml), treated with *N*-bromosuccinimide (1.08 g, 6 mmol) was boiled under reflux. The deep-red colour of the suspension disappeared within *ca.* 5 min, white solid (succinimide) was rapidly deposited, and hydrogen bromide was evolved. After further 10 min refluxing and several hours storage of the reaction mixture at room temperature, the succinimide as filtered off, the filtrate washed with water to neutrality and the solvent removed under reduced pressure. The residual pale-yellow viscous oil gave prisms of **2** (1.13 g, 63%) (from light petroleum), identical (mixed m.p. 157–159 °C and IR spectrum) with material obtained in a).

4'-ax-Bromospirodiisophora-3',6-dione (**2**) did not yield ketonic derivatives under the standard conditions, being substantially recovered after treatment with semicarbazide or benzenesulpho-

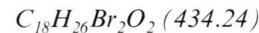
nylhydrazide by the procedures specified for the parent diketone **1** [2]. 2,4-Dinitrophenylhydrazine was recovered quantitatively after its attempted action on **2**.

2',4'-diox-Dibromospirodiisophora-3',6-dione (3)

a) From spirodiisophora-3',6-dione

A stirred solution of **1** (5.52 g, 20 mmol) in glacial acetic acid (60 ml) containing 60% hydrobromic acid (0.5 ml) was treated dropwise during 30 min with M bromine in glacial acetic acid (44 ml, 44 mmol), which was decolourized immediately. The liquid was stirred into ice-water (300 ml) and the precipitated pale-yellow solid (crude: m.p. 140–150 °C, 8.5 g, 97%) collected, washed with water, air-dried and crystallized from ethanol (3 ml per g, recovery 70%) giving prisms of **3**, m.p. 173–175 °C.

IR: 2975–2900 vs, 2870 vs, 1465 s, 1410 m (CH₃, CH₂), 1725 vs br (CO), 1400 ms, 1375 s (CMe₂), 1275 s, 1230 s, 1185, 1175 s d, 1150 ms, 1140 ms, 1125 ms, 920 vs, 785 m, 715 m, 675 m cm⁻¹.



Calcd	C 49.8	H 6.0	Br 36.8,
Found	C 50.0	H 6.0	Br 37.1 M 434.

b) From 4'-ax-bromospirodiisophora-3',6-dione

(i) A stirred solution of **2** (1.78 g, 5 mmol) in glacial acetic acid (25 ml) – 60% hydrobromic acid (0.25 ml) was brominated as above (5 ml M bromine). The crude product (1.69 g, 78%) gave platelets of **3** (from ethanol), identical with the above material.

(ii) A suspension of **2** (1.78 g, 5 mmol) – N-bromosuccinimide (3.56 g, 20 mmol) in chloroform (50 ml) gave, by procedure b) described for **2** (above), prisms of **3** (1.39 g, 64%), identical with the above material.

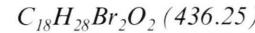
Resistance of spirodiisophor-6-one (15) to bromination

When the reactant **15** [1] was subjected to the standard treatment with 1 mole of bromine, decolorization occurred only initially and slowly. After being kept at room temperature for 30 min, the red fuming liquid was stirred into ice-water. The yellow resinous precipitate gave, on crystallization from light petroleum (b.p. 40–60 °C), prisms of recovered **15** (83%), identified by mixed m.p. 61–62 °C and IR spectrum [1].

2',4'-diox-Dibromo-3'-ax-hydroxyspirodiisophor-6-one (4)

To a stirred solution of **3** (4.34 g, 10 mmol) in anhydrous ether (150 ml), lithium aluminium hydride (0.38 g, 10 mmol) was added in 5 portions over 15–20 min; hydrogen was evolved. Stirring at room temperature was continued for 12 h, the excess of the reducing agent destroyed by the careful addition of cold water and 3 M hydrochloric acid, the product extracted with ether, and the extracts washed with water to neutrality. After the removal of the solvent, the pale-yellow viscous (sometimes granular) residue was dissolved in ethanol–light petroleum (10 and 15 ml respectively). The resulting plates (m.p. 190–195 °C, 2.7 g, 62%) gave, on further crystallization from the same solvents, prisms (2.3 g, 54%) of **4**, m.p. 193–195 °C.

IR: 3460 vs (OH), 2990–2900 vs br, 1490 ms, 1455 vs, 1410 s (CH₃, CH₂), 1710 vs br (CO), 1385 ms, 1375 s (CMe₂), 1360 ms, 1280–1265 s d, 1250 s, 1235, 1225 s d, 1110 s, 1050 ms, 1020 ms, 960 ms, 860 ms, 840 s, 750 vs, 705 vs cm⁻¹.



Calcd	C 49.6	H 6.5	Br 36.6,
Found	C 49.4	H 6.45	Br 35.9 M 436.

Re-oxidation to 3

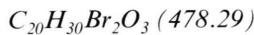
A stirred solution of **4** (0.88 g, 2 mmol) in glacial acetic acid (8 ml) was treated dropwise at room temperature with Kiliani's 10% chromic acid [33] (5 ml, 4 mmol), and stirring continued for 1 h. It was then treated with 3% aqueous sodium sulphite to discharge the olive green colour of the reaction mixture. The resulting white precipitate (m.p. 175 °C, 0.78 g, 89%) gave, on crystallization from ethanol (6 ml), prisms (0.50 g, 57%) of **3**, identified by mixed m.p. and IR spectrum.

2',4'-diox-Dibromo-3'-ax-hydroxyspirodiisophor-6-one. Acetyl derivative (5)

A solution of **4** (0.44 g, 1 mmol) in acetic anhydride (8 ml) was boiled under reflux for 30 min (or set aside at room temperature for 12 h, with addition of 60% perchloric acid, 6 drops), then stirred into warm water (40 ml). The crude product (m.p. 220–225 °C, 0.35 g, 73%) gave prisms (0.24 g, 50%) of **5**, m.p. 227–229 °C (from acetone–light petroleum, 1:1).

IR: 2980–2880 vs, 1480 ms, 1455 s (CH₃, CH₂), 1750 vs (CO, acyl), 1720 vs (CO, ring), 1230–1215 vs br (C–O, ester), 1395 s, 1380 vs (CMe₂),

1370 vs, 1025 vs cm^{-1} and numerous peaks in the fingerprint range.



Calcd C 50.2 H 6.3,
Found C 50.2 H 6.4.

3,5-Dinitrobenzoyl derivative (6)
($\text{Ar} = C_6H_3(NO_2)_2$ -3,5)

A solution of **4** (0.44 g, 1 mmol) in pyridine (10 ml), treated with 3,5-dinitrobenzoyl chloride (0.25 g, 1 mmol), was kept at room temperature for 6 h, then stirred into ice-water (100 ml) containing concentrated hydrochloric acid (10 ml). The resulting pink solid (0.53 g) gave, on crystallization from acetone (12 ml), buff microprisms (0.37 g, 59%) of **6**, m.p. $>300^\circ\text{C}$.

IR: 3100 w (Ar), 2960–2870 s, 1465 s (CH_3 , CH_2), 1735 vs (CO, acyl), 1705 vs (CO, ring), 1630 ms ($\text{C}=\text{C}$), 1550 vs, 1345 vs (N–O), 1270 vs (C–O, ester), 1145 vs (C–N), 720 s, 715 vs (1,3,5-trisub. Ar) cm^{-1} .



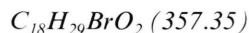
Calcd C 47.6 H 4.8 N 4.4,
Found C 47.9 H 4.9 N 4.5.

4'-ax-Bromo-3'-ax-hydroxyspirodiisophor-6-one (7)

a) Action of excess of lithium aluminium hydride on the 2',4'-dibromo-3',6-dione (3)

A solution of **3** (1.09 g, 2.5 mmol) in anhydrous ether (75 ml) was added dropwise during 3–6 min at room temperature to a stirred suspension of lithium aluminium hydride (0.38 g, 10 mmol) in the same solvent (25 ml) and the stirred mixture boiled under reflux for 30 min. This gave, by the usual isolation procedure (see above), prisms (0.78 g, 87%) of **7**, m.p. 197–199 $^\circ\text{C}$ (from ethanol–light petroleum).

IR: 3520 vs (OH), 2980 vs–2890 s, 1490 ms, 1410 ms (CH_3 , CH_2), 1710 vs br (CO), 1400 ms, 1375 ms (CMe_2), 1350 ms, 1305 ms, 1250 s, 1070 s, 1035 vs, 960 ms, 830 ms, 790 ms, 730 ms cm^{-1} .



Calcd C 60.5 H 8.2 Br 22.4,
Found C 60.8 H 8.2 Br 22.3 M 357.

b) Action of excess of lithium aluminium hydride on 2',4'-dibromo-3'-hydroxyspirodiisophor-6-one (4)

A solution of **4** (0.44 g, 1 mmol) in anhydrous ether (75 ml) was added to lithium aluminium hydride (0.15 g, 4 mmol) in the same solvent (25 ml) (as described above, but 24 h at room temperature). This gave by the usual isolation procedure,

prisms (0.31 g, 86%) of **7**, identical with material obtained in a).

c) Action of sodium borohydride on 4'-bromospirodiisophora-3',6-dione (2)

A stirred solution of **2** (1.78 g, 5 mmol) in (warmed) ethanol (60 ml) was treated at room temperature in portions with sodium borohydride (1.90 g, 50 mmol). The effervescent reaction mixture was set aside at room temperature for 12 h, then stirred into ice-concentrated hydrochloric acid (10 ml). The white precipitate (1.15 g) gave, on crystallization from ethanol, prisms (1.0 g, 56%) of **7**, identical with material obtained in a).

4'-Bromo-3'-hydroxyspirodiisophor-6-one.
Acetyl derivative (8)

A solution of **7** (0.36 g, 1 mmol) in acetic anhydride (10 ml) was treated dropwise at room temperature with 60% perchloric acid (6 drops, temperature rise), set aside at room temperature for 12 h, then stirred into warm water (50 ml). The oily globules solidified on storage at 0 $^\circ\text{C}$ (m.p. 210–215 $^\circ\text{C}$, 0.25 g, 63%) and gave, on crystallization from acetone–light petroleum (5 ml each) prisms (0.20 g, 50%) of **8**, m.p. 224–226 $^\circ\text{C}$.

IR: 2970–2880 vs, 1485–1455 ms mult (CH_3 , CH_2), 1730 vs (CO, acyl), 1710 vs (CO, ring), 1245–1200 vs mult (C–O, ester), 1415 ms, 1400 s (CMe_2) cm^{-1} .



Calcd C 60.1 H 7.8,
Found C 60.15 H 8.0.

3,5-Dinitrobenzoyl derivative (9)

($\text{Ar} = C_6H_3(NO_2)_2$ -3,5)

A solution of **7** (0.36 g, 1 mmol) in pyridine (10 ml), treated with 3,5-dinitrobenzoyl chloride (0.58 g, 2.5 mmol) was kept at 100 $^\circ\text{C}$ for 30 min, then stirred into ice-water (100 ml) containing concentrated hydrochloric acid (10 ml). The precipitate (0.60 g) gave, on crystallization from acetone–light petroleum (1:1), ivory prisms (0.31 g, 55%) of **9**, m.p. 198–201 $^\circ\text{C}$.

IR: 3110 w (Ar), 2990–2880 s, 1465 s (CH_3 , CH_2), 1730 vs (CO, acyl), 1705 s (CO, ring), 1630 ms ($\text{C}=\text{C}$), 1550 vs, 1350 vs (N–O), 1275 vs (C–O, ester), 1160 vs (C–N), 730 s, 720 s (1,3,5-trisub. Ar) cm^{-1} .



Calcd C 54.45 H 5.7 N 5.1,
Found C 54.3 H 5.7 N 5.0.

Favorski Reaction

4',4',7,7-Pentamethylbicyclo[2.2.2]octan-6-one-2-spiro-1'-cyclopentane-3'- ϕ -eq-carboxylic acid (**10**)

A solution of 4'-bromospirodiisophtora-3',6-dione (**2**) (3.55 g, 10 mmol) in ethanol (30 ml) was treated with 3 M sodium hydroxide (20 ml), boiled under reflux for 10 min, and most of the solvent removed under reduced pressure. The residual clear liquid was stirred into ice-water (100 ml) and acidified with concentrated hydrochloric acid. The precipitated white gum was extracted with ether, the extracts washed with water to neutrality, and the solvent removed. The residual pale-yellow oil was dissolved in light petroleum (10 ml); the liquid very slowly deposited prisms (1.15–1.5 g, 40–50%) of **10**, m.p. 214–216 °C.

IR: 2800, 2700 ms sh, 950 ms br (CO₂H), 2980–2800 vs br, 1470, 1460 s d, 1430 s, 1410 s (CH₃, CH₂), 1720–1700 vs mult (CO, ring and CO₂H), 1395 m, 1370 s (CMe₂), 1350 vs, 1325 vs, 1270 vs, 1245 vs, 1225 vs, 825 m, 670 ms cm⁻¹.

C₁₈H₂₈O₃ (292.42)

Calcd	C 73.9	H 9.65,
Found	C 74.0	H 9.7 M 292.

3'- ϕ -ax-Carboxylic acid (**11**)

The foregoing procedure gave, after 3 h refluxing and identical work-up, massive prisms (30%) of **11**, m.p. 201–202 °C (from light petroleum).

IR: 3200 s br, 840–825 m br (CO₂H), 2960 vs, 2860 s sh, 1470–1460 ms d (CH₃, CH₂), 1730 vs (CO, CO₂H), 1695 s (CO, ring), 1355 m, 1320 m, 1265 ms, 1175 s cm⁻¹.

C₁₈H₂₈O₃ (292.42)

Calcd	C 73.9	H 9.65,
Found	C 74.1	H 9.8.

Formation of both 3'- ϕ -eq- and 3'- ϕ -ax-conformers (**10**, **11**)

A stirred solution of **2** (3.55 g, 10 mmol) in dioxan (30 ml) was treated dropwise at room temperature with 1.5 M sodium carbonate (15 ml) and refluxed for 6 h. The liquid was added to ice-water (100 ml) and acidified with concentrated hydrochloric acid. The resulting solidified precipitate (2.9 g) gave, on crystallization from methanol (2 ml per g), prisms (1.7 g, 60%) of a mixture of **10** and **11**, the former predominating: it was separated by fractional crystallization from methanol, affording prisms of the less soluble 3- ϕ -eq-isomer **10**, m.p. 214–218 °C. Partial evaporation of the combined filtrates deposited mixed crystals of **10** and **11** of melting range 160–200 °C.

Isomerization of 3'- ϕ -eq- (**10**) to 3'- ϕ -ax-isomer (**11**)

A solution of **10** (0.58 g, 2 mmol) in ethanol (20 ml), treated with 3 M sodium hydroxide (250 ml) was refluxed for 5 h. It was distilled to small volume under reduced pressure, the residual liquid stirred into ice-water (100 ml) and acidified with concentrated hydrochloric acid. The resulting precipitate (m.p. 190–215 °C, 0.46 g, 79%) gave prisms (0.38 g, 66%) of the 3'- ϕ -ax-isomer **11**, m.p. 201–202 °C, identified by IR spectrum.

p-Nitrobenzyl ester derivatives of **10** and **11**

A solution of the 3'- ϕ -eq-isomer **10** (0.58 g, 2 mmol) in ethanol (18 ml), treated successively with 1.5 M sodium carbonate (5 ml, 7.5 mmol) and *p*-nitrobenzyl bromide (0.54 g, 2.5 mmol), was boiled under reflux for 1 h, added to ice-water (100 ml) and basified with 3 M sodium hydroxide until a precipitate appeared (0.77 g). This gave microprisms (0.60 g, 70%) of the *p*-nitrobenzyl-ester, m.p. 135–136 °C (from acetone).

C₂₅H₃₃NO₅ (427.55)

Calcd	C 70.2	H 7.8	N 3.3,
Found	C 70.0	H 7.7	N 3.3.

The 3'- ϕ -ax-isomer **11** gave, by the foregoing procedure, massive prisms (74%) of the *p*-nitrobenzyl-ester of **11**, m.p. 125–128 °C (from acetone).

Found	C 70.4	H 7.9	N 3.3.
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4',4',7,7-Pentamethylbicyclo[2.2.2]octan-6-one-2-spiro-1'-cyclopentane-3'- ϕ -eq-carboxylic methyl ester (**12**)

a) By the action of diazomethane on the 3'- ϕ -eq-carboxylic acid (**10**)

To a stirred solution of **10** (0.58 g, 2 mmol) in anhydrous ether (100 ml), ethereal diazomethane (from 50 mmol toluene-*p*-sulphonylmethylnitrosamide, "Diazald" in *ca.* 75 ml anhydrous ether) [16] was slowly added. Slight effervescence occurred initially, and the transient yellow colour of the solution finally persisted. The liquid was set aside at room temperature for 12 h, the remaining excess of the reagent destroyed by the addition of 3 M acetic acid, and the washed ethereal solution evaporated in a vacuum. Crystallization of the residual pale-yellow oil from light petroleum (15 ml) gave elongated needles (0.57 g, 93%) of the methyl ester **12**, m.p. 131–133 °C.

IR:	2960 vs–2890 s,	1460 m,	1435 m	(CH ₃ ,
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CH_2), 1725 vs, 1710 s sh (CO), 1405 m, 1375 ms (CMe_2), 1265 m, 1170 s (C—O, ester) cm^{-1} .

$\text{C}_{19}\text{H}_{30}\text{O}_3$ (306.45)

Calcd C 74.5 H 9.9,
Found C 74.7 H 10.1 M 306.

b) By the action of sodium methoxide on 4'-bromospirodiisophora-3',6-dione (2)

A solution of **2** (0.72 g, 3 mmol) in methanol (35 ml), treated with solid sodium methoxide (0.54 g, 10 mmol), was refluxed for 15 min, added to water (50 ml) and extracted with ether. Evaporation of the washed neutral extracts gave a colourless oil, which was dissolved in light petroleum, filtered through alumina (12 \times 2 cm), and the column eluted with the same solvent. Removal of the solvent left a colourless resin which solidified on storage, and gave needles (0.23 g, 35%) of **12**, m.p. 131–133 °C (from light petroleum), identical with material obtained in a).

3'- ϕ -eq-Carboxylic ethyl ester (13)

The use of ethanol–sodium ethoxide in the foregoing procedure gave massive needles (24%) of the ethyl ester **13**, m.p. 105–107 °C (from light petroleum). – It crystallized very slowly and incompletely; the highly viscid pale yellow resin remaining on spontaneous evaporation of the mother liquors gave an IR spectrum identical with that of crystalline **13**, but failed to solidify on prolonged storage at 0 °C.

IR: 2950 vs–2870 s, 1460 m (CH_3 , CH_2), 1725 vs, 1705 s sh (CO), 1400 w, 1395 m (CMe_2), 1260 m, 1170 s (C—O, ester) cm^{-1} .

$\text{C}_{20}\text{H}_{32}\text{O}_3$ (320.48)

Calcd C 75.0 H 10.1,
Found C 75.0 H 10.4.

Resistance of 12 and 13 to hydrolysis

The foregoing esters **12** and **13** (1 mmol) were largely recovered after their solution a) in ethanol (10 ml) – concentrated hydrochloric acid (10 ml) was boiled for 3 h; b) in ethanol (10 ml) – 3 M sodium hydroxide (10 ml) was boiled for 1.5 h (identified by IR spectra).

4,4',4",7,7-Pentamethylbicyclo[2.2.2]octan-6-one-2-spiro-1'-cyclopent-2'-ene-3'-carboxylic acid (14)

a) By the action of sodium hydroxide

A solution of 2',4'-dibromospirodiisophora-3',6-dione (**3**) (4.34 g, 10 mmol) in ethanol (100 ml), treated with 3 M sodium hydroxide

(200 ml), was boiled under reflux for 30 min, then distilled to *ca.* half volume under reduced pressure. The residual liquid was added to ice-water (300 ml) and acidified with concentrated hydrochloric acid. The resulting precipitate (m.p. 148–154 °C, 2.47 g, 85%) gave on crystallization from ethanol (2 ml per g, recovery 50%), prisms of **14**, m.p. 168–170 °C. – The compound dissolved in M sodium hydroxide on warming and was precipitated by hydrochloric acid as a gelatinous present-ly granular material.

IR: 3180 s br, 945–900 m mult (CO_2H), 2980 vs–2870 s, 1460 ms, 1425 m br (CH_3 , CH_2), 1725 s (CO of CO_2H), 1680 vs (CO, ring), 1620 ms ($\text{C}=\text{C}$), 1240 ms, 1210 ms sh (C—O, ester), 1365 m, 1345 m (CMe_2), 1270 s br, 1190 m, 775, 750, 730 s t, 665 ms cm^{-1} .

$\text{C}_{18}\text{H}_{26}\text{O}_3$ (290.41)

Calcd C 74.45 H 9.0,
Found C 73.9 H 9.1 M 290.

b) By the action of sodium carbonate

A stirred solution of **3** (0.9 g, 2 mmol) in dioxan (10 ml) was treated dropwise at room temperature with 1.5 M sodium carbonate (25 ml), then refluxed for 1.5 h, and added to ice-water (100 ml). The resulting solidified precipitate (0.39 g) gave prisms (0.28 g, 48%) of **14** (from ethanol), identical with material obtained in a).

c) By the action of sodium methoxide or ethoxide

A solution of **3** (1.74 g, 4 mmol) in methanol (25 ml), treated with sodium (1.15 g, 0.05 g atom) in methanol (25 ml) was refluxed for 3 h, distilled to small volume, and the residual liquid added to ice-water (100 ml). Acidification gave a precipitate (1.03 g), affording prisms (0.87 g, 75%) of **14** (from methanol), identical with material obtained in a). The use of ethanol in the foregoing procedure gave **14** in 48% yield.

d) By the action of pyridine

A solution of **3** (1.1 g, 2.5 mmol) in anhydrous pyridine (10 ml) was boiled under reflux for 24 h, then stirred into ice-water (100 ml) containing concentrated hydrochloric acid (10 ml). The precipitated soft resin solidified on storage at 0 °C (0.50 g) and gave prisms (0.32 g, 43%) of **14** (from ethanol–light petroleum), identical with material obtained in a).

p-Nitrobenzyl ester of 14

The acid **14** gave, by the procedure specified for

10 (see above), needles (88%) of the *p*-nitrobenzyl ester, m. p. 156–158 °C (from light petroleum).

IR: 2960 vs–2870 s, 1455 m br (CH₃, CH₂), 1710 vs (CO), 1525 vs, 1345 s (N–O), 770 s, 735 s (*p*-disub. Ar), 1230 vs cm^{−1}.

C₂₅H₃₁NO₅ (425.53)

Calcd C 70.6 H 7.3 N 3.3,
Found C 70.1 H 7.3 N 3.2.

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