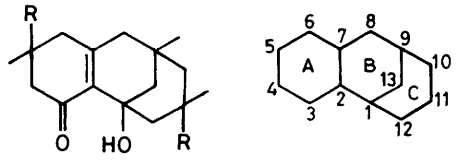
Diisophorone and Related Compounds. Part 23.[1] A Rearrangement of the Tricyclo[7.3.1.0^{2,7}]tridecane to the Bicyclo[4.2.1]nonane-7-spiro-2'-(tetrahydrofuran) Ring System

Frederick Kurzer* and Anthony A. Allen
Royal Free Hospital School of Medicine, University of London, London NW3 2PF

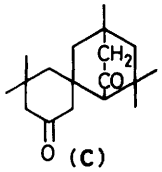
3,4-Dioxo-2,7-epoxydiisophoran-1-ol, a compound of the tricyclo[7.3.1.0^{2,7}]tridecane ring system, is converted by hydrogen peroxide in acidic media into a keto acid of the bicyclo[4.2.1]nonane-7-spiro-2'-(tetrahydrofuran) ring system by skeletal changes involving a Baeyer–Villiger oxidation, a recyclisation, and a pinacol rearrangement. Other members of this bridged ring structure are accessible from the keto acid by appropriate transformations. Their chemical and spectral properties, including the results of two-dimensional carbon-13 NMR measurements, are in accord with the structural assignment to the new ring system.

The majority of chemical transformations involving diisophorones (**A**) occur at the *ortho*-fused rings A/B of their tricyclo[7.3.1.0^{2,7}]tridecane ring system (**B**),† with preservation of both the structure and conformation of the carbon skeleton.[2] The only skeletal rearrangements (as distinct from various structural extensions[4–6]) so far encountered occur in the reversible isomerisation of diisophorones (**A**) and the spirodiketones (**C**),[7] and in the conversion of 4,8-dibromodiisophorone-1-carboxylic acids into derivatives of tricyclo[6.3.1.0^{2,6}]dodecane (*e.g.* **D**) by a Favorski ring contraction.[8] We now report a rearrangement of the tricyclo[7.3.1.0^{2,7}]tridecane carbon framework of diisophorone to the new bicyclo[4.2.1]nonane-7-spiro-2'-(tetrahydrofuran) ring system (**E**) under the conditions of the Baeyer–Villiger oxidation.[9]



(**A**)

(**B**)



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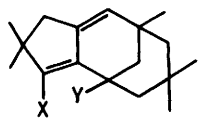
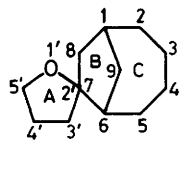
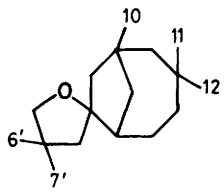


(**D**)



(**E**)



(**F**)

3,4-Dioxo-2,7-epoxydiisophoran-1-ol (**1**),[10] the product of the successive epoxidation and selenium dioxide oxidation of diisophorone (**A**), is readily cleaved[10] by alkaline hydrogen peroxide to the dicarboxylic acid (**1a**) by the familiar *ortho*-diketone scission.[11] Under acidic conditions, however, a more deep-seated structural change, (**B**)→(**E**), involving a pinacol rearrangement, is found to occur.

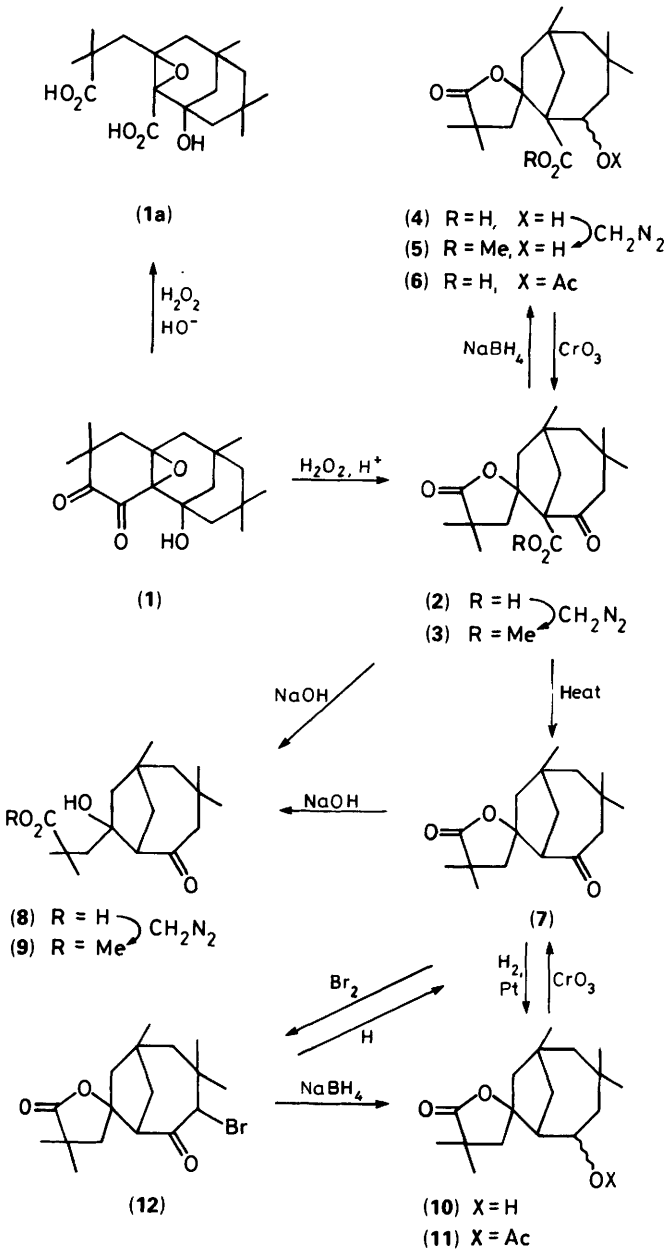
Thus, treatment of the epoxydiketol (**1**) with 30% hydrogen peroxide in glacial acetic or anhydrous formic or propionic acid at 100 °C (acting effectively as peroxy-acids[9,12]) gave good yields of a product, $C_{18}H_{26}O_5$, arising by the net gain of one atom of oxygen, and formulated as the substituted bicyclo-[4.2.1]nonane-7-spiro-2'-(tetrahydrofuran) (**2**). The proposed structure, one of several possible alternatives, is based on a consideration of the chemical and spectral properties of (**2**), and of a group of its transformation products (**3**)–(**12**). It is confirmed decisively by the results of two-dimensional carbon-13 NMR measurements (see below), which demonstrate the presence, in (**2**) and (**7**), of the central five-membered ring B, and its attachments.

The oxidation product (**2**) was a carboxylic acid convertible by diazomethane into its methyl ester (**3**). Its ready decarboxylation to the neutral oxolactone (**7**) by thermolysis in boiling toluene, or above its melting point is compatible with the attachment of the carboxy group at a tertiary carbon atom. This facile decarboxylation appears to be promoted by the adjacent oxo substituent,[13] since the 5-hydroxy analogue (**4**) was not decarboxylated under these conditions. It is recalled that diisophorone-1-carboxylic acids which lack this activation are also thermostable.[2] The formation of an intermediate 'anti-Bredt' enol may therefore play a role in promoting the observed decarboxylation (**2**)→(**7**). The absence of a free hydroxy group in (**2**) and its decarboxylation product (**7**) was in accord with their failure to undergo acetylation.

The action of potassium borohydride reduced the 5-oxo- (**2**) to the 5-hydroxy-carboxylic acid (**4**). This gave the methyl ester (**5**) and the 5-acetyl derivative (**6**) by the standard methods and was reconvertible into the original oxoacid (**2**) by chromic acid oxidation. The methyl ester (**5**) was also obtained by direct reduction of its precursor (**3**).

These reactions confirm the presence of the ketone function [in (**2**)], and the integrity of the structure and conformation of the ring system (**E**) throughout the changes. Parallel reactions were realised with the decarboxylated analogue (**7**); its 5-oxo group was functionalised (giving, for example, an oxime and hydrazone) and reduced by catalytic hydrogenation. The resulting hydroxy lactone (**10**) gave an acetyl derivative (**11**) and was reconvertible in good yield into the starting material (**7**) by

† Simplified nomenclature based on the trivial name 'diisophorane for the parent hydrocarbon continues in use.[2,3]



Scheme 1.

oxidation. On treatment with thionyl chloride in pyridine, it did not undergo dehydration but gave moderate yields of a sulphite ester.

The presence of a γ-lactone ring in the structures of (**2**) and its transformation products is consistent with the results of their hydrolytic cleavage by alkali; the decarboxylated key compound (**7**) was ring-opened to the bicyclic hydroxycarboxylic acid (**8**), which was further characterised as the methyl ester (**9**) and recoverable therefrom by alkaline hydrolysis. The same product (**8**) arose from both the carboxylic acid (**2**) and its methyl ester (**3**), lactone scission being accompanied by simultaneous decarboxylation.

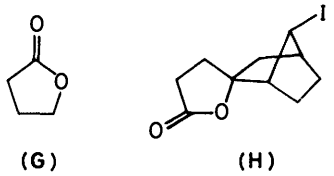
The action of bromine (1 mol equiv.) in glacial acetic acid on the oxolactone (**7**) gave the α-bromoketone (**12**). The proposed location of its halogen substituent is in accord with the demonstrated preferential attack of bromine at methylene groups activated by an adjacent oxo function in model structures,[14] and receives indirect support from the failure of the 5-acetoxy analogue (**11**) [of (**7**)] to absorb bromine under identical conditions. Catalytic hydrogenation of (**12**), or reduction with zinc in glacial acetic acid regenerated the starting material (**12**)→(**7**); sodium borohydride effected the same reaction, with simultaneous reduction of the 5-oxo group (**12**)→(**10**).

Infrared Spectra.—The IR spectral data are in accord with the foregoing interpretations. The 5-oxo group [of (**2**), (**3**), (**7**), and (**12**)] produces an intense band at *ca.* 1 685 cm^{-1}, which disappears upon reduction; the resulting secondary alcohols (**4**), (**5**), and (**10**) display hydroxy absorption near 3 500 cm^{-1}. The prominent peak at 1 735–1 770 cm^{-1} found in all spectra except those of the ring-opened products (**8**) and (**9**) is assigned to the 5′-carbonyl moiety of the γ-lactone ring, agreeing in its frequency with relevant precedents,[15] including the parent tetrahydrofuran-2-one (**G**, ν_{CO} 1 774 cm^{-1} in CCl_4). It persists as the only band of the oxo range in the hydroxy lactone (**10**), which contains none but the lactone carbonyl grouping.

The key carboxylic acid (**2**) produces the expected strong carboxy band at 3 300 cm^{-1} and weak absorptions in the 2 600–2 800 cm^{-1} range, but its major carboxy CO absorption appears to merge with that of the lactone carbonyl group. Its methyl ester (**3**), however, does give rise to three distinct peaks, corresponding individually to its three carbonyl functions. Scission of the γ-lactone ring of (**7**) restores the characteristic absorption near 3 500 cm^{-1} of the regenerated hydroxy group, not only in the free acid (**8**), but more significantly also in its methyl ester (**9**), where any contribution from a carboxy-hydroxy group is excluded.

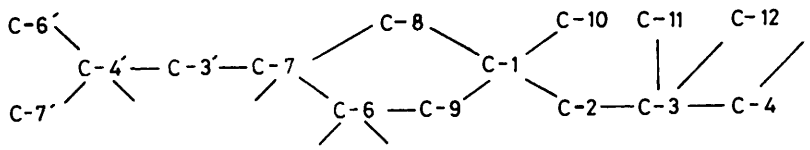
Carbon-13 NMR Spectra.—Clear evidence in support of structure (**E**) for the present ring system was obtained from the results of two-dimensional ^{13}C NMR measurements by the INADEQUATE technique.[16] The numerical data displayed in Table 1 provide consistent carbon connectivities for the two prototypes (**2**) and (**7**), establishing the presence of their five-membered carbocyclic core, and tracing the sites of attachment of the two additional rings. The unequivocal assignments thus obtained furnish, at the same time, guidelines for the interpretation of the ^{13}C NMR spectra of the group of compounds as a whole. These are presented in the usual way[17,18] in accordance with their proposed assignments (Table 2). In the following brief discussion, some of the salient features of the spectral data are commented on, and the correlation between structure and spectral characteristics emphasised.

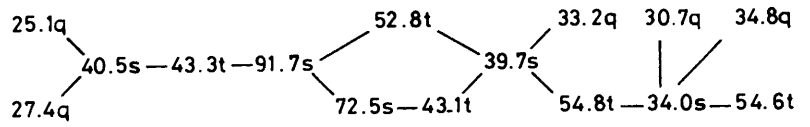
Quaternary carbon atoms. The three low-field carbonyl singlets not identified by the two-dimensional NMR technique are readily distinguished by reference to those of comparable structures. The lowest-field singlet, appearing near δ 210, is assigned to the 5-oxo-carbon, agreeing in its chemical shift with the carbonyl signal of cycloheptanone (δ 212.6[19]). It is replaced by a doublet upon reduction of the 5-oxo group [*e.g.* (**2**)→(**4**); (**7**)→(**10**)], and undergoes the expected[18,20,21] small upfield displacements under the influence of an adjacent 4-bromo or 6-tertiary carboxy substituent. The singlet near δ 180, persisting throughout the series, arises from the γ-lactone carbonyl carbon; its chemical shift approaches that of the carbonyl carbon in butanolide (**G**, δ 178.4[22]) and of the closely comparable spiro-γ-



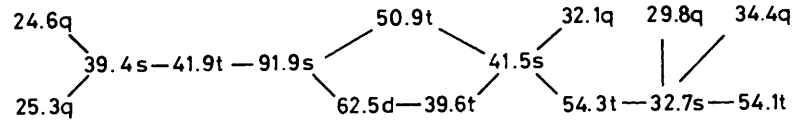
(**G**) (**H**)

Table 1. Two-dimensional ^{13}C NMR spectra and carbon connectivities of compounds (2) and (7).





(2)



(7)

Table 2. Carbon NMR spectra and their assignment.[a]

Compound[b]	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
(2)	39.7 s	54.8 t	34.0 s	54.6 t	205.6 s	72.5 s	91.7 s	52.8 t	43.1 t	33.2 q
(3)	39.7* s	54.9 t	33.8 s	54.7 t	205.9 s	73.3 s	91.5 s	53.5 t	43.4 t	33.2 q
(4)	38.6 s	57.9† t	31.6 s	46.8 t	72.1 d	64.9 s	93.1 s	54.4† t	41.3 t	33.6 q
(5)	38.6* s	58.0† t	31.5 s	46.6 t	72.1 d	64.7 s	93.0 s	54.3† t	41.3 t	33.6 q
(7)	41.5 s	54.3 t	32.7 s	54.1 t	211.3 s	62.5 d	91.9 s	50.9 t	39.6 t	32.1 q
(10)[c]	40.7* s	57.3† t	31.5 s	46.5 t	70.4 d	55.6 d	94.7 s	55.3† t	38.8 t	33.3 q
(10)[d]	42.3* s	55.4† t	31.5 s	45.7 t	68.3 d	58.3 d	94.6 s	52.0† t	37.7 t	33.0 q
(12)	42.4* s	51.5 t	36.2 s	65.9 d	203.1 s	62.8 d	93.1 s	51.2† t	40.0 t	32.6 q
(8)[e]	39.9 s	57.0 t	30.4 s	55.4 t	211.7 s	68.9 d	82.0 s	53.5 t	35.9 t	31.6 q
(9)[e]	40.1 s	57.3 t	30.5 s	55.5 t	211.9 s	69.1 d	81.9 s	53.8 t	36.0 t	31.6 q

Compound[b]	C-11 (*ax*)	C-12 (*eq*)	C-13	C-14	C-3′	C-4′	C-5′	C-6′ (*ax*)	C-7′ (*eq*)
(2)	30.7 q	34.8 q	172.5 s	—	43.3 t	40.5 s	181.3 s	25.1 q	27.4 q
(3)	31.3 q	34.4 q	168.3 s	52.2 q	43.2 t	40.6* s	181.2 s	25.0 q	27.5 q
(4)	31.9 q	37.2 q	177.9 s	—	42.9 t	40.7* s	182.5 s	25.5 q	27.1 q
(5)	31.8 q	37.2 q	174.1 s	52.2 q	43.2 t	40.5* s	181.6 s	25.7 q	27.0 q
(7)	29.8 q	34.4 q	—	—	41.9 t	39.4 s	181.2 s	24.6 q	25.3 q
(10)[c]	31.9 q	37.4 q	—	—	42.9 t	40.7* s	182.5 s	25.8 q	26.2 q
(10)[d]	31.5 q	36.0 q	—	—	43.4 t	42.3* s	181.7 s	25.7 q	26.0 q
(12)	28.7 q	33.2 q	—	—	43.1 t	40.6* s	180.9 s	25.4 q	26.3 q
(8)[e]	25.7 q	37.2 q	—	—	32.8 t	45.2 s	183.2 s	24.8 q	25.3 q
(9)[e]	25.8 q	37.3 q	—	52.0 q	32.8 t	45.2 s	178.4 s	24.8 q	25.6 q

[a] Proton noise-decoupled chemical shifts and first order multiplicities of the individual signals are given. Chemical shifts are given in δ (ppm) downfield from $SiMe_4$. The solvent was deuteriochloroform throughout. [b] The numbering of the ring system is given in structure (**E**), and that of the exocyclic carbon atoms in (**F**). C-13 and C-14 refer to the carbonyl and methyl carbon of the 6-methoxycarbonyl group. [c] Major stereoisomer. [d] Minor stereoisomer. [e] In compounds (**8**) and (**9**) the 7-substituent is numbered so that its carbon atoms correspond to the positions in the tetrahydrofuran ring from which they originate, to facilitate comparisons. *·† Figures may be interchanged for the same compound.

lactone of iodonorbornane (**H**, δ 176[23]). The third low-field singlet (δ *ca.* 172–178) vanishes on decarboxylation and is therefore associated with the exocyclic 13-carboxy carbon; on esterification it undergoes the usual[18,21,24] small upfield shift (by δ *ca.* 4).

The singlet appearing consistently near δ 93, shown by the carbon connectivities to arise from the central spiro-carbon, agrees in its chemical shift with that of the closely comparable spiro-position in (**H**) (δ 87.7[23]). Ring opening [to (**8**) or (**9**)] is attended by a distinct upfield displacement (to δ 82), *i.e.* of the same order as that observed (δ 8–12) on exchanging the acyloxy for a free hydroxy group at the quaternary 1-bridgehead carbon in diisophorone.[1,17,25,26] The assignment of the C-6 singlet is in accord with its susceptibility to changes in the adjacent 5-oxo-function [in (**4**) or (**5**)], and by its replacement by a doublet upon decarboxylation [in (**7**), (**10**), or (**12**)]. Two of the three high-field singlets are too closely spaced (at δ *ca.* 40) to be distinguished with certainty and are marked in Table 2 accordingly; the moderate deshielding of C-4′ (to δ 45) upon ring-opening is noteworthy.

Methine groups. Unequivocal assignments are available for the sole doublet for structures incorporating only one tertiary carbon atom [*e.g.* (**4**) or (**5**)], thus providing the means of identifying the two doublets of (**10**) and (**12**).

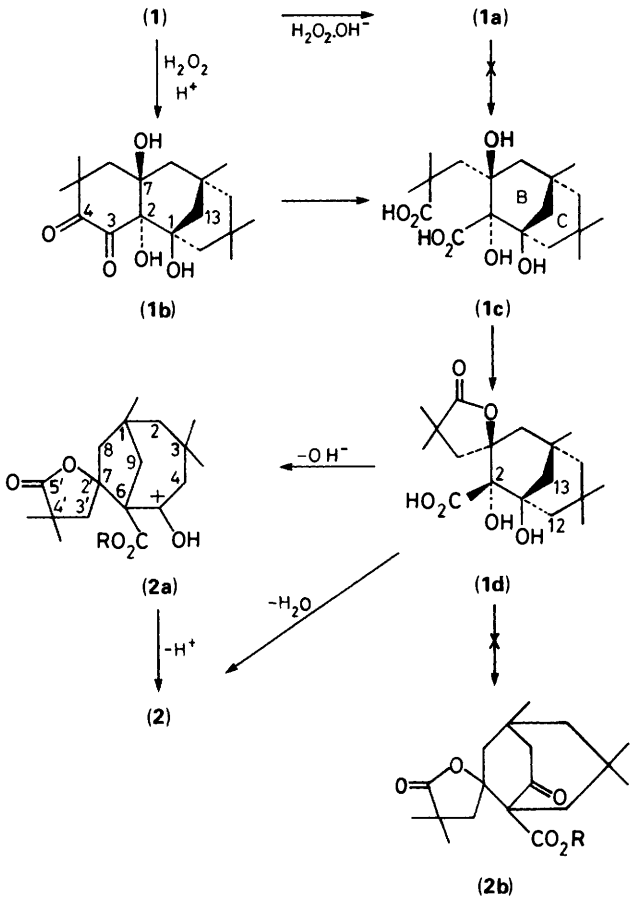
Methylene groups. The triplets form a very closely spaced group of three signals near δ 55, and another of two signals near δ 42. The latter are collectively attributable, according to the carbon connectivities in (**2**) and (**7**), to C-3′ and C-9. The signal appearing constantly at δ 43.2 is allotted to C-3′, the position more remote than C-9 from structural changes at the bicyclo-[4.2.1]nonane skeleton (at C-4,5,6 of rings B/C). On ring opening [to (**8**) or (**9**)], this C-3′ methylene moiety becomes part of an aliphatic side chain, its shielding now matching that of the comparable C-3 carbon in 2,2-dimethylbutanoic acid (CH_3CH_2-CMe_2CO_2H, δ 33.7[27]). The susceptibility of the 9-methylene carbon to changes at the adjacent bridgehead is illustrated by its moderate shielding when decarboxylation occurs at C-6 [in (**7**) and (**10**)].

At lower field, the 4-methylene triplet is characterised by its distinct upfield displacement (by *ca.* 7 ppm) on reduction of the adjacent 5-oxo group, as has also been established for cyclohexanone[28] and cycloheptanone.[29] In agreement with their invariant structural environment in all the compounds, the 2- and 8-methylene carbons produce signals of fairly constant chemical shifts, which are, however, too closely spaced to be reliably distinguished from one another. The signal at slightly higher field is in each case attributed to C-8, as is established in the case of (**2**) and (**7**) by the carbon connectivities.

Methyl groups. The definitive assignments of the five quartets to the individual exocyclic methyl groups, provided by the INADEQUATE technique in respect of (**2**) and (**7**), are readily extended by analogy to the other members of the ring system. The remarkable constancy of the chemical shift of the 10-methyl carbon is ascribed to the relative remoteness of this grouping from structural variations elsewhere in the molecule. The resonances of the 3- and 4′-*gem*-dimethyl carbons resemble numerically those of analogously located methyl groups in a wide range of tricyclo[7.3.1.$0^{2,7}$]tridecanes (**A**, **B**)[17,18] and tricyclo[6.3.1.$0^{2,6}$]dodecanes (**D**).[8] Within each pair of quartets (C-6′,7′ and C-11,12), the signal at lower field is allotted to the equatorial methyl carbon, a distribution that has been established for model cyclohexanes.[17,30].

Mechanism.—The conversion of the epoxydiketone (**1**) into the spirane structure (**2**), clearly a complex multi-stage process, may be accounted for by the reaction sequence outlined in Scheme 2. In the initial phase, the key intermediate (**1c**) arises from (**1**) by the scission of the epoxide ring, and Baeyer–Villiger oxidative cleavage[9] of the 3,4-dioxo-grouping [in (**1b**)]. The conversion of (**1c**) into products of the required molecular formula $C_{18}H_{26}O_5$ by loss of two molecules of water could occur directly in several ways, resulting in at least eight possible alternative structures (not shown), none of which is entirely compatible with all the properties of the products (**2**)–(**7**) and (**10**)–(**12**). The actual course of the reaction involves a 1,2-rearrangement, being explicable in terms of (*a*) the direct formation of the γ-lactone ring from the two *gem*-7-substituents [of (**1c**)] by dehydrative cyclisation and (*b*) a pinacol rearrangement at the substituted 1,2-diol moiety [of (**1c**) or (**1d**)], in which the 13-methylene group migrates to the 2-position, and the possible involvement of a carbonium ion of type (**2a**) in the ultimate step.[31,32] The possible alternative pinacol rearrangement, in which the 12-methylene functions as the migrating group, would give rise to bicyclo[3.2.2]nonane structures [*e.g.* (**2b**)]; this is clearly excluded by the evidence of the two-dimensional ^{13}C NMR measurements.

The foregoing interpretation is compatible with the stereochemical characteristics of the reactions. The cyclohexane rings



Scheme 2.

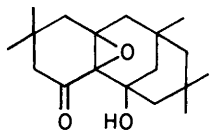
(A/B) of the decalin moiety assume, in the unstrained parent tricyclo[7.3.1.$0^{2,7}$]tridecane framework (**B**), the *trans*-chair conformation, as is confirmed by the results of X-ray analysis.[33] In the starting material (**1**) of the present reaction, rings A and B are flattened into approximate half-chair conformations by the 2,7-epoxide ring (situated above their common plane, *i.e.* opposite ring C). Rupture of this ring at its alternative C–O bonds will produce the two 2,7-diols of opposite configuration, by the well established[34] preferred diaxial *trans*-addition process. The overall course of the reaction indicates that the 2α,7β-diaxial diol (**1b**), with its ring B in the boat conformation, is the favoured stereoisomer, from which the key intermediate (**1c**) arises by scission of the 3,4-dioxo group. In the subsequent pinacol rearrangement at the 1,2α-diol moiety, it is the 13-methylene group in the *trans*-configuration to the leaving 2α-*ax*-hydroxy, rather than the 12-methylene (in *cis*-orientation) that participates, in accord with established steric principles,[31,35] in the migration step of the rearrangement, resulting in the observed formation of the bicyclo[4.2.1] (**2**) rather than the isomeric bicyclo[3.2.2]nonane (**2b**) ring system. This argument is not invalidated if ring B of (**1c**) reverted to the chair form after ring A fission, (**1b**)→(**1c**), as is indeed likely: the 2- and 7-hydroxy groups, though now in equatorial conformation, still preserve their spatial positions relative to the plane of ring B.

The configuration of the 7β-hydroxy group in (**1c**) determines also the orientation of ring A in the final product (**2**), with its hetero-1′-oxygen *above* the plane of ring B. In the newly formed structural framework (**E**), the cycloheptane ring C is flexible, as is also to a limited degree the five-membered γ-lactone ring A. It is therefore as yet not possible to specify the position (α or β) relative to the plane of these rings, of the axial and equatorial

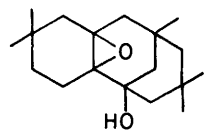
components of the 3- and 4′-*gem*-dimethyl groups, since these are reversed upon conformational inversion of the rings. The individual compounds no doubt assume the overall conformation least subject to steric hindrance.

Attempts to isolate intermediates of this proposed sequence were not successful, but experimental support for the postulated opening phase was provided by the observed changes in the IR spectrum of the reacting system. Thus, the initial cleavage of the 2,7-epoxy ring [of (**1**)] is indicated within the first 30–60 seconds, by the broadening of the hydroxy absorption (at 3 530 cm^{-1}), with transient splitting into a triple peak (consistent with the generation of additional hydroxy groups), and the simultaneous disappearance of the sharp peaks centred at 875 cm^{-1} associated with the epoxide function. The distinct yellow colour of the 3,4-diketone (**1**), persisting during these changes, next fades, while the intense single dioxo band (at 1 720 $^{-1}$) widens and divides as the ring is cleaved; the overall process is completed within 3–5 min.

A possible oxidative cleavage of the 3,4-oxo grouping as the first step, (**1**)→(**1a**), is excluded, because the resulting bicyclo[3.3.1]nonanedicarboxylic acid (**1a**), separately obtainable by the *alkaline* peroxide oxidation of (**1**),[10] was unaffected under the acidic oxidising conditions and is therefore unlikely to function as an intermediate in the present reaction. A requirement for the initial scission of the epoxide ring, (**1**)→(**1b**), appears to be the presence of the adjacent 3,4-dioxo moiety, since no comparable reaction occurs with 2,7-epoxydiisophoran-1-ol-3-one (**J**) or its 3-deoxo-analogue (**K**); indeed, the



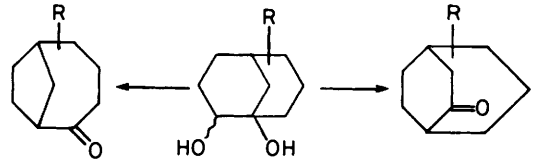
(J)



(K)

latter is synthesised[36] from diisophor-2(7)-en-1-ol precisely under the conditions of the present oxidative rearrangement. The reaction is of course also inhibited when the 1-hydroxy-group of the starting material (**1**) is blocked, *e.g.* by acetylation.

Conclusion.—The outstanding properties of the tricyclic ring system (**B**) of diisophorones (**A**) are its ready formation from monocyclic precursors, and its high stability even under severe conditions.[2] The carbon skeleton maintains its structural and conformational integrity in almost all its numerous known reactions, but does become susceptible to rearrangement upon introduction of specific substituents in appropriate positions.[7,8] The present rearrangement, (**1**)→(**2**), is again clearly the result of the uniquely favourable distribution of suitable structural features within the reactant, and provides the first synthetic approach to the novel bicyclo[4.2.1]-nonane-7-spiro-2′-(tetrahydrofuran) ring system. Although the synthesis is confined, by its specific nature, to a single example, the resulting oxocarboxylic acid (**2**) is a versatile source of a wider range of members of this new ring system. The prospect of applying analogous pinacol rearrangements



(M) (L) (N)

to bicyclo[3.3.1]nonane-1,2-diols (**L**), providing comparable synthetic routes to bicyclo[4.2.1]nonanes (**M**) and bicyclo-[3.2.2]nonanes (**N**),[37] adds general interest to the present observations.

Experimental

General.—Light petroleum had b.p. 60–80 °C unless otherwise specified. Pyridine was the commercial anhydrous grade. M.p.s are uncorrected.

Molecular weights were determined mass spectrometrically using an AEI MS 902 instrument at 70 eV. IR spectra were recorded on a Unicam SP 1000 instrument, using KBr discs. Unassigned peaks of IR spectra are not listed, except for the prototypes (**2**), (**7**), (**8**), and (**10**). Carbon-13 NMR spectra were determined on a Bruker WM 250 Fourier transform instrument operating at 62.89 MHz, with tetramethylsilane as the internal standard.

1,3,3,4′,4′-*Pentamethyl*-5,5′-*dioxobicyclo*[4.2.1]*nonane*-7-*spiro*-2′-(*tetrahydrofuran*)-6-*carboxylic acid* (**2**).—2,7-Epoxy-1-hydroxydiisophorane-3,4-dione (**1**)[10] (1.53 g, 5 mmol) was dissolved in glacial acetic acid (12 ml) with warming; the yellow solution was slowly treated with 30% hydrogen peroxide (9.05 ml, 80 mmol) and heated on a steam bath. When the yellow colour was discharged (*ca.* 5 min), more peroxide (2.25 ml, 2 mmol) was added and heating at 100 °C continued for 30 min. The cooled liquid was stirred into water (300 ml) and acidified (to pH 1–2) with 3M hydrochloric acid. The turbid liquid deposited, on storage for 1 day at room temperature and finally at 0 °C, a white solid (yield 65–70%), which gave on crystallisation from benzene (15 ml per g, recovery 80%), prismatic needles of the *acid* (**2**), m.p. 159–160 °C (decomp) (Found: C, 67.4; H, 8.1; *M*, 322. $C_{18}H_{26}O_5$ requires C, 67.0; H, 8.1%; *M*, 322); ν_{max} 3 390–3 380s (d), 2 600–2 400w (m), 930s (CO_2H), 2 970s, 2 870m (sh), 1 470ms, 1 460m (CH_3,CH_2), 1 390m, 1 370m, 1 360m (CMe_2), 1 760vs (CO of γ-lactone), 1 685ms (sh), 1 675s (CO), 1 270s, 1 240s, 1 220s (sh) (C–O), 1 330m, 1 110s, 1 090s, 980s, 755s, and 700ms cm^{-1}. To observe the initial changes in the IR spectrum of the reacting species (see Mechanism section), samples of the liquid were withdrawn at 30 s, later at 1 min intervals, and the solid was isolated by precipitation as above, washed, and rapidly vacuum-dried.

The use of 99% formic or 99% propionic acid as the reaction medium gave the same product (**2**) in 60 or 70% yield, respectively. In contrast, a solution of (**1**) (0.31 g, 1 mmol) in glacial acetic acid (15 ml), treated with ammonium persulphate (1.15 g, 5 mmol) in water (10 ml) and kept at 100 °C was not decolourised (20 min), the reactant being substantially recovered.

The keto acid (**2**) is soluble in 3M sodium hydroxide and reprecipitated by acetic or hydrochloric acid. It is readily soluble in acetone and ethanol, but nearly insoluble in light petroleum. It did not undergo catalytic hydrogenation in glacial acetic acid in the presence of finely divided platinum,[38] and was recovered (60%) on attempted acetylation by acetic anhydride-perchloric acid in glacial acetic acid.[2]

The following compounds failed to react under the foregoing oxidation conditions. (i) Diisophorone (**A**) and (ii) its 2,7-epoxide were recovered (*ca.* 75% after 1 h). (iii) The yellow colour of a solution of 1-acetoxy-2,7-epoxydiisophorane-3,4-dione[10] was discharged very slowly (fading after 20 min, colourless after 35 min), but no solid product was isolable. (iv) 3-(2-Carboxy-2,2-dimethylethyl)-2,3-epoxy-1-hydroxy-5,7,7-trimethylbicyclo[3.3.1]nonane-2-carboxylic acid (**1a**)[10] was recovered (55%) after its hot solution in glacial acetic acid had been treated with 30% hydrogen peroxide (15 mol equiv.) and kept at 100 °C for 15 min.

6-*Methoxycarbonyl Analogue* (**3**) (*Methyl Ester*) *of* (**2**).—To a stirred ethereal solution of diazomethane (prepared[39] from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide, 'Diazald,' (2.15 g, 10 mmol) was added dropwise at 0 °C a solution of (**2**) (0.64 g, 2 mmol) in dry ether (40 ml); initially the yellow colour was discharged and nitrogen evolved. After storage at room temperature (1 h), the excess of the reagent was destroyed by the addition of 3M acetic acid, and the ethereal layer washed until neutral and evaporated *in vacuo*.[10] The residual colourless oil solidified in contact with light petroleum and gave prisms of the *ester* (**3**), m.p. 134–137 °C (75%, from ethanol) (Found: C, 67.35; H, 8.3; *M*, 336. $C_{19}H_{28}O_5$ requires C, 67.9; H, 8.3%; *M*, 336); ν_{max} 2 980s, 2 915m (sh), 1 465m (d), 1 440m (CH_3,CH_2), 1 390m, 1 370m (CMe_2), 1 770vs (CO of γ-lactone), 1 740vs (CO of CO_2Me), 1 685s (CO ring), and 1 225s (C–O) cm^{-1}. Unlike its parent acid (**2**), (**3**) was unaffected on being boiled in toluene solution (4 h) (see below). It was recovered (70%) after its solution in ethanol (0.2 g in 6 ml)—concentrated hydrochloric acid (2 ml) was refluxed for 4 h.

1,3,3,4′,4′-*Pentamethylbicyclo*[4.2.1]*nonane*-7-*spiro*-2′-(*tetrahydrofuran*)-5,5′-*dione* (**7**).—A solution of (**2**) (0.64 g, 2 mmol) in (sodium-dried) toluene (12 ml) was boiled under reflux for 4 h. The liquid was evaporated under reduced pressure and the residual oil treated with light petroleum (5–10 ml), when it solidified (yield 65–72%). Crystallisation from the same solvent gave small prisms of the *spiro compound* (**7**), m.p. 95–97 °C (Found: C, 73.0; H, 9.2; *M*, 278. $C_{17}H_{26}O_3$ requires C, 73.4; H, 9.3%, *M*, 278); ν_{max} 2 960s, 2 890m, 1 465m, 1 455m (CH_3,CH_2), 1 390m, 1 365m (CMe_2), 1 760vs (CO of γ-lactone), 1 685s (CO ring), 1 235s (C–O), 1 295m, 1 210m, 1 130m, 1 090m, 970m, and 925s cm^{-1}. The keto-lactone (**7**) was recovered (64%) after treatment with zinc dust in boiling acetic acid for 3 h, and after attempted acetylation by acetic anhydride–perchloric acid in glacial acetic acid.

Derivatives of the Keto-lactone (**7**).—The 2,4-*dinitrophenylhydrazone*, obtained from equimolar amounts of (**7**) and 2,4-dinitrophenylhydrazine (1 mmol) in ethanol (20 ml)–concentrated hydrochloric acid (5 ml) (boiling for 3 h), formed deep yellow needles (70%), m.p. 198–201 °C (from ethanol) (Found: C, 60.6; H, 6.6; N, 12.0. $C_{23}H_{30}N_4O_6$ requires C, 60.3; H, 6.55; N, 12.2%).

Oxime. A solution of (**7**) (1.11 g, 4 mmol) and hydroxylamine hydrochloride (0.56 g, 8 mmol) in ethanol (15 ml)–pyridine (3 ml) was boiled under reflux for 4 h. Addition to ice–water containing concentrated hydrochloric acid (3 ml) gave a soft precipitate solidifying to a powder (yield 75–85%) which afforded needles of the oxime, m.p. 165–168 °C (decomp., shrinking from 145 °C) (from ethanol–water, 3:2) (Found: C, 69.6; H, 9.1; N, 4.9; *M*, 293. $C_{17}H_{27}NO_3$ requires C, 69.6; H, 9.2; N, 4.8%; *M*, 293); ν_{max} 3 285m (br), 3 110w (OH, oxime), 2 965vs, 2 885ms (sh), 1 470m, 1 460m (CH_3,CH_2), 1 390m, 1 365m (CMe_2), 1 765vs (CO of γ-lactone), 1 225ms (C–O), and 970s (N–O, oxime) cm^{-1}. Crystallisation of the crude material from benzene–light petroleum (1:3) gave microprisms, m.p. 148–152 °C (sintering from 142 °C), with an almost identical IR spectrum. The two products may be the *syn*- and *anti*-forms of the oxime.

5-*Hydroxy*-1,3,3,4′,4′-*pentamethyl*-5′-*oxobicyclo*[4.2.1]-*nonane*-7-*spiro*-2′-(*tetrahydrofuran*) (**10**).—A solution of (**7**) (0.56 g, 2 mmol) in glacial acetic acid (8 ml) was hydrogenated over Adams' catalyst[38] (0.15 g) (uptake 85 cm^3 in 45 min; calc: 28 + 45 cm^3 at NTP), and the product isolated by dilution of the filtered solution with water (120 ml). Crystallisation from a large volume of light petroleum gave platelets (70–80%) of (**10**), m.p. 160–162 °C (Found: C, 72.7; H, 9.8; *M*, 280. $C_{17}H_{28}O_3$ requires C, 72.9; H, 10.0%; *M*, 280); ν_{max} 3 525s (OH), 2 950s, 2 890m (sh), 1 470m, 1 455m (CH_3,CH_2), 1 390m, 1 365m (CMe_2), 1 735vs (CO of γ-lactone), 1 240s (d) (C–O), 1 325ms, 1 145m, 1 110m, 1 050s, 925s, and 715m cm^{-1}. The product did not undergo further catalytic hydrogenation in glacial acetic acid in the presence of perchloric acid. It was recovered (60%) after its solution in ethanol (1 mmol in 10 ml), treated with 3M sodium hydroxide (5 ml), was boiled under reflux for 4 h.

Reoxidation to the 5,5′-*diketone* (**7**). A stirred solution of (**10**) (0.28 g, 1 mmol) in acetone (10 ml) was treated dropwise with Kiliani's 10% chromic acid (2 ml), kept at room temperature for 15 min, then treated with sulphur dioxide, and the green liquid added to water (100 ml). The resulting crystalline precipitate (75%) was (**7**), identified by mixed m..p. and IR spectroscopy.

5-*Acetoxy*-1,3,3,4′,4′-*pentamethylbicyclo*[4.2.1]*nonane*-7-*spiro*-2′-(*tetrahydrofuran*)-5′-*one* (**11**).—A solution of (**10**) (0.56 g, 2 mmol) in glacial acetic acid (10 ml) was treated with acetic anhydride (1.5 ml) and dropwise with 60% perchloric acid (0.3 ml), set aside at room temperature for 1 h, then added to water. The precipitate gave needles of the *acetoxy compound* (**11**), m.p. 136–137 °C (75%, from light petroleum) (Found: C, 70.9; H, 8.9. $C_{19}H_{30}O_4$ requires C, 70.8; H, 9.3%); ν_{max} 2 955s, 2 880m (sh), 1 470m (CH_3,CH_2), 1 390m, 1 360m (CMe_2), 1 765vs (CO of γ-lactone), 1 720vs (CO, Ac), and 1 250vs (C–O) cm^{-1}.

Bis{(1,3,3,4′,4′-*pentamethyl*-5′-*oxobicyclo*[4.2.1]*nonane*-7-*spiro*-2′-(*tetrahydrofuran*)-5-*yl*} Sulphite.—To a solution of (**10**) (0.28 g, 1 mmol) in pyridine (6 ml) at 0 °C, thionyl chloride (0.36 g, 3 mmol) was added dropwise with cooling. The brown liquid was set aside at 0 °C, then at room temperature (20 min each), and stirred into ice–hydrochloric acid. The precipitate gave white opaque prisms of the *sulphite ester* (46%), m.p. 166–169 °C (from ethanol) (Found: C, 67.8; H, 8.7; S, 5.2. $C_{34}H_{54}O_7S$ requires C, 67.3; H, 8.9; S, 5.3%); ν_{max} 2 975s, 2 885m (sh), 1 475–1 455m (mult) (CH_3,CH_2), 1 765vs (CO of γ-lactone), 1 390m, 1 370m (CMe_2), 1 230ms (C–O), and 1 140m (?S=O) cm^{-1}.

7-(2-*Carboxy*-2,2-*dimethylethyl*)-7-*hydroxy*-1,3,3-*trimethylbicyclo*[4.2.1]*nonan*-5-*one* (**8**).—(i) *From the ketocarboxylic acid* (**2**). A solution of (**2**) (0.64 g, 2 mmol) in ethanol (8 ml)–3M sodium hydroxide (5 ml) was boiled under reflux for 3 h. The yellow liquid was stirred into water (150 ml) and acidified with concentrated hydrochloric acid, when a solid separated slowly. Crystallisation from benzene (15 ml per g) gave needles (45–62%) of (**8**), m.p. 140–142 °C (shrinking from 130 °C) (Found: C, 69.1; H, 9.5; *M*, 296. $C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5%, *M*, 296); ν_{max} 3 450s (OH), 2 960s, 1 475m, 1 460s (CH_3,CH_2), 1 390s, 1 360s (sh) (CMe_2), 1 730vs (CO of CO_2H), 1 710s (CO), 3 160w (br), 1 345s, 1 230s, 1 200s, 1 165s, 1 070s, and 885–870m (mult) cm^{-1}.

(ii) *From the keto carboxylic ester* (**3**). Alkaline hydrolysis of the methyl ester (**3**) under the foregoing conditions gave the same product (**8**) (yield, 48%), identified by IR spectroscopy.

(iii) *From the keto lactone* (**7**) (*superior method*). The reactant (**7**) (2.78 g, 10 mmol) was dissolved in ethanol (18 ml)–3M sodium hydroxide (5 ml) with slight warming, and the pale yellow liquid set aside at room temperature for 12 h. It was then stirred into hot water (100 ml)–3M hydrochloric acid (12 ml): the resulting turbidity coagulated to a white solid [m.p. 142–145 °C; yield 75%, pure (**8**) by IR spectroscopy]. The use of boiling ethanolic alkali (3 h) gave inferior yields.

7-(2-*Methoxycarbonyl*-2,2-*dimethylethyl*)-7-*hydroxy*-1,3,3-*trimethylbicyclo*[4.2.1]*nonan*-5-*one* (**9**).—A solution of (**8**) (0.60 g, 2 mmol) in diethyl ether (20 ml) was treated at room temperature with ethereal diazomethane (from 24 mmol of Diazald[39]). After storage at room temperature (30 min), the

standard work-up [see (3), above] gave a residual oil, which was dissolved in light petroleum, affording needles (45%) of the *ester* (9), m.p. 85–87 °C (Found: C, 69.4; H, 9.0; *M*, 310. $C_{18}H_{30}O_4$ requires C, 69.7; H, 9.7%; *M*, 310); ν_{max} 3 500s (OH), 2 995s, 2 890m (sh), 1 480s, 1 475s, 1 460s, 1 445m (CH_3,CH_2), 1 400m, 1 380s (CMe_2), and 1 705vs (CO) cm^{-1}. The methyl ester (9) was reconverted into the parent acid (8) by alkaline hydrolysis (50% ethanolic 1.5M sodium hydroxide; reflux for 3 h; yield 52%).

5-Hydroxy-1,3,3,4′,4′-pentamethyl-5′-oxobicyclo[4.2.1]*nonane-7-spiro-2′-(tetrahydrofuran)-6-carboxylic acid* (4).—A solution of (2) (3.22 g, 10 mmol) in ethanol (50 ml) was treated at room temperature in portions with potassium borohydride (1.08 g, 20 mmol). The effervescing mixture was kept for 8 h at room temperature, then stirred into water and acidified with 3M hydrochloric acid. The slowly precipitated solid was collected after further storage (crude yield 72–80%) and crystallised from light petroleum–benzene–ethanol (6:3:1), affording the solvated *acid* (4) as needles or white opaque prisms, m.p. 240 °C (decomp. from 230 °C) (Found: C, 64.9; H, 8.8. $C_{18}H_{28}O_5 \cdot C_2H_5OH$ requires C, 64.9; H, 9.2%). Desolvation was effected by refluxing a suspension of the solvate in anhydrous toluene (3 mmol in 15 ml) for 3 h, and removing most of the solvent under reduced pressure. The solid gave, on crystallisation from dioxane–light petroleum, prisms (50–60%) of (4), m.p. 250–252 °C (decomp. from *ca.* 240 °C) (Found: C, 66.8; H, 8.7. $C_{18}H_{28}O_5$ requires C, 66.7; H, 8.6%); ν_{max} 3 495m (OH), 3 315–3 245m (br), 2 700–2 550m (mult) (CO_2H), 2 965s, 2 900s (sh), 2 865m (sh), 1 470m, 1 440w (CH_3,CH_2), 1 390m, 1 370m (CMe_2), 1 765s (CO of γ-lactone), 1 730vs (CO of CO_2H), and 1 230ms (C–O) cm^{-1}.

Reactions of the Hydroxy-carboxylic Acid (4).—*Stability to alkali.* Compound (4) was recovered (75%) after its solution (1 mmol) in ethanol (10 ml)–1.5M sodium hydroxide (4 ml) had been refluxed for 4 h.

Reoxidation to (2). A stirred solution of (4) (solvate, 0.37 g, 1 mmol) in acetone (10 ml) was treated dropwise with Kiliani's 10% chromic acid (2 ml, 1.7 mmol), the liquid turning olive green immediately. After storage for 2 h at room temperature, the mixture was added to water (60 ml), when crystalline (2) appeared slowly (yield, 75–85%), identified by IR spectroscopy.

Acetyl derivative (6). A solution of (4) (0.37 g, 1 mmol) in glacial acetic acid (8 ml) was treated with acetic anhydride (1 ml) and 60% perchloric acid (10 drops), set aside at room temperature for 2 h, then stirred into water. The precipitated resin solidified and gave prisms (65%) of (6), m.p. 227–230 °C (from ethanol–light petroleum) (Found: C, 65.8; H, 8.4. $C_{20}H_{30}O_6$ requires C, 65.6; H, 8.2%); ν_{max} 3 190–3 085m, 2 710–2 440w (CO_2H), 2 970s, 2 870m, 1 465m (CH_3,CH_2), 1 395m, 1 380m (CMe_2), 1 740vs (CO of γ-lactone), 1 720s, 1 710s (sh) (CO), and 1 230 (C–O) cm^{-1}.

Methyl 5-Hydroxy-1,3,3,4′,4′-pentamethyl-5′-oxobicyclo[4.2.1]*nonane-7-spiro-2′-(tetrahydrofuran)-6-carboxylate* (5).—(i) A solution of (4) (0.37 g, 1 mmol) in diethyl ether (15 ml) was treated with ethereal diazomethane (prepared from 12 mmol of Diazald[39]) and set aside at room temperature (1 h). The standard work-up gave prismatic needles (70–80%) of the *ester* (5), m.p. 210–212 °C (from ethanol) (Found: C, 67.4; H, 9.0; *M*, 338. $C_{19}H_{30}O_5$ requires C, 67.45; H, 8.9%; *M*, 338); ν_{max} 3 505s (OH), 2 960s, 2 870m, 1 470m, 1 460–1 440m (mult) (CH_3,CH_2), 1 390m, 1 365m (CMe_2), 1 740s (CO of γ-lactone), 1 725vs (CO of CO_2Me), and 1 240s (C–O) cm^{-1}.

(ii) A solution of the methyl ester (3) (0.34 g, 1 mmol) in ethanol (15 ml)–methanol (1 ml) was treated with potassium borohydride (0.16 g, 3 mmol), set aside for 8 h, then added to water (80 ml) and acidified with 3M hydrochloric acid. The crystalline precipitate was (5), identified by IR spectroscopy and mixed m.p. (yield, 70%).

Reactions of the Hydroxy Methyl Ester (5).—*Hydrolysis.* A solution of (5) (0.34 g, 1 mmol) in ethanol (10 ml)–3M sodium hydroxide (2 ml) was boiled under reflux for 3 h, then diluted with water and acidified with 3M hydrochloric acid. The resulting precipitate was (4), identified by IR spectroscopy (yield 60%).

Oxidation. A stirred solution of (5) (0.34 g, 1 mmol) in acetone (15 ml) was treated with Kiliani's 10% chromic acid (1.75 ml, 1.5 mmol). Addition of the olive green mixture to water (80 ml) gave a turbid liquid gradually depositing crystalline (3), identified by IR spectroscopy and mixed m.p., 135–136 °C (from ethanol) (yield, 85%).

4-Bromo-1,3,3,4′,4′-pentamethylbicyclo[4.2.1]*nonane-7-spiro-2′-(tetrahydrofuran)-5,5′-dione* (12).—A stirred solution of (7) (1.39 g, 5 mmol) in glacial acetic acid (25 ml)–60% hydrobromic acid (0.3 ml) at *ca.* 60 °C was treated with 2M bromine in glacial acetic acid (2.75 ml, 5.5 mmol), which was rapidly decolourised. The lemon yellow solution was set aside at room temperature for 12 h, then stirred into 0.25M hydrochloric acid (180 ml). The white precipitate separating slowly gave, on crystallisation from light petroleum, needles (65–72%) of the *dione* (12), m.p. 128–130 °C (Found: C, 57.4; H, 7.3; Br, 21.8; *M*, 356, 358, equal intensity. $C_{17}H_{25}BrO_3$ requires C, 57.2; H, 7.0; Br, 22.5%; *M*, 357); ν_{max} 2 985s, 2 920m (sh), 1 470s, 1 460m (CH_3,CH_2), 1 765vs (CO of γ-lactone), 1 680s (CO, ring), 1 390m, 1 370m (CMe_2), and 1 240s (C–O) cm^{-1}. The use of 3 mol equiv. of bromine, and reaction times of 48 h (room temperature) gave the same product in diminished yield (26%). The 7-acetoxy-lactone (11) did not undergo bromination under the foregoing conditions: it failed to decolourise 1 mol equiv. of bromine, even on brief heating to 100 °C, and was substantially recovered (70%).

Reactions of the α-Bromo Diketone (12).—*Reduction to* (7). (i) A solution of (12) (0.36 g, 1 mmol) in glacial acetic acid (12 ml) was hydrogenated at room temperature over Adams' catalyst,[38] hydrogen uptake being complete after 20 min. The usual work-up gave (7) (yield 64%), identified by IR spectroscopy and mixed m.p. (ii) A boiling solution of (12) (1 mmol) in glacial acetic acid (8 ml) was treated with zinc dust (2 × 0.4 g, at 20 min interval). After boiling for 45 min, the clear supernatant liquid gave, on dilution and the usual work-up, the keto lactone (7), identified as above (yield 68%).

Reduction to (10). To a solution of (12) (1 mmol) in ethanol (20 ml), sodium borohydride (0.15 g, 4 mmol) was added and the effervescing reaction mixture kept at room temperature for 2 h. The liquid was stirred into 0.25 M sodium hydroxide (100 ml); the resulting turbidity changed, on storage and stirring, to a precipitate of (10), identified by IR spectroscopy and mixed m.p., 160–162 °C (from light petroleum) (yield 65%).

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