Intramolecular Reactions Involving Positions C(2), C(6) and (C2), C(7) in the Bicyclo[3.3.1]nonane Ring System

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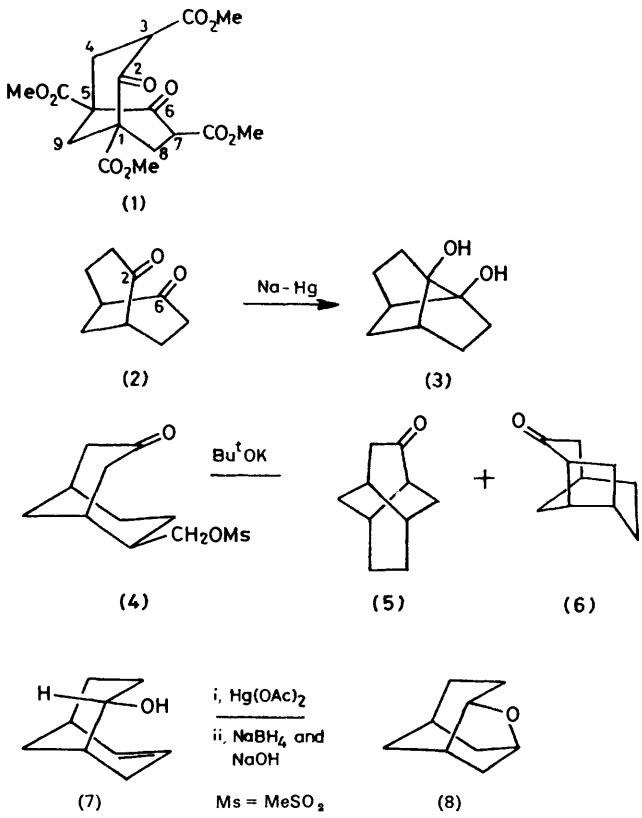
Reactions likely to involve C(2)–C(6) and C(2)–C(7) intramolecular reactions in bicyclo[3.3.1]nonane derivatives are discussed in terms of the conformations available to the ring system. While *endo*-6-hydroxybicyclo[3.3.1]-nonan-2-one (11) incorporated three deuterium atoms (excluding the hydroxy-group) on heating with NaOD, the *exo*-isomer (17) exchanged the six hydrogens adjacent to the oxygenation functions but not the carbinyl proton. Evidence is presented favouring a stereospecific base-induced 2,6-hydride migration, most probably proceeding *via* a twin-twist boat transition state. Treatment of 6,6-ethylenedioxy-2-methoxymethylenebicyclo-[3.3.1]nonane (36) with aqueous HCl in acetone produced 2-hydroxyprotoadamantan-10-one (38) in high yield. This process resulted from hydrolysis of the oxygenated groups thereby liberating the *endo*-keto-aldehyde intermediate (37) which underwent subsequent intramolecular aldol condensation between the C(2) aldehyde and C(7).

In their two pioneering papers on bicyclo[3.3.1]nonane chemistry, Meerwein *et al.*[1,2] prepared the tetraester (1) and were able directly to link C(3) and C(7) to synthesise the first derivative of tricyclo[3.3.1.$0^{3,7}$]nonane (noradamantane). They furthermore attempted to insert a tenth carbon between these sites to obtain a derivative of tricyclo[3.3.1.$1^{3,7}$]decane (adamantane), a process later achieved successfully by Böttger[3] and adapted to the synthesis of the parent hydrocarbon by Prelog and Seiwerth.[4] Subsequently reactions of these types have become widely used to synthesise a variety of noradamantane and adamantane structures. Meerwein was also able to hydrolyse (1) to the diketone (2) and cyclise between C(2) and C(6) to produce (3), the first example of the tricyclo[4.3.0.$0^{3,7}$]nonane (brexane) ring system.[2,5]

Bicyclo[3.3.1]nonane and many of its derivatives are now known to adopt a twin-chair conformation (in either the solid,[6] solution,[7] or gas[8] phases) flattened to overcome non-bonding repulsions between the *endo*-3 and *endo*-7 hydrogen atoms. This proximity of C(3) and C(7) also allows transannular hydride shifts to occur between these sites.[9]

Alternative conformations potentially available to the skeleton are the chair-boat, twin-boat, and twin-twist boat.[7,10] Introduction of an *endo*-C(3) substituent generally forces that ring into a boat conformation.[11] Relief of some of the hydrogen interactions in the twin-boat would produce the twin-twist boat where C(2) and C(6) are much closer together, and Meerwein's cyclisation of (2) to (3) indicates that a conformation of this type is accessible to the skeleton under appropriate conditions. More recently this conformation has been invoked to rationalise the formation of bicyclo[3.3.1]non-1-ene from the mesylate (methanesulphonate) of *endo*-2-hydroxybicyclo[3.3.1]nonane-1-carboxylic acid,[12] and also to explain the formation of *exo*-2,*endo*-6-dihydroxybicyclo-[3.3.1]nonane on borohydride reduction of the diketone (2).[13]

Hamon and Young[14] have recently reported a further



important closure involving C(2) and C(6) resulting in the first synthesis of a tricyclo[4.4.0.$0^{3,8}$]decane (twistane) derivative from the bicyclo[3.3.1]nonane skeleton whereby the keto-mesylate (4) was cyclised to twistan-4-

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one (5) and the isomer (6). An examination of molecular models suggests that the ideal conformation for the former closure is related to the twin-twist boat, with one ring flattened because of the enolate group. This closure predominated over the alternative C(2) and C(8) process resulting in formation of (6).

Equilibration studies on two 3-substituted bicyclo-[3.3.1]nonanes gave ΔG^0 values of 2.7 and 2.5 kcal mol^{-1} * for the twin-chair to chair-boat conversion,[15] while force-field calculations by Schleyer for the parent hydrocarbon gave enthalpy values of 2.5 kcal mol^{-1} for this process and a value of 5.7 kcal mol^{-1} for the chair-boat to twin-boat conversion. Use of the Allinger force field gives slightly lower values in each case.[16] The latest calculations on this ring system indicate that the twin-twist boat is a lower energy conformation than the classical twin-boat.[17]

Treatment of the *endo*-alcohol (7) with mercury(II) acetate in aqueous tetrahydrofuran (THF) (followed by demercuriation) resulted [18] in formation of 2-oxatricyclo[4.3.1.$0^{3,8}$]decane (2-oxaprotoadamantane) (8). This C(2)—C(7) closure can be achieved most easily with the alcohol group in a boat conformation whereas the non-observed C(2)—C(6) closure would require the higher energy twin-twist boat conformation. It is also noteworthy that this closure took precedence over hydration of the double bond. For example, similar treatment of α-terpineol in aqueous THF gives terpin hydrate whereas in anhydrous THF cyclisation to 1,8-cineole is favoured.[19]

The implication that C(2)—C(7) intramolecular closures are especially favourable is furthermore supported by three such preparations of protoadamantan-4-one [20] and by the wide range of 2,7-diheteroprotoadamantanes synthesised by Ganter [21] using this type of closure.

DISCUSSION

The available data on the potential conformations of the bicyclo[3.3.1]nonane ring system and their relative energies confirm that intramolecular processes between C(3) and C(7) will be commonplace but that in appropriate circumstances other processes will occur. We discuss here our investigation into carrying out intramolecular reactions between C(2)—C(6) and C(2)—C(7) using 2,6-disubstituted bicyclo[3.3.1]nonanes synthesised from the diketone (2).

Transannular Hydride Migrations.—Schaefer and Lark [22] have demonstrated that bicyclo[3.3.1]nonan-2-one incorporates up to 3 atoms of deuterium per molecule [at C(1) and C(3)] when heated with D_2O–NaOD, while Marvell *et al.* conclude that the rates of exchange at these two sites are comparable (under basic conditions) from their study of the 3,3-dimethyl derivative.[23] The *endo*-ketol (11) and *exo*-ketol (17) would both be expected to show a similar uptake of three deuterium atoms under similar conditions.

The synthesis of the two ketols from the diketone (2) is summarised in Scheme 1. The stereochemistry of the various *exo*- and *endo*-bicyclo[3.3.1]nonan-2-yl derivatives was supported in each case by the half-peak width of the 2-methine ^1H n.m.r. signal, characteristic values being 15—22 Hz for *endo*-substituted compounds and 6—7 Hz for the *exo*-epimers. A detailed explanation of these values and their interpretation is presented in the Experimental section.

Preparation of the *endo*-ketol (11) was straightforward but synthesis of the epimer (17) proved more difficult. Treatment of *endo*-2-tosyloxybicyclo[3.3.1]nonane with 90% aqueous dimethylformamide (68 h; 78 °C) followed by lithium aluminium hydride treatment of the resulting mixture of olefin and formate results in an acceptable yield of the *exo*-alcohol.[24] Compound (13) proved to be remarkably resistant to this inversion process, but complete conversion into a mixture of the olefin (14) and *exo*-alcohol (16) was achieved by extension of the reaction time and adding 1.1 molar equivalent of sodium acetate to the first step of the process.

As an alternative approach, the olefin (14) was prepared using sodium ethoxide and a check made that no rearrangement had taken place during the elimination by hydrolysis to the keto-olefin. The spectral properties of this material were in accord with those reported [23] for (20) rather than for bicyclo[3.3.1]non-7-en-2-one, and hydrogenation gave bicyclo[3.3.1]nonan-2-one identical with a genuine sample.

The olefin (14) was then elaborated into the *exo*-ketol (17) as illustrated in Scheme 1. This procedure was based on the report by Schaefer [25] that lithium aluminium hydride reduction of *exo*-2,3-epoxybicyclo[3.3.1]nonane gave the *exo*-2-alcohol in high yield. Similar treatment of the epoxide (15) followed by hydrolysis provided the required *exo*-ketol (17).

In passing, it should be mentioned that prolonged heating of the epoxide with lithium aluminium hydride under reflux caused partial reduction of the acetal group yielding the diol (21). This unexpected cleavage was also experienced when the hydroxy-acetal (10) was treated under similar forcing conditions.

Deuteriation of the ketols gave clear-cut incorporation in each case (see Table). While the *endo*-ketol (11)

% Deuterium content

Compound	$[^2H_0]$	$[^2H_1]$	$[^2H_2]$	$[^2H_3]$	$[^2H_4]$	$[^2H_5]$	$[^2H_6]$	$[^2H_7]$	$[^2H_8]$	^2H per mole
(12)	1.4	3.0	19.3	74.5	0.8	0.4	0.6			2.74
(18)	0.4	0.9	1.1	2.8	9.2	29.7	55.1	0.6	0.2	5.33
(19)	2.0	0.3	2.0	5.2	14.9	38.0	37.6			4.95
(2)	85.2	0.4	9.1	0.8	1.3	1.7	1.5			0.43

exchanged the three expected hydrogen atoms to produce (12), the *exo*-ketol (17) exchanged six hydrogen atoms giving (18). The work-up procedure ensured that –OD was exchanged to –OH before measurement by mass spectrometry.[26]

The position of the deuterium atoms in (18) was established by oxidation to the deuteriated diketone (19), causing only a slight loss of label, then exchanging (19) to re-obtain the starting diketone (2) which contained

* 1 cal = 4.184 J.

virtually no deuterium (see Table). Since the ketol (18) clearly showed a carbinyl ^1H n.m.r. signal (1 H, s, δ 3.96) the *endo*-hydrogen on C(6) had not undergone exchange, and therefore the three ' extra ' deuterium atoms must have been located on C(5) and C(7).

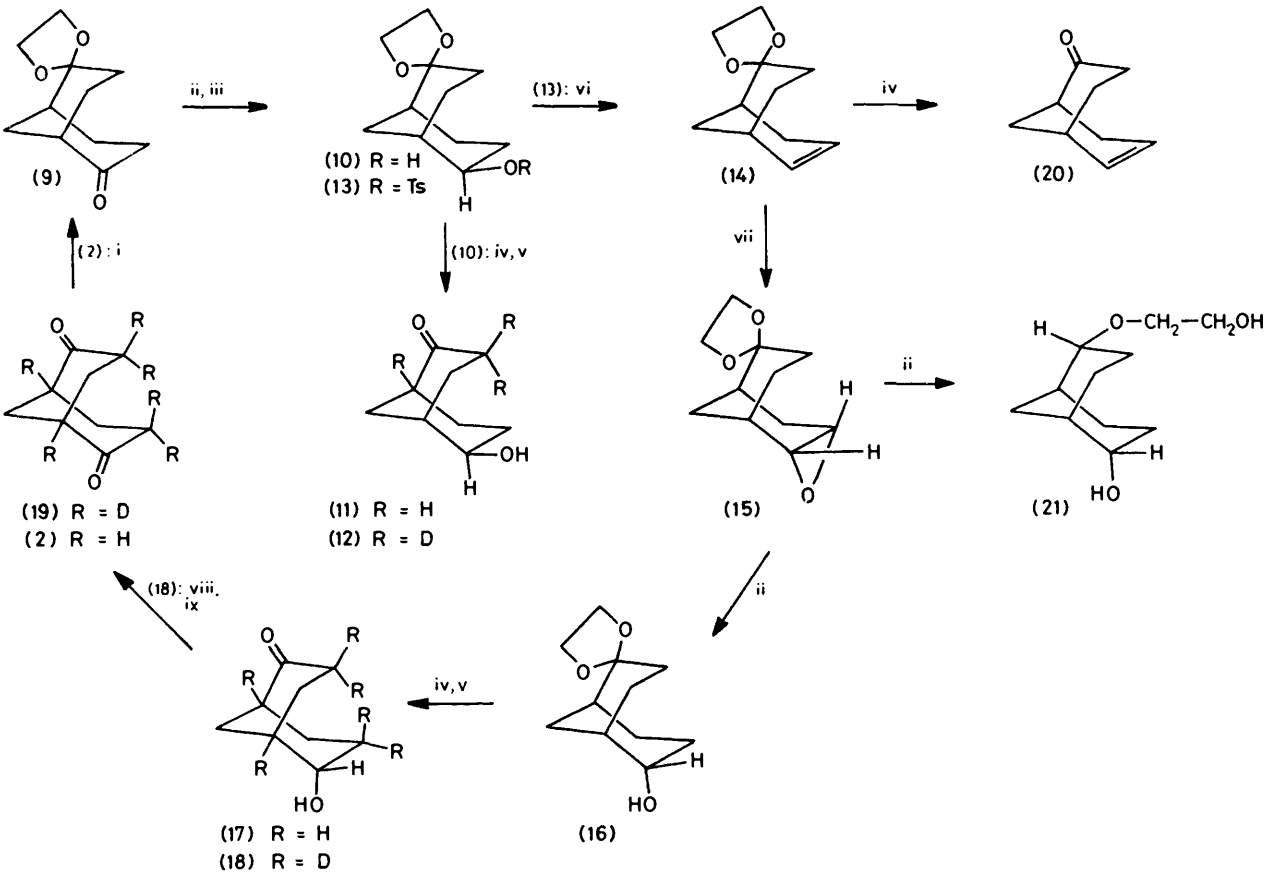
This surprising result indicates that a mechanistic pathway must be available to (17) which permits exchange of protons on C(1), C(3), C(5), and C(7) but not on C(6). Four potential processes (i)—(iv) allowing incorporation of greater than three deuterium atoms per molecule are discussed below.

(i) Homoenolisation between C(2) and C(6) would allow interconversion of the *exo*-alcohol and carbonyl groups and thus allow incorporation of seven deuterium atoms. The experimental conditions used are much less severe than those used to bring about homoenolisation in camphenilone,[27] and this process does not explain the lack of exchange of the carbinyl proton.

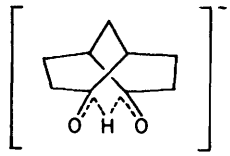
(ii) Homoenolisation between C(2) and C(7) would only allow incorporation of five deuterium atoms.

(iii) Disproportionation of the ketol to the diketone (2) and the diol can be discounted on the grounds that the ketol (17) was not epimerised to (11) under the conditions used and that neither ketol could be detected in a control experiment using an equimolar mixture of the diketone and diol.

(iv) A stereospecific base-induced intramolecular 2,6-hydride shift would allow interconversion of functionality at C(2) and C(6) and yet retain the carbinyl proton in the ketol (17). Together with the usual exchange adjacent to the carbonyl group, this process would allow incorporation of six deuterium atoms as experimentally observed. The most probable transition state for this process would be the twin-twist boat represented by structure (22).



SCHEME 1 Synthesis and deuteriation of *exo*- and *endo*-6-hydroxybicyclo[3.3.1]nonan-2-one. Reagents: i, $CH_2OH{\cdot}CH_2OH$, *p*-$MeC_6H_4SO_3H$; ii, $LiAlH_4$; iii, *p*-$MeC_6H_4SO_2Cl$, C_5H_5N; iv, *p*-$MeC_6H_4SO_3H$, Me_2CO; v, NaOD–D_2O–dioxan; vi, NaOEt; vii, *m*-chloroperbenzoic acid; viii, Jones reagent; ix, NaOH–H_2O–MeOH

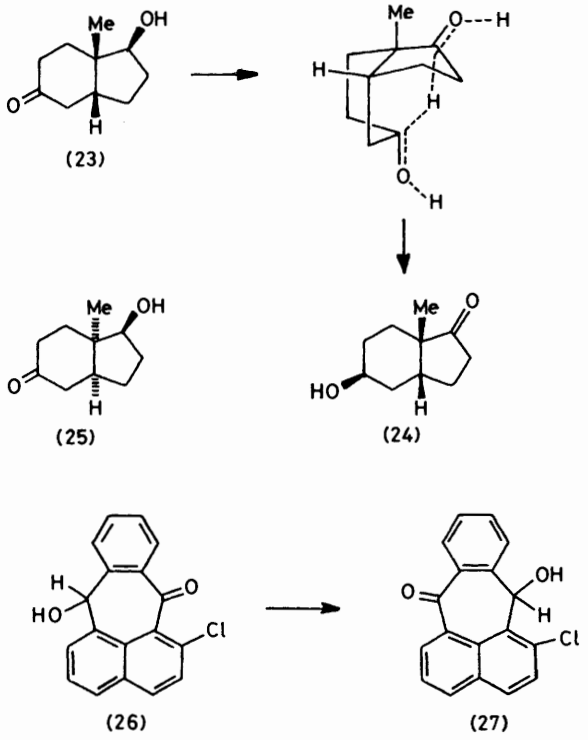


(22)

Two related reactions which add support to process (iv) are shown in Scheme 2. Acklin and Prelog [28] have reported that the hydroxyhydrindanone (23) was isomerised to (24) on Grade I neutral alumina. Since the diastereoisomer (25) was unaffected, it was proposed that the conversion had taken place by an intramolecular

1,5-hydride shift involving the transition state shown. Furthermore, Lansbury and Saeva [29] have reported on the kinetics of the conversion of (26) into (27) when treated with alkali metal butoxides. By use of n.m.r. spectroscopy, they found the rate-determining step to be the transannular hydride shift of the initially formed alkoxide with an activation energy (48 °C) of *ca.* 24 kcal mol^{-1}.

In the bicyclo[3.3.1]nonane skeleton itself, the facility of C(3)—C(7) hydride shifts has already been mentioned. The base-induced isomerisation of the 3,7-substituted analogue of the ketol (17), namely *exo*-7-hydroxybicyclo[3.3.1]nonan-3-one, has been studied in detail by Parker, Watt, and their co-workers [30] who report an



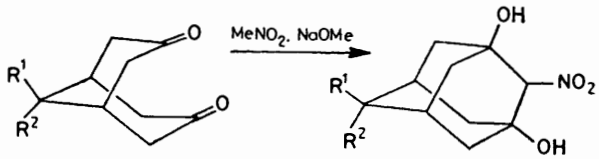
SCHEME 2

activation energy (113 °C) of 19.4 kcal mol^{-1}. Watt [31] has further demonstrated a base-induced C(3)—C(9) hydride shift in *endo*-3-hydroxy-7,7-dimethylbicyclo-[3.3.1]nonan-9-one, while earlier reports also implicate C(2)—C(8) shifts in this ring system.[13,32]

These observations add further support to the view that the deuteriation of the *exo*-ketol (17) proceeds by process (iv).

Intramolecular Cyclisation Reactions.—Formation of a nitroadamantane occurs when the bicyclo[3.3.1]nonane-3,7-diones (28) are treated with nitromethane and sodium methoxide,[33] and accordingly several attempts were made to perform the parallel reaction on the diketone (2) which would provide a twistane derivative. In each case, the only identifiable material recovered was (2).

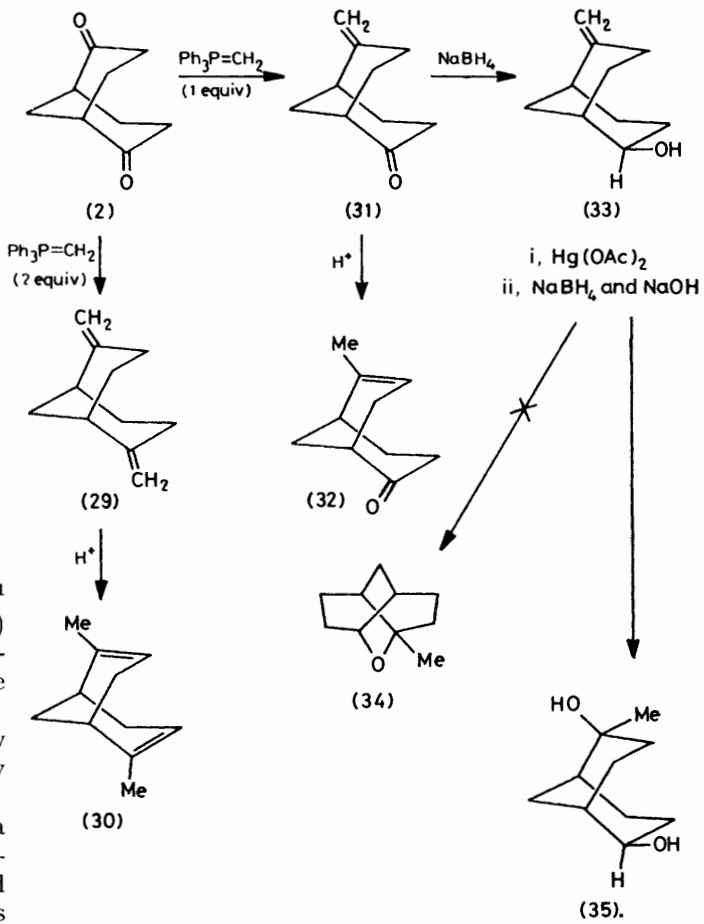
Stetter and his co-workers have also carried out a variety of carbonium ion initiated closures of 7-methylenebicyclo[3.3.1]nonan-3-one and 3,7-dimethylenebicyclo[3.3.1]nonane to the corresponding adamantane derivatives.[34] Similar transannular addition occurs in



(28)

a; R^1 = Me, R^2 = $CHCl_2$
b; R^1 = R^2 = H

reactions of 1,3,5,7-tetramethylenecyclo-octane with electrophilic reagents.[35] Comparable reactions with the 2,6-disubstituted bicyclo[3.3.1]nonanes would give twistane derivatives, but treatment of either the diene (29) [36] or the keto-olefin (31) with strong acids instead isomerised the olefinic bond(s) to the thermodynamically preferred position inside the bicyclic skeleton (see Scheme 3).

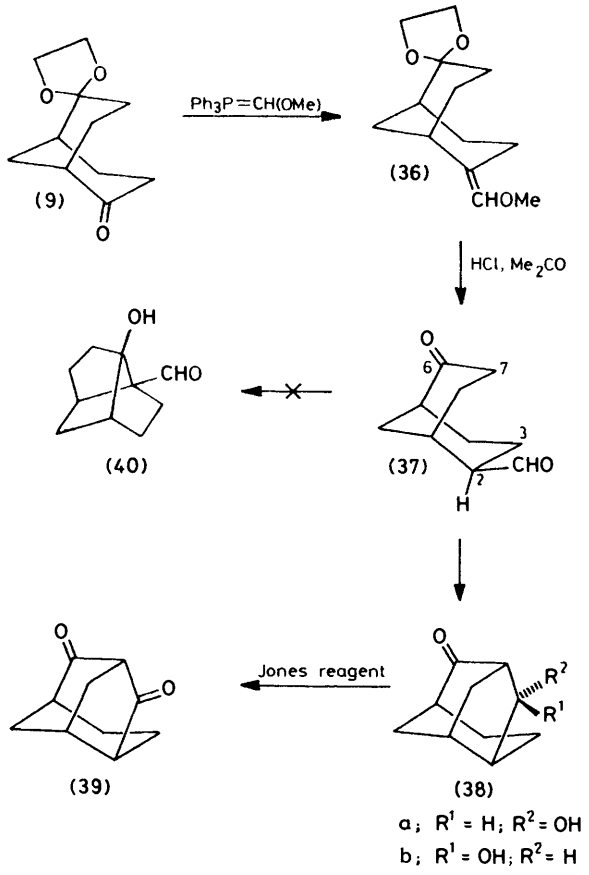


SCHEME 3 Reactions of 2,6-disubstituted bicyclo[3.3.1]nonanes

Reduction of (31) provided the *endo*-alcohol (33) which was subjected to Brown's mercury(II) acetate reaction.[37] By analogy with the alcohol (7), it would be expected that intramolecular trapping of the carbonium ion

produced on mercuriation would produce the oxatwistane (34). However, under aqueous conditions, hydration took place to give the diol (35), and even under anhydrous conditions no (34) was detected. These findings provide further evidence for the facility of C(2)—C(7) over C(2)—C(6) closure since intramolecular cyclisation of (7) was able to compete with the potential hydration reaction, whereas the alcohol (33) did not undergo intramolecular closure even under anhydrous conditions.

Reaction of the keto-acetal (9) with triphenylmethoxymethylenephosphorane gave a 45% yield of the enol ether (36). As in the case of 2-methoxymethylene-7-methylenebicyclo[3.3.1]nonane [14] the ^{1}H n.m.r. spectrum did not discriminate between the two possible geometrical isomers of the enol ether group. Treatment of (36) with hydrochloric acid–aqueous acetone gave a high yield of the protoadamantane ketol (38). This remarkable one-flask conversion (see Scheme 4) involves hydrolysis of both the acetal and enol ether groups to give the *endo*-keto-aldehyde (37) which subsequently undergoes an acid-catalysed aldol condensation.



SCHEME 4

Hydrolysis of the enol ether functionality of (36) would be expected to yield predominantly an *endo*-aldehyde group on either kinetic or thermodynamic grounds. As illustrated elsewhere in this report, attack on bicyclo-[3.3.1]nonane derivatives normally takes place on the *exo*-face, while under equilibrating conditions the *endo*-aldehydic group would be equatorial in the double-chair conformation and therefore be the more stable. These expectations are borne out by the high yield obtained in the cyclisation which could only involve this isomer. The keto-aldehyde could in principle undergo two aldol condensations: closure between the C(2) aldehyde and C(7) to give the protoadamantane (38), or closure between C(2) and C(6) to the brexane (40). As foreshadowed by the earlier results, the former process is the favoured one.

It was hoped that use of milder conditions might allow isolation of the intermediate keto-aldehyde (37) with a view to carrying out an intramolecular pinacol closure, thus affording entry into the twistane system, but this was not achieved. Hydrolysis of (36) with ether saturated with 70% perchloric acid did, however, appear preferentially to liberate the aldehydic group.[38]

Evidence for the assignment of the protoadamantane structure (38) was gained principally from i.r. and ^{1}H and ^{13}C n.m.r. data. In particular, the data on the carbinyl ^{1}H n.m.r. signals indicated the *endo*-alcohol (38a) to be the minor and the *exo*-alcohol (38b) to be the major products on the basis of $W_{\frac{1}{2}}$ values expected from coupling to adjacent protons. The ^{13}C data fully supported the presence of two epimeric alcohols except that one C–H signal was obscured by other signals.

Conclusive evidence was obtained by oxidation of the ketol mixture to yield only one product, protoadamantane-2,10-dione (39). In this process, both carbinyl signals were lost in the ^{1}H n.m.r. spectrum and the i.r. spectrum showed loss of OH and gain of cyclopentanone $\rangle$C=O, plus retention of the earlier six-membered ring absorption. Analytical and ^{13}C n.m.r. data fully supported structure (39).

As discussed earlier, several syntheses of protoadamantan-4-one from 3,7-disubstituted bicyclo[3.3.1]nonanes have been reported, but the majority of entries to this ring system are from suitable adamantane precursors.[39] The present synthesis provides substitution at positions less commonly obtained by these other methods.

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus. U.v. spectra were recorded on a Unicam SP 800 instrument. I.r. and ^{1}H n.m.r. spectra were recorded for solutions in CCl_4 except where stated otherwise. ^{1}H and ^{13}C N.m.r. data are reported as chemical shifts (δ) relative to internal $SiMe_4$.

Stereochemistry of Bicyclo[3.3.1]*nonan-2-yl Derivatives.*—The existence of the bicyclo[3.3.1]nonane skeleton in the twin-chair conformation can be inferred from the appearance of ' abnormal ' methylene i.r. bands [40] at *ca.* 1 490 and 2 990 cm^{-1}. These are only present when C(3) and C(7) are unsubstituted and there are no sp^2 carbon atoms in the two three-carbon bridges.

In a twin-chair conformation, an *exo*-2-derivative has the C(2) methine hydrogen equatorial in a chair cyclohexane. The *endo*-2 epimer has an axial hydrogen. By analogy with

cyclohexane derivatives, an axial proton surrounded by two equatorial and one axial protons should have a larger $W_{\frac{1}{2}}$ for its ^1H n.m.r. signal than an equatorial proton similarly surrounded. In practice, typical values reported herein (and elsewhere [41]) were $W_{\frac{1}{2}}$ 15—22 Hz for the *endo*-epimers (axial ^1H) and $W_{\frac{1}{2}}$ 6—7 Hz for the *exo*-epimers (equatorial ^1H).

For derivatives containing an sp^2 centre in one of the three-carbon bridges, the i.r. bands were lost but without necessarily changing from the twin-chair conformation. As similar $W_{\frac{1}{2}}$ values were found for the C(2) methine proton, this ring at least must still be a chair cyclohexane.

6,6-*Ethylenedioxybicyclo*[3.3.1]*nonan*-2-*one* (9).—The monoacetal (9) was prepared from the diketone (2) [13] by a procedure similar to that of Musso [42] and separated from the diacetal and unchanged (2) by column chromatography on neutral alumina: $\nu_{max.}$ (film) 1 710 and 1 110 cm^{-1}; δ (^1H) 1.5—2.7 (12 H, m) and 3.9 (4 H, s).

6,6-*Ethylenedioxy*-endo-2-*hydroxybicyclo*[3.3.1]*nonane* (10).—The keto-acetal (9) (1.0 g) was stirred in ether (15 ml) with lithium aluminium hydride (0.2 g) for 1 h. Saturated sodium sulphate solution was added dropwise and the resulting precipitate washed several times with ether. Evaporation of solvent from the dried combined extracts gave an oil (0.9 g) which slowly crystallised. Recrystallisation (petrol–ethyl acetate) followed by sublimation gave 6,6-*ethylenedioxy*-endo-2-*hydroxybicyclo*[3.3.1]*nonane*, m.p. 79—81 °C (Found: C, 66.5; H, 9.35. $C_{11}H_{18}O_3$ requires C, 66.85; H, 9.15%); $\nu_{max.}$ 3 620, 2 980, 1 480, 1 120, and 1 050 cm^{-1}; δ (^1H) 1.64 (1 H, s, exchanged with D_2O) and 3.91 (5 H, s, acetal and carbinyl-H).

endo-2-*Acetoxy*-6,6-*ethylenedioxybicyclo*[3.3.1]*nonane*.—The *endo*-alcohol (10) (1 mmol), acetic anhydride (0.8 ml), and pyridine (0.8 ml) were warmed for 30 min, then the cooled solution was carefully poured into saturated sodium hydrogencarbonate solution (5 ml) and set aside for 30 min before extraction with ether. Evaporation of the dried extracts gave endo-2-*acetoxy*-6,6-*ethylenedioxybicyclo*[3.3.1]-*nonane* which was purified by distillation at 70 °C and 0.5 mmHg (Found: C, 64.75; H, 8.4. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%); $\nu_{max.}$ 2 980, 1 730, 1 480, 1 245, 1 240, 1 105, 1 045, and 1 030 cm^{-1}; δ (^1H) 1.94 (3 H, s), 3.85 (4 H, s), and 4.81 (1 H, m, $W_{\frac{1}{2}}$ 21 Hz). This half peak width confirms that the precursor was the *endo*-alcohol, in which the carbinyl proton signal was obscured. The stereochemistry is that expected from attack on the less-crowded *exo*-face. (For example see the reduction of bicyclo[3.3.1]-nonan-2-one.[43])

endo-6-*Hydroxybicyclo*[3.3.1]*nonan*-2-*one* (11).—The hydroxyacetal (10) (0.66 g) was heated for 2 h in refluxing acetone (40 ml) containing toluene-*p*-sulphonic acid monohydrate (20 mg). The cooled mixture was diluted with ether and washed with saturated potassium carbonate solution. Removal of solvent from the dried solution gave a waxy hygroscopic solid (0.45 g) purified further on alumina to give endo-6-*hydroxybicyclo*[3.3.1]*nonan*-2-*one* (11) (0.43 g), m.p. 170—172 °C (Found: C, 69.85; H, 9.25. $C_9H_{14}O_2$ requires C, 70.1; H, 9.15%); $\nu_{max.}$ 3 620, 1 710, 1 060, and 1 040 cm^{-1}; δ (^1H) 2.15 and 2.38 (13 H, m), and 3.9 (1 H, m, $W_{\frac{1}{2}}$ 16 Hz). The tosylate of (11), m.p. 83—84 °C (Found: C, 62.45; H, 6.65. $C_{16}H_{20}O_4S$ requires C, 62.3; H, 6.55%) had $\nu_{max.}$ (paraffin mull) 1 710, 1 600, 1 500, and 1 185 cm^{-1}; δ (^1H) 2.47 (3 H, s), 4.67 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz), 7.45 (2 H, d, J 8.5 Hz), and 7.89 (2 H, d, J 8.5 Hz).

6,6-*Ethylenedioxy*-endo-2-*tosyloxybicyclo*[3.3.1]*nonane* (13).—The hydroxyacetal (10) reacted with toluene-*p*-sulphonyl chloride in pyridine at 0 °C to give 6,6-*ethylenedioxy*-endo-2-*tosyloxybicyclo*[3.3.1]*nonane* (13), m.p. 103.5—105.5 °C (from petrol–ethyl acetate) (Found: C 61.35; H, 6.9. $C_{18}H_{24}O_5S$ requires C, 61.35; H, 6.85%); $\nu_{max.}$ 1 595, 1 495, 1 480, 1 190, 1 170, and 1 100 cm^{-1}; δ (^1H) 2.42 (3 H, s), 3.80 (4 H, s), 4.58 (1 H, m, $W_{\frac{1}{2}}$ 22 Hz); 7.28 (2 H, d, J 8.5 Hz), and 7.81 (2 H, d, J 8.5 Hz).

Attempted Inversion of (13).—(a) The *endo*-2-tosylate (13) (3.5 g) was heated in 90% aqueous dimethylformamide (100 ml) at 78 °C for 184 h. The cooled solution was poured into water (150 ml), extracted with ether, and the extracts dried and filtered. Lithium aluminium hydride (1 g) was added and the mixture stirred for 15 min. Saturated sodium sulphate solution was added and the resulting precipitate washed several times with ether. Removal of solvent from the dried combined extracts gave a colourless oil (1.6 g).

Chromatography on alumina gave the unsaturated acetal (14) (0.4 g), the *endo*-hydroxy-acetal (10) (0.3 g), and *endo*-2-hydroxybicyclo[3.3.1]non-6-ene (0.2 g); $\nu_{max.}$ (film) 3 400, 3 040, 1 060, and 705 cm^{-1}; δ (^1H) 3.68 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz) and 5.68 (2 H, m). Further elution gave an oil (0.6 g) which was probably (i.r.) *endo*-6-hydroxy-*endo*-2-tosyloxybicyclo-[3.3.1]nonane. (b) The tosylate (13) (6.5 g) was heated with sodium acetate (1.83 g) in 90% aqueous dimethylformamide (200 ml) for 96 h at 78 °C. Similar work up as in (a) gave a colourless oil (2.6 g). Chromatography on alumina gave the unsaturated acetal (14) (1.11 g) and the *exo*-hydroxy-acetal (16) (1.4 g). (c) The tosylate (13) (0.35 g) was heated with sodium acetate (0.4 g) in 100% dimethylformamide (10 ml) for 130 h at 78 °C. Similar work up as in (a) gave a pale yellow oil (0.24 g) comprising (14), 25%; (13), 50%; and (16), 25%. Despite a five-fold molar excess of sodium acetate, the large amount of unchanged material indicated that water was a necessary reagent for the inversion reaction.

6,6-*Ethylenedioxybicyclo*[3.3.1]*non*-2-*ene* (14).—The tosyloxyacetal (13) (40 g) was added to a solution of sodium (10 g) in dry ethanol (500 ml) under dry nitrogen and the solution refluxed for 10 days. The cooled mixture was added to water (500 ml) and extracted with petrol (1 × 500 ml, 3 × 150 ml). The combined extracts were washed and dried. Removal of solvent gave a colourless oil (21 g). Chromatography on alumina gave 6,6-ethylenedioxybicyclo-[3.3.1]non-2-ene (14) (12 g) as an oil [44] (Found: C, 73.2; H, 9.15. Calc. for $C_{11}H_{16}O_2$: C, 73.3; H, 8.95%); $\nu_{max.}$ (film) 1 650, 1 120, 770, and 725 cm^{-1}; δ (^1H) 3.87 (4 H, s), and 5.67 (2 H, d, J 4 Hz). Further elution gave 2-*ethoxy* 6,6-*ethylenedioxybicyclo*[3.3.1]*nonane* as an oil (8.5 g) (Found: C, 69.0; H, 10.0. $C_{13}H_{22}O_3$ requires C, 69.0; H, 9.8%); $\nu_{max.}$ (film) 1 140 and 1 080 cm^{-1}; δ (^1H) 1.15 (3 H, t, J 7 Hz), 3.25 (1 H, m), 3.37 (2 H, q, J 7 Hz), and 3.8 (4 H, s).

Bicyclo[3.3.1]*non*-6-*en*-2-*one* (20).—The unsaturated acetal (14) (1.5 g) was hydrolysed as described for (11). A pale yellow liquid (0.9 g) was obtained which was purified on alumina to give bicyclo[3.3.1]non-6-en-2-one [23] (20) (0.7 g) as an oil (Found: C, 79.4; H, 9.0. Calc. for $C_9H_{12}O$ C, 79.3; H, 8.9%); $\nu_{max.}$ 3 040, 1 710, 1 100, and 695 cm^{-1}; $\lambda_{max.}$ (ethanol) 295 nm (ε 19.8), $\lambda_{max.}$ (hexane) 294 nm (ε 15); δ (^1H) 5.83 (2 H, d, J 4 Hz). The u.v. data confirm that no rearrangement had taken place during the elimination step; lit.,[23] $\lambda_{max.}$ 293 nm (ε 15), compared with

$\lambda_{max.}$ 301 nm (ε 198) for bicyclo[3.3.1]non-7-en-2-one. Furthermore, hydrogenation of the unsaturated ketone (20) (H_2; 5% Pd/C) in ethyl acetate (8 h) gave bicyclo[3.3.1]-nonan-2-one identical (i.r. and g.l.c.) with an authentic sample.

exo-2,3-*Epoxy*-6,6-*ethylenedioxybicyclo*[3.3.1]*nonane* (15).—A solution of 85% *m*-chloroperoxybenzoic acid (2.4 g) in chloroform (30 ml) was added to the unsaturated acetal (14) (2 g) in chloroform (10 ml) and the mixture stirred for 15 h at room temperature. 10% Sodium sulphide solution was added dropwise until the mixture gave no colouration with moist starch-iodide paper. The chloroform layer was then washed with saturated sodium hydrogencarbonate solution (4 × 20 ml) and brine (1 × 30 ml), and dried. Removal of solvent gave a pale yellow oil (2.23 g). A pure sample of exo-2,3-*epoxy*-6,6-*ethylenedioxybicyclo*[3.3.1]-*nonane* (15) was obtained by thick layer chromatography (Found: C, 67.55; H, 8.45. $C_{11}H_{16}O_3$ requires C, 67.35; H, 8.3%); $\nu_{max.}$ 1 110 and 1 040 cm^{-1}; δ (^1H) 2.88 (2 H, m, $W_{\frac{1}{2}}$ 16 Hz) and 3.85 (4 H, s).

exo-2-*Hydroxy*-6,6-*ethylenedioxybicyclo*[3.3.1]*nonane* (16).—The epoxyacetal (15) (0.98 g) and lithium aluminium hydride (0.85 g) were stirred in ether (50 ml) for 7 days at room temperature. Saturated sodium sulphate solution was added dropwise, then the precipitate washed successively with ether and ethyl acetate. Evaporation of solvent from the dried extracts gave an oil (0.8 g) which was purified on neutral alumina to give exo-2-*hydroxy*-6,6-*ethylenedioxy-bicyclo*[3.3.1]*nonane* (16) (0.75 g) (Found: C, 66.85; H, 9.2. $C_{11}H_{18}O_3$ requires C, 66.85; H, 9.15%); $\nu_{max.}$ 3 630, 1 120, 1 100, 1 060, and 990 cm^{-1}; δ (^1H) 3.9 (5 H, s, acetal and carbinyl protons). The tosylate of (16) had $\nu_{max.}$ (film) 1 735, 1 250, and 1 040 cm^{-1}; δ (^1H) 1.95 (3 H, s), 3.82 (4 H, s), and 4.80 (1 H, m, $W_{\frac{1}{2}}$ 6 Hz). This $W_{\frac{1}{2}}$ value confirms the precursor to be the *exo*-alcohol, in which the carbinyl signal was obscured.

exo-2-*Hydroxy*-endo-6-(2-*hydroxyethoxy*)*bicyclo*[3.3.1]-*nonane* (21).—The foregoing reduction of (15), if carried out in refluxing ether for 4 days, gave an oil purified on alumina to give exo-2-*hydroxy*-endo-6-(2-*hydroxyethoxy*)*bicyclo*-[3.3.1]*nonane* (21) (Found: C, 66.1; H, 10.25. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.05%); $\nu_{max.}$ (film) 3 360, 1 480, 1 105, 1 070, 1 050, 980, and 950 cm^{-1}; δ (^1H) ($CDCl_3$) m centred on 1.75 (14 H; 2 H exchanged with D_2O) and 3.3—3.9 (6 H, m). The *diacetate* of (21) was obtained as an oil under similar conditions to those used for the alcohol (10) (Found: C, 63.6; H, 8.6. $C_{15}H_{24}O_5$ requires C, 63.35; H, 8.5%); $\nu_{max.}$ (film) 1 735, 1 250, and 1 040 cm^{-1}.

endo-2-*Hydroxy*-endo-6-(2-*hydroxyethoxy*)*bicyclo*[3.3.1]-*nonane*.—Reduction of *endo*-2-hydroxy-6,6-ethylenedioxy-bicyclo[3.3.1]nonane (10) under similar conditions to those which produced (21) gave a colourless oil, of identical t.l.c. behaviour to (21). $\nu_{max.}$ (film) 3 400, 1 480, 1 115, 1 105, 1 060, 1 040, 965, 950, 910 cm^{-1}.

exo-6-*Hydroxybicyclo*[3.3.1]*nonan*-2-*one* (17).—The hydroxyacetal (16) (0.72 g) was hydrolysed as described for (11). Removal of solvent gave a waxy hygroscopic solid (0.51 g) which was purified on neutral alumina to give exo-6-*hydroxybicyclo*[3.3.1]*nonan*-2-*one* (17) (0.49 g), m.p. 153—156 °C (Found: C, 69.95; H, 9.1. $C_9H_{14}O_2$ requires C, 70.1; H, 9.15%); $\nu_{max.}$ 3 620, 1 710, 1 125, 1 050, and 970 cm^{-1}; δ (^1H) 2.20 and 2.45 (12 H, m), 3.09 (1 H, s, exchanged with D_2O), and 3.95 (1 H, m, $W_{\frac{1}{2}}$ 6 Hz). The *tosylate* of (17) had m.p. 111—113 °C (from petrol–ethyl acetate) (Found: C, 62.5; H, 6.7. $C_{16}H_{20}O_4S$ requires C, 62.3; H, 6.55%); $\nu_{max.}$ (paraffin mull) 3 060, 1 700, 1 595, 1 495, 1 190, and 1 175 cm^{-1}; δ (^1H) 2.47 (3 H, s), 4.7 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz), 7.4 (2 H, d, J 8.5 Hz), and 7.8 (2 H, d, J 8.5 Hz).

Deuteriation of the endo-*Ketol* (11).—The *endo*-ketol (11) (29 mg) and a solution of sodium (36 mg) in dioxan (1.5 ml) and deuterium oxide (1.5 ml) were heated for 72 h at 95 °C. The solvents were removed under reduced pressure and the residue was washed with D_2O (0.5 ml) and then ether (3 × 5 ml). The combined ether layers were then washed with D_2O (2 × 0.5 ml) and brine (2 × 5 ml), and dried. Solvent was removed to give a waxy solid (25 mg) purified on neutral alumina to give the deuteriated *endo*-ketol (12) (20 mg). This had identical g.l.c. properties to the starting material (11); $\nu_{max.}$ 3 640, 2 150, 1 705, 1 055, and 1 030 cm^{-1}; δ (^1H) ($CDCl_3$) 3.9 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz).

The deuterium content of (12) and the other compounds was determined mass spectrometrically on an A.E.I./M.S. 902 instrument and converted for isotope effects by the procedure described by Biemann;[45] results are shown in the Table in the Discussion section.

Deuteriation of the exo-*Ketol* (17).—The *exo*-ketol (17) treated as above gave the deuteriated *exo*-ketol (18); $\nu_{max.}$ ($CDCl_3$) 3 650, 2 150, 1 705, and 1 055 cm^{-1}; δ (^1H) ($CDCl_3$) 3.96 (1 H, s, $W_{\frac{1}{2}}$ 3 Hz).

In the i.r. spectrum of (18), the C–O– stretching bands, which are different in position and intensity to those of (17), superficially resemble those of the *endo*-epimer (12). However, treatment of (17) with sodium hydroxide in water–dioxan under identical conditions was found not to have caused any epimerisation (g.l.c. and i.r.). This change in the i.r. spectrum arises from changes due to the C–D bonds surrounding the C–O group, since the conversion of the *endo*-ketol (11) into (12), where no such replacement occurs, caused no substantial change in C–O frequency.

[$^2H_6$]*Bicyclo*[3.3.1]*nonane*-2,6-*dione* (19).—The deuteriated *exo*-ketol (18) (10 mg) was treated in ice-cold acetone (1 ml) with Jones reagent (3 drops).[†] The solution was diluted with water (2 ml) and extracted with ether (2 × 2 ml). The dried extracts were washed with saturated sodium hydrogencarbonate solution (2 × 1 ml). Concentration of the dried solution gave the dione (19) which was purified by sublimation. It had identical g.l.c. properties to dione (2); $\nu_{max.}$ 2 150, 1 710, 1 185, 1 115, and 1 090 cm^{-1} (see Table for deuterium content).

Exchange Reaction of (19) *to* (2).—The dione (19) (3.6 mg) was refluxed under nitrogen with aqueous 4M sodium hydroxide (1 ml) and methanol (1.5 ml) for 12 h. The solution was diluted with water and extracted with ether. Concentration of the dried solution gave the dione (2) which was identical (g.l.c.) with an authentic sample (see Table for deuterium content).

Attempted Disproportionation Experiment.—Authentic samples of the dione (2) (15 mg) and *endo*-2,*endo*-6-dihydroxybicyclo[3.3.1]nonane[13] (15 mg) were heated with a solution of sodium (38 mg) in dioxan (1.5 ml) and water (1.5 ml) in a sealed ampoule for 72 h at 95 °C. Gas chromatography (QF1 and SE30) revealed that both compounds were still present but neither the ketol (11) nor (17) was present.

2,6-*Dimethylbicyclo*[3.3.1]*nona*-2,6-*diene* (30).—2,6-Dimethylenebicyclo[3.3.1]nonane[36] (29) (0.1 g) was stirred at room temperature in 50% sulphuric acid (2.5 ml) for 4 days; the mixture was then diluted with water and extracted with ethyl acetate and the extracts were dried (Na_2CO_3). G.l.c. examination of the crude product (10% FFAP; 140 °C)

showed no peaks compatible with alcohol products (hydration or transannular hydration) but one major hydrocarbon peak, 2,6-dimethylbicyclo[3.3.1]nona-2,6-diene [46] (30) t_R (29) 1.00, t_R (product) 1.14 (Found: C, 89.5; H, 10.7. Calc. for $C_{11}H_{16}$: C, 89.1; H, 10.9%); $\nu_{max.}$ (film) 3 020, 1 675, and 805 cm^{-1}; δ (^1H) ($CDCl_3$) 2.5—2.7 (8 H, m), 2.7—3.4 (6 H, m), and 5.1—5.3 (2 H, m).

6-*Methylenebicyclo*[3.3.1]*nonan-2-one* (31).—The diketone (2) was treated as in the preparation of (29),[36] but using only one equivalent of Wittig reagent. The oily product, 6-*methylenebicyclo*[3.3.1]*nonan-2-one* (31), was separated from unchanged (2) and the diene (29) by column chromatography (Found: C, 79.7; H, 9.7. $C_{10}H_{14}O$ requires: C, 79.95; H, 9.4%); $\nu_{max.}$ (film) 3 075, 1 710, 1 645, and 890 cm^{-1}; δ (^1H) ($CDCl_3$) 1.5—2.2 and 2.2—2.8 (each m, total 12 H), and 4.6—4.8 (2 H, m).

6-*Methylbicyclo*[3.3.1]*non-6-en-2-one* (32).—The ketone (31) (0.1 g) was stirred at room temperature for 20 h in 32% hydrochloric acid (3 ml). Ice was added, then the mixture extracted with ether (4 × 10 ml). The combined extracts were washed ($NaHCO_3$), dried (Na_2CO_3), and evaporated to give a sweet smelling oil, comprising one major peak on g.l.c. (SE-30) with t_R only slightly longer than that of (31), 6-*methylbicyclo*[3.3.1]*non-6-en-2-one* (32) (Found: C, 80.5; H, 9.7. $C_{10}H_{14}O$ requires C, 79.95; H, 9.4%); $\nu_{max.}$ (film) 3 020, 1 710, 1 680, and 790 cm^{-1}; δ (^1H) ($CDCl_3$) 1.6—2.1 (m) and 2.1—2.8 (m) (total 13 H), and 5.3—5.6 (1 H, m).

The same product was formed when (31) was heated at 100 °C for 2 h in 20% sulphuric acid.

endo-2-*Hydroxy*-6-*methylenebicyclo*[3.3.1]*nonane* (33).—Sodium borohydride (0.1 g) was added to a stirred solution of the ketone (31) (0.1 g) in methanol (5 ml) at room temperature. The mixture was stirred for several hours and then worked up in the usual manner yielding an oil, endo-2-*hydroxy*-6-*methylenebicyclo*[3.3.1]*nonane* (33) as the sole product. A g.l.c.-purified sample had m.p. 46—48 °C (Found: C, 79.1; H, 10.8. $C_{10}H_{16}O$ requires C, 78.9; H, 10.6%); $\nu_{max.}$ (film) 3 400, 3 085, 1 650, 1 065, 1 055, and 885 cm^{-1}; δ (^1H) 1.1—2.5 (12 H, m), 3.15—3.35br (1 H, s, exchanged with D_2O), 3.5—4.0 (1 H, m, $W_{\frac{1}{2}}$ 15 Hz), and 4.6 (2 H, s).

exo-2,endo-6-*Dihydroxy*-2-*methylbicyclo*[3.3.1]*nonane* (35).—The *endo*-alcohol (33) (0.1 g) was dissolved in a mixture of peroxide-free tetrahydrofuran (THF) (3 ml) and water (1 ml). Mercury(II) acetate (0.4 g) was added and the clear solution stirred for 0.5 h, before addition of sodium hydroxide solution (3M; 1 ml) followed by a solution of sodium borohydride (0.5M) in aqueous sodium hydroxide (3M; 1 ml). The mixture was saturated with sodium chloride, the THF layer separated off, and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried (Na_2CO_3) and solvent distilled off to give a viscous oil which crystallised when set aside for a long time to give exo-2,endo-6-*dihydroxy*-2-*methylbicyclo*[3.3.1]*nonane* (35), m.p. 148—149 °C (Found: C, 70.55; H, 10.6. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.7%); $\nu_{max.}$ (film) 3 420 and 1 060 cm^{-1}; δ (^1H) (CD_3SOCD_3) 1.07 (3 H, s), 1.1—2.3 (12 H, m), 3.35 (1 H, s, >COH, exchanged with D_2O), 3.57br (1 H, s, $W_{\frac{1}{2}}$ 20 Hz), and 4.40 and 4.45 (1 H, d, >COH, coupled, exchanged with D_2O). G.l.c. (5% LAC) showed a small amount of unchanged alcohol (33) in the mother liquors.

A similar reaction of (33) in anhydrous THF gave neither the oxatwistane (34) nor the diol (35). The i.r. spectrum of the crude products was roughly similar to the starting material, while g.l.c. indicated two peaks with very long retention time believed to be due to products resulting from bimolecular condensations of (33).

6,6-*Ethylenedioxy*-2-*methoxymethylenebicyclo*[3.3.1]*nonane* (36).—Methoxymethyl(triphenyl)phosphonium chloride (4.12 g, 0.012 mol) was stirred as a slurry under dry nitrogen in anhydrous ether (70 ml), then n-butyl-lithium in hexane (0.012 mol) added by syringe. After 15 min, 6,6-ethylenedioxybicyclo[3.3.1]nonan-2-one (9) (1.96 g, 0.010 mol) in dry ether (15 ml) was added whereupon a white precipitate was formed immediately. The mixture was refluxed for 2 h then extracted with water and ether, the extracts were dried (Na_2CO_3), and the solvent was evaporated off to give a red–brown viscous oil. Column chromatography (alumina; 5% ether in petrol) gave the enol ether (36) as a labile oil (1.00 g, 45%); $\nu_{max.}$ (film) 1 675, 1 105, and 910 cm^{-1}; δ (^1H) 1.3—2.9 (12 H, m), 3.47 (3 H, s, OMe), 3.83 (4 H, s, $-O\cdot CH_2\cdot CH_2\cdot O-$), and 5.62 (1 H, s, $=CHOMe$).

2-*Hydroxyprotoadamantan*-10-*one* (38).—The enol ether (36) (0.63 g, 2.8 mmol) was added to a stirred solution of acetone (10 ml) and 2M aqueous hydrogen chloride (5 ml) and the mixture refluxed overnight. Acetone was evaporated off and the residue thoroughly extracted with chloroform. The combined extracts were washed ($NaHCO_3$), dried (Na_2CO_3), and evaporated to give the *exo*- and *endo*-isomers of 2-*hydroxyprotoadamantan*-10-*one* (38) as a white solid (0.36 g, 77%), m.p. 210—215 °C (Found: C, 72.3; H, 8.5. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5%); $\nu_{max.}$ (paraffin mull) 3 420, 1 695, 1 110, and 1 070 cm^{-1}; δ (^1H) ($CDCl_3$) 1.4—2.1 (7 H, m), 2.1—2.9 (5 H, m), 3.5br (1 H, s, exchanged with D_2O), 4.13 s, $W_{\frac{1}{2}}$ 3 Hz, *exo*-C*H*OH), and 4.30, 4.35, 4.40, and 4.45 (q, *endo*-C*H*OH) carbinyl; total integration of two C*H*OH signals, 1 H; ratio *exo* : *endo* = 1.35 : 1.00; δ (^{13}C, $CDCl_3$) 18.2 (t), 20.7 (t), 23.7 (t), 25.1 (t), 31.2 (t), 31.9 (t), 33.1 (d), 33.2 (d), 34.8 (t), 35.0 (d), 37.0 (t), 44.2 (d), 45.1 (d), 58.2 (d), 61.2 (d), 75.4 (d, CHOH), 76.6 (d, CHOH), 215.9 (s, C=O), and 217.3 (s, C=O) p.p.m.; twentieth signal, CH, obscured).

Protoadamantane-2,10-*dione* (39).—The mixture of ketols (38) (0.50 g, 3 mmol) was stirred in acetone (25 ml) and oxidised with Jones reagent at 0 °C. After the usual work-up, the crude products were extracted into chloroform. Evaporation of the dried extracts gave *protoadamantane*-2,10-*dione* (39) (0.39 g, 78%), which was further purified by sublimation, m.p. (sealed capillary) 267—270 °C (Found: C, 72.85; H, 7.25. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.4%); $\nu_{max.}$ (paraffin mull) 1 705 and 1 755 cm^{-1}; δ (^1H) ($CDCl_3$) 1.2—2.5 (8 H, m), 2.5—3.0 (3 H, m), and 3.15 (1 H, s, $W_{\frac{1}{2}}$ 8 Hz), δ (^{13}C) ($CDCl_3$) 20.8 (t), 23.9 (t), 29.6 (t), 31.3 (d, C-8), 37.7 (t), 44.2 (d), and 45.3 (d) (C-3 and C-6), 66.6 (d, C-1), 206.6 (s, C-2), and 214.5 (s, C-10).

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