Di-isophorone and Related Compounds. Part 5.[1] 2,7-Epoxydi-isophoranes: Oxiran Cleavage by Perchloric Acid

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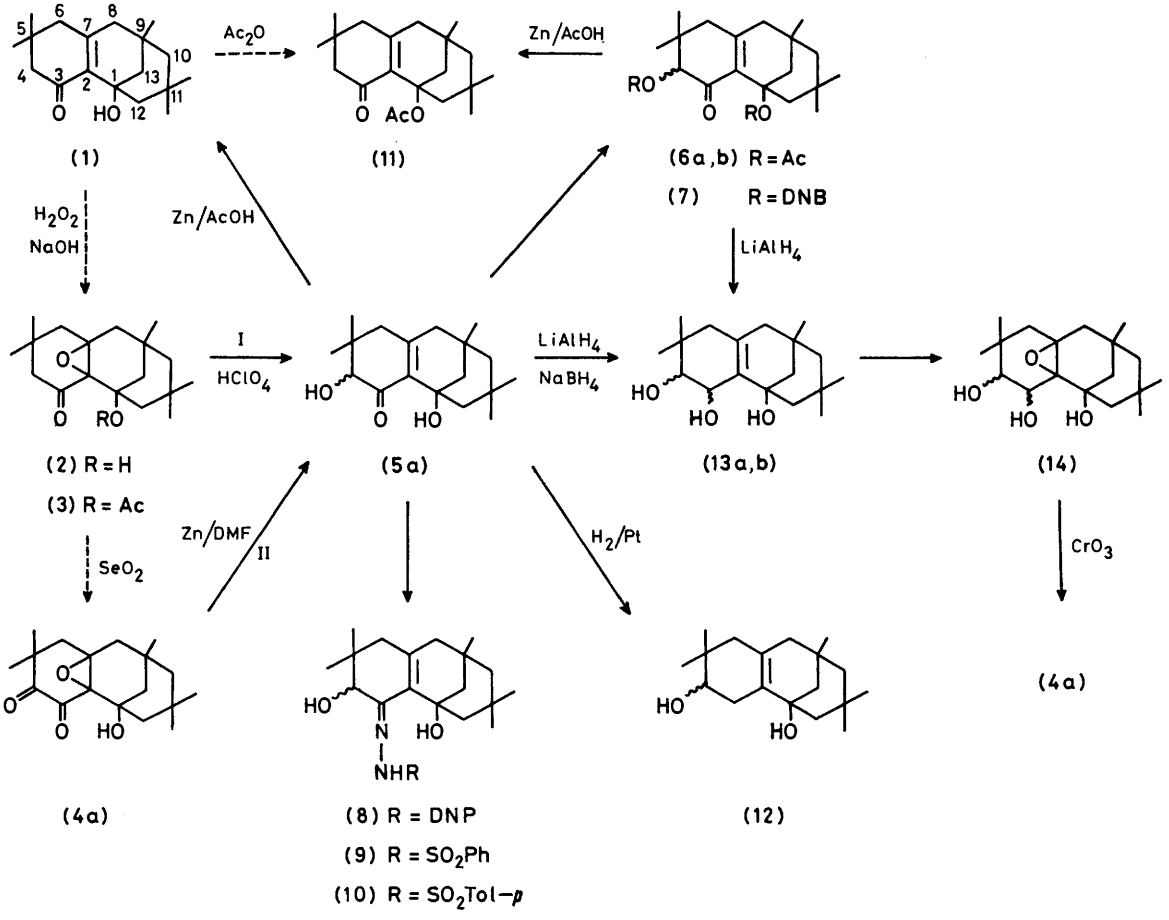
Perchloric acid slowly converts 2,7-epoxy-1-hydroxydi-isophoran-3-one into 1,4-dihydroxydi-isophor-2(7)-en-3-one, the structure of which is in accord with its alternative formation from 2,7-epoxy-1-hydroxydi-isophorane-3,4-dione by reduction with zinc in dimethylformamide. The 1,4-dihydroxy-3-one yields monoketonic and diacyl derivatives, including two stereoisomeric 1,4-diacetates. Its hydrogenation produces di-isophor-2(7)-ene-1,4-diol, while zinc in acetic acid regenerates the parent 1-hydroxydi-isophor-2(7)-en-3-one. Reduction of the 1,4-dihydroxy-3-one with lithium aluminium hydride or sodium borohydride yields two of the possible four stereoisomeric di-isophor-2(7)-ene-1,3,4-triols.

THE 2(7)-olefinic bond in di-isophoranes [*e.g.* (1)] [2] is relatively inert, but undergoes epoxidation under suitable conditions.[3] The resulting 2,7-oxirans [*e.g.* (2)] are useful intermediates for effecting further changes in the di-isophorane structure. Examples of reductive processes which occur with or without opening of the oxiran ring have already been described.[3] A further general 2,7-epoxide ring scission in di-isophoranes is now reported.†

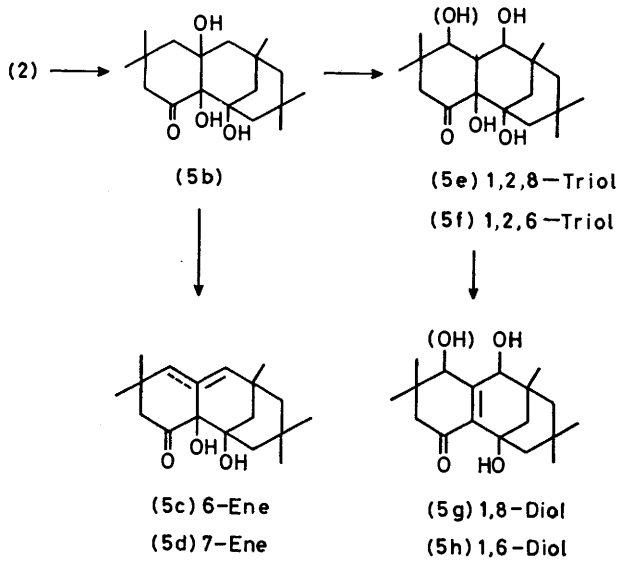
Nucleophilic ring opening of epoxides is a general reaction [4a,5] that is favoured by the attendant release of strain energy of the three-membered ring.[5,6] Examples include the conversion of epoxides into halogenohydrins by halogen acids,[4b,5] into 1,2-diol monoesters by carboxylic acids,[4c] and into 1,2-diols by acid-catalysed hydration; [4d] the wide applicability of these reactions has been demonstrated [4,5,7] and their mechanism and stereochemical course elucidated.[4-6] In the 2,7-position



SCHEME 1

† The nomenclature adopted in this paper is based on that proposed in Part 1 [2] of this series. Application of the IUPAC rules would name, for example, compound (1) as 5-hydroxy-2,2,-7,7,9-pentamethyl-2,3,5,6,7,8,9,10-octahydro-5,9-methanobenzocyclo-octen-4(1*H*)-one.

of di-isophorane, however, the normally highly reactive oxiran ring appears to be stabilised, presumably by the operation of steric effects. Neither hydrohalogen nor carboxylic acids proved readily applicable to the fission



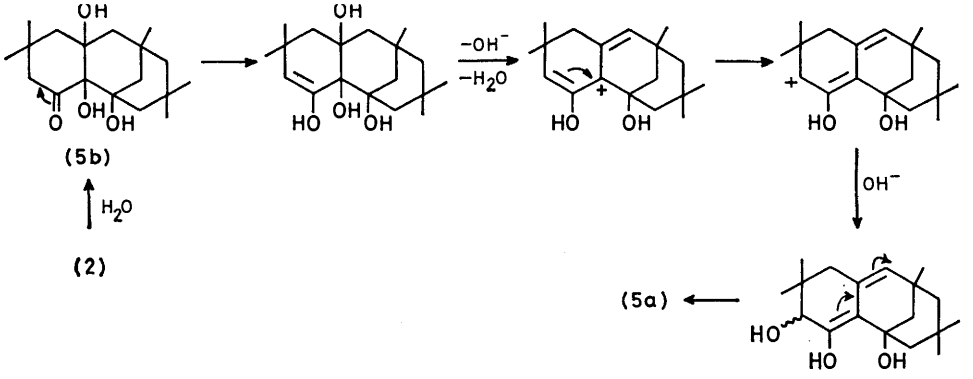
SCHEME 2

of di-isophoran-2,7-epoxides: treatment of 2,7-epoxy-1-hydroxydi-isophoran-3-one (2) with hydrochloric or hydrobromic acid gave non-crystallisable oils, while boiling acetic acid or anhydride were without action on the oxiran ring [in (2)], effecting merely acetylation of the 1-hydroxy-group.[3] However, the attempted hydration of (2) led to observations of interest (Scheme 1).

Perchloric acid promotes the hydration of the oxiran ring under mild conditions in high yield, and has proved especially useful in cleaving steroid epoxides.[7b] Its action on 2,7-epoxy-1-hydroxydi-isophoran-3-one (2) in acetone at room temperature did not terminate at the hydration stage, however, but gave a product (35—42%) to which the 1,4-dihydroxydi-isophor-2(7)-en-3-one structure (5a) has been assigned. 1-Acetoxy-2,7-epoxydi-isophoran-3-one[2] (3) gave the same dihydroxyketone (5a) with simultaneous deacetylation.

The composition ($C_{18}H_{28}O_3$) and molecular weight (292) of the product showed that the net reaction was an isomerisation, probably involving a hydration and dehydration stage, together with possible rearrangements. Structures (5c and d) arising directly by dehydration of the postulated initial intermediate 1,2,7-triol (5b) were at variance with the spectral properties of the product (Scheme 2). The 1,8- or 1,6-dihydroxy-3-oxo-structures (5g and h) derived from the rearranged intermediates (5e and f), although accounting for all the observed properties, were rejected in favour of structure (5a), when the product was found to be also accessible by the controlled reduction of 2,7-epoxy-1-hydroxydi-isophorane-3,4-dione (4a)[1] by the action of zinc in boiling dimethylformamide (DMF). Since the resulting dihydroxyketone was itself reducible to (1) under more vigorous conditions (see below), it had retained the 3-oxo-group and is therefore the 1,4-dihydroxy-3-one (5a).

The i.r. spectrum of (5a) includes two intense bands (at 3 495 and 3 465 cm^{-1}) attributable to two hydroxy-groups, and two peaks (at 1 655 and 1 630 cm^{-1}) indicative of an αβ-unsaturated ketone system forming part of a six-membered ring. Hydrogen bonding is apparent from the displacement of both hydroxy and carbonyl absorptions towards lower frequencies. The u.v. spectrum of (5a) featured an absorption maximum at 250 nm, agreeing with the value (249 nm) calculated according to the Fieser–Woodward correlations.[8] Structures (5c and d) which lack the αβ-unsaturated ketonic moiety are thus excluded by the spectroscopic evidence alone.

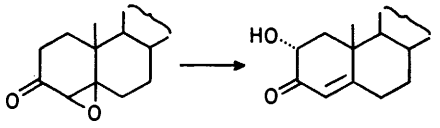


SCHEME 3

The conversion of 2,7-epoxy-1-hydroxydi-isophoran-3-one into the 1,4-dihydroxy-3-one [(2) ⟶ (5a)] involves structural changes almost identical with those occurring in the acid-induced epoxide scission of 4β,5-epoxy-17β-hydroxy-5β-androstan-3-one (15) to 2α-hydroxytestosterone (16);[9] no consideration, however, has been given to the mechanism of this transformation.

If, in accordance with numerous precedents,[4d,5,6,7b] the initial stage of the present reaction is the hydration of the epoxide ring of (2), subsequent essential steps are a dehydration involving the 7-hydroxy-group [of (5b)]

and the migration of the 2-hydroxy-group to the 4-position. A possible order of these events, with the attendant enolisations, is outlined in Scheme 3, but other sequences differing in detail are possible. The mechanism accounts for the observation that several 2,7-epoxydi-isophoranes closely related to (2) failed to react analogously with perchloric acid. These included

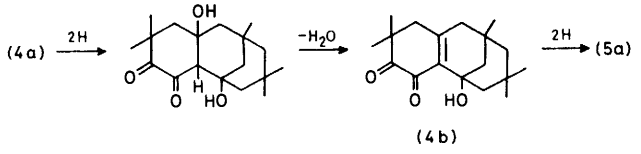


(15) (16)

2,7-epoxydi-isophoran-1-ol and its 1-chloro-analogue, which lack the 3-oxo-group participating in the mechanism, and 2,7-epoxy-1-hydroxydi-isophorane-3,4-dione (4a), in which the 4-position is blocked.

In the reductive formation of the 1,4-dihydroxy-3-one [(4a) ⟶ (5a)], the epoxide ring appears to be opened *before* the 4-oxo-group is reduced, since the yellow colour due to the α-diketone system fades only gradually, and reaction is complete with its disappearance. However, the postulated intermediate 1-hydroxydi-isophor-2(7)-ene-3,4-dione (4b), which has been prepared by several other methods,[10] has not been isolated in the present reaction.

There is evidence that both stereoisomers of (5a), differing in the configuration of their 4-hydroxy-group, arise from (4a) [and possibly also from (2)], and that the axial conformer predominates. Thus, the perchloric acid-catalysed [11] acetylation of the purified 1,4-dihydroxy-3-one [(5a); m.p. 115—118°] derived from



(4b)

SCHEME 4

either (2) or (4a), gave a diacetate [(6a); m.p. 131°], the i.r. spectrum of which includes *three* peaks in the region 1 230—1 260 cm^{-1} (ester C–O). An epimeric diacetate [(6b); m.p. 180°] having only *two* peaks in the same range was obtained from the crude (liquid) zinc-reduction product of (4a), consisting at this stage presumably of a mixture of *both* 4-hydroxy-epimers (5a). On the assumption that the 1-acetoxy-substituent of (6) is associated with one peak in each of the observed group of bands, the 4-acetoxy-group gives rise to *two* bands in (6a), and to *one* band in (6b), suggesting [12] that its conformation is axial in (6a) and equatorial in (6b); that of the 4-hydroxy-group in the purified parent 1,4-dihydroxy-3-one (5a) [which yields (6a) exclusively] is consequently also axial. The precise configuration of ring A, at present unknown, determines the spatial position of the 4-substituent relative to the plane of the ring. Models indicate that the partially flexible ring A is likely to assume a conformation in which the axial 4-substituent is below its plane [*i.e.* 4α-hydroxy- for (5a)].

Depending on the reagent employed, the reduction of (5a) affords one of several products. Zinc in acetic acid selectively reduced the 4-hydroxy-function, converting the dihydroxyketone (5a) or its diacetate (6a) into 1-hydroxydi-isophor-2(7)-en-3-one [(1) or its acetate (11)]. The result is in accord with the ready reductive elimination of allylic hydroxy- [13] or acetoxy-groups [13,14] from comparable steroid structures under these conditions, and with the known [1,3] inability of the reagent to reduce (1) or (11) any further.

Catalytic hydrogenation of (5a) removed, as in the parent (1) [15,16] and other compounds of this series,[17] the 3-oxo-function, giving di-isophor-2(7)-ene-1,4-diol (12) in moderate yield. The selective reduction of this function to a secondary hydroxy-group was effected by the use of metal hydrides. Lithium aluminium hydride and sodium borohydride gave, respectively, the stereoisomeric 1,3,4-triols (13a), m.p. 98—100°, and (13b), m.p. 221—223°; they are regarded as differing in the configuration of the newly introduced epimeric 3-hydroxy-group. The diacetate (6a) underwent reduction with lithium aluminium hydride with simultaneous deacetylation to produce the same triol (13a), although in lower yield.

Successive epoxidation and mild oxidation by chromic acid [18] reconverted the triols into 2,7-epoxy-1-hydroxydi-isophorane-3,4-dione in good overall yield [(13) ⟶ (14) ⟶ (4a)]. Use af a specimen of the 1,4-dihydroxy-3-one (5a) originating from 2,7-epoxy-1-hydroxydi-isophoran-3-one (2) by method I, gave the starting material (4a) for its synthesis by method II, thus proving the retention of the structure and steric configuration of the ring system throughout the changes.

EXPERIMENTAL

General information is given in Part 1 [2] concerning standard procedures, apparatus, reagents, solvents, and abbreviations. Catalytic hydrogenations were performed at room temperature and atmospheric pressure. Light petroleum had b.p. 60—80° unless otherwise stated. Unassigned peaks of the i.r. spectra are not recorded, except for compound (5a).

1,4-*Dihydroxydi-isophor*-2(7)-*en*-3-*one* (5a).—*Method I: from* 2,7-*epoxy*-1-*hydroxydi-isophoran*-3-*one* (2).[3] A stirred solution of the epoxide (2) (1.46 g, 0.005 mol) in acetone (30 ml) was treated dropwise at room temperature with 60% perchloric acid (2 ml), then set aside for 3—4 days. The resulting brown liquid was poured with stirring into water–3N-Na_2CO_3 (to neutralise the acid); the resinous precipitate, which hardened on storage, gave on crystallisation from light petroleum pale yellow *prisms* (0.51—0.62 g, 35—42%), m.p. 118—121° (Found: C, 73.6; H, 9.5. $C_{18}H_{28}O_3$ requires C, 74.0; H, 9.6%); $\nu_{max.}$ 3 495s and 3 465s (OH), 2 980s, 2 890s, 2 865s, 1 475s, 1 470s, 1 460s, and 1 410s (CH_3 and CH_2), 1 390s, 1 375s, and 1 370s (·CMe_2), 1 655vs (CO), 1 630s (C=C), and 1 350s, 1 340s, 1 310s, 1 260s, 1 235s, 1 205s, 1 160s, 1 130s, 1 095s, 1 055s, 1 050s, 995s, 895s, 850m, 820m, and 680m cm^{-1} (unassigned);

$\lambda_{max.}$ 250 nm (log ε 3.90); *m/e* 292s (M^+), 277s ($M^+ - 15$), 221vs ($M^+ - 71$), 203m ($M^+ - 71 - 18$), 175ms, and 121ms.

The use of 1-acetoxy-2,7-epoxydi-isophoran-3-one [3] in the foregoing procedure (but quantity of perchloric acid doubled, and time of reaction 12 days) also gave (5a) (32%), identified by mixed m.p. and its i.r. spectrum.

The *following* epoxides failed to react under the influence of perchloric acid, being substantially recovered in each case: 2,7-epoxydi-isophoran-1-ol [3] (conditions as above); 1-chloro-2,7-epoxydi-isophorane [3] (after treatment for 5 days in tetrahydrofuran); and 2,7-epoxy-1-hydroxydi-isophorane-3,4-dione [1] (after treatment for 1 or 5 days in acetone).

Method II: from 2,7-epoxy-1-hydroxydi-isophorane-3,4-dione (4a). A stirred solution of the dione (4a) (3.06 g, 0.01 mol) in dimethylformamide–water (48 ml; 3 : 1 v/v), treated with zinc dust (5 g), was boiled under reflux for 8 h. The mixture was filtered, the zinc washed with a little boiling dimethylformamide, and the pale yellow filtrate reduced to half bulk under vacuum, and then stirred into water. The brown resinous material was extracted with ether, and the washed neutral extracts evaporated. The resin gave, on crystallisation from light petroleum, large lustrous *prisms* (0.53—0.70 g, 18—24%), m.p. 115—116° (Found: C, 73.8; H, 9.9%), identified by mixed m.p. and its i.r. spectrum. The filtrate after recrystallisation deposited very slowly further prisms (m.p. 68—70°; 0.70 g, 25%) of 1-hydroxydi-isophor-2(7)-en-3-one (1), identified by its i.r. spectrum.[2]

Reactions of 1,4-*Dihydroxdi-isophor*-2(7)-*en*-3-*one* (5a).—(a) The dihydroxyketone (5a) was substantially recovered after treatment with anhydrous oxalic acid at 190—195 °C for 2 h.

(b) *Action of zinc.* A solution of the dihydroxyketone (5a) (0.58 g, 0.002 mol) in boiling glacial acetic acid (20 ml) was treated with zinc dust (0.8 g, 0.012 mol). After refluxing for 2.5 h, the decanted liquid was stirred into ice–water. The crystalline solid which separated slowly was 1-hydroxydi-isophor-2(7)-en-3-one (1) (52%), identified by its i.r. spectrum.[2]

(c) *Catalytic hydrogenation.* A solution of the dihydroxyketone (5a) (0.58 g, 0.002 mol) in glacial acetic acid (20 ml) was hydrogenated over Adams catalyst,[19] and the filtered liquid added to water (300 ml) and partly neutralised with 3N-NaOH (20 ml), when the initial cloudiness coagulated to a white solid. Crystallisation from light petroleum gave felted needles (0.19—0.26 g, 34—46%) of 1,4-*dihydroxydi-isophor*-2(7)-*ene* (12), m.p. 150—152° (Found: C, 78.1; H, 10.8. $C_{18}H_{30}O_2$ requires C, 77.7; H, 10.8%); $\nu_{max.}$ 3 360vs br (OH), 2 950s, 2 890s, and 1 460m (CH_3 and CH_2), 1 395m and 1 370m (·CMe_2), and 1 040vs cm^{-1} (C–O of OH).

(d) *Action of lithium aluminium hydride.* A solution of the dihydroxyketone (5a) (0.58 g, 0.002 mol) was added to a stirred suspension of lithium aluminium hydride (0.23 g, 0.006 mol), both in anhydrous ether, and the mixture was boiled under reflux for 2 h, then worked up in the usual manner.[3] The residual oil solidified rapidly to give needles (0.38 g, 64%) of *di-isophor*-2(7)-*ene*-1,3,4-*triol* (13a), m.p. 98—100° (from light petroleum) (Found: C, 73.5; H, 10.0. $C_{18}H_{30}O_3$ requires C, 73.5; H, 10.2%); $\lambda_{max.}$ 208 nm (log ε 3.66); $\nu_{max.}$ 3 515—3 385vs br (OH), 2 960vs, 2 890vs, 1 470m, and 1 450m (CH_3 and CH_2), 1 395m, 1 385m, and 1 370s (·CMe_2), and 1 040vs cm^{-1} (C–O of OH). Acetylation of (13a) under the usual conditions ($HClO_4$-catalysed, see immediately below) gave an oil that could not be crystallised.

(e) *Action of sodium borohydride.* A stirred solution of the dihydroxyketone (5a) (1.46 g, 0.005 mol) in methanol (60 ml) was treated dropwise at room temperature with sodium borohydride (1.9 g, 0.05 mol) in water–1N-NaOH (12.5 ml; 4 : 1 v/v) when effervescence occurred. After storage at room temperature for 12 h, the liquid was poured with stirring into water. The (air-dried) white precipitate (m.p. 223—225°; 85%) gave the 1,3,4-*triol* (13b) as white opaque microprisms, m.p. 221—223° (from light petroleum) (0.95—1.05 g, 64—72%) (Found: C, 71.2; H, 10.0. $C_{18}H_{30}O_3 \cdot \frac{1}{2}H_2O$, requires C, 71.3; H, 10.2%); $\nu_{max.}$ 3 400—3 200vs mult (OH), 2 960—2 860vs mult, 1 475, and 1 465vs d (CH_3 and CH_2), 1 385s and 1 365vs (·CMe_2), and 1 050vs cm^{-1} (? C–O of OH).

(f) *Epoxidation and oxidation of* (13b).—A solution of the 1,3,4-triol (13b) (0.88 g, 0.003 mol) and *m*-chloroperbenzoic acid (0.57 g, 0.0033 mol) in chloroform (25 ml) was boiled under reflux for 1 h, washed with aqueous $NaHCO_3$ and water (to neutrality), and evaporated under reduced pressure. The residual colourless oil was dissolved in acetone (10 ml) and treated dropwise with stirring with Kiliani's chromic acid [18] (3.0 ml, 0.004 oxidising equivalents) at room temperature. After stirring for 15 min, dilution with warm water produced a yellow precipitate (0.41 g, 45%), which gave the hydroxydiketone (4a), m.p. and mixed m.p. 159—161° (from light petroleum), identified by its i.r. spectrum.[1]

1,4-*Dihydroxydi-isophor*-2(7)-*en*-3-*one* (5a).—*Derivatives.* Each of the following ketonic and hydroxylic derivatives was separately prepared from specimens of the 1,4-dihydroxy-3-one (5a) that had been obtained by methods I and II; their identities were established by their mixed m.p.s and i.r. spectra.

2,4-*Dinitrophenylhydrazone* (8).—The standard procedure [2] gave large deep red *prisms* (68%), m.p. 238—240° (decomp.) (from ethanol) (Found: C, 61.7; H, 7.0; N, 11.7. $C_{24}H_{32}N_4O_6$ requires C, 61.0; H, 6.8; N, 11.9%); $\nu_{max.}$ 3 500mw (OH), 3 200s d (NH), 2 950—2 850s, 1 465ms, and 1 425s (CH_3 and CH_2), 1 612vs (C=N), and 835ms and 740m cm^{-1} (Ar).

Phenylsulphonylhydrazone (9). A boiling solution of the dihydroxyketone (5a) (0.29 g, 0.001 mol) and benzenesulphonyl hydrazide (0.21 g, 0.0012 mol) in ethanol (10 ml) was treated dropwise with concentrated hydrochloric acid (0.25 ml), and boiling under reflux continued for 2 h. Gradual dilution with water (15 ml) and storage deposited a solid, which was recrystallised to afford opaque *microprisms* (0.20 g, 45%), m.p. 188—189° (darkening from 150°) (from ethanol–light petroleum, 1 : 3) (Found: C, 64.55; H, 7.7; N, 6.1; S, 6.9. $C_{24}H_{34}N_2O_4S$ requires C, 64.6; H, 7.6; N, 6.3; S, 7.2%); $\nu_{max.}$ 3 270vs, br (? OH, NH), 2 960—2 860vs, 1 470, 1 450, and 1 430vs, br mult (CH_3 and CH_2), 1 635s (C=N), 1 395vs and 1 370vs (·CMe_2), 1 165vs, br (SO_2), and 755s and 685s cm^{-1} (Ar). In the absence of hydrochloric acid, starting material was recovered (60%).

p-*Tolylsulphonylhydrazone* (10). Prepared as for the phenylsulphonylhydrazone (9), this derivative formed silky needles (70%), m.p. 197—198° (from ethanol–light petroleum; 1 : 2; 100 ml) (Found: C, 65.5; H, 8.1; N, 6.2. $C_{25}H_{36}N_2O_4S$ requires C, 65.2; H, 7.8; N, 6.1%); $\nu_{max.}$ 3 415s and 3 090s (OH and NH), 2 970—2 860vs and 1 470—1 450s mult (CH_3 and CH_2), 1 635m (C=N), 1 600m

and 820—810ms mult (Ar), 1 385ms and 1 365s (·CMe_2), and 1 165vs cm^{-1} (SO_2).

1,4-*Bis*-(3,5-*dinitrobenzoate*) (7). A solution of the dihydroxyketone (5a) (0.58 g, 0.002 mol) in pyridine (15 ml) was treated with 3,5-dinitrobenzoyl chloride (1.15 g, 0.005 mol), kept at 100 °C for 45 min, and then poured with stirring into ice–concentrated hydrochloric acid (15 ml). The rust brown precipitate was washed with Na_2CO_3 to give cream prismatic *needles* (1.05 g, 78%), m.p. 189—192° (from acetone–ethanol–light petroleum, 1 : 1 : 2) (Found: C, 56.6; H, 4.6; N, 7.9. $C_{32}H_{32}N_4O_{13}$ requires C, 56.6; H, 4.7; N, 8.2%); $\nu_{max.}$ 3 120s, 730, and 715vs d (Ar), 2 970—2 890vs mult, 1 465s, and 1 425m (CH_3 and CH_2), 1 740vs and 1 715vs (CO of acyl groups), 1 690vs (CO), 1 630vs (C=C), 1 395ms and 1 365s (·CMe_2), and 1 290, 1 275, and 1 260vs, t cm^{-1} (C–O ester).

1,4-*Diacetoxydi-isophor*-2(7)-*en*-3-*one* (6a; ?4α).—(a) *Preparation*. A solution of the dihydroxyketone (5a) (0.58 g, 0.002 mol) in glacial acetic acid–acetic anhydride (11.5 ml; 15 : 3 v/v) was treated with 60% perchloric acid (10 drops) with external cooling, set aside at room temperature for 1.5 h, then poured with stirring onto ice. The solidified product gave minute opaque *prisms* (0.54 g, 72%), m.p. 131—133° (from ethanol, with addition of drops of water) (Found: C, 70.1; H, 8.6. $C_{22}H_{32}O_5$ requires C, 70.2; H, 8.5%); $\lambda_{max.}$ 246 nm (log ε 3.98); $\nu_{max.}$ 2 960s, 2 900s, and 1 475s (CH_3 and CH_2), 1 395s and 1 370s (·CMe_2), 1 745vs, 1 730vs, 1 260vs, d, 1 240vs, and 1 235vs (C–O ester), 1 685vs (CO), and 1 645s cm^{-1} (C=C). The same product (6a) was obtained (46%) when (5a) was refluxed in acetic anhydride for 3 h.

The diacetate (6a) failed to undergo catalytic hydrogenation, in the absence or presence of small amounts of 60% perchloric acid, starting material being recovered nearly quantitatively in each case.

(b) *Action of zinc*. A solution of the diacetate (6a) (0.38 g, 0.001 mol) in boiling glacial acetic acid (15 ml) was treated with zinc dust (0.65 g, 0.01 mol) in 3 portions at intervals of 5 min. After boiling for 30 min, the decanted solution was stirred into ice–water to precipitate 1-acetoxydi-isophor-2(7)-en-3-one (11) (0.25 g, 80%), identified by its mixed m.p. 125—127° [15] and i.r. spectrum.

(c) *Action of lithium aluminium hydride*. Treatment of the diacetate (6a) (0.002 mol) with lithium aluminium hydride (0.01 mol) by the procedure given for (5a) (see above) gave the triol (13a) (35%), identified by its mixed m.p. 98—100° and i.r. spectrum.

1,4-*Diacetoxydi-isophor*-2(7)-*en*-3-*one* (6b; ?4β).—Acetylation, as described for (6a), of the total resinous uncrystallised dihydroxyketone (5a) prepared by method II, gave a yellow precipitate, which afforded lustrous *prisms*, m.p. 188° (from ethanol, with addition of a few drops of water) [overall yield from (4a), 15%] (Found: C, 70.3; H, 8.9%); $\nu_{max.}$ 2 950—2 860vs, 1 435s, and 1 415s (CH_3 and CH_2), 1 740—1 720vs (CO of AcO), 1 675vs (CO), 1 630s (C=C, conjug.), 1 390vs, and 1 370vs (·CMe_2), and 1 260 and 1 245vs br cm^{-1} (C–O, ester).

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