Diisophorone and Related Compounds, Part 27 [1]

Nucleophilic Reactions of 1-Halogenodiisophoranes

Frederick Kurzer* and C. Richard Duffner

Royal Free Hospital School of Medicine (University of London), London NW 3

Z. Naturforsch. 45b, 1314–1323 (1990); received February 19, 1990

1-Halogenodiisophoranes, Production, Nucleophilic Reactions, Tricyclo[7.3.1.0^2-7]tridecanes, Enol-acetylation

The action of nucleophiles on 1-halogenodiisophoranes, obtained by several methods from the corresponding 1-hydroxy or 1-alkoxy compounds, replaces their bridgehead 1-halogen by hydroxy, alkoxy or acetoxy groups. The semiquantitative results show that the high solvolysis and hydrolysis rates of the 1-halogenodiisophor-2(7)-en-3-ones contrast markedly with the low reactivities of their 3-deketo analogues. Perchloric acid-catalyzed acetylation of diisophor-2(7)-en-1-ol-3-ones yields, by enolisation of the 3-keto-group, 1,3-diacetoxydiisophora-2,7-dienes in addition to the usual 1-monoacetates.

Introduction

Diisophorone (1) is a readily accessible compound [2] of the tricyclo[7.3.1.0^2-7]tridecane ring system (A), the three-dimensional bridged carbon skeleton (C) of which incorporates the bicyclo[3.3.1]nonane structure B: the detailed knowledge of the chemistry of this simpler bicyclic pattern [3] has provided guidelines for the study of the less familiar tricyclic diisophorane-system. The 1-bridgehead position, situated in an almost identical structural environment in both ring systems, is of particular interest as a directly comparable reactive centre.

In the diisophorone structure (C), the bicyclo[3.3.1]nonane moiety is slightly distorted, the 2(7)-double bond partially flattening ring B, without however appreciably deflecting the bridgehead C-1 bond. Ring A and the peripheral methyl groups present steric obstacles to approaching reagents, but the activating influence of the 2(7)-en-3-one system is likely to enhance 1-bridgehead activity. The expectation that 1-halogenodiisophorones should undergo nucleophilic substitution with retention of the ring-system has been realized in their alkaline hydrolysis [14] and aminolysis [15]. In special circumstances, however, the bridgehead may participate in rearrangement, as is exemplified by a pinacol transformation of a 1,2-diol [16]. The present account of solvolysis and allied reactions of 1-halogenodiisophoranes supplements and extends our previous observations. Since the systematic names of compounds of the present series are excessively long and cumbersome, we continue to use our proposed [2] simplified nomenclature based on the term ‘diisophorane’ for the parent hydrocarbon (5,5,9,11,11-pentamethyltricyclo[7.3.1.0^2-7]tridecane).
Results and Discussion

Production of 1-halogenodiisophoranes

The required 1-halogenodiisophoranes were accessible by several methods, including extensions of those due to Kabas and Rutz [14], who obtained 1-chlorodiisophorone (3) from the corresponding alcohols by the action of thionyl chloride or concentrated hydrochloric acid. The former has proved to be the more generally applicable reagent, affording both 3 and its 3-deketo analogue (12), as well as their 5,11-bisnor-homologues (4, 13) in excellent yield. The corresponding 1-bromo compounds, however, were not obtainable by the parallel use of thionyl bromide, mixtures of brominated products being obtained. In another approach, 1-chlorodiisophor-2(7)-enes (e.g. 12) were accessible by the removal of the 3-keto-function from the pre-formed chloroketone (e.g. 3) by catalytic hydrogenation, which occurred without affecting the 1-halogen substituent.

The action of concentrated hydrohalogen acids on the alcohols, though an excellent method for producing 3 [14], is more limited in its applicability. The 5,11-bisnor-homologue (2) and diisophoranes lacking the 3-keto-function (e.g. 10) reacted only slowly and incompletely. 1-Bromodiisophor-2(7)-en-3-one (5) was obtainable from 1 in high yield (70%) by the use of 45% hydrobromic acid, but here again, the procedure failed with the lower homologue (2) and the 3-deketo-compounds (10, 11). When successful, the reaction is remarkable in that the water-insoluble non-basic starting materials (e.g. 1) dissolve rapidly in the concentrated hydrochloric acid at room temperature to give deep-red solutions, from which the insoluble products separate gradually, arising presumably from intermediate carbonium ions (e.g. D); their participation in the Koch-Haaf carboxylation, and in the alkylation of 1-hydroxydiisophor-2(7)-enes by trialkyl orthoformates has previously been postulated [2].

Another effective route to 1-bromodiisophor-2(7)-en-3-one (5) was the interaction of the 1-methoxy compound (6, R' = Me) with acetyl bromide-stannic chloride: this application of Suzuki and Morita’s method [17] has already proved successful in producing the 1-chloro-analogue (3) [2]. The action of phosphorus tribromide (on 1) proved of limited utility, affording only small and variable yields (up to 17%) of the 1-bromo-compound 5.

Although 3 gave a 2,4-dinitrophenylhydrazone, the formation of ketonic derivatives from the 1-halogenodiisophorones was usually attended by partial loss of halogen, presumably by nucleophilic attack by the nitrogenous reagent (NH₂NHR, NH₂OH, NH₂NHCXNH₂), and was therefore unsuitable for their general characterization.

The spectral properties (UV, IR) of 3, 12 and 19...
their congeners are in accord with their formulation (see Experimental). The $^{13}$C NMR spectra of the 3-ketones 3–5 have already been incorporated in our wider surveys correlating these spectral characteristics [18, 19]. Spectra of diisophoranes lacking the 3-oxo-function, previously unreported, are now exemplified by those of 10, 12, and 14; they are readily interpreted by reference to fully assigned $^{13}$C NMR spectra of related structures [18, 19], including that of the prototype 1 (shown in Table I for comparison). In the 3-deoxo-compounds (10, 12, 14), modifications in the spectra are confined to signals of carbon atoms in the immediate vicinity of the structural change at C-3. Thus, the new 3-methylene carbon produces a high-field triplet (δ, 21–24 ppm), agreeing in its chemical shift with those of comparable centres in cyclohexenes [20]. The removal of the electron-attracting 3-keto group is further attended by a distinct up-field displacement of the C-4 signal, consistent with the increased electron density at this adjacent centre; the same, though progressively smaller effects are apparent at C-5 and C-6. The carbon atoms flanking the 2(7)-double bond, now no longer part of an a-enone system, display nearly equal chemical shifts in the range characteristic of alkylated cyclohexenes [20, 21]. Elsewhere in the molecule, the chemical shifts of the signals remain substantially unaffected, especially those of C-9, 10 and 11, remote from the structural change, and of the extranuclear methyls.

The previously unrecorded spectra of the a,ß-unsaturated keto ethers 6 (Alk = Me, Et) arising in the present solvolyses, and in the acid-catalyzed alkylation of 1 by trialkyl orthoformates [2], resemble closely that of 1. Except for minor changes in the chemical shifts of the 1-carbon atom bearing the modified substituent, and of the spatially proximate 12-methylene grouping, the spectra are almost identical.

**Table I. $^{13}$C NMR spectra of diisophorane derivatives.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
<th>C-8</th>
<th>C-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71.4 s</td>
<td>135.4 s</td>
<td>200.7 s</td>
<td>51.8 t *</td>
<td>32.2 s</td>
<td>45.7 t</td>
<td>157.5 s</td>
<td>46.6 t *</td>
<td>32.4 s</td>
</tr>
<tr>
<td>6b</td>
<td>76.7 s</td>
<td>134.9 s</td>
<td>196.2 s</td>
<td>52.4 t</td>
<td>32.3 s</td>
<td>47.0 t</td>
<td>158.7 s</td>
<td>45.9 t</td>
<td>32.3 s</td>
</tr>
<tr>
<td>6c</td>
<td>76.5 s</td>
<td>134.6 s</td>
<td>196.2 s</td>
<td>52.5 t</td>
<td>32.3 s</td>
<td>47.4 t</td>
<td>157.9 s</td>
<td>46.0 t</td>
<td>32.4 s</td>
</tr>
<tr>
<td>10</td>
<td>73.3 s</td>
<td>*129.3 s</td>
<td>20.6 t</td>
<td>36.5 t</td>
<td>28.8 s</td>
<td>44.3 t</td>
<td>*131.9 s</td>
<td>44.1 t</td>
<td>32.2 s</td>
</tr>
<tr>
<td>14c</td>
<td>78.0 s</td>
<td>*131.5 s</td>
<td>21.1 t</td>
<td>35.7 t</td>
<td>29.0 s</td>
<td>*44.5 t</td>
<td>*132.2 s</td>
<td>44.1 t</td>
<td>32.9 s</td>
</tr>
<tr>
<td>12</td>
<td>75.6 s</td>
<td>*130.5 s</td>
<td>23.6 t</td>
<td>35.8 t</td>
<td>28.8 s</td>
<td>*44.6 t</td>
<td>*131.1 s</td>
<td>*44.0 t</td>
<td>*33.0 s</td>
</tr>
<tr>
<td>17c</td>
<td>80.7 s</td>
<td>132.2 s</td>
<td>123.6 s</td>
<td>43.0 t</td>
<td>30.1 s</td>
<td>44.8 t</td>
<td>143.1 s</td>
<td>133.8 d</td>
<td>35.8 s</td>
</tr>
<tr>
<td>19c</td>
<td>82.9 s</td>
<td>132.8 s</td>
<td>120.0 d</td>
<td>39.9 t</td>
<td>30.0 s</td>
<td>44.2 t</td>
<td>136.9 s</td>
<td>132.5 d</td>
<td>36.2 s</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-10</th>
<th>C-11</th>
<th>C-12</th>
<th>C-13</th>
<th>C-14</th>
<th>C-15</th>
<th>C-16</th>
<th>C-17</th>
<th>C-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52.1 t</td>
<td>31.4 s</td>
<td>50.3 t</td>
<td>44.6 t</td>
<td>26.8 q</td>
<td>29.7 q</td>
<td>28.2 q</td>
<td>32.7 q</td>
<td>37.1 q</td>
</tr>
<tr>
<td>6b</td>
<td>52.4 t</td>
<td>31.4 s</td>
<td>42.9 t</td>
<td>45.4 t</td>
<td>27.7 q</td>
<td>29.6 q</td>
<td>28.4 q</td>
<td>33.0 q</td>
<td>37.2 q</td>
</tr>
<tr>
<td>6c</td>
<td>52.5 t</td>
<td>31.4 s</td>
<td>*45.4 t</td>
<td>*44.0 t</td>
<td>27.8 q</td>
<td>29.6 q</td>
<td>28.5 q</td>
<td>33.0 q</td>
<td>37.2 q</td>
</tr>
<tr>
<td>10</td>
<td>53.0 t</td>
<td>31.8 s</td>
<td>*48.9 t</td>
<td>*48.0 t</td>
<td>25.8 q</td>
<td>31.0 q</td>
<td>28.1 q</td>
<td>33.1 q</td>
<td>37.3 q</td>
</tr>
<tr>
<td>14c</td>
<td>53.3 t</td>
<td>31.4 s</td>
<td>*46.9 t</td>
<td>*44.6 t</td>
<td>25.8 q</td>
<td>31.3 q</td>
<td>28.3 q</td>
<td>33.5 q</td>
<td>37.4 q</td>
</tr>
<tr>
<td>12</td>
<td>52.1 t</td>
<td>*33.8 s</td>
<td>51.4 t</td>
<td>50.9 t</td>
<td>25.2 q</td>
<td>31.4 q</td>
<td>28.0 q</td>
<td>32.9 q</td>
<td>37.0 q</td>
</tr>
<tr>
<td>17c</td>
<td>49.2 t</td>
<td>31.5 s</td>
<td>49.1 t</td>
<td>43.8 t</td>
<td>25.6 q</td>
<td>*30.2 q</td>
<td>28.6 q</td>
<td>*30.3 q</td>
<td>37.2 q</td>
</tr>
<tr>
<td>19c</td>
<td>51.9 t</td>
<td>31.5 s</td>
<td>48.5 t</td>
<td>44.3 t</td>
<td>26.0 q</td>
<td>29.1 q</td>
<td>*30.4 q</td>
<td>*30.7 q</td>
<td>37.4 q</td>
</tr>
</tbody>
</table>

* Chemical shifts are given in ppm (δ) from TMS as internal standard. The solvent was deuteriochloroform. The spectra of 1 [18] and 19 [29] are included for comparison: 6: R' = CH₃, Additional signal of the 1-methoxy-group: δ, 49.4 q; 6: R' = CH₂CH₃, Additional signals of the 1-ethoxy-group: δ, 57.0 t (CH₃), 16.1 q (CH₃); 14: R' = CH₂CH₂CH₂, Additional signals of the 1-ethoxy-group: δ, 57.0 t (CH₃), 16.0 q (CH₃); 17: Additional signals of the 1-acetyl [δ, 168.7 s (CO), 21.9 q (CH₃)] and 3-acetyl group: [168.8 s (CO), 21.2 q (CH₃)]; 19: Additional signals of the 1-acetyl-group: δ, 169.2 s (CO), 22.7 q (CH₃); * + ++ Signals may be interchanged horizontally.
Solvolysis and Allied Reactions

The interaction of the 1-chloro (3, 4) and 1-bromo (5) ketones with sodium alkoxide in the appropriate alcohol occurred exceptionally rapidly, giving excellent yields of 1-alkoxydiisophor-2(7)-en-3-ones (6, 7; R' = Me, Et, iPr) within minutes at room temperature. In contrast, solvolysis of their 3-deoxo analogues (12, 13) occurred at an infinitely lower rate. Sodium alkoxide in the appropriate alcohol was virtually without action at room temperature, and only 5–10% conversion (12 → 14) was achieved after several hours at the boiling point of the medium.

Hydrolysis of the 1-halogenoketones (3, 5) by sodium hydroxide in aqueous dioxan gave the parent β-ketol (1) as the sole product (90% after 1 h at 100 °C; slower using calcium carbonate). The use of alkali in aqueous ethanol under various conditions gave mixtures of the 1-ethoxy (6, R' = Et) and 1-hydroxy compounds (1), the former generally predominating. Here again, the 3-deketo-analogues reacted less rapidly, though the rate differences were less extreme. Hydrolysis of 12 in 0.75 M sodium hydroxide in boiling 85% aqueous ethanol, for example, was complete within 10 h, yielding 1-ethoxy-(14, R' = Et) and 1-hydroxy-diisophor-2(7)-ene (10) (ca. 4:1; total 75%). The use of methanol and 2-propanol gave comparable results.

Acylation of Diisophorones

Diacetyl derivatives. The acylation of diisophorone β-ketols (e.g. 1, 2), normally terminating with the production of 1-monoacyl derivatives (e.g. 8) [14, 24, 25], is now shown to proceed to diacylated products under conditions conducive to enolization of their 3-keto group. Enol acetylation is effected specifically by isopropenyl acetate [26] and is promoted when the action of acetic anhydride is catalyzed by perchloric acid: steroid ketones and quinones have been converted into enol acetates by these reagents [26].

The perchloric acid-catalyzed acetylation of the β-ketols (1, 2) gave products that were separable into mono and diacetyl derivatives. Isopropenyl acetate effected the same change, but was without action on the preformed monoacetyl compounds; attempts to achieve exclusive diacetylation by its means were not successful.

The mono-substitution products are the known 1-acetoxy compounds (e.g. 8) [14]. The diacetyl derivatives are formulated as 1,3-diacetoxydiisophora-2,7-dienes (17, 18). Their IR spectra include an intense broad or twinned peak at 1725–1755
cm⁻¹, corresponding to two acetyl carbonyl groups; the characteristic enone absorption [14, 27] has disappeared. Comparison of the observed position of the UV absorption maximum (17: λ, 246 nm) with those calculated by the Fieser-Woodward rules [28] for homo- and heteroannular systems of conjugated double bonds (λ, 273, 244 nm, respectively) confirm the distribution of the diene-system (in 17, 18) over rings A and B. Alkaline hydrolysis reconverted the diacetate 17 into the parent β-ketol 1.

The ¹³C NMR spectrum of the diacetyl-derivative 17 (Table I) is readily assigned by reference to the established chemical shifts of diisophorones in general [18, 19, 30], and those of the monoacetate 8 [18] and conjugated dienes in particular [18, 29], and is in accord with the proposed structure. Its resemblance to that of 1-acetoxydiisophora-2,7-diene (19) (included in Table I for comparison) is remarkably close [29], while any deviations from that of the 1-acetoxy-ketone (8) are accountable in terms of the structural differences.

Conclusion

The production of 1-halogenodiisophoranes (3–5, 12, 13) from the corresponding hydroxy (1, 10) and alkoxy compounds (6), and their reconversion thereeto by nucleophiles shows that the structure and configuration of the diisophorane skeleton is preserved throughout the 1-bridgehead substitution processes (e.g. 1 → 3 → 6 → 3 → 1). It illustrates once again [24] the stability and steric integrity of this ring-system under these conditions, contrasting with the ring contraction [30] and aromatization [31] processes that it is capable of undergoing when attacked elsewhere in the molecule. – Enolization of the 3-keto-group of diisophoranes has been repeatedly postulated [24, 25, 32] as part of the mechanism of their interconversions; the isolation and characterization of the present diacylated products provides concrete evidence for the existence of such structures.

Experimental

The simplified nomenclature employed is that adopted in Part 1 [2], which also gives general information concerning standard procedures, reagents, solvents and abbreviations. Light petroleum had b.p. 60–80 °C unless otherwise stated. Perchloric acid was the “Analar” grade, s.gr. 1.54 (60–62% HClO₄). The equipment and procedures used in the measurement of the ¹³C NMR spectra are specified in Part 17 [25]. Unassigned peaks of the IR spectra are not recorded except for the key compounds 3, 5 and 17.

Thin layer chromatography (TLC) was carried out using plates coated with a 250 μ slurry of Silica Gel G (Merck, after Stahl) and activated by heating to 100 °C for 1 h. The solvent systems used were (a) light petroleum and benzene, 1:4 and (b) benzene and ethyl acetate, 4:1. Plates were developed by spraying with 50% sulphuric acid and heating at 100 °C.

Production of 1-halogenodiisophoranes

1-Chlorodiisophor-2(7)-en-3-one (3) (1-chloro-5,5,9,11,11-pentamethyltricyclo[7.3.1.0²7]tridec-2(7)-en-3-one)

Method I: Use of thionyl chloride. – A solution of 1 [2] (2.76 g, 10 mmol) in anhydrous chloroform (25 ml) at 0 °C was treated dropwise with thionyl chloride (1.78 g, 15 mmol), and the liquid, protected against moisture, set aside at 0 °C for 3 days. The deep-yellow fluorescing liquid was evaporated below 30 °C in a vacuum (removing all thionyl chloride), the residue dissolved in light petroleum (b.p. 40–60 °C, 50 ml), filtered through alumina (12×1.5 cm), and the column exhaustively eluted with benzene – light petroleum (4:1, 300–400 ml). The pale-yellow solid obtained on removal of the solvent gave, on crystallization from methanol (8 ml per g), or ethanol (4 ml per g) or light petroleum (10 ml per g, recovery above 80% in each case), prisms of 3, m.p. 128–130 °C. Lit. m.p. 135–136 °C [14] (yield 2.35-2.7 g, 84–92%). UV (EtOH): λmax 243 nm (log ε 3.97). IR (KBr): 2950 vs – 2850 s, 1470, 1465 s d (CH₃, CH₂), 1675 vs (CO), 1625 s (C = C, conjug), 1385 ms, 1270 ms, 1180 m, 1135 ms, 965 ms, 900 ms, 705 mw cm⁻¹.

C₁₈H₂₅ClO (294.8)

Caled C 73.35 H 9.2 Cl 12.0
Found C 73.1 H 9.4 Cl 12.2

Method II: Use of hydrohalogen acid. – Finely powdered 1 [2] (11.04 g, 40 mmol) was added to stirred concentrated hydrochloric acid (200 ml), when solution occurred within 10–15 min (transient deep-red colour). The liquid became turbid, and white solid began to separate. After 24 h stirring at room temperature, the precipitate was collected, rinsed with 50% ethanol, and crystallized as above, giving 3, identical (mixed m.p., IR)
with material obtained in I (yield, 9.2–10.15 g, 78–86%).

2,4-Dinitrophenylhydrazone. – A solution of 3 (0.29 g, 1 mmol) and 2,4-dinitrophenylhydrazine (0.22 g, 1.1 mmol) in ethanol (12 ml) – concentrated hydrochloric acid (0.15 ml, 1.5 mmol) was boiled under reflux for 30 min, then reduced in volume. The solid (0.21 g, 45%) gave orange microprisms of the derivative, m.p. 173–174 °C (decomp.) (from ethanol).

C_{74}H_{31}ClN_{4}O_{4} (475.0)
Calcd C 60.7 H 6.5 Cl 7.5 N 11.8,
Found C 61.0 H 6.8 Cl 7.0 N 12.4.

1-Chloro-5,11-bisnordiisophor-2(7)-en-3-one (4)

Method I:
A solution of 2 (2.48 g, 10 mmol) in chloroform (15 ml) was treated at room temperature with thionyl chloride (1.43 g, 12 mmol) in chloroform (10 ml), and stirred at room temperature for 2 h, and at 50 °C for 1 h. The standard work-up (see 3, above) gave a pale-yellow solid (2.4 g); crystallization from ethanol (10 ml) with dropwise addition of water gave needles (1.6-1.9 g, 60-70%) of 4, m.p. 113-115 °C. Lit. m.p. 102-103 °C. UV: \( \lambda_{\text{max}} 241 \text{ nm (log } \varepsilon 4.13) \). IR: 2950 vs, 2900, 2880 vs d, 1465 s, 1410 s (CH\(_3\), C\(\text{F}\)), 1660 vs (CO), 1615 s (C = C, conjug), 840 ms, 825 m, 775 s (?C-C\(\text{Cl}\)) cm\(^{-1}\).

C\(_{16}\)H\(_{23}\)ClO\(_2\) (266.8)
Calcd C 72.1 H 8.6 Cl 13.3,
Found C 71.6 H 8.4 Cl 13.45.

Method II:
Dissolution of 2 (10 mmol) in concentrated hydrochloric acid (50 ml), interaction at room temperature for 24 h, and standard work-up (see above) gave mixtures containing, according to TLC, 15–20% of 4 (compare ref. [14]).

1-Chlorodiisophor-2(7)-ene (12)

Method I:
Treatment of 10 (15 mmol) [14, 33] by this procedure, followed by vacuum distillation gave a colourless mobile liquid (b.p. 110–112 °C/1.0 mm Hg). It solidified on storage and afforded needles (3.0 g, 60%) of 12, m.p. 56–57 °C (from ethanol). Lit. m.p. 60-61 °C [14]. IR: 2970-2890 vs, 2850 vs d, 1460 vs (CH\(_3\), CH\(_2\)), 1660 vs (CO), 1615 s (C=C, conjug), 840 ms, 775 s (\(? \text{C-Cl}\)) cm\(^{-1}\).

C\(_{18}\)H\(_{29}\)Cl (280.9)
Calcd C 77.0 H 10.3 Cl 12.6,
Found C 76.6 H 10.3 Cl 13.0.

Method III: Hydrogenation of the Haloketone.
A solution of 3 (1.48 g, 5 mmol) in glacial acetic acid (30 ml) was shaken in an atmosphere of hydrogen over Adams’ catalyst [34] (0.15 g) at room temperature for 3 h. The filtered liquid was stirred into ice, neutralized with 10 M sodium hydroxide, and the product extracted with ether. Removal of the solvent from the washed dried extracts gave a mobile oil (1.2 g, 85%), which consisted, after vacuum distillation and crystallization, of 12, identical with material obtained in I.

I-Chloro-5,11-bisnordiisophor-2(7)-ene (13)

Method I: Treatment of 11 (4.68 g, 20 mmol) by this procedure, followed by vacuum distillation gave a colourless mobile oil (b.p. 114–116 °C/1.0 mm Hg). It solidified on storage and afforded needles (3.0 g, 60%) of 13, m.p. 43–45 °C (from 85% ethanol). IR: 2950–2910 vs, 2870 vs, 1460 s, 1445 s sh (CH\(_3\), CH\(_2\)), 835 vs, 810 ms, 770 vs and 760 s sh (\(? \text{C-Cl}\)) cm\(^{-1}\).

C\(_{18}\)H\(_{25}\)BrO (339.3)
Calcd C 63.7 H 8.0 Br 23.6,
Found C 64.1 H 8.1 Br 23.1.

Method IV: Use of phosphorus tribromide. A solution of 1 (2.76 g, 10 mmol) in anhydrous benzene (400 ml) containing anhydrous pyridine (5 drops) was treated at 0–5 °C with vigorous swirling with phosphorus tribromide (5.42 g, 20 mmol). The mixture was set aside at 0 °C for 12 h, and at room temperature for 4 h, then slowly treated with ice-water (100 ml) and the organic phase washed to neutrality (sodium bicarbonate, water) and eva-
porated in a vacuum. The solution of the resulting reddish-brown resin in ethanol (10 ml) slowly deposited solid (m.p. 87–92 °C) which gave prisms of 5 (from ethanol), identical with material obtained in method II (yield, 17%). The filtrates contained only intractable gums.

Method V. Use of acetyl bromide – stannic chloride. A stirred solution of 6 (R' = Me) (0.58 g, 2 mmol) in acetyl bromide (1.0 g, 8 mmol), treated at 0 °C with stannic chloride (4 drops), was stirred at 0 °C for 30 min and at 25 °C for 3 h, and the liquid diluted with ice-water (5 ml). The precipitated resin hardened rapidly on stirring and gave prisms of 5 (from ethanol), identical with material obtained in method II (yield, 0.44 g, 65%).

Solvolyses

In this and the following two sections, selected representative experiments exemplify the typical behaviour of the compounds concerned.

1-Halogenodiisophor-2(7)-en-3-ones (3, 5)

Ethanolysis. – A solution of 3 (1.48 g, 5 mmol) or 5 (1.70 g, 5 mmol) in anhydrous ethanol (12 ml) was treated with one of sodium (0.138 g, 6 mg atom) in ethanol (6 ml) and set aside at room temperature for 1 h. The yellow liquid (depositing sodium chloride after a few min) was stirred into 3 M hydrochloric acid (100 ml), and the product extracted with ether. The washed dried extracts gave, on evaporation, a residue forming prisms (85–90%) of 1-ethoxydiisophor-2(7)-en-3-one (6, R' = Et), m.p. 101–103 °C (from light petroleum, b.p. 40–60 °C, or from 65% aqueous ethanol), identical with material obtained by trialkyl orthoformate alkylation [2]. Examination of the reacting mixture by TLC or by the usual work-up showed that solvolysis was substantially complete after 5 min.

The same procedure employing the appropriate alcohols as solvolytic reagents gave the following homologues: 6 (R' = Me): m.p. 87–88 °C (yield, 75–80%), 6 (R' = isoPr): m.p. 97–99 °C (yield, 70–85%), each identical with authentic material [2].

1-Alkoxy-5,11-bisnordiisophor-2(7)-en-3-ones (7, R' = Me, Et, isoPr)

These were obtained from 4 by solvolysis (as described for 3, above) and comprise the following examples:

The methoxy-homologue (7, R' = Me) formed elongated prisms (yield, 80%), m.p. 109–110 °C (from light petroleum, b.p. 40–60 °C). UV: $\lambda_{\text{max}}$ 243 nm (log ε 3.98). IR: 2960–2870 vs, 2830 s sh, 1460, 1440 s d, 1420 s, 1395 s, 1380 s (CH$_3$, CH$_2$), 1660 vs (CO), 1615 vs (C=C, conjug), 1085 vs br (C–O–C) cm$^{-1}$.

C$_{17}$H$_{25}$O$_2$ (262.4)

Calcd C 77.9 H 9.9,
Found C 77.4 H 10.0.

Its 2,4-dinitrophenylhydrazone formed deep-red prisms (75%), m.p. 194–195 °C (from ethanol – ethyl acetate).

C$_{23}$H$_{30}$N$_4$O$_5$ (442.5)

Calcd C 62.4 H 6.8 N 12.7,
Found C 62.4 H 7.0 N 12.7.

Its oxime, prepared from the ketone and hydroxylamine hydrochloride (1.0 and 1.2 mmol) by 3 h refluxing in ethanol (6 ml) – pyridine (1 ml), and addition to ice-water (50 ml) formed opaque microprisms (80%), m.p. 224–225 °C (from ethanol). IR: 3250 vs vbr (OH), 2960–2860 vs, 2820 vs sh, 1460 vs br, 1380 vs (CH$_3$, CH$_2$), 1620 s (C = N), 1130 s, 1095, 1090 vs br (C–O–C) cm$^{-1}$.

C$_{17}$H$_{25}$NO$_2$ (277.4)

Calcd C 73.6 H 9.8,
Found C 73.3 H 9.8.

The ethoxy-homologue (7, R' = Et) formed needles (yield, 70%), m.p. 78–80 °C (crystallized successively from light petroleum, b.p. 40–60 °C, then 60% aqueous ethanol). UV: $\lambda_{\text{max}}$ 243 nm (log ε 3.86). IR: 2940–2850 vs, 1465 s, 1385, 1380 s d (CH$_3$, CH$_2$), 1675 vs br (CO), 1620 s (C=C, conjug), 1120 ms, 1080 s (C–O–C) cm$^{-1}$.

C$_{18}$H$_{29}$O$_2$ (276.4)

Calcd C 78.3 H 10.1,
Found C 78.1 H 10.3.

2,4-Dinitrophenylhydrazone: Deep-red prisms, m.p. 171–172 °C (decomp), (from ethyl acetate – ethanol).

C$_{24}$H$_{32}$N$_4$O$_5$ (456.5)

Calcd C 63.2 H 7.0 N 12.3,
Found C 63.3 H 6.85 N 12.0.

Oxime: Lustrous platelets (80%), m.p. 178–179 °C (from ethanol), IR: 3280 vs vbr (OH), 2970–2890 vs, 1460 vs br, 1380 vs (CH$_3$, CH$_2$), 1630 s (C=N), 1130 s, 1080 vs vbr (C–O–C) cm$^{-1}$.

C$_{18}$H$_{25}$NO$_2$ (291.4)

Calcd C 74.2 H 10.0 N 4.8,
Found C 74.3 H 10.1 N 4.9.
The isopropoxy-homologue (7, R’ = isoPr) formed thin flakes, m.p. 117–118 °C (from ethanol–water, 3:2) (yield, 55%). UV: λ_max 243 nm (logε 3.96). IR: 2970–2880 vs, 1460 str, 1380 str (CH₃, CH₂), 1680–1665 vs (CO), 1615 s (C = C, conj), 1125 vs, 1095 s (C – O – C) cm⁻¹.

C₁₉H₃₀O₂ (290.4)  
Calcd C 78.6 H 10.3,  
Found C 78.9 H 10.2.

2,4-Dinitrophenylhydrazone: Scarlet prisms (60%), m.p. 181–182 °C (decomp) (from ethanol).

C₂₅H₃₄N₄O₅ (470.5)  
Calcd C 63.8 H 7.2 N 11.9,  
Found C 63.8 H 7.3 N 11.8.

Oxime: Rectangular prisms (75%), m.p. 177–178 °C (from ethanol). IR: 3330 vs br (OH), 2970–2880 vs mult, 1460–1445 s mult, 1430 ms, 1385 vs (CH₃, CH₂), 1630 m (C = N), 1130–1120 vs, 1090 ms (C – O – C) cm⁻¹.

C₁₉H₃₁N₂O₂ (305.45)  
Calcd C 74.8 H 10.2 N 4.6,  
Found C 74.3 H 10.1 N 4.6.

1-Chlorodiisophor-2(7)-ene (12):  
(a) A solution of 12 (1.40 g, 5 mmol) in methanol (15 ml) containing sodium methoxide (6 mmol) was set aside at room temperature for 24 h, then boiled under reflux for 2 h, forming a yellow liquid depositing traces of sodium chloride. In the usual isolation procedure, the starting material was recovered (ca. 85%).  
(b) Comparable observations were made using sodium ethoxide in ethanol. After further 18 h boiling, the starting material (b.p. 114–116 °C/1.5 mm Hg) was recoverable (56%), identified by IR and TLC.

1-Chloro-5,11-bisnordiisophor-2(7)-ene (13):  
(c) The same observations were made using 13 in conjunction with sodium methoxide (see (a)). After further 18 h boiling, the starting material (b.p. 114–116 °C/1.5 mm Hg) was recoverable (56%), identified by IR and TLC.  
(d) Ethanolysis of 13 gave analogous results, except that the production of 15 (R’ = Et) in ca. 10% yield after 20 h refluxing was demonstrable by TLC.

Hydrolysis

1-Bromodiisophor-2(7)-en-3-one (5)  
Action of aqueous alkali–dioxan. – A solution of 5 (0.68 g, 2 mmol) in dioxan (15 ml) – water (15 ml), treated with 10 M sodium hydroxide (0.6 ml, 6 mmol) was kept at 100 °C (under nitrogen) for 1 h. The greenish-yellow liquid was stirred into ice – 3 M hydrochloric acid (20 ml). The white solid gave, on crystallization from light petroleum (b.p. 40–60 °C), prisms (80%) of 1, m.p. 84–85 °C, identical with authentic material [2].

1-Chlorodiisophor-2(7)-en-3-one (3)  
(a) Action of aqueous alkali–dioxan gave results identical with those described in the foregoing paragraph.  
(b) Action of aqueous-ethanolic alkali. – The stirred orange two-phase system of a solution of 3 (0.6 g, 2 mmol) in ethanol (10 ml) and 10 M sodium hydroxide (2.5 ml) was boiled under reflux for 1 h. It was added to M hydrochloric acid (75 ml) and the product extracted with ether. The yellow residue obtained therefrom on evaporation solidified on storage and had, according to TLC, the following composition: 1, RF = 0.45 (10–20%); 6 (R’ = Et), RF = 0.37 (50–60%); polymeric isophorone, RF = 0.1–0 (10–15%). Crystallization from light petroleum (b.p. 40–60 °C) gave prisms (0.3 g, 50%) of 6 (R’ = Et), m.p. 101–103 °C.

1-Chlorodiisophor-2(7)-ene (12)  
A solution of 12 (1.40 g, 5 mmol) in ethanol (12 ml) – 5 M sodium hydroxide (2 ml, 10 mmol) was boiled under reflux for 12 h. The yellow liquid containing deposited sodium chloride was stirred into M hydrochloric acid (60 ml) and extracted with ether. The semicrystalline residue therefrom (1.1 g) was separated chromatographically: the appropriate fractions gave, on crystallization, the following products: 1, RF = 0.45 (10–20%); 6 (R’ = Et), RF = 0.37 (50–60%); polymeric isophorone, RF = 0.1–0 (10–15%). Crystallization from light petroleum (b.p. 40–60 °C) gave prisms (0.3 g, 50%) of 6 (R’ = Et), m.p. 101–103 °C.

Acetalysis

1-Chlorodiisophor-2(7)-en-3-one (3)  
A solution of 3 (4.42 g, 15 mmol) and urea (2.7 g, 45 mmol) in glacial acetic acid (150 ml) was kept at 100 °C for 48 h. The orange-red liquid was
stirred into ice-water, neutralized with sodium carbonate and extracted with ether. The orange oil obtained therefrom on evaporation solidified on storage (4.2 g). Its solution in light petroleum (b.p. 40–60 °C) – benzene (1:1) was filtered through alumina, and the column eluted with the same solvent mixture. The product therefrom, gave, on crystallization from ether – light petroleum, prisms of the 1-acetoxy-compound 8, m.p. 125–126 °C (2.6 g, 55%) [14], identified by IR (see below).

1-Chlorodiisophor-2(7)-ene (12)

The use of this reactant (4.2 g, 15 mmol) in the foregoing procedure gave a pale-yellow resin consisting, according to TLC, principally of 16, together with some 10. Its solution in light petroleum (b.p. 40–60 °C) was chromatographed, and the alumina column (40×2.5 cm) successively eluted with light petroleum (b.p. 40–60 °C, 250 and 750 ml), and exhaustively with benzene–light petroleum (1:4). The first eluate gave a colourless mobile oil (1.0 g) which failed to crystallize and was not identified. The second and third eluate gave solid (2.5 g) which consisted, after crystallization from ethanol–water (4:1), of prisms (2.28 g, 50%) of 1-acetoxydiisophor-2(7)-ene (16), m.p. 52–53 °C. IR: 2960–2860 vs, 1460–1435 m mult (CO of Ac), 1385 m, 1365 s (C = C, conjug), 1395 m sh, 1370 vs (CMe2), 1255, 1215, 1195 vs d (C – O – C, ester), 1145 s, 1095 ms, 1045 ms br, 1015 m cm−1.

C20H30O3 (304.5)
Calcd C 78.9 H 10.5,
Found C 78.4 H 10.5.

Acetylation of diisophorones

Diisophor-2(7)-en-1-ol-3-one (1)

(a) Perchlorid acid – catalyzed acetylation. – A stirred solution of 1 (8.28 g, 30 mmol) in acetic anhydride (50 ml) at 0 °C was treated dropwise with perchlorid acid (20 drops) dissolved in acetic anhydride (15 ml) during 30 min. The yellow, later deep-red liquid was stored at 0 °C for 3 days, then added dropwise to ice – 10 M sodium hydroxide (100 ml, 1 mol). The orange semisolid precipitate hardened to a yellow solid on storage, was washed with water, air-dried and dissolved in ethanol (20 ml). The resulting pale-yellow crystals were subjected to fractional crystallization from the same solvent and gave, as the less soluble fraction (m.p. 119–121 °C, total 4–4.8 g, 42–50%), 1-acetoxydiisophor-2(7)-en-3-one (8) as prisms, m.p. 124–125 °C (from ether, 6 ml per g, recovery 90%; from ethanol, 6 ml per g, recovery 60%). Lit. m.p. [14] 125–127 °C. UV: λmax 250 nm (log ε 3.87). IR: 2950 vs – 2870 s, 1460–1435 m (CH3, CH2), 1730 vs (CO of Ac), 1725 vs (CO of Ac), 1660 vs (CO, ring), 1630 s (C = C, conjug), 1395 ms, 1370 vs (CMe2), 1260 vs br, 1245 vs (C–O–C, ester) cm−1.

C20H30O3 (318.4)
Calcd C 75.5 H 9.4,
Found C 75.65 H 9.5.

The monoacetate (8) was substantially recovered after treatment with hydroxylamine hydrochloride by the standard procedure (see 7, above). It also failed to give a 2,4-dinitrophenylhydrazone.

The more soluble fractions from the ethanol filtrates (3.45–4.3 g, 32–40%) gave, on successive crystallization from ether or ethanol, then ethanol–water (6 and 4 ml per g, recovery 80%), prisms of 1,3-diacetoxydiisophora-2,7-diene (17), m.p. 75–77 °C. UV: λmax 246 nm (log ε 4.42). IR: 2940–2870 s, 1475 ms br, 1445 ms br (CH3, CH2), 1750 vs, 1730 vs (CO of 2 Ac), 1655 m (C = C, conjug), 1395 m sh, 1370 vs (CMe2), 1255, 1245 vs d, 1215, 1195 vs d (C–O–C, ester), 1145 s, 1095 ms, 1040 vs, 1025 s, 1015 m tr, 980 m cm−1.

C20H30O4 (360.5)
Calcd C 73.3 H 8.9,
Found C 73.6 H 8.9.

(b) Action of isopropenyl acetate. – A stirred solution of 1 (2.76 g, 10 mmol) in isopropenyl acetate (25 ml) was treated (under dry nitrogen) with concentrated sulphuric acid (3 drops, colour change to deep-yellow), boiled under reflux for 2 h, and two-thirds of the liquid distilled off under reduced pressure (under nitrogen). The residual brown liquid was diluted with ether (120 ml) and washed neutral with 5% sodium bicarbonate, 10% sodium chloride and water (removal of some tar). The dried solution gave, on evaporation under reduced pressure, an oil solidifying at 0 °C, which was fractionated as above, into 8, m.p. 118–120 °C (44%) and 17, m.p. 72–75 °C (25%).

Attempts to convert 8 into 17 by this procedure were unsuccessful, the reactant being largely recovered, but some 1 and resin were also formed.

5,11-Bisnordiisophor-2(7)-en-1-ol-3-one (2)

Acetylation of 2 (3.72 g, 15 mmol) by procedure (a) gave a crude resinous product, which was extracted with ether. The washed dried extracts gave on evaporation a brown viscous resin which was chromatographed in light petroleum on alumina, the column (2×35 cm) being eluted successively with light petroleum (1 l), light petroleum–benzene (4:1) and (3:2) (1 l each). Of the three fractions obtained on evaporation of the eluates (A:
0.3 g, B: 2.1 g, C: 1.6 g), the first was resinous and uncrystallizable.

Crystallization of B from ethanol (6 ml) gave prisms (1.70 g, 34%) of 1,3-diacetoxy-5,11-bisnor-diisophor-2(7)-en-3-one (18), m. p. 102–103 °C. UV: \( \lambda_{\text{max}} \) 246 nm (log \( e \) 3.93). IR: 1465 s, 1445, 1440 ms d, 1385, 1370 vs d (CH\(_3\), CH\(_2\)), 1755–1730 vs (CO of acetate), 1625 vs br, 1590 ms (C = C, conjug), 1250 vs br (C–O–C, ester) cm\(^{-1}\).

C\(_{18}\)H\(_{26}\)O\(_4\) (332.4)
Calcd C 74.5 H 9.0.
Found C 73.9 H 9.0.

We thank Mrs. J. E. Hawkes and Mrs. F. B. Galloway, of the University of London NMR Spectroscopy Service at King's College, London, for the production of the \(^{13}\)C NMR spectra.