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Diisophorone and Related Compounds. Part 12[1] Synthesis of 4-Bromodiisophorones and Their Reactions with Nucleophiles

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4-Bromodiisophor-2(7)-en-1-ol-3-one (**2**) is accessible by the action of hydrobromic acid on 2,7-epoxydiisophoran-1-ol-3-one (**1**), and is convertible into the corresponding 1-carboxylic acid (**9**) by the *Koch-Haaf* reaction. Nucleophilic substitution displaces the halogen in both the 4-bromoketol (**2**) and the 4-bromoketo-acid (**9**). Amongst the products thus obtained, 4-hydroxy-1-carboxydiisophor-2(7)-en-3-one (**11**) is of special interest as a source of the 3,4-diketo-1-carboxylic acid (**13**).

(Keywords: Diisophorone; Tricyclo[7.3.1.0^{2,7}]tridecanes)

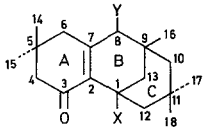
Diisophoron und verwandte Verbindungen, 12. Mitt.:
Synthese von 4-Bromdiisophoronen und ihre Reaktion mit Nucleophilen

4-Bromdiisophor-2(7)-en-1-ol-3-on (**2**) ist durch Einwirkung von Bromwasserstoffsäure auf 2,7-Epoxydiisophoran-1-ol-3-on (**1**) erhältlich und wird mittels der *Koch-Haaf*-Reaktion zur entsprechenden 1-Carbonsäure (**9**) umgesetzt. Durch nucleophile Reagenzien wird das Halogen sowohl im 4-Bromketol (**2**) als auch in der 4-Bromoketosäure (**9**) substituiert. Unter den so erhältlichen Produkten ist das 4-Hydroxy-1-carboxydiisophor-2(7)-en-3-on als Ausgangsmaterial für die 3,4-Diketo-1-säure (**13**) von zusätzlichem Interesse.

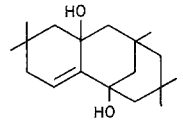
Introduction

The halogenation of diisophorone [diisophor-2(7)-en-1-ol-3-one (**A**) for nomenclature, see Ref.[2]] is a convenient means of introducing reactive centres into specific positions of this three-dimensional structure, at which further reactions may be studied. Our examination of the readily accessible 1-chloro- (**B**)[3] and 8-bromo-diisophorones (**C**)[3,4] from this point of view has shown that nucleophilic substitution of the

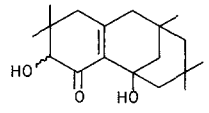
halogen may proceed normally[5,6], or may be attended by migration[7,8], partial aromatisation[1,4], or intramolecular condensation[9]. The way for investigating comparable substitutions at the 4-position in diisophorone has now been opened by the provision of a route to the novel 4-bromodiisophorones **2** and **9**. Nucleophilic replacement of their 4-bromo-substituent is found to take place normally; it provides reference compounds that have proved useful for solving structural and configurational problems concerning their 4-hydroxy-analogues (e.g. **7**, **11**) and 8-isomers (see Part 13, subjoined, and Refs. [7,8,10]).



A: X=OH; Y=H
B: X=Cl; Y=H
C: X=OH; Y=Br



D



E

Results and Discussion

Despite the inertness of its bridged 2,7-olefinic bond[2], diisophor-2(7)-en-1-ol-3-one (**A**) is readily convertible into the 2,7-epoxide **1**[11]. The ring-cleavage of epoxides by a variety of reagents is a versatile synthetic method, the mechanism and stereochemical course of which have been extensively studied[12,13].

Several examples of its use for modifying the diisophorone-structure have been described; they include the conversion of the 2,7-epoxide **1** into 1,4-dihydroxydiisophor-2(7)-en-3-one (**E**) by perchloric acid[10], into 1,7-dihydroxydiisophor-2-ene (**D**) by hydrazine (*Wharton* reaction)[11], and the regeneration of the parent ketol **A** by metal reduction[11]. However, our past attempts[10] to cleave the oxirane-ring (of **1**) with hydrohalogen acids, under conditions that yield halohydrins from epoxides[12,13], produced merely intractable resins.

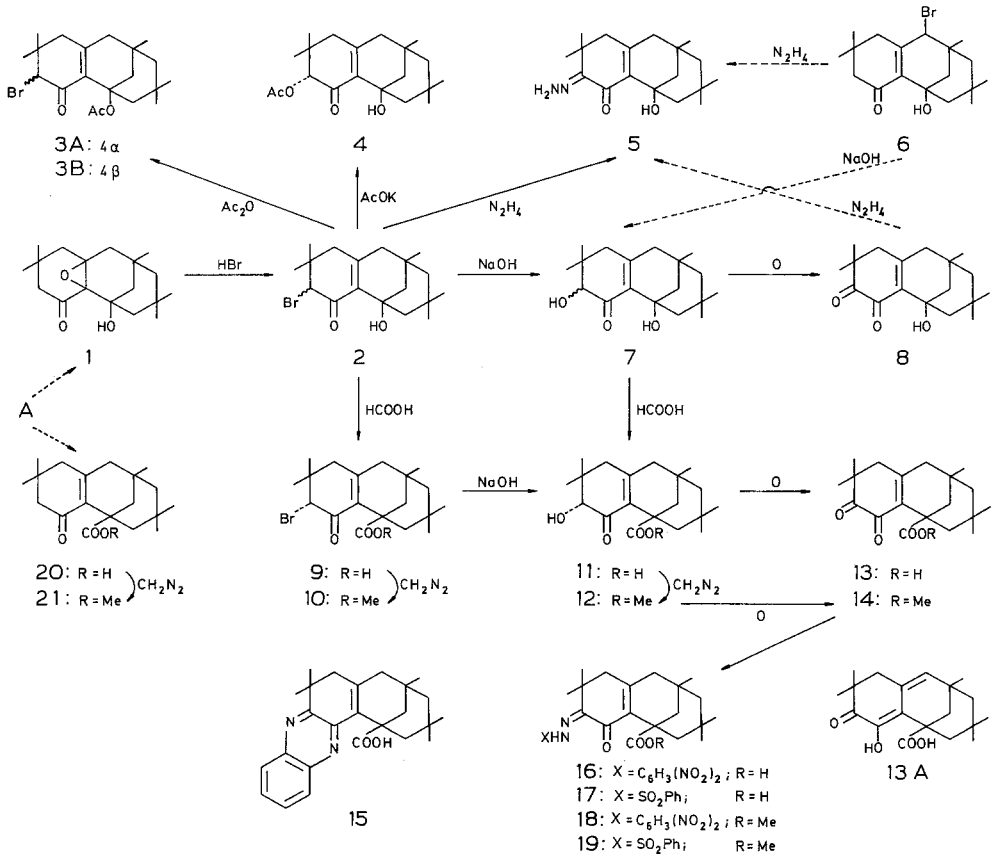
It has now been found that the action of hydrobromic acid on **1** under mild conditions readily opens the oxirane ring, and simultaneously introduces bromine at C-4. The formal resemblence of the effect of hydrobromic and perchloric acid[10] (see above) on **1** is noteworthy.

Thus, the action of 60% hydrobromic acid in glacial acetic acid on 2,7-epoxydiisophoran-1-ol-3-one (**1**) at room temperature gave a product (ca. 50%) consisting of a mixture of the epimeric 4α- and 4β-bromodiisophor-2(7)-en-1-ol-3-ones (**2**), the former predominating. Its i.r. spectrum resembled that of the authentic 8-bromo-isomer[3,4] **6**, but was clearly distinct therefrom in the "finger print" range; beyond

1 200 cm^{-1}, the i.r. spectra of both the 4- and 8-bromo-compounds **2** and **6** and their parent ketol **A** are remarkably similar. The mass spectrum of **2** displayed only weak signals of the molecular ion (*m*/e, 356, 354); the prominent peaks indicated the initial removal of ring C by the usual[14] loss of the fragment C_5H_{11} (*m*/e 71), followed by the ejection of bromine. The fragmentation pattern thus resembles that of the 8-bromo-isomer **6**, which has been interpreted in detail[14].

The location of the bromine-substituent at C-4 (in **2**) is in accord with both the chemical and ^{13}C-nmr spectral evidence. Nucleophilic replacement of the halogen by acetolysis or hydrazinolysis gave good yields of 4α-acetoxydiisophor-2(7)-en-1-ol-3-one (**4**) or the 4-hydrazone **5**, respectively, both known compounds of established structure[7,10]. It is recalled that the 8-bromo-isomer **6** yields the *same* 4-substituted products (**4**, **5**) under these conditions[7]; however, this does not invalidate

Scheme 1



the present reasoning in favour of structure **2**, since the authentic 8-bromo-isomer **6**[4] is distinct from **2**, and undergoes these nucleophilic reactions effectively with simultaneous migration of the substituent[7]. Further, the apparent sole production of the 4α-acetoxy-epimer **4** in the acetolysis of the 4αβ-bromoketol **2** is consistent with the fact that its 4β-epimer is an uncrystallisable oil[10], and therefore escapes isolation. Unlike its 4-hydroxy-analogue **7**[10], the 4-bromoketol **2** did not yield a 2,4-dinitrophenylhydrazone under the standard conditions[2].

The action of alkali on 4-bromodiisophor-2(7)-en-1-ol-3-one (**2**) gave 3,4-diketodiisophor-2(7)-en-1-ol **8**, evidently by air oxidation of the primarily formed 4-hydroxy-compound **7**; the latter was isolable by performing the reaction in an atmosphere of nitrogen. Although yields were low in either case, the observations add to the evidence supporting the formulation of **2**. Acetylation of **2** gave both the 4α- and 4β-bromo-1-acetoxy-derivatives **3 A, B**, which differed in their physical properties (except the mass spectra) and were separable by fractional crystallisation; the more abundant fraction (ca. 65%) is regarded as the 4α-epimer.

Table 1. *^{13}C-Nmr spectrum of 4-bromodiisophor-2(7)-en-1-ol-3-one* (**2**)[a, b]

Compound Carbon no.	**A**	**2**[c]	
1	71.4 s	71.2	72.0 s
2	135.4 s	133.6	134.4 s
3	200.7 s	193.2	— s
4	51.8 t	63.6	61.9 d
5	*32.2 s	37.1	36.1 s
6	45.7 t	*45.5	46.1 t
7	157.5 s	157.0	158.9 s
8	44.6 t	*42.5	41.1 t
9	*32.4 s	32.3	32.2 s
10	52.1 t	52.3	— t
11	31.4 s	31.6	31.7 s
12	50.3 t	50.3	49.7 t
13	46.6 t	46.3	46.7 t
14	26.8 q	26.6	28.1 q
15	29.7 q	26.1	24.5 q
16	28.2 q	28.6	29.2 q
17	32.7 q	32.7	32.8 q
18	37.1 q	37.1	37.0 q

[a] The spectrum of the parent ketol **A** is given for comparison[15].

[b] Chemical shifts are in ppm downfield from *TMS*. The numerical values supersede those previously listed[15].

[c] The more intense signal is shown first.

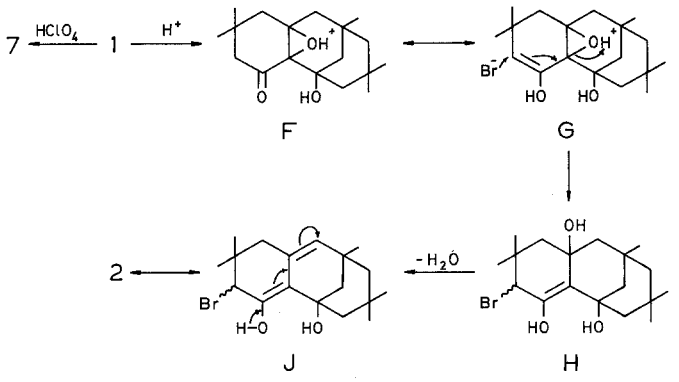
* Signals may be interchanged (vertically).

The ^{13}C-nmr spectrum of 4-bromodiisophor-2(7)-en-1-ol-3-one (**2**), interpreted by reference to the assigned spectrum of the parent ketol **A**[15] (see Table 1), provides the following structural information: Due to the presence of both epimeric forms of the compound, the spectrum contains twice the expected number of signals, grouped in closely spaced pairs; the more intense set is thought to be associated with the predominating 4α-epimer. The location of the bromo-substituent at C-4 is confirmed by its effect of displacing the singlet of the adjacent 3-keto-carbon upfield (from 200.7 in **A** to 193.2 ppm in **2**), and that of the adjacent 5-carbon downfield (from 32.2 or 32.4 to 37.1 ppm); neither displacement occurs on passing from the parent ketol **A** to its 8-bromo-derivative **6**[15]. Furthermore, the characteristic C-4 triplet of **A** at 51.8 ppm[15] gives way (in **2**) to a doublet (at lower field). The quartets are provisionally assigned, in analogy with those of **4** and **7**[15], so as to reflect the maximum influence of the 4α-axial bromine substituent on the spatially most proximate equatorial 15-methyl-carbon.

Mechanism. The formation of **2** from the epoxide **1** proceeds by a mechanism, in which the scission of the oxirane-ring clearly plays an essential role. The failure of the parent ketol **A** to react under identical conditions emphasises this point. In acidic media, oxirane rings are generally cleaved by the addition of a proton and the appropriate anion to their oxygen and an adjacent carbon atom, respectively, by an S_N1 mechanism resulting in a racemic product[12,13,16]. In the present example, direct attack at the carbon atoms of the oxirane-ring appears to be sterically disfavoured: access to these positions from the α-face of rings A/B is restricted by ring C, especially by its 17ax-methyl substituent projecting below the plane of rings A/B of the folded structure. Recently, the conversion of 8-bromo- (**6**) into 4-hydroxydiisophor-2(7)-en-1-ol-3-one (**7**) by alkali has been accounted for by an S_N2''-mechanism, involving a direct attack of the anion at C-4[7]. An analogous interpretation of the present reaction (Scheme 2) envisages attack by bromide at C-4 of the protonated enolised reactant **G**. Concomitant epoxide-fission, displacement of the double bond (resulting in **H**), loss of the elements of water (forming **J**), and reversal of the enolisation to the more stable αβ-unsaturated keto-system completes the process. Since the anion may approach C-4 from above or below the plane of ring A, both epimers of the product are formed. The relative complexity of this process and consequent scope for the occurrence of side-reactions is held to be responsible for the moderate yields obtained, and for the persistent formation of resins.

The foregoing mechanism may also operate in the formally analogous conversion of the epoxide **1** into 4-hydroxydiisophor-2(7)-en-1-ol-3-one (**7**) by perchloric acid[10], in which case a hydroxy-anion functions as the attacking species at C-4 (in **G**): this alternative is preferable to the original interpretation[10] in that it does not invoke the sterically disfavoured initial hydration.

Scheme 2



The availability of **2** has also made the corresponding 4-bromo-1-carboxylic acid (**9**) and its congeners readily accessible. These were required as reference compounds in connexion with the assignment of structures to their 8-substituted position isomers (see Part 13, subjoined), and as intermediates in the synthesis of the 3,4-diketocarboxylic acid **13**. Moreover, carboxylic acids of this series are generally less soluble, more highly crystalline and less liable to resinification than are ketols and other functional derivatives, and are correspondingly more easily manipulated in the experimental work.

The introduction of carboxyl-groups at tertiary carbon atoms by the *Koch-Haaf* reaction[17,18] has been applied successfully to the synthesis of diisophorone-1-carboxylic acids. 1-Carboxydiisophor-2(7)-en-3-one (**20**) and its 5,11-bisnor-analogue were first obtained by its means[5], on treatment of the 1-chloro-compounds (e.g. **B**) with anhydrous formic acid in sulphuric acid at 0° in the presence of one equivalent of silver sulphate for the disposal of the displaced chloride ion. However, since the reaction proceeds by the addition of nascent carbon monoxide to the intermediate carbonium ion[17], the 1-chloro-group (of **B**) is replaceable in the absence of silver ions, and 1-hydroxy- and 1-alkoxy-groups are displaced with equal facility. The simplified procedure has made the 1-carboxylic acid **20** directly obtainable in quantity from the parent ketol **A** (see Experimental), and has proved effective in the production of the substituted analogues **9** and **11**; (see also Part 13, subjoined). With careful control of the conditions, 4-bromo-1-carboxydiisophor-2(7)-en-3-one was obtainable by the *Koch-Haaf* carboxylation (**2** → **9**) in high yield. The product was sterically uniform: originating presumably from the more abundant 4α-epimer of the starting material **2**, it is regarded as the 4α-bromo-compound.

A further object was the synthesis of the 3,4-diketo-1-carboxylic acid **13** for its comparison with the parent 3,4-diketol **8**[8]. It was obtained from the 4-bromo-compound by way of 4-hydroxy-1-carboxydiisophor-2(7)-en-3-one (**11**), which was accessible in good yield by the action of alkali on the 4α-bromo-acid **9**. The contrasting difficulty of converting the corresponding 4-bromoketol **2** into the 1,4-dihydroxyketone **7** by alkaline hydrolysis (see above) is noteworthy. The resulting 4-hydroxy-acid **11** was the 4α-epimer containing varying small quantities of the 4β-form, as shown by the results of its acetylation, with or without prior esterification (to **12**) (see Part 13, subjoined).

An alternative route to the 4-hydroxy-acid **11** was the *Koch-Haaf* carboxylation of diisophor-2(7)-ene-1,4-diol-3-one (**7**). However, the production of this 1,4-diol [from 8-bromodiisophor-2(7)-en-1-ol-3-one, **6**][7] tends to be erratic, and its carboxylation (to **11**) was in this instance attended by much resinification, resulting in low overall yields. Although this route was therefore less suitable for preparative purposes, it was still significant in confirming the formulation of the compounds **7**, **9**, and **11** of both reaction sequences.

Kiliani oxidation[19a] of the 4-hydroxy-3-keto-acid **11** thus obtained gave satisfactory yields of 3,4-diketo-1-carboxydiisophor-2(7)-ene (**13**). Unlike the comparable 3,4-diketol **8**[8], it did not separate from acidic media as a stable enolic form (**13 A**). Its properties reflected the presence of the extended conjugated system comprising an αβ-diketo-group adjacent to an olefinic bond. The compound was distinctly yellow, and gave rise to a group of four intense peaks at 1 725–1 635 cm^{-1} in the i.r., and to a broad absorption band centred at 257 nm in the u.v. range. It reacted with phenylene diamine[20] with formation of a substituted quinoxaline (**15**). Like the 3,4-diketol **8**[8], it readily gave monoarylhydrazones, formulated analogously as 4-hydrazono-derivatives (**16**, **17**). The potential usefulness of the 3,4-diketo-grouping (in **13**) as a point of attack for cleaving ring A[20] of the diisophorone molecule is noteworthy.

The ketocarboxylic acids **9**, **11**, and **20** were converted into the corresponding methyl esters **10**, **12**, and **21** by diazomethane[19b]. Under the mild conditions of this reaction, esterification proceeded smoothly and in better yield than in the *Fischer-Speier* procedure[21] previously employed[5]. Reconversion into the acids (e.g. **21** → **20**) occurred upon acid hydrolysis by a method that has been described for the production of the comparable 2,6-diketoadamantane-1,5-dicarboxylic acid[22]. In contrast, the methyl esters were remarkably resistant to alkaline hydrolysis, the model ester **21** being unaffected by boiling aqueous-ethanolic N-alkali (1 h). The greatly reduced saponification rates observed on passing from primary to tertiary carboxylic acid esters (e.g.

ethyl propionate to pivaloate, $Me_3C \cdot COOEt$) have been noted, and have been ascribed to steric causes[23].

3,4-Diketo-1-methoxycarbonyldiisophor-2(7)-ene (**14**) was obtained by the parallel *Kiliani* oxidation of the 4-hydroxy-methyl ester **12**. The more obvious route, viz. esterification of the 3,4-diketo-acid **13** by diazomethane was inapplicable, because it resulted in simultaneous spiro-oxirane formation at C-4, a reaction that will be described in another connection. The diketo-ester **14** gave the usual hydrazono-derivatives **18** and **19**, but unaccountably failed to yield a quinoxaline (corresponding to **15**).

In contrast to its ready hydrolysis to the 4-hydroxy-acid **11**, the 4-bromo-acid **9** failed to undergo acetolysis on treatment with potassium acetate in acetic acid. Since the corresponding 4-bromoketol, as well as the 8-bromo-isomer react readily under identical conditions (**2**, **6** → **4**), it is concluded that the 4-bromo-substituent (in **9**) is sufficiently stabilised by the proximate carboxyl group in this instance.

The structures assigned to the keto-acids now described were completely corroborated by the characteristics of their ^{13}C-nmr spectra. For reasons of conciseness and more effective comparison, the spectra (except that of **2**, above) are recorded and discussed in conjunction with those of the isomeric 8-substituted series (see Part 14, subjoined).

Experimental

The nomenclature employed is that adopted in the initial paper of this series[2]. This gives general information concerning standard procedures, reagents, solvents, and equipment. Light petroleum had b.p. 60–80° unless otherwise specified. Formic acid used in the *Koch-Haaf* reaction was the anhydrous 98–100% material. Except for key-compounds, unassigned peaks of the i.r. spectra are not recorded.

4-Bromodiisophorone

4-Bromodiisophor-2(7)-en-1-ol-3-one (**2**)

A stirred solution of 2,7-epoxydiisophoran-1-ol-3-one[11] (**1**, 8.76 g, 0.03 mol) in glacial acetic acid (180 ml) was treated at room temperature dropwise with 60% hydrobromic acid (45 ml) during 45 min. The yellow liquid was set aside for 1 h, then stirred into ice-water (1.2 l). The solidified pale-yellow granular material (occasionally still somewhat soft after 24–48 h) was collected, washed with water and air-dried (8.5–9 g). Crystallisation from light petroleum (b.p. 40–60°, 15–20 ml per g) gave prisms of **2**, m.p. 119–120° (4.5–5.5 g, 42–52%, in two or three successive crops). (Found: C 60.8; H 7.7; Br 22.3. $C_{18}H_{27}BrO_2$ requires C 60.9; H 7.6; Br 22.5%). ν_{max} 3 480 s (OH), 2 950 vs–2 850 s, 1 460 ms, 1 415 s br (CH_3, CH_2), 1 645 vs (CO), 1 625 vs (C : C conjug.), 1 395 ms, 1 375 vs ($\cdot CMe_2$), 690 s (? Br), 1 325 m, 1 305 ms, 1 290 s d, 1 190, 1 180, 1 160 m t, 1 100 mw, 1 080 mw, 1 050 vs, 1 000 m, 950 mw, 915 m cm^{-1}. λ_{max} 263 nm (log ε 3.97); 207 (3.46). *m/e* 356, 354 w (M^+), 285, 283 vs (M^+-71), 204 m (M^+-71-Br), 341, 339 m, 286, 284 s, 205, 203 s, 189 s.

Spontaneous evaporation of the final filtrates gave an uncrystallisable sticky resin (representing nearly half the yield), of which more than one quarter still consisted of **2**. This was not isolable as such, but by subjecting the total resin to the *Koch-Haaf* reaction, 4-bromo-1-carboxydiisophor-2(7)-en-3-one (**9**, or preferably its methyl ester, **10**; for details see below) were obtainable in ca. 25% yield. The final motherliquors therefrom gave again intractable resins.—Alternatively, acetylation of the total resin gave **3** in low yield (5–10%).—The total resin did apparently not contain appreciable quantities of diisophorone (**A**, i.e. the ultimate starting material) because it failed to give a 2,4-dinitrophenylhydrazone under the standard conditions[2].

The 4-bromoketol (**2**) failed to yield a 2,4-dinitrophenylhydrazone by the standard procedure[2], the reagent being largely recovered.

Diisophor-2(7)-en-1-ol-3-one (**A**, 0.02 mol), subjected to the action of hydrobromic acid under the above conditions, was recovered (80%).

1-Acetoxy-4α-(and β)-bromodiisophor-2(7)-en-3-one (**3 A**, **3 B**)

A solution of **2** (1.42 g, 0.004 mol) in glacial acetic acid (18 ml)—acetic anhydride (9 ml) was treated (external ice-cooling) with 60% perchloric acid (12 drops), set aside at room temperature for 3 h, and the yellow liquid stirred into warm water (300 ml). The white resin solidified on storage (m.p. 132–137°, 1.4 g); it was crystallised from light petroleum, giving small prisms (0.51 g, 64%) of **3 A**, m.p. 174–176°. (Found: C 59.9; H 7.5; Br 20.4. $C_{20}H_{29}BrO_3$ requires C 60.5; H 7.3; Br 20.1%.) ν_{max} 2 960 vs–2 860 s, 1 460 ms, 1 425 ms (CH_3, CH_2); 1 720 vs (C : O of *Ac*), 1 675 vs (CO), 1 630 s (C : C conjug.), 1 390 ms, 1 370 vs (·CMe_2), 1 255 vs, 1 240 vs (C—O ester), 695 ms (? Br) cm^{-1}. *m/e* 398, 396 vw (M^+), 355, 353 vw (M^+-43, *Ac*), 339, 337 w (M^+-59, *Ac*O), 323, 321 w (M^+-59-16), 317 w (M^+-Br), 258 s (M^+-Br-59), 257 vs max (M^+-Br-59-1), 242 w (M^+-Br-59-16), 285 w, 283 w, 276 ms, 274 ms, 202 m, 201 ms.

The motherliquors therefrom deposited the epimeric **3 B** as prisms, m.p. 142–145° (8–18%) (from ethanol). (Found: C 60.2; H 7.4; Br 21.6%.) ν_{max} 2 950–2 860 vs, 1 470–1 425, 1 410 s mult (CH_3, CH_2), 1 725 vs (C : O of *Ac*), 1 660 vs (CO), 1 625 s (C : C conjug.), 1 395 s–1 370 vs mult (·CMe_2), 1 260, 1 245 vs br (C—O ester), 715 ms (? Br) cm^{-1}. *m/e*, as the foregoing, **3 A**.

After being treated in pyridine (10 ml) with acetic anhydride (3 ml), the reactant (**2**, 0.003 mol) was recovered (90% after 24 h at room temperature, and 70% after 1.5 h at 100°).

4α-Acetoxydiisophor-2(7)-en-1-ol-3-one (**4**, by acetolysis)

A solution of **2** (1.78 g, 0.005 mol) and potassium acetate (1.5 g, 0.015 mol) in glacial acetic acid (12 ml) was boiled under reflux for 1 h, white solid separating after 15 min. Addition of the suspension to ice-water (200 ml) precipitated a curdy solid (1.4 g, 84%: pure **4** by i.r.), which gave prisms (1.03 g, 64%) of **4**, m.p. 106–108° (from light petroleum), identical (mixed m.p., i.r.) with authentic material[7].

The crystallisation filtrates gave, on spontaneous evaporation, an orange resin. This was acetylated (glacial acetic acid, acetic anhydride, 6 ml each; 60% perchloric acid, 6 drops; 2 h at room temperature, followed by addition to water). Dissolution of the resulting resin in light petroleum gave as two successive crops (i) 1,4β-diacetoxydiisophor-2(7)-en-3-one (0.19 g, 10%), identified by mixed m.p. 185–186° and i.r. spectrum[10] (ii) its 1,4α-epimer (0.15 g, 8%), identified by mixed m.p. 130–132° and i.r. spectrum[10].

4-Hydrazonodiisophor-2(7)-en-1-ol-3-one (**5**)

A solution of **2** (1.78 g, 0.005 mol) in hydrazine hydrate (8 ml) was boiled under reflux for 20 min. The yellow turbid liquid was added to ice-water; the precipitated pale-red soft resin was rinsed with water, and immediately added to boiling ethanol (10 ml). The yellow crystalline solid (m.p. 155°, 0.85 g, 56%) which separated was **5** (from ethanol), identical (mixed m.p. 160–162°, i.r.) with authentic material[7].

1,4α-Dihydroxydiisophor-2(7)-en-3-one (**7**) (Alkaline Hydrolysis of **2**)

A solution of **2** (1.78 g, 0.005 mol) in dioxan (20 ml) was treated *under nitrogen* at room temperature during 15 min dropwise with *N*-sodium hydroxide (7.5 ml, 0.0075 mol). After continued stirring under nitrogen for 45 min, the clear yellow liquid was added to ice-water (100 ml) containing 3 *N*-sodium hydroxide (10 ml). A pale-yellow precipitate appeared on stirring, resinified, and changed to a pale-yellow soft solid (1.1 g) which was dissolved in light petroleum. The faintly yellow microprisms which separated fairly rapidly were **7** (0.47 g, 32%), identified by mixed m.p. 116–118° and i.r. spectrum[7,10]. The reactant was substantially recovered after a shorter reaction time (20 min).

In the absence of the inert atmosphere, the hydrolysis yielded a crude product, which gave on crystallisation as above, a first crop of **8** as yellow microprisms (0.18 g, 13%), identified by mixed m.p. 260–262° and i.r. spectrum[8].—Two subsequent crops (0.41 g, 28%) were **7**. Attempts to isolate any 1,4β-epimer by acetylation (see Ref.[7]) of the residual resins remaining from the crystallisation filtrates were unsuccessful, giving only intractable oils.

4-Bromodiisophorone-Carboxylic Acid

1-Carboxydiisophor-2(7)-en-3-one (**20**)

(a) Into a stirred precooled (0°) mixture of concentrated sulphuric acid (400 ml)—formic acid (10 ml, added dropwise), finely powdered diisophor-2(7)-en-1-ol-3-one (13.8 g, 0.05 mol) was introduced slowly (30 min), each portion being allowed to dissolve (deep red colour) before the next was added. To the orange liquid, more formic acid (50 ml) was added dropwise (2 h, effervescence) with external ice-cooling (internal temperature ca. 5°) and stirring continued for 1 h, when effervescence nearly ceased. Addition of the liquid to ice-water (3 l) gave a white precipitate (crude: m.p. 223–225°, ca. 13.5 g, 90%), which was crystallised from ethanol (10 ml per g, recovery 80%) affording **20**, m.p. 244–246°, identical (i.r.) with authentic material[5]. λ_{max} 247 nm ($\log \varepsilon$ 3.96); λ_{infl} 206 nm (3.04). *m/e* 304 m (M^+), 287 m (M^+-17, OH), 286 s (M^+-17-1), 259 m (M^+-45, COOH), 258 s (M^+-45-1), 216 w (M^+-71-17), 215 m (M^+-71-17-1), 201 s (max).

(b) The use of 1-chlorodiisophor-2(7)-en-3-one[3] (1.47 g, 0.005 mol) and concentrated sulphuric acid (50 ml)—formic acid (10 ml) as in (a) (addition of formic acid, from 0° to room temperature; 45 min, effervescence and fumes of hydrogen chloride) produced a white solid (m.p. 222°, 1.45 g, 95%) which gave prismatic needles of **20**, identical with authentic material[5].

(c) 1-Ethoxydiisophor-2(7)-en-3-one[5] similarly gave **20** in 75% yield.

1-Methoxycarbonyldiisophor-2(7)-en-3-one (**21**)

A swirled suspension of finely powdered **20** (3.04 g, 0.01 mol) in ether (200 ml) was treated at room temperature during 3–5 min with ethereal diazomethane

(from toluene-*p*-sulphonylmethylnitrosamide, "Diazald"[19b], 0.025 mol). The remaining suspended reactant dissolved rapidly and the liquid effervesced; during the addition of the first half of the reagent, the yellow colour was discharged, but this persisted thereafter. After 2 h storage at room temperature, the remaining diazomethane was destroyed by an excess of 3*N*-acetic acid (effervescence) and the latter neutralised with aqueous 1.5*M*-sodium carbonate. The washed neutral ethereal solution gave, on evaporation under reduced pressure, a pale-yellow resin which solidified rapidly. Crystallisation of the white solid from light petroleum gave massive prisms of **21**, m.p. 114–117° (2.55 g, 80%), identified by its i.r. spectrum[5]. *m/e* 318 m (M^+), 287 m (M^+-31, O*Me*), 286 s (M^+-31-1), 259 m (M^+-59, COO*Me*), 258 s (M^+-59-1), 216 w (M^+-71-31), 215 m (M^+-71-31-1), 201 s (max), 243 m, 189 w, 187 w.

Like its parent carboxylic acid **20**[5], the methyl ester **21** did not yield a 2,4-dinitrophenylhydrazone under the standard conditions[2].

The methyl ester **21** (0.64 g, 0.002 mol) was recovered (95%) after being boiled in ethanol (15 ml)—3*N*-sodium hydroxide (7.5 ml) for 1 h.

Reconversion into the acid. A solution of **21** (1.59 g, 0.005 mol) in warm glacial acetic acid (15 ml) was treated with concentrated hydrochloric acid (10 ml), the clear colourless liquid boiled under reflux for 2 h, then stirred into ice-water (200 ml). The precipitate (m.p. 225–230°, 1.36 g, 90%, pure by i.r.) was **20**, m.p. 245–246° (from ethanol).

4α-Bromo-1-carboxydiisophor-2(7)-en-3-one (**9**)

To stirred concentrated sulphuric acid (100 ml), maintained at 0° to —5°, formic acid (2 ml) was added dropwise during 10 min (effervescence), followed by **2** (3.55 g, 0.01 mol) in small portions, the solid being each time allowed to dissolve before more was added (total, ca. 1 h). More formic acid (18 ml) was then added dropwise in the same temperature range with continued stirring (ca. 1.5 h). The gently effervescing liquid was added to ice-water (300 ml), the finely divided white precipitate collected and washed with water (by suspension) (m.p. 205–210°, ca. 3.5 g, 90%). Crystallisation from acetone (35 ml per g) or acetone-ethanol gave felted silky needles of **9**, m.p. 231–232° (in 2–3 successive crops, 72–84%). (Found: C 59.2; H 7.2; Br 21.6. $C_{19}H_{27}BrO_3$ requires C 59.5; H 7.05, Br 20.9%.) ν_{max} 2 950–2 850 vs, 1 470 ms, 1 425 ms (CH_3, CH_2), 2 660–2 650 m t, 2 550 mw d (COOH), 1 690 vs (CO of COOH), 1 665 vs (CO), 1 635 s (C : C conjug.), 1 395 m, 1 380 ms (·C*Me*$_2$), 1 295 s, 1 190 m, 1 155 m, 725 mw, 685 mw cm^{-1}. λ_{max} 260 nm (log ε 3.72). *m/e* 384, 382 w (M^+), 366, 364 m (M^+-18, OH-1), 323, 321 m (M^+-45, COOH-16), 303 w (M^+-Br), 286 m (M^+-Br-17, OH), 285 s (M^+-Br-17-1), 258 s (M^+-Br-45, COOH), 257 vs (max) (M^+-Br-45-1), 215 m (M^+-Br-71-17), 259 s, 188 m.—The success of the reaction depends particularly on the low temperature range employed; this requirement was more easily met by working on a small scale.

Stability of **2** *to concentrated sulphuric acid.* A solution of **2** (0.003 mol) in concentrated sulphuric acid (20 ml), kept at 0°–5° for 2 h, and stirred into ice water gave a precipitate of the starting material (recovery of recrystallised product, 80%) substantially unchanged in its epimeric composition (by ^{13}C nmr spectrum).

Attempted Acetolysis of **9**. 4α-Bromo-1-carboxydiisophor-2(7)-en-3-one (**9**) was recovered (70–80%) after being treated with potassium acetate in acetic acid under conditions which resulted in acetolysis of **2** (see above).

4α-Bromo-1-methoxycarbonyldiisophor-2(7)-en-3-one (**10**)

A suspension of **9** (1.92 g, 0.005 mol) in ether (120 ml) was treated with ethereal diazomethane (from "Diazald"[19b], 0.025 mol) and the crude product isolated as described for **21** (see above). Having first formed a clear colourless resin, it quickly solidified and gave, on crystallisation from a relatively large volume of light petroleum, massive prisms (1.7 g, 85%) of **10**, m.p. 169–170°. (Found: C 59.9; H 7.3; Br 20.6. $C_{20}H_{29}BrO_3$ requires C 60.5; H 7.3; Br 20.1%.) ν_{max} 2 950–2 860 vs, 1 470, 1 450, 1 440 ms t, 1 425 ms (CH_3, CH_2), 1 735 vs br (C:O ester), 1 665 vs (CO), 1 640 s (C:C conjug.), 1 395 ms, 1 380 vs (·CMe_2), 1 240 vs br (C—O ester); numerous sharp peaks below 1 300, including the following prominent ones: 1 290 ms, 1 185 s, 1 155 ms, 1 090 ms, 1 055 s, 1 000 m, 900 m, 800 mw, 750 ms, 685 m cm^{-1}. λ_{max} 261 nm (log ε 3.76). *m/e* 398, 396 w (M^+), 367, 365 w (M^+-31, *Me*O), 366, 364 mw (M^+-*Me*O-1), 339, 337 w (M^+-59, COO*Me*), 317 w (M^+-Br), 286 s (M^+-Br-31), 258 m (M^+-Br-59), 257 vs (max) (M^+-Br-59-1), 215 w (M^+-Br-71-31), 187 m (M^+-Br-71-59), 287 m, 201 ms.

1-Carboxy-4-hydroxydiisophor-2(7)-en-3-one (**11**)

(a) *By Action of Sodium hydroxide on* **9**. A solution of **9** (5.75 g, 0.015 mol) in 3*N*-sodium hydroxide (20 ml, 0.06 mol)—water (60 ml) was boiled under reflux for 20 min. The pale-yellow (sometimes turbid) liquid was cooled to room temperature and added to ice-water (250 ml) containing concentrated hydrochloric acid (10 ml). The white precipitate (crude: m.p. 185–195°, 4.1–4.3 g, 85–90%; satisfactory i.r.) gave, on crystallisation from ethanol—light petroleum (1:5), minute prisms of **11**, m.p. 216–220° (as 3–4 successive crops, total ca. 70%.) (Found: C 71.3; H 8.9. $C_{19}H_{28}O_4$ requires C 71.25; H 8.75%). ν_{max} 3 400 vs (OH), 2 960 vs–2 870 s, 1 445 ms, 1 425 ms (CH_3, CH_2), 2 600 w (COOH), 1 720 vs (CO of COOH), 1 665 vs (CO), 1 640 s (C:C conjug.), 1 395 m–1 370 s mult (·CMe_2), 1 235 vs, 1 185 s, 1 140 vs, 1 065 s, 1 000 s (group of diagnostic peaks, distinction from **20**[5]), 3 190 s br, 695 s cm^{-1}. λ_{max} 247 nm (log ε 3.85), λ_{infl} 210 (3.28). *m/e* 320 m (M^+), 303 ms (M^+-17, OH), 302 s (M^+-17-1), 275 m (M^+-45, COOH), 249 s (M^+-71), 204 m (M^+-71-45), 276 ms, 259 m, 221 vs (max), 203 m, 202 m, 164 s.

(b) *By Koch-Haaf Reaction of* **7**. To stirred cooled concentrated sulphuric acid (75 ml), formic acid (1.5 ml) was added dropwise (5–10 min), the temperature being maintained below 6°, followed by **7** (2.92 g, 0.01 mol) (45–60 min), each small portion being allowed to dissolve before the next was added (successive colour change to pale-green, then deep reddish-brown). More formic acid (5 ml) was added dropwise (30 min), again below 6°. The liquid was stirred a further 30 min, then added to ice-water (300 ml), giving a pale-brown resinous precipitate which disintegrated to a greyish-brown powder on storage (24–72 h). It was collected, washed with water, air-dried (m.p. ca. 180°, 1.28–1.6 g, 40–50%) and afforded **11** (from ethanol—light petroleum) identical (mixed m.p. 218–224°, i.r.) with material obtained in (a). *M* (by high resolution mass spectroscopy). Found: 320.1991. Calc. 320.1987.

1-Methoxycarbonyldiisophor-2(7)-en-4-ol-3-one (**12**)

A solution of **11** (0.96 g, 0.003 mol) in ether (150 ml) was treated with ethereal diazomethane (from "Diazald"[19b], 0.02 mol), and the product isolated as described for **21** (see above). The resulting yellow oil solidified on storage (48 h) and gave massive prisms (total, 0.65 g, 65%) of **12**, m.p. 114–116° (from light

petroleum). (Found: C 71.5; H 9.1. $C_{20}H_{30}O_4$ requires C 71.85; H 9.0%.) ν_{max} 3 490 vs (OH), 2 940 vs–2 860 s, 1 465 ms, 1 440 ms (CH_3, CH_2), 1 730 vs (C:O ester), 1 670 vs (CO), 1 645 s (C:C conjug.), 1 400 m sh, 1 390 ms (·CMe_2), 1 245–1 235 vs br (C—O ester) cm^{-1}. λ_{max} 248 nm (log ε 3.98), λ_{infl} 206 (3.33). *m/e* 334 s (M^+), 303 m (M^+-31, O*Me*), 302 vs (M^+-31-1), 275 m (M^+-59, COO*Me*), 274 vs (M^+-59-1), 263 m (M^+-71), 262 vs (M^+-71-1), 234 vs, 217 vs, 179 vs, 178 vs, 177 s.

3,4-Diketodiisophorone Carboxylic Acid

3,4-Diketo-1-carboxydiisophor-2(7)-ene (**13**)

A stirred solution of **11** (3.20 g, 0.01 mol) in acetone (80 ml) was treated dropwise during 5 min with *Kiliani*'s 10% chromic acid[19a] (7.5 ml, 0.015 g-atom O) (colour change to olive-green, then reddish-brown), and stirring at room temperature continued for 20 min. The supernatant orange-yellow solution was decanted from the dark deposit and the latter rinsed and stirred with a little more acetone. (The residue was water soluble with dark-blue colour, and was discarded). The combined liquids were evaporated to half volume under reduced pressure at room temperature and stirred into ice-water (250 ml). The resulting pale-yellow precipitate tended to resinify, but resolidified on storage and was collected and washed with water (crude: crystalline powder, m.p. between 190° and 200°, 2.05–2.55 g, 65–80%). Crystallisation from acetone—light petroleum (20 ml each, per g) gave yellow microprisms of **13**, m.p. 212–214° (1.6 g, 50%). (Found: C 71.65; H 8.35. $C_{19}H_{26}O_4$ requires C 71.7; H 8.2%.) ν_{max} 2 970–2 860 vs, 1 480–1 465 s (CH_3, CH_2), 2 650 m, 2 540 m (COOH), 1 725 vs, 1 705 vs br, 1 665 vs, 1 635 vs (C:O of COOH and CO·CO·C:C), 1 395 ms–1 380 s mult (·CMe_2), 1 285 s, 1 270 s, 1 185 m, 1 155 m, 1 060 s, 985 m, 945–930 m, 870 m, 720 m cm^{-1}. λ_{max} 257 nm (log ε 3.66), 206 (3.52). *m/e* 318 s (M^+), 301 s (M^+-17, OH), 273 s (M^+-45, COOH), 246 s (M^+-71-1), 230 s (M^+-71-17), 229 s (M^+-71-17-1), 275 s, 255 s, 216 vs, 201 s.

3,4-Diketo-1-carboxydiisophor-2(7)-ene: Derivatives

4-(2',4'-Dinitrophenylhydrazone) (**16**). A solution of **13** (0.32 g, 0.001 mol) in warm ethanol (10 ml) was treated with one of 2,4-dinitrophenylhydrazine (0.24 g, 0.0012 mol) in the same solvent (10 ml) containing concentrated hydrochloric acid (10 drops), and the clear liquid heated to boiling, when an orange crystalline precipitate separated at once. Crystallisation from ethoxyethanol (25 ml) gave deep orange-red prisms (60%) of **16**, m.p. 278° (decomp.). (Found: C 60.3; H 6.2; N 10.9. $C_{25}H_{30}N_4O_7$ requires C 60.2; H 6.0; N 11.2%.)

4-Benzenesulphonylhydrazone (**17**). A solution of **13** (0.32 g, 0.001 mol) and benzenesulphonylhydrazide (0.26 g, 0.0015 mol) in ethanol (12 ml) containing concentrated hydrochloric acid (2 drops) was boiled under reflux for 1 h. The yellow liquid was evaporated to half-volume, diluted with water to incipient turbidity, and separation of the crystalline product later completed by further addition of water. Crystallisation from ethanol gave faintly yellow felted needles (60–70%) of **17**, m.p. 174–176°. (Found: C 63.75; H 6.9; N 6.1. $C_{25}H_{32}N_2O_5S$ requires C 63.6; H 6.8; N 5.9%.) ν_{max} 3 180 ms (NH), 3 080 ms, 755, 720, 685 ms (*Ar*), 2 950 vs–2 880 s, 1 470, 1 450 ms (CH_3, CH_2), 2 650 m, 2 540 m (COOH), 1 710 s sh (CO of COOH), 1 695 vs br (CO), 1 625 vs br (C:N/C:C conjug.), 1 395 ms, 1 370 vs (·CMe_2), 1 055 ms br (?SO_2) cm^{-1}.

Quinoxaline Derivative (**15**). A solution of **13** (0.32 g, 0.001 mol) and *o*-phenylenediamine (0.14 g, 0.00125 mol) in ethanol (12 ml) was boiled under reflux for 1.5 h, distilled to half-volume, then stirred into ice-water; acidification with concentrated hydrochloric acid coagulated the precipitate (crude: m.p. 238–245°, 0.29 g, 75%). Crystallisation from ethanol—light petroleum (recovery, 80%) gave refractive platelets of **15**, m.p. 259–261°. (Found: C 76.6; H 7.9; N 7.2. $C_{25}H_{30}N_2O_2$ requires C 76.9; H 7.7; N 7.2%.) ν_{max} 3100 ms, 765 vs sh, 755 vs (*Ar*), 2970–2880 vs, 1470 ms, 1415 s (CH_3, CH_2), 2650 m t (COOH), 1700 vs br (CO of COOH), 1650 m (? C : N/C : C conjug.) cm^{-1}. *m/e* 390 s (M^+), 372 m (M^+-18, OH-1), 345 w (M^+-45, COOH), 301 m (M^+-71-17-1), 347 s, 346 vs, 290 s, 289 vs (max).

3,4-Diketo-1-methoxycarbonyldiisophor-2(7)-ene (**14**)

A stirred solution of **12** (1.67 g, 0.005 mol) in acetone (40 ml) was treated dropwise with *Kiliani*'s 10% chromic acid[19a] (5 ml, 0.01 g-atom O), and stirring continued for a total of 20 min. The yellow acetone solution was decanted, and the deep greenish-blue deposit rinsed with further portions of acetone. The combined solution was evaporated to small volume and added to ice-water. The pale-yellow resin, which solidified presently (m.p. 165–170°, 80%, nearly pure by i.r.) gave, on crystallisation from light petroleum (ca. 500 ml per g, with addition of acetone, 15 ml; recovery 60–70%), yellow prismatic needles of **14**, m.p. 174–176°. (Found: C 72.1; H 8.4. $C_{20}H_{28}O_4$ requires C 72.3; H 8.4%). ν_{max} 2970 vs–2870 s sh, 1470 ms, 1445 ms, 1425 ms (CH_3, CH_2), 1735 vs, 1720 vs sh (C : O ester), 1665 vs, 1630 vs (diCO/C : C conjug.), 1395 ms, 1380 s (·CMe_2), 1240 vs br (C—O ester) cm^{-1}. λ_{max} 257 nm (log ε 3.87), 210 (3.48). *m/e* 332 m (M^+), 301 w (M^+-31, *Me*O), 300 w (M^+-31-1), 273 s (M^+-59, COO*Me*), 272 s (M^+-59-1), 245 s (M^+-71-15-1), 230 m (M^+-71-31), 229 s (M^+-71-31-1), 201 ms (M^+-71-59-1), 244 vs.

The following derivatives were obtained from **14** by the procedures given for **16** and **17**:

4-(2',4'-Dinitrophenylhydrazone) (**18**), golden-yellow microplatelets (80%), m.p. 238–240° (from ethoxyethanol-ethanol). (Found: C 60.65; H 6.35; N 10.8. $C_{26}H_{32}N_4O_7$ requires C 60.9; H 6.25; N 10.9%).

4-Benzenesulphonylhydrazone (**19**), faintly yellow rectangular prisms (80%), m.p. 143–144° (from ethanol—light petroleum). (Found: C 63.9; H 7.1; N 5.7. $C_{26}H_{34}N_2O_5S$ requires C 64.2; H 7.0; N 5.8%.) ν_{max} 3150 ms (NH), 3080 ms, 760 ms, 720 s, 685 s (*Ar*), 2970 vs–2870 s, (1470 ms, 1455 s, 1445 ms) t (CH_3, CH_2), 1735 vs (C : O ester), 1630 vs br (? CO/C : N/C : C conjug.), 1395 s, 1370 vs br (·CMe_2), 1270–1240 vs br mult (C—O ester), 1050 vs br (? SO_2) cm^{-1}.

Unlike the 1-carboxylic acid **13** (see above) the methyl ester **14** failed to yield a quinoxaline derivative, being recovered (75%) after being boiled under reflux with *o*-phenylenediamine (1.5 mol) in ethanol for 2 h.

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