Monatshefte für Chemie 115, 809—823 (1984)

Monatshefte für Chemie
Chemical Monthly

Diisophorone and Related Compounds. Part 13[1] Nucleophilic Reactions of 8-Bromodiisophorone-1-carboxylic Acid

Frederick Kurzer* and **Jayantilal N. Patel**

Royal Free Hospital School of Medicine (University of London), London, England

(Received 22 November 1983. Accepted 19 December 1983)

8-Bromo-1-carboxydiisophor-2(7)-en-3-one is obtainable from diisophorone by successive monobromination and *Koch-Haaf* carboxylation, performed in either sequence. Nucleophilic replacement of its 8-bromo-substituent by acetolysis or methanolysis occurs with simultaneous migration, resulting in the 4-acetoxy- or 4-methoxy-compounds, respectively. In contrast, alkaline hydrolysis yields the 8-hydroxy-compound as main-product; this serves as the precursor of 3,8-diketodiisophor-2(7)-ene-1-carboxylic acid. The configuration of the 4- and 8-substituents is tentatively assigned on the basis of i.r. spectral data.

(Keywords: Diisophorone; 8-Bromo-1-carboxydiisophor-2(7)-en-3-one, synthesis and nucleophilic reactions of; Tricyclo[7.3.1.0^{2,7}]tridecanes)

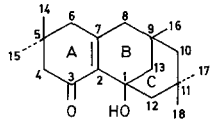
Diisophoron und verwandte Verbindungen, 13. Mitt.: Nucleophile Reaktionen von 8-Bromdiisophoron-1-carbonsäure

8-Brom-1-carboxydiisophor-2(7)-en-3-on ist aus Diisophoron durch Monobromierung und *Koch-Haaf*-Carboxylierung zugänglich; die Reaktionen sind in beliebiger Reihenfolge ausführbar. Nucleophiler Austausch des 8-Brom-Substituenten durch Acetolyse und Methanolyse erfolgt unter gleichzeitiger Isomerisierung, wobei 4-Acetoxy- oder Methoxy-Verbindungen entstehen. Im Gegensatz dazu liefert alkalische Hydrolyse hauptsächlich die 8-Hydroxyl-Verbindung; diese dient als Ausgangsmaterial für die Darstellung der 3,8-Diketodiisophor-2(7)-en-1-carbonsäure. Vorläufige Konfigurationen der 4- und 8-Substituenten werden auf Grund von IR-Spektren vorgeschlagen.

Introduction

The action of nucleophiles on 8-bromodiisophor-2(7)-en-1-ol-3-one (**1**) produces 4- rather than 8-substituted products; the replacement and

its attendant (apparent) migration have been interpreted by a mechanism of the S_N2'' type[2]. With the object of further exploring the scope of this reaction and the validity of its interpretation, the nucleophilic replacement of halogen in 8-bromo-1-carboxydiisophor-2(7)-en-3-one (**3**) by hydrolysis, acetolysis and alcoholysis have been investigated. Parallel work[1] dealing with the isomeric 4-bromo-ketols and -carboxylic acids has provided information essential for the formulation of the present series of compounds.



A

Results and Discussion

8-Bromo-1-carboxydiisophor-2(7)-en-3-one (**3**) required as starting material was accessible from the parent ketol **A**, the ultimate source of all diisophorone derivatives, by consecutive 8-monobromination and 1-carboxylation, performed in either order. In the first sequence, the bromocarboxylic acid **3** arises by *Koch-Haaf* carboxylation[3] of authentic 8-bromodiisophor-2(7)-en-1-ol-3-one (**1**)[4,5]. This approach is significant in establishing the location of the bromine substituent at C-8, but is the less suitable synthesis for preparative purposes, because its carboxylation stage requires exceptionally strict control of the reaction conditions difficult to maintain except on a small scale.—The reverse sequence involves the monobromination of the readily accessible 1-carboxydiisophor-2(7)-en-3-one (**2**)[1,6]: as in diisophorone (**A**) itself[4,5], monohalogenation thus attacks the 8-position first. Rapid 4,8-dibromination appears to compete with the main reaction even in the absence of an excess of halogen, but is minimised by performing the bromination very slowly in dilute solution.

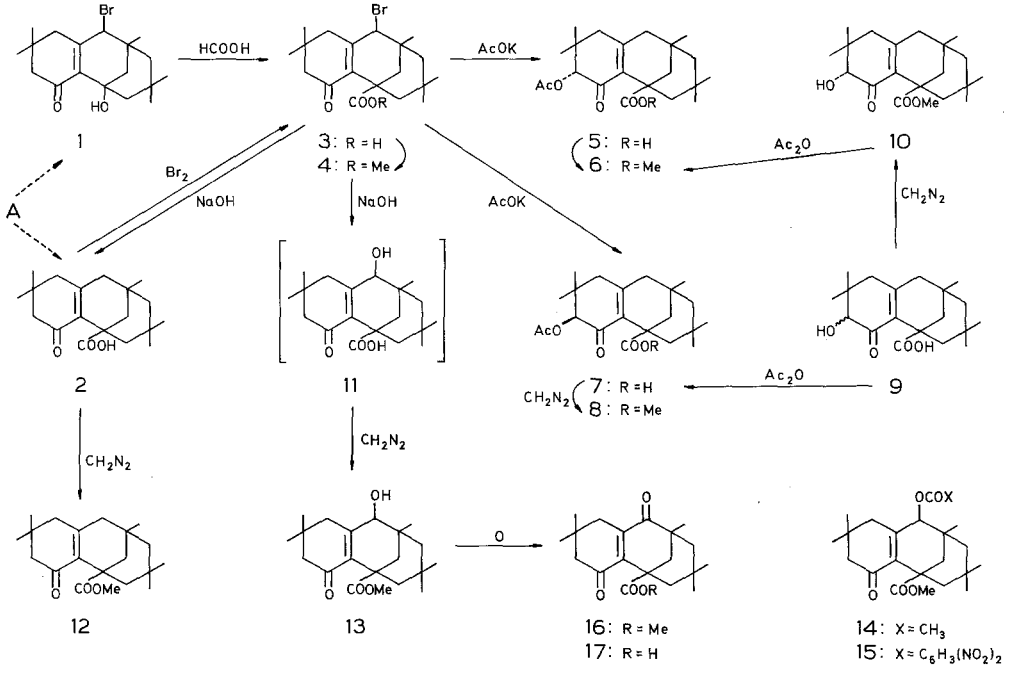
8-Bromo-1-carboxydiisophor-2(7)-en-3-one (**3**) displayed the expected i.r. and u.v. spectral properties (see Experimental). The ^{13}C-nmr spectrum of its methyl ester (**4**, obtained nearly quantitatively by means of diazomethane[7a]) confirmed the 8-location of the bromo-substituent (see Part 14, subjoined). Its mass spectrum, displaying weak signals of the molecular ion (384, 382), was consistent with the fragmentation of the molecule by successive loss of the halogen-, hydroxy-, carboxy- and C_5H_{11}-moieties, the last originating from ring C (of **A**). The methyl ester **4** decomposed analogously, with ejection of the corresponding methoxy- and methoxycarbonyl-fragments.

Acetolysis

In dealing with the nucleophilic substitution reactions of the 8-bromo-acid **3**, it is expedient to begin with its acetolysis, which provides reference compounds of established structure used in formulating other substitution products.

Acetolysis of the 8-bromo-acid **3**, like that of the 8-bromoketol **1**[2], occurred with apparent migration of the substituent, yielding 4-substituted products. Thus, the action of potassium acetate in boiling acetic acid on **3** gave a readily separable mixture of two products, the major being formulated as 4α-acetoxy-1-carboxydiisophor-2(7)-en-3-one (**5**, m.p. 198–200°), and the minor as its 4β-acetoxy-epimer (**7**, m.p. 267–270°). The epimers differed in their solubility, m.p. and i.r. spectra, but gave identical mass spectra. The major epimer incorporated one mole of ethanol of crystallisation which was only slowly removed at 140 °C in a vacuum. Each epimer (**5**, **7**) was separately converted by diazomethane into its methyl ester (**6**, **8**): this pair of isomers had identical m.ps. (188—190°), but showed a pronounced m.p. depression in admixture. Their i.r. spectra were distinct, but their mass spectra, like those of the pair of parent acids, were identical.

Scheme 1



The formulation of the two acetolysis products (**5**, **7**) and their methyl esters (**6**, **8**) as 4-acetoxy-compounds is founded on the fact that they may each be related to authentic 4-hydroxy-1-carboxydiisophor-2(7)-en-3-one (**9**)[1], as follows:

(i) Acetylation of **9** gave low yields (up to 10%) of its 4-acetoxy-derivative identical with the *minor acetolysis product*, m.p. 267–270°, of **3**. The filtrates of this (authentic) acetylation product gave only viscid resins, from which the epimeric 4-acetoxy-compound was not isolable. No reference compound was therefore available for immediate comparison with the major acetolysis product (of **3**).

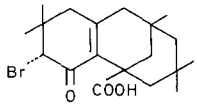
(ii) However, this was identifiable indirectly as follows: The 4-hydroxycarboxylic acid **9** was convertible into its (sterically uniform) methyl ester **10**[1] in good yields by diazomethane. On acetylation, this gave a product identical with the methyl ester of the *major acetolysis product*, m.p. 198–200°.

The foregoing observations lead to the following mutually interdependent conclusions: Firstly, the 4-hydroxycarboxylic acid **9**[1], which serves as the source of *both* epimeric reference compounds **7** and **6**, is itself a mixture of its 4α- and 4β-forms, one of which predominates greatly. The configuration of its major and minor constituent is undecided at this stage, but the preponderance of the 4α-hydroxy-epimer may reasonably be surmised from the origin[1,8] of the 4-hydroxy-acid **9** from 4α-precursors, and is in fact confirmed in the sequel.— Secondly, the two acetolysis products of the 8-bromo-1-carboxylic acid **3**, being each separately relatable to the 4αβ-hydroxy-1-carboxylic acid **9**, are the epimeric forms of 4-acetoxy-1-carboxydiisophor-2(7)-en-3-one (**5**, **7**); their possible 8-acetoxy-structure is thereby excluded, a conclusion that is confirmed by their ^{13}C-nmr spectra (see Part 14, subjoined).

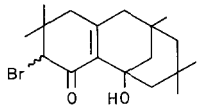
The configurations of the 4-substituents in the epimer-pairs (**5**, **7** and **6**, **8**) are finally assigned, as in a previous example[8], by reference to the multiplicity of the ester C—O stretching band near 1 200 cm^{-1} in their i.r. spectra[9]. The major acetolysis product (and its methyl ester), producing doubly or triply peaked bands, are accordingly formulated as the axial 4α-epimers (**5**, **6**), while the corresponding minor products, associated with single peak bands, are the equatorial 4β-forms (**7**, **8**). As a consequence, the hydroxy-acid **9**, giving high yields of a 4α-(**9** → **10** → **5**) and low yields of a 4β-derivative (**9** → **7**), is seen to consist mostly of its 4α-conformer.

In attempting to confirm the formulation of the acetolysis products **5** and **7** by an unequivocal synthesis, the acetolysis of 4α-bromo-1-carboxydiisophor-2(7)-en-3-one (**B**)[1] was the obvious choice. However, this 4-bromo-compound unexpectedly failed to react, being recovered

(70–80%) after treatment with potassium acetate in acetic acid under both the standard and varied conditions. Since acetolysis of the 8-bromocarboxylic acid **3** and of the 4-bromoketol **C** is so readily accomplished, the contrasting behaviour of the 4-bromo-acid **B** is presumably to be ascribed to a deactivating influence of the 1-carboxy-group on the more proximate 4-bromo-substituent.



B



C

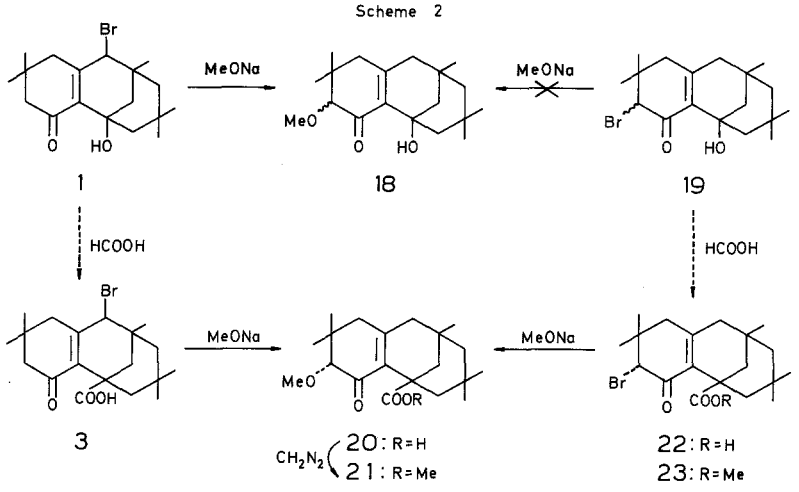
In the hope of obtaining the individual epimeric forms of 4-hydroxy-1-carboxydiisophor-2(7)-en-3-one (**9**), the isolated 4α- and 4β-acetoxy-compounds (**5**, **7**) were each subjected to alkaline hydrolysis. However, the reactions gave much intractable resinous product, and lack of starting material in quantity prevented the optimisation of the experimental conditions. 4β-Acetoxy-1-carboxydiisophor-2(7)-en-3-one (**7**) gave a product (ca. 50%) indistinguishable from the 4αβ-hydroxy-acid **9**. The 4α-acetoxy-epimer **5** surprisingly gave 1-carboxydiisophor-2(7)-en-3-one (**2**) as the only isolable solid (30–35%), which was identified as such[1,6], or as its methyl ester **12**[1,6], after treatment with diazomethane.

Alcoholysis

Methanolysis of 8-bromodiisophorones, the second example of nucleophilic substitution, was also attended by the apparent 8 → 4 migratory process. Thus, the action of methanolic sodium methoxide on 8-bromo-1-carboxydiisophor-2(7)-en-3-one (**3**) gave moderate yields of a product identified as the 4-methoxy-1-carboxylic acid **20** on the grounds that methanolysis of the 4-bromocarboxylic acid **22** gave the same methoxycarboxylic acid **20** even more readily in better yield. The parallel methanolysis of the methyl ester **23** gave **21**, identical with 4-methoxy-1-methoxycarbonyldiisophor-2(7)-en-3-one obtainable by the action of diazomethane on **20**. The ^{13}C-nmr spectral evidence was in accord with the 4-methoxy-structure of both the acid **20** and its methyl ester **21**, and indicated that both products were sterically uniform 4α-axial epimers (see Part 14, subjoined).

To obtain data for comparison, the corresponding bromoketols **1** and **19** were also subjected to methanolysis. **1** gave, in addition to much intractable resinous material, modest yields of a product which consisted, according to its ^{13}C nmr-spectrum, of near-equimolar quantities of 4α (and β)-methoxydiisophor-2(7)-en-1-ol-3-one (**18**). In attempts to obtain the same compound from the 4-

Scheme 2



bromoketol **19**[1] (in analogy with the substitution **22** → **20**), the resinous nature of the products precluded the isolation of any identifiable material. In producing a 4-substituted product from the 8-bromoketol **1**, the methanolysis falls into line with the hydrolysis, acetolysis, and hydrazinolysis (of **1**) previously described[2].

Alkaline Hydrolysis

The action of aqueous alkali on 8-bromo-1-carboxydiisophor-2(7)-en-3-one (**3**) differed from the other nucleophilic replacements at C-8 so far examined in that the usual 8 → 4 migration did *not* occur. The product consisted of approximately equal quantities of the 8-hydroxycarboxylic acid **11** and 1-carboxydiisophor-2(7)-en-3-one (**2**). Although small amounts of the latter were obtainable by fractional crystallisation, a satisfactory separation of the mixture (**2**, **11**) could not be effected. This was possible, however, after conversion of the total hydrolysis product into the corresponding methyl esters (**12**, **13**), each of which was isolable pure in 35–40% yield.

One of these was identified as 1-methoxycarbonyldiisophor-2(7)-en-3-one (**12**) by its comparison with authentic material[6]. The other was, according to its composition, and spectral and other properties, 8-hydroxy-1-methoxycarbonyldiisophor-2(7)-en-3-one (**13**). Its possible 4-hydroxy-structure was excluded by the fact that its acetyl-derivative was non-identical with *either* epimeric 4-acetoxydiisophorone ester (**6**, **8**). On the basis of its origin, its ^{13}C-nmr spectrum, and its ready oxidation to the 3,8-diketo-ester **16**, it was identified as the 8-hydroxy-isomer **13**. It was sterically uniform, the hydroxy-group assuming very probably the 8β-(pseudo)axial configuration. Thus, the 8-acetoxy-

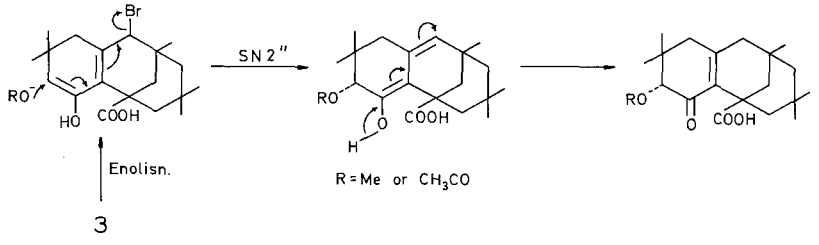
compound **14**, obtained from **13** by acetylation, exhibited the triply-peaked i.r. absorption band near 1 200 cm^{-1}, held[9] to be indicative of axial acetoxy-groups. By analogy, other 8-substituted diisophorones are regarded as 8β-axial conformers also.

The hydroxy-acid **11** corresponding to the methyl ester **13** remains unknown; attempts to obtain the pure material from its isolated methyl ester **13** have so far failed. Alkaline hydrolysis of diisophorone-1-carboxylic methyl esters occurs only slowly[1]; in the present instance, the necessary prolonged alkaline treatment of **13** was attended by oxidation to the 3,8-diketo-acid **17** or material contaminated with it. The ester **13** resisted the action of ethanolic hydrochloric acid; acid hydrolysis under conditions[10] that have proved successful[1] for producing the parent acid **2** from its methyl ester **12**, was also inapplicable because it caused partial aromatisation of the reactant.

The formation, in the alkaline hydrolysis of **3**, of the debrominated parent keto-acid **2** was an unexpected parallel reaction that occurred invariably in near-equimolar quantities. That this product (**2**) was not accidentally introduced with the starting material **3** (which is itself produced from **2** by monobromination) was confirmed by using carefully purified and analysed reactant. The mechanism of this seemingly reductive process will be considered in the context of reactions of di- and tri-halogenated diisophorones. It is clearly not an isolated case, as is shown by the analogous conversion of the 4α-acetoxy-compound **5** into **2** by alkali (see above).

3,8-Diketo-1-methoxycarbonyldiisophor-2(7)-ene (**16**) was obtained from **13** in good yield by *Kiliani* oxidation[7b] and afforded the parent 3,8-diketo-acid **17** on alkaline hydrolysis. The distribution of the conjugated olefinic 1,4-diketo-system over two rings (in **16**, **17**) is consistent with the position of their u.v. absorption maximum (272, 270 nm, respectively), which matches that of the analogously distributed $\Delta^{8,9}$-7,11-dione-grouping in steroids (270 nm)[11]. Further support for the structure of **16** and **17** (and hence of their precursor **13**) was provided by their ^{13}C-nmr spectra (see Part 14, subjoined). Unlike their 3,4-diketo-analogues[1], the

Scheme 3



3,8-dione ester **16** and acid **17** did not yield 2,4-dinitrophenylhydrazones. In the case of diisophorone-1-carboxylic acids, this reaction is known[1,6] to fail at the 3-keto-, but to proceed readily at the 4-keto-position; the failure of the 8-keto-function to react may be due to the proximity of the folded ring C, even though significant steric hindrance is not obviously apparent.

Mechanism

With one exception, the nucleophilic replacements of the 8-bromo-substituent in diisophorone-1-carboxylic acids resemble those of comparable 8-bromoketols (e.g. **1**)[2] in being attended by an apparent **8** → **4** migration. They are therefore interpreted, as before[2], in terms of an S_N2''-mechanism. The proposed reaction sequence (Scheme 3) closely follows the stages previously outlined for the bromoketol **1** and is therefore not discussed in detail; it is applicable to both the acetolysis and methanolysis. In contrast, the hydrolysis of the 8-bromo- (**3**) to the 8-hydroxy-acid (**11**) is a simple replacement, for which an S_N1-mechanism involving carbonium ions appears to be the most acceptable interpretation; a concerted substitution process is clearly prevented by the rigidity of the C-8 centre and by the steric hindrance (to rear approach of the reacting species at C-8) exerted by the three-dimensional molecule as a whole.

The ^{13}C-nmr spectra of the substituted diisophorone-1-carboxylic acids now described provided additional, and in some instances, decisive support for the suggested structural assignments. For the sake of brevity and easier comparison, the spectra of both 4-[1] and 8-substituted carboxylic acids are presented collectively in the subjoined report (Part 14).

Experimental

Standard procedures, reagents, solvents, and equipment are as given in Part 12[1] and previously[12]. Unassigned peaks of i.r. spectra are not recorded except for key-compounds.

8-Bromodiisophorone-Carboxylic Acid

8-Bromo-1-carboxydiisophor-2(7)-en-3-one (**3**)

(a) *By monobromination of 1-carboxydiisophor-2(7)-en-3-one.* A stirred solution of the reactant **2** (3.04 g, 0.01 mol) in glacial acetic acid (250 ml) containing a few drops of 60% hydrobromic acid was treated dropwise with *M*-bromine in the same solvent (10.5 ml, 0.0105 mol, diluted to 100 ml with more acetic acid) over 3 h. Addition of the colourless liquid to ice-water (1.5 l) gave a white precipitate (m.p. 206–208°, ca. 2.9 g, 75%), forming prisms of **3**, m.p. 204–206° (from methanol, or from ethanol—water, recovery 70–80%). (Found:

C 59.2; H 7.3; Br 20.7. $C_{19}H_{27}BrO_3$ requires C 59.5; H 7.05; Br 20.9%.) ν_{max} 2 960–2 860 vs, 1 420, 1 410 s d (CH_3, CH_2), 2 650 ms, 2 540 ms (COOH), 1 700 vs vbr (CO of COOH), 1 670 vs (CO), 1 640 ms sh (C : C conjug.), 1 390 ms, 1 370 vs (·CMe_2), 1 465 s, 1 300–1 270 vs br, 1 210 m, 1 125 ms, 1 080 mw, 955 ms, 905 ms, 785 mw, 720 ms, 695 mw, 675 mw cm^{-1}. λ_{max} 256 nm (log ε 4.05), 209 (3.59). *m/e* 384, 382 w (M^+), 303 m(M^+-Br), 287 m (M^+-Br-16), 286 s (M^+-Br-17, OH), 258 s (M^+-Br-45, COOH), 215 m (M^+-Br-71-17), 187 s (M^+-Br-71-45), 243 vs, 203 s, 202 vs (max).

The bromination is performed very slowly in very dilute solution to avoid possible di-and trihalogenation. On the 0.1 molar scale, the volume of acetic acid was reduced to 700 and 120 ml.

(b) *From 8-bromodiisophor-2(7)-en-1-ol-3-one, by the Koch-Haaf reaction.* To a cooled (0°) stirred solution of formic acid (2 ml) in concentrated sulphuric acid (100 ml), the reactant **1** (3.55 g, 0.01 mol) was added during 5–10 min, and the deep-yellow liquid treated dropwise during 1.5 h at 0° (external cooling) with 100% formic acid (18 ml), the effervescence being allowed to subside between additions. The liquid was stirred into ice, and the resulting precipitate (3–3.5 g) crystallised from light petroleum (b.p. 40–60°), affording **3** as opaque prisms (1.72 g, 45%), identical with material produced in (a) (by mixed m.p. 204–205° and i.r. spectrum). The reaction failed when performed in the presence of 1 mol of silver sulphate.

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

A stirred solution of **3** (1.92 g, 0.005 mol) in ether (120 ml) was treated at room temperature during 3–5 min with ethereal diazomethane (from toluene-*p*-sulphonylmethylnitrosamide, "Diazald"[7a], 0.025 mol), the initial portions of which were decolourised (with effervescence). The pale-yellow solution was set aside for 3 h, then worked up in the usual manner[1]. The crude product formed at first a clear colourless resin, which solidified partially to a white solid on storage; crystallisation from light petroleum gave ivory prisms (total, 1.72 g, 87%) of **4**, m.p. 136–138°. (Found: C 60.15; H 7.4; Br 20.3. $C_{20}H_{29}BrO_3$ requires C 60.5; H 7.3; Br 20.1%.) ν_{max} 2 960 vs–2 870 s, 1 470 s, 1 440 s (CH_3, CH_2), 1 735 vs (CO of COO*Me*), 1 660 vs (CO), 1 635 ms (C : C conjug.), 1 395 ms, 1 380 vs (·CMe_2), 1 245, 1 225 vs d (C—O ester) cm^{-1}. *m/e* 398, 396 w (M^+), 317 ms (M^+-Br), 286 s (M^+-Br-31, *Me*O), 258 ms (M^+-Br-59, COO*Me*), 187 s (M^+-Br-71-59) (max), 287 s, 259 ms, 244 m, 216 m, 204 m, 203 m, 202 s.

Acetolysis

8-Bromo-1-carboxydiisophor-2(7)-en-3-one. Acetolysis

A solution of **3** (7.65 g, 0.02 mol) and anhydrous potassium acetate (5.9 g, 0.06 mol) in glacial acetic acid (60 ml) was boiled under reflux for 1 h (severe "bumping" after ca. 15 min) and the orange suspension stirred into ice-water (500 ml). The white precipitate coagulated on storage for 12 h to a resinous, later solid and friable material. It was collected, washed to neutrality, and air-dired (crude, m.p. 80–85°, ca. 6.5 g). The faintly brown powder was dissolved in ethanol—light petroleum (10 and 50 ml); the liquid deposited fairly rapidly microcrystalline 4β-acetoxy-1-carboxydiisophor-2(7)-en-3-one (**7**), m.p. 267–270° (0.6–0.9 g, 8–12%), identical (mixed m.p., i.r. spectrum) with authentic material (by acetylation of **9**, see below). (Found: C 69.7; H 8.5%.)

The filtrate therefrom slowly deposited during 2–3 days, minute prisms (2.9–3.7 g, 36–45%) of solvated *4α-acetoxy-1-carboxydiisophor-2(7)-en-3-one* (**5**), m.p. 198–200°. (Found: C 67.6; H 8.4. $C_{21}H_{30}O_5 \cdot C_2H_5OH$ requires C 67.65; H 8.8%.) ν_{max} 3450 m br (OH of *Et*OH?), 2960–2870 vs, 1475 s (CH_3, CH_2), 2720–2640 w (COOH), 1735, 1705 vs br (CO of COOH, *Ac*O), 1680 vs (CO), 1640 s (C:C conjug.), 1395–1380 s br (·CMe_2), 1265, 1230 vs br (C—O of *Ac*O), 1065 ms, 1025 m, 815 m, 695 ms cm^{-1}. Its mass spectrum was identical with that of the authentic 4β-epimer **7** (see below).—The final motherliquors gave, on spontaneous evaporation at room temperature, a yellow to buff solid residue which was, according to its i.r. spectrum, almost pure 4α-acetoxy-compound **5**.

The material was desolvated by being kept at ca. 145° (b.p. of xylene) at 1 mm for 6 h, forming an opaque crystalline powder. (Found: C 69.1; H 8.2. $C_{21}H_{30}O_5$ requires C 69.6; H 8.3%.) Its i.r. spectrum was unchanged after desolvation (confirming that this major fraction **5** was not merely solvated **7**).

4β-Acetoxy-1-methoxycarbonyldiisophor-2(7)-en-3-one (**8**)

A stirred suspension of **7** (0.36 g, 0.001 mol) in ether (50 ml) was treated with ethereal diazomethane (20 ml, from 0.01 mol "Diazald" [7a]) and worked up in the usual manner[1]. The residual crude solid produced a mass of opaque felted needles (0.28 g, 75%) of **8**, m.p. 187–189° (from light petroleum). (Found: C 69.9; H 8.5. $C_{22}H_{32}O_5$ requires C 70.2; H 8.5%.) ν_{max} 2955 vs–2890 s, 1435 ms (CH_3, CH_2), 1730 vs br (C:O of COO*Me* and *Ac*O), 1675 vs (CO), 1645 ms (C:C conjug.), 1390, 1370 s (·CMe_2), 1240 vs br (C—O ester), 1170 m, 1155 m, 1125 m, 1060, 1050 s d, 1000 m, 920 mw, 790 mw, 750 mw cm^{-1}. The finger-print range is given in detail to show the distinctness of **8** and **6**. *m/e* 376 m (M^+), 345 w (M^+-31, *Me*O), 344 s (M^+-31-1), 317 w (M^+-59, COO*Me*), 316 s (M^+-59-1), 274 m (M^+-71-31), 262 m (M^+-71-43, *Me*CO), 284 m, 256 m, 241 m, 234 vs max, 201 m, 199 s, 178 s.

4α-Acetoxy-1-methoxycarbonyldiisophor-2(7)-en-3-one (**6**)

Prepared from solvated **5** (0.005 mol) as described for the 4β-epimer **8**, the white residual crude product gave lustrous prismatic needles (1.35 g, 72%) of **6**, m.p. 188–191° (from light petroleum, with addition of a little acetone). (Found: C 69.8; H 8.7%.) For i.r. and mass spectrum, see reference compound **6**, below. Its mass spectrum was identical with that of **8**. The mixed m.p. of **6** and **8** was depressed by ca. 30° below that of their identical m.ps.

4β-Acetoxy-1-carboxydiisophor-2(7)-en-3-one (**7**, reference compound)

A solution of **9**[1] (0.64 g, 0.002 mol) in (warm) glacial acetic acid—acetic anhydride (8 ml each) was cooled to room temperature, and treated with external cooling with 60% perchloric acid (8 drops). The pink liquid was set aside for 2 h, then stirred into water (100 ml). The resinous precipitate failed to solidify on storage (72 h) and was isolated by ether extraction. The residual pale brown oil obtained from the washed neutral extracts was dissolved in ethanol—light petroleum; the solution slowly deposited minute prisms (0.10 g, 14%) of **7**, m.p. 265–268° (from the same solvents). (Found: C 68.5; H 8.4. $C_{21}H_{30}O_5$ requires C 69.6; H 8.3%.) ν_{max} 2960–2870 vs, 1465 ms (CH_3, CH_2); 2650 mw (COOH), 1740 vs, 1700 vs (C:O of ester and COOH), 1675 vs (CO), 1640 s (C:C, conjug.), 1390 ms–1375 s br (·CMe_2), 1230 vs br (C—O of ester), 1295 s, 1055 s, 935 m, 790 mw, 715 mw cm^{-1}. *m/e* 362 w (M^+), 344 m (M^+-18, OH-1), 316 m (M^+-46, COOH-1), 302 w (M^+-45-15, *Me*), 286 s (M^+-59, *Ac*O-17), 274 m (M^+-71-17), 258 s (M^+-59-45), 243 s, 220 m, 215 ms, 201 vs, max.

Spontaneous evaporation of the mother liquors gave an orange sticky resin (0.5 g) which failed to yield crystalline material on its attempted conversion into the corresponding 1-methyl ester by diazomethane.

4α-Acetoxy-1-methoxycarbonyldiisophor-2(7)-en-3-one (**6**, reference compound)

A solution of **10**[1] (0.67 g, 0.002 mol) in glacial acetic acid—acetic anhydride (8 ml each) was treated at room temperature with 60% perchloric acid (8 drops), set aside for 2 h, then stirred into warm water (200 ml). The resulting crude white solid gave, on crystallisation from light petroleum (120 ml), lustrous needles (total, 0.54 g, 72%) of **6**, m.p. 187–190°. (Found: C 70.5; H 8.75. $C_{22}H_{32}O_5$ requires C 70.2; H 8.5%.) ν_{max} 2 950 vs–2 890 s, 1 435 s (CH_3, CH_2), 1 745, 1 725 vs br d (C:O of COO*Me*, *Ac*O), 1 685 vs (CO), 1 645 s (C:C, conjug.), 1 395 s, 1 375 vs (·C*Me*$_2$), 1 255–1 235 vs vbr tr (C—O, ester), 1 190 ms, 1 135 s, 1 090 ms, 1 060 s, 1 045 ms d, 995 ms, 965 mw, 920, 910 mw d, 875 w, 820 ms, 745 w, 685 mw cm^{-1} (fingerprint range given in full to show distinctness of **6**, **8**, and **14**). *m/e* 376 m (M^+), 345 w (M^+-31, *Me*O), 344 s (M^+-31-1), 317 w (M^+-59, COO*Me*), 316 s (M^+-59-1), 274 m (M^+-71-31), 262 m (M^+-71-43, *Me*CO), 284 m, 256 m, 241 m, 234 s max, 201 m, 199 s, 178 s.

Action of Alkali on **7**

A solution of **7** (1.09 g, 0.003 mol) in *M*-sodium hydroxide (20 ml, 0.02 mol) was kept at 100° for 30 min. Addition of the yellow liquid to ice-water, and acidification with conc. hydrochloric acid produced a colloidal precipitate which coagulated on addition of solid sodium chloride (crude: m.p. 195–200°, 0.8 g). Its solution in ethanol—light petroleum rapidly deposited microcrystalline (0.46 g, 48%) **9**, identical (mixed m.p. 210–212°, i.r.) with authentic material[1]. A later crop (0.1 g) was, according to its i.r. spectrum, a mixture of the same product **9**, and **2**[1,6].

Action of Alkali on **5**

Identical experiments using the 4α-epimer **5** resulted in a crude product (0.7 g) which gave, on crystallisation as above, microprisms (0.29 g, 32%) of **2**, identical (mixed m.p. 228–230°, i.r.) with authentic material[1,6]. I.r. spectra indicated that subsequent crops (ca. 0.3 g) were mostly the same compound admixed with some **9**.

Alternatively, the total crude hydrolysis product was treated in ether (45 ml) with diazomethane (from 0.06 mol "Diazald"[7a]) by the standard procedure. Crystallisation of the semisolid crude product from light petroleum gave lustrous prisms (0.32 g, 34%) of **12**, identical (mixed m.p. 120–121°, i.r.) with authentic material[1,6]. The filtrates therefrom gave only sticky resins.

Alcoholysis

4αβ-Methoxydiisophor-2(7)-en-1-ol-3-one (**18**)

A solution of **1**[4,5] (3.55 g, 0.01 mol) in methanol (50 ml), treated with one of sodium (0.51 g, 0.022 g atom) in methanol (25 ml) was boiled under reflux for 2 h. The turbid liquid was distilled to half volume under reduced pressure, then stirred into ice-water containing concentrated hydrochloric acid (5 ml). The precipitated white resinous product was rinsed with water, air-dried and dissolved in light petroleum (10 ml), yielding prismatic needles (0.98 g, 32%) of **18**, m.p. 90–93°. (Found: C 74.3; H 9.9. $C_{19}H_{30}O_3$ requires C 74.5; H 9.8%.) ν_{max}

3500 vs (OH), 2950–2850 vs, 1470 ms, 1420 ms br (CH_3, CH_2), 1640, 1625 vs d (CO), 1605 s sh (C:C, conjug.), 1395 ms, 1370 s (·CMe_2) cm^{-1}. λ_{max} 254 nm (log ε 3.69). Spontaneous evaporation of the crystallisation filtrates gave only orange viscid intractable resins.

The use of **19**[1] in the foregoing procedure (or use of 0.015 g atom of sodium, 30 min refluxing) gave, in each case, a sticky orange-brown resin from which no crystalline material was isolable.

1-Carboxy-4-methoxydiisophor-2(7)-en-3-one (**20**)

(a) *Methanolysis of the 4-bromo-analogue* **22**. A suspension of **22**[1] (1.92 g, 0.005 mol) in hot methanol (25 ml) cleared on addition of a solution of sodium (0.25 g, 0.011 g atom) in methanol (15 ml). The yellow liquid was boiled under reflux for 2 h, and gave after the usual work-up, a white precipitate (m.p. 215–220°, 1.35 g, 80%, nearly pure by i.r.). Crystallisation from acetone—light petroleum (20 ml each), produced lustrous needles (total, 40%) of **20**, m.p. 246–248°. (Found: C 71.5; H 8.7. $C_{20}H_{30}O_4$ requires C 71.85; H 9.0%.) ν_{max} 2950–2890 vs–2815 s br, 1470 ms, 1425 ms (CH_3, CH_2), 2650 s, 2540 s (COOH), 1690 vs br (CO of COOH), 1660 vs (CO), 1635 s (C:C, conjug.), 1390, 1375 m (·CMe_2) cm^{-1}. λ_{max} 250 nm (log ε 3.96), 205 (3.40). *m/e* 334 vw (M^+), 317 w (M^+-17, OH), 316 m (M^+-17-1), 289 s (M^+-45, COOH), 330 vw, 304 s, 288 m, 273 m, 271 s, 248 m, 220 vs, max.

(b) *Methanolysis of the 8-bromo-analogue* **3**. The use of **3** in the foregoing procedure gave a low-melting crude product (m.p. ca. 80°, 1.4 g, unidentifiable by i.r.) which on crystallisation (as in a) gave two successive crops (25%) of **20** (identical by mixed m.p. 242–246° and i.r.). The filtrates therefrom gave a higher proportion of pale-yellow resin than in (a).

4-Methoxy-1-methoxycarbonyldiisophor-2(7)-en-3-one (**21**)

(a) *Methanolysis of the 4-bromo-analogue* **23**. A solution of **23**[1] (1.98 g, 0.005 mol) in (warm) methanol (30 ml) was treated with one of sodium (0.125 g, 0.0055 g atom) in methanol (12 ml) and boiled under reflux for 2.5 h. It gave, after the usual work-up, a white resin, which was rinsed with water, air-dried, and dissolved in light petroleum (b.p. 40–60°). The crystalline solid gave prismatic needles of **21**, m.p. 127–130° (from the same solvent, total, 1.12 g, 64%). (Found: C 72.6; H 9.4. $C_{21}H_{32}O_4$ requires C 72.4; H 9.2%.) ν_{max} 2970 vs, 2910–2800 s br, 1475 ms, 1440 ms (CH_3, CH_2), 1730 vs (CO of COO*Me*), 1665 vs (CO), 1640 s (C:C, conjug.), 1395 ms, 1380 ms (·CMe_2), 1250 vs br (C—O ester) cm^{-1}. λ_{max} 251 nm (log ε 3.85).

(b) *Esterification of* **20**. A swirled suspension of **20** (0.67 g, 0.002 mol) in ether (30 ml) was treated with ethereal diazomethane (50 ml; from 0.02 mol "Diazald"[7a]). It gave, upon the usual work-up, a pale-yellow oil which was dissolved in light petroleum (b.p. 40–60°) and deposited needles (0.43 g, 62%) of **21**, identical with material obtained in (a).

Alkaline Hydrolysis

8-Bromo-1-carboxydiisophor-2(7)-en-3-one (**3**): *Action of Alkali*

(A) *Hydrolysis*. A solution of **3** (7.66 g, 0.02 mol) in 0.75 *M* sodium hydroxide (80 ml, 0.06 mol) was boiled under reflux for 45 min. The clear pale-orange liquid was added to ice-water (300 ml) containing concentrated hydrochloric acid (12 ml, 0.12 mol) and the white precipitate collected, washed (to neutrality) and

air-dried (m.p. in range 190–210°, 4.7–5.3 g). The crude product from two experiments, dissolved in acetone (80 ml)—light petroleum (10–15 ml), deposited 3–4 successive crystalline crops of approximately equal weight (m.p. range 195–205°, 190–200°, 180–190°, respectively, total 8.8–10.0 g, 70–80%); they were mixtures of **2** and **11** in about equal parts, the former predominating in the initial, and the latter in the final fractions. Recovery in the crystallisation was almost quantitative, the final motherliquors giving a solid deposit on complete spontaneous evaporation. The mixture was not separable effectively by fractional crystallisation, but this was possible in the case of their methyl esters (see below).

Alternatively, crystallisation of the crude material from ethanol—light petroleum (3 ml each, per g) produced a small initial crop which gave, after a further crystallisation from the same solvents, almost entirely **2** (8–12%), identified by mixed m.p. 232–234° and i.r. spectrum[1,6].

In confirmatory experiments, the use of analysed specimens of **3** (Found: Br, 21.3; 21.0) gave the same results. This established that **2** had not been present in the starting material, and that its isolation in the present reaction was not fortuitous.—The same product mixture was obtained (crude, 85%) when the reaction was performed in boiling 0.5 *N*-sodium hydroxide during 10 min.

(B) *Conversion into methyl esters.* The combined total crystallised powdered solids (from A, 4.7 g, 0.015 mol, calc. for average M.Wt. 312) were suspended in ether (120–150 ml) and treated in portions with ethereal diazomethane (from 0.03 mol "Diazald"[7a]). The reaction mixture effervesced gently and the remaining suspended reactant dissolved. The pale-yellow solution was set aside for 3 h, the excess of the diazomethane destroyed with 3 *N*-acetic acid and the washed (sodium carbonate, water) ethereal solution evaporated under reduced pressure. The residual oil solidified rapidly to a crystalline solid; it was dissolved in light petroleum (successive portions, total ca. 1 l). The crystals separating slowly during 24–48 h (m.p. ca. 130°, 1.75–2.25 g, 35–45%) (filtrate: F) gave, on crystallisation from the same solvent (recovery 80%), massive square prisms of *8-hydroxy-1-methoxycarbonyldiisophor-2(7)-en-3-one* (**13**), m.p. 134–136°. (Found: C 71.7; H 8.9. $C_{20}H_{30}O_4$ requires C 71.85; H 9.0%.) ν_{max} 3 510 vs (OH), 2 950–2 860 vs, 1 465 s, 1 440 s (CH_3, CH_2), 1 715 vs br (C : O, ester), 1 660 vs (CO), 1 645 s sh (C : C, conjug.), 1 395 ms, 1 375 vs (·CMe_2), 1 270–1 260 vs q vbr (C—O ester), 1 190 ms d, 1 165 ms, 1 150 ms, 1 115 ms, 1 055 s, 1 030 vs, 995 m, 970 m, 955 m, 905 mw, 805 m, 755 m cm^{-1}. λ_{max} 247 nm (log ε 3.97). *m/e* 334 m (M^+), 319 w (M^+-15, *Me*), 303 s (M^+-31, *Me*O), 275 s (M^+-59, COO*Me*), 258 m (M^+-59-17, OH), 204 s (M^+-71-59), 219 s max, 218 ms, 202 s.

Filtrates F (which deposited no further material on storage) were evaporated to one-third volume; the yellow liquid slowly deposited crystalline material (2–3 successive crops, total 1.4–1.9 g, 30–40%), which gave on crystallisation from methanol—light petroleum, prisms of **12** (identified by mixed m.p. and i.r.[1,6]).—The final motherliquors gave, on spontaneous evaporation at room temperature only intractable sticky resins.

Esterification by this procedure of *initial* crops of the hydrolysis product A tended to give more of **12**, while that of later and *final* crops produced almost entirely **13**, though still in moderate yield (up to 56%).

8-Acetoxy-1-methoxycarbonyldiisophor-2(7)-en-3-one (**14**)

A solution of **13** (0.67 g, 0.002 mol) in glacial acetic acid and acetic anhydride (4 ml each) was treated at room temperature with 60% perchloric acid (4 drops),

set aside for 2 h, then stirred into water (100 ml). The white precipitate, collected after 24 h, gave minute prisms (0.56 g, 75%) of **14**, m.p. 175–178° (from light petroleum). (Found: C 70.0; H 8.75. $C_{22}H_{32}O_5$ requires C 70.2; H 8.5%.) ν_{max} 2 970 vs–2 880 s, 1 465 s, 1 435 s (CH_3, CH_2); 1 735–1 720 vs mult (C : O, diester), 1 670–1 665 vs (CO), 1 645 ms sh (C : C, conjug.), 1 395 ms, 1 370 vs br (·CMe_2), 1 245–1 220 vs mult vbr (C—O, diester) cm^{-1}. *m/e* 376 mw (M^+), 344 w (M^+-31, *Me*O-1), 333 w (M^+-43, *Me*CO), 302 vs max (M^+-43-31), 274 s (M^+-43-59, COO*Me*), 261 s (M^+-71-43-1), 214 s (M^+-71-59, *Ac*O-31-1), 343 w, 284 s, 203 m, 201 m.

8-(3',5'-Dinitrobenzoyl)oxy-1-methoxycarbonyldiisophor-2(7)-en-3-one (**15**)

A solution of **13** (0.67 g, 0.002 mol) in (warm) pyridine (10 ml) was treated with 3,5-dinitrobenzoyl chloride (0.58 g, 0.0025 mol) and kept at 100° for 1 h. The precipitate obtained on stirring the liquid into ice-water containing concentrated hydrochloric acid (12 ml) gave faintly yellow microprisms (0.6 g, 58%) of **15**, m.p. 210–211° (from ethanol—light petroleum). (Found: C 61.7; H 6.2; N 5.2. $C_{27}H_{32}N_2O_9$ requires C 61.4; H 6.1; N 5.3%.) ν_{max} 2 950 vs–2 850 s, 1 470–1 455 s mult (CH_3, CH_2), 1 730, 1 715 vs d br (C : O, diester), 1 670 vs (CO), 1 630 ms (C : C, conjug.), 1 550 vs, 1 345 vs br, 730, 720 vs d (NO_2), 1 395 vs sh, 1 375, 1 365 s d (·CMe_2), 1 270–1 250 vs mult (C—O, diester) cm^{-1}.

3,8-Diketodiisophorone-Carboxylic Acid

1-Methoxycarbonyldiisophor-2(7)-ene-3,8-dione (**16**)

A stirred solution of **13** (1.67 g, 0.005 mol) in acetone (40 ml) was treated dropwise at room temperature with *Kiliani*'s 10% chromic acid[7b] (6 ml, 0.012 g atom O) during 10 min, and stirring continued for another 15 min. The orange liquid was decanted from a dark-blue deposit which was extracted with further small portions of acetone. The combined extracts were evaporated to small volume and stirred into ice-water; the pale yellow precipitate gave minute lemon-yellow prisms of **16**, m.p. 148–150° (total, 75%) (from light petroleum, ca. 30 ml per g). (Found: C 72.1; H 8.4. $C_{20}H_{28}O_4$ requires C 72.3; H 8.4%.) ν_{max} 2 950 vs–2 870 s, 1 470 s, 1 430 s (CH_3, CH_2), 1 730 vs d br (C : O, ester), 1 675–1 665 vs mult (di-CO), 1 645 m sh (C : C, conjug.), 1 395 m, 1 370 s (·CMe_2), 1 245 vs br, 1 225 vs (C—O, ester), 1 190 s, 1 165 vs, 1 135, 1 125 s, 1 045 vs, 970 s, 895 m, 800 m, 750 m cm^{-1}. λ_{max} 272 nm (log ε 3.94); 218 (3.65). *m/e* 332 m (M^+), 301 m (M^+-31, *Me*O), 273 s (M^+-59, COO*Me*), 272 s (M^+-59-1), 257 m (M^+-59-16, O), 245 m (M^+-71-16), 230 m (M^+-71-31); 235 vs (max), 218 s, 217 s. The compound **16** failed to yield a 2,4-dinitrophenylhydrazone under the standard conditions.

1-Carboxydiisophor-2(7)-ene-3,8-dione (**17**)

(A) *By hydrolysis of its methyl ester.* A warm solution of **16** (0.66 g, 0.002 mol) in ethanol (12 ml) was slowly treated with 3 *M*-sodium hydroxide (12 ml) and boiled under reflux for 5 h. The orange liquid was added to ice-water (60 ml) and acidified with concentrated hydrochloric acid, giving a pale-yellow precipitate (m.p. 212–218°, 0.46–0.52 g, 75–85%). Crystallisation from ethanol—light petroleum (1 : 4) gave pale-yellow microprisms of **17**, m.p. 236–238° (60–70%). (Found: C 71.6; H 8.4. $C_{19}H_{26}O_4$ requires C 71.7; H 8.2%.) ν_{max} 2 950 vs–2 870 s, 1 465 ms, 1 410 s (CH_3, CH_2), 2 640 m, 2 520 m (COOH), 1 708, 1 700 vs d (C : O, COOH), 1 675 vs (CO), 1 645 ms sh (C : C, conjug.), 1 395 m, 1 370 ms (·CMe_2),

1 275 vs, 1 195 vs, 1 160 vs, 965 ms, 720 s cm^{-1}. λ_{max} 270 nm (log ε 3.84), λ_{plat} 215–224 (3.55). *m/e* 318 m (M^+), 301 m (M^+-17, OH), 300 s (M^+-17-1), 273 s (M^+-45, COOH), 272 s (M^+-45-1), 257 s (M^+-45-16), 230 m (M^+-71-17), 229 s (M^+-71-17-1), 274 vs, 244 s, 217 vs (max).—The compound **17** failed to yield a 2,4-dinitrophenylhydrazone under the standard conditions.

(B) *By oxidation of (impure) 8-hydroxy-1-carboxydiisophor-2(7)-en-3-one* (**11**). A stirred solution of (impure) **11** (i.e. late and final crops of the alkaline hydrolysis product of **3**, see above) (3.2 g, ca. 0.01 mol) in glacial acetic acid (30 ml) or acetone (80 ml) was oxidised with *Kiliani*'s 10% chromic acid[7b] as above. The crude product (m.p. 208–212°, ca. 2.4 g, 75%) gave **17** (60%, in two successive crops) (from ethanol—light petroleum), identical with product obtained in (A).—When the *total* crude product of the alkaline hydrolysis of **3** was used as starting material in this oxidation, the resulting **17** contained appreciable quantities (up to ca. 40%) of **2**.

(C) *By prolonged action of alkali on* **13**. A solution of **13** (0.67 g, 0.002 mol) in ethanol (15 ml) was slowly treated with 3 *M*-sodium hydroxide (12 ml) and the pale-yellow liquid boiled under reflux for 7 h, more ethanol (5 ml) being added after 3 h. It was stirred into ice-water (80 ml) and acidified with concentrated hydrochloric acid. The resulting pale-yellow precipitate was **17**, m.p. 228–230° (from ethanol—light petroleum) (0.38 g, 60%), identical with material obtained in (A).

The same results were obtained (yield, 50%) by performing the hydrolysis in ethanolic *M*-sodium ethoxide (7 h). Shorter periods of boiling (ethanolic alkali) gave either the starting material (30 min) or resulted in incomplete reaction (3 h). The 8-hydroxy-3-keto-1-carboxylic acid **11** was not obtained.

Resistance of **13** *to mineral acid.* The reactant **13** was recovered (75%), after its solution in ethanol—concentrated hydrochloric acid (0.03 mol in 22.5 and 2.5 ml, respectively) had been boiled under reflux for 2 h.

References

[1] Part 12, preceding paper.

[2] *Davies P. R., Kurzer F., Morgan A. R.*, Monatsh. Chem. **111**, 1097 (1980).

[3] *Koch H., Haaf W.*, Liebig's Ann. **618**, 251 (1958); ibid. **638**, 111, 122 (1960); Org. Synth. **44**, 1 (1964); Coll. Vol. **5**, 20 (1973); *Stetter H., Schwarz M., Hirschhorn A.*, Chem. Ber. **92**, 1629 (1959); *Stetter H., Mayer J., Schwarz M., Wulff C.*, ibid. **93**, 226 (1960); *Stetter H., Wulff C.*, ibid. **93**, 1366 (1960).

[4] *Kabas G., Rutz H. C.*, Tetrahedron **22**, 1219 (1966).

[5] *Furth B., Kossanyi J., Morizur J. P., Vandewalle M.*, Bull. Soc. chim. France **1967**, 1428.

[6] *Duffner C. R., Kurzer F.*, Tetrahedron **34**, 1251 (1978).

[7] *Fieser L. F., Fieser M.*, Reagents for Organic Synthesis. New York: Wiley. (a) Vol. 1, p. 191 (1967), Vol. 2, p. 102 (1969); (b) Vol. 1, p. 144 (1967).

[8] *Allen A. A., Kurzer F., Morgan A. R.*, J.C.S. Perkin I **1980**, 733.

[9] *Fieser L. F., Fieser M.*, Steroids, p. 171. New York: Reinhold. 1959.

[10] *Prelog V., Seiwerth R.*, Ber. dtsch. chem. Ges. **74**, 1644 (1941); *Stetter H., Bänder O. E.*, Chem. Ber. **88**, 1535 (1955).

[11] *Dorfman L.*, Chem. Rev. **53**, 47, 67 (1953).

[12] *Allen A. A., Duffner C. R., Kurzer F.*, Tetrahedron **34**, 1247 (1978).