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Diisophorone and Related Compounds. Part 17 [1] Synthesis and Nucleophilic Reactions of 4,8-Dibromodiisophorones

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4,8-Dibromodiisophor-2(7)-en-1-ol-3-one is obtained by dibromination of the parent ketol, or by monobromination of the 4- or 8-bromo-analogues. It is converted, by *Koch-Haaf* carboxylation, into 4,8-dibromodiisophor-2(7)-en-3-one-1-carboxylic acid, which is also accessible by bromination of the appropriate preformed diisophorone-1-carboxylic acids. The existence of the dibromoketol in two stereoisomeric forms is traced to conformational differences of its 4-substituent.

Acetolysis of the 4,8-dibromo-1-carboxylic acid or its methyl ester occurs exclusively at the 8-position, but hydrazinolysis removes both halogen substituents, with formation of 4-hydrazono-diisophorones. The ^{13}C-nmr spectra reflect the structural and conformational changes. A general fragmentation pattern accounts for the behaviour of the individual compounds under electron impact.

(Keywords: Diisophorones, 4,8-dibromo-derivatives; ^{13}C NMR-spectra; MS; Tricyclo[7.3.1.0^{2,7}]tridecanes)

Diisophoron und verwandte Verbindungen. 17. Mitt.
Synthese und nucleophile Reaktionen von 4,8-Dibromdiisophoronen

4,8-Dibromdiisophor-2(7)-en-1-ol-3-on wird durch Dibromierung des Stamm-Ketols oder durch Monobromierung seiner 4- oder 8-Monobrom-Derivate erhalten. Mittels *Koch-Haaf*Carboxylierung wird es in die entsprechende 1-Carbonsäure umgewandelt, die auch durch Bromierung von vorgebildeten Carbonsäuren zugänglich ist. Stereoisomere Formen des Dibromketols unterscheiden sich durch die Konformation ihres 4-Substituenten.

Die Acetolyse der 4,8-Dibrom-1-carbonsäure beschränkt sich auf ihren 8-Substituenten; Hydrazinolyse entfernt hingegen beide Halogen-Atome unter Bildung von 4-Hydrazono-diisophoronen. Die ^{13}C-Kernresonanz-Spektren stimmen mit den Struktur- und Konfigurations-Änderungen überein. Das massenspektrometrische Verhalten der verschiedenen Verbindungen wird an Hand eines allgemeinen Fragmentations-Schemas erörtert.

Introduction

Diisophorone (**1**) may be selectively halogenated at its 1- [2], 4- [3], or 8-position [2, 4, 5] to yield reactive intermediates suitable for the study of further transformations of its three-dimensional alicyclic structure. Attack by nucleophiles at the new reactive centres may occur in one of several ways, resulting in substitution with [6, 7] or without [8, 9] isomerisation, partial aromatisation [4, 10], or intramolecular condensation [11]. Our examination of 4- [3] and 8-bromo-diisophorones [5, 6, 10] from this point of view has now been extended to the 4,8-dibrominated series, exemplified by the parent ketol (**2**) and the ketocarboxylic acid (**8**). The novel features of their production, reactions and properties are correlated satisfactorily with those of their mono-halogeno-analogues.

Results and Discussion

4,8-Dibromodiisophor-2(7)-en-1-ol-3-one (**2**) was readily obtainable by dibromination of diisophorone (**1**) by molecular bromine in glacial acetic acid. It also arose in high yield in the monobromination of authentic 4-bromo- [3] (**4**) or 8-bromo-diisophor-2(7)-en-1-ol-3-one [2, 4] (**3**), a fact that provides direct proof of the location of its halogen substituents. Since monobromination of the parent ketol **1** yields the 8-bromo-compound **3**, dibromination is seen to occur successively at the 8- and 4-position of the molecule; exclusive 4-bromination requires a different synthetic approach [3].

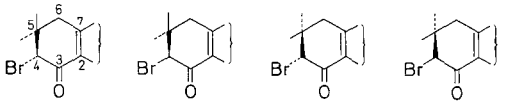
4,8-Dibromodiisophor-2(7)-en-1-ol-3-one (**2**) thus obtained was a mixture of two stereoisomers in the approximate ratio 2:1. This was shown by its ^{13}C-nmr spectrum, which contained twice the expected number of signals, grouped in closely spaced line-pairs, the intensity of one partner being in each case about twice that of the other. Unlike the parent 4,8-dibromoketol **2**, which was inseparable by crystallisation, its 1-acetyl-derivative was readily fractionated into its constituent epimers (**5 A**, **5 B**). In its existence as two stereoisomers, **2** resembles its 4-monobromo-analogue **4** [3], but differs from the sterically uniform 8-monobromo-isomer **3**. The seat of the observed isomerism (of **2**) is therefore ascribed to configurational differences centred at the 4-substituent. The fact that monobromination of the sterically pure **3** yielded the epimeric 4,8-dibromodiisophorone-mixture **2** supports this interpretation (see stereochemical aspects, below).

4,8-Dibromodiisophor-2(7)-en-3-one-1-carboxylic acid (**8**) was similarly obtained in high yields by halogenation of the appropriate preformed carboxylic acid (**6** [8, 3], **10** [5], **11** [3]); dibromination of the readily accessible parent keto-acid **6** under the standard conditions

provides the most expedient preparative method. In another approach, *Koch-Haaf* [12] carboxylation of **2** gave the required dibromocarboxylic acid **8** in 85% yields. Its 1-methyl-ester **9** was obtained by esterification using diazomethane [13] (82%), or by dibromination of the parent ester [3] (**7**, 80%). Both the acid **8** and ester **9**, regardless of their source, were sterically uniform and are assigned the 4α,8β-configuration (see below).

Stereochemical Aspects

As has been discussed in another connexion [14], the partially flattened ring A of diisophorone may, by a bond-"flip" at C(4)—C(5), assume one of two possible pseudo-chair conformations, each of which may bear a 4-substituent in the axial or equatorial configuration (**2A**—**2D**)*. The conformation of ring A, in which C-5 appears above the plane bounded by carbon atoms C-2, 3, 6, 7 (i.e. as in **2A, 2B**) may reasonably be favoured, because its 5,5-gem-dimethyl-group exerts no steric hindrance on ring C (located on the opposite side of the plane of rings A/B); the alternative structure (**2C**, **2D**) represents more crowded molecules in which the 5α-ax-methyl approaches the 17α-ax-methyl-group of ring C closely. The observed stereoisomerism is therefore ascribed to epimerism of the 4-substituent, and not to conformational changes of ring A itself. On this basis, the two stereoisomeric 4,8-dibromodiisophor-2(7)-en-1-ol-3-ones (**2**) (and their acetates **5**) are represented with reasonable probability, though without formal proof, as the epimeric pairs **2A** and **2B.**



2A : 4α-ax **2B** : 4β-eq **2C** : 4α-eq **2D** : 4β-ax

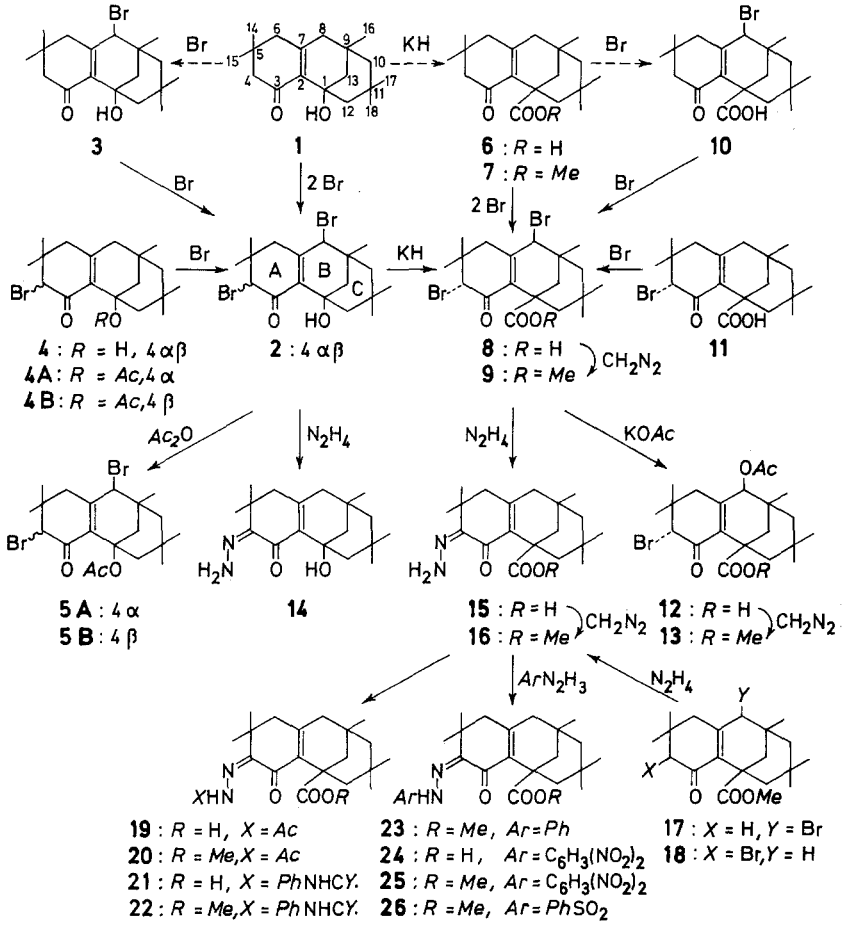
It is further proposed that the more abundant isomer of the 4,8-dibromoketols **2** and **5**, as well as the sterically uniform 4,8-dibromocarboxylic acids **8** and **9** bear their 4-bromo-substituent in the 4α-ax-configuration. This assignment is supported by several observations and arguments:

Thus, the preponderance of the 4α-ax- over the 4β-eq-forms in 1,4-diacetoxydiisophor-2(7)-en-3-one [15] and 4-acetoxydiisophor-2(7)-en-3-one-1-carboxylic acid [5] has been suggested by ir spectral evidence; the conclusion was

* In the ensuing discussion, the designation *axial* and *equatorial* as applied to 4-, 5- and 8-substituents are understood to allow for any deviation from true *ax-* and *eq*-conformation due to ring distortion caused by the 2(7)-double bond. The term "above the plane of rings A/B" refers to the space opposite to that subtended by ring C.

extended to the 4-bromoketol **4** [3] by reference to relevant chemical interconversions. In the present 4,8-dibromo-compounds, the distance between the fixed 8β-eq- and the 4-substituent is somewhat greater for the 4α-ax- than the 4β-eq-configuration. Moreover, the 8β-eq- and 4β-eq-bromine atoms are both situated on the same side above the plane of rings A/B, while 4α-ax-bromine emerges below this plane, with its bond directed almost opposite to that of the 8β-eq-bond, factors that would presumably favour the formation and stability of 4α-ax,8β-eq-dibromo-epimers. Finally, the assignment is in accord with the generalisation, established by *Corey* [16] and elaborated by *Djerassi* [17], that kinetically controlled bromination of cyclohexanones (including ketosteroids) introduces the halogen in the axial conformation. In the absence of appreciable steric interaction between such axial bromine and proximate substituents (as is the case in the present diisophorones), the kinetically controlled reaction product is also the thermodynamically more stable one.

Scheme 1



It remains to account for the contrasting behaviour upon dibromination of the ketol **1** and the ketocarboxylic acid **6**, **7**, the former producing a pair of stereoisomers, but the latter the sterically uniform (4α-ax-) compound, all in high yield. In rationalising this difference in terms of the only structural distinction between the compounds concerned, it is noted that the C-1 and C-4β-eq-bonds of the three-dimensional carbon framework emerge above the plane of rings A/B, ca. 4 Å apart, in directions roughly parallel to one another. The relatively bulky 1-carboxy- or 1-methoxycarbonyl-group (of **6** or **10**) may thus obstruct the attack by the reagent along the 4β-eq-axis, favouring the entry of the substituent in the less hindered 4α-ax-configuration. In contrast, the smaller 1-hydroxy-group does not entirely prevent the formation of the 4β-eq-stereomer, which thus appears as the minor product.

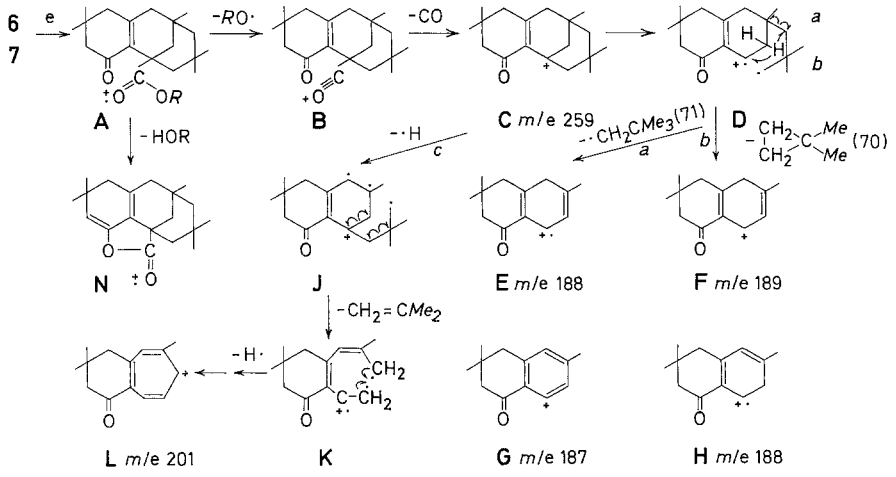
In the *Koch-Haaf* carboxylation (**2** → **8**), the 4αβ,8β-dibromoketol **2**, containing a maximum of 60% of the major stereoisomer, is converted in better than 80% yield into the sterically uniform 4,8-dibromoketocarboxylic acid **8**, implying the epimerisation of one of the constituents of the stereoisomer mixture **2**. The comparable 1-carboxylation of the 4αβ-monobromoketol (**4** → **11**) [3] is attended by the same steric readjustment. On the basis of the foregoing discussion, the minor 4β-eq-bromo-stereoisomer is regarded to epimerise to the more stable conformer, resulting in the sterically uniform 4α-ax-compound. The isomerisation process is explicable, as are comparable examples frequently encountered among steroid α-bromoketones [18], by a mechanism involving the transient enolisation [19] of the α-bromoketo-function of the epimerising species in the highly acidic medium.

Fragmentation Under Electron Impact

The mass spectra of the diisophorone carboxylic acids (**6**, **8**, **10**, **11**) and their methyl esters reveal a common fragmentation pattern, comprising essentially the loss of the extranuclear attachments, and the fission and removal of ring C of the carbon skeleton by one or more of three alternative pathways. Its main-features are outlined, for the sake of conciseness, by reference to the bromine-free prototype **6** (Scheme 2); in its later stages, the fragmentation resembles that of the β-ketols of this series, which has been interpreted in detail by *Kossanyi* et al. [20]. Thus, the molecular ion **A** loses its carboxyl-group by the successive detachment [21] of a hydroxyl radical and carbon monoxide, resulting in the carbonium ion **C**. Removal of ring C therefrom proceeds by the loss of the neopentyl radical (. CH_2CMe_3; pathway *a*) or of 1,1-dimethylcyclopropane (pathway *b*), involving the inter- or intramolecular transfer of a hydrogen radical (from C-13 of **D**) respectively. The resulting fragments

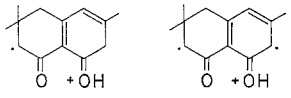
(**E**, **F**), revealed by their high intensity peaks, are found side by side (e.g. in **8**, **10**, **17**), but path *a* appears to be marginally favoured. A third mode of fragmentation, leading to the formation of the condensed tropylium cation **L** (pathway *c*) contributes significantly to the decomposition pattern, as is demonstrated by the high (and sometimes maximum) intensity of the peak (*m*/e 201) associated with this species. Further prominent signals indicate the direct loss of the elements of water from the acids (**6**, **8**, **10**, **11**), or of methanol from their methyl esters, in accord with the favourable position of their (tautomerised) 3-keto- and 1-carboxy(or methoxycarbonyl)-groups for cyclisation to the lactones (e.g. **N**) [21]; their continued scission is visualised to produce entities of type **E**—**H** (not detailed in Scheme 2).

Scheme 2



The mass spectra of the 4-(and 8)-monobromo- and 4,8-dibromo-acids combine the characteristics of the prototype **6** with those related to the ejection of the halogen substituents: Thus, the formation of bicyclic species corresponding to **E** and **F** (but diminished by 1 or 2 atoms of hydrogen, respectively), and of condensed tropylium cations (**L**) are again conspicuous features of the fragmentation process; those originating from the 8-bromo-compounds by a pathway analogous to **A** → **E**, **F**, are illustrated (**G**, **H**). Signals due to lighter fragments are generally too numerous to be assigned with confidence; the decomposition terminates no doubt in tropylium ions of the type identified by *Kossanyi* et al. [20] in the fragmentation of the *β*-ketols. The 4,8-dibromoketol (**2**, **5**) is similarly cleaved with formation, as precursors of the terminal tropylium ions, of the molecular ions **P** and **Q**. The retention of the original 1-hydroxy-group (of **2**) in the molecular ions (**P**, **Q**), compared with the early removal of the 1-carboxy-group (from **6** etc.) distinguishes the two fragmentation patterns. Although there appears

to be some latitude in the order of the fragmentation events for the individual compounds, a bromo-substituent is clearly ejected more readily from the 8- than from the 4-position of diisophorone. Thus, bromine is absent in all the fragments arising from the 8-substituted compounds (**10**, **17**), but persists in some of those from the 4-bromo-isomers (**11**, **18**). The stepwise loss of halogen from the 4,8-dibromo-compounds (**2**, **5**, **8**, **9**) is regarded to follow the same pattern. The greater mobility of the 8- over that of the 4-bromo-substituent under electron impact thus provides a parallel to its superior chemical reactivity.



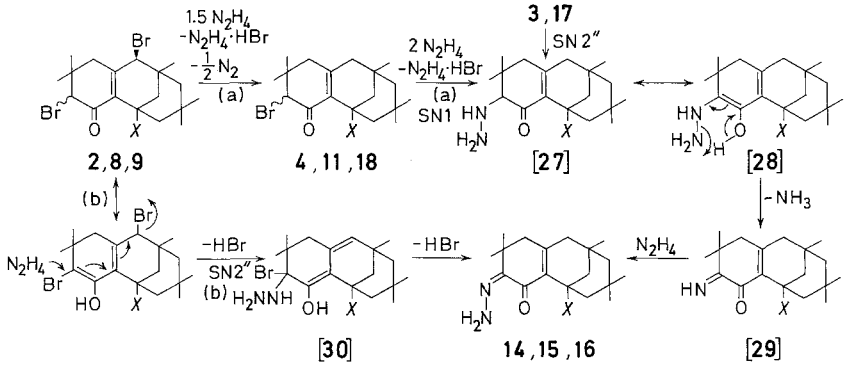
P : *m/e* 204 **Q** : *m/e* 203

Nucleophilic Reactions

Acetolysis of the carboxylic acid **8** by potassium acetate—acetic acid occurred exclusively at the 8-position, producing excellent yields of the 8-acetoxy-4-bromo-acid **12**. Its formulation, based on the demonstrated [3] inertness towards acetolysis of the 4-monobromoacid **11**, is confirmed by the ^{13}C-nmr data (see below). Although the 4,8-dibromoketol **2** appeared to undergo acetolysis also, as judged from the separation of potassium bromide, the resulting mixture of stereoisomers formed an intractable viscid resin from which no material suitable for characterisation was isolable.

Hydrazinolysis: The action of hydrazine on **2** gave excellent yields of 4-hydrazonodiisophor-2(7)-en-1-ol-3-one (**14**), the structure of which has been established previously [6]. The carboxylic acid **8**, its methyl ester **9** as well as its 4- and 8-monobromo-analogues (as their methyl esters **17**, **18**) similarly yielded in each case the 4-hydrazono-1-carboxylic acid (**15**, or its methyl ester **16**).

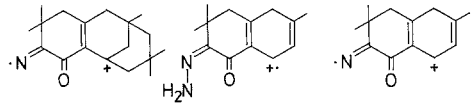
Scheme 3



The observations are interpreted by a mechanism (Scheme 3) which combines a reductive removal of the 8-bromo-substituent [22] by hydrazine with the reaction sequence proposed by *Hauptmann* et al. [23] for the comparable conversion of phenacyl bromide into 2-phenylglyoxal monohydrazone ($R'COCHBrR \rightarrow R'CO.CR=NNH_2$), (pathway *a*, via **27–29**); the reduction may not necessarily be the first stage. Since, however, the action of nucleophiles on 8-bromodiisophorones has on several occasions [5–7] resulted in effective 4-substitution by an SN2″-mechanism, it is tempting to consider the alternative pathway *b* for the hydrazinolysis of the 4,8-dibromo-compounds **2**, **8**, and **9**: in this sequence, the initial concerted entry of the hydrazino-moiety at C-4 and expulsion of bromine at C-8 by the SN2″-mechanism yields the transient intermediate **30**, from which the observed products (**14–16**) could arise directly by loss of hydrogen bromide. This more direct route (*b*) is inapplicable, however, to the 4- and 8-monobromo-analogues, a fact that may possibly explain their slower and less complete hydrazinolysis.

The 4-hydrazono-1-carboxylic acid and its ester (**15**, **16**) gave the expected derivatives on acylation (viz. **19**, **20**), and on addition of phenyl isocyanate or isothiocyanate (**21**, **22**; $Y=O,S$). Their 3-keto-group was inert towards ketonic reagents: on further treatment with substituted hydrazines they yielded, by the established [3, 6, 7] exchange process, the 4-ω-aryl(or arylsulphonyl)hydrazono-compounds (**23–26**). Since hydrazines other than the parent base (e.g. $PhNHNH_2$) failed to effect hydrazinolysis in bromodiisophorones (e.g. **9**), this "transhydrazination" is a useful indirect route to the more highly substituted examples. Their structure is assigned on the basis of that proved [6] for 4-ω-phenylsemicarbazonodiisophor-2(7)-en-1-ol-3-one.

The mass spectra of the 4-hydrazonocarboxylic acids **15**, **16** may be interpreted by fragmentation patterns modelled on that of the parent acid **6**. The removal of the carboxyl-group precedes that of the hydrazono-moiety, which appears to persist well into the later stages of the fragmentation. Ring C is again cleaved from the tricyclic system as the neopentyl radical (*m/e* 71) or 1,1-dimethylcyclopropane (*m/e* 70). Typical stages of the decomposition, common to all examples, are indicated by identifiable fragments such as **R**, **S**, and **T**, from which a fragmentation pattern analogous to that of Scheme 2 may be constructed (but is not detailed here).



R : *m/e* 271 **S** : *m/e* 216 **T** : *m/e* 201

^{13}C-*Nmr Spectra*

The ^{13}C-nmr spectra of the compounds now described are displayed in the usual way [14, 24] in accordance with their proposed assignments (Table 1). Those of the two stereoisomeric 1-acetoxy-4-bromodiisophor-

2(7)-en-3-ones [3] (**4A**, **4B**) not previously recorded, are included for comparison. A close correlation emerges between the spectral data of the 4,8-dibromo-compounds, their 4- and 8-monobromo-analogues (**4**, **11**; **3**, **10**), and their ultimate parent ketol and carboxylic acid (**1**, **6**), a fact that provided helpful guidelines for the interpretation of the new spectra. The reasoning leading to the assignment of the reference spectra of the parent structures (**1**, **6**) is on record [14, 24]; comments concerning the present data are therefore confined to their relevance to structural questions and to brief comparisons.

The ^{13}C-nmr spectra of the 4,8-dibromo-ketols **2** and **5** and -1-carboxylic acids **8** and **9** do not differ significantly from one another, except in the resonances of their 1-bridgehead carbon bearing the changed substituent. Their two doublets, though closely spaced, are assignable by reference to the known [14, 24] chemical shifts of the individual doublets of the 4- and 8-monobromo-compounds (**4**, **11** and **3**, **10**). The 8β-eq-bromo-substituent modifies the spectra in a manner previously seen in **3** [24] and **10** [14]: the adjacent C-9 carbon is deshielded (by 4–5 ppm), while the triplets of the proximate C-6, 10, 12 and 13-carbons are displaced upfield to different degrees. This shielding effect on C-12 and C-13 is further enhanced in the 1-acetates (**5A**, **5B**) and 1-carboxylic acids (**8**, **9**), as has previously been observed in comparable structures [24]. The acetolysis product of **8** is identified as the 8-acetoxy-4-bromo-isomer **12** on the grounds that it is the lower field doublet associated with C-8 that is displaced (to 74.6 ppm) upon substitution, while the chemical shift of C-4 remains unaffected.

The existence of two stereoisomeric forms of 4,8-dibromodiisophorone and its acetate (**2**, **5**), as well as the 4-monobromo-analogues **4**, due to epimerism at C-4, is reflected in their ^{13}C-nmr spectra. Corresponding carbon atoms of the stereoisomer-pairs give rise to signals of chemical shifts which, though consistently distinct, differ on average by less than 1 ppm, except those of the doublets of the stereoisomeric centre (C-4). Three of the five quartets display the usual [14, 24] chemical shifts of the 16-, 17- and 18-carbon atoms and are allotted accordingly; the two that remain for C-14 and C-15 of the isomer-pairs (**2**; **5A**, **5B**; **4A**, **4B**) may in principle be distributed in four permutations and do not *a priori* provide information concerning the configuration of the 4-bromo-substituent in the individual epimers. Their consistent assignment may be arrived at on the basis of the following postulate: The 14β-ax- and 15α-eq-methyl carbons occupy spatial positions nearly symmetrical with respect to a 4β-eq-substituent; when entering the molecule, the latter should therefore displace the relevant quartets (of the parent diisophorone **1**) approximately equally. In contrast, a 4α-ax-substituent occupies a position entirely non-equivalent with respect to the 5-gem-dimethyl carbon atoms (C-14, 15), so that its introduction should exert an unequal effect upon them. One of the four possible dispositions of the numerical data satisfies these requirements most closely (see Table 1, compounds **2**, **4**), and may,

Table 1. *Chemical shifts of* ^{13}C*-nmr signals of diisophorones and their assignments*

Compound[a]		C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
		Bromoketols and their Acetates									
2	4α-ax	72.0 s	133.3 s	194.5 s	62.0 d	*36.6 s	+40.0 t	153.3 s	65.1 d	*36.1 s	49.3 t
2	4β-eq	71.4 s	134.4 s	194.0 s	64.5 d	*37.7 s	+43.0 t	152.6 s	64.7 d	*37.1 s	50.2 t
5A	4α-ax	78.8 s	132.6 s	189.8 s	63.2 d	*37.0 s	40.3 t	150.2 s	64.8 d	*36.1 s	47.9 t
5B	4β-eq	78.7 s	133.6 s	189.1 s	64.3 d	*38.2 s	43.8 t	149.6 s	66.6 d	*37.4 s	48.9 t
4A	4α-ax	79.8 s	133.3 s	188.6 s	65.8 d	37.5 s	*45.1 t	154.4 s	*43.5 t	32.6 s	52.1 t
4B	4β-eq	80.0 s	132.4 s	188.8 s	63.3 d	36.2 s	*45.5 t	155.4 s	*41.6 t	32.5 s	52.3 t
		Bromocarboxylic Acids									
8		45.6 s	134.7 s	190.5 s	63.0 d	34.8 s	41.3 t	151.7 s	66.1 d	36.5 s	47.0 t
9		44.7 s	133.3 s	190.2 s	61.0 d	34.5 s	*40.2 t	151.6 s	64.5 d	36.2 s	47.1 t
13[b]		44.4 s	135.8 s	189.9 s	60.6 d	34.7 s	*39.9 t	151.0 s	74.6 d	36.1 s	49.6 t
		4-Hydrazono-Compounds									
14[c]		71.4 s	138.4 s	184.8 s	137.4 s	37.3 s	*46.0 t	156.2 s	*45.0 t	32.4 s	52.3 t
15		45.2 s	*138.2 s	183.8 s	*137.1 s	37.8 s	+45.6 t	153.7 s	+45.3 t	○30.7 s	52.6 t
16		44.6 s	*139.1 s	183.1 s	*136.0 s	37.7 s	+45.4 t	154.9 s	+45.3 t	○30.6 s	52.5 t
20[b]		44.7 s	136.6 s	183.4 s	143.4 s	39.1 s	+45.6 t	159.1 s	+45.1 t	○30.6 s	52.2 t

Table 1 (continued)

Compound[a]		C11	C12	C13	C14	C15	C16	C17	C18	C19	C20
2	4α-ax	31.6 s	47.8 t	+37.9 t	23.2 q	28.1 q	32.3 q	32.6 q	35.7 q		
2	4β-eq	31.5 s	49.0 t	+38.7 t	24.1 q	27.7 q	31.3 q	33.0 q	36.3 q		
5 A	4α-ax	31.1 s	45.4 t	35.6 t	23.4 q	28.1 q	32.4 q	32.7 q	36.0 q	170.2 s	21.7 q
5 B	4β-eq	30.9 s	45.9 t	36.5 t	22.4 q	29.0 q	31.5 q	33.0 q	36.5 q	169.8 s	21.7 q
4 A	4α-ax	31.1 s	46.3 t	*43.8 t	24.2 q	29.0 q	28.4 q	32.4 q	37.3 q	169.8 s	21.9 q
4 B	4β-eq	31.3 s	45.9 t	*43.8 t	25.0 q	27.8 q	29.6 q	32.5 q	37.3 q	170.4 s	22.0 q
8		30.2 s	40.3 t	35.8 t	23.3 q	27.7 q	31.8 q	33.7 q	35.1 q	178.1 s	
9		30.0 s	*39.8 t	34.8 t	22.7 q	28.1 q	31.6 q	33.4 q	35.0 q	176.1 s	52.1 q
13		29.7 s	*39.2 t	*38.0 t	24.1 q	28.1 q	26.7 q	31.1 q	36.9 q	176.4 s	51.9 q
14		31.5 s	50.0 t	46.3 t	+27.3 q	+27.9 q	28.4 q	32.7 q	37.1 q		
15		○30.3 s	45.1 t	42.5 t	27.4 q	×28.4 q	×28.6 q	32.9 q	37.7 q	179.3 s	
16		○30.0 s	44.2 t	41.4 t	26.8 q	×28.1 q	×28.4 q	32.7 q	37.4 q	177.6 s	51.7 q
20		○30.0 s	44.0 t	41.2 t	26.2 q	27.5 q	28.4 q	32.6 q	37.3 q	176.8 s	51.9 q

* + × ○ Signals may be exchanged in a horizontal line

[a] Spectra were determined in deuteriochloroform, except those of the sparingly soluble free acids **8** and **15**, for which deuteriopyridine was used

[b] Additional signals: **13**: C-21, 170.6 s; C-22, 20.8 q. **20**: C-21, 174.5 s; C-22, 19.7 q

[c] This spectrum [14] is included for comparison

moreover, be extended to the examples occurring exclusively in the 4α-ax-forms (**8**, **9**, **13**). It suggests that the 4-bromo-substituent shields the 5-gem-dimethyl-carbons, and that the effect is greatest between the 4α-ax-bromo- and 14β-ax-methyl substituent.

The spectra of the 4-hydrazono-1-carboxylic acid and its derivatives **15**, **16** and **20** combine the features of those of the 4-hydrazono-ketol **14** [24] and the parent carboxylic acid **6** and **7** [14]. The introduction of the 4-hydrazono-group replaces the familiar 4-methylene triplet (at ca. 52 ppm) by a low-field singlet, which appears in the appropriate hydrazono-carbon range [25] at ca. 137 ppm. A simultaneous electron drift towards the ketonic centre distinctly shields C-3 (by ca. 15 ppm), while C-5 and C-2 undergo smaller deshielding; the magnitude of the effects are similar in both the β-ketol **14** [24] and the 1-carboxylic acid.

Experimental

The nomenclature employed is that adopted in Part 1 [26] of this series. This also gives general information concerning standard procedures, apparatus, reagents, solvents and abbreviations. Light petroleum had b.p. 60–80° unless otherwise specified. Pyridine was the commercial anhydrous grade.

The ^{13}C-nmr spectra were determined on a Bruker WM 250 *Fourier* Transform instrument operating at 62.89 MHz, and the broad band proton noise decoupled and DEPT spectra recorded. The internal standard was *TMS*, and the solvent deuteriochloroform or deuteriopyridine. Mass spectra were obtained on an AEI MS-902 instrument operating at 70 eV. Unassigned peaks of ir spectra are not recorded except for the key-compounds **2**, **8** and **15**, and for **5A** and **5B** (to distinguish the epimers).

Synthesis

4α,β-8β-Dibromodiisophor-2(7)-en-1-ol-3-one (**2**)

(i) *From diisophor-2(7)-en-1-ol-3-one* ("Diisophorone", **1**). A stirred solution of **1** (13.8 g, 0.05 mol) in glacial acetic acid (250 ml) containing 60% hydrobromic acid (1 ml) was treated dropwise at room temperature during ca. 1.5 h with 0.5 *M* bromine in the same solvent (200 ml, 0.1 mol), and the yellow liquid added to ice-water (2 l). The pale yellow semisolid precipitate hardened on storage (72 h), was collected, washed with water and air-dried (m.p. 99–101°; above 90%). It gave, on crystallisation from light petroleum (b.p. 40–60°), microcrystalline needles (13.9–15.5 g; 64–72%) of **2**, m.p. 104–106° (Found: C 49.2, H 5.9, Br 36.5. $C_{18}H_{26}Br_2O_2$ requires C 49.8, H 6.0, Br 36.8%). ν_{max} 3 510 vs (OH); 2 960 vs–2 880 s, 1 470 s, 1 420 s br (CH_3, CH_2); 1 645, 1 640 vs d (CO); 1 615 s (C=C conjug.); 1 395 m, 1 370 vs (. CMe_2); 1 330 s, 1 305 s, 1 285 s, 1 180 s, 1 050 vs, 995 m, 950 m d, 915 m, 875 mw, 685 s cm^{-1}. *m/e* 436, 434, 432 vw (M^+); 365, 363, 361 vs (*M*-71); 355, 353 ms (*M*-Br); 285, 283 s (*M*-Br-70); 284, 282 s (*M*-Br-71); 274 m (*M*-2 Br); 218 vs max (*M*-2 Br-56, $CH_2=CMe_2$); 204 ms (*M*-2 Br-70 = **P**); 203 ms (*M*-2 Br-71 = **Q**); 313, 311 ms, 259 ms, 232 s, 205 ms, 201 m, 189 s.

Alternatively, the final acetic acid solution was gradually diluted with crushed ice until the separation of the product was complete. The resulting microprisms,

m.p. 85–88°, obtained in near-quantitative yield, were suitable for further synthetic use without purification. However, the uncrystallised material tends to decompose and can be kept only for short periods.

(ii) *From 4α,β-bromodiisophor-2(7)-en-1-ol-3-one* (**4**) [3]. A stirred solution of **4** (1.78 g, 0.005 mol) in glacial acetic acid (30 ml)—60% hydrobromic acid (0.2 ml) was treated dropwise with 0.33 *M* bromine in the same solvent (15 ml, 0.005 mol) during 1 h, the bromine being decolourised as fast as it was added. Isolation and crystallisation as described in (i) gave **2** (total, 1.62 g, 75%), identical (mixed m.p. 98–101°, ir.) with material obtained in (i).

(iii) *From 8-bromodiisophor-2(7)-en-1-ol-3-one* (**3**) [4, 6]. The same result was obtained when **3** (0.005 mol) was used in the foregoing procedure, the 4,8-dibromoketol **2** resulting in 65–75% yield.

4,8-Dibromodiisophor-2(7)-en-1-ol-3-one (**2**): *Acetylation*

A solution of **2** (2.17 g, 0.005 mol) in glacial acetic acid (20 ml), treated with acetic anhydride (10 ml), then dropwise with 60% perchloric acid (0.4 ml), was set aside at room temperature for 2 h, then stirred into warm water (200 ml). The supernatant aqueous phase was decanted from the pale-yellow resin, which was covered with water and gradually solidified. It was dissolved in light petroleum, and gave successive crops of crystals (each 0.5–0.3 g). The first two fractions gave, on crystallisation from the same solvent, minute prisms (0.57 g, 24%) of 1-acetoxy-4β,8-dibromodiisophor-2(7)-en-3-one (**5 B**), m.p. 168–170° (Found: C 50.2, H 5.9, Br 33.4. $C_{20}H_{28}Br_2O_3$ requires C 50.4, H 5.9, Br 33.6%). ν_{max} 2960 vs–2860 s, 1470 ms (CH_3, CH_2), 1730 vs (CO of *Ac*), 1680 vs (CO, ring), 1625 m (C=C conjug.), 1390 m, 1370 s (.CMe_2), 1250, 1240 vs br (C—O of *Ac*), 1165 ms, 1140 m, 1100 m, 1030 vs, 970 mw, 950 mw, 930 w, 910 w, 860 w, 810 w, 720 mw, 700 m and 685 mw cm^{-1}. *m/e* 397, 395 m (*M*-Br), 364, 362, 360 w (*M*-71-43, *Ac*), 337, 335 s (*M*-Br-59, *Ac*O-1), 281, 279 vs (*M*-Br-59-56, $CH_2=CMe_2$-1), 267, 265 s (*M*-Br-71-59), 202 vs max (*M*-2 Br-71-43), 186 s (**P**-18, H_2O); 355, 353 w.

The later crops gave massive needles (0.83 g, 35%) of the 4α,8-dibromo-epimer (**5 A**), m.p. 104–108° (Found: C 49.6, H 5.8, Br 33.2%). ν_{max} 2950 vs–2850 s, 1475 ms (CH_3, CH_2), 1725 vs (CO of *Ac*), 1665 vs (CO, ring), 1615 m (C=C conjug.), 1395 m, 1375 s (.CMe_2), 1255, 1240 vs br (C—O of *Ac*), 1170 m, 1135 m, 1100 m, 1030 vs, 955 mw, 925 mw, 865 w and 690, 680 w d cm^{-1}. Spontaneous evaporation of the mother-liquors gave a crystalline residue consisting essentially of **5 A**.

4α,8β-Dibromo-1-carboxydiisophor-2(7)-en-3-one (**8**)

(i) *From 1-carboxydiisophor-2(7)-en-3-one* (**6**) [3, 8]. A stirred solution of **6** (13.7 g, 0.045 mol) in glacial acetic acid (500 ml) containing 60% hydrobromic acid (1 ml) was treated dropwise during 3–4 h with 0.5 *M* bromine in glacial acetic acid (200 ml, 0.1 mol) which was decolourised immediately. The yellow (sometimes orange) liquid was stirred into ice-water (ca. 3 l), the resulting finely divided ivory precipitate collected and washed with water to neutrality. The air-dried product (m.p. between 200 and 208°, 90–95%, pure by ir.) was crystallised by dissolution in ethanol (successive portions, total 250 ml), and dilution of the filtered liquid with an equal volume of light petroleum (recovery 70% in successive crops) or with hot water (100 ml) (recovery 80% in one crop), giving microprisms of **8**, m.p. 218–222° (Found: C 49.2, H 5.75, Br 34.1. $C_{19}H_{26}Br_2O_3$ requires C 49.4, H 5.6, Br 34.6%). ν_{max} 2970 vs–2870 s, 1480–1455 s mult (CH_3, CH_2), 2640 ms d, 2540 m (COOH), 1705 vs br (CO of COOH), 1680 vs br (CO), 1630 ms (C=C conjug.), 685 s (? Br);

1395 s, 1375 vs (.CMe_2); 1325 ms, 1280 vs br, 1230 s, 945 ms, 905 s, and 790 mw cm^{-1}. *m/e* 464, 462, 460 vw (M^+), 419, 417, 415 vw (*M*-45, COOH), 383, 381 vs (*M*-Br), 365, 363 vs (*M*-Br-18, H_2O), 295, 293 s (*M*-Br-71-17), 267, 265 s (*M*-Br-71-45), 214 s (*M*-2 Br-71-17), 201 vs (**L**), 200 s (**L**-1), 187 vs max (**H**-1), 186 vs (**G**-1); 337, 335 vs, 216 s.

(ii) *From 4-bromo-1-carboxydiisophor-2(7)-en-3-one* (**11**) [3]. The reactant (1.53 g, 0.004 mol) was dissolved in glacial acetic acid (60 ml) with heating. The solution was allowed to cool (to just above room temperature to keep the reactant dissolved) and was brominated (0.004 mol) and isolated as above, affording microprisms of **8** (1.0 g, 54%), identical (mixed m.p. 214–216°, ir.) with material prepared in (i). Spontaneous evaporation of the mother liquors deposited up to 35% of the starting material.

(iii) *From 8-bromo-1-carboxydiisophor-2(7)-en-3-one* (**10**) [5]. The use of **10** in the foregoing procedure gave **8** (75%, identified by mixed m.p. and ir.).

(iv) *From 4,8-dibromodiisophor-2(7)-en-1-ol-3-one* (**2**) (By *Koch-Haaf* carboxylation [12]). The reactant (**2**) (2.17 g, 0.005 mol) was dissolved in stirred concentrated sulphuric acid (100 ml) at 0°, and the deep-yellow solution treated dropwise with 100% formic acid (20 ml), the temperature being maintained near 0° by external cooling (ca. 2 h, effervescence). After another hour's stirring, the liquid was added to ice-water (1.5 l), the white precipitate collected and washed with water to neutrality. Crystallisation as above gave prisms (2.0 g, 85%) of **8**, identical (mixed m.p., ir.) with material obtained in (i–iii).

4α,8β-Dibromo-1-methoxycarbonyldiisophor-2(7)-en-3-one (**9**)

(i) *From the 1-carboxylic acid* (**8**). A stirred suspension of **8** (2.31 g, 0.005 mol) in ether (150 ml) was treated in portions with ethereal diazomethane (from 0.012 mol 'Diazald' [13]). The solid dissolved with effervescence; the colour of the reagent was initially discharged but later persisted. After 3 hours' storage at room temperature, the excess of diazomethane was destroyed with 3 *M* acetic acid, the liquid washed to neutrality (sodium carbonate, water), and the ether removed in a vacuum. The faintly yellow solid residue gave, on crystallisation from light petroleum (ca. 150 ml), ivory prisms (1.95 g, 82%) of **9**, m.p. 143–145° (Found: C 50.6, H 6.0, Br 33.0. $C_{20}H_{28}Br_2O_3$ requires C 50.4, H 5.9, Br 33.6%). ν_{max} 2960 vs–2880 s, 1480 ms, 1450 ms (CH_3, CH_2), 1740 vs (C=O of ester), 1670 vs (CO), 1395 m, 1380 ms (.CMe_2), 1245 s (C—O, ester), 685 ms (? Br) cm^{-1}. *m/e* 478, 476, 474 w (M^+), 419, 417, 415 w (*M*-59, COO*Me*), 397, 395 s (*M*-Br), 366, 364 ms (*M*-Br-31, O*Me*), 338, 336 m (*M*-Br-59), 285 w (*M*-2 Br-31), 257 vw (*M*-2 Br-59), 202 s (**L** + 1), 200 ms (**L**-1), 186 s (**G**-1); 365, 363 vs max, 337, 335 ms, 229 s.

(ii) *From 1-methoxycarbonyldiisophor-2(7)-en-3-one* (**7**) [3, 8]. A stirred solution of **7** (3.18 g, 0.01 mol) in glacial acetic acid (100 ml)—60% hydrobromic acid (0.2 ml) was brominated (room temperature, 1 h, 0.33 *M* bromine in H*Ac*, 0.02 mol), and the pale orange liquid stirred into ice water (500 ml). The white precipitate gave, on crystallisation from acetone-light petroleum (ca. 4 ml each, per g), prisms (3.8 g, 80%) of **9**, identical (mixed m.p. 142–144°, ir.) with material obtained in (i).

The use of 3 moles of bromine in the foregoing procedure gave the same product in 64% yield, but produced in some cases, mixtures of of **7** and the 4,4,8-tribromo-methyl ester (e.g. in ca. 60 and 20% yield), which were separable by fractional crystallisation from acetone.

Acetolysis

8-Acetoxy-4α-bromo-1-carboxydiisophor-2(7)-en-3-one (**12**)

A solution of **8** (4.62 g, 0.01 mol) and anhydrous potassium acetate (5.9 g, 0.06 mol) in glacial acetic acid (60 ml) was boiled under reflux for 1 h. White solid separating after a few minutes caused severe bumping. The suspension was stirred into ice-water (300 ml), the white precipitate collected and washed to neutrality (m.p. 80–90°, 3.5 g). Dissolution in ethanol-light petroleum (5 and 25 ml) gave successive crops of crystals (total 1.85–2.3 g, 42–52%) and a final yellow sticky resin (R). The solid gave, on further crystallisation from the same solvents (recovery ca. 50%), microprisms of **12**, m.p. 247–248° (Found C 56.7, H 6.6, Br 18.4. $C_{21}H_{29}BrO_5$ requires C 57.2, H 6.6, Br 18.1%). ν_{max} 3 480–3 420 ms br (?OH), 2 970–2 870 vs, 1 475 ms (CH_3, CH_2), 2 640–2 620 ms d, 2 540 ms (COOH), 1 735 vs, 1 700, 1 695 vs d (C=O of *Ac*O, COOH), 1 675 vs (C=O), 1 645 ms sh (C=C conjug.), 1 395 m, 1 375 s (. C*Me*$_2$), 1 225 vs br (C—O) cm^{-1}. *m/e* 442, 440 vw (M^+), 399, 397 w (*M*-43, CH_3CO .), 382, 380 vw (*M*-43-17, OH), 318 vs max (*M*-Br-43), 316 m (*M*-Br-45, COOH), 302 m (*M*-Br-59, CH_3COO .), 294, 292 m (*M*-71-59-18), 273 m (*M*-Br-71-17), 257 s (*M*-Br-59-45), 201 s (**L**), 187 s (**H**-1), 301 s.

Treatment of the resin R with diazomethane gave the crystalline methyl ester **13** (see immediately below) in yields indicating the presence of up to 10% of **12** in the resin.

8-Acetoxy-α-bromo-1-methoxycarbonyldiisophor-2(7)-en-3-one (**13**)

(i) *From the carboxylic acid* **12**. A suspension of **12** (0.88 g, 0.002 mol) in ether (150 ml) was treated with ethereal diazomethane (from 0.04 mol 'Diazald' [13]), when solution occurred with effervescence. The yellow liquid was set aside at room temperature for 3 h, and gave upon the usual work-up (see above), a white solid. This produced, on crystallisation from light petroleum (with addition of a little acetone), microprisms (0.51 g, 56%) of **13**, m.p. 219–221° (Found: C 57.6, H 6.9. $C_{22}H_{31}BrO_5$ requires C 58.0, H 6.8%). ν_{max} 2 960 vs–2 870 s, 1 470 s, 1 440 s (CH_3, CH_2), 1 740–1 720 vs br (C=O of *Ac*O, COO*Me*), 1 670 vs br (C=O), 1 645 s (C=C conjug.), 1 395 ms, 1 370 vs br (. C*Me*$_2$), 1 260–1 210 vs vbr (C—O of *Ac*O, COO*Me*), 1 165 vs, 1 045 vs, 1 020 vs, 980 vs cm^{-1}. *m/e* 456, 454 w (M^+), 425, 423 w (*M*-31, O*Me*), 424, 422 w (*M*-32, *Me*OH), 397, 395 w (*M*-59, *Ac*O or COO*Me*), 295, 293 ms (*M*-71-59-31), 201 ms (**L**), 187 ms (**H**-1); 333 vs, 301 vs, 283 vs max, 255 vs.

(ii) *From 4,8-dibromo-1-methoxycarbonyldiisophor-2(7)-en-3-one* (**9**). A solution of **9** (2.38 g, 0.005 mol) and potassium acetate (2.95 g, 0.03 mol) in glacial acetic acid (30 ml) was boiled under reflux for 1 h, then stirred into ice water. The white precipitate, collected and washed neutral, which tended to resinify, was dissolved in acetone (10 ml)—light petroleum (20 ml). The product crystallising in successive fractions (total, 1.05 g, 47%) was **13**, identical with material obtained in (i).

Attempted acetolysis of 4,8-dibromodiisophor-2(7)-en-1-ol-3-one (**2**) under the standard conditions (see above) (time of refluxing, 1 h or 20 min), though attended by the separation of potassium bromide, produced resinous semisolids which were uncrystallisable from light petroleum, eventually forming yellow viscous sticky resins.

Hydrazinolysis

4-Hydrazonodiisophor-2(7)-en-1-ol-3-one (**14**)

A solution of **2** (2.17 g, 0.005 mol) and hydrazine hydrate (1.0 g, 0.02 mol) in ethanol (20 ml) was boiled under reflux for 2 h. The deep-red liquid was added to water, and the precipitated yellow resin immediately added to boiling ethanol (10 ml). The solution deposited deep yellow prisms (1.15–1.3 g, 75–85%) of **14**, identical (mixed m.p. 160–162°, ir.) with material obtained analogously [6] from the 8-bromo-compound (**3**).

1-Carboxy-4-hydrazonodiisophor-2(7)-en-3-one (**15**)

Finely powdered **8** (4.62 g, 0.01 mol), suspended in hydrazine hydrate (15 g, 0.3 mol) was rapidly heated to boiling under reflux. The initially clear liquid became turbid suddenly (1 min); addition of ethanol (5 ml) produced a deep-yellow clear solution which was boiled for 5 min. Addition to ice—3 *M*-hydrochloric acid (100 ml) gave a pale-yellow precipitate, which was collected, washed neutral, and air-dried (m.p. 190–195°, 2.5–2.8 g, 75–85%). Crystallisation from ethanol (ca. 30 ml per g, recovery 60%) gave pale-yellow felted needles of **15**, m.p. 236–238° (Found: C 68.8, H 8.7, N 8.6. $C_{19}H_{28}N_2O_3$ requires C 68.7, H 8.4, N 8.4%). ν_{max} 3 445 vs, 3 270 m (NH_2), 2 945 vs–2 860 s, 1 465 m (CH_3, CH_2), 2 650 m, 2 540 mw (COOH), 1 700–1 690 vs d (CO of COOH), 1 640 ms, 1 625 s (C=N, CO ring), 1 565 s (? NH), 1 390, 1 375 ms (. CMe_2), 1 295 s, 1 215 m, 1 175 m, 1 135 mw, 1 105 mw, 1 085 m, 985 mw, 955 mw, 865 m, 805 m, 720 mw cm^{-1}. *m/e* 332 w (*M*$^+$), 315 ms (*M*-17, OH), 271 vs (*M*-45, COOH-16, NH_2), 244 s (*M*-70-18, H_2O), 243 vs (*M*-71-18), 216 ms (*M*-71-45), 201 s (*M*-70-45-16), 187 vs max (*M*-70-45-30, ? = NNH_2), 289 s. In the initial crystallisation, the crude powder is advantageously added in one portion *to* the boiling ethanol, in which it dissolves instantly, but then reappears rapidly in a now less soluble crystalline form.

4-Acetylhydrazono-1-carboxydiisophor-2(7)-en-3-one (**19**)

A solution of **15** (0.66 g, 0.002 mol) in warm pyridine (8 ml), treated with acetic anhydride (1 ml), was kept at 100° for 2 min, then at room temperature for 3 h, and added to ice-concentrated hydrochloric acid (8 ml). The precipitate gave pale-yellow microprisms (85%) of **19**, m.p. 254–257° (from ethanol—light petroleum) (Found: C 67.0, H 8.0, N 7.4. $C_{21}H_{30}N_2O_4$ requires C 67.4, H 8.0, N 7.5%). ν_{max} 3 230 s, 1 560 ms br (NH), 2 950 vs–2 860 s mult, 1 475 ms, 1 440 ms–1 410 s (CH_3, CH_2), 2 650–2 630 mw d, 2 540 w (COOH), 1 715, 1 710 vs vbr (CO of *Ac*, COOH), 1 620 vs (C=N, CO ring), 1 395 s, 1 375 vs (. CMe_2), 1 285 vs br (C—O of *Ac*) cm^{-1}. *m/e* 374 vw (*M*$^+$), 357 mw (*M*-17, OH), 356 ms (*M*-18, H_2O), 314 w (*M*-17-43, *Ac*), 313 vw (*M*-18-43), 299 w (*M*-17-58, *Ac*NH), 271 m (*M*-58-45, COOH), 258 vs max (*M*-71-45), 201 vs (*M*-70-58-45).

1-Carboxy-4-(4'-phenylsemicarbazono)diisophor-2(7)-en-3-one (**21**, *Y* = O)

A solution of **15** (0.66 g, 0.002 mol) in warm pyridine (10 ml), treated with phenyl isocyanate (0.36 g, 0.003 mol), was kept at 100° for 2 min, then at room temperature for 1 h, and stirred into ice—concentrated hydrochloric acid (10 ml). The derivative, **21**, *Y* = O, formed a pale-yellow crystalline powder (60%), m.p. 263–265° (decomp.) (from a fairly large volume of acetone-ethanol) (Found: C 69.1, H 7.4, N 9.6. $C_{26}H_{33}N_3O_4$ requires C 69.2, H 7.3, N 9.3%). ν_{max} 3 250 m, 1 535 vs br (NH), 2 950 vs–2 860 s, 1 450 s (CH_3, CH_2), 2 655 mw (COOH),

1 700 vs br (CO of COOH), 1 615 s (CO ring/C=N), 1 390 mw, 1 375 m (. CMe_2), 760 m, 695, 690 w d (*Ph*) cm^{-1}.

The *4-(4'-phenylthiosemicarbazono)*—analogue (**21**, $Y=S$), similarly obtained (65%) by the use of phenyl isothiocyanate (0.34 g, 0.0025 mol), formed a deep-yellow crystalline powder, m.p. 275–277° (decomp.) (from a fairly large volume of acetone—ethanol) (Found: C 66.7, H 7.3, N 8.8. $C_{26}H_{33}N_3O_3S$ requires C 66.8, H 7.1, N 9.0%). ν_{max} 3 310 s, 3 290 s, 1 540 vs (NH), 2 950 vs–2 860 s, 1 430 vs (CH_3, CH_2), 2 660 mw, 2 530 w (COOH), 1 700 vs (CO of COOH), 1 615 vs (CO ring/C=N), 1 595 ms (C=C conjug.), 1 390 ms, 1 375 s (. CMe_2), 755 mw, 695 m (*Ph*) cm^{-1}.

1-Carboxy-4-(2',4'-dinitrophenylhydrazono)diisophor-2(7)-en-3-one (**24**)

A hot solution of **15** (0.50 g, 0.0015 mol) in ethanol (8 ml) was treated with one of 2,4-dinitrophenylhydrazine (0.40 g, 0.002 mol) in ethanol (10 ml)—concentrated hydrochloric acid (1 ml). On being heated for 1–2 min, the liquid rapidly deposited an orange crystalline solid (m.p. 278°, 0.45 g, 60%, pure by i.r.) (filtrate F), forming **24** as a brick-red crystalline powder, m.p. 278–280° (decomp.) (from ethoxyethanol), identical with authentic material [3]. (Found: C 60.15, H 6.2, N 11.0. Calc. for $C_{25}H_{30}N_4O_7$: C 60.2, H 6.0, N 11.2%). 2,4-Dinitrophenylhydrazine (ca. 40%) was recovered on partial evaporation of filtrate F.

4-Hydrazono-1-methoxycarbonyldiisophor-2(7)-en-3-one (**16**)

(i) *From 4,8-dibromo-1-methoxycarbonyldiisophor-2(7)-en-3-one* (**9**). A solution of **9** (4.76 g, 0.01 mol) in hot ethanol (50 ml), treated with hydrazine hydrate (2.0 g, 0.04 mol) was boiled under reflux for 20 min. Within the first minute, the clear liquid turned turbid and deposited colourless droplets (of saturated aqueous hydrazine bromide) on the walls of the flask. The mixture was distilled to half volume under reduced pressure, and stirred into ice—concentrated hydrochloric acid (5 ml); the pale-yellow precipitate, obtained nearly quantitatively, gave silky yellow needles (2.6–2.9 g, 75–85%) of **16**, m.p. 178–180° (from ethanol) (Found: C 69.2, H 8.8, N 8.1. $C_{20}H_{30}N_2O_3$ requires C 69.4, H 8.7, N 8.1%). ν_{max} 3 380 vs, 3 225 ms (NH_2), 2 950 vs, 2 895 vs–2 855 s br, 1 460 s (CH_3, CH_2), 1 745 vs (CO of COO*Me*), 1 645 s, 1 630 s (C=N, CO ring), 1 560 s br, 1 520 vs (? NH), 1 385, 1 375 s d (. CMe_2), 1 230 vs (C—O of COO*Me*) cm^{-1}. *m/e* 346 vw (M^+), 315 w (*M*-31, O*Me*), 299 w (*M*-31-16, NH_2), 287 w (*M*-59, COO*Me*), 271 vs max (*M*-59-16), 244 s (*M*-71-31), 216 s (*M*-71-59), 201 s (*M*-70-59-16), 187 vs (*M*-70-59-30, ? = NNH_2), 303 s, 272 s, 243 vs.

(ii) *From the monobromo-analogues.* When **17** [5] or **18** [3] was subjected to hydrazinolysis under the foregoing conditions, the same 4-hydrazono-compound **16**, identified by mixed m.p. and ir., was obtained in 62 and 48% yield, respectively.

(iii) *From the corresponding carboxylic acid* (**15**). A solution of **15** (1.66 g, 0.005 mol) in diethyl ether (30 ml) was treated with ethereal diazomethane (from 'Diazald' [13], 0.02 mol). Spontaneous evaporation of the liquid at room temperature left a dark-yellow solid, which gave **16**, m.p. 180–182° (from ethanol) (1.3 g, 75%).

4-Hydrazono-1-methoxycarbonyldiisophor-2(7)-en-3-one (**16**): *Derivatives*

The compound gave the following derivatives by the methods used for the 1-carboxylic acid (**15**):

The *4-acetyl-derivative* (**20**) formed ivory felted needles (65%), m.p. 143–144° (from light petroleum) (Found: C 67.4, H 8.2, N 7.3. $C_{22}H_{32}N_2O_4$ requires C 68.0, H 8.25, N 7.2%). ν_{max} 3250, 3240 s d, 1565 m (NH), 2950 vs–2850 s mult, 1470 ms, 1440–1415 ms (CH_3, CH_2), 1740 vs, 1730 vs sh (CO of COO*Me*, *Ac*), 1705 vs, 1620 vs (C=N/CO ring), 1390 ms, 1375 s (. C*Me*$_2$), 1285 s (C—O of *Ac*), 1245 vs (C—O of COO*Me*) cm^{-1}. *m/e* 388 w (M^+), 357 w (*M*-31, O*Me*), 345 s (*M*-43, *Ac*), 329 w (*M*-59, COO*Me*), 317 mw (*M*-71), 271 w (*M*-59-58, *Ac*NH), 258 s (*M*-71-59), 215 w (*M*-71-59-43), 201 vs (*M*-70-59-58). 257 vs max (*M*-59-72, ? = NNH*Ac*), 243 w, 187 m (*M*-70-59-72).

The *4-(4'-phenylsemicarbazono)-compound* (**22**, $Y = O$) formed pale-yellow minute prisms (0.45 g, 48%), m.p. 194–196° (from ethanol—light petroleum) (Found: C 69.3, H 7.5, N 9.4. $C_{27}H_{35}N_3O_4$ requires C 69.7, H 7.5, N 9.0%). ν_{max} 3380 vs, 3230 ms, 1530 vs (NH), 2945 vs–2850 ms, 1445 vs, 1415 m (CH_3, CH_2), 1720 vs (CO of COO*Me*), 1705 vs (?CO of NHCO), 1620 vs mult (CO ring/C=N), 1390 ms, 1370 s (. C*Me*$_2$), 1265 vs (C—O of COO*Me*), 750 s, 695 w (*Ph*), 1080 s, 985 m cm^{-1}.

The *4-(4'-phenylthiosemicarbazono)-compound* (**22**, $Y = S$) formed deep-yellow prisms (40%), m.p. 201–202° (from acetone—light petroleum) (Found: C 67.1, H 7.5, N 8.9. $C_{27}H_{35}N_3O_3S$ requires C 67.4, H 7.3, N 8.7%). ν_{max} 3295 vs, 1520 vs (NH), 2955 vs–2865 s, 1470–1430 ms mult (CH_3, CH_2), 1730 vs (CO of COO*Me*), 1620–1610 ms (CO ring/C=N), 1390, 1370 ms (. C*Me*$_2$), 1240 s (C—O of COO*Me*), 745 m, 700 m (*Ph*), 1150 vs br cm^{-1}.

1-Methoxycarbonyl-4-ω-phenylhydrazonodiisophor-2(7)-en-3-one (**23**)

A solution of **16** (0.69 g, 0.002 mol) and phenylhydrazine (0.27 g, 0.0025 mol) in ethanol (10 ml) containing concentrated hydrochloric acid (0.3 ml) was boiled under reflux for 10 min. The deep-orange liquid was evaporated to half volume and stirred into ice water. The solidified precipitate gave successive crops of crystals (from ethanol, ca. 15 ml). The initial fraction (0.23 g, 28%) was **23**, m.p. 166–168° (from light petroleum) (Found: C 73.3, H 8.1, N 6.6. $C_{26}H_{34}N_2O_3$ requires C 73.9, H 8.1, N 6.6%). ν_{max} 2950 vs–2860 ms, 1465, 1435 m (CH_3, CH_2), 1745 vs (CO of COO*Me*), 1640 mw, 1600 s (CO ring/C=N), 1585 s, 1530 vs (?NH), 1395 m, 1370 m (. C*Me*$_2$), 1235 vs (C—O of COO*Me*), 770, 760 mw d, 705 m (*Ph*) cm^{-1}. *m/e* 422 vs max (M^+), 391 ms (*M*-31, *Me*O), 363 m (*M*-59, COO*Me*), 292 m (*M*-71-59), 271 s (*M*-59-92, *Ph*NH), 257 s (*M*-59-106, ? = NNH*Ph*), 201 s (*M*-70-59-92), 186 ms (*M*-71-59-106), 407 m, 348 ms, 347 vs; (unusually intense molecular ion). Subsequent fractions (total up to 0.26 g, 40%) consisted of 1-methoxycarbonyldiisophor-2(7)-en-3-one (**7**), m.p. 115–118° (from light petroleum), identified by i.r. [3, 8].

The 4-ω-phenylhydrazono-compound (**23**) was not directly accessible by hydrazinolysis of **9**, using phenylhydrazine. The reactant **9** was recovered (ca. 80%) after being boiled with phenylhydrazine (4 mol) for 1 h in the absence or presence of concentrated hydrochloric acid (0.25 ml per 15 ml ethanol).

4-(2',4'-Dinitrophenylhydrazono)-1-methoxycarbonyldiisophor-2(7)-en-3-one (**25**)

A hot solution of **16** (0.52 g, 0.0015 mol) in ethanol (6 ml) was treated with one of 2,4-dinitrophenylhydrazine (0.40 g, 0.002 mol) in ethanol (8 ml)—concentrated hydrochloric acid (1 ml) and boiled for ca. 1 min. The product, which separated at

once (m.p. 242–244°, 0.62 g, 80%) gave yellow microplatelets of **25**, m.p. 240–242° (from ethoxyethanol—ethanol), identical with authentic material [3]. (Found: C 60.9, H 6.4, N 11.0. Calc for $C_{26}H_{32}N_4O_7$: C 60.9, H 6.25, N 10.9%).

4-Benzenesulphonylhydrazono-1-methoxycarbonyldiisophor-2(7)-en-3-one (**26**)

A solution of **16** (0.69 g, 0.002 mol) and benzenesulphonylhydrazide (0.43 g, 0.0025 mol) in ethanol (25 ml) containing concentrated hydrochloric acid (0.25 ml) was boiled for 10 min, then stirred into ice-water, and the solidified resin crystallised from light petroleum. The first fraction (0.24 g, 25%) was **26**, m.p. 137–139° (from ethanol—light petroleum), identified by ir [3]. Lit. m.p. [3] 143–144°. Subsequent fractions (0.23 g, 36%) gave prisms of **7**, m.p. 115–117° (from light petroleum), identified by ir [8]. On more prolonged boiling (30 min), a more resinous crude product was obtained, from which lower yields (ca. 20% each) of the foregoing two products (**26**, **7**) were isolable.

Additional Mass Spectra

The mass spectra of the following relevant compounds are re-determined and interpreted in accordance with the fragmentation pattern of Scheme 2.

1-Carboxydiisophor-2(7)-en-3-one (**6**) [3]. *m*/e 304 ms (M^+), 287 vs (*M*-17, OH), 286 vs (*M*-18, H_2O), 259 vs (*M*-45, COOH), 216 ms (*M*-71-17), 201 vs (**L**), 189 vs (**F**). 271 vs, 258 vs max, 215 vs, 203 vs, 202 vs.

1-Methoxycarbonyldiisophor-2(7)-en-3-one (**7**) [3]. *m*/e 318 m (M^+), 287 mw (*M*-31, O*Me*), 286 s (*M*-32, *Me*OH), 259 m (*M*-59, COO*Me*), 216 w (*M*-71-31), 201 s (**L**), 189 w (**F**). 258 s, 243 ms.

8-Bromo-1-carboxydiisophor-2(7)-en-3-one (**10**) [5]. *m*/e 384, 382 vw (M^+), 303 ms (*M*-Br), 286 vs (*M*-Br-17, OH), 285 m (*M*-Br-18, H_2O), 258 vs (*M*-Br-45, COOH), 215 s (*M*-Br-71-17), 201 vs max (**L**), 188 ms (**H**), 187 vs (**G**), 287 vs, 243 vs, 189 vs.

8-Bromo-1-methoxycarbonyldiisophor-2(7)-en-3-one (**17**) [5]. *m*/e 398, 396 w (M^+), 317 s (*M*-Br), 286 s (*M*-Br-31, O*Me*), 258 vs (*M*-Br-59, COO*Me*), 201 vs max (**L**), 188 s (**H**), 187 vs (**G**), 318 s, 287 s, 259 vs, 189 s.

4-Bromo-1-carboxydiisophor-2(7)-en-3-one (**11**) [3]. *m*/e 384, 382 mw (M^+), 367, 365 m (*M*-17, OH), 366, 364 s (*M*-18, H_2O), 339, 337 w (*M*-45, COOH), 303 w (*M*-Br), 286 s (*M*-Br-17), 285 vs (*M*-Br-18), 258 vs (*M*-Br-45), 215 m (*M*-Br-71-17), 201 m (**L**), 187 m (**E**-1). 323, 321 m, 259 s, 257 vs max, 202 s, 189 m.

4-Bromo-1-methoxycarbonyldiisophor-2(7)-en-3-one (**18**) [3]. *m*/e 398, 396 m (M^+), 366, 364 ms (*M*-32, *Me*OH), 339, 337 w (*M*-59, COO*Me*), 317 w (*M*-Br), 286 vs (*M*-Br-31), 258 s (*M*-Br-59), 215 m (*M*-Br-71-31), 201 vs (**L**), 187 m (**E**-1). 287 s, 257 vs max.

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