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DIISOPHORONE AND RELATED COMPOUNDS—II[1]

1-ALKOXY- AND 1-CARBOXY-DIISOPHORANE DERIVATIVES

C. RICHARD DUFFNER and FREDERICK KURZER*

Royal Free Hospital School of Medicine (University of London), 8 Hunter Street, London WC1N 1BP, England

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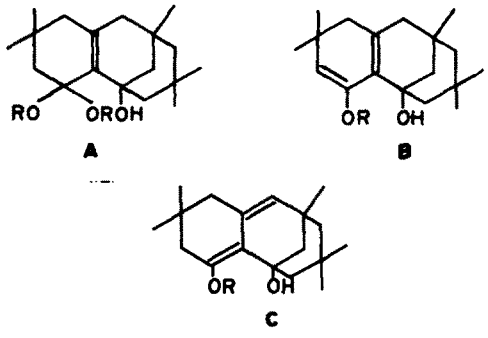
Abstract—The acid catalysed interaction in dioxan of trialkyl orthoformates with diisophor-2(7)-en-1-ol-3-one, diisophor-2(7)-en-1-ol, and their bisnor-homologues, provides the corresponding 1-alkoxy-compounds. Their structure is established by the identity of 1-methoxydiisophor-2(7)-en-3-one obtained by this method, and by the action of sodium methoxide on 1-chlorodiisophor-2(17)-en-3-one. The latter is regenerated from 1-methoxy(or ethoxy) diisophor-2(7)-en-3-one by the action of stannic chloride-acetyl chloride. Catalytic hydrogenation reduces the 3-keto-function in 1-alkoxydiisophor-2(7)-en-3-ones to a methylene unit; simultaneous removal of the 1-alkoxy-group in the case of the 1-isopropoxy-homologue yields the penultimate parent hydrocarbon of this series, diisophor-2(7)-ene.

The combined action of silver sulphate and formic acid in concentrated sulphuric acid on 1-chlorodiisophor-2(7)-en-3-one (and its bisnor-homologue) produces the corresponding 1-carboxylic acids. These are also obtainable by the hydrolysis of the 1-cyano-compound, and are esterifiable by the standard methods.

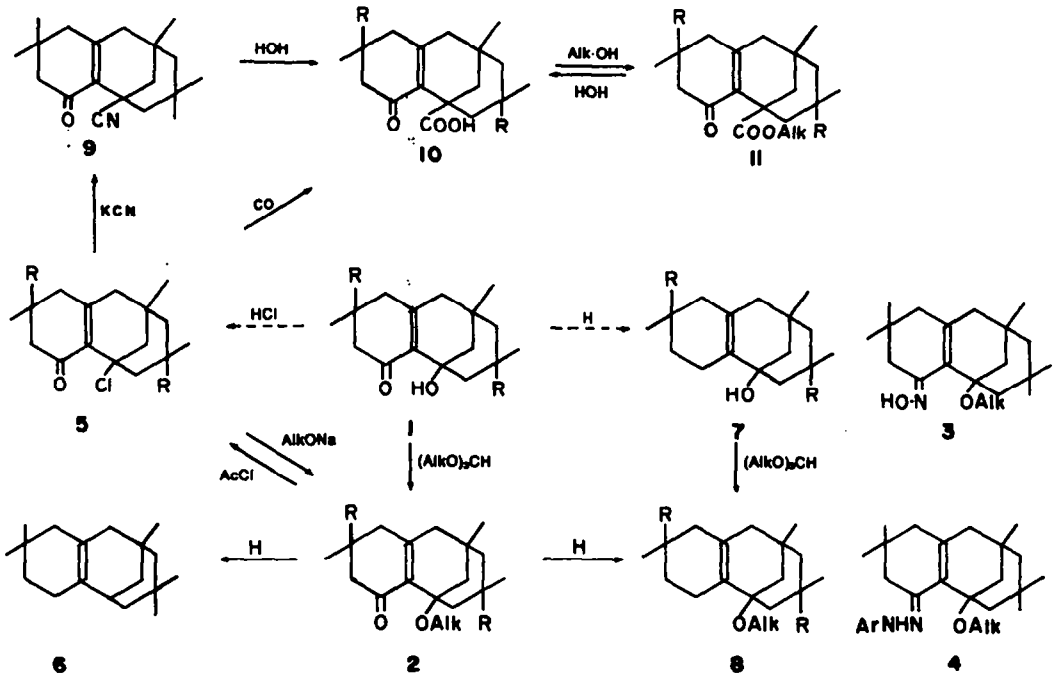
The recognition of diisophorones (1) as unsaturated ketols[2,3] was one of the earliest contributions to the information that led eventually to the assignment of their accepted structure.[1] Conversely, the successful formulation of this molecule, and a precise knowledge of the relation of the substituents to each other, has stimulated further work on the effect of modifying or replacing these functions. This paper describes substitution reactions at the C(1)-tertiary bridgehead in the diisophorane structure, resulting in the formation of 1-alkoxy- and 1-carboxy-diisophorane derivatives.[4]

While searching for suitable methods of blocking the keto-function in diisophor-3-ones with protecting groups, we examined the possible use of triethyl orthoformate for this purpose. The reaction, which normally converts[5] aldehydes and ketones into the corresponding acetals and ketals, took an unexpected course, providing a new route to 1-alkoxydiisophoranes (2, 8).

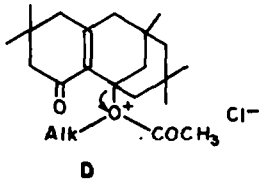
Thus, the acid-catalysed interaction of diisophor-2(7)-en-ol-3-one or its lower homologue (1, R=Me, H) and an excess of trialkyl orthoformate (3–4 mole) in boiling dioxan prodeeded with striking fluorescence, and produced the corresponding 1-alkoxy-compounds (2) in 50–65% yield. Neither triethyl ortho-acetate $[(EtO)_3C{\cdot}OH]$ nor tetraethyl orthocarbonate $[(EtO)_4C]$ was capable of effecting the same reaction. The formulation of the products, suggested by their composition, spectral properties, and chemical behaviour, was confirmed by the identity of the 1-OMe compound (2, R=Alk=Me) with authentic material, obtained by the action of sodium methoxide on 1-chlorodiisophor-2(7)-en-3-one[3] (5, R=Me). The orthoformate alkylation was also applicable to 1-hydroxydiisophor-2(7)-enes (7→8), showing that the adjoining 3-keto-group (in 2) is not directly concerned in the reaction. Although occurring more slowly, it gave even better yields, and proved to be the method of choice for producing 1-alkoxydiisophor-2(7)-enes (8a–d). 1-Acetoxy- and 1-bromo-diisophor-2(7)-en-3-one underwent neither alkylation nor ketalisation, being largely recovered after treatment with triethyl orthoformate under the standard conditions; it thus appears that the usual[5,6] formation of ketals (A) or enol-ethers (B, C) arising therefrom by loss of alcohol, is altogether disfavoured in the present instance, possibly by the operation of steric factors.



The IR spectra of the 1-alkoxydiisophor-2(7)-en-3-ones (2) display the usual characteristics of their alkane moieties.[1] The OH absorption of diisophor-2(7)-en-1-ol-3-ones (1, R=Me, H) has disappeared, as have the effects of H-bonding. The peaks due to the CO-group and the conjugated olefinic bond, barely resolved in the spectrum of diisophorone (1, R=Me; 1640–1625 cm^{-1}), and appearing as a massive doublet in that of its 5, 11-bisnor-homologue (1, R=H; 1645, 1625 cm^{-1}), are here found as distinct absorptions at *ca.* 1665 and 1625 cm^{-1}, the former having been displaced, in the absence of H-bonding, towards higher wave numbers. The spectra of the 1-alkoxydiisophor-2(7)-enes (8) resemble closely those of the corresponding 2(7)-en-3-ones (2), except for the expected disappearance of the intense absorption bands of the β-enone system. The UV spectra of 2 display maxima at 243–245 nm (log ϵ, *ca.* 4), absent in those of 8, and are in accord with the β-enone structure of the former products (2). The NMR spectrum of 2 (R=Alk=Me) shows a sharp singlet at 3.08 δ (3H), attributed to the 1-OMe-group; the methylene and methyl regions resemble those of 1 (R=Me).[7]



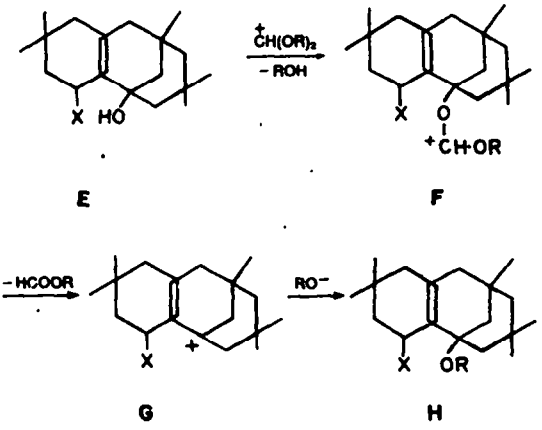
The 1-alkoxydiisophor-2(7)-en-3-ones (2) gave ketonic derivatives, including oximes (3) and 2,4-dinitrophenylhydrazones (4) by the standard methods (Tables 2 and 3). They were convertible into 1-chlorodiisophor-2(7)-en-3-one (5, R=Me) in high yield (80%) by the action of acetyl chloride in the presence of stannic chloride. The reaction effects the same replacement at the bridgehead of bicyclo[2.2.2] octanes;[8] since bromine or iodine are introduced by the action of the appropriate acetyl halides,[8] the latter are the effective reagents, and are likely to participate in the substitution by a mechanism[9] involving the formation and scission of an oxonium ion of type D; recombination of the resulting C-1 carbonium ion and halide anion would provide the observed product (5).



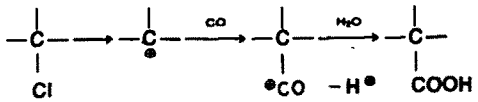
D

Catalytic hydrogenation of 1-alkoxydiisophor-2(7)-en-3-ones (2) reduced, as in diisophorone,[3,10] the 3-keto- to a methylene function, providing an alternative route to 1-alkoxydiisophor-2(7)-enes (8). The identity of compounds obtained by both methods (7, 2→8; R=Me, Alk=Me, Et) furnishes additional proof for the structural assignments. 1-Isopropoxydiisophor-2(7)-en-3-one (2, R=Me, Alk=isoPr) behaved anomalously in that its 1-alkoxy-group was simultaneously removed during the reduction. The resulting liquid diisophor-2(7)-ene (6) may be regarded as the penultimate parent hydrocarbon of the present class of compounds. Its IR spectrum, displaying solely the absorption characteristics of the unsubstituted diisophorane ring-system, served to confirm the spectral assignments[1] to its alkane moieties.

Little information appears to be available concerning the action of trialkyl orthoformates as alkylating agents. A precedent relevant to the present alkylation is the conversion of 3β-hydroxy- into 3β-alkoxy-Δ⁵-sterols by the use of trialkyl orthoformates in conjunction with perchloric acid.[11] The alkylation of the tertiary OH-group (in 1, 7) is likely to occur by a replacement process in which the substituents are exchanged in their entirety: trialkyl orthoformates are known[12] to form stable tertiary carboxonium salts (e.g. $[HC(OEt)_2]^+BF_4^-$) and should therefore be capable of undergoing an acid-catalysed dissociation of the type $H(COR)_3 \rightleftarrows HC(OR)_2^+ + OR^-$, providing the dialkylcarbonium cation as the effective reagent. Its function in a sequence of stages such as E→F→G→H would account for the production of the observed products, and for the failure of 1-bromo- and 1-acetoxy-diisophor-2(7)-en-3-ones to afford the 1-alkoxy-compounds. A similar mechanism has been proposed[11] for the alkylation of 3β-hydroxy-Δ⁵-sterols. If more generally applicable, the orthoformate alkylation would provide a desirable route to ethers derived from tertiary and bridgehead alcohols, that are not readily accessible by other methods,[13] and further work is in progress to gain a better understanding of its nature and scope.



In conclusion, we report the synthesis, by two methods, of diisophorone-1-carboxylic acids, which were of interest as potential intermediates in further changes. In the Koch–Haaf reaction[14,15] carboxylation is effected at a tertiary C atom by the action of formic acid in concentrated sulphuric acid, with or without admixture of other solvents. A modification of this synthesis, used for converting bromo- into carboxy-adamantanes,[16,17] proved suitable for preparing the desired compounds (**10**) in the present series. 1-Chlorodiisophor-2(7)-en-3-one or its 5, 11-bisnor-homologue (**5**; R=Me, H), on being treated in concentrated sulphuric acid with an excess of formic acid in the presence of an equivalent of silver sulphate, afforded the corresponding 1-carboxylic acids (**10**, R=Me, H) in excellent yields. The mechanism of the reaction is likely to involve the generation of the carbonium ion (**J**) by the removal, from **5**, of the 1-halogen substituent as silver chloride; the process is completed, as established by the originators[14] of this synthesis, by the addition of carbon monoxide, followed by interaction with water:



(J)

The absence of rearrangement in the diisophorone skeleton under the conditions of this reaction is noteworthy. This was shown by the observation that diisophor-2(7)-en-1-ol-3-one (**1**, R=Me) was unaffected by concentrated sulphuric acid at low temperatures, and by the confirmation of the structure of the 1-carboxylic acid (**10**, R=Me) by reactions proceeding under entirely different conditions: thus, the action of potassium cyanide on 1-chlorodiisophor-2(7)-en-3-one (**5**, R=Me) in dimethylformamide gave excellent yields of the 1-cyano-compound (**9**, R=Me); its hydrolysis by alkali produced the 1-carboxylic acid (**10**), identical with material obtained in the Koch-Haaf reaction.

The acids (**10**) were esterifiable by the standard method[18] to their methyl and ethyl esters (**11**, R=Me, H; Alk=Me, Et), and were recoverable therefrom by hydrolysis. The high m.ps of the acids (**10**), contrasting with the fusion at low temperatures of their esters (**11**), are attributable to the usual pairing of carboxylic acid molecules by hydrogen bonding. The acids were unaffected by pyrolysis at 200–250°; neither they nor the esters gave 2,4-dinitrophenylhydrazones. Their spectral properties are in accord with their assigned structure. Thus, the high intensity absorption maximum (λ_{max}, 247 nm) in the UV spectrum of **10** (R=Me) indicates the retention of the β-enone system. The IR spectra of both acids (**10**) and esters (**11**) contained the expected absorption characteristics, including three distinct prominent peaks due to the carboxy-carbonyl- and ring-carbonyl groups, and the 2(7)-double bond (Experimental). The esters (**11**) gave rise to an unusually large number of sharp peaks in the 1200–700 cm^{-1} range; they are recorded in full for reference in one example (**11**, R=Alk=Me).

EXPERIMENTAL

General information is given in the foregoing paper[1] concerning standard procedures, apparatus, reagents, solvents and abbreviations. Catalytic hydrogenations were performed at room temp. and atmospheric pressure.

1-*Alkoxydiisophorane derivatives*

1-Alkoxydiisophor-2(7)-en-3-ones **2**. The following general procedure was employed for preparing **2a–2e** (Table 1).

Diisophor-2(7)-en-1-ol-3-one (**1**, R=Me; 2.76 g, 0.01 mole), dissolved in dioxan (20 ml), was treated with trialkyl orthoformate (0.03 mole), followed by a soln of conc. H_2SO_4 (3 drops) in dioxan (2 ml), and boiled under reflux for 1 hr. The pale to deep greenish-yellow fluorescing liquid was evaporated in a vacuum, and the residual fluorescent oil (which solidified on storage at room temp. in most cases) dissolved in light petroleum (10–20 ml). The product separated slowly as large prisms (usually requiring prolonged storage), and was recrystallised from the same solvent (for **2a**, **2b**: *ca.* 10 ml per g, recovery 70–80%). The final light petroleum mother liquors from the crude material generally gave only viscid greenish-yellow intractable oils.

Oximes (**3**) *and 2,4-Dinitrophenylhydrazones* (**4**) of the foregoing 1-alkoxydiisophor-2(7)-en-3-ones (**2a–e**) were obtained by the procedure given in Part I[1] and are listed in Tables 2 and 3.

The 2,4-dinitrophenylhydrazone **4a** had the following IR spectrum: 3330 m (NH); 3100 w, 852 ms, 740 ms (Ar); 2950–2870 s, 1440–1425 s mult (CH_3, CH_2); 1620 vs (C=N); 1380 m sh, 1365 ms (·CMe_2): 1110 s, 1085 s (C–O–C); 1595 vs, 1525 s, 1510 s, 1335 vs br, 1315 vs, 1265 s, 1220 ms, 1135 s, 925 ms, 835 mw cm^{-1}.

1-Acetoxydiisophor-2(7)-en-3-one[3,19] was substantially recovered after treatment with triethyl orthoformate under the above standard conditions (after 1 or 6 hr boiling), as was 1-bromodiisophor-2(7)-en-3-one[19] (56%). Compound **1** (R=H), though apparently undergoing the reaction in low yield, gave a liquid product that has so far not been isolated in a satisfactory pure state.

Treatment of **1** (R=Me) in boiling dioxan with triethyl orthoacetate (3.75 mole) under the foregoing conditions was not attended by the fluorescent yellow-green luminous colour typical of the orthoformate reaction. Starting material was substantially recovered after 2 hr boiling, and after subsequent addn of catalytic quantities of H_2O and 3 hr further boiling. When tetraethyl orthocarbonate[20] (4 mole) was used under the same conditions, the bulk of **1** (R=Me) was again recovered.

1-Methoxydiisophor-2(7)-en-3-one **2a**. A soln of **5** (2.95 g, 0.01 mole; R=Me) in anhyd MeOH (25 ml) was treated with Na (0.275 g, 0.012 g. atom) in MeOH (12 ml) and the yellow liquid set aside at room temp. for 24 hr. It was then stirred into 3*N* HCl (75 ml) and ether (50 ml), and extracted with the same solvent. Evaporation of the washed dried (Na_2SO_4) extracts under reduced pressure gave a pale-yellow oil, which was dissolved in light petroleum, filtered through alumina (12 × 2 cm), and the column eluted with the same solvent. Removal of the solvent left a nearly colourless resin solidifying at room temp. which gave prisms (1.89 g, 65%) of **2a**, identical (m.m.p., IR spectrum, tlc) with material specified in Table 1.

1-Chlorodiisophor-2(7)-en-3-one **5** (R=Me). A stirred mixture of **2a** (0.58 g, 0.002 mole) and acetyl chloride (0.32 g, 0.004 mole) was treated at 0° with stannic chloride (4 drops). Stirring at 0° was continued for 30 min and at 25° for 3 hr, a white ppt separating after *ca.* 1 hr and increasing with time. The mixture was diluted at 0° with H_2O (5 ml); the ppt gave, on crystallisation from EtOH, plates (0.47 g, 80%) of **5** (R=Me), m.p. and m.m.p. 128–130°. Lit.[3] m.p. 135–136° (Also identified by IR spectrum[19] and tlc).

The use of the 1-OEt homologue **2b** (0.002 mole) in this procedure (but using more acetyl chloride; 1.2 g, 0.015 mole) gave **5** (R=Me) (78%), identified as above.

1-Methoxydiisophor-2(7)-ene **8a**. (a) Compound **2a** (1.45 g, 0.005 mole) in glacial AcOH (25 ml) was hydrogenated over Adam's catalyst[21] (0.2 g). The shaken mixture absorbed H_2 fairly rapidly (340–380 cc in 2 hr). The filtered liquid was diluted with H_2O, neutralised with 40% KOH (ice), and exhaustively extracted with ether. Evaporation of the washed dried (Na_2SO_4) extracts gave a mobile liquid (1.25 g, containing according to tlc, up to 10% by-products). Vacuum distillation gave **8a** (70%) (Table 1).

Applied to **2b**, the foregoing procedure afforded **8b** in 75% yield.

(b) A soln of **7**[10] (R=Me; 1.31 g, 0.005 mole) in dioxan (10 ml)

Table 1. 1-*Alkoxydiisophor-2(7)-en-3-ones* (2) and 1-*alkoxydiisophor-2(7)-enes* (3)

Compd.	R	Alk	mp.[a] or bp.[c] Yield	Molecular Formula	Found %	Reqd. %	UV:λ_{max} nm(log ε)	IR : ν cm^{-1}
2a	Me	Me	87-88 65%	$C_{19}H_{30}O_2$	C,78.4 H,10.45	78.6 10.3	245 (3.91)	2950vs-2850s, 1465m, 1415ms (CH_3,CH_2); 1665vs (CO); 1625s (C=C); 1390ms, 1375s (·CMe_2); 1105ms,1085vs (C·O·C); 1325ms, 1285ms, 1275ms, 980mw, 965mw, 935m, 675w.
2b	Me	Et	100-101 55%	$C_{20}H_{32}O_2$	C,79.7 H,10.4	78.95 10.5	245 (3.93)	2950-2860vs br, 1445ms br, 1410ms (CH_3,CH_2); 1660vs (CO); 1620s (C=C); 1390s, 1375s (·CMe_2); 1115vs, 1075vs (C·O·C); 1340mw, 1325mw, 1285ms, 1265ms, 1190m, 1165m, 1000, 995mwd, 960mw, 700w, 670w.
2c	Me	nPr	85-87 56%	$C_{21}H_{34}O_2$	C,79.0 H,10.65	79.2 10.7	245 (3.92)	2950vs-2840ms, 1470, 1450md, 1415m (CH_3,CH_2); 1660vs (CO); 1625s (C=C); 1390ms, 1375s (·CMe_2); 1115ms, 1080s (C·O·C); 1340, 1330mwd, 1290, 1280m d, 1265m, 1045ms, 1010m, 962mw, 675w
2d	Me	isoPr	97-99 85%[b]	$C_{21}H_{34}O_2$	C,78.8 H,10.4	79.2 10.7	245 (3.91)	2960-2880vs, 1475s (CH_3,CH_2); 1675vs br (CO); 1635s (C=C); 1390, 1375s (·CMe_2); 1135s, 1120vs d, 1055vs (C·O·C); 1330s, 1305m, 1280, 1270s d, 1185m, 1170s, 1010s, 970m, 935m, 650m.

2e ~~~	Me	nBu[c]	57–58 45%	$C_{22}H_{36}O_2$	C,79.0 H,11.1	79.5 10.8	245 (3.92)	2960–2880vs, 1470s (CH_3,CH_2); 1675vs br (CO); 1635s (C=C); 1395ms, 1375s (·CMe_2); 1110m, 1090s (C·O·C); 1280, 1270ms d, 1195, 1185s d, 1140ms, 1050ms, 967w, 655w.
8a ~~~	Me	Me	142–144/ 7mm 80%	$C_{19}H_{32}O$	C,82.8 H,11.9	82.6 11.6		2955–2860vs, 1460s br (CH_3,CH_2); 1390ms, 1365s (·CMe_2); 1095s, 1075vs (C·O·C); 1340ms, 1305m, 1275mw, 1245mw, 1200mw, 1175m, 975m, 930mw.
8b ~~~	Me	Et	64–65 80%	$C_{20}H_{34}O$	C,82.55 H,11.7	82.8 11.7	206 (3.73)	2960–2750vs mult, 1460s (CH_3,CH_2); 1395s, 1365s (·CMe_2); 1100s, 1075vs (C·O·C); 1340m, 1305m, 1250m, 1235m, 1200m, 1170–1160m mult, 1115s; 1025, 1005, 995, 985m quartet, 940w.
8c ~~~	H	Me	76–78/ 3mm 80%	$C_{17}H_{28}O$	C,82.1 H,11.6	82.3 11.3		2960–2860vs, 1460s br, 1380m (CH_3,CH_2); 1080vs br (C·O·C); 1295m, 960mw, 920w.
8d ~~~	H	Et	121–123/ 2.5mm 85%	$C_{18}H_{30}O$	C,82.2 H,11.6	82.4 11.45		2970–2850vs br, 1460s br, 1380ms br (CH_3,CH_2); 1110s, 1095s, 1075s (C·O·C); 1295ms, 1015m, 990mw, 945w.

[a] From light petroleum, b.p.40–60° [b] Prepared by solvolysis of the 1-chloro-compound
[c] Excess of tri-n-butyl orthoformate was removed in a vacuum (7mm, ca.100°).

NMR Spectra

2a ~~~ : 0.74 δ (3H), 0.92 δ (3H), 1.01 δ (6H), 1.06 δ (3H), 3.08 δ (sharp singlet, 3H). No signals below 3.10δ.

2b ~~~ : 0.74 δ (3H); 0.92 δ (3H), 1.01 δ (6H), 1.06 δ (3H), a ca.18 line irregular multiplet, centred at 3.2 δ (2H). No signals below 3.7δ.

2d ~~~ : 0.72 δ (3H); 0.90 δ (3H), 1.00 δ (6H), 1.07 δ (3H), broadened doublet at 0.96 δ (3H) and 1.17 δ (3H) having J = 12.9 cps. Quintet centred at 3.63 δ (each line broadened or further split) having approximate line separations of 6 cps (1H). No other signals below 2.5δ.

Table 2. *Oximes (3) of 1-alkoxydiisophor-2(7)-en-3-ones*

Compd.	Alk	mp.[a] Yield	Molecular Formula	Found %	Reqd. %	IR : ν cm^{-1} [b]
3a	Me	199-200° 80%	$C_{19}H_{31}NO_2$	C,74.7 H,10.0 N,4.65	74.75 10.2 4.6	3300vs (OH); 2960vs-2860s, 1465, 1455ms, 1440ms, 1430ms (CH_3,CH_2); 1630ms (C=N); 1386m, 1370s (·CMe_2); 1105ms 1075s (C·O·C); 1325m, 1280m, 1265m, 1035ms, 975, 965ms d, 925ms, 905ms, 890ms, 780mw, 720w, 692w.
3b	Et	223-226° 78%	$C_{20}H_{33}NO_2$	C,75.7 H,10.6 N, 4.4	75.2 10.35 4.4	3330vs (OH); 2950-2900vs br, 1467s br (CH_3,CH_2); 1630m (C=N); 1390ms, 1370vs (·CMe_2); 1105s, 1075vs (C·O·C)
3c	n-Pr	192-195° 67%	$C_{21}H_{35}NO_2$	C,75.8 H,10.25 N, 4.3	75.7 10.5 4.2	3370-3340vs (OH); 2960-2880vs, 1470-1460s (CH_3, CH_2); 1640m (C=N); 1390m sh, 1370s (·CMe_2); 1105s, 1080s (C·O·C)
3d	iso-Pr	198-199° 90%	$C_{21}H_{35}NO_2$	C,75.0 H,10.4 N, 4.6	75.7 10.5 4.2	3320vs br (OH); 2960vs-2860s, 1475-1465ms (CH_3, CH_2); 1630m (C=N); 1390m sh, 1375s (·CMe_2); 1045vs (C·O·C).
3e	n-Bu	188-189° 56%	$C_{22}H_{37}NO_2$	C,76.1 H,10.8 N, 4.0	76.1 10.7 4.0	3370-3320vs br (OH); 2950-2860vs br, 1465s (CH_3, CH_2); 1640mw (C=N); 1395m sh, 1370vs (·CMe_2); 1105s, 1070vs (C·O·C)

[a] From EtOH (e.g. 10ml/g for 3a , 25ml/g for 3b

[b] The IR spectrum of 3a is given in full; only the assigned peaks are given for 3b - 3e

Table 3. 2,4-*Dinitrophenylhydrazones* (4) *of* 1-*alkoxydiisophor*-2(7)-*en*-3-*ones*

Compd.	Alk	m.p.[a] Yield	Molecular Formula	Found %	Reqd. %	IR : [c]
4a	Me	188-190° 85%	$C_{25}H_{34}N_4O_5$	C,63.4 H, 7.2 N,12.2	63.8 7.2 11.9	See Experimental
4b	Et	173-175° 90%	$C_{26}H_{36}N_4O_5$	C,64.2 H, 7.1 N,11.7	64.5 7.4 11.6	3300ms (NH); 3080m, 840, 835m d, 720ms (Ar); 1620, 1600vs d (C=N); 1130, 1115vs d, 1085, 1075vs d (C·O·C).
4c	nPr	146-147° 90%	$C_{27}H_{38}N_4O_5$	C,64.6 H, 7.5 N,11.6	65.1 7.6 11.2	3305ms (NH); 3105m, 840, 835ms, 742s (Ar); 1620, 1595vs br d (C=N); 1115vs, 1080vs br (C·O·C).
4d	isoPr	190-192 [b] 90%	$C_{27}H_{38}N_4O_5$	C,64.8 H, 7.8 N,11.8	65.1 7.6 11.2	3310ms (NH); 3100m, 840, 835s d, 740s (Ar), 1625-1595 vs mult (C=N); 1145-1115vs mult, 1080vs (C·O·C)
4e	nBu	186-187 [b] 60%	$C_{28}H_{40}N_4O_5$	C,66.1 H, 7.9 N,10.65	65.6 7.8 10.9	3340ms (NH); 3110m, 850, 835ms d, 742s (Ar); 1615, 1595vs d (C=N); 1110vs, 1080vs (C·O·C)

[a] From EtOH (e.g. 100ml/g for 4a) [b] From ethyl acetate (e.g. 20ml/g for 4d)

[c] The IR spectrum of 4a is given in full in the Experimental. For 4b-e, only the assigned peaks are given (but alkane absorptions are excluded).

was treated successively with trimethyl orthoformate (2.12 g, 0.02 mole) and conc. H_2SO_4 (2 drops, in 2 ml dioxan). The colourless liquid was boiled under reflux for 3 hr, diluted with benzene (50 ml), washed with H_2O, and the solvents removed under reduced pressure. The residual oil, redissolved in benzene, was filtered through alumina (1.5 × 17 cm), and completely eluted with light petroleum. Removal of the solvent, and vacuum distillation gave **8a** as a colourless liquid (1.10 g, 80%) (Table 1).

Homologues **8b–d** were obtained by the same procedure and are specified in Table 1.

1-Isopropoxydiisophor-2(7)-en-3-one **2d**

Catalytic hydrogenation. A soln of **2d** (1.60 g, 0.005 mole) in glacial AcOH (30 ml) was hydrogenated over Adam's catalyst[21] (0.2 g). The uptake of H_2 (350–380 cc, 0.015 mole, allowing for the uptake of the catalyst) slowed up and ceased after 2–3 hr. Then Pt was filtered off, the filtrate stirred into ice (100 g), neutralised with solid Na_2CO_3, and extracted with ether. The residue obtained on removal of the solvent was redissolved in light petroleum (b.p. 60–80°), filtered through alumina (2 × 10 cm), and completely eluted. Removal of the solvent left an oil (1.11 g, 90%, uniform by tlc) which gave, on vacuum distillation, *diisophor-2(7)-ene* (**6**) as a colourless mobile liquid, b.p. 106–108°/2.5 mm. (Found: C, 87.6; H, 12.3. $C_{18}H_{30}$ requires: C, 87.8; H, 12.2%) IR: 2960–2850 vs, 1470–1458 vs br (CH_3, CH_2); 1390 s, 1365 vs (·CMe_2); 785 m, 760 mw br cm^{-1}.

1-Carboxydiisophorane derivatives

1-Carboxydiisophor-2(7)-en-3-one **10** (R=Me)

A stirred soln of "Analar" Ag_2SO_4 (3.12 g, 0.01 mole) in conc H_2SO_4 (200 ml) at room temp. was treated, over a 3 hr period portionwise with finely powdered **5** (R=Me;[3] 2.95 g, 0.01 mole) while HCOOH (100%, 15 ml) was added dropwise (effervescence). As each portion of solid was added, it dissolved rapidly, while a finely divided white ppt of AgCl appeared. Stirring was continued until effervescence ceased (*ca.* 1 hr), the AgCl removed by filtration through a sintered glass funnel, and rinsed with conc H_2SO_4 (2 × 20 ml). The pale-pink filtrate was slowly stirred into ice-water (800 ml); the ppt was collected at 0° (m.p. 225–227°, 3.05 g, 100%) and rinsed with H_2O. Crystallisation from EtOH (8 ml per g, recovery 70%) gave prisms of **10** (R=Me), m.p. 232–234° (Found: C, 74.4; H, 9.0. $C_{19}H_{28}O_3$ requires: C, 75.0; H, 9.2%). IR: 3090 m, 930 m br (OH of COOH); 2950–2860 vs, 1465 m, 1410 s (CH_3, CH_2); 1700 vs br (CO of COOH); 1665 vs (CO, ring); 1640 s (C=C); 1385 m, 1375 s (·CMe_2); 1275 vs br (COOH); 2650 m, 2530 mw, 1190 m, 1155 m, 1085 w, 720 ms cm^{-1}. UV: 247 nm (log ε 4.00). Substantially the same result was obtained when all the reactant (**5**, R=Me) was added to the Ag_2SO_4 soln in the first 10 min, and the HCOOH added gradually afterwards, as above.

The acid **10** (R=Me) failed to give a 2, 4-dinitrophenylhydrazone, the reagent being recovered (90%) after the usual procedure.[1] It was recovered (80%, crystallised from EtOH) after being melted at 260° and kept at 250–200° for 15 min.

Diisophor-2(7)-en-1-ol-3-one (**1**, R=Me; 2.76 g, 0.01 mole) dissolved slowly in stirred conc. H_2SO_4 (30 ml) at 0°, and was recovered nearly quantitatively (mixed m.p., IR[1]) on addition of the golden yellow liquid to ice. However, more or less complete destruction of **1** (R=Me) occurred in higher temp. ranges.

1-Methoxycarbonyldiisophor-2(7)-en-3-one **11** (R=Alk=Me)

A soln of **10** (R=Me; 0.61 g, 0.002 mole) in MeOH (15 ml) was boiled under reflux during 4 hr while anhyd. HCl was passed through. Most of the solvent was removed in a vacuum, the residual liquid diluted with H_2O, neutralised with 3*N* NH_4OH, and the oily product extracted with ether. Evaporation of the washed dried extracts left a resin which solidified on storage, and gave **11** (R=Alk=Me) as prisms, m.p. 116–118° (0.48 g, 75%) (from MeOH–H_2O, 4 and 2 ml). (Found: C, 76.1; H, 9.6. $C_{20}H_{32}O_3$ requires: C, 75.5; H, 9.4%). IR: 2930–2850 vs br; 1470–1440 s mult, 1425 ms (CH_3, CH_2); 1735 vs (CO of COOMe); 1660 vs (CO, ring); 1635 s (C=C); 1390 ms, 1375 s, (·CMe_2); 1235 vs br (C–O ester); 1155 vs, 1125 ms, 1085 m, 1050 s, 990 m, 970–950 w mult, 930 w, 905 w, 890 mw, 870 w, 795 w d, 750 m, 735 mw cm^{-1}.

1-Ethoxycarbonyldiisophor-2(7)-en-3-one **11** (R=Me, Alk=Et)

The use of EtOH gave, by the foregoing procedure, prisms (85%) of **11** (R=Me, Alk=Et), m.p. 71–73° (from EtOH–H_2O). (Found: C, 75.4; H, 9.6. $C_{21}H_{32}O_3$ requires: C, 75.9; H, 9.6%). IR: 2930–2850 vs, 1470 ms, 1415 ms (CH_3, CH_2); 1728 vs (CO of COOEt); 1660 vs (CO, ring); 1640 s (C=C); 1395 ms, 1380 ms br (·CMe_2); 1240–1225 vs br mult (CO, ester); 1300 ms, 1160 vs, 1055 vs, 755 m cm^{-1}. Only the more prominent of the numerous peaks between 1200 and 700 cm^{-1} are given. The ester failed to yield a 2,4-dinitrophenylhydrazone by the standard procedure.[1]

1-Carboxy-5, 11-bisnordiisophor-2(7)-en-3-one **10** (R=H)

This was prepared as described for **10** (R=Me, see above) from 1-chloro-5, 11-bisnordiisophor-2(7)-en-3-one[19] (2.67 g, 0.01 mole). This was introduced in portions (*ca.* 0.2 g) during 3 hr, while HCOOH (100%, 15 ml) was added dropwise over the same period. Each portion of solid dissolved slowly (5–10 min, measurable in the initial stages), while AgCl appeared at the same rate. Stirring was continued for 1 hr; the usual work-up gave a white ppt, which was boiled with EtOH (2 × 15 ml) and a little AgCl filtered off. The filtrate deposited solid (m.p. 200–201°, 2.0–2.2 g, 74–80%), which gave **10** (R=H) as prisms, m.p. 203–205° (from EtOH, 8 ml per g) (Found: C, 73.3; H, 8.3. $C_{17}H_{24}O_3$ requires: C, 73.9; H, 8.7%). IR: 2950–2875 vs, 1470 s, 1450 ms, 1425 s, 1395, 1385 s, d (CH_3, CH_2); 1695 vs (CO of COOH); 1665 vs (CO ring); 1640 s (C=C); 1290 vs–1275 s br (COOH); 940 mw br (OH of COOH); 2640 s, 1180 m, 1155 m, 1040 w d, 970 mw, 755 mw, 730 ms cm^{-1}.

1-Methooxcarbonyl-5, 11-bisnordiisophor-2(7)-en-3-one **11** (R=H, Alk=Me)

This was obtained by the standard esterification prodcedure (see above) and formed lustrous platelets (75–85%), m.p. 81–82° (from EtOH–H_2O) (Found: C, 73.8; H, 8.95. $C_{18}H_{28}O_3$ requires: C, 74.5; H, 9.0%). IR: 2930–2860 vs br, 1470–1458 s mult, 1440 s, 1380 s (CH_3, CH_2); 1738 vs (CO of COOMe); 1665 vs (CO, ring); 1630 s (C=C); 1240 vs br (C–O ester); 1185 s, 1145 s, 1120 s, 1045 s, 990 ms, 910 m, 760 s, 750 ms d cm^{-1}.

1-Ethoxycarbonyl-5, 11-bisnordiisophor-2(7)-en-3-one **11** (R=H, Alk=Et)

This formed lustrous platelets (80%), m.p. 86–87° (from EtOH–H_2O, 5 ml each per g, recovery 80%) (Found: C, 74.9; H, 9.3. $C_{19}H_{28}O_3$ requires: C, 75.0; H, 9.2%). IR: 2950 vs–2850 s, 1470 ms, 1390 ms, 1380 s (CH_3, CH_2); 1735 vs br (CO of COOEt); 1668 vs (CO, ring); 1635 s (C=C); 1235 vs br (CO ester); 1180 s, 1140 vs, 1115 s, 1040 s, 875 mw, 750 ms cm^{-1}.

1-Cyanodiisophor-2(7)-en-3-one **9**

A soln of **5** (R=Me;[3] 5.90 g, 0.02 mole) and finely powdered KCN (1.95 g, 0.03 mole) in dimethylformamide (60 ml) was boiled under reflux for 2 hr and the resulting red liquid stirred into H_2O. The resinous ppt solidified on storage and was collected, after the destruction of the excess of the cyanide by the addition of aq. NaClO. Crystallisation from light petroleum (b.p. 60–80°) gave opaque ivory prisms (3.65–4.1 g, 64–72%) of **9**, m.p. 123–126° (Found: C, 79.4; H, 9.0; N, 4.5. $C_{19}H_{27}NO$ requires: C, 80.0; H, 9.5; N, 4.9%) IR.: 2965 vs, 2910–2880 s br, 1470 s, 1440 m (CH_3, CH_2); 1390 s, 1377 s (·CMe_2); 2245 m (CN); 1660 vs (CO); 1635 s (C=C); 1420 m, 1290 m, 1275 m, 1200 w, 1160 w, 1135 w, 960 w cm^{-1}.

Alkaline hydrolysis. A soln of **9** (0.58 g, 0.002 mole) in EtOH (15 ml)—3*N* NaOH (10 ml) was boiled under reflux for 4 hr, diluted with H_2O (20 ml), and acidified.

The ppt, collected at 0° (0.29 g, 48%) was the 1-carboxy-compound, **10** (R=Me), identified by mixed m.p. 230–232° and IR spectrum (see above). The reaction did not occur under the influence of ethanolic (60%) 2*N* HCl, the reactant being recovered (48%) after 5 hr boiling.

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