Ethyl 2-Methyl-4-oxocyclohex-2-enecarboxylate (Hagemann's Ester) as a Precursor to Alkyl-substituted 3-Methylcyclohexenones

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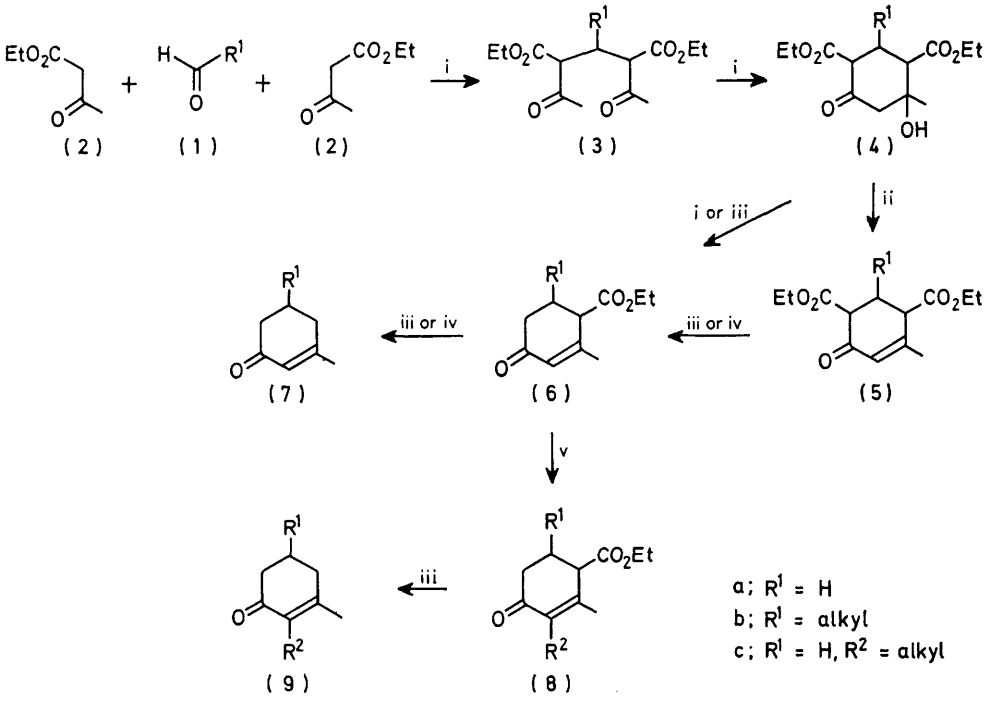
4-Alkyl-3-methylcyclohex-2-enones have been prepared from ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate (Hagemann's ester) *via* the alkylation of its ethylene glycol acetal. Various routes to 6-alkyl-3-methylcyclohex-2-enones from Hagemann's ester have been explored; a particularly convenient route to these unsaturated ketones utilised the isomeric keto-ester, ethyl 4-methyl-2-oxocyclohex-3-enecarboxylate as starting material. The alkylation of ethyl 2-methyl-4-pyrrolidinocyclohexa-1,3-dienecarboxylate, the fully conjugated dienamine derived from Hagemann's ester, yielded 2-alkyl-3-methylcyclohex-2-enones after hydrolysis and de-ethoxycarbonylation. An improved preparation of Hagemann's ester is reported. The preparation of 4-alkyl- and 6-alkyl-3-methylcyclohex-2-enones complements the existing procedures to 2-alkyl- and 5-alkyl-3-methylcyclohex-2-enones.

JASMINE odourants, which according to Boelens possess a characteristic substitution profile round a central carbon atom,[1] include materials as diverse as 3-methyl-2-(*cis*-pent-2-enyl)cyclopent-2-enone (*cis*-jasmone), ethyl 2-acetyloctanoate, and 2-n-pentylcinnamaldehyde.[2]

side chains found in the jasmones themselves (pentyl, hexyl, *cis*-pent-2-enyl).

Ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate (Hagemann's ester) (6a) was the starting material of choice since it has been frequently used for the preparation of 2-alkyl-3-methylcyclohex-2-enones (9c).[4] In



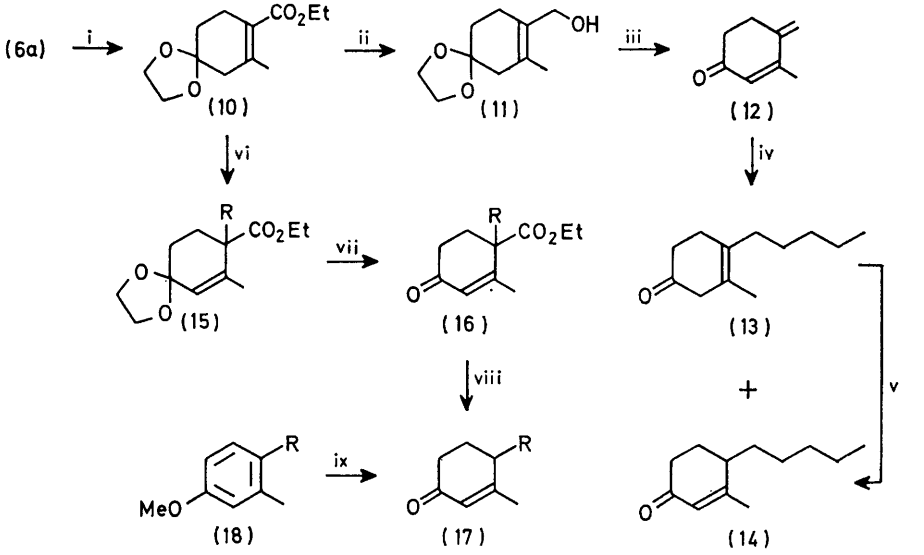
Reagents: i, piperidine; ii, *p*-$MeC_6H_4SO_3H$–benzene; iii, KOH–EtOH; iv, H_2SO_4–H_2O–AcOH; v, EtONa–EtOH, RX

In order to gain more insight into the odour–structure relationships in this area, we decided to prepare a series of 3-methylcyclohex-2-enones alkylated at different positions (2, 4, 5, and 6) round the ring. This also enabled us to test Boelens' hypothesis, as only the 2-substituted materials lie within the postulated requirements for a jasmine odour.[3] The substituents investigated have been limited to three unbranched groups (butyl, pentyl, hexyl), one branched chain primary group (isopentyl), and one allylic group (3-methylbut-2-enyl), all of which bear a close similarity to the alkyl

addition, by substituting an aliphatic aldehyde (1b) for formaldehyde, it is possible to prepare 5-alkyl-3-methylcyclohex-2-enones (7b) by the same sequence of reactions.[5] The formation of 4-alkyl- and 6-alkyl-3-methylcyclohexenones from the vinylogous β-keto-ester (6a) would thus complement existing procedures and greatly increase the synthetic potential of this readily prepared material.[6]

4-*Alkyl*-3-*methylcyclohex*-2-*enones*.—To prepare the compounds of the 4-series, Hagemann's ester (6a) was converted into 3-methyl-4-methylenecyclohex-2-enone

(12). Good yields of acetal (10) could not be achieved by any of the published procedures;[7] a modification of that of Baggiolini *et al.*[7a] did, however, provide satisfactory results. Following reduction of acetal (10), deacetalisation, and dehydration of allylic alcohol (11) were achieved using hydrochloric acid in tetrahydrofuran; the αβγδ-unsaturated ketone (12) was obtained as a pale yellow oil ($\nu_{C=O}$ 1 675 cm^{-1}) which polymerised slowly on standing. With the ready 1,4-addition of organocuprates to αβ-unsaturated carbonyl compounds[8] well established, Marshall *et al.* studied the regioselectivity of lithium dimethylcuprate addition to alicyclic dienones,[9] and demonstrated that 1,6-addition is the preferred mode of reaction. Treatment of dienone (12) with lithium di-n-butylcuprate yielded a mixture

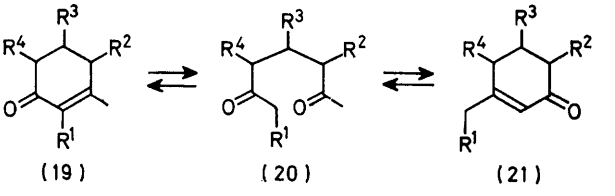


Reagents: i, $HOCH_2CH_2OH$–*p*-$MeC_6H_4SO_3H$–benzene; ii, $LiAl(OCH_2CH_2OMe)_2$–benzene; iii, HCl–THF; iv, Bu^n_2CuLi–CuI–Et_2O–hexane; v, H^+; vi, Pr^i_2NLi–THF,RI; vii, *p*-$MeC_6H_4SO_3H$–H_2O–acetone; viii, KOH–EtOH; ix, Li–NH_3–EtOH,H_3O^+–EtOH–EtOAc

of two ketones in which the βγ-unsaturated isomer (13) predominated. Treatment with acid effected isomerisation[10] to the fully conjugated enone (14), isolated in 49% yield from dienone (12).

A more convenient synthetic route utilises the α-alkylation of an αβ-unsaturated ester.[11] Reaction of acetal (10) with lithium di-isopropylamide at −10° produced the corresponding anion,[12] which, on treatment with the appropriate alkyl iodide, yielded the tertiary acetal-ester (15) in high regiospecificity, *ca.* 75% of a single alkylation product being obtained. Following deacetalisation, saponification and decarboxylation were accomplished only on prolonged refluxing (48 h) in ethanolic potassium hydroxide. This difficulty supports the prior observations of Nasipuri *et al.* who demonstrated the relative ease of saponification of C-3 substituted esters (8c) in comparison with their C-1 analogues (16).[13] The ketonic product obtained was a mixture of the desired 4-alkyl-3-methylcyclohexenone (17) together with the isomeric 6-alkyl-3-methylcyclohexenone (24) in a 6 : 4 ratio. Following separation on a spinning-band distillation column, all five 4-alkyl compounds (17) were successfully isolated in a pure state by this route.

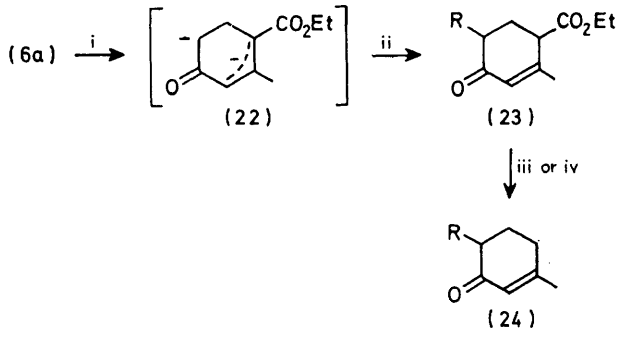
The invariable production of a mixture of 4- and 6-alkyl materials by this route is probably due to a base-catalysed retro-Aldol reaction, followed by cyclisation in the opposite manner [(19) ⟶ (20) ⟶ (21); R^1 = R^3 = R^4 = H, R^2 = alkyl], a reaction whose importance was first noted by Lacey.[14] To confirm the position of the alkyl substituent in one of the ketones (17), a synthetic sequence which utilised aromatic intermediates has been employed.[15] Friedel–Crafts acylation of *m*-cresyl methyl ether using 3-methylbutanoyl chloride–aluminium chloride produced a mixture of 3-methyl-4-(3-methyl-1-oxobutyl)- and 5-methyl-2-(3-methyl-1-oxobutyl)-anisole. Clemmensen reduction of these ketones yielded a mixture of 3-methyl-4-(3-methylbutyl)- and 5-methyl-2-(3-methylbutyl)-anisole, which were separated by fractional distillation on a



spinning-band column. The major component was shown to be the 3,4-disubstituted anisole (18) by the presence in the n.m.r. spectrum of two protons *ortho* to the methoxy-group. Following the well established Birch reduction of 3,4-dialkyl substituted anisoles to 3,4-dialkylcyclohexenones (but not to 4,5-dialkylcyclohexenones),[16] 3-methyl-4-(3-methylbutyl)anisole gave 3-methyl-4-(3-methylbutyl)cyclohex-2-enone (17; R = 3-methylbutyl) in fair yield; the material prepared by

this method was identical with the major product obtained *via* the alkylation of acetal (10).

6-Alkyl-3-methylcyclohex-2-enones.—The alkylation of the dianion (22) [17] from Hagemann's ester was envisaged



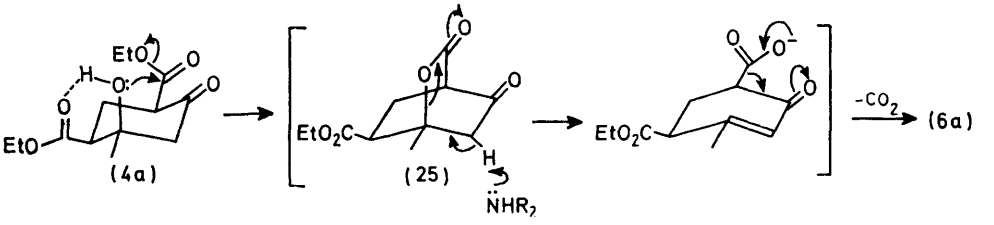
Reagents: i, Pr^i_2NLi–THF; ii, RX; iii, KOH–EtOH; iv, H_2SO_4–H_2O–AcOH.

as a straightforward method of introducing a substituent at C-5 (23), and so generating a 6-alkyl-3-methylcyclohex-2-enone (24) as the final product. Despite the high specificity in the actual alkylation reaction (*ca.* 75% of a single alkylation product), a mixture of substituted cyclohexenones was invariably obtained as the final product, the ratio of alkylation products being dependent on both the method of saponification and decarboxylation and the duration of the reaction. Typical reaction products contained, apart from de-ethoxycarbonylated starting material (29) (<5%), 2-alkyl-3-methylcyclohex-2-enone (9c) (<5%), 6-alkyl-3-methylcyclohex-2-enone (24) (30—50%), and 4-alkyl-3-methylcyclohex-2-enone (17) (15—40%). As previously, the formation of a mixture of ketones (17) and (24) is best explained in terms of the retro-Aldol–recyclisation sequence [(19) ⟶ (20) ⟶ (21); $R^1 = R^2 = R^3 = H$, R^4 = alkyl].[14]

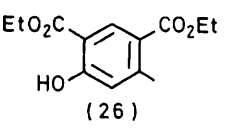
An alternative approach to the compounds of the 6-series utilises the alkylation of compound (5a), readily obtained by treatment of the aldol (4a) with toluene-*p*-sulphonic acid in benzene. This material, a crystalline solid, m.p. 77—80°, is the first isolable product when the condensation of 2 equiv. of acetoacetic ester and 1 equiv. of formaldehyde is carried out in the presence of piperidine at low temperatures. Its structure has been the source of considerable dispute,[18] but the presence of signals in the i.r. and n.m.r. spectra characteristic of a tertiary hydroxy group,[19] identify the product as the aldol (4a) and not as the isomeric 1,5-diketone (3a).

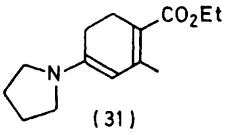
Compound (5a), which combines the elements of a β-keto-ester and a vinylogous β-keto-ester, clearly possesses some potential in alkylation studies. In our preliminary study, alkylation of the sodium enolate of (5a) produced, after acid-catalysed saponification (to minimise rearrangement) and decarboxylation, a 4 : 1 mixture of 2-alkyl-3-methylcyclohex-2-enone (9c) and 6-alkyl-3-methylcyclohex-2-enone (24).

In contrast to the acid-catalysed dehydration of aldol (4a) to enone (5a), base-catalysed dehydration of (4a) produced Hagemann's ester (6a) directly; no evidence for the intermediacy of enone (5a) in the base-catalysed reaction has been found despite the claims of many authors.[5,6] Therefore the reaction may be better discussed in terms of bicyclic intermediates [*e.g.* (25)].[20] The ease and simplicity of the transformation [(4a) ⟶ (6a)] suggested that the piperidine present in the original condensation reaction might be equally capable of this decarboxylative dehydration. This proved to be correct, since on heating the crude reaction mixture containing aldol (4a) in the presence of piperidine, Hagemann's ester (6a) was obtained directly and reproducibly in yields of 59—61%, a considerable improvement on the earlier procedures.[6] The residues from the



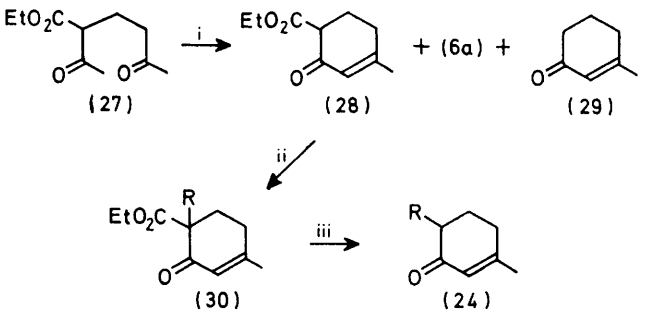
preparation of Hagemann's ester carried out in this way contained a variable quantity of a crystalline phenol, identified as diethyl 4-hydroxy-6-methylbenzene-1,3-dicarboxylate (26) on the basis of its spectroscopic data.





An alternative approach to the target 6-alkyl ketones has been successful using ethyl 4-methyl-2-oxocyclohex-3-enecarboxylate (28), a β-keto-ester isomeric with Hagemann's ester, as starting material. Ethyl 2-acetyl-5-oxohexanoate (27), the product of the Michael condensation between ethyl acetoacetate and methyl vinyl ketone, is reported [21] to cyclise in a two-stage procedure to β-keto-ester (28), the direction of cyclisation thus following the generally accepted rule of utilising the carbonyl function of the original Michael acceptor.[22] This procedure, in our hands, gave a 40% yield of distilled product, containing a mixture of the possible cyclisation products, β-keto-ester (28), Hagemann's ester (6a), and 3-methylcyclohex-2-enone (29) in the

ratio 85 : 10 : 5. Despite considerable endeavour, no cyclisation conditions have been found which produced β-keto-ester (28) uncontaminated with δ-keto-ester (6a); the 1,5-diketone (27) was best cyclised in concentrated sulphuric acid containing a small quantity of water to yield 72% of a distilled product containing enones (28) and (6a) in a ratio of 88 : 12. Product analysis was based on the vinyl proton signal (δ 5.7) in the n.m.r. spectrum, Δδ being increased by the addition of the shift reagent $Eu(fod)_3$.



Reagents: i, H_2O–H_2SO_4; ii, NaOEt–EtOH,RX; iii, H_2SO_4–H_2O–AcOH

A number of other procedures for the preparation of ethyl 4-methyl-2-oxocyclohex-3-enecarboxylate (28) have been briefly investigated. The condensation of 1,3-dichlorobut-2-ene with ethyl acetoacetate gave ethyl 2-(3-chlorobut-2-enyl)-3-oxobutanoate [23] but cyclisation in concentrated sulphuric acid gave β-keto-ester (28) together with appreciable quantities of 3-methylcyclohexenone (29). Furthermore the acid-catalysed Robinson annelation reaction [24] between ethyl acetoacetate and methyl vinyl ketone yielded a mixture of 1,5-diketone (27) and Hagemann's ester (6a).

Alkylation of ethyl 4-methyl-2-oxocyclohex-3-enecarboxylate (28), *via* its sodium enolate, proceeded without difficulty, and the corresponding alkylated esters (30) were readily obtained. It is evident from their n.m.r. spectra, which lack a signal at δ 3.15 (H-1), that alkylation has taken place at that position: the presence of an unchanged vinyl proton signal at δ 5.7 rules out C-3 alkylation. Saponification and decarboxylation, best accomplished using acidic conditions, yielded the desired 6-alkyl-3-methylcyclohexenones (24). The acidic conditions offer two advantages: first, the problem of the presence in the reaction mixture of an isomeric 2-alkyl compound, produced from the Hagemann's ester (6a) invariably present, was thereby surmounted, as an alkylated Hagemann's ester (8c) is not so readily saponified and decarboxylated under acidic conditions.[6b] Secondly, the retro-Aldol–recyclisation reaction proceeds much more slowly under acidic conditions.[14] Thus the 6-alkyl-3-methylcyclohex-2-enones (24) were obtained essentially free from isomeric impurities.

This general pattern was not followed when 3-methylbut-2-enyl chloride was used as the alkylating agent. Although the alkylation step proceeded in above average yield due to the higher activity of the allylic halide, saponification, and decarboxylation under acidic conditions led to a mixture of three products in the ratio 16 : 3 : 1. Based on the spectroscopic data for the purified materials, these compounds have been identified as 2,7-dimethyltetralin,[25] 2,7-dimethylnaphthalene,[26] and a dehydro-3-methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone. Recourse, however, to basic saponification and decarboxylation did yield 3-methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone, which was purified by spinning-band distillation.

The synthesis of the terpene (±)-piperitone (3-methyl-6-isopropylcyclohex-2-enone) [27] by the above method (using isopropyl bromide as the alkylating agent) established beyond doubt that 6-alkyl-3-methylcyclohex-2-enones (24) are indeed being produced. This route, which utilises compound (28) as a common intermediate, is superior to the alternatives used hitherto.[28]

The removal of the ethoxycarbonyl group present in the alkylated β-keto-esters and δ-keto-esters has generally been carried out using classical procedures (KOH–EtOH, H_2SO_4–H_2O–AcOH), preference being given to whichever reagent performed better in small-scale experiments. De-ethoxycarbonylations [(16) ⟶ (17), (30) ⟶ (24)] using certain of the reagents introduced in the last decade (NaCl–H_2O–DMSO, NaCl–H_2O–DMF) [29a] gave poorer yields than the classical procedures. The use of boric anhydride,[29b] however, did give good, if somewhat inconsistent, results in the preparation of Hagemann's ester (6a).

2-*Alkyl*-3-*methylcyclohex*-2-*enones*.—The five 2-alkyl-3-methylcyclohex-2-enones [(6a) ⟶ (8c) ⟶ (9c)] were prepared using published procedures.[30] The production of small quantities (*ca.* 15%) of C-1 alkylated products (16) together with the desired C-3 alkylated material (8c) [13] in no way diminishes the usefulness of the above synthetic sequence, as the different rates of saponification allow easy separation. In this instance, the retro-Aldol–recyclisation reaction is less important: the rearrangement product (21; R^1 = alkyl, R^2 = R^3 = R^4 = H) is a monosubstituted cyclohexenone, and it has been conclusively demonstrated that the thermodynamically more stable product is the dialkyl-substituted starting material.[31]

An alternative route to the 2-alkyl-3-methylcyclohex-2-enones could utilise the solid, fully conjugated dienamine (31).[21b,32] Pandit *et al.*[33] have studied the alkylation of alicyclic dienamines with allylic halides and demonstrated that *N*-alkylation followed by aza-Cope rearrangement and direct *C*-alkylation at the β-position are the two most common modes of reaction. Alkylation of ethyl 2-methyl-4-pyrrolidinocyclohexa-1,3-dienecarboxylate (31) with 3-methylbut-2-enyl chloride gave, after hydrolysis, a moderate yield of enone ester alkylated in the 3-position (8c); regiospecificity is good, <5% of any other alkylated product being obtained. Base-catalysed saponification, followed by decarboxyl-

ation, yielded 3-methyl-2-(3-methylbut-2-enyl)cyclohex-2-enone (9c; R^2 = 3-methylbut-2-enyl).*

5-Alkyl-3-methylcyclohex-2-enones.—In contrast to the three other series of substituted cyclohexenones in which a common intermediate was alkylated to produce a group of congeners, the ketones of the 5-series (7b) were produced by condensing individual aldehydes with two equivalents of acetoacetic ester. When the reaction was carried out at 0°, the intermediate aldols (4b) could be readily isolated;[5] however by raising the reaction temperature to 90°, one of the ethoxycarbonyl groups could be removed with great facility. By analogy with the ready conversion of the unsubstituted aldol (4a) to Hagemann's ester (6a), it would be anticipated that the ester function β to the carbonyl group would be lost.[34] Confirmation that δ-keto-esters (6b) were indeed formed, was obtained from the absence of chelated hydroxy absorption in the i.r. and n.m.r. spectra, and the non-formation of ferric chloride complexes.

With respect to the individual aldehydes required for the condensation reaction, 4-methylpentanal was prepared using modifications to the procedure of Brunner *et al.*[35] Attempts to prepare 4-methylpent-3-enal by the condensation of isobutene with acetaldehyde [36] and by the deconjugation of 4-methylpent-2-enal [37] were not successful.

The spectral data of all the substituted cyclohexenones are in accordance with their structures; their mass spectra will be the subject of a separate publication. The groups of four isomeric compounds could not generally be separated by g.l.c., the 4- and 5-alkyl compounds having identical retention times under a wide range of conditions. The use of a liquid crystal phase (*p*-phenylene bis-4-n-heptyloxybenzoate) in its nematic form did however separate the mixtures into four well resolved peaks.

The odours of these substituted cyclohexenones have been considered in detail elsewhere.[3]

EXPERIMENTAL

I.r. spectra were measured with a Unicam SP 2000 instrument and u.v. spectra with a Unicam SP 8000 instrument. ^{1}H N.m.r. spectra were recorded on a Varian A-60A instrument for solutions in deuteriochloroform (unless otherwise stated), with tetramethylsilane as internal standard. Mass spectra were obtained with an AEI MS 902 instrument at 70 eV. G.l.c. analyses were performed on a Pye 104 instrument [9 ft glass column packed with 3% FFAP on Chromosorb G (100—120 mesh)]. n-Butyllithium was used as a 1.58M solution in hexane. DNP = 2,4-dinitrophenylhydrazone.

Ethyl 2-Methyl-4-oxocyclohex-2-enecarboxylate (Hagemann's Ester) (6a).—To a mixture of ethyl acetoacetate (2) (2 082 g, 16.0 mol) and piperidine (80 ml) contained in a 5-l bolt-head flask was added with stirring, paraformaldehyde (240.2 g, 8.0 mol. equiv.) at such a rate that the moderately exothermic reaction did not cause the temperature to exceed 70° (1.0—1.5 h). The mixture was then heated to 80—90° whereby refluxing commenced accompanied by the copious evolution of carbon dioxide. Heating was continued for 6 h by which time 60—65% of the theoretical amount of gas had been evolved. The low boiling ' heads ' and water were removed under reduced pressure at the water pump. Subsequent distillation gave ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate [6] as a yellow oil, b.p. 116—118° at 2.4 mmHg (881.2 g, 4.84 mol, 60.5%); phenylhydrazone (from aqueous ethanol), m.p. 71—73°. The DNP was obtained in dimorphic forms, as dark red platelets (from methanol or ethanol) transition point 98.1°, m.p. 110°, or as orange-red crystals (from cyclohexane or benzene), m.p. 110°.

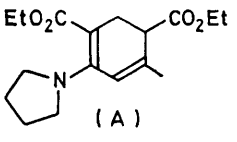
Wiped film evaporation (b.p. 75° at 5×10^{-3} mmHg) of the distillation residues gave a variable yield of a viscous orange-brown oil. Following basic extraction, *diethyl 4-hydroxy-6-methylbenzene-1,3-dicarboxylate* (26) crystallised from aqueous ethanol as glistening flakes, m.p. 50—51° (lit.,[38] 51°); $\nu_{max.}$ (melt) 3 450, 3 150, 1 718, and 1 678 cm^{-1}; δ 1.39 (6 H, dt, *J ca.* 7 Hz, CH_2CH_3), 2.53 (3 H, s, $ArCH_3$), 4.29 (4 H, dq, *J ca.* 7 Hz, CH_2CH_3), 6.65 and 8.27 (2 H, 2 × s, Ar-H), and 11.87 (OH); M^+ 252.

Ethyl 2-Methyl-4,4-ethylenedioxycyclohex-1-enecarboxylate (10).—Hagemann's ester (6a) (236.9 g, 1.3 mol), ethylene glycol (267.0 g, 240 ml, 4.3 mol), toluene-*p*-sulphonic acid (6.0 g), and benzene (1.2 l) were refluxed under a Dean–Stark trap for 24 h. A second charge of catalyst (6.0 g) was added and the mixture refluxed under the trap for a further 24 h. The cooled mixture was washed with 2% aqueous sodium hydrogencarbonate solution (1 × 1 l), and with water (2 × 500 ml), dried over anhydrous sodium carbonate, and concentrated (314.1 g). Fractional distillation gave ethyl 2-methyl-4,4-ethylenedioxycyclohex-1-enecarboxylate [7,12] as an oil, b.p. 120—126° at 1.7 mmHg (241.6 g, 1.07 mol, 82.1%).

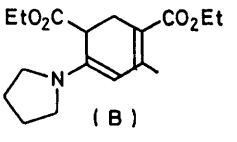
4,4-Ethylenedioxy-1-hydroxymethyl-2-methylcyclohexene (11).—To acetal ester (10) (105.0 g, 0.46 mol) was added dropwise over 7 h at 20° a solution of sodium bis-(2-methoxyethoxy)aluminium hydride (175.8 g, 0.87 mol) in dry benzene (75 g). The mixture was allowed to stand at room temperature for 24 h, and then decomposed by pouring onto crushed ice (1 kg). The products were extracted with benzene (2 × 500 ml); the combined benzene extracts were washed with brine (1 × 250 ml), dried ($MgSO_4$), and concentrated (46.9 g). The aqueous extract was reduced in volume to 300 ml and extracted with benzene in a continuous extraction unit for 16 h; further crude product (33.4 g) was thus obtained. Fractional distillation gave 4,4-ethylenedioxy-1-hydroxymethyl-2-methylcyclohexene [7b] as a yellow oil, b.p. 112—114° at 0.6 mmHg (62.4 g, 0.34 mol, 73.6%).

3-Methyl-4-methylenecyclohex-2-enone (12).—Allylic alcohol (11) (40.2 g, 0.22 mol), 10% w/w hydrochloric acid (42 ml), and tetrahydrofuran (180 ml) were stirred vigorously at 20° for 4 h. The reaction mixture was carefully neutralised with solid sodium hydrogencarbonate. Excess of toluene was then added, and the mixture distilled at atmospheric

* A straightforward route to 6-alkyl-3-methylcyclohex-2-enones (24) should be possible in principle if enone (5a) reacts with pyrrolidine to form dienamine (A); the u.v. spectrum of the



(A)



(B)

product showed a single prominent maximum at 383 nm, very close to that exhibited by dienamine (31). It appears that isomer (B) is formed in preference to the cross-conjugated compound (A).

pressure until a head temperature of 108° had been reached. The toluene solution thus obtained was concentrated and then distilled to give 3-methyl-4-methylenecyclohex-2-enone [7] as a viscous oil, b.p. 90—92° at 15 mmHg (19.9 g, 0.16 mol, 74.7%); $\nu_{max.}$ (film) 1 675, 1 634, 1 592, 871, and 795 cm^{-1}; $\lambda_{max.}$ (EtOH) 272 nm (log ε 4.18); δ 2.03 (3 H, d, *J ca.* 1.5 Hz, CH_3C=C), 2.2—3.1 (4 H, complex, CH_2CH_2), 5.27br (2 H, s, C=CH_2), 5.80 (1 H, q, *J ca.* 1.5 Hz, HC=C); *m/e* 122 (M^+).

4-Alkyl-3-methylcyclohex-2-enones (17).—A typical procedure is described for the synthesis of 3-methyl-4-(3-methylbutyl)cyclohex-2-enone. To dry tetrahydrofuran (500 ml) held at −10° under nitrogen was added with stirring di-isopropylamine (32.4 g, 0.32 mol) over 10 min, 2,2-bipyridyl (2 mg); [39] and a solution of n-butyl-lithium (0.32 mol) in hexane. The bright red solution containing lithium di-isopropylamide was stirred for 15 min before acetal-ester (10) (36.0 g, 0.16 mol) was added dropwise over 35 min. The mixture was stirred for a further 20 min before 3-methylbutyl iodide (70.3 g, 0.355 mol) was added dropwise over 20 min. After stirring for 1 h at −10°, the mixture was quenched with water (500 ml), concentrated to remove the solvents, and a mixture of water (200 ml) and ether (200 ml) added. The organic phase was separated, the aqueous phase was acidified (dilute hydrochloric acid), and extracted with ether (2 × 200 ml). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to yield the crude alkylated acetal-ester (15; R = 3-methylbutyl) (39.4 g).

The crude product was refluxed with toluene-*p*-sulphonic acid (1.5 g) in aqueous acetone (300 ml AnalaR acetone, 6 ml distilled water) for 3 h. The reaction was neutralised with 10% aqueous sodium carbonate solution, and then poured into ice–water (500 ml). The ethereal extracts (3 × 75 ml) of the mixture were washed with brine, dried ($MgSO_4$), and concentrated to give *ethyl 2-methyl-1-(3-methylbutyl)-4-oxocyclohex-2-enecarboxylate* (16; R = 3-methylbutyl) (32.1 g). A purified sample was isolated by preparative g.l.c., $\nu_{max.}$ (film) 1 733, 1 684, and 1 627 cm^{-1}; δ 0.81 [6 H, d, *J ca.* 5 Hz, $CH(CH_3)_2$], 1.15 (3 H, t, *J ca.* 7 Hz, CH_2CH_3), 0.9—2.4 (*ca.* 9 H, complex, ring and chain protons), 1.87 (3 H, d, *J ca.* 1 Hz, C=CCH_3), 4.03 (2 H, q, *J ca.* 7 Hz, CH_2CH_3), and 5.70 (1 H, q, *J ca.* 1 Hz, C=CH) (Found: M^+, 252.172 6. $C_{15}H_{24}O_3$ requires *M*, 252.172 5).

The crude product (29.9 g) was gently refluxed with alcoholic potassium hydroxide [from 85% potassium hydroxide (14.5 g) and 90% aqueous ethanol (410 ml)] under nitrogen for 48 h. The mixture was concentrated, added to a mixture of ether (200 ml) and water (200 ml), and acidified (pH 4.0) with dilute hydrochloric acid. The organic phase was separated, and the aqueous phase extracted with ether (3 × 50 ml). The combined organic extracts were washed with 10% aqueous sodium hydrogencarbonate solution and brine, dried ($MgSO_4$), and concentrated (21.4 g) to yield a 6 : 4 mixture of 4-(3-methylbutyl)- (17) and 6-(3-methylbutyl)-3-methylcyclohexenones (24). Spinning-band distillation gave *3-methyl-4-(3-methylbutyl)cyclohex-2-enone* as an oil, b.p. 75° at 0.4 mmHg (11.37 g, 0.06 mol, 39%), $\nu_{max.}$ (film) 1 679 and 1 629 cm^{-1}; $\lambda_{max.}$ (hexane) 226 nm (log ε 4.15); δ 0.87 [6 H, d, *J ca.* 5 Hz, $CH(CH_3)_2$], 1.06—1.74 (4 H, complex, chain CH_2), 1.80—2.51 (6 H, complex, ring CH_2 and 2 × CH), 1.89 (3 H, d, *J ca.* 1 Hz, C=CCH_3), and 5.62 (1 H, q, *J ca.* 1 Hz, C=CH) (Found: M^+, 180.150 4. $C_{12}H_{20}O$ requires *M*, 180.151 4).

The following cyclohexenones were also prepared by this method: *4-butyl-3-methylcyclohex-2-enone*, b.p. 82° at 1.4 mmHg (34%) (Found: M^+, 166.136 4. $C_{11}H_{18}O$ requires *M*, 166.135 8); *3-methyl-4-pentylcyclohex-2-enone* (43%), b.p. 72° at 0.15 mmHg (Found: M^+, 180.150 7; $C_{12}H_{20}O$ requires *M*, 180.151 4); *4-hexyl-3-methylcyclohex-2-enone* (40%), b.p. 84° at 0.1 mmHg (Found: M^+, 194.167 0. $C_{13}H_{22}O$ requires *M*, 194.167 1); and *3-methyl-4-(3-methylbut-2-enyl)cyclohex-2-enone* (27%), b.p. 82° at 2.0 mmHg (Found: M^+, 178.136 3. $C_{12}H_{18}O$ requires *M*, 178.135 8).

3-Methyl-4-pentylcyclohex-2-enone (14).—To a suspension of cuprous iodide (15.2 g, 0.08 mol) in dry ether (220 ml) was slowly added under nitrogen a solution of n-butyl-lithium (0.16 mol) in hexane. The dark green suspension was stirred at 0° for 5 min before 3-methyl-4-methylenecyclohex-2-enone (12) (8.55 g, 0.07 mol) in dry ether (80 ml) was added dropwise over 30 min. The reaction mixture was decomposed with a solution of ammonium chloride to which ammonia had been added (650 ml; pH 8). Air was bubbled through the reaction mixture until the deep blue colour of the cuprammonium complex had developed fully in the aqueous phase. The organic layer was separated, and the aqueous phase extracted with ether (2 × 100 ml). The combined extracts were washed with saturated ammonium chloride solution (2 × 200 ml), dried ($MgSO_4$), and concentrated (15.76 g) to give predominantly *3-methyl-4-pentylcyclopent-3-enone* (13), $\nu_{max.}$ (film) 1 723 cm^{-1}; δ 0.90 (3 H, t, *J ca.* 5 Hz, terminal CH_3), 1.32br (6 H, s, chain CH_2), 1.67 (3 H, s, C=CCH_3), and 2.08—2.69 (8 H, complex, 4 × CH_2); furthermore the spectrum did not show any signal due to an olefinic proton; M^+ 180.

The mixture was chromatographed on Grade I acidic alumina [increasing proportions of ether in light petroleum (b.p. 40—60°) as eluant] and yielded a fraction containing the conjugated ketone (11.96 g). Fractional distillation on a spinning-band column gave 3-methyl-4-pentylcyclohex-2-enone as an oil, b.p. 72° at 0.15 mmHg (6.14 g, 0.034 mol, 48.6%), $\nu_{max.}$ (film) 1 678 and 1 629 cm^{-1}; $\lambda_{max.}$ (hexane) 226 nm (log ε 4.19); δ 0.89 (3 H, t, *J ca.* 5 Hz, CH_2CH_3), 1.07—1.70 (8 H, complex, alkyl side chain), 1.70—2.49 (5 H, complex, ring protons), 1.88 (3 H, d, *J ca.* 1 Hz, C=CCH_3), and 5.66 (1 H, m, *J ca.* 1 Hz, C=CH); M^+ 180, identical in all respects with material prepared by a different method.

3-Methyl-4-(3-methylbutyl)anisole (18; R = 3-*methylbutyl*). A mixture of 3-methyl-4-(3-methyl-1-oxobutyl)- and 5-methyl-2-(3-methyl-1-oxobutyl)anisole were reduced (Clemmensen reaction) to 3-methyl-4-(3-methylbutyl)- and 5-methyl-2-(3-methylbutyl)-anisole. The isomeric compounds were separated by spinning-band distillation: 3-methyl-4-(3-methylbutyl)anisole was obtained as an oil, b.p. 117—119° at 10 mmHg, $\nu_{max.}$ (film) 1 612 and 1 250 cm^{-1}; δ(CCl_4) 0.93 [6 H, d, *J ca.* 5 Hz, $CH(CH_3)_2$], 1.0—1.8 [3 H, complex, $CH_2CH(CH_3)_2$], 2.22 (3 H, s, $ArCH_3$), 2.22—2.63 (2 H, complex, $ArCH_2$), 3.67 (3 H, s, OCH_3), 6.51 (1 H, dd, H-6), 6.58 (1 H, d, H-2), and 6.92 (1 H, d, $J_{5,6}$ *ca.* 10 Hz, H-5); M^+ 192.

3-Methyl-4-(3-methylbutyl)cyclohex-2-enone (17; R = 3-*methylbutyl*).—3-Methyl-4-(3-methylbutyl)anisole (18) (9.6 g, 0.05 mol) in dry ether (50 ml) was cooled to −40° and liquid ammonia (75 ml) was slowly added with stirring. The homogeneous solution was stirred for 5 min and lithium shot (1.6 g) was added over 10 min. After stirring for a further 10 min, absolute ethanol (18 ml) was added dropwise over 15 min. The mixture was then allowed to evaporate

overnight. Ether (30 ml) and water (30 ml) were added to the mixture, the organic layer was separated, and the aqueous layer extracted with ether (2 × 100 ml). The combined organic layers were washed with brine, and concentrated (9.3 g). The intermediate dihydro-compound was refluxed with ethyl acetate (80 ml), ethanol (40 ml), and 10% w/w hydrochloric acid (30 ml) for 1.25 h. The mixture was diluted with water (250 ml), and extracted with ether (3 × 50 ml). The combined ether layers were washed with brine, dried ($MgSO_4$), and concentrated (8.1 g). Short-path distillation yielded the cyclohexenone (5.09 g), purified by spinning-band distillation, b.p. 124—125° at 8 mmHg (1.21 g), identical in all respects with the material prepared by an alternative method.

Alkylation of the Dianion (22) *from Hagemann's Ester*.—A solution of lithium di-isopropylamide (0.2 mol) in dry tetrahydrofuran (200 ml) was prepared at −10° as described under (17). Ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate (6a) (18.2 g, 0.1 mol) was added over 15 min, followed by 15 min stirring; n-butyl bromide (15.1 g, 0.11 mol) was then added and stirring continued for a further 3 h. The reaction mixture was quenched with cold water (300 ml), neutralised with 10% w/w hydrochloric acid, and extracted with ether (3 × 200 ml). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated (20.1 g).

Typical basic hydrolysis. The crude product (10.0 g) was refluxed with alcoholic potassium hydroxide [from 85% potassium hydroxide (17.0 g) and 90% aqueous ethanol (150 ml)] for 12 h. The mixture was concentrated, added to ether (75 ml)–water (75 ml), and acidified (pH 4) with dilute hydrochloric acid. The organic layer was separated, washed with 10% sodium hydrogencarbonate solution and brine, dried ($MgSO_4$), and concentrated (8.2 g). Following distillation, g.l.c.–m.s. examination demonstrated the presence of 3-methylcyclohex-2-enone (29) (1.0%), 2-butyl-3-methylcyclohex-2-enone (9c; R^2 = Bu) (3.2%), 6-butyl-3-methylcyclohex-2-enone (24; R = Bu) (31.5%), and 4-butyl-3-methylcyclohex-2-enone (17; R = Bu) (28.2%).

Typical acidic hydrolysis. The crude product (10.0 g), concentrated sulphuric acid (5 ml), water (5 ml), and glacial acetic acid (20 ml) were stirred and refluxed for 12 h and then left at room temperature overnight. After dilution with water (60 ml), the organic material was taken up in ether (3 × 25 ml). The combined ethereal layers were washed with 10% sodium hydrogencarbonate solution, and brine, dried ($MgSO_4$), and concentrated (8.7 g). After distillation, g.l.c.–m.s. examination showed the presence of 3-methylcyclohex-2-enone (29) (2.3%), 2-butyl-3-methylcyclohex-2-enone (9c; R^2 = Bu) (4.1%), 6-butyl-3-methylcyclohex-2-enone (24; R = Bu) (48.4%), and 4-butyl-3-methylcyclohex-2-enone (17; R = Bu) (17.4%).

Diethyl 4-Hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (4a).—This material was obtained by the method of Rabe;[18] it crystallised from aqueous ethanol as long needles, m.p. 77—80° (sealed tube) (lit.,[18] 79°), $\nu_{max.}$ (KBr disc) 3 535, 1 737, 1 714, and 1 706sh cm^{-1}; δ 1.27 (6 H, overlapping t, *J ca.* 6 Hz, 2 × CH_2CH_3), 1.30 [3 H, s, C(OH)-CH_3], 2.15—3.45 (6 H, complex, ring protons), 3.52 [C(OH)-CH_3], 4.17 (4 H, overlapping q, *J ca.* 6 Hz, 2 × CH_2CH_3), and 12.3 (enolic OH); M^+ 272.

Diethyl 4-Methyl-6-oxocyclohex-4-ene-1,3-dicarboxylate (5a).—The aldol (4a) (27.2 g, 0.1 mol), toluene-*p*-sulphonic acid (2.5 g), and benzene (250 ml) were refluxed under a Dean–Stark trap until water no longer separated (*ca.* 8 h). The major portion of the solvent was evaporated under reduced pressure, the resulting concentrate was washed with 10% aqueous sodium hydrogencarbonate solution, and brine, dried ($MgSO_4$), and concentrated (23.2 g).

Short-path distillation gave diethyl 4-methyl-6-oxocyclohex-4-ene-1,3-dicarboxylate[18] as a pale yellow oil, b.p. 124—126° at 0.4 mmHg (22.1 g, 0.09 mol, 87%), $\nu_{max.}$ (film) 1 742, 1 727, 1 677, and 1 635 cm^{-1}; $\lambda_{max.}$ (EtOH) 230 nm (log ε 4.15); δ 1.24 (6 H, overlapping t, *J ca.* 7 Hz, 2 × CH_2CH_3), 1.97 (3 H, d, *J ca.* 1 Hz, C=CCH_3), 1.97—2.61 (2 H, complex, ring CH_2), 2.97—*ca.* 3.50 (2 H, complex, ring CH), 4.14 (4 H, overlapping q, *J ca.* 7 Hz, 2 × CH_2CH_3), and 5.82 (1 H, m, *J ca.* 1 Hz, HC=C); M^+ 254; DNP (from benzene–ethanol), m.p. 165—167°. On refluxing with phenylhydrazine solution, compound (5a) gave tan needles, m.p. 193—194°, M^+ 296.

Compound (5a) (1.27 g, 5 mmol), pyrrolidine (0.43 g, 6 mmol), toluene-*p*-sulphonic acid (0.05 g), and benzene (10 ml) were refluxed under a Dean–Stark trap until no more water collected (*ca.* 6 h). The mixture was washed with sodium hydrogencarbonate solution, and dried ($MgSO_4$). Concentration gave *diethyl 4-methyl-6-pyrrolidinocyclohexa-3,5-diene-1,3-dicarboxylate* as a light yellow oil, b.p. 155—157° (decomp.) at 0.7 mmHg, $\nu_{max.}$ (film) 1 727, 1 676, and 1 609 cm^{-1}; $\lambda_{max.}$ (EtOH) 383 nm (log ε 4.48); δ 1.20 (6 H, overlapping t, 2 × CH_2CH_3), 1.70—2.05 (6 H, m, CH_2CH_2 and 2 × H-2), 2.18 (3 H, d, C=CCH_3), 3.05—3.50 (4 H, m, CH_2NCH_2), 4.06 (4 H, q, 2 × CH_2CH_3), and 4.47 (1 H, s, H-5); M^+ 307.

Alkylation of Diethyl 4-Methyl-6-oxocyclohex-4-ene-1,3-dicarboxylate (5a).—To a stirred solution of sodium ethoxide in ethanol [prepared from sodium (1.15 g, 0.05 g-atom) in absolute ethanol (50 ml)] was added at room temperature a solution of compound (5a) (12.71 g, 0.05 mol) in absolute ethanol (50 ml). 3-Methylbutyl iodide (9.9 g, 0.05 mol) was then added over 10 min. The mixture was refluxed with stirring for 1.5 h. The excess of ethanol was removed under reduced pressure, the resulting slurry diluted with water (100 ml), and then acidified with 25% hydrochloric acid. The organic material was taken up in ether, and the aqueous phase extracted with ether (3 × 25 ml). The combined ether extracts were washed with brine and concentrated (12.2 g). The crude product (5 g), acetic acid (30 ml), water (6 ml), and concentrated sulphuric acid (4 ml) were refluxed for 5 h; on cooling, the reaction mixture was diluted with water (150 ml). The organic phase was separated and the aqueous phase extracted with ether (3 × 25 ml). The bulked organic phases were washed with sodium hydrogencarbonate solution and brine, dried ($MgSO_4$), and concentrated (2.4 g). Following distillation, g.l.c.–m.s. examination indicated the presence of 3-methylcyclohex-2-enone (29) (20.5%), 3-methyl-2-(3-methylbutyl)-cyclohex-2-enone (9c; R^2 = 3-methylbutyl) (35.0%), 3-methyl-6-(3-methylbutyl)cyclohex-2-enone (24; R = 3-methylbutyl) (8.5%), and 3-methyl-4-(3-methylbutyl)-cyclohex-2-enone (17; R = 3-methylbutyl) (1.2%).

Ethyl 4-Methyl-2-oxocyclohex-3-enecarboxylate (28).—Ethyl 2-acetyl-5-oxohexanoate (27)[21] (100.1 g, 0.5 mol) was added to a mixture of concentrated sulphuric acid (300 ml) and water (10 ml) held at −10°. The rate of addition was adjusted such that the temperature of the mixture was maintained between −10 and −5° (*ca.* 3 h). The mixture was allowed to warm to room temperature (1.5 h) and then poured slowly onto ice–water (700 ml), the temperature

being maintained below 35° during the quenching procedure. The organic material was extracted with ether (3 × 200 ml) followed by toluene (1 × 200 ml). The combined organic extracts were washed with 10% aqueous sodium hydrogencarbonate solution until just alkaline, and then with brine to neutrality, dried ($MgSO_4$), and concentrated (75.1 g). Fractional distillation yielded ethyl 4-methyl-2-oxocyclohex-3-enecarboxylate [21] as a pale yellow oil, b.p. 99—101° at 0.5 mmHg (65.8 g, 0.36 mol, 72%); DNP (from ethanol), m.p. 117°; phenylhydrazone (from aqueous ethanol), m.p. 122—123° (lit.,[23] 123°), which on refluxing in ethanol gave the corresponding pyrazolone, m.p. 178—180° (lit.,[23] 199—201°), M^+ 226.

6-Alkyl-3-methylcyclohex-2-enones (24).—A typical procedure is described for the synthesis of 6-butyl-3-methylcyclohex-2-enone. To a stirred solution of sodium ethoxide [prepared by dissolving sodium (11.5 g, 0.5 g-atom) in ethanol (350 ml)] was added at room temperature dropwise over 1 h, ethyl 4-methyl-2-oxocyclohex-3-enecarboxylate (28) (91.9 g, 0.5 mol). n-Butyl bromide (68.5 g, 0.5 mol) was added over 1 h with vigorous stirring and the mixture then refluxed for 2 h. The excess of ethanol was evaporated under reduced pressure, and the resulting slurry diluted with water (300 ml). After the mixture had been acidified with 25% hydrochloric acid, the organic phase was taken up in ether (150 ml), and the aqueous phase extracted with ether (3 × 150 ml). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to yield *ethyl 1-butyl-4-methyl-2-oxocyclohex-3-enecarboxylate* (30; R = Bu) (112.0 g). A purified sample was isolated by preparative g.l.c. $\nu_{max.}$ (film) 1 737, 1 684, and 1 647 cm^{-1}; δ 0.85 (3 H, t, *J ca.* 5 Hz, terminal CH_3), 1.15 (3 H, t, *J ca.* 7 Hz, $CO_2CH_2CH_3$), 1.09—2.55 (10 H, complex, 5 × CH_2), 1.86 (3 H, d, *J ca.* 1 Hz, C=CCH_3), 4.04 (2 H, q, *J ca.* 7 Hz, $CO_2CH_2CH_3$), and 5.71 (1 H, q, *J ca.* 1 Hz, C=CH) (Found: M^+, 238.156 5. $C_{14}H_{22}O_3$ requires *M*, 238.156 9).

The crude alkylated ester (111.5 g), concentrated sulphuric acid (60 ml), water (60 ml), and glacial acetic acid (200 ml) were stirred and refluxed for 5 h, and then left at room temperature overnight. After dilution with water (600 ml), the organic products were taken up in ether (3 × 150 ml). The combined ethereal layers were washed with 10% sodium hydroxide solution till just alkaline, then with brine to neutrality, dried ($MgSO_4$), and concentrated (64.4 g). Distillation gave *6-butyl-3-methylcyclohex-2-enone* as an oil (41.5 g, 0.25 mol, 50%), b.p. 108—110° at 6 mmHg (lit.,[40] 95—96° at 4 mmHg), $\nu_{max.}$ (film) 1 673 and 1 640 cm^{-1}; $\lambda_{max.}$ (hexane) 224 nm (log ε 4.18); δ 0.86 (3 H, t, *J ca.* 5 Hz, terminal CH_3), 1.10—1.57 (6 H, complex, side chain CH_2), 1.57—2.45 (5 H, complex, ring CH_2 and CH), 1.89 (3 H, d, *J ca.* 1 Hz, C=CCH_3), and 5.66 (1 H, q, *J ca.* 1 Hz, C=CH) (Found: M^+, 166.135 0. $C_{11}H_{18}O$ requires *M*, 166.135 8).

The following ketones were also prepared by this method: *3-methyl-6-pentylcyclohex-2-enone* (51%), b.p. 103—106° at 3 mmHg (Found: M^+, 180.150 6. $C_{12}H_{20}O$ requires *M*, 180.151 4); *3-methyl-6-(3-methylbutyl)cyclohex-2-enone* (33%),[40] b.p. 105—108° at 3.5 mmHg (Found: M^+, 180.151 0. $C_{12}H_{20}O$ requires *M*, 180.151 4); *6-hexyl-3-methylcyclohex-2-enone* (48%), b.p. 80—81° at 0.1 mmHg (Found: M^+, 194.167 7. $C_{13}H_{22}O$ requires *M*, 194.167 1).

3-Methyl-6-isopropylcyclohex-2-enone (30%),[37,40] b.p. 102—104° at 9 mmHg, prepared by this route, was identical in all respects (except optical activity) with piperitone isolated from Eucalyptus dives oil.

Saponification and Decarboxylation of Ethyl 4-Methyl-1-(3-methylbut-2-enyl)-2-oxocyclohex-3-enecarboxylate (30; R = 3-(3-*methylbut-2-enyl*).—Alkylated ester (30; R = 3-methylbut-2-enyl) (111.7 g) was treated with concentrated sulphuric acid, water, and glacial acetic acid as described in the previous section. After an identical work-up procedure, the crude product (55.2 g) was shown by g.l.c. to be a mixture of three products: compounds A (79.8%), B (5.1%), and C (15.1%). By a combination of fractional distillation and column chromatography the major components were obtained in a pure state. On the basis of its spectroscopic data, compound C, m.p. 95—96°, $\lambda_{max.}$ (hexane) 270, 276, 307, 317, and 321 nm (log ε 3.65, 3.67, 2.56, 2.39, and 2.36), M^+ 156, was identified as 2,7-dimethylnaphthalene.[26] Similarly, compound A, $\nu_{max.}$ (film) 2 900, 1 600, 1 504, 1 460, 1 440, 1 379, 809, and 796 cm^{-1}, $\lambda_{max.}$ (EtOH) 264, 270, 273, and 279 nm (log ε 2.75, 2.92, 2.90, and 2.98), M^+ 160, was identical with 2,7-dimethyltetralin.[25] Compound B (<90% purity), M^+ 176, had a breakdown pattern consistent with a dehydro-3-methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone.

Alkylated ester (30; R = 3-methylbut-2-enyl) (105.0 g) was refluxed with alcoholic potassium hydroxide [from 85% potassium hydroxide (21.0 g) and 90% aqueous ethanol (400 ml)] for 6 h, cooled, and the precipitated salts filtered off. The viscous oil obtained after concentration of the filtrate was taken up in a mixture of water and ether (5 : 1 v/v). The mixture was acidified with dilute hydrochloric acid and extracted with ether (3 × 125 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated (83.0 g). The crude product was transferred to a distillation flask and heated under vacuum (20—30 mmHg) until decarboxylation was complete, indicated by a sharp decrease in pressure. *3-Methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone* (24; R = 3-*methylbut-2-enyl*) was obtained in a pure state by spinning-band distillation (30.2 g, 0.17 mol, 41%), b.p. 75—77° at 0.3 mmHg, $\nu_{max.}$ (film) 1 672 and 1 638 cm^{-1}; $\lambda_{max.}$ (hexane) 224 nm (log ε 4.14); δ 1.57, 1.65 [2 × 3 H, 2 × s, =$C(CH_3)_2$], 1.87 (3 H, d, *J ca.* 1 Hz, C=CCH_3), 1.80—2.65 (7 H, complex, ring protons and side chain CH_2), 5.03 [1 H, q, CH=$C(CH_3)_2$], and 5.69 (1 H, m, *J ca.* 1 Hz, C=CH) (Found: M^+, 178.135 5. $C_{12}H_{18}O$ requires *M*, 178.135 8).

2-Alkyl-3-methylcyclohex-2-enones (9c).—These materials were prepared following the general directions of Edgar *et al.*[30] In general, the crude alkylated esters were used in the next stage without purification. The following were characterised: *ethyl 2-methyl-3-pentyl-4-oxocyclohex-2-enecarboxylate* (8c; R^2 = pentyl), b.p. 128—129° at 0.3 mmHg, $\nu_{max.}$ (film) 1 739, 1 675, and 1 636 cm^{-1}; δ 0.85br (3 H, s, terminal CH_3), 1.22 (3 H, t, *J ca.* 7 Hz, $CO_2CH_2CH_3$), *ca.* 1.25 (6 H, complex, alkyl side chain), 1.94 (3 H, s, C=CCH_3), 2.06—2.60 (6 H, complex, ring CH_2 and C=CCH_2), 3.27 (1 H, t, CH), and 4.10 (2 H, q, *J ca.* 7 Hz, $CO_2CH_2CH_3$) (Found: M^+, 252.172 8. $C_{15}H_{24}O_3$ requires *M*, 252.172 5); and *ethyl 2-methyl-3-(3-methylbut-2-enyl)-4-oxocyclohex-2-enecarboxylate* (8c; R^2 = 3-methylbut-2-enyl), b.p. 132—133° at 0.4 mmHg, $\nu_{max.}$ (film) 1 740, 1 676, and 1 637 cm^{-1}; δ 1.22 (3 H, t, *J ca.* 7 Hz, CH_2CH_3), 1.60, 1.64 [2 × 3 H, 2 × s, =$C(CH_3)_2$], 1.90 (3 H, s, C=CCH_3), 2.0—2.65 (4 H, complex, ring CH_2), 2.97br (2 H, d, =CCH_2C=), 3.25 (1 H, t, *J ca.* 5 Hz, CH), 4.12 (2 H, q, *J ca.* 7 Hz, CH_2CH_3), and 4.82br (1 H, t, C=CH) (Found: M^+, 250.157 1. $C_{15}H_{22}O_3$ requires *M*, 250.156 9). The following cyclohexenones were prepared by this method: *2-butyl-3-methylcyclohex-2-enone* (39%), b.p. 69° at 0.7 mmHg (Found: M^+, 166.136 3.

$C_{11}H_{18}O$ requires M, 166.135 8); 3-*methyl*-2-*pentylcyclohex*-2-*enone* (44%),[30] b.p. 81° at 0.4 mmHg (Found: M^+, 180.150 3. $C_{12}H_{20}O$ requires M, 180.151 4); 3-*methyl*-2-(3-*methylbutyl*)*cyclohex*-2-*enone* (39%), b.p. 84° at 0.7 mmHg (Found: M^+, 180.151 8. $C_{12}H_{20}O$ requires M, 180.151 4); 2-*hexyl*-3-*methylcyclohex*-2-*enone* (49%),[41] b.p. 90° at 0.7 mmHg (Found: M^+, 194.167 3. $C_{13}H_{22}O$ requires M, 194.167 1); 3-*methyl*-2-(3-*methylbut*-2-*enyl*)*cyclohex*-2-*enone* (63%), b.p. 97° at 0.5 mmHg (Found: M^+, 178.136 6. $C_{12}H_{18}O$ requires M, 178.135 8).

Alkylation of Ethyl 2-*Methyl*-4-*pyrrolidinocyclohexa*-1,3-*dienecarboxylate* (31).—Enamine (31) [21b] (32.0 g, 0.136 mol), 3-methylbut-2-enyl chloride (13.0 g, 0.124 mol), and acetonitrile (165 ml) were mixed together thoroughly, and then left at 0° for 65 h. The solvent was evaporated under reduced pressure, and the crude product was refluxed with glacial acetic acid (24 ml), water (24 ml), and sodium acetate (12 g) for 4 h. The mixture was diluted with water and extracted with ether (3 × 75 ml). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated (22.1 g). Distillation gave, after a forerun of Hagemann's ester (6a) (6.3 g), ethyl 2-methyl-3-(3-methylbut-2-enyl)-4-oxocyclohex-2-enecarboxylate (8c; R^2 = 3-methylbut-2-enyl) (13.6 g, 0.054 mol, 53%, based on reacted enamine), b.p. 130—133° at 0.5 mmHg, identical with material obtained by an alternative method.

Base-catalysed saponification, followed by thermal decarboxylation during distillation, gave 3-methyl-2-(3-methylbut-2-enyl)cyclohex-2-enone (9c; R^2 = 3-methylbut-2-enyl) (5.2 g, 0.029 mol, 54%), b.p. 96—97° at 0.5 mmHg.

4-*Methylpentanal*.—4-Methylpentanal diethyl acetal [35] (262.7 g, 1.5 mol) was added dropwise to a stirred, distilling dilute sulphuric acid solution (2% v/v, 400 ml) held in a round-bottomed flask fitted with a short Vigreux column and a condenser set for downward distillation. The two-phase steam-distillate was extracted with ether (3 × 100 ml), and the combined ether layers were washed with water, dried ($MgSO_4$), and concentrated (132.1 g). Distillation gave 4-methylpentanal as a piquant liquid (80.9 g, 0.81 mol, 54%), b.p. 120° at 761 mmHg.

5-*Alkyl*-3-*methylcyclohex*-2-*enones* (7b).—These materials were prepared following the general directions of Horning *et al.*[5] In general the crude alkylated aldols (4b) were saponified and decarboxylated to cyclohexenones (7b) directly. An intermediate monoalkylated ester could also be isolated: to a mixture of ethyl acetoacetate (260.3 g, 2.0 mol) and piperidine (10 ml) was added with stirring, heptanal (114.2 g, 1.0 mol) at such a rate that the temperature did not exceed 70°. The mixture was then heated at 80—90° for 1 h. The low boiling ' heads ' and water were removed under reduced pressure. Distillation gave *ethyl* 6-*hexyl*-2-*methyl*-4-*oxocyclohex*-2-*enecarboxylate* (6b; R^1 = hexyl) [34] as a pale yellow liquid (221.1 g, 0.83 mol, 83%), b.p. 138—140° at 1.0 mmHg, $\nu_{max.}$ (film) 1 742, 1 683, and 1 646 cm^{-1}; δ 0.87br (3 H, s, terminal CH_3), 1.23 (3 H, dt, $CO_2CH_2CH_3$), 1.25br (10 H, s, side chain CH_2), 1.52—2.55 (*ca.* 4 H, complex, ring CH_2 and CH), 1.93 (3 H, overlapping t, *J ca.* 1 Hz, C=CCH_3), 4.15 (2 H, q, $CO_2CH_2CH_3$), 5.81 (1 H, m, *J ca.* 1 Hz, C=CH) (Found: M^+, 266.189 0. $C_{16}H_{26}O_3$ requires M, 266.188 2). The following cyclohexenones were prepared by this method: [5] 5-*butyl*-3-*methylcyclohex*-2-*enone* (55%), b.p. 91° at 1.2 mmHg (Found: M^+, 166.135 1. $C_{11}H_{18}O$ requires M, 166.135 8); 3-*methyl*-5-*pentylcyclohex*-2-*enone* (53%), b.p. 94° at 0.6 mmHg (Found: M^+, 180.151 0. $C_{12}H_{20}O$ requires M, 180.151 4); 3-*methyl*-5-(3-*methylbutyl*)*cyclohex*-2-*enone* (47%), b.p. 110° at 1.6 mmHg (Found: M^+, 180.150 5. $C_{12}H_{20}O$ requires M, 180.151 4); 5-*hexyl*-3-*methylcyclohex*-2-*enone* (45%), b.p. 113° at 1.3 mmHg (Found: M^+, 194.167 1. $C_{13}H_{22}O$ requires M, 194.167 1)

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