Tetrahedron, 1966, Vol. 22, pp. 2319 to 2329. Pergamon Press Ltd. Printed in Northern Ireland

STUDIES IN SESQUITERPENES—XXVI

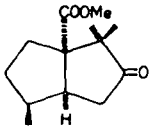
SYNTHESIS OF 2,2,6-TRIMETHYL-3-OXO-1-CARBOMETHOXY-BICYCLO[0,3,3]OCTANE, A DEGRADATION PRODUCT OF PATCHOULI ALCOHOL

R. K. GUPTA, M. C. CHACO and SUKH DEV
Department of Organic Chemistry, Indian Institute of Science, Bangalore and
National Chemical Laboratory, Poona, India

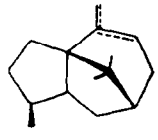
(*Received* 11 *November* 1965; *in revised form* 15 *January* 1966)

Abstract—The synthesis of the title compound is described and results of some experiments on the degradation of patchouli alcohol are reported.

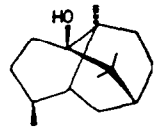
BICYCLO keto ester (I), described by Büchi *et al.*[1,2] as a degradation product of patchoulenes (II)—the hydrocarbons derived from patchouli alcohol[3] (III)—provided an important clue to the size of ring B in the patchoulenes. Since the bicyclo keto ester (I) contains twelve carbon atoms of the patchouli alcohol,[4] synthetic support



I



II

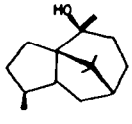


III

for its structure was considered desirable and the present paper describes its total synthesis. The scheme is outlined in Fig. 1.

The condensation of 2-carbethoxy-5-methyl-cyclopentanone (V)[5] with α-bromo-propionic ester to give VI was affected following the directions of Jones and Linstead.[6] The elaboration of the carbonyl function in VI into the desired methylidene carboxylic ester side chain, as in IXb, could be achieved by a number of reactions: e.g.,

[1] G. Büchi and R. E. Erickson, *J. Amer. Chem. Soc.* **78**, 1262 (1956).
[2] G. Büchi, R. E. Erickson and N. Wakabayashi, *J. Amer. Chem. Soc.* **83**, 927 (1961).
[3] M. Dobler, J. D. Dunitz, B. Gubler, H. P. Weber, G. Büchi and J. Padilla, *Proc. Chem. Soc.* 383 (1963).
[4] The bicyclo keto ester (I) appeared attractive for elaborating the molecule of patchouli alcohol, which was considered, at the time this work was started, to possess the structure[1,3] IV.



IV

[5] A simplified procedure for the preparation of diethyl α-methyladipate from diethyl adipate in 73% yield and which does not necessitate the isolation of intermediates, is described in the Experimental.
[6] R. L. Jones and R. P. Linstead, *J. Chem. Soc.* 616 (1936).

Reformatsky,[7,8] Knoevenagel[9,10] or *via* condensation with ethoxyacetylene.[11] In view of the susceptibility of Reformatsky and Knoevenagel reactions to steric factors, ethoxyacetylene condensation was preferred, as it has been used with success even in cases of sterically hindered carbonyl compounds.[12–16] Condensation of ethoxyacetylene magnesium bromide with the keto ester (VI) yielded the acetylenic lactone

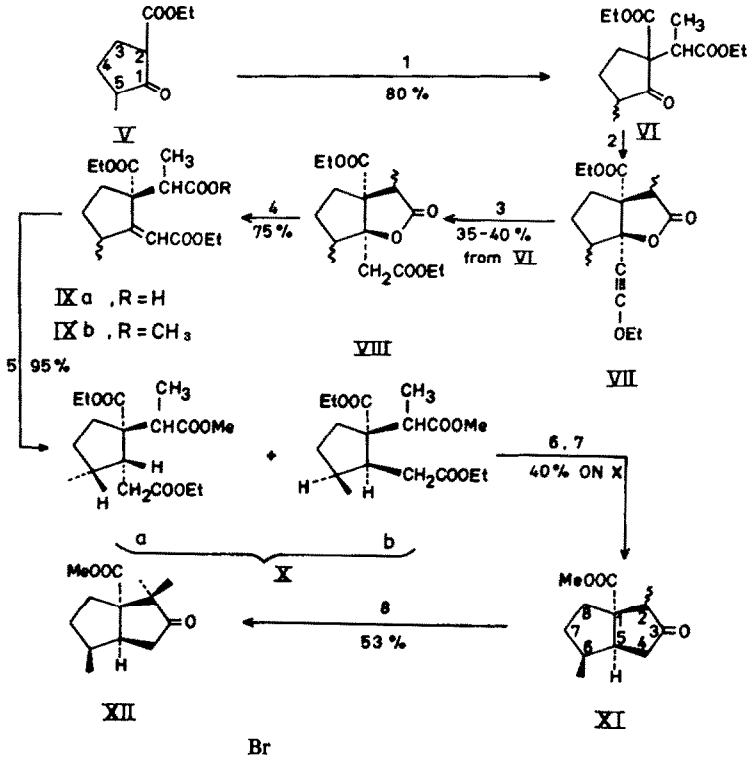


FIG. 1.

[7] R. L. Shriner in *Organic Reactions* Vol. 1; p. 1. Wiley, New York (1942).

[8] A. Surrey, *Name Reactions in Organic Chemistry* p. 200. Academic Press, New York (1961).

[9] Ref. 8, p. 147.

[10] V. Migridichian, *The Chemistry of Organic Cyanogen Compounds* pp. 319–348. Reinhold, New York (1947).

[11] J. F. Arens, *Advances in Organic Chemistry, Methods and Results* 2, pp. 117–212. Interscience, New York (1960).

[12] L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, *J. Amer. Chem. Soc.* **74**, 4974 (1952).

[13] G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, *J. Amer. Chem. Soc.* **76**, 1715 (1954).

[14] J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta* **40**, 1438 (1957).

[15] A. Lardon, O. Schindler and T. Reichstein, *Helv. Chim. Acta* **40**, 666 (1957).

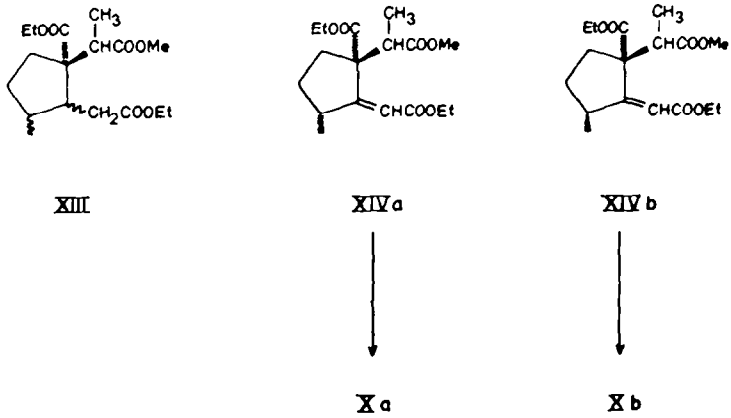
[16] S. A. Szpilfogel, W. J. Vander Burg, C. M. Siegmann and D. A. van Drop, *Rec. Trav. Chim.* **77**, 157 (1958).

(VII), which without further purification, was hydrated with aqueous sulphuric acid to furnish a product, which analysed for $C_{16}H_{24}O_6$ and showed in the IR spectrum bands at 1779 (γ-lactone) and 1730–1740 cm^{-1} (ester). These data are in accord with the expected structure VIII. The stereochemistry for the ring-junction, as shown in VIII, is based on *cis*-bicyclo[0,3,3]octane being far more stable than *trans*-bicyclo[0,3,3]-octane,[17] and consequently the lactonization of hydroxy acetylenic ester is consistent only with a *cis*-ring closure. This, however, has no bearing on subsequent steps.

The above lactone (VIII), being a β-hydroxy acid derivative, on ring-opening underwent smooth elimination[18] to the required unsaturated acid (IXa) which was converted into the methyl ester (IXb). The ester, $C_{17}H_{26}O_6$, displayed spectral characteristics ($\nu^{C=O}$ 1728, $\nu^{C=C}$ 1642 cm^{-1}; λ_{max}^{ETOH} 222 mμ, log ε 3·92) expected of structure IXb.

Reduction of IXb was attempted without success over Adam's PtO_2 catalyst, under varying conditions of temperature (20°, 70°, 125°, 150°), pressure (atmospheric, 500 and 800 lb/□″), reaction times (7 hr to 48 hr) and catalyst ratio (1:20 to 1:10). Nishimura, in 1960, introduced rhodium-platinum (3:1) oxide[19] as a hydrogenation catalyst[20–23] and its use proved most rewarding yielding a mixture of saturated esters (XIII).

Regarding the stereochemistry of XIII, it appears that catalytic hydrogenation involves the addition of two atoms of hydrogen from the same side i.e. from the sterically less-hindered side of the unsaturated substrate.[24,25] On this basis, the stereochemistry of XIII would depend on the configuration of the methyl at C_5 (XIVa and/or XIVb) in IXb. Thus, the product of catalytic hydrogenation should be a mixture of Xa and



XIII XIVa XIVb

Xa Xb

[17] J. W. Barrett and R. P. Linstead, *J. Chem. Soc.* 436 (1935); 611 (1936).

[18] Similar cases have been recorded: W. E. Bachmann and G. D. Johnson, *J. Amer. Chem. Soc.* **71**, 3463 (1949); B. Belleau, *Ibid.* **73**, 5149 (1951); W. S. Johnson, R. G. Christiansen and R. E. Ireland, *Ibid.* **79**, 1995 (1957).

[19] S. Nishimura, *Bull. Chem. Soc. Japan* **33**, 566 (1960).

[20] S. Nishimura, T. Onoda and A. Nakamura, *Bull. Chem. Soc. Japan* **33**, 1356 (1960).

[21] S. Nishimura, *Bull. Chem. Soc. Japan* **34**, 32, 1544 (1961).

[22] S. Nishimura and K. Mori, *Bull. Chem. Soc. Japan* **36**, 318 (1963).

[23] S. Nishimura and H. Taguchi, *Bull. Chem. Soc. Japan* **35**, 353, 873 (1963).

[24] R. L. Burwell, *Chem. Revs.* **57**, 895 (1957).

[25] S. Siegel and M. Dunkel in *Advances in Catalysis* Vol. **9**, pp. 15–24. Academic Press, New York (1957).

Xb.[26] In Xb, which has the desired methyl configuration at C_5, the propionate and acetate side chains are *cis*-oriented, whereas in Xa, which has the unwanted configuration at C_5, the vicinal ester side-chains are *trans*-oriented. As in the ethoxyacetylene condensation the attack on the carbonyl function has resulted in the lactone (VIII) in which the two five-membered rings are, in all probability *cis*-locked, the configuration of the methyl at C_5 in IX is likely to be the same as in XIVb. Consequently, it is reasonable to expect Xb to be the main product of hydrogenation.

As Barrett and Linstead[17] have demonstrated that Dieckmann cyclization of diethyl cyclopentyl-1,2-diacetate (with sodium dust in benzene) furnishes the *cis*-keto and that the *trans*-isomer, under similar conditions, fails to cyclize, compound XIII was subjected to Dieckmann cyclization with the expectation that only *cis*-isomer (Xb) would undergo cyclization. The crude product was hydrolysed with aqueous AcOH–HCl and the resulting material re-esterified (diazomethane) to give the desired keto ester (XI) in an overall yield of 40% (based on XIII).

Structure XI is supported by its IR spectrum: $\nu^{C=O}$ 1750–1728 cm^{-1}, ν^{-CH_2CO-} 1408 cm^{-1}. Though this product shows a single peak in GLC under a variety of conditions, it is clear from its PMR spectrum[27] that it is about a 1:1 mixture (as disclosed by two signals for $COOCH_3$ protons at 216 and 221 c/s) of two isomers. This is further supported by the occurrence of three doublets centred at 56, 58 and 62 c/s (J = 9, 7 and 8 c/s respectively) and assignable to CH_3—CH, in the PMR spectrum. Since the fusion of the two rings must be *cis* (as required by its mode of preparation), the two isomers can differ only, in the stereochemistry at C_2 (because, as discussed previously the configuration of methyl at C_5 is, in all probability, as shown in Xb). This difference is of no consequence in the synthesis of XII as the asymmetry at C_2 will be lost in the final product.

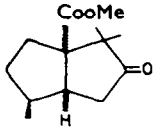
The final step in the synthesis of XII, *viz.* the introduction of a methyl at C_2 in XI, could be achieved in accordance with the work of Corey and Cantrall.[28] Thus, the keto ester (XI) on treatment with trityl sodium and methyl iodide readily furnished a monomethylated product, $C_{13}H_{20}O_3$ in which the methylation had occurred at the desired centre. The IR spectrum shows a *gem*-dimethyl group at 1360, 1380 cm^{-1} and CH_2 α to C=O at 1408 cm^{-1}. The PMR spectrum (Fig. 2) is fully consistent with the structure XII and supports our previous contention that the isomers of XI differ only in the stereochemistry at C_2. The PMR spectrum (Fig. 3) does not show any evidence[29] for the presence of isomers, the assignment of signals is shown in Fig. 3.

[26] These conclusions are not dependent on the configuration at C_3 in XIV, as a consideration of the alternative configuration at C_3 would lead to the mirror images of XIVa and XIVb.

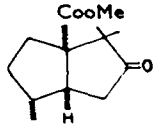
[27] All PMR spectra were taken on 10–20% solutions in CCl_4 on a Varian A-60 spectrometer; the signals are recorded in c/s from tetramethylsilane (internal standard) as zero.

[28] E. J. Corey and E. W. Cantrall, *J. Amer. Chem. Soc.* **81**, 1745 (1959).

[29] Had the isomers of XI differed in configuration of methyl at C_6, it is reasonable to expect that the



i



ii

mixture of (i) and (ii) should show at least some difference in the chemical shifts for $COOCH_3$ or CH_3—CH in the PMR spectrum of XII.

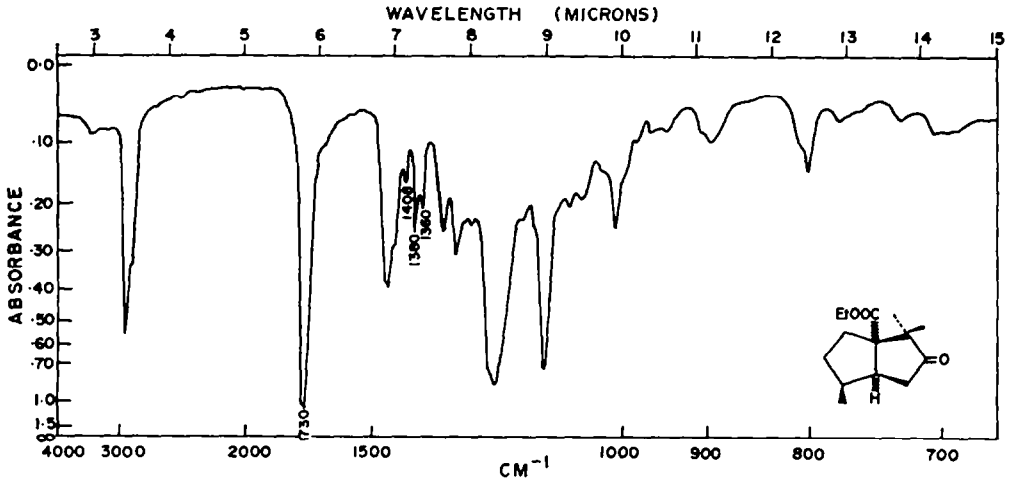


FIG. 2 IR spectrum of keto ester XII

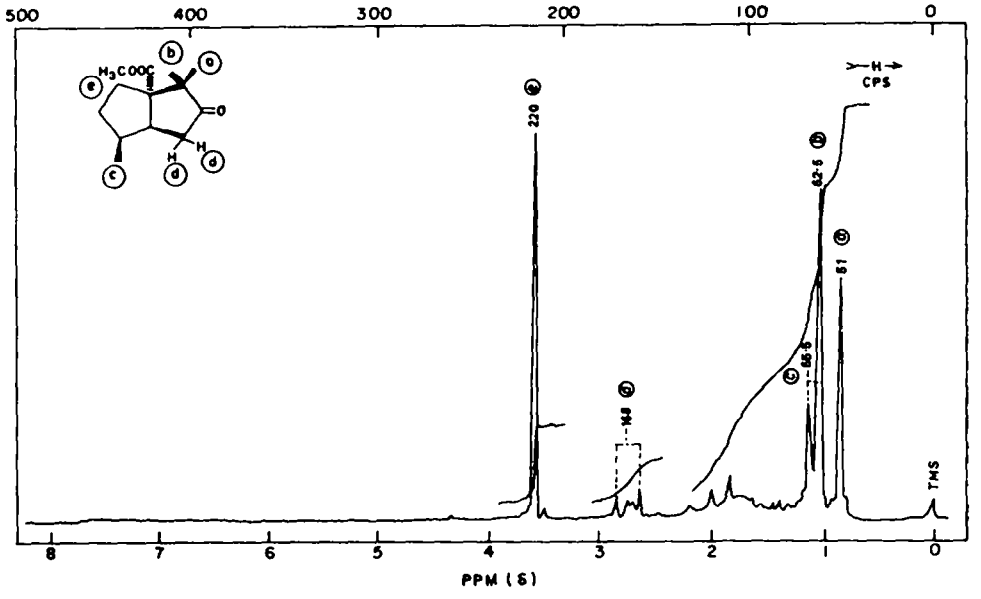


FIG. 3 PMR spectrum of keto ester XII

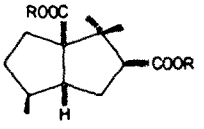
Thus, the total synthesis of 2,2,6-trimethyl-3-oxo-1-carbomethoxy-bicyclo[0,3,3]-octane[30] (XII) has been achieved and the stereochemistry is based on reasonable deductions and should represent the (±)-form of compound I obtained by Büchi *et al.*[1,2]

Some experiments on the degradation of patchouli alcohol

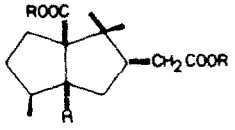
As pointed out earlier,[4] the keto ester (I) appeared attractive for elaborating the

[30] The IR spectrum of our synthetic compound was sent to Prof. G. Büchi for comparison with his product, who kindly informed us (Feb. 20, 1963) that though the curves are very similar they are not superimposable. He further pointed out that their sample was never absolutely pure as there was neither GLC nor TLC available in those days, but further observed that all important peaks are identical.

molecule of patchouli alcohol, which was considered at the time this work was started, to possess the structure IV. Two routes starting from the keto ester (I) and passing either through the dimethyl bisnorpatchouli dicarboxylate (XVb) or dimethyl nor-patchouli dicarboxylate (XVIb) were envisaged for the purpose. When the structure of patchouli alcohol was revised to III, it became apparent that the synthetic routes from keto ester (I) *via* XVb or XVIb to patchouli alcohol were no longer feasible. However, some degradation experiments on patchouli alcohol were carried out and we give below some of the relevant results obtained during this work.

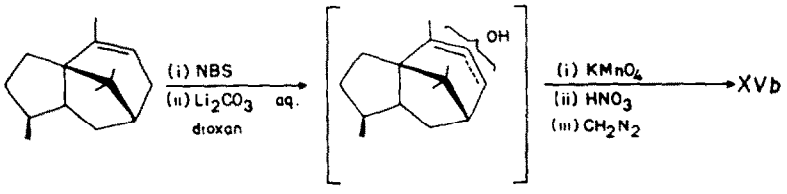


XVa, R = H
XVb, R = Me



XVIa, R = H
XVIb, R = Me

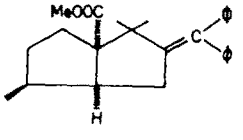
Since the known procedure[2] for the degradation of patchouli alcohol to XVa, did not, in our hands, furnish workable yields of XVa, an alternative procedure (XVII → XVIII → XVb) was worked out giving XVb in an overall yield of 7–10% from the patchoulene mixture[2] [containing ~65% α-patchoulene (XVII)].



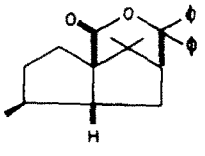
XVII XVIII

The diacid XVIa was obtained from the same patchoulene mixture, by its ozonolysis followed by nitric acid oxidation. The structure of the product, $C_{14}H_{22}O_4$, m.p. 242–244° is clearly supported by the PMR spectrum (Fig. 4) of its methyl ester.

The availability of dimethyl bisnorpatchoulidicarboxylate (XVb) prompted us to degrade it to keto ester (I) according to the procedure of Büchi *et al.*[2] for direct comparison with our synthetic material. These authors describe a two-stage (Barbier-Wieland degradation) preparation of I from XVb and passing through diphenylethylene (XIX), which was isolated as a solid, m.p. 154–155°, λ_{max}^{EtOH} 227 mμ (ε, 11,200). By following the procedure of these authors a crystalline compound answering the above characteristics could be easily obtained. However, ozonolysis of this compound failed



XIX



XX

in our hands and the product was recovered unchanged. As a matter of fact Büchi *et al.*[2] state that chromic acid oxidation of XIX could not be affected and the cleavage

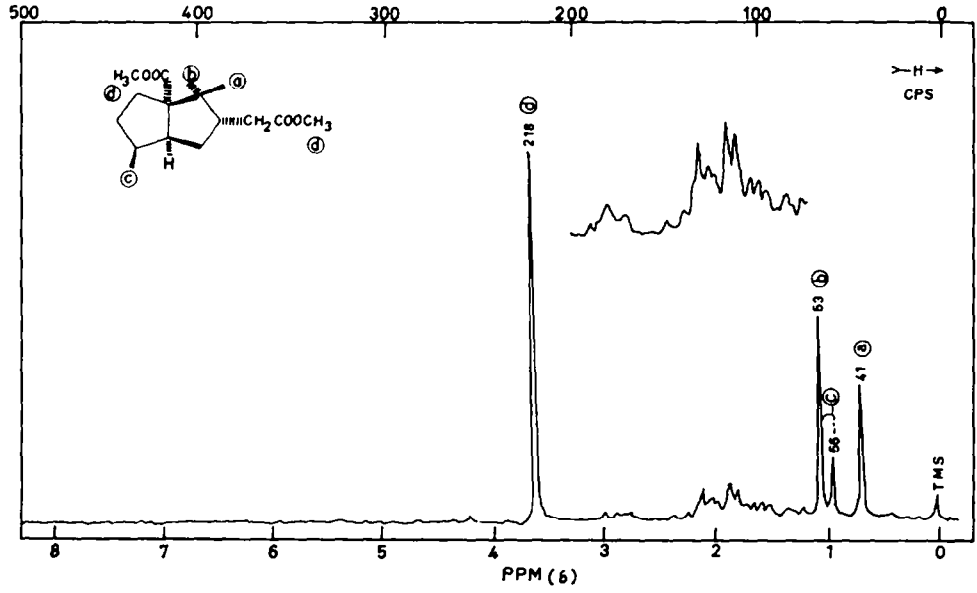


FIG. 4 PMR spectrum of dimethyl norpatchoulidicarboxylate (XVIb)

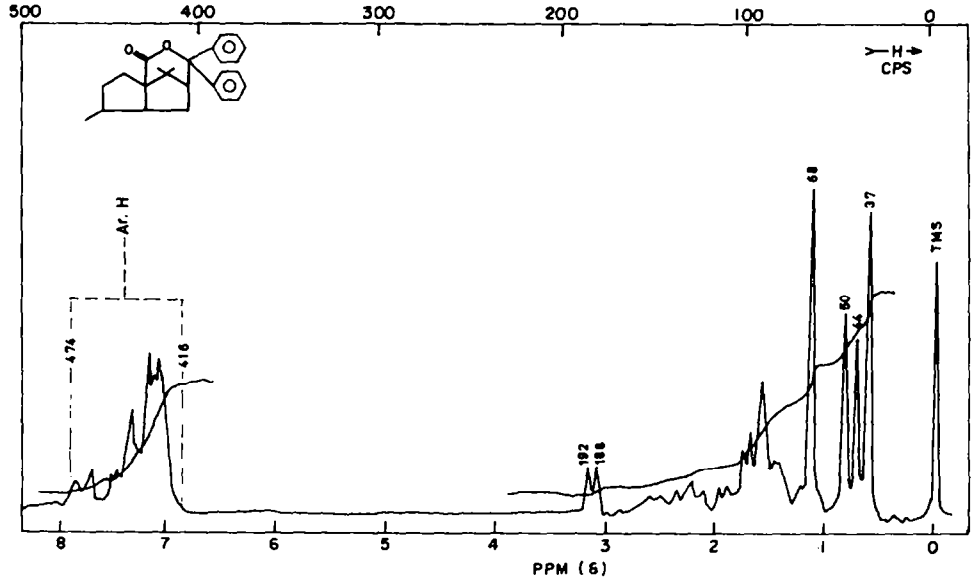


FIG. 5 PMR spectrum of δ-lactone (XX)

was ultimately achieved by ozonolysis under drastic conditions. In view of this and the abnormally low UV absorption[31] of the compound, structure XIX appeared unreliable, a contention which was proved by a study of its PMR spectrum (Fig. 5). As expected on mechanistic considerations,[32] the spectrum clearly indicates a δ-lactone

[31] Normal value λ_{max} 250 mμ: F. E. King and G. Jones, *J. Chem. Soc.* 658 (1955); J. D. Cocker and T. G. Halsall, *Ibid.* 4262 (1956).

[32] e.g. cf. G. Stork and R. Berslow, *J. Amer. Chem. Soc.* **75**, 3291 (1953).

(XX). However, XIX and XX cannot be distinguished on the basis of combustion analysis or IR spectrum.

EXPERIMENTAL

All the b.ps are uncorrected. M.ps were determined on a Koffler hot stage microscope and are uncorrected. All solvent extracts were finally washed with brine, before drying (Na_2SO_4).

IR spectra were taken on a Perkin–Elmer infracord (model 137E) and Perkin–Elmer infrared spectrophotometer (model 221) either as smears (liquids) or in nujol (solids), unless stated to contrary. GLC analyses were carried out on "Aerograph" (model A-350-B) or on a Perkin–Elmer vapour fractometer (model 154D) using H_2 as carrier gas.

Synthesis of keto ester XII

Diethyl α-methyladipate.[33–36] Diethyl adipate (50·5 g, 0·25 mole) was added to a suspension of NaH (50%; 14·6 g, 0·3 mole) in benzene (300 ml). The flask was fitted with a reflux condenser the top of which, through a $CaCl_2$ guard, was connected to a Hg pop valve. The reaction was started by adding a small amount of EtOH (1 ml) followed by gentle warming. Within a short time a vigorous reaction started, which was kept under control by occasional cooling in an ice-bath. When evolution of H_2 ceased, the contents of the flask were refluxed (water bath) for 5 hr. Benzene–EtOH mixture (90 ml) was distilled off from the reaction mixture in a stream of N_2 and freshly distilled MeI (60 g, 0·4 mole) was added and the mixture left at room temp till the solid cake had completely dissolved (swirling was required to break the cake in the beginning). The reaction mixture was next refluxed (18 hr), cooled to room temp and dry EtOH (75 ml) and Na (1 g) added. After the complete dissolution of Na, the product was refluxed for 90 min, cooled, acidified with aqueous AcOH (1:1) and the product worked up as usual. Removal of solvent and fractionation furnished the desired diethyl α-methyladipate: b.p. 101–102°/1·2 mm, n_D^{25} 1·4290, yield 39·0 g (73% based on diethyladipate). The IR spectrum of the product was identical with that of the product prepared by the ethoxide cleavage of pure 2-methyl-2-carbethoxy-cyclopentanone.

2-Carbethoxy-5-methylcyclopentanone (V).[6] This was prepared following essentially the directions of Jones and Linstead.[6] To the pulverized Na (8·3 g, 0·35 g atom) in dry benzene (150 ml) was added diethyl α-methyladipate (50 g, 0·23 mole) in one lot. The reaction was started by adding dry EtOH (1 ml) followed by gentle warming. A brisk reaction started with the evolution of H_2. When the evolution of H_2 had subsided, the reaction mixture was heated (waterbath) under reflux for 21 hr and then worked up to give the desired keto ester: b.p. 80–81°/1·5 mm, n_D^{25} 1·4451, yield 28·5 g (73%). IR spectrum: >=O 1751, 1721 cm^{-1}.

If NaH was substituted for Na dust in the above experiment the yield was improved to 88%.

Ethyl 2-carbethoxy-2-(α-methylpropionate) 5-methyl-cyclopentanone (VI).[6] The above keto ester (42·5 g, 0·25 mole) was added slowly to a well-stirred suspension of pulverized Na (6·9 g, 0·32 g atom) in dry toluene (200 ml) at 1–4° (ice-bath) and then allowed to attain room temp (~28°). The reaction mixture was then heated on a steam bath for 3 hr and later in an oil bath (110–115°) for 1 hr. The product was cooled to 3–5° (ice bath) and ethyl α-bromopropionate (54·3 g, 0·3 mole) was added dropwise under brisk stirring. After the addition, the reaction mixture was allowed to attain room temp and heated under reflux (5 hr) in an oil bath. The product was chilled (ice-salt bath) and water (150 ml) was added slowly under stirring and the whole worked up in the usual manner, the final extracts being washed with aqueous AcOH. The solvent was removed (under suction) and the product fractionated to give the desired keto ester (VI): b.p. 136–138°/2·5 mm, n_D^{25} 1·4540, yield 53·1 g (80%). IR spectrum: >=O 1751, 1727 cm^{-1}.

3-Methyl-1-carbethoxy-2-carbethoxymethyl-2-hydroxycyclopentyl-α-propionic acid lactone (VIII). To a solution of EtMgBr, prepared from Mg (5·8 g, 0·24 g atom) and EtBr (30 g, 0·27 mole) in absolute ether (200 ml) under N_2, ethoxyacetylene[37,38] (15·4 g, 0·22 mole) in dry ether (100 ml) was

[33] R. Cornubert and C. Borrel, *Bull. Soc. Chim. Fr.* [4], **47**, 301 (1930).
[34] L. Bouveault and R. Locquin, *Bull. Soc. Chim. Fr.* [4], **3**, 441 (1908).
[35] L. Bouveault and R. Locquin, *Bull. Soc. Chim. Fr.* [4], **3**, 432 (1908).
[36] W. Dieckmann, *Liebig's Ann.* **317**, 69 (1901).
[37] G. Eglinton, E. R. H. Jones, B. L. Shaw and M. C. Whiting, *J. Chem. Soc.* 1860 (1954).
[38] E. R. H. Jones, G. Eglinton, M. C. Whiting and B. L. Shaw in *Organic Syntheses* Vol. **34**; p. 46. J. Wiley, New York (1954).

added slowly with brisk mechanical stirring. When the evolution of ethane ceased, dry thiophene-free benzene (100 ml) was added to the milky suspension of ethoxyacetylene magnesium bromide to form a clear solution. The reaction flask was cooled (ice-salt) and refilled with fresh dry N_2. The keto ester (VI; 27·0 g, 0·1 mole) in benzene (100 ml) was then added slowly, dropwise (2 hr), under brisk stirring. A light brown colour developed which deepened as time lapsed. Stirring was continued for 5 hr at this temp (ice-salt) and the reaction mixture then left overnight (12 hr) at room temp (~25°). The stirring was repeated for another 2 hr under cooling of an ice-salt bath and the complex decomposed by adding cold saturated NH_4Cl aq (200 ml). The ether–benzene layer was separated and washed with water (75 ml × 2). The combined aqueous portions were thoroughly extracted with ether (50 ml × 5) and the extracts combined with the ether–benzene layer, washed with brine (50 ml × 3), dried and the solvent removed. The residue was dissolved in peroxide-free dioxan (200 ml) and H_2SO_4aq (20 ml, ~3·6N H_2SO_4) added. There was immediate evolution of heat, but the reaction did not become vigorous. The hydration was allowed to proceed (18 hr) at room temp and then excess H_2SO_4 was neutralized with 10% $NaHCO_3$ aq. Most of the dioxan–water was removed under suction at 74–76°, water (100 ml) added to the residue and the organic material thoroughly extracted with ether (50 ml × 6). The extract was washed with water (50 ml × 2), dried and the solvent removed. The dark brown residue (25·2 g), was rapidly distilled (free flame) through a short (5 cm) Vigreux column at <1 mm to give a yellow oil (19·0 g) which was fractionated:

Fr. No.	b.p./mm	n_D^{30}	Yield (g)
1	80–132°/0·7	1·4524	4·36
2	132–170°/0·6 mostly 157–162°/0·6	1·4759	12·10
3	158–160°/0·6 (middle cut of Fr. 2)	1·4748	0·83

Fractions 2 and 3 constituted the desired lactone (VIII). Fr. 3 was analysed: (Found: C, 61·62; H, 7·30. $C_{16}H_{24}O_4$ requires: C, 61·53; H, 7·70%).

Ethyl 2-carbethoxy-2-(α-methyl-propionate) 5-methyl-cyclopentylidene acetate (IXb). A mixture of the above γ-lactone (12·0 g, 0·038 mole), MeOH (500 ml) and 10% NaOH aq (30 ml, 0·075 mole) was heated (waterbath) under reflux for 2½ hr under protection of CO_2 (KOH guard tube). Most of the MeOH was removed under suction (water pump) at a bath temp ≯50°. Water (100 ml) was added to the residue and the organic material extracted with ether (40 ml × 3). The combined ether extract was washed with 10% $NaHCO_3$aq (25 ml × 1), water and dried. Removal of solvent gave a neutral liquid (0·8 g) which was not investigated further.

The alkaline washings and the original aqueous portions were combined, acidified with HClaq and the product taken up in ether (50 ml × 4). The extract was washed with water (20 ml × 2), dried and treated with a slight excess of ethereal solution of diazomethane. After 2 hr the excess diazomethane was destroyed by the addition of a few drops AcOH and worked up to give a mobile liquid which was fractionated:

Fr. No.	b.p./mm	n_D^{30}	Yield (g)
1	Up to 121°/0·6	1·4560	0·54
2	121–135°/0·6 mostly 132–133°/0·6	1·4635	8·62
3	132–133°/0·6 (middle cut of Fr. 2)	1·4642	0·68

Fractions 2 and 3 constituted the desired product (IXb). Fraction 3, λ_{max}^{EtOH} 222 mμ (log ε 3·92), was analysed: (Found: C, 61·9; H, 7·85. $C_{17}H_{26}O_6$ requires: C, 62·5; H, 7·97%).

Ethyl 2-carbethoxy-2 (α-methyl propionate) 5-methylcyclopentyl acetate (X)—*Preparation of catalyst*—Rhodium chloride (1·0 g), chloroplatinic acid (0·52 g) and $NaNO_3$ (20 g) were mixed in a 100 ml Pyrex beaker. Water (5 ml) was added and the mixture well stirred to an almost homogeneous mass. The contents of the beaker were first heated slowly to dryness with a free flame and then heated strongly until fusion started. Heating was continued at this temp until evolution of fumes ceased; heat was maintained for an additional 20 min and the product worked up to give the catalyst as a pale brown powder, yield 0·75 g.

Hydrogenation. The unsaturated ester (IXb; 2·45 g, 0·0075 mole) was hydrogenated at room temp (27°) and press (710 mm) in glacial AcOH (50 ml) over pre-reduced Rh–Pt (3:1) catalyst. The H_2 uptake ceased after absorption of 194 ml H_2 (0·99 mole equiv of gas) in 10 hr. The reaction mixture yielded X as a mobile liquid: b.p. 143–145°/0·6 mm, n_D^{30} 1·4610, d_4^{30} 1·0842, M_D 83·03 (Calc. 83·49), yield 2·35 g (95%). (Found: C, 61·98; H, 8·82. $C_{17}H_{28}O_6$ requires: C, 62·20; H, 8·60%.) IR spectrum: ester 1739–1718 cm^{-1}.

2,6-*Dimethyl*-3-*oxo*-7-*carbomethoxybicyclo*[0,3,3]*octane* (XI). To compound X (5·43 g, 0·016 mole) in dry benzene (50 ml), NaH (50%; 2·3 g, 0·48 mole) was added. The reaction was started by adding a few drops of anhydrous EtOH followed by heating on a steam bath resulting in a brisk reaction with evolution of H_2. When the evolution of gas ceased, the contents were heated (waterbath) under reflux (6 hr) in an atmosphere of H_2 (evolved). The reaction mixture was worked up as usual, dried and the solvent removed. The residue, so obtained, was taken up in AcOH (25 ml), HClaq (1:2, 75 ml) added and the product refluxed for 3 hr in the atmosphere of evolved CO_2. Most of HCl–AcOHaq was removed under red. press. from a steam bath. The residue was diluted with water (20 ml) and extracted with ether (50 ml × 3). The combined ether extracts were washed with 5% NaOHaq (10 ml × 5) and the alkaline extracts acidified with HClaq. The product was extracted with ether (20 ml × 5) and the combined extracts dried and treated with a slight excess of ethereal diazomethane and worked up to give an oil which was fractionated:

Fr. No.	b.p./mm	n_D^{30}	$FeCl_3$ test	Yield (g)
1	96–105°/0·5 mostly 96–97°/0·5	1·4660	−ve	1·40
2	105–130°/0·5 mostly 130°/0·5	1·4684	−ve	1·42

Fraction 1 (1·40 g) was converted into its *semicarbazone* (pyridine method) m.p. 172–176° (dec), yield 1·15 g; this was recrystallized from EtOH to give a product (0·95 g), m.p. 176–178° (dec). (Found: N, 15·70. $C_{13}H_{21}O_3N_3$ requires: N, 15·53%.)

A mixture of pure, powered semicarbazone (1·25 g), oxalic acid (3·6 g), water (20 ml) and toluene (35 ml) was refluxed with brisk stirring for 3 hr and then worked up to yield pure XI, b.p. 94°/0·6 mm, n_D^{30} 1·4690, yield 0·896 g. (Found: C, 68·25; H, 8·59. $C_{12}H_{18}O_2$ requires: C, 86·50; H, 8·57%.)

2,2,6-*Trimethyl*-3-*oxo*-1-*carbomethoxy-bicyclo* [0,3,3]octane (XII). To a solution of XI (330 mg, 1·57 mmole) in ether (10 ml), an ether solution of trityl sodium[39] (0·13N; 20 ml, 2·6 mmole) was added slowly, under brisk stirring, in an atmosphere of N_2. The reaction mixture was stirred for 1 hr and a faint red colour, indicating the presence of slight excess of reagent, persisted. At this stage MeI (3 ml) was added in one lot and stirring continued for 18 hr at room temp (27°). Excess MeI and solvent were removed (under suction) at room temp, water (10 ml) added to the residue and the product extracted with ether (15 ml × 5). The extract was washed with water (10 ml × 2) and dried. Removal of solvent furnished a product (1·32 g) which was chromatographed over neutral alumina[40]/II (15 g, 20 cm × 1 cm):

Frac. 1: Pet. ether (50 ml × 3)	902 mg of hydrocarbons
Frac. 2: Pet. ether (25 ml × 2)	28 mg of XII
Frac. 3: Pet. ether/50% benzene (25 ml)	217 mg of XII
Frac. 4: Pet. ether/50% benzene (25 ml × 3)	27 mg of XII
Frac. 5: Benzene–2% MeOH (25 ml × 4)	64 mg?

Fractions 2–4 were combined and distilled at a temp below 150° (bath) at 1 mm. The mobile distillate was redistilled to give pure XII, b.p. (bath) 108–113°/0·5 mm, yield 187 mg (53%). It showed a single peak in GLC (20% diethylene glycol polysuccinate, 200°, 2 metre). (Found: C, 69·61; H, 8·84. $C_{13}H_{20}O_3$ requires: C, 69·61; H, 8·92%.)

Degradation experiments on patchouli alcohol

Patchoulenes (II)[3]. Patchouli alcohol (6·12 g, 0·027 mole) in dry pyridine (100 ml) was treated with freshly distilled $POCl_3$ (70 ml) and the contents gently refluxed (6 hr) under anhydrous conditions.

[39] W. B. Renfrow and C. R. Hauser in *Organic syntheses* Col. Vol. 2; p. 607. Wiley, New York (1943).

[40] E. Lederer and M. Lederer, *Chromatography* p. 24. Elsevier, London (1957).

The reaction mixture was worked up[3] to yield an olefinic mixture, b.p. 103–105°/2·5 mm, n_D^{30} 1·5034, yield 4·83 g (84%). Its GLC (column: 20% carbowax 1500 on celite, 2 metre; temp 160°; gas press: 15 psi) exhibited 4 peaks: γ-patchoulene (peak No. 1, 13%), α-patchoulene (peak No. 3, 69%) and β-patchoulenes (peak No. 2 and 4, 16%) with relative retention times of 1, 1·6, 1·4 and 2·22 min respectively.

Dimethyl bisnorpatchoulidicarboxylate (XVb). Patchoulenes (5·1 g, 0·025 mole), N-bromosuccinimide (4·9 g, 0 027 mole), benzoyl peroxide (250 mg) and dry CCl_4 (75 ml) after heating under reflux for 2 hr yielded the crude bromide as a brown liquid. This was dissolved in pure dioxan (80 ml), water (20 ml) and Li_2CO_3 (0·93 g, 0·012 mole) was added and the mixture refluxed (18 hr) on a steam bath. The unreacted Li_2CO_3 (~120 mg) was filtered off and the filtrate diluted with water (50 ml) and extracted with ether (50 ml × 2). The extract was washed with water (30 ml × 2) and dried. Removal of solvent left a brown residue which was distilled, b.p. 88–120°/0·5 to 0·8 mm, yield 4·57 g.

The above product (4·57 g) was suspended in aqueous acetone (60 ml; 5 parts acetone and 1 part water) and powdered $KMnO_4$ (13·4 g, 0·084 mole) was added, in small lots of about 1 g each, under brisk stirring during 1 hr. Stirring was continued for 4 hr and the precipitated MnO_2 was filtered off and washed successively with water (25 ml × 2), ether (25 ml × 2) and 10% Na_2CO_3aq (15 ml × 1). The combined filtrates were acidified with HClaq and the two layers separated, and the lower aqueous layer extracted with ether (25 ml × 2). The ether layer was extracted with 10% Na_2CO_3 aq and the combined extracts acidified with HClaq. The acidic material, so liberated, was extracted with ether (25 ml × 4), washed with water (10 ml × 2) and dried. Removal of solvent furnished a gum (2·54 g).

Water (6 ml) was added to the above gummy acid (2·54 g) and heated under reflux in an oil bath (138 ± 2°). Nitric acid (d = 1·42, 15 ml) was added slowly and cautiously (from the top of the condenser) to this refluxing mixture. After 30 min, more HNO_3 (3 ml) was added and refluxing continued for another 30 min. The reaction mixture was allowed to attain room temp and then poured into cold water (50 ml). The resulting milky suspension was extracted with ether (25 ml × 4) and the extract washed with small portions (~7 ml) of water until the washings were almost neutral. The ether solution was dried, esterified (diazomethane) and processed as usual. Removal of solvent furnished a mobile liquid which was distilled, b.p. 150–172°/4 mm, yield 1·3 g. GLC of this material indicated the presence of 4 components out of which the required compound (peak No. 3) constituted the major (60%) portion which was isolated from this mixture by preparative GLC (column: 9 ft × 1″, 20% diethylene glycol polysuccinate on Chromosorb W; 200°; N_2, 25 lbs/□″). The product was distilled: b.p. 131°/2 mm, n_D^{30} 1·4750, yield 560 mg. (Found: C, 67·11; H, 9·16. $C_{15}H_{24}O_4$ requires: C, 67·13; H, 9·02%.) IR spectrum (CCl_4): ester 1738–1725 cm^{-1}. PMR spectrum: two quaternary methyls (two 3H singlets and 47 and 63 c/s); one CH_3—CH (a 3H doublet centred at 56 c/s, J = 6 c/s); two $COOCH_3$ (two 3H singlets at 215 and 217 c/s). Its IR spectrum (CCl_4) was superimposable on that of an authentic sample.[2]

Dimethyl nor-patchouli-dicarboxylate (XVIb). A solution of patchoulenes (8·1 g, 0·04 mole) in purified AcOEt (100 ml) was ozonized at −10° (ice–salt) with a current of ozonized O_2 (output of O_3 ~80 mg/hr) till no more O_3 was absorbed (10 hr; KI–AcOH test). The solvent was removed by suction at a temp below 30°. The residual pale yellow ozonide was taken up in AcOH (30 ml), mixed with 1% H_2O_2aq (35 ml) and left at room temp for 90 min. The mixture was then heated at ~60° for 1 hr and finally on a steam-bath for 2 hr. The reaction mixture was worked up to give 3·80 g of an acidic product.

The above material (3·8 g) was oxidized with HNO_3, as for XVb. The resulting gum (2·2 g) was dissolved in formic acid (5 ml) and stored at ~0° for 2 days, and the separated crystals filtered off, washed with a little formic acid and dried, m.p. 238–242°, yield 180 mg. Recrystallization from EtOH–pet. ether yielded pure XVIa, m.p. 242–244°, yield 140 mg. (Found: C, 65·91; H, 8·86. $C_{14}H_{22}O_4$ requires: C, 66·14; H, 8·66%.) Mixed m.p. with an authentic sample[2] of XVa m.p. 225–227°) was 190–197°.

Its *dimethyl ester* from diazomethane (Found: C, 68·14; H, 9·39. $C_{16}H_{26}O_4$ requires: C, 68·05; H, 9·28%) showed in the GLC (column: 20% diethylene glycol polysuccinate on Chromosorb W, 5 ft; temp, 200°; flow, 50 ml/min) a single peak of +97% purity; the relative retention times of XVb and XVIb were 1 and 1·88 min under the above conditions.

Acknowledgemnet—The authors are grateful to Prof. G. Büchi for the supply of an authentic sample of bisnorpatchouli dicarboxylic acid (XVa) and, comparison of our synthetic keto ester (XII) with his product.