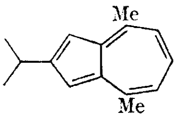
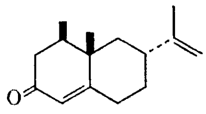
The Total Synthesis of Racemic Isonootkatone (α-Vetivone)

By JAMES A. MARSHALL,* HERMANN FAUBL, and THOMAS M. WARNE, JUN.
(*Department of Chemistry, Northwestern University, Evanston, Illinois* 60201)

THE recent work of Endo and de Mayo,[1] and independent findings in our own laboratory[2] have shown that α-vetivone (XIV), long regarded as a relative of vetivazulene (I), must now be formulated as an isomer of nootkatone (II).[3] For this reason we have suggested that this compound be renamed isonootkatone.[2] We now present a total synthesis of racemic isonootkatone by a route (Chart) which fully confirms the suggested structure.



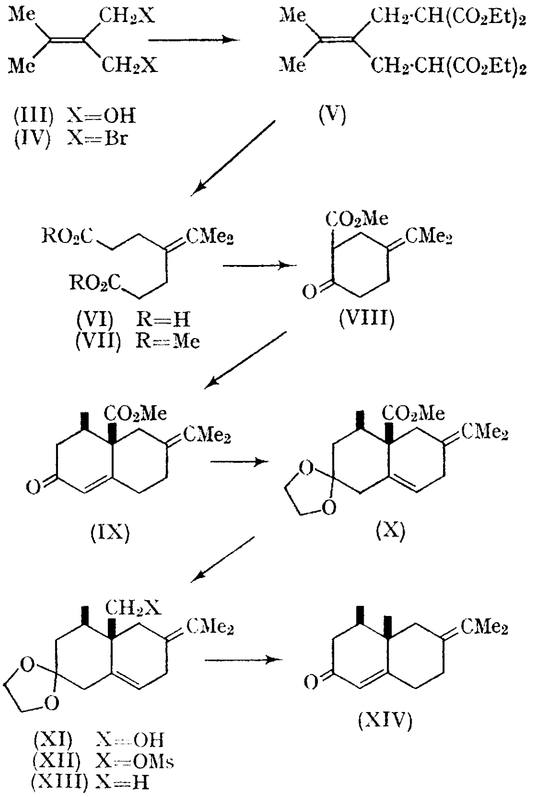
(I)



(II)

Diethyl isopropylidenemalonate,[4] upon reduction with lithium aluminium hydride afforded the corresponding diol (III) [b.p. 78° at 0·2 mm.; δ (CCl_4) 4·18 (OH), 4·14 (CH_2·O), and 1·74 p.p.m. (vinyl CH_3)†]. The dibromide, a powerful lachrymator obtained by treating diol (III) with PBr_3 in ether–hexane–pyridine, yielded the tetra-ester (V) *via* alkylation with an excess of diethyl sodiomalonate in 1,2-dimethoxyethane. Subsequent hydrolysis and decarboxylation converted (V) into diacid (VI) and this compound, in turn, gave the corresponding diester (VII) [b.p. 87—95° at 0·2—0·3 mm.; $\lambda_{\max}^{(\text{film})}$ 5·76 (ester CO), 8·35, 8·53, 9·63, and 10·10 μ.]. Dieckmann cyclization of the diester with sodium hydride in 1,2-dimethoxyethane afforded methyl 5-isopropylidene-2-oxocyclohexanecarboxylate (VIII) [b.p. 67—75° at 0·03—0·04 mm.; δ(CCl_4) 12·13 (enol O*H*), 3·76 (OC*H*$_3$), and 1·68 p.p.m. (two vinyl C*H*$_3$'s)]. Robinson annelation of this cyclic β-keto-ester occurred smoothly upon treatment first with *trans*-pent-3-en-2-one[5] in the presence of 0·1 molar equivalent of methanolic sodium methoxide at 0° to effect the Michael addition, and then with an excess of the same base at room temperature for eighteen hours to complete the aldol cyclization. The resulting product [b.p. 65—100° (bath temperature) at 0·05—0·1 mm.; $\lambda_{\max}^{(\text{film})}$ 5·79 (ester CO), 5·99 (ketone CO), 6·13 (C=C), 8·18, 8·48, 9·10, 10·05, 11·45, and 11·77 μ; δ(CCl_4) 5·90 (vinyl H), 3·67 OC*H*$_3$), 1·70, 1·76 (two vinyl C*H*$_3$'s), and 1·02 p.p.m. (C*H*$_3$ doublet, *J* 6 c./sec.)] solidified upon refrigeration and appears to be mainly the bicyclic keto-ester (IX). In our initial synthetic planning we felt that steric and electronic factors in the aforementioned Michael addition would favour the transition state orientation depicted in (XV). This arrangement leads ultimately to the bicyclic keto-ester (IX) with a *cis*-relationship between the methoxycarbonyl and methyl groups. The findings reported here tend to confirm our analysis. Additional work relating to this point is currently in progress.

CHART



Unsaturated ketone (IX) afforded the ethylene ketal derivative (X) [$\lambda_{\max}^{(\text{film})}$ 5·79 (ester CO), 8·18, 8·83, 9·20, 10·03, 10·49, 11·05, and 12·64 μ;

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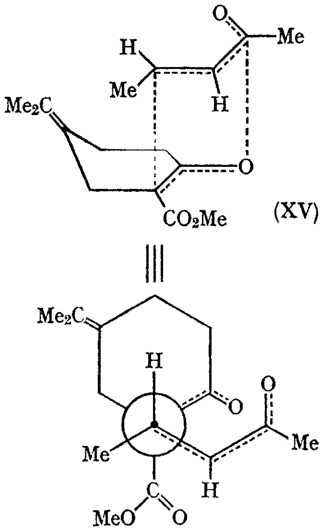
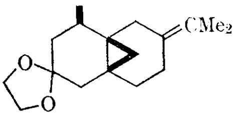
† With Me_4Si as internal reference throughout.

$\delta(\mathrm{CCl_4})$ 5·42 (vinyl H, $w_{h/2}$ 8 c./sec.), 3·88 ($\mathrm{OC}H_2\cdot\mathrm{C}H_2\mathrm{O}$), 3·62 ($\mathrm{OC}H_3$), 1·62, 1·72 (two vinyl $\mathrm{C}H_3$'s), and 0·98 p.p.m. ($\mathrm{C}H_3$ doublet, *J* 6 c./sec.)] upon treatment with ethylene glycol and a trace of toluene-*p*-sulphonic acid in refluxing benzene (Dean–Stark water trap). Reduction of the ester (X) with ethereal lithium aluminium hydride gave the alcohol (XI) [$\lambda_{\max}^{(\mathrm{film})}$ 2·92 (OH), 8·90, 9·16, 9·50, 10·10, 10·50, and 12·58 μ; $\delta(\mathrm{C_5H_5N})$ 5·55 (vinyl H, $w_{h/2}$ 7 c./sec.), 5·03 (OH), 3·88 ($\mathrm{C}H_2\mathrm{O}$ and $\mathrm{OC}H_2\cdot\mathrm{C}H_2\mathrm{O}$), 1·75, 1·60 (vinyl $\mathrm{C}H_3$'s), and 1·18 p.p.m. ($\mathrm{C}H_3$ doublet, *J* 6 c./sec.)]. The methanesulphonate derivative (XII) yielded a mixture of the S–O and C–O cleavage products (XI) and (XIII) upon reduction with lithium in ammonia–ethanol. Racemic isonootakatone (XIV) could be readily isolated by chromatography on silica gel after hydrolysis of the crude ketal mixture. The infrared and n.m.r. spectra and the gas-chromatographic retention time of the material thereby secured exactly matched those of natural isonootkatone isolated from vetivert acetate.[2]



(XV)

Treatment of the methanesulphonate derivative (XII) with ethereal lithium aluminium hydride led to none of the desired hydrogenolysis product (XIII). A cyclopropane derivative [$\delta(\mathrm{CCl_4})$ 3·50 ($\mathrm{OC}H_2\cdot\mathrm{C}H_2\mathrm{O}$), 1·58 (vinyl $\mathrm{CH_3}$), 0·98 ($\mathrm{C}H_3$ doublet, *J* 6 c./sec.), and 0·25 p.p.m. (cyclopropane $\mathrm{CH_2}$, centre of AB quartet)], presumably (XVI), was the predominant product of this reduction.



(XVI)

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[1] K. Endo and P. de Mayo, *Chem. Comm.*, 1967, 89.
[2] J. A. Marshall and N. H. Andersen, *Tetrahedron Letters*, 1967, 1611.
[3] W. D. Macleod, jun., *Tetrahedron Letters*, 1965, 4779.
[4] A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, 1938, **60**, 2644.
[5] H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, 1966, **31**, 2138.