The Total Synthesis of Racemic Patchouli and *epi*-Patchouli Alcohol[†]

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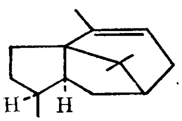
THE elegant conversion of homocamphor to α-patchoulene (I)[1] constitutes a formal total synthesis of the well known sesquiterpene, patchouli alcohol (II), since the transformation of (I) → (II) had previously been effected.[2] The latter transformation involved, at one stage, a novel and fortuitous rearrangement of oxido-α-patchoulene to a hydroxy-derivative of (II).

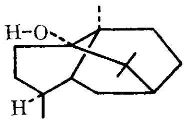
We report a short, direct, total synthesis of racemic patchouli alcohol. The synthesis illustrates the synthetic potentialities inherent in the generalized reaction, (III) → (IV) and suggests the effect of stereochemical factors on this reductive cyclization process.[3] We also report the preparation of racemic *epi*-patchouli alcohol, unknown from natural sources.

Condensation of methyl vinyl ketone with (V)[4] afforded the adduct (VI) (93%)[‡,§] [b.p. 85—87°/0·2 mm., the dinitrophenylhydrazone (DNP) m.p. 186—188°] which was quantitatively reduced (Pd–C) to the dihydro-derivative, (VII) (DNP, m.p. 144—156°). Equilibration (sodium methoxide–methanol) gave a 30 : 70 mixture of the epimers (VII) : (VIII) from which the latter (m.p. 42—43°) was obtained by fractional crystallization from hexane. Repetition of the epimerization twice more gave (VIII) in 65% overall yield from (VII).

Reaction of (VIII) with vinyl-lithium in tetrahydrofuran provided the alcohol (IX), which was cleanly converted (HCl–$CHCl_3$) into a chloride (X), whose allylic relationship with its progenitor is clearly revealed in its n.m.r. [τ (CCl_4) 4·59 (1H, t, *J* 8·5), 6·02 (2H, d, *J* 8·5 c./sec.), 8·50 (3H, br s)] spectrum. Attempted catalytic hydrogenation of the double bond in (X) also caused extensive hydrogenolysis of the chlorine function. Thus, reaction of (X) with H_2–Rh–Al_2O_3 gave[5] primarily a mixture of the ketones, (XI) and (XII), which at this stage were separated analytically (gas chromatography).

Solvolysis (H_2O–dioxan) of (X) yielded (85%) the alcohol (XIII) which was hydrogenated


(I)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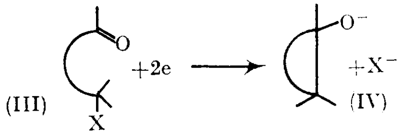

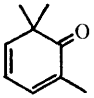
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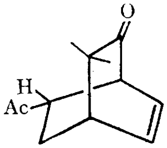
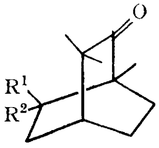
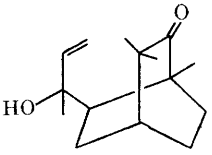


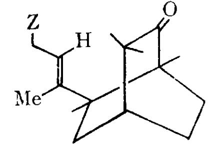
(VI)



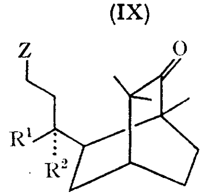
(VII) R^1=H, R^2=Ac
(VIII) R^1=Ac, R^2=H



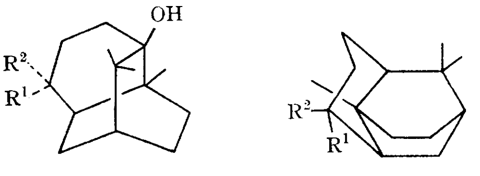
(IX)



(X) Z=Cl
(XIII) Z=OH



	R^1	R^2	Z
(XI)	Me	H	OH
(XII)	H	Me	H
(XIV)	H	Me	OH
(XV)	Me	H	OH
(XVI)	H	Me	Br
(XVII)	Me	H	Br



(II) R^1 = Me, R^2 = H
(XVIII) R^1 = H, R^2 = Me.

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[‡] All numbered compounds (VI)—(XVII), with the exception of the labile (IX), (X), XVI), and (XVII), gave combustion analyses within 0·3% of theory. All compounds gave parent peaks in their mass spectra in accord with theory. The structural assignments are, in every case, also in accord with the i.r. and n.m.r. spectra.

[§] The orientation as well as the *endo*-configuration (with respect to the ethylene bridge) of the adduct was first assigned by analogy with the results of other Diels–Alder reactions of compound (V) (ref. 4). Epimerization of (VI) gave a 1 : 1 ratio of *endo* : *exo* isomers. The stereoselectivity of the dihydro-stage is ascribed to a non-bonded 2,6-repulsion of the *endo*-hydrogen by the acetyl group, present in (VII) but absent in (VIII).

(Pd–C–EtOAc–$NaNO_2$)[6] to a mixture of saturated alcohols, with only minor losses due to hydrogenolysis of the hydroxy-function. The epimers, (XIV) (phenylurethane m.p. 145°) and (XV) (phenylurethane m.p. 165°) were obtained by chromatography on Florisil. Their assignments follow from the subsequent reactions.

Treatment of (XIV) with PBr_3 gave (92%) the bromo-ketone, (XVI) which with sodium in tetrahydrofuran gave the ketone (XII), and traces of an oily saturated carbinol, whose i.r. and mass spectra and v.p.c. retention time are similar to, but discernably different from, those of authentic patchouli alcohol. We assign structure (XVIII), 1-*epi*-patchouli alcohol to this compound.

Similar treatment of the bromo-ketone (XVII) [85% from carbinol (XV) and PBr_3] gave (55%) a 1 : 1 mixture of two isomers, readily separable by preparative gas chromatography. The compound of lower retention time was (XI), whilst the other, m.p. 39—40°, was identified as (±)-patchouli alcohol (II) by the complete correspondence of its i.r., n.m.r., and mass spectra with those obtained from an authentic sample of the (−)-enantiomer, furnished by Professor Buchi.

The ratio of the reductive cyclization to reductive cleavage¶ varies significantly in the two bromo-ketones [*ca.* 1 : 1 in the case of (XVII) and 1 : 10 in the case of (XVI)]. Formation of (XVIII) necessitates the creation of two axially oriented methyl groups, mutually disposed in a 1,3-relationship. The formation of patchouli alcohol, (II) involves the generation of one axial methyl group but the particularly serious 1,3-diaxial methyl–methyl repulsion is avoided.

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¶ Examples of reductive cleavage, to the near exclusion of reductive cyclization have previously been reported (see ref. 3*a*). A high-yield reductive cyclization has been reported in an instance which did not involve the creation of any serious non-bonded interactions such as the 1,3-diaxial Me–H interaction present in (II). Also, that case (see ref. 3*b*) involved the use of magnesium rather than sodium as the reducing metal. Reactions of (XVI) and (XVII) with magnesium lead to a high recovery of starting material.

[1] G. Buchi, W. D. McCleod, and J. Padilla O., *J. Amer. Chem. Soc.*, 1964, **86**, 4438.

[2] G. Buchi, R. E. Erickson, and N. Wakabayashi, *J. Amer. Chem. Soc.*, 1961, **83**, 927.

[3] For some early studies dealing with this type of reductive cyclization see: (*a*) H. O. House, J. J. Riehl, and C. G. Pitt, *J. Org. Chem.*, 1965, **30**, 650; (*b*) S. J. Etheredge, Thesis, Columbia University, 1965. For some very recent, conceptually related reactions see: (*c*) P. K. Freeman, V. N. M. Rao, D. G. George, and G. L. Fenwick, *J. Org. Chem.*, 1967, **32**, 3958; (*d*) R. R. Sauers, R. M. Hawthorne, and B. I. Dentz, *ibid.*, 1967, **32**, 4071.

[4] T. L. Brown, D. Y. Curtin, and R. R. Fraser, *J. Amer. Chem. Soc.*, 1958, **80**, 4339.

[5] *Cf.* G. Ham and W. Coker, *J. Org. Chem.*, 1964, **29**, 194.

[6] *Cf.* H. Dart and H. Henbest, *J. Chem. Soc.*, 1960, 3053.