Manool-derived Diterpenic Hydrocarbons and Related Products

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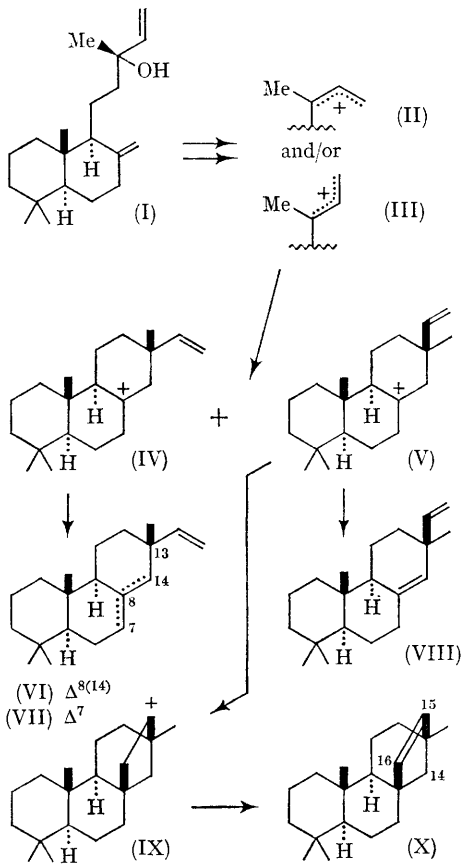
IN continuation of our studies of the total synthesis of diterpenic natural products and in an attempt to simulate the probable route of biosynthesis (*vide infra*) of some tri-[1] and tetra-carbocyclic diterpenes,[2] an investigation of the solvolysis of manool (I) was undertaken.[3]

Heating a formic acid–chloroform (1 : 1) solution of manool (I) under reflux for 3 hr. and lithium aluminium hydride treatment of the resultant mixture of hydrocarbons and esters produced the pimaradiene isomer (XI)[4] (29%), the sandaracopimaradiene isomer (XII)[4] (21%), the rimuene isomer (XIII)[5] (>5%), and a saturated alcohol (11%), m.p. 114—115°, $[\alpha]_D$ −0·019° (*c* 0·11, MeOH), δ($CDCl_3$) 2·90 broad one-proton singlet (hydroxymethine).† The hydrocarbons were identified by comparison with authentic samples, while the alcohol was shown to possess constitution (XIV) by the following reactions. Acetylation yielded the ester (XV), m.p. 81—83°, $[\alpha]_D$ −0·31° (*c* 0·045, MeOH), μ (KBr) 5·75s, δ 4·42 broad one-proton singlet (acetoxymethine), whose lithium aluminium hydride reduction reverted it to the alcohol (XIV). Jones oxidation of the latter yielded ketone (XVI), m.p. 104—105°, o.r.d. (MeOH) negative Cotton effect, μ 5·75s, whose Wolff–Kishner reduction yielded hibane [dihydro-(X)].[6] These facts and the non-identity of the ketone with 15- or 16-ketohibane[6] proved it to be 14-hibone (XVI). Furthermore, its transformation exclusively to alcohol (XIV) on reduction with lithium aluminium hydride and a variety of other hydrides by analogy with the specificity attending hydride reductions of bicyclo[3,2,1]-octan-8-one[7] and its methyl derivative (*vide infra*) suggested the alcohol to be 14α-hibol (XIV).

While no naturally occurring pimaradienes were isolable from the manool (I) formolysis mixture, several could be prepared by simple, chemical conversions of the diene products. In contrast to a previous report,[4] treatment of (XII), (VI), or (VII) with hydrogen chloride in chloroform at 0° yielded an equilibrium mixture of *ca.* 6 : 2 : 1 of the three substances, respectively. Exposure of (XIII)—prepared most efficiently (>50%) by extended formic acid treatment of (XII)—to hydrogen chloride in glacial acetic acid at room temperature and subsequent treatment with ethanolic potassium hydroxide led to rimuene (XVII)[5,8] (>5%), identical with an authentic specimen. In view of the previous total synthesis of manool (I)[9] these transformations constitute

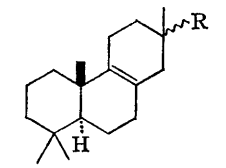
† Satisfactory elemental analyses were obtained for all new compounds.

formal total syntheses of the plant hydrocarbons sandaracopimaradiene (VI),[10,11] isopimaradiene (VII),[12] and rimuene (XVII).[5,8,11,13]

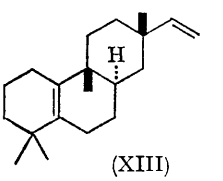


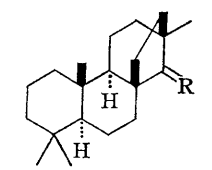
The formation of a *ca.* 1:1 mixture of 13-epimers of tricyclic dienes from the manool formolysis indicated destruction of the asymmetry in the manool (I) side-chain prior to ring formation [*i.e.* the intermediacy of (II) and/or (III)]. This was confirmed by the observation of a room temperature solvolysis of (I) for short reaction time yielding predominantly a mixture of uncyclized allyl formate isomers (XVIII) and (XIX). While the production of the tricyclic formolysis compounds is reminiscent of the likely biosynthesis of the natural hydrocarbons, the origin of the lone tetracyclic product (XIV formate) appears to bear little resemblance to the biosynthesis of its structural relative, hibaene (X).

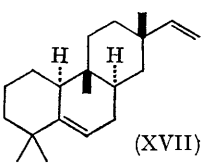
Three explanations of the genesis of the tetracycle can be offered. One, the (I)–(II and/or III)–(V)–(IX)–(XX)–(XIV formate) route, is unlikely in view of the unprecedented nature of a 1,3-hydride shift [(IX)→(XX)] creating a trigonal



(XI) R=β-vinyl
(XII) R=α-vinyl

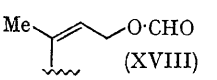




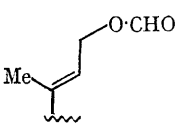


(XIV) R=α-OH,β-H
(XV) R=α-OAc,β-H
(XVI) R=O

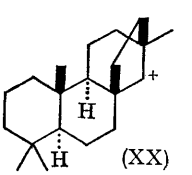
centre at the most strained carbon bridge of a bicyclo[3,2,1]octane system. Furthermore, the necessary intermediacy of cation (V), the conjugate acid of (VIII) and (XI), suggests that these substances also lie on the path to (XIV formate). However none of the latter could be found among the ester products of a formic acid treatment of (XI).



(XVIII)



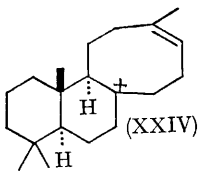
(XIX)



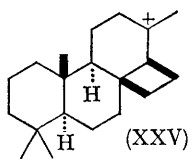
A second explanation, the (XVIII and/or XIX)–(XXI)–(XXII)–(XXIII)–(XX)–(XIV formate) route, proved untenable upon recovery of (XXIII) from its formic acid treatment[14] under conditions identical with those of the manool formolysis. Finally, the most inviting and mechanistically most intriguing interpretation is represented by the (I)–(II)–(XXIV)–(XXV)–(XX)–(XIV formate) route, wherein the extraordinary stereospecificity of the formation of the

fourth ring of the tetracyclic product is attributable to the sterically induced exclusivity of buckling of the cyclo-octenyl moiety toward its α-face in the crucial (XXIV)→(XXV) step. While no direct proof of the preferred, third explanation is available, confirmation of the last steps of the proposed route come from the following study of the solvolysis of a model compound.

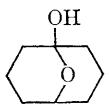
Acetylation of (XXVI)[15] produced the keto-acetate (XXVII) (85%). Treatment of the latter with excess of methylmagnesium iodide and re-acetylation of the product yielded the hydroxy-acetate (XXVIII) (72%), whose exposure to toluene-*p*-sulphonyl chloride in pyridine at 100° led to a mixture (85%) of (XXIX) containing 20% of exocyclic double bond isomer. Hydrolysis of the acetates, followed by treatment with toluene-*p*-sulphonyl chloride in pyridine produced pure sulphonate (XXX) (76%), m.p. 47—48°. Solvolysis of this sulphonate in formic acid in the presence of sodium formate at 75° for 2 hr. followed by lithium aluminium hydride treatment yielded alcohol (XXXI) (71%), m.p. 60—61° (sublimation at *ca.* 45°), δ 3·57 broad one-proton doublet (*J* 4·5 c./sec.) (hydroxymethine). Jones oxidation of the alcohol yielded ketone (XXXII) (92%), μ (neat) 5·75s (semicarbazone, m.p. 226—229°), whose reduction with a variety of hydrides re-liberated the alcohol (XXXI).



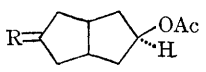
(XXIV)



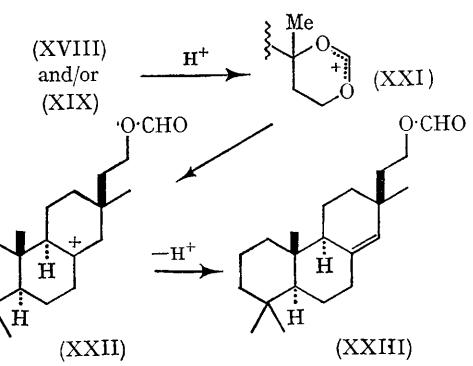
(XXV)



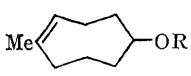
(XXVI)



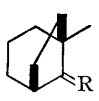
(XXVII) R=O
(XXVIII) R=α-OH,β-Me



(XXII) (XXIII)



(XXIX) R=Ac
(XXX) R=Ts



(XXXI) R=α-OH,β-H
(XXXII) R=O

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[1] L. Ruzicka, *Experientia*, 1953, **9**, 357.
[2] E. Wenkert, *Chem. and Ind.*, 1955, 282.
[3] An earlier study (S. Bory and C. Asselineau, *Bull. Soc. chim. France*, 1961, 1355) was left in an inconclusive state. A related study on agathadiol has been reported by O. E. Edwards and R. S. Rosich, Abstracts of Papers Presented at the 150th Meeting of the Amer. Chem. Soc. (Atlantic City, New Jersey, U.S.A., September 13–17, 1965), 24S.
[4] R. F. Church and R. E. Ireland, *J. Amer. Chem. Soc.*, 1963, **28**, 17.
[5] J. D. Connolly, R. McCrindle, R. D. H. Murray, and K. H. Overton, *J. Chem. Soc.* (*C*), 1966, 273.
[6] Y. Kitahara and A. Yoshikoshi, *Bull. Chem. Soc. Japan*, 1965, **38**, 735.
[7] A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, 1960, **82**, 4299; A. C. Cope, S. Moon, C. H. Park, and G. L. Woo, *ibid.*, 1962, **84**, 4865; C. S. Foote and R. B. Woodward, *Tetrahedron*, 1964, **20**, 687.
[8] R. E. Corbett and S. G. Wyllie, *J. Chem. Soc.* (*C*), 1966, 1737.
[9] D. B. Bigley, N. A. J. Rogers, and J. A. Barltrop, *J. Chem. Soc.*, 1960, 4613; G. Büchi and K. Biemann, *Croat. Chem. Acta*, 1957, **29**, 163; G. Ohloff, *Annalen*, 1958, **617**, 134; *Helv. Chim. Acta*, 1958, **41**, 845; E. Wenkert, J. R. Mahajan, M. Nussim, and F. Schenker, *Canad. J. Chem.*, 1966, **44**, 2575.
[10] R. A. Laidlaw and J. W. W. Morgan, *J. Chem. Soc.*, 1963, 644.
[11] R. E. Corbett and R. A. J. Smith, *J. Chem. Soc.* (*C*), 1967, 300.
[12] H. Erdtman and L. Westfelt, *Acta Chem. Scand.*, 1963, **17**, 1826; E. Wenkert, P. W. Jeffs, and J. R. Mahajan, *J. Amer. Chem. Soc.*, 1964, **86**, 2218 (reference 5c); L. Westfelt, *Acta Chem. Scand.*, 1966, **20**, 2841; P. K. Grant, C. Huntrakul and D. R. J. Sheppard, *Austral. J. Chem.*, 1967, **20**, 969.
[13] For total syntheses of racemic (VI) and (XVII) see R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, 1963, **28**, 6, and R. E. Ireland and L. N. Mander, *ibid.*, 1967, **32**, 689, respectively.
[14] *Cf.* W. Herz, A. K. Pinder, and R. N. Mirrington, *J. Org. Chem.*, 1966, **31**, 2257.
[15] H. Moell and O. Schlichting, Ger. Pat. 1,029,368 (*Chem. Abs.*, 1960, **54**, 10901).