$[\alpha]_D$ −1°. Found for $C_{25}H_{35}BrO_6$: C, 58.77; H, 6.79; Br, 15.55; O, 18.67) which was treated with zinc dust in isopropyl alcohol to afford Δ^5-pregnene-3β,17α,19-triol-20-one 3,17-diacetate (XIX) (m.p. 228–229°, $[\alpha]_D$ −48°. Found for $C_{25}H_{36}O_6$: C, 69.10; H, 8.66; O, 22.36). Hydrolysis of XIX gave the 3β-alcohol XX (m.p. 245–247°, $[\alpha]_D$ −63°. Found for $C_{23}H_{34}O_5$: C, 70.59; H, 8.53; O, 20.62) which underwent Oppenauer oxidation (10 min.) to furnish 19-hydroxy-17α-acetoxyprogesterone (XXI) (m.p. 252–254°, $[\alpha]_D$ +72°, λ_{max} 242 mμ, log ϵ 4.17. Found for $C_{23}H_{32}O_5$: C, 71.38; H, 8.36; O, 20.34). Oxidation of XXI to the 19-acid XXII (m.p. 166–168°, $[\alpha]_D$ +116°, λ_{max} 244 mμ, log ϵ 4.18. Found for $C_{23}H_{30}O_6$: C, 68.72; H, 7.60; O, 23.56) and treatment with acid gave 19-nor-17α-acetoxyprogesterone[18] (XXIII) (m.p. 227–229°, $[\alpha]_D$ +18°, λ_{max} 239 mμ, log ϵ 4.23).

(18) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6110 (1958).

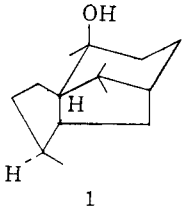
A. BOWERS
RESEARCH LABORATORIES R. VILLOTTI
SYNTEX, S. A. J. A. EDWARDS
APARTADO POSTAL 2679 E. DENOT
MÉXICO, D. F. O. HALPERN

RECEIVED JUNE 13, 1962

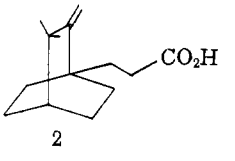
SYNTHESIS OF PATCHOULI ALCOHOL[1]

Sir:

After structural studies on the tricyclic sesquiterpene patchouli alcohol (1)[2] were complete we initiated work directed toward a synthesis of this natural product and the related patchoulione (**19**), a substance with highly desirable olfactory properties. A synthesis verifying both structure and absolute configuration of 1 is now presented.



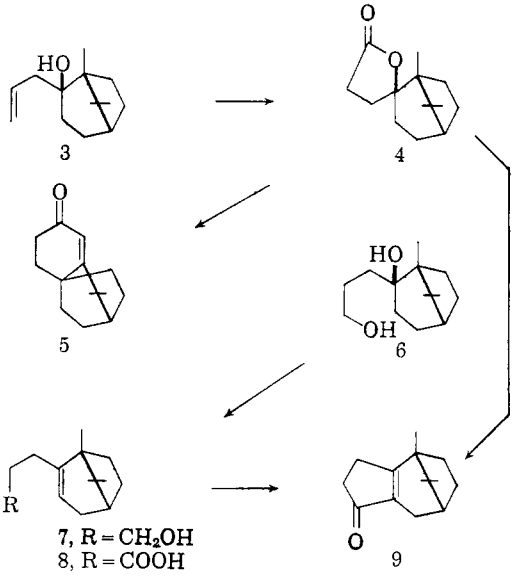
1



2

Addition of allylmagnesium chloride to (−)-homocamphor[3] (prepared from (+)-camphor) gave the carbinol (**3**) (80%), m.p. 36–36.5°, $[\alpha]_D$ −20° (all in $CHCl_3$) which on treatment with diborane[4] followed by oxidation with Jones' reagent[5,6] was converted to the spirolactone (**4**) (54%), m.p. 89–90°, $[\alpha]_D$ −45°, $\nu_{max}^{CCl_4}$ 1770 cm.$^{-1}$. Dehydration in the presence of 1% $ZnCl_2$ in hot acetic anhydride–acetic acid solution (3:1) furnished the *meso*-ketone (**5**), (10%), m.p. 101–103°, λ_{max}^{EtOH} 247 mμ (ϵ 14,500), $\nu_{max}^{CCl_4}$ 1665, 1615 cm.$^{-1}$, n.m.r. (all in CCl_4) at 4.25 (1H singlet); 8.82 τ (6H singlet) and the desired cyclopentenone (**9**) (40%) m.p. 100°, λ_{max}^{EtOH} 246 mμ (ϵ 13,000), $\nu_{max}^{CCl_4}$ 1695, 1635 cm.$^{-1}$, three methyl resonance peaks in the n.m.r. spectrum at 8.95, 9.05 and 9.15 τ. The latter ketone (**9**) was nearly completely racemized, indicating reversible isomerization of **8** and the *meso*-acid (**2**) prior to cyclization. This was avoided as follows: Hydroboration of **3** followed by oxidation with hydrogen peroxide gave the diol (**6**), m.p. 138–139°, $[\alpha]_D$ −25° identical with the product available by reduction of **4** with lithium aluminum hydride which was monoacetylated, dehydrated with phosphorus oxychloride in pyridine and the resulting acetate reduced with lithium aluminum hydride to the unsaturated alcohol (**7**). Oxidation with chromium trioxide furnished the acid (**8**), m.p. 81–82°, n.m.r. signals at −2.2 (1H), 4.9 (1H broad), 9.0 (3H), 9.08τ (6H) (over-all yield 3 to 8, 65%).

Treatment of its acid chloride with aluminum chloride in carbon disulfide afforded **9**, m.p. 110°, $[\alpha]_D$ −149° (41%).



Wittig condensation[7] with triphenylphosphinemethylene in peroxide free tetrahydrofuran furnished an unstable liquid diene (**10**), λ_{max}^{EtOH} 256 mμ which on hydrogenation over Raney nickel W2 in ethyl acetate gave an olefin, over-all yield **9** to **11**, 38%, $[\alpha]_D$ −42°. Identity with β-patchoulene (**11**) was established by comparison of infrared and n.m.r. spectra, optical rotation and retention time in the gas chromatogram.

The tricyclic skeleton of patchouli alcohol (**1**) had to be constructed from **11** using some version of the Wagner–Meerwein rearrangement. Direct isomerization was ruled out because the equilibrium between **11** and **20** is quantitatively in favor of **11**. Epoxidation of **11** with peracetic acid produced the liquid epoxide (**12**) (99%), $[\alpha]_D$ −8° which was isomerized with boron fluoride in ether solution (20°, 5–10 min.) to the unsaturated alcohol (**13**) (57%), m.p. 30–31°, $[\alpha]_D$ −14°,

(1) Terpenes XVII.

(2) G. Büchi, R. E. Erickson and N. Wakabayashi, *J. Am Chem. Soc.*, **83**, 927 (1961).

(3) H. Favre and J.-C. Richer, *Can. J. Chem.*, **37**, 417 (1959); H. Rupe and C. Frey, *Helv. Chim. Acta*, **27**, 627 (1944).

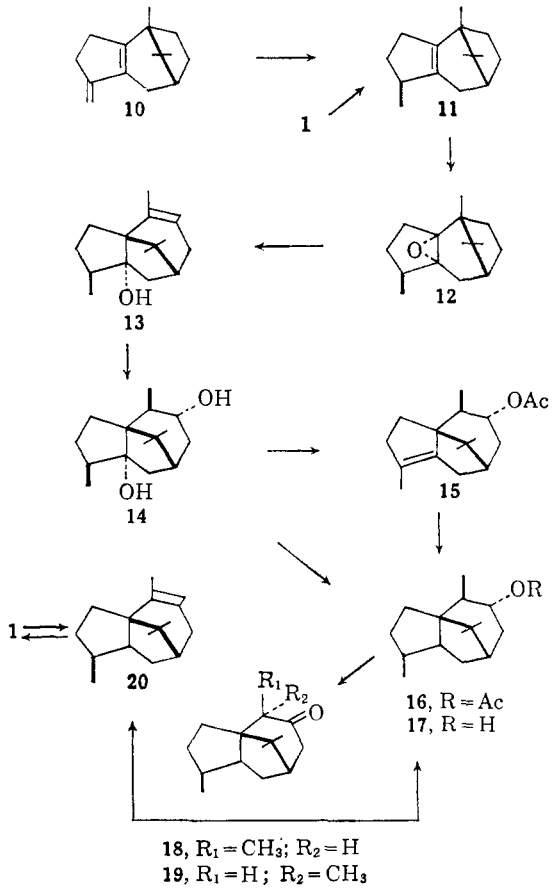
(4) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959.)

(5) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(6) *Cf.* oxidation of secondary boranes to ketones, R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959); H. C. Brown and C. P. Garg, *ibid.*, **83**, 2951 (1961).

(7) U. Schöllkopf, *Angew. Chem.*, **71**, 260 (1959).

n.m.r. at 4.57 broad ($>C=C<^{H}$); 7.73 (OH), 8.38 ($CH_3-\underset{|}{C}=\underset{|}{C}-$), doublet centered at 9.0 (J 6 cs., $CH_3-\underset{|}{CH}$), 9.05, 9.14τ ($CH_3-\underset{|}{C}-CH_3$). Hydroboration–oxidation led to the diol (**14**) (45%), m.p. 112–113°, $[\alpha]_D$ −2° subsequently transformed to the liquid acetate (**15**) (87%), $[\alpha]_D$ +39° with acetic anhydride in hot pyridine. The position of the double bond in **15** was revealed by its n.m.r. spectrum: doublet at 5.4 (1H, J 6 cs.), 8.15 (3H), 8.55 (3H), doublet at 8.85 (3H, J 6 cs.), 8.97, 9.20 τ (6H) with no olefinic protons. Catalytic reduction of **15** afforded the liquid acetate (**16**) (98%), $[\alpha]_D$ −3° which with lithium aluminum hydride gave the alcohol (**17**) (87%) m.p. 97–97.5°, $[\alpha]_D$ −7° identical in every respect with an alcohol obtained from α-patchoulene (**20**) by hydroboration–oxidation. Catalytic reduction of the diol (**14**) over platinum in acetic acid containing some perchloric acid yielded the alcohol (**17**) in one operation.



The synthesis of patchoulione (**19**) was completed by chromic acid oxidation of **17** to the ketone (**18**) (97%), m.p. 25–26°, $[\alpha]_D$ +13° followed by epimerization with alkali to **19** (60%), m.p. 48–50° identical (infrared, mixture m.p. and rotation) with an authentic sample of patchoulione (**19**). Pyrolysis of **16** at 350° afforded a mixture of two liquid olefins in a ratio of 4:1. The major isomer, $[\alpha]_D$ +51° had n.m.r. at 4.95 (broad, $-\underset{|}{C}=\underset{|}{C}-H$); 8.37 ($CH_3-\underset{|}{C}=\underset{|}{C}-$); doublet centered at 9.10 (J 6 cs.) 9.05; 9.11 τ ($CH_3-\underset{|}{C}-CH_3$) and was spectroscopically (infrared and n.m.r.), vapor chromatographically and polarimetrically identical with authentic α-patchoulene (**20**). Preferential formation of **20** agrees with the postulate of double bond character in the transition state of the pyrolytic elimination[8] because the other isomer is destabilized by 1,3-methyl interaction. We have previously described[1] a conversion of α-patchoulene (**20**) to patchouli alcohol (**1**) and since total syntheses of (+)-camphor have been accomplished the transformations[9] described constitute a total synthesis.

Financial support by the National Institutes of Health (RG9186) and by Firmenich and Cie, Geneva, is gratefully acknowledged.

(8) C. H. DePuy and R. W. King, *Chem. Revs.*, **60**, 431 (1960).
(9) G. Komppa, *Ber.*, **36**, 4332 (1903); *Ann.*, **370**, 209 (1909).
(10) National Institutes of Health Predoctoral Fellow 1960–1962.

DEPARTMENT OF CHEMISTRY G. BÜCHI
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASSACUSETTS WILLIAM D. MACLEOD, JR.[10]
RECEIVED JULY 12, 1962

STEROIDS. CC.[1] SPECTRA AND STEREOCHEMISTRY, PART III.[2] STEROIDAL 5,6-EPOXIDES

Sir:

Epoxidation of Δ^5-steroids frequently produces both the 5α,6α- and 5β,6β-epoxides, the former stereochemistry normally being assigned to that isomer which preponderates. Proof of structure has hitherto rested on further chemical reactions and molecular rotation differences.[3]

An examination of Dreiding models of the stereoisomeric 5,6-epoxides suggested that the angles (ϕ) subtended by the epoxidic C—H bonds with the C—H bonds at C_7 (Table I) are sufficiently different to permit a differentiation between the α- and β-epoxides to be made through a study of J_{HH} values, providing that the Karplus correlation,[5] relating J_{HH} to ϕ is valid for these cases.[6]

(1) Steroids. CXCIX, L. H. Knox, E. Velarde, S. Berger and D. Cuadriello, *Chem. and Ind.*, in press, 1962.
(2) Part II, A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736 (1962).
(3) A survey of the literature and collected data[4] reveals that the β-epoxide is more dextrorotatory than the α. However, this requires both compounds for the comparison. An apparent exception concerns the epoxides of 17β-carboxy-$\Delta^{5,16}$-androstadiene-3β-ol acetate methyl ester, where the correct specific rotation of the β-epoxide, −7° (ref. 4c, p. 1167), is erroneously given as −70° (ref. 4c, p. 1171) and repeated elsewhere as the incorrect value (ref. 4a, p. 78).
(4) (a) A. Petit and J. P. Mathieu, "Tables de Constantes et Données Numériques. 6. Constantes Sélectionnées. Pouvoir Rotatoire Naturel. I. Stéroïdes," Masson et Cie., Paris, 1956; (b) A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959); (c) L. Ruzicka, E. Hardegger and C. Kauter, *Helv. Chim. Acta*, **27**, 1164 (1944).
(5) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(6) It has been shown recently[7] that in the rigid steroid molecule, the constants of the Karplus equations need to be much larger, at least for the steroidal 2- and 4-acetoxy-3-ketones examined. Table I also includes therefore calculated J values according to these modified equations.[7]
(7) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).