Chem. Pharm. Bull.
16(1) 43—51 (1968)

UDC 547.597.07 : 582.542.2

Synthesis of Cyperene, Cyperotundone, and Patchoulenone1)

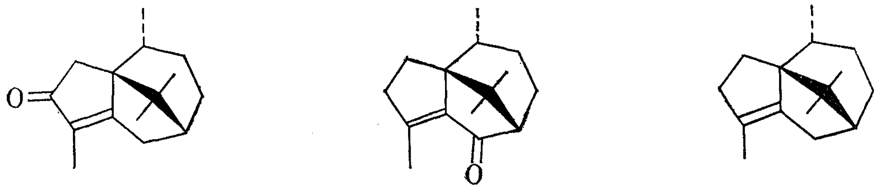
Hiroshi Hikino, Kunio Ito, Keitaro Aota,
and Tsunematsu Takemoto

*Pharmaceutical Institute, Tohoku University School of Medicine*2)

(Received March 8, 1967)

Isopatchoul-9-en-5α-ol (VII) was hydrogenated using nickel catalyst in methanol to give 10α(H)-isopatchoulan-5α-ol (XII). Dehydration of the alcohol (XII) formed 10-*epi*-cyperene (IV) which on oxidation yielded 10-*epi*-cyperotundone (V). The alcohol (VII) was converted into 9α-acetoxy-10α(H)-isopatchoul-4-ene (XVII) *via* 10α(H)-isopatchoulane-5α,9α-diol (XIV) by known methods. Hydrolysis of the unsaturated acetate (XVII) afforded 10α(H)-isopatchoul-4-en-9α-ol (XIX) which was oxidized to yield isopatchoul-4-en-9-one (XXI). Wolff-Kishner reduction of the ketone (XXI) furnished cyperene (III) which on oxidation gave cyperotundone (I) and patchoulenone (II).

Cyperotundone is a sesquiterpenic constituent of *Cyperus* species (Cyperaceae), *i.e.*, *C. scariosus* R. Brown, *C. articulatus* Linné, and *C. rotundus* Linné.3) We have recently elucidated the structure and absolute configuration of this substance as represented by formula I from analytical studies4) and, in relation, deduced the stereostructures II and III for its congeners, patchoulenone and cyperene, respectively,2) both being also the constituents of *C. rotundus*.5,6) The present communication describes a synthesis verifying both structure and absolute configuration of the natural products (I, II, and III), along with preparation of their epimers (IV and V).



I II III

Chart 1

A convenient point of departure for the synthesis was isopatchoul-9-en-5α-ol (VII) which had been prepared as an intermediate *en route* for the total synthesis of patchouli alcohol.7) The first phase of the synthesis was concerned with the hydrogenation of the starting material (VII).

The alcohol (VII) was prepared by treatment of β-patchoulene epoxide (VI) with boron trifluoride,7) when the diol (VIII) was also obtained. Hydrogenation of the C-9:C-10 double

---

1) This paper is Part XVIII in the series on Sesquiterpenoids. Preceding paper, Part XVII: H. Hikino, Y. Sakurai, S. Numabe, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 39 (1968).

2) Location: *Kita-4-bancho, Sendai.*

3) For the general aspects of the research, refer to H. Hikino, K. Aota, and T. Takemoto, *Tetrahedron*, **23**, 2169 (1967).

4) H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 628 (1965); **14**, 890 (1966).

5) O. Motl, B. Trivedi, V. Herout, and F. Šorm, *Chem. & Ind.* (London), **1963**, 1284; B. Trivedi, O. Motl, V. Herout, and F. Šorm, *Collection Czechoslov. Chem. Communs.*, **29**, 1675 (1964).

6) B. Trivedi, O. Motl, J. Smolíková, and F. Šorm, *Tetrahedron Letters*, **1964**, 1197.

7) G. Büchi and W.D. MacLeod, Jr., *J. Am. Chem. Soc.*, **84**, 3205 (1962); G. Büchi, W.D. MacLeod, Jr., and J. Padilla O., *ibid.*, **86**, 4438 (1964).

bond in the isopatchoulane skeleton has already been performed on α-patchoulene (IX).4) Thus, it was observed that the ethylenic linkage was unaffected on hydrogenation with palladized charcoal in methanol but was hydrogenated over the same catalyst in ethyl acetate, when the addition of hydrogen to the double bond took place from the less hindered β-side of the molecule to furnish the saturated hydrocarbon with the 10α-methyl group (X). Therefore, it was initially considered that on hydrogenation under the same conditions, the unsaturated alcohol (VII) had to give the saturated alcohol having the 10α-methyl group (XI). However, attempts to hydrogenate the alcohol (VII) under various conditions, *i.e.*, with palladium-on-carbon or platinum oxide in methanol or ethyl acetate at room temperature under ordinary pressure, failed recovering the starting material (VII). Further, hydrogenation was carried out over platinum oxide in acetic acid resulting in hydrogenolysis to yield a saturated hydrocarbon which received no further attention. Then the alcohol (VII) was hydrogenated over Raney nickel in methanol at an elevated tempereature under pressure affording the saturated alcohol (XII) together with a saturated hydrocarbon (XIII). The relative yields of the two products (XII and XIII) varied from lot to lot, and in a particular instance, only the hydrogenolyzed product (XIII) was obtained. The configuration at C-10 of the alcohol (XII) was unknown at this stage and deduced later (*vide infra*). Treatment of the saturated alchool (XII) with a hot mixure of acetic anhydride and pyridine afforded an unsaturated hydrocarbon, which was not identical with cyperene (III) in optical rotation, infrared and nuclear magnetic resonance (NMR) spectra, and retention times in vapor phase chromatography. Since the NMR spectra of the hydrocarbon showed the presence of a newly formed olefinic methyl, a secondary methyl, and two tertiary methyls but no olefinic hydrogens, these functional groups being the same as those of cyperene (III), the unsaturated hydrocarbon was considered to be most probably a stereoisomer of cyperene (III). Further detailed examinations of the proton resonance revealed that the chemical shifts (9.26 and 8.94τ) of the two tertiary methyl singnals were in agreement with the corresponding ones in cyperene (III), but the line position (8.95τ) of the secondary methyl signal suffered a remarkable downward shift as compared with the corresponding one in cyperene (III)(see Table I). Previously we have assumed that α- and β-methyl groups at C-10 or C-11 in

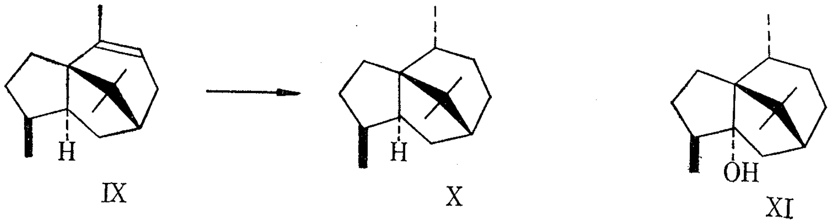


Chart 2

TABLE I

Compounds	Chemical shifts of the methyl protons (in τ-values)			
	C-12	C-13	C-15(α)	C-15(β)
Cyperotundone (I)	8.83	9.25	9.39	
Cyperene (III)	9.06	9.25	9.20	
10-*epi*-Cyperotundone (V)	8.79	9.29		8.84
10-*epi*-Cyperene (IV)	8.94	9.26		8.95
The unsaturated alcohol (XIX)	9.01	9.22		8.91
The unsaturated acetate (XVII)	8.97	9.20		8.85
The unsaturated alcohol (XXII)	8.94	9.25	9.02	

isopatchoul-4-ene derivatives cannot be equivalent and a β-methyl is fairly deshielded, whilst an α-methyl is rather shielded, since Dreiding models show that the 10α- and 11α-methyls or the 10β- and 11β-methyls are similarly situated with respect to the double bond at C-4:C-5, and an α-methyl is more above the plane of the double bond than its counterpart, a β-methyl.$^{4)}$ This assumption, however, may possibly be the reverse, since the anomaly on the shielding effect of the ethylenic linkage in bicyclo[2,2,1]heptene has recently been observed.$^{8)}$ Validity of this assumption in the present cases will be confirmed later (*vide infra*). Therefore, the deshielded chemical shift (8.95τ) of the secondary (*i.e.*, C-10) methyl group indicated it to be oriented in a β-configuration, the unsaturated hydrocarbon is consequently concluded to be 10-*epi*-cyperene (IV). This was further supported by the fact that the mass spectrum of the hydrocarbon (IV) was identical with that of cyperene (III). Oxidation of the hydrocarbon (IV) with *t*-butyl chromate gave the cyclopentenone (V) with the spectral characteristics (λ_{max} 245.5 mμ (log ε 4.09), ν_{max} 1704 and 1664 cm^{-1}), which were compatible with those of cyperotundone (I). In the NMR spectrum, similar shielding effects on the C-10 and C-11 methyl signals to those found in the congeners were again observed (see Table I). The deshielded chemical shift (8.84τ) of the C-15 methyl protons shows the C-10 methyl group to be β-oriented. Formulation of 10-*epi*-cyperotundone (V) was further justified by the identical mass spectrum with that of cyperotundone (I) and also by the very similar circular dichroism curve to that of the epimer (I). Based on the above facts, it is now clear that hydrogen was unexpectedly delivered by Raney nickel from the less accessible α-side of the unsaturated alcohol (VII) to give the epimeric alcohol (XII) but not the disired one (XI). Although this cannot be fully rationalized, at least part of the reason may be explained by the affinity of the nickel catalyst to the hydroxyl group α-situated.

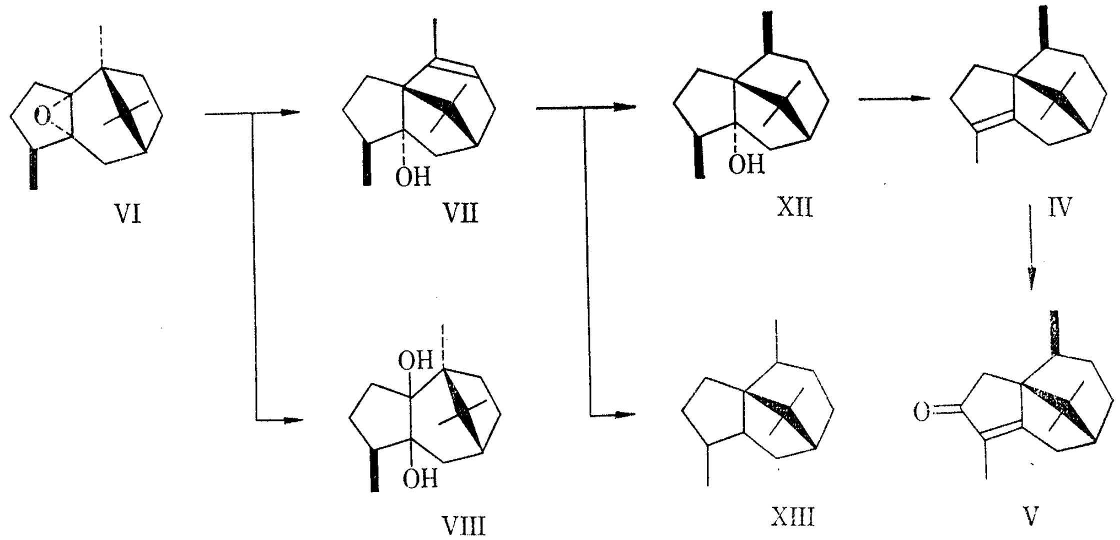


Chart 3

Since initial efforts to convert the unsaturated alcohol (VII) to the saturated alcohol (XI) through catalytic hydrogenation failed, an alternative route was attempted. Treatment of the diol (XIV) with a refluxing mixture of acetic anhydride and pyridine for 12 hours furnished, slightly contrary to the earlier claim,$^{7)}$ a mixture of four acetates. The most polar product was concluded to be the mono-acetate (XV) from the spectral properties demonstrating the presence of a tertiary hydroxyl and a secondary acetoxyl group, the C-9 hydrogen signal having a down-field shift (-1.15 ppm) as compared with that of the starting diol(XIV). The next polar product was the diacetate (XVI) as evidenced by the spectral characteristics

---

8) K. Tori, K. Aono, Y. Hata, R. Muneyuki, T. Tsuji, and H. Tanida, *Tetrahedron Letters*, **1966**, 9.

which showed the presence of a tertiary and a secondary acetoxyl group. The remaining of the product was confirmed to be a mixture of the two acetates (XVII and XVIII) from its NMR spectrum. On prolonged reaction of the diol (XIV) with a refluxing mixture of acetic anhydride and pyridine, the monoacetate (XV) was not found in a reaction product probably by its further transformation to the other acetates (XVI—XVIII). In order to avoid the formation of the by-products (XV and XVI), the diol (XIV) was treated with acetic anhydride alone under reflux yielding a mixture of the same unsaturated acetates (XVII and XVIII). However, it was observed that the relative ratio of the undesired acetate (XVIII) to the desired acetate (XVII) increased in this case. As separation of these two unsaturated acetates (XVII and XVIII) was impracticable, the mixture was hydrolyzed with lithium aluminum hydride to give a mixture of unsaturated alcohols, which could be efficiently separated by chromatography into its components. The major product was the required unsaturated alcohol (XIX) having the C–4:C–5 double bond, as verified by a resonance peak due to a vinyl methyl but no vinyl hydrogen peak in the NMR spectrum. The minor product had the NMR spectrum which exhibited the presence of a trisubstituted ethylenic linkage with a methyl group on it. This finding is only compatible with the structure XX for the minor product. Therefore, it is evident that treatment with acetic anhydride would initiate elimination of the C–5 hydroxyl in the diol (XIV) toward the formation of a double bond at C–4:C–5 and bring about migration of it to the C–3:C–4 position where it is conceivably thermodynamically more stable.

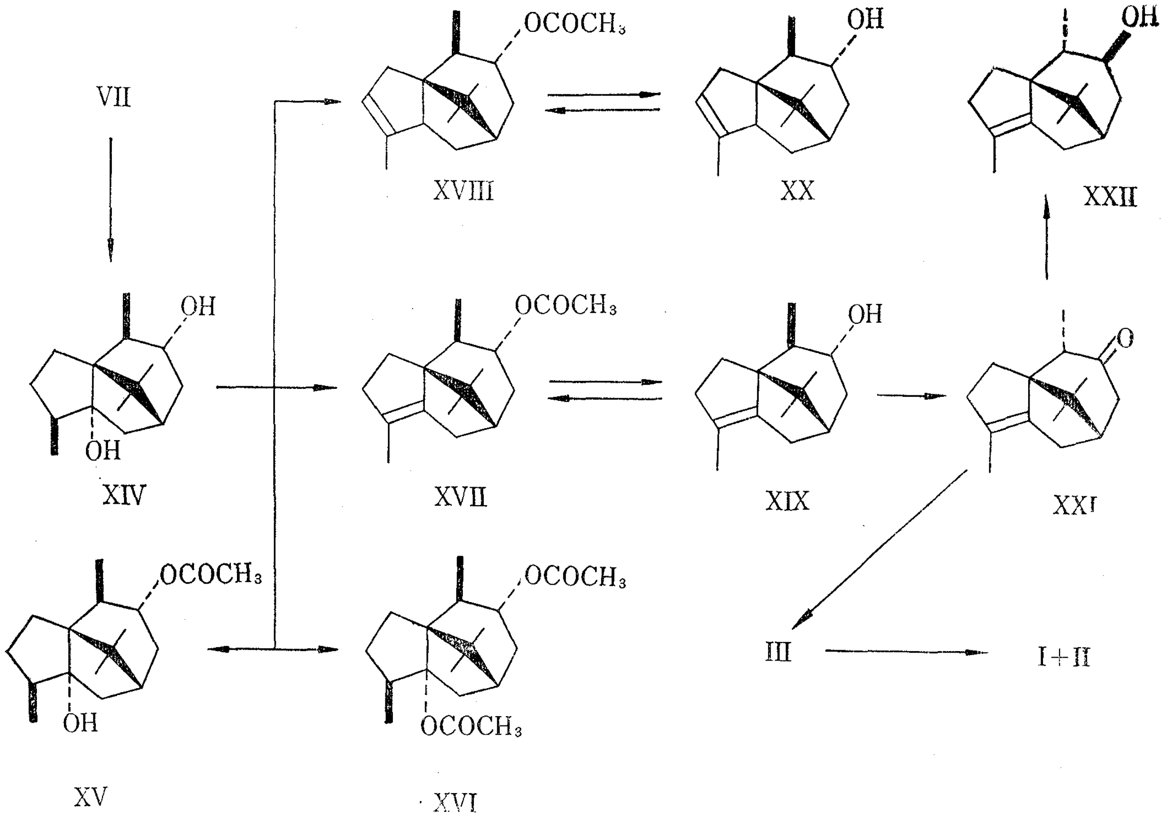


Chart 4

Now, we must discuss about the configurations at C–9 and C–10 of a series of compounds (XIV, XV, XVI, XVII, and XIX). Although Büchi, *et al.*[7] previously described that the diol obtained from the unsaturated alcohol (VII) by hydroboration–oxidation had the stereochemistry (XIV), no detailed discussion was made about this assignment. The establishment of these configurations is quite essential for the confirmation of the absolute configuration at C–10 of the natural products (I, II, and III). This has been achieved in the subsequent way.

Since the A– and B–rings in these compounds are rigidly fixed, the only flexible point is the geometry of the C_8–C_9–C_{10} fragment in the C–ring which must exist in any of the conformations ranging from a chair form (a) to a boat form (c).[9] The Newman projections, along the C_8–C_9 bond, corresponding to the various conformations are shown below the perspective diagrams. The conformation of the C–ring may be determined from the couplings of the C–9 hydrogen to its neighboring hydrogens. All three of these coupling constants[10] are observed to increase with increase in the bulkiness of the C–5 and C–9 substituents in the order XIX, XVII, XIV, XV, and XVI (see Table II), and these increments appear to reflect a corresponding change in the conformation of the C–ring. These increases in the C–9 proton couplings are best explained in terms of a non–bonded interaction between a 9α(axial)–oxygen function and the 5α– and 6α–substituents, which distorts the C–ring from a chair conformaton (a) towards a boat conformation (c) until the steric interactions are relieved. A β(equatorial)–oxygen function at C–9 would not explain this distortion. Further, of the four possible substitution patterns at C–9 and C–10 in these compounds, only the assigned configurations (*i.e.*, 9α–hydroxyl or acetoxyl, and 10β–methyl) are consistent with

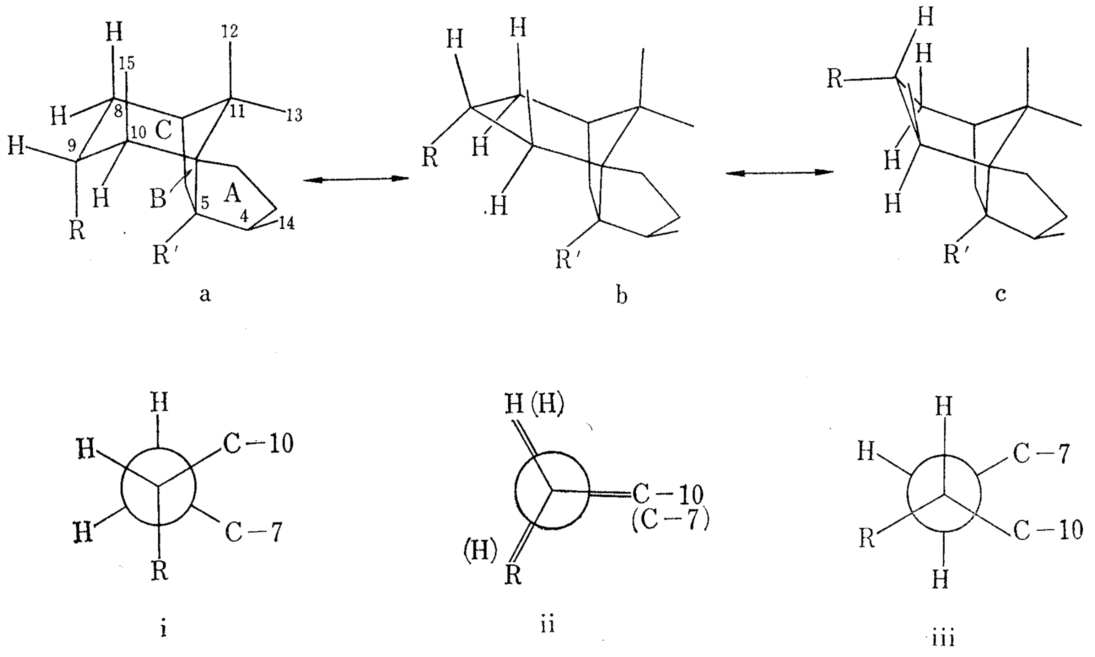


Chart 5

TABLE II

Compounds	Apparent coupling constants (cps)		
	$J_{9\beta,8\beta}$	$J_{9\beta,8\alpha}$	$J_{9\beta,10\alpha}$
The unsaturated alcohol (XIX)	4	~0	~0
The unsaturated acetate (XVII)	5	~0	~0
The diol (XIV)	8	~0	~0
The diol monoacetate (XV)	9	2	2
The diol diacetate (XIV)	10	4	4

TABLE III

Arbitrary assigned dihedral angles(°)			Calculated coupling constants (cps)		
$\phi_{9\beta,8\beta}$	$\phi_{9\beta,8\alpha}$	$\phi_{9\beta,10\alpha}$	$J_{9\beta,8\beta}$	$J_{9\beta,8\alpha}$	$J_{9\beta,10\alpha}$
50	70	70	4	1	1
40	80	80	6	0.3	0.3
30	90	90	7	0	0
20	100	100	9	0.5	0.5
10	110	110	10	2	2
0	120	120	10	4	4
10	130	130	10	7	7

---

[9] Compounds XIX and XVII have a double bond at C–4:C–5.

[10] Coupling constants are assumed to be equal to the observed splittings.

the observed change of the coupling constants of the C–9 hydrogen signal as the C–9 and C–5 substituents are made more bulky. Comparison with the coupling constants calculated from the dihedral angles by the Williamson–Johnson version[11] of the Karplus equation (see Table III) indicate that the conformation of the C–ring changes from that near projection i, in the compound XIX, to that near projection ii, in the compound XVI. After the establishment of the β–configuration of the C–10 methyl groups in these compounds, the observed deshielded chemical shifts (8.85 and 8.91τ) of the C–15 proton signals in the compounds XVII and XIX confirmed our earlier assignment[4] of the methyl groups at C–10 and C–11 in the cyperene skeleton. The natural products (I, II, and III), whose NMR signals for the C–15 protons appear in the higher field, are also verified as having the C–10 methyl group in the α–configuration.

When the unsaturated alcohol (XIX) was oxidized with chromic acid (Brown reagent[12] and Jones reagent[13]), an unsaturated ketone was obtained whose spectral properties agreed with the expected structure XXI but the configuration at C–10 was unknown at this stage. It was found that the C–10 methyl group in this ketone had α–configuration, since the NMR signal due to the C–10 methyl was essentially unchanged on passing from carbon tetrachloride to benzene solution demonstrating the methyl group adjacent to the carbonyl to be equatorially oriented.[14] Therefore, it was concluded that the initially produced ketone evidently had suffered epimerization at C–10 during the course of reaction and isolation to give the ketone(XXI). This was further confirmed by its conversion by means of lithium aluminum hydride into a new unsaturated alcohol. In accordance with the assignment for the C–10 methyl group of the original ketone (XXI), the NMR signal of the C–9 hydrogen of the new alcohol occurred as a sextet ($J_1=J_2=10$, $J_3=7$ cps) which indicated that the C–9 hydroxyl group was situated in an equatorial–like (*i.e.*, β–) configuration and the C–10 methyl group also in an equatorial–like (*i.e.*, α–) configuration in the C–ring with a slightly deformed chair conformation. With the deshielding effect of an equatorial hydroxyl group in a cyclohexane ring to a vicinal equatorial methyl protons in mind, the line position (9.02τ) of the C–15 methyl signal in the NMR spectrum revealed that the C–10 methyl group was α–situated. These results are all consistent with the stereochemistry (XXII) for the new alcohol.

The ketone (XXI) was reduced by the procedure of Wolff–Kishner and the hydrocarbon thus obtained was found to be indistinguishable in every respect, including optical rotation, with the natural cyperene (III). Oxidation of cyperene (III) to cyperotundone (I) has already accomplished by Merali, *et al.*[15] and Nigam[16] in their structural studies. To complete the present synthesis, the hydrocarbon (III) was oxidized with *t*–butyl chromate to afford two unsaturated ketones which were shown to be identical with the natural cyperotundone (I) and patchoulenone (II).

Experimental[17]

Rearrangement of β–Patchoulene Oxide with Boron Trifluoride Etherate——β–Patchoulene oxide (VI) (41.0 g) in ether (200 ml) was treated with BF_3–Et_2O (6 ml) by the methods previously reported[7] to give an oil (42.2 g) which was chromatographed on alumina (800 g).

---

11) K.L. Williamson and W.S.Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).

12) H.C. Brown and C.P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

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

14) N.S. Bhacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden–Day, Inc., San Francisco, 1964, p. 159.

15) S.B. Merali, P.S. Kalsi, K.K. Chakravarti, and S.C. Bhattacharyya, *Tetrahedron Letters*, **1965**, 4053.

16) C. Nigam, *J. Pharm. Sciences*, **54**, 1823 (1965).

17) Melting points are uncorrected. Specific rotations were measured in $CHCl_3$ solution. NMR spectra were determined at 60 Mcps in CCl_4 solution *vs.* Me_4Si as internal standard. Chemical shifts are indicated in τ values and coupling constants (J) in cps units.

Elution with light petroleum–benzene (4:1) afforded fractions containing an alcohol (26.2 g) which was submitted to rechromatography over silica gel (500 g). Light petroleum–benzene (4:1) eluate yielded the unsaturated alcohol (VII)⁾[7] which crystallized on standing, IR (liquid) cm^{-1}: 3560 (hydroxyl), 1647, 830, 816, 797 (trisubstituted ethylenic linkage), NMR: singlet (3H) at 9.11τ ($C\underline{H}_3$–C⋖), singlet (3H) at 9.03τ ($C\underline{H}_3$–C⋖), doublet (3H) at 8.98τ (J=6, $C\underline{H}_3$–CH⟨), unresolved peak (3H) at 8.33τ ($C\underline{H}_3$–C=C), broad peak (1H) at 4.52τ (–CH_2–C$\underline{H}$=C–CH_3).

Successive elution with benzene gave a crystal paste (2.6 g) which on crystallization from AcOEt furnished the diol (VIII) as colorless prisms, mp 110°, $[\alpha]_D$ −70.1°(c=5.4), *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.45; H, 10.96, IR (CCl_4) cm^{-1}: 3650, 3520 (hydroxyl), NMR: singlet (3H) at 9.22τ ($C\underline{H}_3$–C⋖), doublet (3H) at 9.19τ (J=5, $C\underline{H}_3$–CH⟨), two singlets (6H) at 8.98, 8.97τ(($C\underline{H}_3)_2$C⟨).

Attempted Hydrogenation of the Unsaturated Alcohol over Palladized Charcoal or Platinum Oxide in Methanol or Ethyl Acetate——The unsaturated alcohol (VII) was stirred in an atmosphere of H_2 (1 atm) at room temperature using 5% Pd–C or PtO_2 in MeOH or AcOEt. In every case, only the starting alcohol (VII) was obtained.

Hydrogenation of the Unsaturated Alcohol over Platinum Oxide in Acetic Acid——The unsaturated alcohol (VII)(130 mg) was hydrogenated over PtO_2 (90 mg) in AcOH (12 ml) at room temperature for 1 day. Working up in the usual way and distillation under reduced pressure furnished a hydrocarbon as a colorless oil, IR: no hydroxyl band, NMR: multiplet (12H) in the region 9.3—9.0τ.

Hydrogenation of the Unsaturated Alcohol over Raney Nickel in Methanol——The unsaturated alcohol (VII)(1.00 g) in MeOH (10 ml) was agitated with Raney Ni (10 ml) under H_2 (initial pressure: 70 atm) at 100° for 30 hr. After filtering off the catalyst, the mixture was evaporated to give an oil (0.94 g) which was chromatographed over silica gel (20 g).

Elution with light petroleum yielded an oil (0.33 g) which on distillation under reduced pressure gave the hydrocarbon (XIII) as a colorless oil, $[\alpha]_D$ −15.0°(c=7.2), IR: no hydroxyl band, NMR: singlet (3H) at 9.23τ ($C\underline{H}_3$–CH⟨), doublet (3H) at 9.06τ (J=6, $C\underline{H}_3$–CH⟨), doublet (3H) at 9.01τ (J=6, $C\underline{H}_3$–CH⟨), singlet (3H) at 8.96τ ($C\underline{H}_3$–C⋖).

Successive elution with benzene afforded a crystal paste (0.57 g) which was crystallized from light petroleum to yield the saturated alcohol (XII) as colorless prisms, mp 39—40°, $[\alpha]_D$ −1.3°(c=3.1), IR (CCl_4) cm^{-1}: 3650, 3520 (hydroxyl), NMR: singlet (3H) at 9.22τ ($C\underline{H}_3$–C⋖), doublet (6H) at 8.96τ (J=6, $C\underline{H}_3$–CH⟨), singlet (3H) at 8.91τ ($C\underline{H}_3$–C⋖).

Dehydration of the Saturated Alcohol with Acetic Anhydride——The alcohol (XII)(200 mg) was allowed to reflux with Ac_2O (0.5 ml) in pyridine (1 ml) for 8 hr. Upon isolation in the usual manner, the product (191 mg) was chromatographed over silica gel (5 g) and fractions eluted with light petroleum afforded, after distillation under diminished pressure, 10-*epi*-cyperene (IV) as a colorless oil, $[\alpha]_D$ +82.2°(c=5.4), MS (m/e): 204 (M^+, base), 189, 175, 161, 147, 133, 119, 105, 91, 79, 69, 55, 41, IR (liquid): no hydroxyl band, NMR: singlet (3H) at 9.26τ ($C\underline{H}_3$–C⋖), doublet (3H) at 8.95τ (J=7, $C\underline{H}_3$–CH⟨), singlet (3H) at 8.94τ ($C\underline{H}_3$–C⋖),unresolved peak (3H) at τ 8.46($C\underline{H}_3$–C=C⟨).

Oxidation of 10-*epi*-Cyperene with *t*-Butyl Chromate——To 10-*epi*-cyperene (IV)(340 mg) in CCl_4 (4 ml) was added a mixture of $CrO_2(O\text{-}t\text{-}Bu)_2$ solution (solution B,⁾[18] 4 ml), AcOH (1 ml), and Ac_2O (0.5 ml) dropwise with stirring at 70° over a period of 30 min and swirling was continued for a further 1 hr. Working up in the customary manner gave an oil (350 mg) which was chromatographed over silica gel (10 g). Elution with light petroleum–benzene (4:1) yielded an oil (120 mg) which on distillation under reduced pressure furnished 10-*epi*-cyperotundone (V) as a colorless oil, CD (c=0.0502, dioxane): $[\theta]_{316}$ −6080, MS (m/e): 218 (M^+, base), 203, 189, 175, 161, 147, 133, 119, 105, 91, 77, 69, 55, 41, UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ mμ (log ε): 245.5 (4.09), IR (liquid) cm^{-1}: 1704, 1664 (cyclopentenone), NMR: singlet (3H) at 9.29τ ($C\underline{H}_3$–C⋖), doublet (3H) at 8.84τ (J=6, $C\underline{H}_3$–CH⟨), singlet (3H) at 8.79τ ($C\underline{H}_3$–C⋖), triplet (3H) at 8.39τ (J=1, $C\underline{H}_3$–C=C–CH_2–).

Hydroboration–Oxidation of the Unsaturated Alcohol——The unsaturated alcohol (VII)(3.5 g) was subjected to hydroboration–oxidation by the procedures previously reported⁾[7] to give the diol (XIV) as colorless needles (from light petroleum), mp 103—104°, $[\alpha]_D$ −2.3°(c=6.7), IR (KBr) cm^{-1}: 3175 (hydroxyl), NMR: singlet (3H) at 9.18τ ($C\underline{H}_3$–C⋖), singlet (3H) at 9.03τ ($C\underline{H}_3$–C⋖), doublet (3H) at 8.92τ (J=7, $C\underline{H}_3$–CH⟨),doublet (3H) at 8.89τ (J=7, $C\underline{H}_3$–CH⟨), doublet (1H) at 6.33τ (J=8, –CH_2–C$\underline{H}$(OH)–CH⟨).

Dehydration of the Diol with Acetic Anhydride——a) The diol (XIV)(1.00 g)in Ac_2O (5 ml) and pyridine (10 ml) was heated under reflux for 12 hr. After isolation with ether in the usual manner, the product (1.16 g) was chromatographed over silica gel (25 g).

Elution with light petroleum–benzene (5:1) gave an oil (452 mg) which was distilled under reduced pressure to yield a mixture of the unsaturated acetates (XVII and XVIII) in the approximate ratio 7:1 (from NMR spectrum) as a colorless oil, IR (liquid) cm^{-1}: 1730, 1242 (acetoxyl).

Subsequent elution with light petroleum–benzene (5:2) afforded an oil (343 mg) which on distillation under reduced pressure gave the diol diacetate (XVI) as a colorless oil, $[\alpha]_D$ +8.7°(c=5.5), IR (liquid) cm^{-1}: 1727, 1243 (acetoxyl), NMR: singlet (3H) at 9.16τ ($C\underline{H}_3$–C⋖), singlet (3H) at 8.93τ ($C\underline{H}_3$–C⋖), doublet

---

18) R.V. Oppenauer and H. Oberrauch, *Anales asoc. quim. argentina*, **37**, 246 (1949)(*C.A.*, **44**, 3909 (1950)).

(3H) at 8.87τ ($J=7$, $\text{C}\underline{\text{H}}_3$–CH⟨), doublet (3H) at 8.78τ ($J=6$, $\text{C}\underline{\text{H}}_3$–CH⟨), two singlets (3H each) at 8.07, 8.04τ ($\text{C}\underline{\text{H}}_3$–CO–O–), sextet (1H) at 5.14τ ($J_1=10$, $J_2=J_3=4$, –CH_2–$\text{C}\underline{\text{H}}(\text{OCOCH}_3)$–CH⟨).

Successive elution with benzene:AcOEt (10:1) yielded an oil (370 mg) which was distilled under diminished pressure to furnish the diol monoacetate (XV) as a colorless oil, $[\alpha]_D$ +1.5°($c=5.2$), IR (liquid) cm^{-1}: 3580 (hydroxyl), 1730, 1222 (acetoxyl), NMR: singlet (3H) at 9.17τ ($\text{C}\underline{\text{H}}_3$–C⋖), doublet (3H) at 8.99τ (J=7, $\text{C}\underline{\text{H}}_3$–CH⟨), singlet (3H) at 8.98τ ($\text{C}\underline{\text{H}}_3$–C⋖), doublet (3H) at 8.84τ ($J=8$, $\text{C}\underline{\text{H}}_3$–CH⟨), singlet (3H) at 8.00 τ ($\text{C}\underline{\text{H}}_3$–CO–O–), sextet (1H) at 5.18τ ($J_1=9$, $J_2=J_3=3$, –CH_2–$\text{C}\underline{\text{H}}(\text{OCOCH}_3)$–CH⟨).

b) The diol (XIV)(214 mg) was allowed to reflux with Ac_2O (1 ml) in pyridine (2 ml) for 24 hr. Upon isolation, the product (250 mg) was placed on a silica gel column (8 g).

Light petroleum–benzene (5:1) eluted a mixture of the unsaturated acetates (XVII and XVIII)(173 mg) in the approximate ratio 6:1 (from NMR spectrum).

Light petroleum–benzene (5:2) eluted the diol diacetate (XVI)(76 mg).

c) The diol (XIV)(500 mg) was refluxed for 5 hr with Ac_2O (5 ml). After isolation, the product was chromatographed on silica gel (10g). Elution with light petroleum–benzene (5:1) afforded a mixture of the unsaturated acetates (XVII and XVIII)(494 mg) in the approximate ratio 5:2 (from NMR spectrum).

Hydrolysis of a Mixture of the Unsaturated Acetates——A mixture of the unsaturated acetates (XVII and XVIII)(440 mg) and LiAlH_4 (80 mg) were dissolved in ether (10 ml). After stirring at room temperature for 2 hr excess hydride was decomposed by dropwise addition of H_2O. Extraction with ether and evaporation of the dried solvent gave a residue (428 mg) which was chromatographed over silica gel (20 g).

Elution with light petroleum–benzene (4:1) and distillation under reduced pressure yielded the alcohol (XIX) as a colorless oil, $[\alpha]_D$ +48.8°($c=3.1$), *Anal.* Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.76; H, 10.98. Found: C, 81.61; H, 10.66, IR (liquid) cm^{-1}: 3380 (hydroxyl), NMR: singlet (3H) at 9.22τ ($\text{C}\underline{\text{H}}_3$–C⋖), singlet (3H) at 9.01τ ($\text{C}\underline{\text{H}}_3$–C⋖), doublet (3H) at 8.91τ ($J=7$, $\text{C}\underline{\text{H}}_3$–CH⟨), singlet (3H) at 8.41τ ($\text{C}\underline{\text{H}}_3$–C=C⟨), doublet (1H) at 6.38τ ($J=4$, –CH_2–$\text{C}\underline{\text{H}}$(OH)–CH⟨).

Further elution with the same solvent and crystallization from light petroleum to give the isomerized alcohol (XX) as colorless needles, mp 112—113°, $[\alpha]_D$ +40.0°($c=3.9$), *Anal.* Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.76; H, 10.98. Found: C, 81.58; H, 10.76, IR (CCl_4) cm^{-1}: 3650, 3400 (hydroxyl), NMR: singlet (3H) at 9.27τ ($\text{C}\underline{\text{H}}_3$–C⋖), singlet (3H) at 9.03τ ($\text{C}\underline{\text{H}}_3$–C⋖), doublet (3H) at 8.95τ ($J=8$, $\text{C}\underline{\text{H}}_3$–CH⟨), unresolved peak (3H) at 8.38τ ($\text{C}\underline{\text{H}}_3$–C=C⟨), doublet (1H) at 6.27τ ($J=5$, –CH_2–$\text{C}\underline{\text{H}}$(OH)–CH⟨), broadened peak (1H) at 4.98τ (band width at half height: 7 cps, –CH_2–$\text{C}\underline{\text{H}}$=C⟨).

Acetylation of the Unsaturated Alcohol——The alcohol (XIX)(100 mg) in pyridine (1 ml) was treated 1 day at room temperature with Ac_2O (0.5 ml). Upon isolation, the product (105 mg) was distilled under reduced pressure to give the unsaturated acetate (XVII) as a colorless oil, $[\alpha]_D$ +41.9°($c=5.2$), *Anal.* Calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_2$: C, 77.82; H, 9.99. Found: C, 77.63; H, 10.15, IR (liquid) cm^{-1}: 1727, 1240 (acetoxyl), NMR: singlet (3H) at 9.20τ ($\text{C}\underline{\text{H}}_3$–C⋖), singlet (3H) at 8.97τ ($\text{C}\underline{\text{H}}_3$–C⋖), doublet (3H) at 8.85τ ($J=7$, $\text{C}\underline{\text{H}}_3$–CH⟨), triplet (3H) at 8.43τ ($J=1$, $\text{C}\underline{\text{H}}_3$–C=C⟨), singlet (3H) at 8.12τ ($\text{C}\underline{\text{H}}_3$–CO–O–), doublet (1H) at 5.37τ ($J=5$, –CH_2–$\text{C}\underline{\text{H}}(\text{OCOCH}_3)$–CH⟨).

Acetylation of the Isomerized Unsaturated Alcohol——The alcohol (XX)(85 mg) in pyridine (1 ml) was treated with Ac_2O (0.5 ml) at room temperature for 1 day. The product (100 mg) isolated in the usual way was distilled under diminished pressure to yield the unsaturated acetate (XVIII) as a colorless oil, $[\alpha]_D$ +24.6°($c=4.2$), IR (liquid) cm^{-1}: 1729, 1238 (acetoxyl), NMR: singlet (3H) at 9.26τ ($\text{C}\underline{\text{H}}_3$–C⋖), singlet (3H) at 8.98τ ($\text{C}\underline{\text{H}}_3$–C⋖), doublet (3H) at 8.87τ (J=7, $\text{C}\underline{\text{H}}_3$–CH⟨), singlet (3H) at 8.03τ ($\text{C}\underline{\text{H}}_3$–CO–O–), doublet (1H) at 5.32τ ($J=7$, –CH_2–$\text{C}\underline{\text{H}}(\text{OCOCH}_3)$–CH⟨), broadened peak (1H) at 4.95τ (band width at half height: 7 cps, –CH_2–$\text{C}\underline{\text{H}}$=C⟨).

Oxidation of the Unsaturated Alcohol with Chromic Acid——a) To a stirred solution of the unsaturated alcohol (XIX)(500 mg) in ether (5 ml) was added $\text{Na}_2\text{Cr}_2\text{O}_7\cdot 2\text{H}_2\text{O}$ (500 mg) in H_2SO_4 (1 ml) and H_2O (4 ml), stirring was continued at room temperature for 2 hr. Isolation by ether extraction gave an oil (423 mg). Chromatography on silica gel (8 g) and elution with light petroleum–benzene (5:1) afforded an oil (279 mg) which on distillation under reduced pressure yielded the unsaturated ketone (XXI) as a colorless oil, $[\alpha]_D$ −43.3°($c=4.4$), *Anal.* Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}$: C, 82.51; H, 10.16. Found: C, 85.15; H, 10.07, IR (liquid) cm^{-1}: 1702 (cyclohexanone), NMR: singlet (3H) at 9.10τ ($\text{C}\underline{\text{H}}_3$–C⋖), singlet (3H) at 8.90τ ($\text{C}\underline{\text{H}}_3$–C⋖), doublet (3H) at 8.78τ ($J=7$, $\text{C}\underline{\text{H}}_3$–CH⟨), slightly multiplying singlet (3H) at 8.42τ ($\text{C}\underline{\text{H}}_3$–C=C⟨), NMR ($\text{C}_6\text{H}_6$): singlet (3H) at 9.27$\tau'$ ($\text{C}\underline{\text{H}}_3$–C⋖), singlet (3H) at 9.14τ' ($\text{C}\underline{\text{H}}_3$–C⋖), doublet (3H) at 8.80τ' ($J=7$, $\text{C}\underline{\text{H}}_3$–CH⟨), slightly multiplying singlet (3H) at 8.56τ' ($\text{C}\underline{\text{H}}_3$–C=C⟨).

b) A solution of H_2CrO_4[13] was added dropwise with stirring to the unsaturated alcohol (XIX)(33 mg) in acetone (1ml) until a persistent orange coloration was given. The reaction mixture was extracted with ether, and the extract shaken with NaHCO_3 solution and then with H_2O and evaporated. Evaporation gave an oil (27 mg) which was chromatographed on silica gel (1 g). Light petroleum–benzene (5:1) eluted the unsaturated ketone (XXI)(11 mg), identified by comparison of IR and NMR spectra.

Reduction of the Unsaturated Ketone with Lithium Aluminum Hydride——To a stirred solution of the ketone (XXI)(63 mg) in ether (5 ml) was added LiAlH_4 (20 mg). The mixture was stirred at room temperature for 30 min, after which the excess hydride was decomposed with H_2O, and the product (57 mg) isolated in the usual way was crystallized from light petroleum to give the isomerized alcohol (XXII) as colorless needles, mp 95—97°, $[\alpha]_D$ +35.6°(c=2.7), IR (CCl_4) cm^{-1}: 3650, 3450 (hydroxyl), NMR: singlet (3H) at 9.25τ ($C\underline{H}_3$–$C\leqslant$), doublet (3H) at 9.02τ (J=7, $C\underline{H}_3$–$CH\langle$), singlet (3H) at 8.94τ ($C\underline{H}_3$–$C\leqslant$), unresolved peak (3H) at 8.43τ ($C\underline{H}_3$–$C{=}C\langle$), sextet (1H) at 6.08τ ($J_1=J_2=10$, $J_3=7$, –CH_2–$C\underline{H}(OH)$–$CH\langle$).

Wolff–Kishner Reduction of the Unsaturated Ketone——The ketone (XXI)(86 mg) and 80% $NH_2NH_2 \cdot H_2O$ (60 mg) in EtOH (1 ml) were refluxed for 2 hr and then KOH (80 mg) and triethylene glycol (1 ml) were added. The mixture was heated to 190° to distilled NH_2NH_2 and H_2O, kept at 190—200° for 1 hr, poured into H_2O, and extracted with ether. The product (64 mg) was chromatographed over alumina (1 g). Elution with light petroleum and distillation under reduced pressure furnished the synthetic cyperene (III) (30 mg) as a colorless oil, $[\alpha]_D$ −24.0°(c=3.7), MS (m/e): 204 (M^+, base), 189, 175, 161, 147, 133, 119, 105, 91, 79, 69, 55, 41, NMR: singlet (3H) at 9.25τ ($C\underline{H}_3$–$C\leqslant$), doublet (3H) at 9.20τ (J=5, $C\underline{H}_3$–$CH\langle$), singlet (3H) at 9.06τ ($C\underline{H}_3$–$C\leqslant$), singlet (3H) at 8.39τ ($C\underline{H}_3$–$C{=}C\langle$).

Oxidation of Cyperene with *t*–Butyl Chromate——A mixture of CrO_2 (O–t–Bu)$_2$ solution (solution B,[13] 4 ml), HOAc (1ml), and Ac_2O (0.5 ml) was added dropwise with swirling to cyperene (III)(340 mg) in CCl_4 (4 ml) at 70° over 30 min and the mixture was allowed to stand at 70° with occasional swirling for 1 hr. Upon isolation in the usual manner, the product (350 mg) was filtered through silica gel (10 g).

Elution with light petroleum gave the recovered cyperene (III)(157 mg).

Successive elution with light petroleum–benzene (10:1) afforded a crystalline mass (15 mg) which was crystallized from light petroleum to give the synthetic patchoulenone (II) as colorless needles, mp 50—52°, $[\alpha]_D$ −118.8°(c=2.8), IR (KBr) cm^{-1}: 1710, 1662 (2–(exo)ethylenecyclopentanone), NMR: doublet (3H) at 9.17τ (J=6, $C\underline{H}_3$–$CH\langle$), singlet (3H) at 9.12τ ($C\underline{H}_3$–$C\leqslant$), singlet (3H) at 9.00τ ($C\underline{H}_3$–$C\leqslant$), triplet (3H) at 8.01τ (J=1, –CH_2–$C(C\underline{H}_3){=}C\langle$), identified by mp, optical rotation, and IR and NMR spectra as the natural patchoulenone.

Further elution with light petroleum–benzene (5:1) gave a crystalline mass (90 mg) which on crystallization from light petroleum furnished the synthetic cyperotundone (I) as colorless needles, mp 45—46°, $[\alpha]_D$ +41.2°(c=5.8), CD (c=0.0529, dioxane): $[\theta]_{314}$ −5380, MS (m/e): 218 (M^+, base), 203, 175, 161, 147, 133, 119, 105, 91, 77, 69, 55, 41, IR (CCl_4) cm^{-1}: 1705, 1667 (cyclopentenone), NMR: doublet (3H) at 9.39τ (J=7, $C\underline{H}_3$–$CH\langle$), singlet (3H) at 9.25τ ($C\underline{H}_3$–$C\leqslant$), singlet (3H) at 8.83τ ($C\underline{H}_3$–$C\leqslant$), triplet (3H) at 8.33τ (J=1, $C\underline{H}_3$–$C{=}C$–CH_2–), identified by mixed mp and comparison of optical rotations, and IR and NMR spectra with the natural cyperotundone.

Acknowldgement We are much indebted to Dr. O. Motl, Czechoslovak Academy of Science, for a generous gift of the natural patchoulenone, to Research Laboratories, Takeda Chemical Industries, Ltd., for the mass spectra, to Analytical Laboratory, Department of Chemistry, this University, for the NMR spectra, and to Analytical Laboratories, this Institute, for the IR and NMR spectra and microanalyses.