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Synthesis of Intermedeol and Related Sesquiterpenoid Studies[1]

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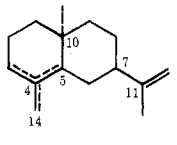
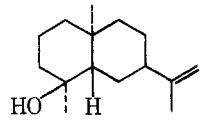
The 10-epieudesmanes (−)-7β,10α-selina-4,11-diene (I) and (+)-5βH,10α-selina-3,11-diene (II) were synthesized from 10α-selina-4,11-dien-3-one (VI) and natural (−)-7β,10β-selina-4,11-diene (I) was further converted into intermedeol (IV). Intermedeol (IV) was transformed into 5βH,10α-eudesmol (XI). On treatment with boron trifluoride etherate, neointermedeol (XV), a close relative of intermedeol, gave δ-selinene, while with thionyl chloride in benzene selina-4,11-diene was obtained.

The recent isolation of the dienes (−)-7β,10α-selina-4,11-diene (I) and (+)-5βH,7β,10α-selina-3,11-diene (II) from *Dipterocarpus alatus* Roxb.[3] and (−)-5β,7β,10α-selina-4(14),11-diene (III) from *Aristolochia indica* Linn.[4] are of particular interest since they can be visualized as arising biogenetically simply by dehydration of intermedeol (IV), the

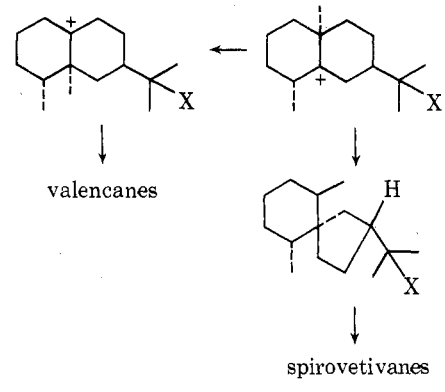


I, $\Delta^{4(5)}$
II, $\Delta^{3(4)}$, 5βH
III, $\Delta^{4(14)}$, 5βH



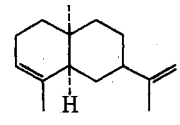
IV

first member of this family to be reported.[5] In fact, diene III was first prepared in 1962,[5b,6] by pyrolysis of intermedeol acetate, but was not recognized as such since, at that time, the configuration at C-7 was thought to be 7βH.[5a] The grapefruit constituent paradisol[7] is now known to be identical with intermedeol[8] and a direct comparison of the dehydration product of paradisol[7] with natural III has shown their identity.[4] Only a few other related 10-epieudesmanes have been reported,[9,10] but this group of sesquiterpenes appears to play an important role as biogenetic precursors to the valencanes and spirovetivanes.[11,12] Marshall and Andersen[12] have concluded from the literature on constituents of eudalene-yielding essential oils that (1) 10-epieudesmanes are more prone to rearrangement and (2) rearrangements always occur from a eudesmane with cis related methyl groupings. These observations were

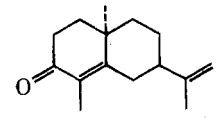


explained by postulating that relief of the strain associated with an axial isopropyl grouping and a 1,3-diaxial methyl interaction provides substantial driving force for the rearrangements.[12]

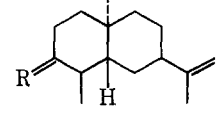
We now report the synthesis of I (21%) and II (13%) together with isomer V (37%) by a modified Wolff–Kishner reduction[13] of the previously reported dienone VI[14] and the further con-



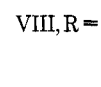
V



VI



VII, R = O

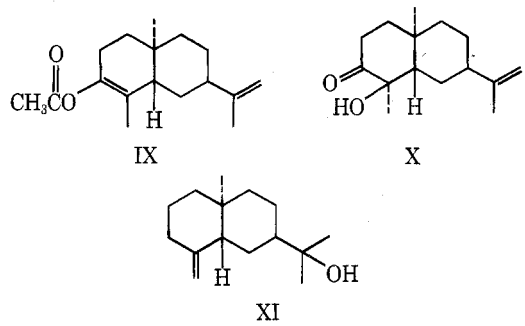
VIII, R = 

version of natural II into intermedeol (IV). The reaction conditions were selected to give the maximum amount of double bond migration. I and II were identical by ir and NMR spectra and by gas chromatography on three columns with authentic samples.[15] Diene V was characterized by its elemental analysis, mass spectrum, and by its ir (ν 1635, 880 cm^{-1}) and NMR [δ 0.87 (3 H), 1.65–1.73 (6 H), 4.72 (2 H), 5.30 (1 H)] spectra. The preference for protonation of the intermediate anion of the hydrazone at C-5 to give cis fused V may be explained as follows. If it is assumed that the orbital at C-5 is sp^3, presumed in the case of metal ammonia reductions of α,β-unsaturated ketones,[16] then continuous overlap with the C-4 sp^2 orbital can be maintained by an α-oriented (cis to C-10 methyl) C-5 orbital. This orientation would be expected to be preferred over the β orientation (leading to II) since the former intermediate, after protonation at C-5, would lead to an all-chair arrangement with an equatorial C-7 isopropenyl group whereas the latter case would lead to the less favorable B-ring twist-boat conformation. Grundon, Henbest, and Scott[17] showed that by using a modification of the Wolff–Kishner reduction procedure involving potassium *tert*-butoxide in refluxing toluene, double bond migration in α,β-unsaturated ketones could be minimized and, in particular, by using the preformed semicarbazone of cholest-4-en-3-one, essentially pure cholest-4-ene was obtained in high yield. When the semicarbazone of VI was subjected to these conditions, the only product detected by gas chromatography and isolation was I, the unrearranged diene.

Epoxidation of natural II[15] with *m*-chloroperbenzoic acid (1 molar equiv) in methylene chloride gave a mixture in which a single epoxide predominated (~80% of products).[18] Attempted separation of this epoxide mixture by chromatography on silica gel led to disappearance of epoxides and formation of a ketone, presumably VII, as the major product. Therefore, the epoxide mixture was reduced with $LiAlH_4$ in THF at 60 °C and only after 16 h were the epoxides consumed. Gas chromatographic analysis indicated the presence of three products in the approximate ratio of 1.5:4.3:1.0. The most abundant product was eluted with benzene/hexane (~1:1) from an alumina column and was shown to be alcohol VIII by its spectral properties and its conversion to the known ketone VII[3,14] by Jones oxidation. The second most abundant reduction product was eluted from the alumina column prior to alcohol VIII, but repeated chromatography over alumina failed to provide it in completely pure form. An analytically pure sample was obtained by preparative gas chromatography and it was found to be identical by ir, NMR, and gas chromatography with natural intermedeol (IV).[5] This represents the first reported synthesis of intermedeol.[19] When intermedeol was first isolated[5b] we were surprised that it showed two bands of equal strength in its ir spectrum at 890 and 910 cm^{-1}; the presence of both these bands has been verified in the spectrum of pure synthetic intermedeol.

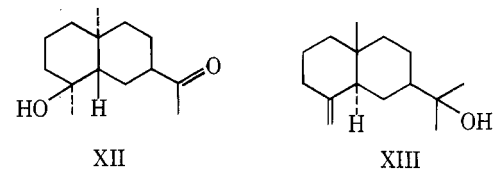
Regiospecific epoxidation of II at the more nucleophilic C-3, C-4 double bond was to be expected,[20] and an examination of Dreiding models clearly indicated that the β face (trans to C-10 Me) is less sterically encumbered. Thus, it is assumed that the major epoxide of II is the β-epoxide. However, this epoxide has no low-energy pathway available to it for reduction by lithium aluminum hydride, and indeed this reaction proceeded at a surprisingly slow rate as indicated above. Alcohol VIII must arise either by axial nucleophilic attack from the α side at the highly hindered C-4 tertiary position, or the epoxide undergoes prior rearrangement to the C-3 ketone, catalyzed by a Lewis acid impurity, which in turn is reduced.[21] Indeed, addition of $AlCl_3$ to the solution enhanced the rate of formation of alcohol VIII. Intermedeol is produced by hydride attack at the secondary C-3 position, but in order for there to be axial epoxide opening an A-ring boat conformation would be involved (presumably the B ring is also in a boat conformation).

An attempt was made to synthesize intermedeol from VI by reductive acylation with lithium/ammonia/*tert*-butyl alcohol and trapping with acetic anhydride to give enol acetate IX, followed by epoxidation with *m*-chloroperbenzoic acid and



alkaline hydrolysis to give X and finally conversion of X to intermedeol. Enol acetate IX was obtained, as expected, in a yield of about 65% and its NMR spectrum showed the characteristic C-4 methyl group at δ 1.43.[22] The ir spectrum of IX was analogous to that reported for its Δ^2 isomer.[23] Epoxidation of IX appeared to proceed without difficulty and the crude epoxide was hydrolyzed with aqueous ethanolic potassium hydroxide[24] to give X, in poor yield, after chromatography on alumina.[25] However, no means was found to efficiently remove the C-3 carbonyl group without disturbing the C-4 hydroxyl group or C-11 double bond.

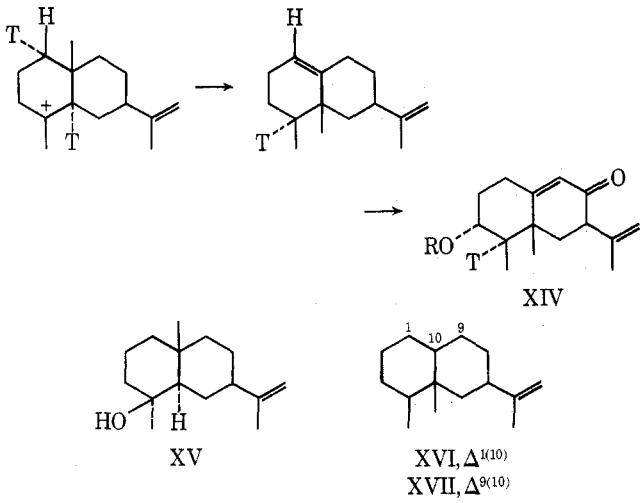
Intermedeol has been converted into 5βH,10α-eudesmol (XI), a material not yet found in nature but presumably an important biogenetic precursor,[11] as follows. Oxidation with potassium permanganate–sodium periodate gave XII as previously described.[5a] Ketol XII was dehydrated to the exocyclic olefin with phosphorus oxychloride in pyridine, then addition of methylmagnesium iodide and the usual workup gave, after chromatography, 5βH,10α-eudesmol (XI), which was similar to but distinguishable from the natural product β-eudesmol (XIII) by thin layer and gas chromatography.[26]



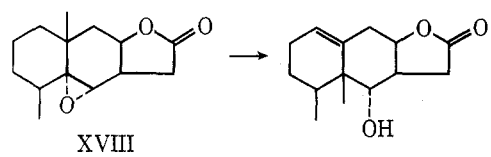
Insufficient quantities of intermedeol (IV) and XI have thus far been available to study their in vitro conversion to spirovetivanes and valencanes, as postulated in the biogenesis of these substances.[11,12]

Recently Brooks and Keates[27] provided in vivo support for the original Robinson postulation[28] that the C-5 methyl group in eremophilane sesquiterpenes arises by migration from C-10 in a precursor of the eudesmanoid skeletal type as outlined for petasin (XIV). Therefore, we attempted an in vitro simulation of this biogenetic pathway using neointermedeol (XV), a close relative of intermedeol, previously isolated by us from a different race of the same plant species that yielded intermedeol.[29] As mentioned above, Marshall and Andersen[12] postulated that in vivo a C-10 → C-5 methyl migration always occurs from a eudesmane with cis related methyl groups. However, in neointermedeol where the C-4 hydroxyl group is instead cis to the C-10 methyl group, the concerted sequence of trans anti parallel shifts (−) α C-1 H; β C-10 Me → β C-5 Me; α C-5 H → α C-4 H; (−) β C-4 OH are possible. In the event, exposure to boron trifluoride etherate for 3 min resulted in the conversion of neointermedeol into δ-selinene (selina-4,6-diene) in excellent yield while treatment with thionyl

chloride in benzene gave selina-4,11-diene as the major product. The latter was identified by the similarity of its ir and NMR spectra to those previously reported[30] and the almost identity of its NMR spectrum with that of its 10 epimer I. However, in the latter case there was indication that a "biogenetic type" rearrangement did occur to a small extent, involving either a C-10 → C-5 methyl migration to give either eremophilene (XVI) or its isomer 7αH-eremophila-9,11-diene (XVII)[31] or rearrangement to a spirovetivane. While



chromatography failed to yield the minor "biogenetic type" product in pure form, fractions enriched in this product were obtained in which the NMR spectra showed high-field methyl doublets and broad olefinic signals at about δ 5.3.[31,32] A number of unsuccessful attempts to effect the in vitro conversion of an eudesmanoid type precursor into an eremophilane type sesquiterpene have been recorded.[33] The only reported successful example of a C-10 → C-5 methyl migration in an eudesmanoid precursor involved the formic acid–acetone treatment of epoxydihydroalantolactone (XVIII).[34] More



XVIII

recently, Hochstetler[35] has shown that 2,2,8,8,10-pentamethyl-1(9)-octalin undergoes acid-catalyzed rearrangement via both a spiro[4.5]decalyl cation system and an angular methyl migration. Thus, in vitro "biogenetic type" rearrangements of simple eudesmanes (or 10-epieudesmanes) to eremophilanes (or valencanes) or spirovetivanes are not readily accomplished and may, in fact, require very rigid conformation features as present in the more highly substituted derivatives. In vivo this conformational rigidity could be enzyme controlled.

Experimental Section[36]

7β,10α-Selina-4,11-diene, 5βH,7β,10α-Selina-3,11-diene, and 5αH,7β,10α-Selina-3,11-diene (V). Ketone VI (4.8 g)[14] and 8 ml of hydrazine hydrate (64% in water) were dissolved in 350 ml of freshly distilled triethylene glycol. To this was added a solution prepared by dissolving 7.6 g of potassium hydroxide in 100 ml of triethylene glycol. The combined solution was heated at 100 °C for 30 min, then the temperature raised to 210 °C over a period of 30 min, where it was maintained for 1 h, during which time hydrazine and water distilled out of the solution.[13] Extraction with petroleum ether (bp 30–60 °C), washing with water, drying ($MgSO_4$), and concentration gave 4.24 g of product which by gas chromatography (Carbowax 20M column) was shown to be composed of, in order of elution, 37% V, 21% I, and 13% II. Repeated column chromatography on 10% silver nitrate–silica gel columns provided analytically pure samples of the three dienes which were eluted with 10% benzene in petroleum ether in the order II, V, and finally I. I and II were identical with authentic samples[3,15] of I and II by gas chromatography (Carbowax 20M column) alone and on admixture, and by superposition of their ir, NMR, and mass spectra. Infrared and NMR spectra of I and II have been previously reported.[3]

Wolff–Kishner reduction of the semicarbazone of VI under the conditions of Grunwald et al.[17] gave only I. Thus, 1.0 g of semicarbazone VI (mp 177–180 °C, lit.[14] mp 177 °C) and 0.8 g of potassium *tert*-butoxide were added to 15 ml of toluene and the solution was refluxed for 90 h. Nitrogen evolution (~89% theoretical) appeared to cease after 68 h. The solution was neutralized with hydrochloric acid and extracted with ether. After the usual workup, gas chromatography and NMR analysis of the crude product indicated the presence of only I. As previously, an analytically pure sample of I was prepared and was identical with I prepared as described above.

Diene V, which showed a single peak by gas chromatography, exhibited the following properties: bp 70 °C (0.1 mm) (bath); mass spectrum 204.1889 (calcd, 204.1878); ir ν_{max} (neat) 1645 and 890 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.88 (3 H, s), 1.66–1.75 (6 H, m), 4.72 (2 H, m), 5.30 (1 H, m).

Synthesis of Intermedeol (IV). To a solution containing 0.994 g of II[15] (88.5% purity by gas chromatography) in 25 ml of methylene chloride at −10 °C was added dropwise a solution containing 0.944 g of *m*-chloroperbenzoic acid in 25 ml of methylene chloride at 0 to −10 °C over a period of 5 min. Gas chromatography indicated reaction to be complete after an additional 20 min of stirring. The methylene chloride solution was then washed successively with a saturated sodium sulfite solution, a sodium bicarbonate solution, then a saturated brine solution. Drying ($MgSO_4$) and concentration with a rotary evaporator gave 0.997 g of the crude epoxide product, gas chromatographic analysis (ratio of peak areas) of which indicated approximately 71% of a single product, <5% unreacted II, and a number of other components, none of which were present in excess of 5%:[18] ν_{max} (film) 880 cm^{-1}; δ (CCl_4) 4.88 (m).

To a solution of 10 ml of tetrahydrofuran, distilled from lithium aluminum hydride, containing 98 mg of the above-mentioned epoxide mixture at 58 °C, was added dropwise (over a period of 30 min) a solution prepared by vigorously stirring 103 mg of lithium aluminum hydride in 10 ml of dry tetrahydrofuran. Gas chromatographic analysis showed disappearance of starting material only after 16 h, when the reaction mixture was quenched with a solution of sodium potassium tartrate, then extracted with ether. Drying and concentration with a rotary evaporator gave 107 mg of crude product, gas chromatographic analysis of which indicated three major products in the ratio 15:23:62, in the order of increasing retention time. The second most abundant constituent showed the same retention time as intermedeol (IV) by gas chromatography. The analytical sample of intermedeol was only obtained after repeated chromatography on neutral alumina (activity I) followed by preparative gas chromatography (Carbowax 20M column). The intermedeol thus obtained was identical with the natural product by ir and NMR spectral comparisons, and in gas chromatographic retention time alone and on admixture.[5]

The most abundant product, VIII, was eluted from the alumina column after intermedeol in benzene/hexane (1:1): δ (CCl_4) 0.83 (3 H, s), 0.95 (3 H, d, J = 6 Hz), 1.68 (3 H, s), 3.68 (1 H, m), 4.83 (2 H, m). Oxidation of VIII with Jones reagent gave ketone VII, mp 43–45 °C (lit.[3] mp 49.5–50 °C), identical by ir and NMR spectra with the spectra of an authentic sample prepared by reduction of VI with lithium in liquid ammonia as previously described.[14]

Attempted Conversion of VI into Intermedeol. Preparation of Ketol X. Ketone VI[14] (5.45 g, 0.025 mol) and 1.85 g (0.025 mol) of *tert*-butyl alcohol were dissolved in 50 ml of anhydrous ether. This solution was added dropwise, over a period of 1 h, to a solution of 250 ml of liquid ammonia to which 0.38 g (0.55 g-atom) of lithium had been added. After stirring for an additional 1 h, the ammonia was allowed to evaporate under anhydrous conditions and when evaporation seemed to cease, 25 ml of anhydrous ether was added to the residue and this solution was allowed to evaporate in a hood. This procedure was repeated in order to remove the last traces of ammonia and finally the residue was taken up in 50 ml of anhydrous ether and this ethereal solution, after vigorous stirring, was slowly dropped (30 min) into 25.5 g (0.25 mol) of freshly distilled acetic anhydride at room temperature under a nitrogen atmosphere. After stirring for an additional 30 min, this solution was rapidly added to a two-phase system of 150 ml of pentane and 150 ml of a saturated sodium bicarbonate solution at 0–5 °C. Solid sodium bicarbonate was added, over a period of 2–3 h, while the temperature was maintained below 5 °C until neutralization was complete. The layers were separated, the aqueous layer was filtered and then extracted with pentane, and the combined

pentane layers were washed sequentially with sodium bicarbonate solution, then saturated brine solution, and finally dried and evaporated to give a crude residue of 6.36 g. Gas chromatography (Carbowax 20 M column) showed in order of increasing retention time 9% of an unidentified substance, 16% VII, 4% unidentified substance, 65% IX, and 6% VI (ratio of peak areas). Chromatography on Merck acid-washed alumina (activity II) gave enol acetate IX in the petroleum ether eluent, ketone VII in the petroleum ether–benzene (9:1) eluent, and the α,β-unsaturated ketone VI in the petroleum ether–benzene (1:1) to benzene eluents. Hot box distillation gave the analytical sample of IX: bp 100–110 °C (bath) (0.1 mm); ν_{max} (neat) 1750, 1685, 1640, 1220, 892 cm^{-1}; δ (CCl_4) 0.92 (3 H, s), 1.43 (3 H, m), 1.72 (3 H, m), 2.03 (3 H, s), 4.85 (2 H, b); positive plain ORD curve.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found C, 77.55; H, 9.90.

To 3.02 g of crude enol acetate in 150 ml of dry chilled ether, 2.37 g of *m*-chloroperbenzoic acid (83.8%) in 40 ml of dry ether was added. After 14 h at 5 °C, gas chromatography showed that little enol acetate had been consumed and the solution was therefore left at 25 °C in the dark for 25 h. Ether was removed with the rotary evaporator and addition of 50 ml of petroleum ether resulted in precipitation of *m*-chlorobenzoic acid, which was removed by filtration. Evaporation of the petroleum ether gave a quantitative yield of crude product: δ (CCl_4) 1.32, 1.73, 2.02, 2.06, 4.85. Gas chromatography suggested decomposition on the column and the crude epoxide was used without further purification. To a solution containing the above crude epoxide in 100 ml of ethanol was added a solution prepared by dissolving 5 g of potassium hydroxide in 25 ml of ethanol and 3 ml of water. The entire solution was stirred at 60 °C for 2 h, then most of the alcohol was removed at reduced pressure and 100 ml of water was added to the residue, which was then extracted with ether. Washing with brine, drying over magnesium sulfate, and evaporation of the ether gave crude product in 95% yield. Gas chromatographic analysis of the crude product indicated the presence of seven products with the hydroxy ketone composing only about 20% of the mixture (based on peak areas). Chromatography on Merck acid-washed alumina (activity II) gave the hydroxy ketone in the benzene eluent as a viscous gum: bp 110–115 °C (0.1 mm) (bath); ν_{max} (neat) 3477, 1714, 1661, 1637, 1069, 1052, and 895 cm^{-1}; δ (CCl_4) 1.16 (3 H, s), 1.18 (3 H, s), 1.73 (3 H, m), 4.86 (2 H, b).

Attempted preparation of the thioketol of X appeared, by NMR analysis, to result in at least partial migration of the isopropenyl double bond, and reduction of the crude product with Raney nickel gave no product corresponding to intermedeol by gas chromatographic analysis. Reduction of X with lithium aluminum hydride in ether resulted in disappearance of the carbonyl group, as detected by ir, but the product could not be converted into the desired secondary tosylate, the characteristic isopropenyl double bond peak at 890 cm^{-1} in the ir having disappeared. Regardless, lithium aluminum hydride reduction of this crude product likewise gave no material with the retention time of intermedeol by gas chromatography.

Conversion of Intermedeol (IV) into 5βH,10α-Eudesmol (XI). Intermedeol (0.134 g) was dissolved in 65 ml of *tert*-butyl alcohol and a solution of 1.02 g of sodium periodate, 0.252 g of potassium carbonate, and 0.03 g of potassium permanganate in 70 ml of water was added with stirring at room temperature. After stirring for 17 h, 120 ml of water was added to the solution which was then extracted with benzene. The combined organic layers were washed with water, then dried over magnesium sulfate. Evaporation of the solvent gave 0.105 g of a yellow oil, which was distilled to give ~80% (peak area, gas chromatography) of ketol XII: bp 115 °C (0.3 mm) (bath); ν_{max} (neat) 3440, 1705, 1455, 1380, 1285, and 910 cm^{-1}; δ ($CDCl_3$) 0.92 (3 H, s), 1.10 (3 H, s), 2.18 (3 H, s).

The ketol was dehydrated as follows. To ketol (0.120 g) dissolved in 4 ml of dry pyridine was added 0.3 ml of phosphorus oxychloride. After mixing, the homogeneous solution was allowed to stand at room temperature for 20 h, then poured over 40 g of ice and the resulting mixture extracted with ether. The ether extracts were washed with water, 2% hydrochloric acid, and again with water until neutral and finally dried over magnesium sulfate, then filtered and evaporated to give 0.111 g of the enone: ν_{max} (neat) 1710, 1450, 1378, 1284, and 887 cm^{-1}; δ ($CDCl_3$) 0.73 (3 H, s), 2.13 (3 H, s), 4.42 and 4.73 (2 H, m).

5βH,10α-Eudesmol (XI) was prepared from the above enone as follows. To 0.275 g of magnesium turnings in 2 ml of dry ether was added 0.1 ml of methyl iodide to initiate the reaction, after which 1.60 g of methyl iodide in 5 ml of dry ether was added drop by drop. Another 2 ml of dry ether was added and after an additional 15 min of stirring, 0.11 g of the above-mentioned enone dissolved in 5 ml of ether was added and the entire solution refluxed for 6 h. The reaction was quenched with a saturated ammonium chloride solution and the mixture was thoroughly extracted with ether. After washing with water and drying, evaporation of the ether extract gave 0.089 g of crude XI (~85% purity by peak areas in gas chromatography).

Chromatography on silica gel gave XI in the hexane–ether (98:2) eluent and distillation, bp 105–110 °C (0.2 mm) (bath), gave a colorless liquid which crystallized on standing, mp 45–50 °C. Further chromatography on alumina (activity II) gave material of mp 62–66 °C in the benzene–ether (1:1) eluent. This alcohol (XI) was shown to be homogeneous by thin layer chromatography (silica gel, 95:5 chloroform–ether) and by gas chromatography on a 3% QF-1 column and not to be identical with an authentic sample of β-eudesmol (XIII): $[\alpha]^{25}D$ −17.5° (*c* 5.00, $CHCl_3$); ν_{max} (neat) 3420, 1640, 1450, 1380, and 890 cm^{-1}; ν_{max} (CCl_4) 3610, 1640, 1455, 1380, and 888 cm^{-1}; δ ($CDCl_3$) 0.76 (3 H, s), 1.26 (6 H, s), 4.51 and 4.76 (2 H, m); mass spectrum 204.1880 (calcd for $M^+ - H_2O$, 204.1878).[26]

Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 81.18; H, 11.83.

Dehydration of Neointermedeol. A. Reaction with Boron Trifluoride Etherate. Neointermedeol[29] (118 mg) was dissolved in 2.5 ml of dry benzene and to this solution was added 0.25 ml of freshly distilled boron triifluoride etherate. After stirring at room temperature for 3 min, 5 ml of water was added, the layers separated, the aqueous layer further extracted with ether, and the combined organic layers washed with water, dried, and concentrated on the rotary evaporator to give 108 mg of crude product, gas chromatograph and NMR of which indicated the presence of approximately 90% δ-selinene. Distillation gave pure δ-selinene (bp 130 °C, 0.06 mm) which was identified by its uv and ir spectra[37] and NMR spectrum: δ ($CDCl_3$) 0.98 (3 H, s), 1.10 (6 H, d, J = 6.5 Hz), 6.2 (1 H, s).

B. Reaction with Thionyl Chloride. Neointermedeol[29] (250 mg) was dissolved in 5 ml of dry benzene to which was added 100 mg of pyridine. After cooling to 5 °C 1.35 g of thionyl chloride was added. After maintaining the solution at 10–20 °C for 90 min, it was poured into an aqueous bicarbonate solution which was extracted with ether. The usual workup gave 0.25 g of crude product, gas chromatography of which showed the absence of starting material but the appearance of one major and two minor peaks of lower retention time. Chromatography on a silver nitrate–silica column gave selina-4,11-diene: δ ($CDCl_3$) 1.05 (3 H, s), 1.62 (3 H, s), 1.75 (3 H, s), 4.75 (2 H, m); ν_{max} (neat) 1640, 887 cm^{-1}.[30] Further elution yielded fractions containing predominantly selina-4,11-diene as determined by gas chromatography and NMR but the NMR spectra showed the presence of high-field doublets at ~δ 0.9 and a broad signal at ~δ 5.3.[31,32]

Registry No.—I, 28290-20-2; II, 60132-29-8; IV, 60064-79-1; V, 60132-30-1; VI, 2303-31-3; VIII, 60132-31-2; IX, 60064-80-4; X, 60064-81-5; XI, 60132-32-3; XII, 60132-33-4; XII enone analogue, 60064-82-6; XV, 5945-72-2.

References and Notes

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Synthesis of a Tetracyclic Ajmalicine Analogue

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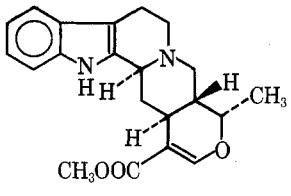
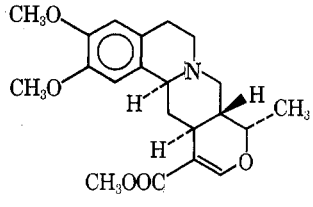
The synthesis of a tetracyclic analogue (**2**) of the heteroyohimbine alkaloid ajmalicine (**1**) is described. The synthesis makes use of a novel alternative to the Korte reaction for the preparation of the dihydropyran ester portion (**11**) of the molecule.

A number of syntheses of indole alkaloid analogues lacking the pyrrole ring of the natural products has been reported.[1] These syntheses were undertaken either with the aim of obtaining medicinally useful substances or as model studies for the synthesis of the natural alkaloids. With the former goal in mind it appeared worthwhile to prepare such a tetracyclic version of the heteroyohimbine alkaloid ajmalicine (**1**)[2] as a potential hypotensive agent.

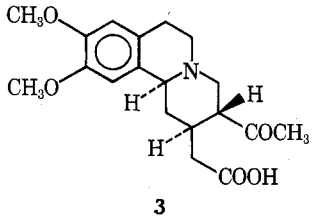


1

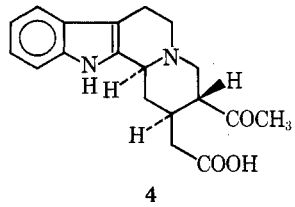


2

We selected **2** as our target, reasoning that it could be prepared from the intermediate **3**, used in van Tamelen's emetine synthesis,[3] by applying the methods developed for the synthesis of ajmalicine from the corresponding indole-containing intermediate **4**, described in the same paper.[3]



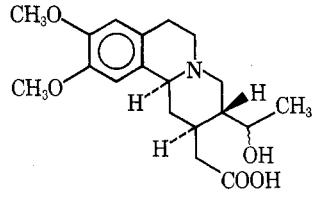
3



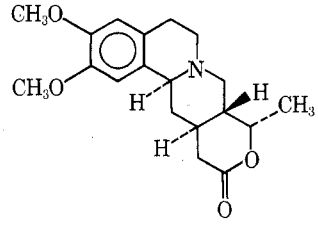
4

Reduction of **3** with sodium borohydride in aqueous potassium hydroxide gave the hydroxy acid **5**. The NMR spectrum of this substance showed that it was a 50:50 mixture of the two epimeric alcohols [a methyl doublet at δ 1.26 (J = 6.75 Hz) collaped on irradiation at δ 4.71, while a doublet at δ 1.30 (J = 6.20 Hz) collapsed on irradiation at δ 4.29].

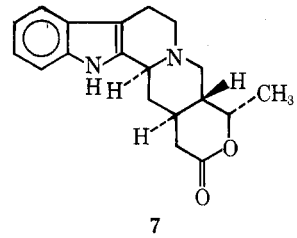
The lactone **6** was prepared from **5** either with 1-cyclohexyl-3-(2-morpholinylethyl)carbodiimide metho-*p*-toluenesulfonate in pyridine or with ethanolic hydrogen chloride. One recrystallization of the crude lactone gave material which was a single isomer (NMR), presumably having the configuration indicated by analogy with van Tamelen's pentacyclic lactone **7** which was converted to ajmalicine.[3] Surprisingly, although a variety of conditions was tried, treatment of **6** with triphenylmethylsodium in dioxane followed by addition of methyl formate did not lead to the formation of the α-hydroxymethylene lactone. van Tamelen found that the lactone **7** underwent condensation under these conditions.[3] Conceivably, in the case of **7**, proton abstraction α to the carbonyl group was facilitated by an intramolecular process involving initial deprotonation of the indole N–H.



5



6



7

We had intended to complete the synthesis of **2** by making use of the Korte reaction,[4] which involves treatment of a hydroxymethylene lactone **8** with methanolic HCl at room