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THE STRUCTURE OF δ-CADINOL—AMORPHAN-3-ENE-9β-OL

Y. T. LIN, Y. S. CHENG and Y. H. KUO
Department of Chemistry, National Taiwan University, Republic of China

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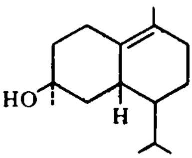
Abstract—The structure of δ-cadinol was established as amorphan-3-ene-9β-ol (VIII) by chemical behavior and spectroscopic data.

δ-CADINOL, a cadalene sesquiterpene alcohol, was first isolated in 1922 from the leaves of *Torreya nucifera* Sieb et Zucc (Taxaceae). Since then, six different structures, I,[1] II,[2] III,[3] IV,[4] V[5] and VI,[6] have been proposed by various workers. Smolders[5] has adduced sound evidence that the olefinic linkage should be located at C_3–C_4. Therefore, structure I, II, III and IV can be excluded. However, δ-cardinol cannot be of the cadinane structure, since structure VII and V have been assigned to α-cadinol[7] and T-cadinol,[8, 6a] respectively, and both structures are well established.

All the known muurolane derivatives have been found to give good yields of crystalline dihydrochlorides, and the yield of muurolene dihydrochloride was always higher than that of cadinene dihydrochloride.[8, 9] But δ-cadinol gave only cadinene dihydrochloride in poor yield (30%, lit.[2] 14%). In addition, bulgarene gave bulgarene dihydrochloride only.[10] Thus, δ-cadinol is unlikely to be a derivative of muurolene (VI) or a derivative of bulgarene. Now we wish to report that the correct structure of δ-cadinol should be amorphan-3-ene-9β-ol (VIII), an amorphene derivative.

Dehydration of δ-cadinol with $SOCl_2$ in pyridine afforded a mixture of hydrocarbons which showed weak terminal methylene absorption in the IR spectrum and five products were obtained by gas chromatography. Three of them (main products) were identified by IR spectra as γ-muurolene, α-muurolene and δ-cadinene in the approximate ratio 25:57:10. Similar result had been obtained by using brosyl chloride in pyridine.[4, 6c] These results indicate the OH group in δ-cadinol is located at C_9, and in an axial orientation.

When δ-cadinol was allowed to react with B_2H_6 in THF followed by oxidation with H_2O_2, two diols, IX and X, were obtained. The former (major) product melted at 127–129°. The NMR spectrum showed a triplet ($J = 7{\cdot}0$ cps) at τ 6·10 for the C_4 proton indicating a diaxial relationship between the C_4 and C_5 protons. The minor product, m.p. 144–145°, with a triplet coupling ($J = 2{\cdot}4$ cps) for the C_4 proton was in good accord with the assigned structure (X). Oxidation of IX with CrO_3 gave a hydroxy ketone (XI) (ν_{max} 3460, 1705 cm^{-1}), m.p. 92–94°, in good yield. Treated with 10% ethanolic NaOH overnight at room temp or under reflux (3 hr), XI gave a product XII, m.p. 148–150°. This alkali treatment converted the ring junction from the unstable amorphane skeleton to the cadinane skeleton, while the secondary Me (C_3Me) remained unchanged. This was proved by a solvent effect, the secondary Me shifted from 9·01 (in $CDCl_3$) to 9·12 (in C_6H_6). The further evidence for proving the



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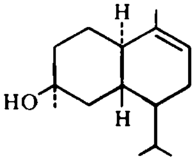

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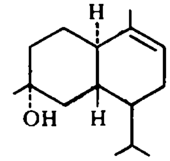

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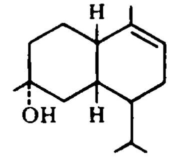

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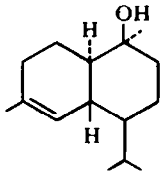

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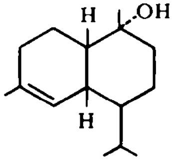

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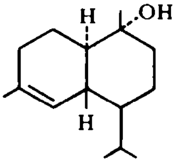

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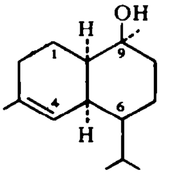

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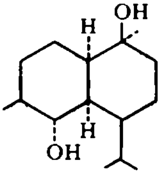

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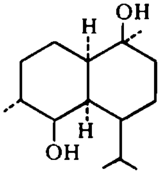

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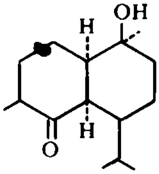

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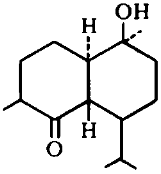

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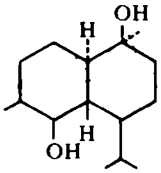

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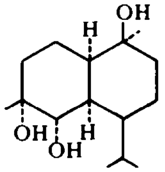

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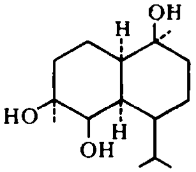

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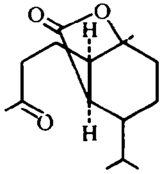
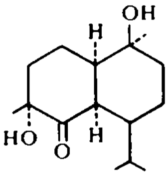


XVI



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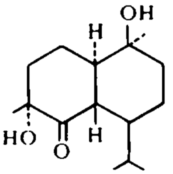

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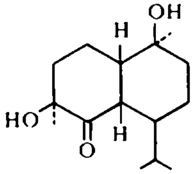

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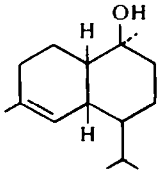

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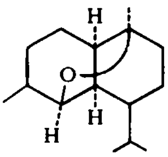
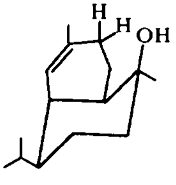


XXI



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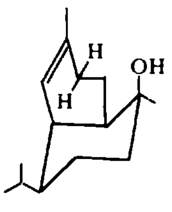

XXIII

secondary Me group to be unchanged was performed by the reduction of XII with $NaBH_4$. The product (XIII) showed the C_4 proton as a doublet of doublets with couplings of $J = 7$ and 3 cps (axial-axial and axial-equatorial coupling).

Additional proof was provided as described below. δ-Cadinol was treated with OsO_4 in pyridine and gave two crystalline compounds, XIV (m.p. 155–157°) and XV (m.p. 149–151°). The former (major) showed NMR absorption at 8·52 (3H, s, $=C(OH)CH_3$), 8·40 (3H, s, $=C(OH)CH_3$), and 5·32 (1H, d, $J = 7{\cdot}5$ cps, $=C(OH)H$). The C_4 proton had coupling constant 7·5 cps which is predicted to be axial-axial coupling. XIV was subjected to oxidation with CrO_3 and pyridine at room temp, and gave a colourless liquid lactone (XVI) (M^+ ion m/e 252) which exhibited IR absorption bands at 1770 cm^{-1} (γ-lactone) and 1720 cm^{-1} (no OH absorption), and NMR spectrum at 8·66 (3H, s, $=C(CH_3)O\underset{\underset{O}{\|}}{C}R$), and 7·95 (3H, s, $CH_3\underset{\underset{O}{\|}}{C}$—).

The $KMnO_4$ oxidation product, ketodiol XVII (m.p. 142–144°), from δ-cadinol was converted into XVIII (m.p. 132–134°) by treating with 10% ethanolic NaOH overnight. While the ketodiol XIX (m.p. 154–156°), obtained from $KMnO_4$ oxidation of T-muurolol (XX), was quantitatively recovered unchanged after alkaline treatment. If δ-cadinol is an epimer of T-muurolol, a similar result would be expected. When IX was treated with an equimolar quantity of brosyl chloride in pyridine at room temp for 3·5 hr, the main product XXI (M^+ ion m/e 222), obtained in good yield, showed strong IR absorption bands at 979 and 952 cm^{-1}, but no bands indicating the presence of OH groups or double bonds. The NMR spectrum of XXI exhibited a sharp singlet at 6·34 for the C_4 proton, indicating the dihedral angle between $H—C_4—C_3—H$ and $H—C_4—C_5—H$ to be approximately 90°. The cyclic ether bridge (XXI) and γ-lactone (XVI) formation must happen across C_4 and C_9. This type of cyclic ether and γ-lactone formation can only be derived from an alcohol possessing a *cis*-fused ring and a OH orientated β-axial (amorphenol) as showed in formula VIII.

By examination of a Dreiding model, the A ring of δ-cadinol is not likely in a quasi-chair conformation (XXII) since the non-bonded interaction between the OH group and the C_2 proton in this conformation is large. It is more likely that δ-cadinol is in the quasi-boat conformation (XXIII). This is supported by the fact that the vinyl proton of δ-cadinol appears as doublet ($J = 6{\cdot}5$ cps).

EXPERIMENTAL

M.ps are uncorrected. NMR spectra were determined at 60 MHz and chemical shifts are given in τ-values, coupling constants (J) in cps.

Isolation of (−)-*δ-cadinol.* The sliced wood of *Taiwania cryptomerioides* Hayata was extracted with acetone at room temp. The combined acetone solution was evaporated to leave oil. The steam volatile fraction was dissolved in ether and extracted with 2% NaOH to remove the acidic component. The neutral fraction was subjected to chromatographic separation on neutral alumina, and (−)-δ-cadinol was eluted from n-hexane-C_6H_6 mixture eluent. The detail purification is described in our previous reports.[11, 12]

Dehydration of δ-cadinol. δ-Cadinol (16·5 mg) was dissolved in pyridine (1 ml) and treated with 0·05 ml $SOCl_2$ at 0–2°. The mixture was stirred for 15 min, then extracted with ether. The organic layer was washed with water and subjected to gas chromatographic separation. The mixture of olefins consisted of five components; two unidentified hydrocarbons (almost the same retention time as α-muurolene), γ-muurolene, α-muurolene and δ-cadinene in the ratio of 25:57:10.

(−)-*Cadinene dihydrochloride from δ-cadinol.* A soln of 100 mg of δ-cadinol in 3 ml of anhyd ether was saturated with anhyd HCl at 5° and the solution kept for 5 hr. The solvent was removed under reduced pressure and dark red viscous residue crystallized from MeOH to yield 30 mg of colourless needles, m.p. 117–118°, no depression upon admixture with an authentic sample of (−)cadinene dihydrochloride.

Amorphan-4α,9β-diol(IX) *and amorphan-4β,9β-diol*(X). 4·5 g BF_3-etherate was added dropwise to a soln of 630 mg δ-cadinol in 10 ml dioxane containing 420 mg $NaBH_4$ and the mixture left at room temp for 90 min. Ice water was then added dropwise till H_2 evolution ceased. The cleavage of the B—R bond was achieved by adding 50 ml 3N NaOH aq and 2·5 ml 30% H_2O_2. After 30 min, the mixture was poured into water (200 ml) and processed as usual. The residual oil partially crystallized on cooling. The solid (IX) was separated and the filtrate dissolved in a small volume of n-hexane C_6H_6 and upon cooling more solid (IX) was deposited. The combined mother liquid was chromatographed on neutral alumina. The hexane eluent gave *amorphan-4β,9β-diol*(X) (20 mg), m.p. 144–145°, which showed IR absorption bands at 3370, 1380, 1360, 1117, 1005, 982, 953 and 864 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CDCl_3}$ 9·07 (6H, d, J = 5·8 cps), 8·94 (3H, d, J = 6·2 cps), 8·80 (3H, s) and 6·24 (1H, t, J = 2·4 cps). The C_6H_6 eluent gave *amorphan-4α,9β-diol*(IX) (the combined solids were 360 mg), m.p. 127–129°, which showed IR absorption bands at 3400, 3350, 1378, 1370, 1138, 1018, 1006, 1000, 937, 705 and 620 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CDCl_3}$ 9·06 (6H, d, J = 5 cps), 8·96 (3H, d, J = 7·1 cps), 8·73 (3H, s) and 6·10 (1H, t, J = 7·0 cps).

Amorphan-4-ene-9β-ol(XI). A soln of 75 mg CrO_3 in 1 ml glacial AcOH containing a few drops of water was added dropwise to a soln of 150 mg amorphan-4α,9β-diol(IX) in 1 ml glacial AcOH, and the mixture left at room temp for 20 min, poured into water and extracted with C_6H_6. The extract was washed with $NaHCO_3$, water and the solvent evaporated. The crystalline residue was recrystallized from n-hexane, yield 68 mg, m.p. 92–94°. It showed IR absorption bands at 3480, 1705, 1390, 1380, 1258, 1160, 1010, 950, 835 and 810 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CDCl_3}$ 9·16, 9·06 (6H, d, J = 6·2 cps), 8·96 (3H, d, J = 6 cps) and 8·78 (3H, s).

Cadinan-4-one-9β-ol(XII). 53 mg of XI was added to 5% methanolic NaOH aq, left overnight, and then dropped into water. The crystals obtained on crystallization gave *cadinan-4-one-9β-ol*(XII), m.p. 150° (45 mg), which dropped to 85° on m.m.p. with starting material (XI). Further alkali treatment of XII, refluxing with 2% BuONa soln for 2 hr or with 20% NaOH aq for 3 hr, only recovered XII. It showed IR absorption bands at 3325, 1694, 1375, 1363, 1200, 1116, 1055, 920 and 700 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CDCl_3}$ 9·27, 9·07 (6H, d, J = 6·0 cps), 9·01 (3H, d, J = 6·0 cps) and 8·74 (3H, s) or $\tau_{ppm}^{C_6H_6}$ 9·12 (3H, d, J = 6·4 cps), 8·90, 8·85 (6H, d, J = 6·0 cps), and 8·73 (3H, s).

Cadinan-4β,9β-diol(XIII). $NaBH_4$ was added in small portions to a soln of *cadinan-4-one-9β-ol*(XII) (54 mg) in 1 ml MeOH, and the soln poured into water. Precipitates appeared, which on recrystallization, had m.p. 154–155° (42 mg). It showed IR absorption bands at 3350, 1370, 1365, 1260, 1107, 910, 749 and 670 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CDCl_3}$ 9·12, 9·10 (6H, d, J = 6·8 cps), 9·01 (3H, d, J = 6·5 cps), 8·70 (3H, s), 6·62 (1H, d, J = 7, 3 cps).

Amorphan-3α,4α,9β-triol(XIV) *and amorphan-3β,4β,9β-triol*(XV). A soln of 432 mg of δ-cadinol in dioxane (10 ml) containing three drops of pyridine was added to a soln of 630 mg of OsO_4 in dioxane (10 ml) and the resulting soln was allowed to stand in the dark for 7 days. H_2S was bubbled into the soln for 20 min, and the resulting black slurry filtered. The solid was washed with hot EtOAc and the combined filtrate concentrated to dryness. The residual thick oil was subjected to neutral alumina chromatographic separation. It gave *amorphan-3β,4β,9β-triol* (5 mg) (XV) and *amorphan-3α,4α,9β-triol* (200 mg) (XIV). The former, m.p. 149–151°, showed IR spectrum absorption bands at 3500, 3380, 1385, 1375, 1150, 1125, 1025, 950, 930 and 898 cm^{-1}. The latter, m.p. 155–157°, showed IR spectrum absorption bands at 3580, 1395, 1385, 1370, 1169, 1101, 1030, 992, 952, 914 and 794 cm^{-1}, NMR spectrum at $\tau_{ppm}^{C_5H_5N}$ 9·08, 9·00 (6H, d, J = 5·5 cps), 8·52, 8·40 (6H, each of s) and 5·52 (1H, d, J = 7·5 cps).

γ-Lactone(XVI) *from* CrO_3 *oxidation*. A suspension of 248 mg CrO_3 in 2 ml pyridine was added dropwise to a soln of 207 mg amorphan-3α,4α,9β-triol(XIV) in 1 ml pyridine over a period of 30 min. The mixture was allowed to stand at room temp for 20 hr, poured into water (35 ml) and extracted with ether. The ether layer was washed with 10% HCl, 10% Na_2CO_3 and finally water. The ether was dried (Na_2SO_4), evaporated and chromatographed on neutral alumina. The C_6H_6 eluent gave 56 mg ketolactone(XVI), liquid, colourless, M^+ ion *m/e* 252, which showed IR absorption bands at 1770, 1720, 1415, 1378, 1360, 1285, 1165, 1115, 1050, 950, 920 and 740 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CCl_4}$ 9·15, 9·05 (6H, d, J = 6·0 cps), 8·66 (3H, s) and 7·95 (3H, s).

Amorphan-3α,9β-diol-4-one(XVII). To a soln of 110 mg of δ-cadinol in 25 ml of purified acetone cooled in an ice-bath, there was added dropwise with stirring, a soln of 600 mg of $KMnO_4$ in water (10 ml). The soln was allowed to warm to room temp and stirred for 10 hr. When unreacted permanganate was destroyed with $NaHSO_3$, the MnO_2 filtered and the filtrate concentrated until all of acetone was removed.

The remaining alkaline aqueous soln was cooled to 0°, acidified with 1% HCl and extracted with ether. The ether soln was washed with dilute $NaHCO_3$, water and dried. The ether was evaporated and the residual solid recrystallized twice from C_6H_6, yield 65 mg, m.p. 142–144°. It showed IR absorption bands at 3478, 3430, 1680, 1375, 1365, 1235, 1074, 1054, 991, 983, 921, 774, 738 and 694 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CDCl_3}$ 9·14, 9·10 (6H, d, J = 6·4 cps), 8·75 (3H, s) and 8·60 (3H, s).

Cadinan-3α,9β-*diol-4-one*(XVIII). XVII (20 mg) was added to 10% ethanolic NaOH aq and left overnight. The mixture was filtered and recrystallized from C_6H_6, yield 10 mg, m.p. 132–134°. It showed IR absorption bands at 3455, 1680, 1240, 1200, 1078, 1063, 1030, 1000, 962 and 690 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CDCl_3}$ 9·16 (6H, d, J = 6·2 cps), 8·93, 8·63 (6H, each of s).

Muurolan-3β,9β-*diol-4-one*(XIX). T-muurolol (260 mg) and 990 mg of $KMnO_4$ was treated as above (for XVII) and gave XIX, m.p. 154–156°, IR absorption bands at 3482, 1695, 1388, 1378, 1170, 1080, 1018 and 702 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CDCl_3}$ 9·18, 9·13 (6H, d, J = 6·2 cps), 8·80, 8·64 (6H, each of s), or $\tau_{ppm}^{C_6H_6}$ 9·24, 9·08 (6H, d, J = 6·0 cps), 9·13, 8·77 (3H, each of s).

XIX (20 mg) was added to 10% ethanolic NaOH aq and the soln poured into water. The crystals were filtered and recrystallized from C_6H_6, yield 15 mg of XIX, identified by comparison of its IR spectrum and m.m.p.

Amorphan-4β,9β-*oxide*(XXI). IX (120 mg) was treated with an equimolar quantity of brosyl chloride in anhyd pyridine at room temp for 3·5 hr. Without removal of solvent, the mixture was chromatographed directly on silica gel, and 85 mg of colourless liquid (XXI) obtained. The product, $C_{15}H_{26}O$ (M^+ ion *m/e* 222), showed IR absorption bands at 1370, 1125, 998, 979, 952, 885, 806 and 777 cm^{-1} and NMR spectrum at $\tau_{ppm}^{CCl_4}$ 9·11, 9·07 (6H, d, J = 6·0 cps), 9·06 (3H, d, J = 4·6 cps), 8·80 (3H, s), 6·34 (1H, s).

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