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DAPHNIPHYLLUM ALKALOIDS. PART II (1). THE ISOLATION AND THE STRUCTURES OF THE ALKALOIDS FROM DAPHNIPHYLLUM MACROPODUM MIQUEL

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In 1909, Yagi (2) isolated from the bark of Daphniphyllum macropodum Miquel (Euphorbiaceae) an amorphous alkaloid, daphnimacrine, $C_{27}H_{41}O_4N$, m.p. 75-84°. Since then no further studies on the alkaloids of this plant appeared to have been made.

We have recently reported the isolation of several new alkaloids from this plant and established the structure of one of them as shown in A* by the X-ray analysis (1).

Since a similar work has also appeared recently (3), we wish to summarize here our recent results on the alkaloids which we have isolated from this same plant.

Column chromatography of the base fraction (217 g.) on neutralized silicic acid (4) furnished the following fractions: fraction 1 ($CHCl_3$, 1.3 g.), fraction 2 ($CHCl_3$, 9.7 g.), fraction 3 ($CHCl_3$, 14.1 g.), fraction 4 [$CHCl_3$-MeOH (50:1), 28.9 g.], fraction 5 [$CHCl_3$-MeOH (20:1), 5.1 g.], fraction 6 [$CHCl_3$-MeOH (20:1), 1.9 g.], fraction 7 [$CHCl_3$-MeOH (20:1), 56 g.], fraction 8 [$CHCl_3$-MeOH (10:1), 3.1 g.], fraction 9 [$CHCl_3$-MeOH (10:1), 36.8 g.],

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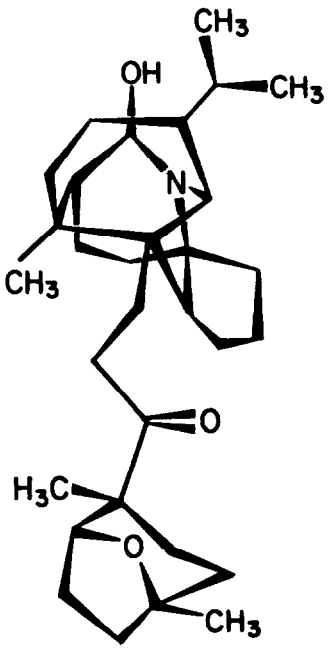
* We now name this alkaloid daphnimacropine.



A

fraction 10 [$CHCl_3$-MeOH (10:1), 17.5 g.], fraction 11 [$CHCl_3$-MeOH (5:1), 17.2 g.], and fraction 12 [$CHCl_3$-MeOH (3:1), 7.4 g.].

Fractions 3 to 5 yielded three alkaloids.

Macrodaphnidine (I), $C_{27}H_{37}O_7N$, had m.p. 150-152° (from acetone-ether), $[\alpha]_D$ +8.3° (c, 1.30, $CHCl_3$), pKa = 7.4 (in 80% methylcellosolve); hydrobromide, m.p. 240-242° (from acetone-chloroform), $[\alpha]_D$ +5.6° (c, 1.34); hydrochloride, m.p. 231-234° (from acetone-methanol); methiodide, m.p. 192-193° (from acetone-methanol).

This alkaloid had a hydroxyl band at 3450 $cm.^{-1}$ and a triplet carbonyl band (1740, 1730, and 1727 $cm.^{-1}$) in its IR spectrum. That one of these carbonyl groups is present as a methylester and the other two, as a secondary and a primary acetate, was demonstrated by the NMR spectrum. It showed

singlets at τ 6.29 (3H, $C\underline{H}_3O$-), at τ 7.96 (3H) and 7.94 (3H) ($C\underline{H}_3CO_2$-), at τ 5.33 (2H, $AcOC\underline{H}_2$-), and a quartet at τ 4.51 (1H, J=7 and 12 cps, $AcOC\underline{H}<$). Furthermore, one secondary methyl group was indicated by a doublet signal at τ 8.94 (J=7 cps). The presence of one hydroxyl, one methoxycarbonyl group, one primary, and one secondary acetate was also supported by the mass spectrum which gave peaks at m/e 487 (M^+) (base peak), 469 (M^+-H_2O) (68%), 428 ($M^+-CO_2CH_3$) (11%), 410 [$M^+-(H_2O+CO_2CH_3)$] (49%), 396 [$M^+-(H_2O+CH_2CO_2CH_3)$] (6%), and 354 [$M^+-(CH_3CO_2H+CH_2CO_2CH_3)$] (8%).

The alkaloid could not be hydrogenated over platinum oxide in acetic acid solution. Acetylation with acetic anhydride-pyridine at room temperature resulted in the recovery of starting material, whereas refluxing with the same reagent for two hours led to a mixture of unidentifiable products. This indicated that the hydroxyl group must be tertiary.

Partial hydrolysis of the alkaloid with methanolic sodium hydroxide furnished a product, $C_{23}H_{33}O_5N$, m.p. 174–176° (from chloroform-ether), $[\alpha]_D$ -26.0° (c, 1.49, $CHCl_3$), $\nu_{max.}$ $cm.^{-1}$ 3320 (OH) and 1740 (ester C=O), m/e 403 (M^+), 385 (M^+-H_2O), 354 [$M^+-(H_2O+CH_2OH)$], and 326 [$M^+-(H_2O+CO_2CH_3)$], showing that both acetoxyl groups were hydrolyzed and the methylester group was intact. Hydrolysis under more drastic conditions led to an unidentified amino acid.

Reduction of the alkaloid with lithium aluminum hydride in ether-dioxane yielded an alcohol which was characterized as the hydrobromide, $C_{22}H_{33}O_4N\cdot HBr$, m.p. 193–194° (from acetone-methanol), with no IR bands in the carbonyl region and no NMR signals due to acetoxyl and methoxyl groups, m/e 357 [$M^+-(HBr+H_2O)$] and 326 [$M^+-(HBr+H_2O+CH_2OH)$].

All these chemical and spectroscopic properties can be accounted for if this alkaloid has structure I. Thus, macrodaphnidine should be identical with yuzurimine* whose structure was recently determined by the X-ray analysis (3).

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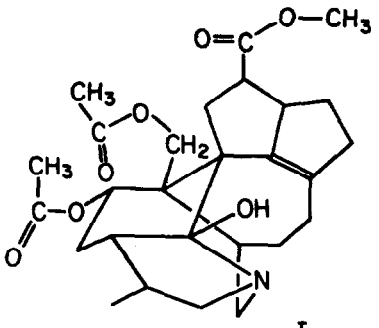
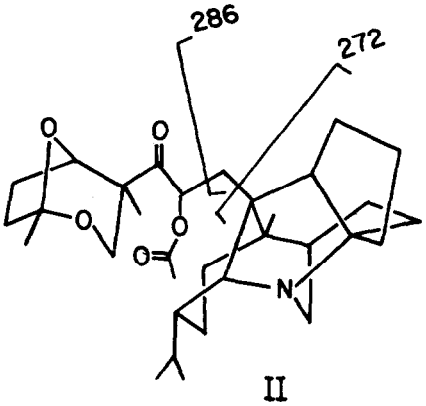
* Sakabe et al. (3) did not record the physical data of this alkaloid itself since they isolated it as the derivatives.



I



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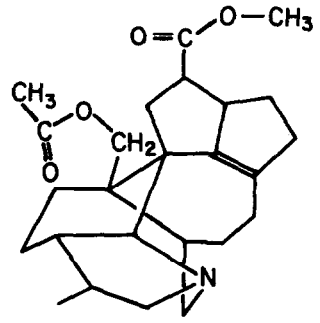

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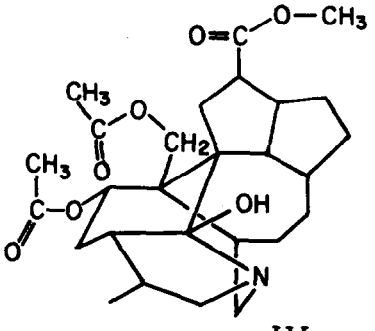

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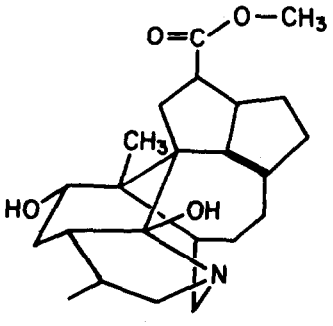

V

Daphniphyllamine (II), $C_{32}H_{49}O_5N$, was isolated as the hydrobromide, m.p. 228-230° (from chloroform-ether), $[\alpha]_D$ +25.8° (c, 1.34), +44.9° (c, 1.92, $CHCl_3$); methiodide, m.p. 276-279° (from acetone-methanol).

The IR spectrum of the hydrobromide showed bands at 1730 (ester C=O) and 1720 $cm.^{-1}$ (saturated open-chain ketone). Its NMR spectrum showed signals due to three tertiary methyls at τ 9.08, 8.92, and 8.53, one isopropyl at τ 9.05 (3H) and 8.85 (3H) (doublets, J=6 cps), and one acetoxyl group at τ 7.87, associated with a proton signal at τ 4.34 (quartet, J=3 and 12 cps, $AcOC\underline{H}<$). The mass spectrum of the methiodide gave fragment peaks at m/e 527 (M^+-CH_3I), 512 [$M^+-(CH_3I+CH_3)$], 484 [$M^+-(CH_3I+CH<^{CH_3}_{CH_3}$)], 469 [$M^+-(CH_3I+CH_3+CH<^{CH_3}_{CH_3}$)], 442, 286, and 272. The latter two fragment peaks are characteristic of daphnimacropine (1) and also daphniphylline (II) (3). Furthermore, all other physical data of this alkaloid are in good agreement with those recorded for daphniphylline, and therefore they should be identical.

Daphmacrine, $C_{32}H_{49}O_4N$, formed a hydrobromide, m.p.>300° (from chloroform-acetone), $[\alpha]_D$ +30.1° (c, 1.79), $\nu_{max.}$ $cm.^{-1}$ 1770 (lactonic C=O), 1730 (ester C=O), and 1229 (ester C-O), m/e 511 (M^+-HBr), 496, 469, 468, 428, 426, 410, 286, 272, and 230, τ 9.01 (3H) and 8.83 (3H) (doublets, J=6 cps, $C\underline{H}_3>^{CH}_{CH_3}$), 8.87 (3H), 8.76 (3H), and 8.50 (3H) (singlet, $C\underline{H}_3-C<$), and 7.88 (3H, singlet, $C\underline{H}_3CO_2-$).

Fraction 9 afforded two alkaloids.

Macrodaphniphyllidine (III), $C_{25}H_{35}O_4N$, crystallized as the hydrobromide, m.p. 305-306° (from acetone-methanol), $[\alpha]_D$ +3.9° (c, 1.11), $\nu_{max.}$ $cm.^{-1}$ 1740 (ester C=O) and 1245 (ester C-O). Its NMR spectrum contained peaks at τ 8.89 (doublet, J=6 cps, $C\underline{H}_3-CH<$), 7.94 ($C\underline{H}_3CO_2-$), 6.30 ($C\underline{H}_3O-$), and 5.55 ($AcOC\underline{H}_2-$), but lacked a signal due to a secondary acetate group. The fragment peaks in the mass spectrum confirmed the presence of a $-CO_2CH_3$ [m/e 354 (M^+-59)] and a $-CH_2OAc$ grouping [m/e 340 (M^+-73)]. On the basis of these spectroscopic data and also its biogenetic relationship to macrodaphnidine (I), structure III was assigned to macrodaphniphyllidine.

Macrodaphnine (IV), $C_{27}H_{39}O_7N$, showed m.p. 180-181.5° (from chloroform-

ether); hydrobromide, m.p. 249-252° (from acetone-methanol), $[\alpha]_D$ -18.4° (c, 1.30), $\nu_{max.}$ cm.$^{-1}$ 3370 (OH), 1740 and 1730 (ester C=O), and 1260 (ester C-O), m/e 471 [M^+-(HBr+H_2O)] and 412, τ 8.88 (3H, doublet, J=7 cps, $C\underline{H}_3$-CH<), 7.92 (6H, singlet, two $C\underline{H}_3CO_2$-), 6.29 (3H, singlet, $C\underline{H}_3O$-), 5.57 (2H, singlet, $AcOC\underline{H}_2$-), and 4.51 (1H, quartet, J=7 and 12 cps, $AcOC\underline{H}$<); hydrochloride, m.p. 215-218° (from chloroform-acetone), $[\alpha]_D$ -14.5° (c, 0.96).

The elemental composition of this alkaloid corresponds to that of a dihydro derivative of macrodaphnidine (I), which was confirmed by the mass fragment peaks at m/e 471 (M^+-H_2O), 412 [M^+-(H_2O+CO_2CH_3)], and 398 [M^+-(H_2O+$CH_2CO_2CH_3$)], all of which are two mass unit higher than the corresponding peaks in the mass spectrum of macrodaphnidine. Its IR spectrum showed bands at 3350 (OH) and 1735 and 1730 (ester C=O) cm.$^{-1}$, and the nature of all the functional groups present was clarified by the NMR signals at τ 9.00 (J=7 cps, $C\underline{H}_3$-CH<), 7.99 (6H, singlet, two $C\underline{H}_3CO_2$-), 6.38 ($C\underline{H}_3O$-), 5.59 (singlet, $AcOC\underline{H}_2$-), and 4.70 (quartet, J=7 and 12 cps, $AcOC\underline{H}$<). These common features of the spectra of this alkaloid and macrodaphnidine confirmed that it has structure IV.

From fraction 11, two alkaloids were isolated.

Daphmacropodine, $C_{32}H_{51}O_4N$, had m.p. 214-215° (from acetone), $[\alpha]_D$ +4.9° (c, 1.11, $CHCl_3$), $\nu_{max.}$ cm.$^{-1}$ 1740 (ester C=O) and 1240 (ester C-O), m/e 513 (M^+), 495, 300, 286, and 272; hydrobromide, m.p. 215-218° (from acetone).

Macrodaphniphyllamine (V), $C_{23}H_{33}O_4N$, showed m.p. 152-153° (from chloroform-hexane), $[\alpha]_D$-51.7° (c, 1.25, $CHCl_3$); hydrobromide, m.p. 229-230° (from acetone), $[\alpha]_D$ -31.2° (c, 0.70).

The IR spectrum of this alkaloid had an ester carbonyl absorption band at 1730 cm.$^{-1}$ in addition to a hydroxyl band at 3400 cm.$^{-1}$ Its mass spectrum gave peaks at m/e 387 (M^+), 369 (M^+-H_2O), 354 [M^+-(H_2O+CH_3)], and 310 [M^+-(H_2O+CO_2CH_3)]. In the NMR spectrum, signals corresponding to a secondary methyl (τ 8.97, doublet, J=7 cps) and a methoxyl group (τ 6.37) were also observed, but absorption due to an acetoxyl group was absent. Instead, a signal (3H, singlet) assignable to a tertiary methyl group appeared at somewhat low field of τ 8.77. These spectroscopic evidence, together with its biogenetic

consideration, leads to the assignment of structure V to macrodaphniphyllamine.

The alkaloids whose structures have not yet been shown in this paper are now being investigated.

Melting points are uncorrected. All compounds described gave satisfactory elemental analyses. Unless otherwise noted, all rotations were taken in methanol solution. The 60 Mc NMR spectra were obtained with Varian A-60 spectrometer using TMS as internal standard. The IR spectra were measured with Perkin-Elmer 337 grating infrared spectrophotometer in KCl or KBr discs.

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