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THE ISOLATION AND STRUCTURES OF TWO NEW ALKALOIDS, MILLIAMINES A AND B, OBTAINED FROM EUPHORBIA MILLII

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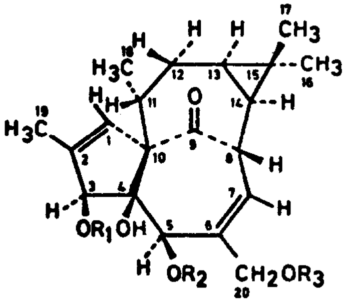
Extensive studies on irritant and cocarcinogenic components of Euphorbia species have been carried out by some groups, recently.[1-5] In this communication we wish to report the isolation and structures of two new alkaloids, milliamines A and B, obtained from the roots of E. Millii Ch. des Moulins (Euphorbiaceae, Japanese name "Hanakirin").

The fresh roots were extracted with methanol. The evaporation of methanolic extracts at 60° under reduced pressure afforded an aqueous residue which was extracted with ether. The ethereal solution was washed with a saturated sodium chloride solution and evaporated to give a residue, which was chromatographed on silicic acid. Some fractions with a positive Dragendorff test afforded milliamines A and B, which were purified as hydrochlorides. The molecular formulas, physical constants, and spectral data of new alkaloids are as follows.

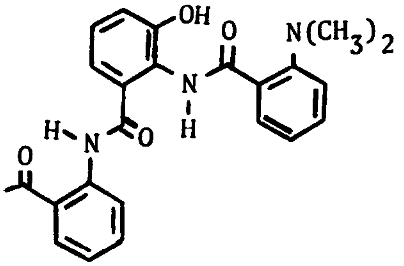
Milliamine A (I, $C_{45}H_{49}N_3O_{10}$): $[\alpha]_D^{25} = +6°$ (c= 1.4, $CHCl_3$); [hydrochloride: m.p. 167-170°; UV (MeOH), 232 (ε, 37300), 260 (21900), 315 (14100), 342 nm (4800); IR (KBr), 2800-3600, 1725, 1690, 1670, 1645, 1610, 1585, 1530, 1310 cm^{-1}]; NMR (60 MHz, $CDCl_3$, δ), 0.5-1.4 (11H, complex pattern), 1.83 (3H, d, J= 1.0 Hz), 2.05 (3H, s), 2.83 (6H, s), 3.55 (1H, exchangeable with D_2O), 3.95 (1H, m), 4.0-4.2 (1H, exchangeable with D_2O), 4.43, 4.80 (2H, AB quartet, J= 13 Hz), 5.80 (1H, s), 6.15 (2H, m), 7.1-7.8 (8H, complex pattern), 8.1-8.3 (2H, m), 8.85 (1H, d of d, J= 10, 1.0 Hz), 9.3-9.8 (1H, br.s, exchangeable with D_2O), 11.6 (1H, br.s, exchangeable with D_2O), 13.3 (1H, br.s, exchangeable with D_2O).

Milliamine B (II, $C_{43}H_{47}N_3O_9$): $[\alpha]_D^{25} = -14°$ (c= 1.4, $CHCl_3$); [hydrochloride: m.p. ∿140°; UV (MeOH), 227 (ε, 43800), 260 (18800), 315 (14600), 342 nm (5000); IR (KBr), 2800-3600, 1710, 1685, 1670, 1650, 1610, 1580, 1520, 1300 cm^{-1}]; NMR (60 MHz, $CDCl_3$, δ), 0.93 (3H, d, J= 6.0 Hz), 1.05 (3H, s), 1.09 (3H, s), 0.5-1.2 (2H, m), 1.76 (3H, d, J= 1.0 Hz), 2.78 (6H, s), 3.65 (1H, m), 3.70 (1H, s, exchangeable with D_2O), 4.0-4.2 (1H, m), 4.0-4.2 (2H, exchangeable with D_2O), 4.72, 4.95 (2H, AB quartet, J= 13 Hz), 5.85 (1H, d, J= 1.0 Hz), 6.12 (1H, m), 6.9-7.8 (8H, complex pattern), 7.9-8.2 (2H, m), 8.79 (1H, d of d, J= 10, 1.0 Hz), 9.50 (1H, br.s, exchangeable with D_2O), 11.7 (1H, s, exchangeable with D_2O), 13.4 (1H, s, exchangeable with D_2O).



<u>I</u> R_1: X, R_2: H, R_3: $COCH_3$

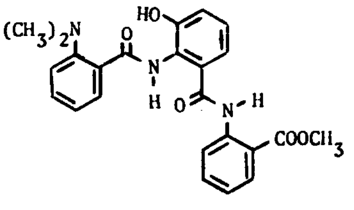
<u>II</u> R_1, R_2: H, R_3: X



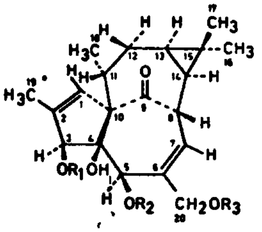
X

The methanolysis of milliamine A <u>I</u> with sodium methoxide-methanol afforded a compound <u>III</u> [$C_{24}H_{23}N_3O_5$: m.p. 160-161°; UV (MeOH), 227 (ε, 41500), 258 (17000), 315 nm (15100); IR (KBr), 3550, 3250, 2400-3000, 1695, 1675, 1620, 1605, 1595, 1500, 1305 cm^{-1}; NMR (60 MHz, acetone-d_6, δ), 2.73 (6H, s), 3.77 (3H, s), 6.8-7.6 (8H, complex pattern), 7.7-8.1 (2H, m), 8.6 (1H, d of d, J= 10, 1.0 Hz), 9.26 (1H, s, exchangeable with D_2O), 11.3 (1H, s, exchangeable with D_2O), 12.9

(1H, s, exchangeable with D_2O)], and a diterpene tetraol (ingenol) IVa, $C_{20}H_{28}O_5$, which yielded a triacetate IVb ($C_{26}H_{34}O_8$) with acetic anhydride-pyridine. The triacetate was shown to be ingenol triacetate,[4)] whose structure was unambiguously established by X-ray analysis.[4)] Methanolysis of the compound III with 6N hydrochloric acid-methanol (V/V, 1:1) gave methyl anthranilate and methyl 3-hydroxy-N-(N',N'-dimethylanthranoyl) anthranilate V ($C_{17}H_{18}N_2O_4$), m.p. 89-90°, which was identical with a compound synthesized from N,N-dimethylanthranilic acid and 3-hydroxyanthranilic acid as illustrated in the scheme. Furthermore, treatment of the hydrochloride of milliamine A with methanol-aqueous sodium bicarbonate gave ingenol monoacetate IVc ($C_{22}H_{30}O_6$). In the nmr spectrum of ingenol monoacetate IVc the signal of two protons on C-20, which appeared at δ 4.10 in ingenol IVa, was observed as an AB quartet at δ 4.25 and 4.80 (J= 13 Hz), indicating that a primary acetoxy group is present in IVc.



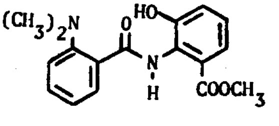
III



IVa R_1, R_2, R_3: H

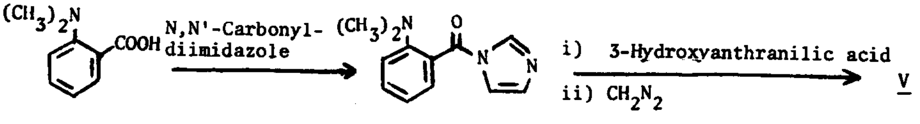
b R_1, R_2, R_3: $COCH_3$

c R_1, R_2: H, R_3: $COCH_3$



V

Scheme



On the basis of these results and the fact that a siglet of one proton attached at C-3 assigned from the nuclear magnetic double resonance experiments (100 MHz)[6] of milliamine B II and IVa appeared at δ 5.80 in milliamine A, it is concluded that the structure of milliamine A is I.

The structure of milliamine B is suggested from results that methanolysis of milliamine B afforded a compound III and ingenol IVa, and that a signal of two protons on C-20 appeared at δ 4.72 and 4.95 as an AB quartet (J= 13 Hz).

Acknowledgment

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References

1) W. Adolf, E. Hecker, A. Balmain, M. F. Lhomme, Y. Nakatani, G. Ourisson, G. Ponsinent, R. J. Pryce, T. S. Santhanakrishnan, L. G. Matyuhina, and I. A. Saltikova, Tetrahedron Letters, 2241 (1970). K. Zechmeister, M. Rohrl, F. Brandl, S. Hechtfischer, W. Hoppe, E. Hecker, W. Adolf, and H. Kubinyi, Tetrahedron Letters, 3071 (1970).

2) M. Gschwendt and E. Hecker, Tetrahedron Letters, 3509 (1969).

3) M. Gschwendt and E. Hecker, Tetrahedron Letters, 567 (1970).

4) K. Zechmeister, F. Brandl, W. Hoppe, E. Hecker, H. J. Opferkuch, and W. Adolf, Tetrahedron Letters, 4075 (1970).

5) P. Narayanan, M. Rohrl, K. Zechmeister, D. W. Engel, W. Hoppe, E. Hecker, and W. Adolf, Tetrahedron Letters, 1325 (1971).

6) We thank Mr. T. Kondo (Department of Agricultural Chemistry, Nagoya University) for the measurement of nmr (100 MHz) spectra.