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SYNTHESIS OF EVONINE FROM EVONINIC ACID AND AN EVONINOL DERIVATIVE

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The 14-membered bislactone ring was constructed starting from dimethyl evoninate (1) and the evoninol derivative (6), leading to the synthesis of evonine (13).

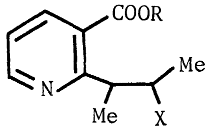
Recently, the structural studies on complex sesquiterpene alkaloids from the Celastraceae family have actively been performed.[1 - 11] Many of these alkaloids are characterized by the presence of the novel structural unit, the bislactone of a large ring (14- or 15-membered ring) consisting of an unsymmetrical pyridine dicarboxylic acid and the sesquiterpene polyalcohol of eudesmane type, as exemplified by a key representative, evonine (13). The common feature of the bislactone structure in these alkaloids is that the aliphatic acid part of the pyridine dicarboxylic acid forms the ester linkage with the C-3 hydroxyl of the sesquiterpene polyalcohol, while the aromatic acid part with the C-15 hydroxyl.

We report here the construction of the 14-membered bislactone ring from the corresponding pyridine dicarboxylic acid (evoninic acid) and the sesquiterpene polyalcohol (evoninol) derivative, leading to the synthesis of evonine (13).

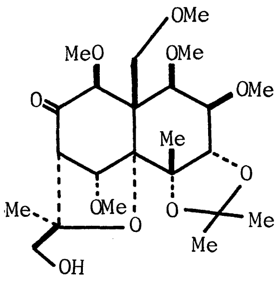
The hydroxy ester (2)[12,13] prepared from dimethyl evoninate (1) by three steps[2d] was converted (Ph_3CCl - Py, 60°, 15 hr) to the trityl derivative (3)[12-14] (95%), which was subsequently hydrolyzed (10% KOH - MeOH, 70°, 12 hr) to the acid (4)[13] (71%). The crude mixed anhydride (5), obtained on treatment of the acid (4) with ethyl chloroformate and triethylamine (DME, room temp., 18 hr) was condensed with the evoninol pentamethyl ether acetonide (6)[2d] (4-dimethylamino-pyridine - Et_3N - DME, 90°, 15 hr) to afford the ester (7)[13,14] (34% based on utilized (6)).

The ester (7) was converted to the hydroxy acid (10)[12-14] by the following sequence of the reactions: i) removal of the trityl group (80% AcOH, 50°, 13 hr) to give the alcohol (8) (82%); ii) oxidation (CrO_3 - Py, 65°, 14 hr) affording the acid (9) (70%); iii) hydrolysis of the acetonide moiety (50% AcOH, 85°, 2.5 hr) (68%).

Formation of the lactone ring was performed by treating the methyl ester (11)[12-14] obtained by



1 : R = Me, X = COOMe
2 : R = Me, X = CH_2OH
3 : R = Me, X = CH_2OCPh_3
4 : R = H, X = CH_2OCPh_3
5 : R = COOEt, X = CH_2OCPh_3



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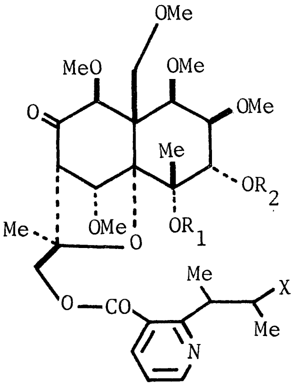
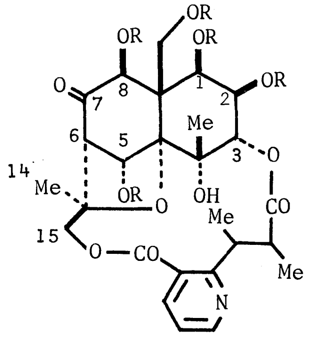


7 : R_1, R_2 = CMe_2, X = CH_2OCPh_3
8 : R_1, R_2 = CMe_2, X = CH_2OH
9 : R_1, R_2 = CMe_2, X = COOH
10 : R_1 = R_2 = H, X = COOH
11 : R_1 = R_2 = H, X = COOMe



12 : R = Me
13 : R = Ac (evonine)

methylation (CH_2N_2) of (10) with sodium hydride (DMF, room temp., 2 hr) to give the bislactone $(12)^{12-14}$ (12%). Demethylation of the methyl ether groups in (12) (BCl_3 - CH_2Cl_2, room temp., 12 hr) followed by acetylation (Ac_2O - Py, 70°, 10 hr) afforded a crystalline compound (35%), identified to be evonine by spectral (ir, nmr, and mass) and thin layer chromatographic comparison.

The above sequence of the reactions forming the bislactone ring would be applicable to the synthesis of other members of Celastraceae alkaloids from their corresponding two components, the pyridine dicarboxylic acid and the sesquiterpene polyalcohol.

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12. Elemental composition of this compound was verified by high resolution mass spectral determination on the molecular ion.
13. Structure assignments are based on ir, nmr, and mass spectral evidence.
14. This amorphous compound was purified by preparative tlc (silica gel).

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