Synthesis of the 'Supposed' Cannivonine: a Constituent of New Brunswick Cranberry Leaves

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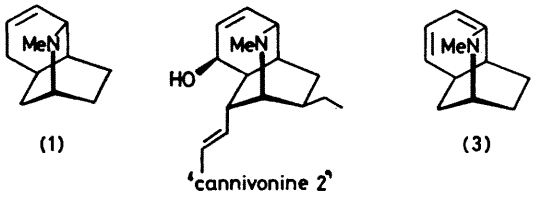
Summary The synthesis of compound (**1**), which possesses the reputed structure of the cranberry alkaloid, cannivonine, has been accomplished through transannular opening of the epoxide (**7**).

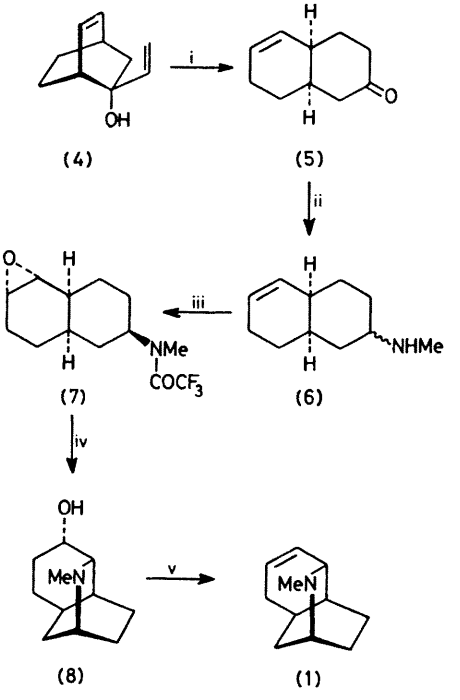
IN 1971 the structure of the first member of a series of alkaloids isolated from extracts of New Brunswick cranberry leaves (*Vaccinium oxycoccus*) was reported.[1] This compound, called cannivonine (**1**) by Jankowski, represented the simplest member of this group. The other

members, such as 'cannivonine 2' (**2**) consist of more highly functionalized versions of the azatricyclo[5.3.1.$0^{3,8}$]-undecene (**1**).



(1) (2) (3)

The rare isoquinuclidine structure exhibited by cannivonine made this compound an intriguing target for synthesis. Moreover, its synthesis appeared crucial to confirming its identity, especially since the proposed structure rested solely on n.m.r. studies and some very questionable degradation results [obtention of the Bredt's rule[2] violating the diene (**3**) had been claimed].[1a] Other anomalies also cast doubt on the structure of the related compound 'cannivonine 2' (**2**).[3]



(4) (5) (7) (6) (8) (1)

SCHEME. i, KH, 18-crown-6, DME, room temp., 14 h; ii, $MeNH_2$·HCl, $NaCNBH_3$, MeOH, room temp., 24 h; iii, (1) $(CF_3CO)_2O$, Na_2CO_3, (2) MCPBA, CH_2Cl_2; iv, K_2CO_3, MeOH, H_2O, reflux, 1·5 h; v, H_3PO_4–P_2O_5, heat.

The sequence used to synthesize cannivonine (**1**) is depicted in the Scheme. The *cis*-$\Delta^{5,6}$-octalin-2-one (**5**), a compound described by Berson,[4] was readily available through Evan's modification of the oxy-Cope rearrangement of the alcohol (**4**).[5,6] Reductive amination of (**5**) by the Borch procedure ($NaCNBH_3$, $MeNH_2$·HCl, MeOH, 24 h at room temperature)[7] provided an isomeric mixture of amines† in 92% yield. These were trifluoroacetylated [$(CF_3CO)_2O$, Na_2CO_3, ether–tetrahydrofuran(THF), 0 °C → room temperature, 94% yield;[8] v.p.c. analysis on 15% C-20M, 60/80 A/W on Chrom. P, 200 °C revealed that this mixture contained 60% of the desired isomer] and separated by medium-pressure liquid chromatography (m.p.l.c.) (32—63 μm Woelm silica with 5% ethyl acetate–hexane) to provide the pure trifluoroacetamide (m.p. 68·5—69·5 °C).‡ Subsequent epoxidation in CH_2Cl_2 (*m*-chloroperbenzoic acid (MCPBA), $NaHCO_3$, 14 h at room temperature) yielded a 70:30 mixture of epoxides.[9] The desired major isomer (**7**) was isolated by m.p.l.c. with 10—20% ethyl acetate–hexane as eluant: ν(film) 1710 cm^{-1}; δ (60 MHz; CCl_4) 3·15—2·80 (m, 5H), 2·75—2·60 (m, 1H), and 2·20—1·10 (m, 12H). Exposure of the protected amino-epoxide (**7**) to refluxing aqueous methanol containing potassium carbonate for 1·5 h led to removal of the trifluoroacetyl protecting group with concurrent ring closure through diaxial epoxide opening to afford the alcohol (**8**)[8]§ as a crystalline compound (m.p. 80—81·5 °C from hexanes) in 91% yield after bulb-to-bulb distillation (107—115 °C oven temperature, 0·08 mmHg): ν(KBr) 3350 cm^{-1}; δ ($CDCl_3$, 100 MHz) 3·70 (m, 1H), 2·52 (m, 1H), 2·35 (s, 3H), 2·24 (m, 1H), and 2·16—1·00 (m, 13H).

The dehydration of (**8**) to the 'supposed' cannivonine proved problematic when attempted by several standard procedures ($MeSO_2Cl$–1,5-diazabicyclo[5.4.0]undec-5-ene, $POCl_3$–pyridine, *etc.*). Even pyrolysis of the *O*-phenyl thiocarbonate of (**8**)[10] was found to lead, as in the above experiments, to undesired non-olefinic rearrangement products.¶ Since it was assumed that these products arose through intramolecular displacement of the potential leaving group by nitrogen with aziridinium ion formation, the dehydration was attempted in anhydrous phosphoric acid, a medium in which nitrogen participation could be prevented through protonation. The desired product (**1**) was indeed obtained when (**8**) was heated in H_3PO_4–P_2O_5[11] for 1·5 h at 200 °C: ^1H n.m.r. δ (100 MHz, $CDCl_3$) 6·20—5·50 (m, 2H), 2·80 (m, 1H), 2·58 (m, 1H), 2·46 (s, 3H), and 2·20—1·00 (m, 10H); ^{13}C n.m.r. δ 130·86, 126·05, 56·53, 49·64, 41·71, 33·92 (2 peaks), 29·89, 26·64, 23·78, and 19·62 p.p.m.; *m/e* (15 eV) 163 (M^+, base peak).

This material was identical to a sample prepared independently from the alcohol (**8**) by a three-step sequence involving Jones oxidation, tosylhydrazone formation, and subsequent decomposition of this hydrazone with an excess of methyl-lithium.[12]

† Reduction of the *N*-methylimine prepared from (**5**) with sodium in ethanol provided substantial amounts of the incorrect isomer (v.p.c. ratio of the *N*-trifluoroacetyl derivatives was 30:70).

‡ A number of attempts were made to effect ring closure of (**6**) through intramolecular aminometallation processes. These experiments have presently met with little success.

§ The amino-alcohol (**8**) has a retention time of 21·7 min on 28% Pennwalt–40% KOH on Gas Chrom R at 192 °C with a helium flow of 54 ml min^{-1}.

¶ The structures of these rearrangement products are presently being investigated.

The spectral data for (**1**) do not agree with those reported for cannivonine. Since our method of synthesis is unambiguous, we can only arrive at the inescapable conclusion that the reported structure for this compound is incorrect. A complete reinterpretation of the spectral data and degradation studies and a reassignment of the structure of cannivonine will thus be needed.

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** Professor D. Evans has informed us in a personal communication that the synthesis of (**1**) has independently been carried out at the California Institute of Technology through a similar reaction sequence and an *X*-ray structure obtained on a derivative of (**8**).

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[5] D. A. Evans and A. M. Golob, *J. Amer. Chem. Soc.*, 1975, **97**, 4765.
[6] The starting bicyclo[2.2.2]oct-2-en-5-one required for the synthesis of (**4**) was prepared by the procedure of P. D. Freeman, D. M. Balls, and D. J. Brown, *J. Org. Chem.*, 1968, **33**, 2211. The 2 : 1 mixture of bicyclic alcohols obtained on addition of vinylmagnesium bromide to this carbonyl compound (ref. 4a) was submitted to rearrangement without prior separation by treatment with 2 equiv. of potassium hydride in dimethoxyethane (DME) and 1·1 equiv. of 18-crown-6 at room temperature for 14 h. The desired octalone (**5**) was then conveniently separated from the unrearranged 'wrong' alcohol by m.p.l.c. on Woelm silica with 7% ethyl acetate–hexane as eluant.
[7] R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, 1971, **93**, 2897.
[8] H. Newman, *J. Org. Chem.*, 1965, **30**, 1287.
[9] The epoxidation of a *cis*-fused bicyclic system on its concave face is not without precedent. See, for example, E. J. Corey and R. Noyori, *Tetrahedron Letters*, 1970, 311 and G. Berti, *Topics Stereochem.*, 1973, **7**, 93.
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[12] R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, 1967, **89**, 5734.