The Total Synthesis of (±)-Tabersonine

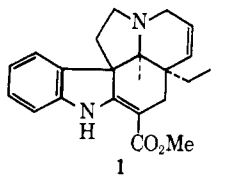
Sir:

Tabersonine (**1**), isolated from *Amsonia tabernaemontana* in 1954 by Le Men,[1] has since been found to play a critical role in the biosynthesis[2] of catharanthine (*Iboga*) and vindoline (*Aspidosperma*), a progenitor of the oncolytic dimeric alkaloids vinblastine (VLB) and vincristine (VCR).[3] To date biosynthetic experiments on *Vinca rosea* involving the feeding of tabersonine have been conducted by labeling the naturally occurring levorotatory enantiomer. The conspicuous absence of the dextrotatory enantiomer from natural sources suggests a possible primary metabolic role and necessitates the preparation of the racemate by a synthetic route.

Modification of Czuba's procedure for the oxidation of 5-bromonicotinamide[4,5] (**2a**) with sodium hypobromite provided 3-amino-5-bromopyridine (**2b**, 79% yield), mp 66–67° (lit.[6] 66–67°). Diazotization of the amine followed by decomposition of the resultant diazonium salt with hot aqueous sulfuric acid gave rise to the known 3-bromo-5-hydroxypyridine (**2c**, 98% yield), mp 166.5–167.5° (lit.[7] 166.5–167.5°). Exposure of the hydroxypyridine to diazomethane[8] in ether–*tert*-butyl alcohol at −15° afforded 3-bromo-5-methoxypyridine (**2d**), mp 30–32° (lit.[9] 33.5–34°). Transformation of halide **2d** into its Grignard reagent by entrainment with ethyl bromide, and subsequent addition of dry acetaldehyde, provided 3-(α-hydroxyethyl)-5-methoxypyridine[10] (**2e**, 79% yield): bp 113–120° (30 μ);[11] mp 44.5–45.5°; nmr δ ($CDCl_3$) 1.45 (3 H, J = 6.5 Hz, d), 3.82 (3 H, s), 4.70 (1 H, broad s, concentration dependent), 5.10 (1 H, J = 6.5 Hz, q), 7.15 (2 H, J = 3 Hz, d), and 8.12 (1 H, J = 3 Hz, t).

Quaternization of secondary alcohol **2e** with benzyl chloride in refluxing acetone afforded pyridinium salt **3**, mp 149.5–150° (98% yield). Employing selective conditions[12] to cause 3-α-hydroxyalkylpyridinium salts to undergo reductive elimination, pyridinium salt **3** was transformed into a mixture of enol ethers **4** by reduction with lithium aluminum hydride in tetrahydrofuran at room temperature. Hydrolysis of the enol ether with aqueous methanolic hydrochloric acid provided enone **5a** previously prepared by an alternate route.[13]

Reduction of enone **5a** with lithium aluminum hydride in tetrahydrofuran produced the allylic alcohol **5b** as an oil: ir ($CHCl_3$) 3550–3100 cm^{-1}.



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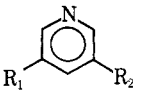
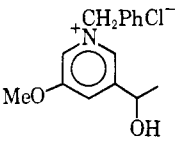


2a, R_1 = Br; R_2 = $CONH_2$
b, R_1 = Br; R_2 = NH_2
c, R_1 = Br; R_2 = OH
d, R_1 = Br; R_2 = OMe
e, R_1 = CHOHMe; R_2 = OMe



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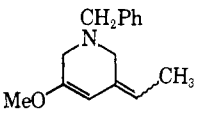

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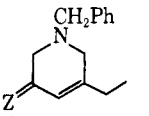
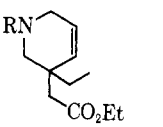
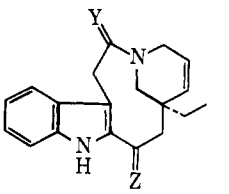


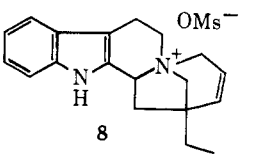
5a, Z = O
b, Z = H, OH



6a, R = CH_2Ph
b, R = CO_2Et



7a, Y = Z = O
b, Y = H_2; Z = H, OH
c, Y = H_2; Z = H, CN
d, Y = H_2; Z = H, CO_2Me
e, Y = Z = H_2



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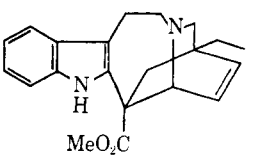

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Exposure of **5b** to ethyl orthoacetate[14] (pivalic acid catalyst) at 140° for 48 hr effected a Claisen rearrangement providing unsaturated ester **6a** (74.5% yield): bp 127–129° (0.01 mm); nmr δ ($CDCl_3$) 0.80 (3 H, J = 7 Hz, t), 1.16 (3 H, J = 7 Hz, t), 1.52 (2-H, J = 7 Hz, q), 2.28 (1 H, J_{AB} = 12 Hz, d), 2.44 (2 H, s), 2.54 (1 H, J_{AB} = 12 Hz, d), 2.78 (1 H, J_{AB} = 17 Hz, d), 3.00 (1 H, J_{AB} = 17 Hz, d), 3.52 (2 H, s), 4.05 (2 H, J = 7 Hz, q), 5.62 (2 H, s), and 7.26 (5 H, s, broad). Facile cleavage of the benzyl group was achieved with ethyl chloroformate in refluxing benzene,[15] giving rise to the carbamate ester **6b** (90% yield): bp 133–134° (1 mm); ir ($CHCl_3$) 1730 (–CO_2Et) and 1695 (–NCO_2Et) cm^{-1}.

The carbamate **6b** was transformed as previously reported employing the following sequence of reagents: (a) potassium hydroxide, methyl Cellosolve at reflux, (b) methanolic hydrogen chloride, (c) 3-indoleacetyl chloride, (d) saponification, and (e) polyphosphoric acid at 85°, thus yielding the tetracyclic unsaturated keto lactam **7a**.[13] Reduction of the keto lactam with lithium aluminum hydride in tetrahydrofuran at room temperature provided a mixture of diastereomeric amino alcohols **7b**, which, upon treatment with methanesulfonyl chloride–pyridine at 0°, gave rise to the crude quaternary salt **8**.[16] Subjection

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(9) K. Clark and K. Rothwell, *J. Chem. Soc.*, 1885 (1960).
(10) All new compounds gave satisfactory combustion analyses and/or mass spectral data.
(11) A forerun of 3-methoxypyridine was also obtained.
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(16) (a) J. Harley-Mason and A. Ur-Rahman, *Chem. Commun.*, 208

of the aforementioned salt to potassium cyanide[16a,17] in hot dimethylformamide[16b,18] produced the ring cleaved α and β nitriles **7c** in a 4:1 ratio, respectively (58% yield).[19] The nitriles could also be prepared *via* the chloroindolenine route[19,16b] from 14,15-dehydroquebrachamine (**7e**).[13] Acid hydrolysis of either nitrile provided 14,15-dehydroquebrachamine, locating the nitrile function at C-16. The respective α and β esters **7d** were prepared from the corresponding nitriles by saponification and subsequent esterification with diazomethane.[16b] The same mixture of esters could be obtained (tlc comparison) by reduction of (−)-tabersonine according to Le Men.[20] Oxidation of the major isomer, α-ester **7d**, with platinum–oxygen in ethyl acetate according to Schmid[21] afforded (±)-tabersonine (hydrochloride, mp 187° dec), whose identity with an authentic sample of (−)-tabersonine[22] was demonstrated by comparative thin layer chromatography and solution infrared, ultraviolet, and mass spectroscopy.

Whereas allocatharanthine (**9**) is produced from tabersonine in hot acetic acid solution, no sign of allocatharanthine was observed (tlc) in the oxidative cyclization.[23] Similar selective oxidations with platinum–oxygen have recently been reported[24] in related systems.

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(1967); (b) J. P. Kutney, W. J. Cretney, P. LeQuesne, B. McKague, and E. Piers, *J. Amer. Chem. Soc.*, **92**, 1712 (1970); (c) J. P. Kutney, N. Abdurahman, C. Gletsos, P. LeQuesne, E. Piers, and I. Vlattas, *ibid.*, **92**, 1727 (1970).

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(22) We wish to thank Professors A. I. Scott and J. Le Men for samples of (−)-tabersonine hydrochloride.

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(25) National Institutes of Health Predoctoral Fellow, 1968–1971.

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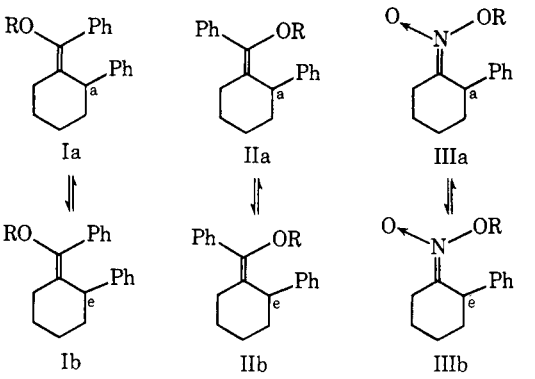
Allylic(1,3) Strain. A Defense

Sir:

In 1965 we published[1] two stereochemical theorems dealing with allylic strain in six-membered rings. These ideas were applied[2,3] among other ways in explaining (a) the preferred conformation in the ground state of molecules such as I, II, and III and (b) the stereochemical consequences of C protonation of I, II, and III (R = H or metal). In essence we contended that the cyclohexane ring in these molecules assumes, dominantly, conformation Ia, IIa, or IIIa in which the phenyl ring is axially oriented in order to minimize the Ph–Ph or Ph–OR interaction, as the case may be, in conformation Ib, IIb, or IIIb. With regard to C



protonation of the enolic forms of these molecules we suggested that protonation occurs "axially" (*i.e.*, from the least-hindered side[4]) and produces largely the cis isomer of benzoyl- or nitro-2-phenylcyclohexane.

These ideas have been criticized recently (a) by Zimmerman and Mariano,[5] who have cast doubt on the validity of the nmr data that formed the experimental underpinning of the A(1,3) strain concept, and (b) by Bordwell and his coworkers,[6–8] who have carried out extensive kinetic studies on the protonation of acinitro compounds such as III (R = alkali metal) and on the deprotonation of the related nitro compounds. These results, together with ultraviolet data, and an examination of molecular models, led the latter workers to conclude[8] that (1) the ground state of III (R = alkali metal) is IIIb and (2) the preferred transition state for the C protonation of II (R = alkali metal) does not have geometry around C-1 similar to that of II.

Whereas we reserve comment on the second conclusion, our recent results, which are discussed below, lead us to reject the first contention, completely.

In connection with the conformational preference of I (R = Ac) and II (R = Ac), we have compared the nmr values of their benzylic protons with those of a series of model compounds in which the orientation of the corresponding hydrogen atom is known (Table I).

The results indicate that our original suggestion is correct, *i.e.*, that the sum of two gauche coupling constants ($J_{AX} + J_{BX}$) as observed for an equatorial benzylic proton is significantly less than the sum of a gauche and trans coupling required for the corresponding axial proton and thus *the width at half-height*[9] *for the benzylic proton is a valid probe* for assessing the conformational preference of I and II, and also undoubtedly of III.

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(7) F. G. Bordwell and K. C. Yee, *ibid.*, **92**, 5933 (1970).

(8) F. G. Bordwell and K. C. Yee, *ibid.*, **92**, 5939 (1970).

(9) The benzylic resonance which is the X of an ABX spin system can display a wide variety of splitting patterns which depend on the chemical shift and coupling constants involved. For clarification purposes the results in Table I are expressed as $J_{AX} + J_{BX}$ since in all systems considered here the line width at half-height or separation of the outside peaks, as the case may be, represent at worst an upper limit for this sum, assuming all coupling constants have the same sign.