

LITHIUM-AMMONIA REDUCTION OF TETRAHYDROCANNABINOLS*

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We wish to report that during the course of our work on tetrahydrocannabinols and their various nitrogen analogs^{1,2} the reduction of compounds I to IV with Li in liquid ammonia furnished their open chain conjugated derivatives, e.g., I gave V. These results are in contrast to those of Birch and Maung³ who have found that metal-ammonia reduction of chromenes gives ortho-isopentenyl phenols, e.g., VIa gave VIIa.

In order to study the difference between our results and those of Birch and Maung³ we prepared⁴ VIb⁵. On treatment with Li-ammonia in a tetrahydrofuran-aniline mixture, VIb gave the unconjugated VIIb as a gum, C₂₀H₃₂O₂, m/e 304; nmr spectrum⁶ (CCl₄) 1.73, 1.80 2 s (6, olefinic methyls); 5.23 m (1, vinylic). These results are similar to Birch and Maung's³ findings on VIa. The difference in the products obtained from chromenes of type VI on the one hand and from I to IV on the other is not so surprising if one considers the stability of various carbanions⁷. Thus, compound VIb on metal-ammonia reduction will give the tertiary carbanion VIIIa, which is more stable in the secondary form VIIb and hence on protonation gives VIIb. Similarly, IV gives the tertiary carbanion IXa. Of the two tertiary carbanions IXa and IXb the isopropyl is more stable than the cycloalkyl and hence IXa protonates to give the end product. On the same basis I, II and III would be expected to give their open chain conjugated derivatives.

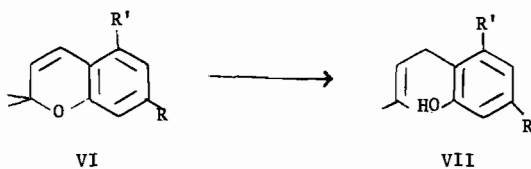
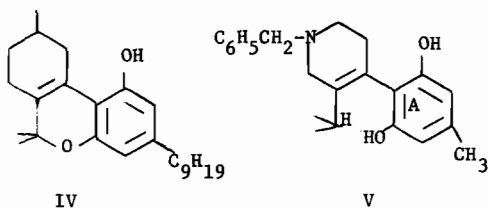
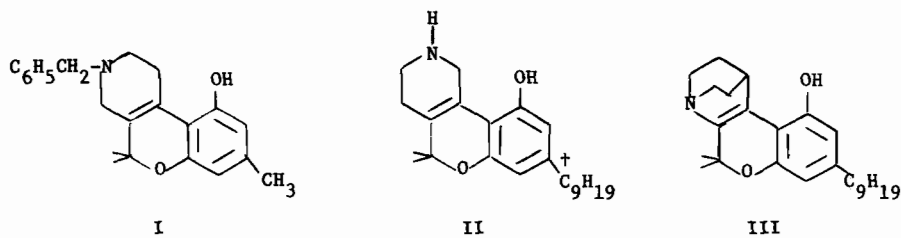
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Compound I dissolved in tetrahydrofuran was reduced with Li (excess) in liquid ammonia to give a solid, m.p. 205-208°, $\lambda_{\text{max}}^{\text{EtOH}}$ 208 nm (ϵ 1510); $\text{C}_{22}\text{H}_{27}\text{NO}_2$, m/e 337. Its nmr spectrum ($\text{C}_6\text{D}_5\text{N}$) showed absorption at 1.07 d (area 6, gem dimethyl group; $J = 7$ cps), 2.25 s (3, aromatic methyl), 2.75 s (4), 2.98 m (1, $J = 7$ cps), 3.32 m (2), 3.74 s (2), 6.7 s (2, aromatic ring A), 7.4 m (5, aromatic), 9.3 br (2, exchangeable with D_2O). The appearance of the two aromatic protons in ring A as a singlet and the two exchangeable protons show clearly that the pyran ring in I is opened. Thus, structure V was assigned to this compound. This was further confirmed by determining its nmr spectrum at 100 megacycles, with no change in the coupling constant of the doublet assigned to the CMe_2 group at 1.07 ppm, and by decoupling the methine multiplet at 2.98 ppm, causing the geminal methyl doublet to collapse. The ultraviolet spectrum is rationalized on the basis that the benzene ring is out of plane with the double bond of the tetrahydropyridine ring.

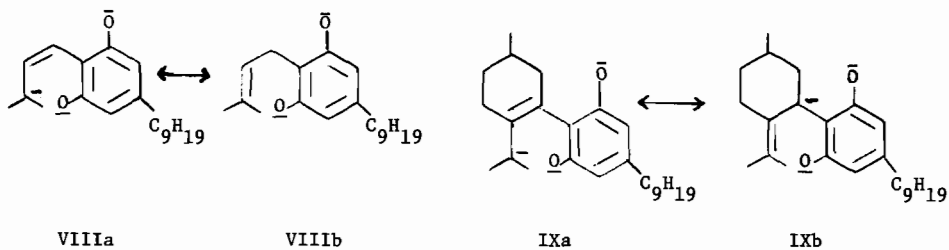
Similarly, the reduction of II and III furnished their respective ring opened derivatives analogous to V. Product from II: m.p. 77-81°; $\text{C}_{23}\text{H}_{37}\text{NO}_2$, m/e 359; $\lambda_{\text{max}}^{\text{EtOH}}$ 280 nm (ϵ 980); nmr spectrum⁸ (CDCl_3) 0.85 m (area 6), 0.91 d (6, gem dimethyl group; $J = 7$ cps), 1.24 m (12), 2.35 m (4), 3.32 m (4) 5.92 (3, exchangeable with D_2O), 6.28 s (2, aromatic). Product from III: HCl Salt; m.p. 236-238° $\lambda_{\text{max}}^{\text{EtOH}}$ 280 nm (ϵ 1880) and 250 nm (ϵ 7540); $\text{C}_{25}\text{H}_{39}\text{NO}_2$, m/e 385; nmr spectrum⁸ (CDCl_3) 0.82 m (area 6), 1.07 d (6, gem dimethyl group; $J = 7$ cps), 1.26 m (12), 1.75 m (4), 2.61, 3.06 m (7), 5.0 br (2, exchangeable with D_2O), 6.32 s (2, aromatic).

Likewise, Adam's tetrahydrocannabinol IV⁹, dissolved in a tetrahydrofuran and aniline mixture, was reduced¹⁰ with Li (excess) in liquid ammonia to give a red gum; $\text{C}_{25}\text{H}_{40}\text{O}_2$, m/e 372; $\lambda_{\text{max}}^{\text{EtOH}}$ 275 nm (ϵ 1600); nmr spectrum⁸ (CDCl_3) 0.87 (area 6), 0.92 d (6, gem dimethyl group; $J = 7$ cps), 0.97 to 1.65 (15), 1.7 to 2.5 (9), 4.79 s (2, exchangeable with D_2O), 6.31 s (2, aromatic); diacetate, $\text{C}_{29}\text{H}_{44}\text{O}_4$, m/e 456 with appropriate spectrum.



a, R' = R = H
b, R' = OH, R = C₉H₁₉

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b, R' = OH, R = C₉H₁₉



[†]C₉H₁₉ = CH(CH₃)CH(CH₃)-n-C₅H₁₁

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2. Carried out for the U.S. Army Edgewood Arsenal under Contract No. DA18-108-AMC-103(A).
3. A.J. Birch and M. Maung, Tetrahedron Letters, 3275 (1967).
4. Satisfactory analytical data have been obtained for all new compounds. The isolated yield of each compound was at least 60%.
5. Chromene VIb was prepared from 5-(3-methyl-2-octyl) resorcinol and 3-hydroxy-3-methyl-1,1-dimethoxybutane according to the general procedure described by W.M. Bandaranaysake, L. Crombie and D.A. Whiting, J. Chem. Soc. (C), 811 (1971).
6. All nmr spectra were determined on a Varian A-60 Spectrophotometer. Values given are in parts per million relative to TMS as an internal standard: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.
7. See for example J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" McGraw-Hill Book Company, New York, N.Y., 1968, p. 142.
8. It is difficult to assign peaks in the aliphatic region because of the complex side chain.
9. R. Adams, S. Mackenzie, Jr., and S. Loewe, J. Am. Chem. Soc., **70**, 664 (1948).
10. The reduction conditions used were the same as in the case of VIb.