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THE BIRCH REDUCTION OF TRYPTAMINE QUATERNARY SALTS

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We wish to report that in the lithium-in-ammonia reductions of tryptamine methiodides, preferential reduction of either the quaternary center or the indole nucleus* can be obtained, depending on whether or not methanol is present during these reductions. Furthermore, the mode of cleavage of the quaternary group (absence of methanol) is dependent upon the nature of the substituent on the indole nitrogen.

Thus treatment of N,N-dimethyl-5-methoxytryptamine methiodide (I) (1) or 5-methoxy-1, N,N-trimethyltryptamine methiodide (II)** with 15 equivalents of lithium in liquid ammonia containing excess methanol afforded the corresponding 4,7-dihydrotryptamine methiodides IV (m.p. 181-183°, 43%) and V (dec. 120°, 46%). In contrast, when I and II were treated with 2 (or more) equivalents of lithium in ammonia in the absence of methanol the reductions followed different courses. With the 1-unsubstituted compound I, a methyl group was cleaved from the quaternary ammonium function, affording N,N-dimethyltryptamine III (60%). However, with the 1-methyl compound II, trimethylamine was cleaved and the unusual spiro-indoline VII (m.p. 197-205°, 83%) was formed.

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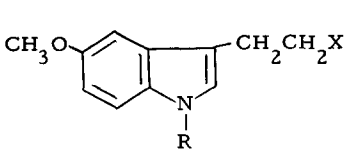
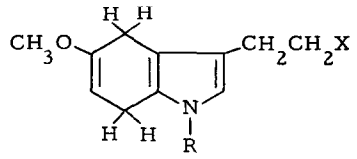
* Birch reduction of indoles has been described in two previous reports (2,3); a more definitive report is in preparation (W.A. Remers, G.J. Gibs, C. Pidacks, and M.J. Weiss).

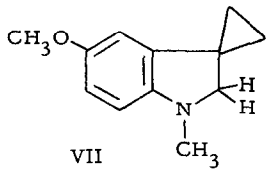
** Prepared from methyl iodide and the corresponding N,N-dimethyltryptamine (4), this quaternary salt had m.p. 192-196°.



I R = H, X = $N(CH_3)_3I$
II R = CH_3, X = $N(CH_3)_3I$
III R = H, X = $N(CH_3)_2$



IV R = H, X = $N(CH_3)_3I$
V R = CH_3, X = $N(CH_3)_3I$
VI R = H, X = $N(CH_3)_2$



VII

The structures of the above products followed from their spectral properties*. For the 4,7-dihydrotryptamines IV-VI, infrared absorption maxima at 6.0 μ were attributed to the vinyl ether function, and the characteristic indole ultraviolet chromophore was absent. The presence in the nmr spectra of one vinyl proton (δ4.75 ppm) and one pyrrole proton (6.41 ppm) confirmed the structures. Spiro-indoline VII had a four-proton multiplet at 0.41-1.83 ppm (⋈) a two-proton singlet at 4.30 ppm (N-CH_2-$\overset{|}{C}$-), and three aromatic protons at 6.13-6.75 ppm. An independent preparation of IV was afforded by reduction of N,N-dimethyl-5-methoxytryptamine III with lithium and methanol in ammonia, followed by treatment of the resulting 4,7-dihydro derivative (VI, m.p. 91-93°, 55%) with methyl iodide.

In the absence of methanol electron addition at the quaternary center apparently occurs in preference to electron addition to the indole nucleus or indole NH bond**. With a quaternary tryptamine salt that has an ind-NH, the quaternary center then undergoes cleavage of a methyl group*** and no reduction of the indole nucleus occurs, even if excess lithium is present****.

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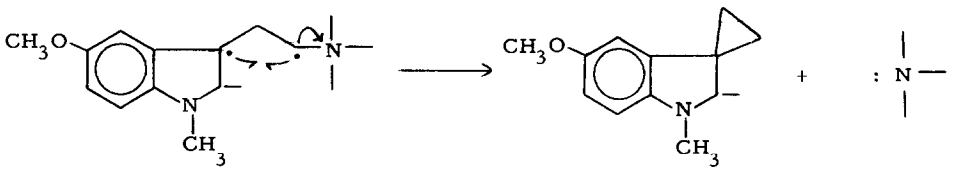
* Satisfactory elemental analyses were obtained on all new compounds (L. Brancone). Nmr spectra were determined in deuteriochloroform (W. Fulmor).

** This observation finds precedence in the reductions of agroclavine methiodide (5) and of a quebrachamine precursor (6).

*** The loss of methyl in preference to most other radicals from quaternary salts is well established (7).

**** Indoles unsubstituted on nitrogen undergo salt formation with alkali metals in ammonia and are not reduced in the absence of a proton source such as an alcohol (3).

However, with a quaternary tryptamine salt that has an ind-N-methyl group, the different course of the cleavage reaction suggests that electron addition to the indole nucleus occurs prior to cleavage, and the cleavage then involves ring formation either simultaneous with, or subsequent to loss of trimethylamine. One reasonable possibility for this transformation is the concerted coupling of unpaired electrons and elimination of trimethylamine depicted in A ⟶ B.



A B

In the presence of methanol the electron which adds to the quaternary center is apparently discharged (transferred to methanol) without cleavage (8). Thus it is possible to effect preferential reduction of the benzene ring in quaternary salts I and II in the presence of excess lithium. Additional evidence for the suppression of quaternary salt cleavage by methanol was found in the behavior of methyl triethylammonium iodide under the same conditions, wherein 84% of the unreacted quaternary salt could be recovered. When methanol was absent the cleavage of the methyl group proceeded rapidly and in high yield (7).

The above-described evidence suggests that the species formed upon addition of an electron to a tryptamine quaternary center has a pre-cleavage lifetime longer than might have been anticipated. This lifetime is at least sufficient to allow the electron to be transferred to methanol. Also, if the cyclization to VII occurs via a radical anion in the indole nucleus, the pre-cleavage lifetime at the quaternary center must be long enough to allow this second electron addition.

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