S. Eguchi for the synthesis of compounds VIb and i, Dr. K. S. Rybalko (Vilar, Moscow) for a sample of desacetoxymatricarin isolated from *Artemesia leucodes*, and Dr. R. E. K. Winter for helpful discussions.

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Received July 31, 1967

Ring Selectivity in the Reduction of Certain Indoles and Quinolines by Lithium and Methanol in Liquid Ammonia

Sir:

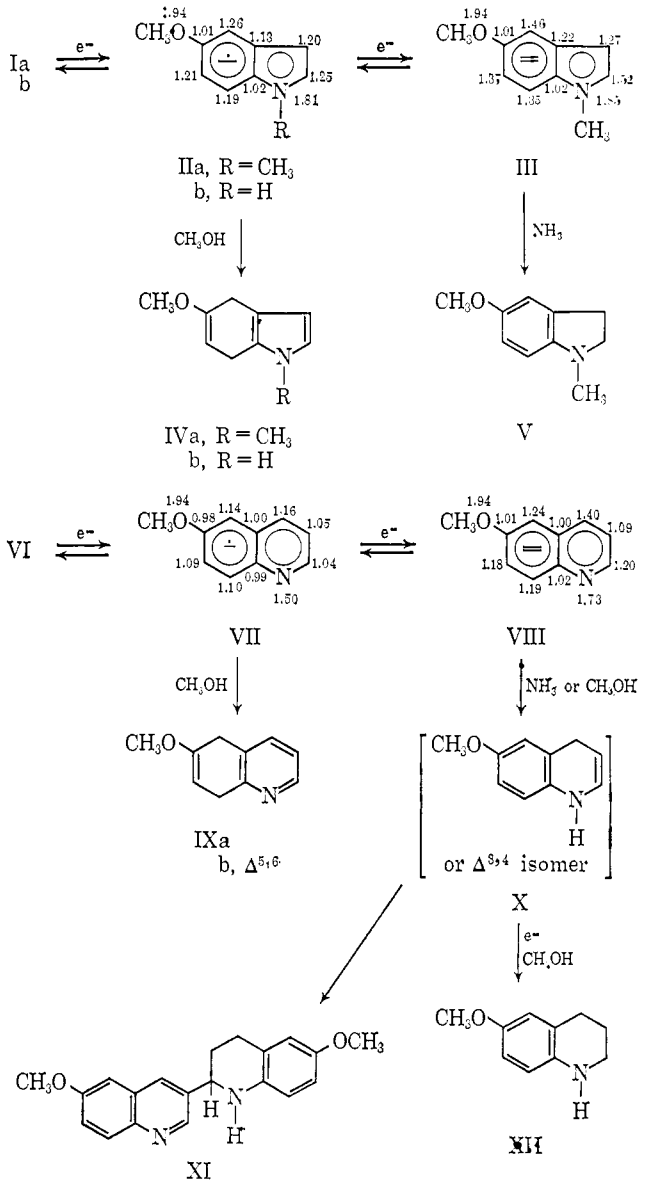
We wish to report that in the reduction of certain indole and quinoline derivatives by lithium and methanol in liquid ammonia the nature of the product is determined by the stage at which the methanol is added. When such compounds are treated with lithium, and methanol is added later or omitted, reduction occurs preferentially in the heterocyclic ring, probably *via* dianion intermediates; however, when excess methanol is present from the beginning of the reaction, reduction occurs in the benzene ring, apparently by interception of radical anion intermediates.

Thus treatment of 10 mmoles of 5-methoxy-1-methylindole (Ia)[1] with 80 mg-atoms of lithium in 200 ml of ammonia (no methanol) for 4 hr, followed by discharge of the excess lithium with ferric ion, afforded indoline V[1] as the sole product (70%). In contrast, if 20 ml of methanol was present prior to the addition of lithium, the reduction was very rapid and the product mixture contained 60% of 4,7-dihydro derivative IVa (n^{25}D 1.5465; nmr: pyrrole protons at δ 6.55 and 5.91, vinyl proton at 4.75, four aliphatic protons at 3.23 ppm), 4% of V, and 8% of Ia.[2,3]

When methanol is added to an ongoing reduction of Ia to V, the formation of IVa supersedes so that the ratio of V to IVa is determined by the time elapsed (10 min to 4 hr) before methanol addition (see Scheme I).

The equilibrium between Ia and its radical anion IIa apparently lies well to the left since Ia decolorizes lithium in ammonia quite slowly. However, methanol (a relatively strong acid) rapidly converts the small concentration of IIa to 4,7-dihydroindole IVa.[4] When methanol is absent, IIa is apparently insufficiently basic to deprotonate ammonia and reduction to IVa does not occur. Instead, the equilibrium between IIa and dianion III is established. This strongly basic dianion

Scheme I



is protonated by ammonia in the pyrrole ring to give indoline V. One reasonable explanation for the difference in the site of protonation between radical anion IIa and dianion III is that these intermediates have different patterns of electron distribution. Indeed, the depicted total π-electron densities, calculated by the LCAO–MO method,[5] reveal this difference and in the case of the dianion give an unequivocal indication of the site of protonation (C-2).

Treatment of 5-methoxyindole (Ib) in ammonia with 4 equiv of lithium results in vigorous reaction until 1 equiv is consumed, and thereafter blue color appears. Addition of methanol to this mixture affords 82% of 4,7-dihydro-5-methoxyindole [IVb, mp 65–68°, nmr: pyrrole protons at δ 6.68 and 6.00 (triplets), vinyl proton at 4.79 ppm]. If excess methanol is present from the beginning, IVb is still the sole product isolated (80%). The difference in behavior of Ib from Ia upon reduction is undoubtedly due to the acidic hydrogen of Ib. Apparently Ib is converted into a salt which is not reduced

(1) J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 1203 (1951).

(2) In all experiments the ammonia was evaporated and the residue was treated with water and ether. The concentrate from the ether phase was compared with purified standards by glpc on a 6-ft Carbowax 20M column at 250°. With indoles the ether extract was totally volatile; however, only the monomeric quinoline products were volatile. Quinoline mixtures were partially resolved by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol system, although some 30–60% of the crude consisted of inseparable polymers. All compounds gave acceptable microanalyses (L. Brancone). Ultraviolet spectra were determined in methanol and nmr spectra were determined in $CDCl_3$ (W. Fulmor).

(3) Both IVa and V are unchanged by lithium amide in ammonia. Although IVa is stable toward excess lithium and methanol, V is reduced further. However, V is stable in the absence of methanol.

(4) For discussion of mechanisms of the Birch reduction see A. P. Krapcho and A. A. Bothner-By, *J. Am. Chem. Soc.*, **81**, 3658 (1959); W. Hückel, *Fortshr. Chem. Forsh.*, **6**, 197 (1966).

(5) The parameters used were suggested in A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1962, p 135.

until sufficient methanol has been added to regenerate the neutral indole,[6] and under these conditions the formation of dianion, which would lead to indoline, is precluded.

Treatment of 6-methoxyquinoline (VI) in ammonia and methanol (conditions as described above) with 5 equiv of lithium afforded 32% of 5,8-dihydro-6-methoxyquinoline [IXa, bp 141–143° (8 mm); λ_{max} 6.0 μ (C=$COCH_3$), 269 mμ (ϵ 4100); nmr: δ 8.41, 7.45, and 7.08 (three protons on pyridine ring with appropriate splitting patterns), 4.83 (triplet, J = 4 cps, vinyl), and 3.58 ppm (four-proton multiplet)], 16% of 7,8-dihydro-6-methoxyquinoline [IXb, λ_{max} 275 mμ (ϵ 5900); picrate mp 164–168°; nmr (for picrate): δ 8.35, 8.01, and 7.80 (three protons on pyridine ring with appropriate splitting patterns), 5.90 (broadened singlet, vinyl), and 3.23 and 2.63 ppm (each a two-proton triplet)], 2.5% of the known[7] 5,6,7,8-tetrahydroquinoline, 5% of 6-methoxy-1,2,3,4-tetrahydroquinoline (XII), and 8% of VI.

In the absence of methanol, VI rapidly consumed 2 equiv of lithium and formed dianion VIII. Addition of methanol then afforded as the main product isolated (35%) unsymmetrical dimer XI [mp 159–160°; λ_{max} 329 and 322 (ϵ 3680), 225 mμ (ϵ 23,400); M^+ at 320; nmr: δ 8.71 and 8.00 (doublets, J = 2 cps, two protons *meta* on pyridine ring), 7.08, 7.30, and 6.97 (three protons on benzene ring), 6.60 (broad, three protons on benzene ring), 3.85 and 3.70 (two three-proton singlets, methoxyls), 2.75 and 2.05 (two two-proton multiplets), and 4.50 ppm (doubled doublet; on addition of HCl to a dimethyl sulfoxide solution of XI this splitting pattern broadened considerably, whereas the splitting patterns of the other aliphatic protons were unchanged, indicating that this proton is next to nitrogen)]. Also isolated were IX (15%) and VI (14%). Repetition of the previous experiment with 5 equiv of lithium did not afford any XI. Instead 32% of 1,2,3,4-tetrahydro-6-methoxyquinoline (XII), 5% of IXa, and 9% of VI were obtained.

With the strongly basic dianion VIII protonation apparently occurs irreversibly on nitrogen. The resulting anion is then converted by further protonation to X or its $\Delta^{3,4}$ isomer.[8] If excess lithium is present, either of these intermediates would be reduced to XII. In the absence of excess lithium, tautomerization followed by dimerization to XI occurs.

When excess methanol is present radical anion VII must be rapidly protonated before it can go to VIII. This protonation appears to be reversible on nitrogen, but irreversible on carbon (C-5) in the benzene ring,[9] leading to IXa and (by isomerization) to IXb.

Similar results were obtained with quinoline. Thus when methanol was present the main product isolated was 5,8-dihydroquinoline [picrate mp 167–169°; nmr (for picrate): δ 5.97 (two vinyl protons) and 8.75, 8.41, and 7.88 ppm (three pyridine-ring protons); 24%]. However, when the methanol was added later (5 equiv of lithium) the main product was 1,2,3,4-tetrahydroquinoline (36%).[10]

(6) This idea was originally advanced by S. O'Brien and D. C. C. Smith [*J. Chem. Soc.*, 4609 (1960)] to explain the superiority of methanol as a proton source in the reduction of indole.

(7) E. Godar and R. Mariella, *J. Am. Chem. Soc.*, **79**, 1402 (1957).

(8) When IXa was treated with lithium amide it was converted back to VI (85%) and underwent no isomerization to X.

(9) Reversal of protonation on nitrogen would be catalyzed by the methoxide formed. When ammonium chloride is substituted for the methanol no IX is formed, although reduction is nearly complete.

(10) Treatment of quinoline with 2 equiv of sodium followed by ammonium chloride (−65° under N_2) afforded 1,2-dihydroquinoline (84%) [W. Hückel and L. Hagedorn, *Chem. Ber.*, **90**, 752 (1957)].

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Received May 31, 1967

Pretazettine[1]

Sir:

Tazettine is considered one of the most common alkaloids of the Amaryllidaceae.[2,3] Structural studies began in 1934[4] and culminated in the assignment of structure I to the alkaloid in 1966.[5] We present evidence that tazettine is not a naturally occurring alkaloid but rather is an artifact derived from the chemical lability of the true alkaloid, pretazettine.

Because of our continuing need for large quantities of tazettine in biosynthetic studies, we selected two standard sources (*Sprekelia formosissima*[6] and *Ismene calithina*[7]) for large-scale isolation of the alkaloid. Using procedures which did not involve chromatography on alumina or any strongly basic conditions, we found the crude alkaloid fraction devoid of tazettine as determined by thin-layer chromatographic criteria.

The major alkaloid, pretazettine ($C_{18}H_{21}NO_5$), is an amorphous substance, $[\alpha]^{24}D$ +180° (*c* 0.2, $CHCl_3$). It affords crystalline hydrochloride [mp 224–225°; $[\alpha]^{24}D$ +30.3° (*c* 0.15, H_2O)] and hydrobromide [mp 224–226°; $[\alpha]^{24}D$ +19.4° (*c* 0.16, H_2O)] salts.[8] Pretazettine is readily converted to tazettine either by chromatography on basic alumina or by treatment with 0.1 *N* sodium hydroxide at 20° for 1 hr. Pretazettine is unstable as the free base and gradually rearranges to tazettine upon standing. An aqueous solution of pretazettine at 70° is converted to tazettine in less than 1 hr.

The chemical and physical properties of pretazettine are in good agreement with those reported by Proskurnina[9] for isotazettine.[10] Pretazettine may be assigned structure II not only from its ready rearrange-

(1) Supported by a grant from the National Institutes of Health (HE 7503).

(2) W. C. Wildman, *Alkaloids*, **6**, 372 (1960).

(3) H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, p 410.

(4) E. Späth and L. Kahovec, *Ber.*, **67**, 1501 (1934).

(5) R. J. Highet and P. F. Highet, *Tetrahedron Letters*, 4099 (1966). Other references on the structure of tazettine include: W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 2962 (1955); T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *ibid.*, 4749 (1956); T. Ikeda, W. I. Taylor, Y. Tsuda, and S. Uyeo, *Chem. Ind.* (London), 1088 (1955); T. Ikeda, W. I. Taylor, Y. Tsuda, and S. Uyeo, *ibid.*, 411 (1956); R. J. Highet and W. C. Wildman, *ibid.*, 1159 (1955); H. Irie, Y. Tsuda, and S. Uyeo, *J. Chem. Soc.*, 1446 (1959); Y. Tsuda and S. Uyeo, *ibid.*, 2485 (1961).

(6) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **88**, 1590 (1955).

(7) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **45**, 315 (1958).

(8) Substantiating elemental analyses, nmr, and mass spectral data have been obtained for all compounds and will be reported in the final paper.

(9) N. F. Proskurnina, *Zh. Obshch. Khim.*, **23**, 3365 (1957).

(10) The name isotazettine is inappropriate since it does not reflect the basic ring system of the alkaloid and introduces confusion when equated with isotazettine (criwelline), tazettinol, and isotazettinol, all of which contain the tazettine ring system but vary in stereochemistry at C_3.