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THE SYNTHESIS OF DEHYDROBUFOTENINE

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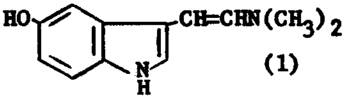
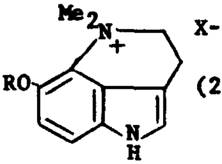
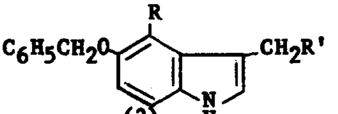
Dehydrobufotenine, the principal indolic constituent from the parotid glands of the South American toad Bufo marinus was originally investigated by Wieland[1] who suggested structure (1). Recently two independent groups[2] almost simultaneously proposed structure (2a) [R = H; X = Cl; the natural substance is isolated from the toad as the hydrochloride] based primarily on nmr data. We now wish to report the synthesis of the novel heterocycle (2a) and its identity with the natural substance, thus confirming the correctness of the latter assignments.



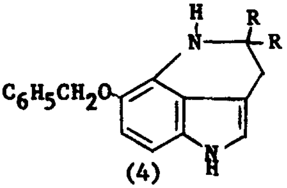
(1)



(2)



(3)



(4)

Our synthetic pathway roughly parallels the route to 1,3,4,5-tetrahydropyrrolo 4,3,2-de quinoline[3], the parent heterocycle. Nitration of 5-benzyloxygramine gave in 70% yield a single product*, m.p. 143-144°, $\lambda_{max}^{CHCl_3}$ 6.62, 7.50μ

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*Satisfactory elemental analyses were obtained for all new compounds. All nmr spectra were measured with tetramethylsilane as the internal standard on a Varian A-60 spectrometer.

(nitro), whose structure was shown to be the 4-nitro derivative[4] (3a) [R = -NO_2; R' = -$N(CH_3)_2$] by the nmr spectrum ($CDCl_3$) which displayed two doublets centered at τ2.67 and 3.06, J = 9 cps each, (two <u>ortho</u> H's at positions 6 and 7) and a singlet at τ 2.85 (H at position 2)[5]

Conversion of the nitrogramine (3) via the quaternary methosulfate to the nitrile (3b) [R = -NO_2; R' = -CN] m.p. 162.5-163.5°, was accomplished in 66% yield.

Reductive cyclization of (3b) to the desired amine (4a) [R = R = H] as described for the parent system[3] was unsuccessful due to the concomitant hydrogenolysis of the protecting benzyl group. The resultant phenolic amine(s) could not be isolated even under acidic conditions. We therefore subjected the nitrile (3b) to ethanolysis with alcoholic hydrogen chloride and obtained the ester (3c) [R = -NO_2; R' = -$CO_2C_2H_5$] m.p. 98-99°, $\lambda_{max}^{CHCl_3}$ 5.75, 6.54, 7.25μ (ester, nitro), in 63% yield. Sodium dithionite reduction of (3c) was accompanied by saponification of the ester group to give the amino acid (3d) [R = -NH_2; R' = -CO_2H] m.p. 140.5-141.5°, in 89% yield, λ_{max}^{KBr} 3.41, 3.87, 4.68, 6.37, 6.64μ (amino acid bands).

Cyclization of (3d) to the lactam (4b) [R,R = O=] was effected with dicyclohexylcarbodiimide in tetrahydrofuran; the product, m.p. 179-180°, $\lambda_{max}^{CHCl_3}$ 2.88, 2.94 (NH), 6.01μ (amide carbonyl), was obtained in 65% yield. Reduction of the lactam (4b) to the amine (4a) with a two-fold excess of diborane[6,7] at room temperature gave an 82% yield of (4a), m.p. 83.5-84.5°, $\lambda_{max}^{CHCl_3}$ 2.81, 2.89, 6.56μ (NH). Treatment of (4a) with a large excess of methyl iodide in an alcoholic potassium hydroxide medium at room temperature gave a 78% yield of the quaternary iodide (2b) [R = $C_6H_5CH_2$-; X = I] m.p. 194.5-196° (dec.), nmr signals ($DMSO_{d6}$): τ 2.30-2.79 (multiplet, 8 aromatic H's), 4.61 (singlet, 2 benzyl H's) 5.85, 6.70 (triplets, 2 ring methylene H's each) and 6.31 (singlet, 6 methyl H's).

Attempted mild hydrogenolysis* of the benzyl compound (2b) returned the

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*Gentle hydrogenations were attempted at first, since dehydrobufotenine hydrochloride is reported (see ref. 1) to be cleaved catalytically to bufotenine in a weakly acidic medium; however the proximity of the two methyl groups to the benzyloxy function apparently shields the (benzyl) C-O bond as well as the (phenyl) C-N linkage of the tetrahydroquinoline system.

starting material; more stringent conditions (methanol solution, 50% by weight of 10% Pd/C, 60°, 6 hrs.) caused a smooth transition to the desired phenol (2c) $\left[R = H,\ X = I\right]$ in 85% yield, m.p. $243.5\text{-}245^{\circ}$ (dec.). To compare the synthetic sample with the available natural material, the hydroiodide was converted to the hydrochloride (2a) $\left[R = H;\ X = Cl\right]$ by a standard procedure[8]. The resulting product, m.p. $237\text{-}238^{\circ}$ (dec.)*, was shown to be identical to natural dehydrobufotenine hydrochloride in all respects (mixture melting point, infrared, ultraviolet and nmr spectra, thin-layer and paper chromatography, and similar comparison of the picrate derivatives of both samples).

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REFERENCES

1. H. Wieland and T. Wieland, Ann., 528, 234 (1937).
2. F. Marki, A. V. Robertson, and B. Witkop, J. Am. Chem. Soc., 83, 3341 (1961); B. Robinson, G. F. Smith, A. H. Jackson, D. Shaw, B. Frydman, and V. Deulofeu, Proc. Chem. Soc., (London) 310 (1961).
3. J. B. Hester, J. Org. Chem. 29, 1158 (1964).
4. For examples and a discussion of the preferential nitration of 5-alkoxyindoles in the 4-position, see W. A. Remers, R. H. Roth and M. J. Weiss J. Org. Chem. 30, 4381 (1965).
5. L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, J. Am. Chem. Soc., 82, 2184 (1960).
6. See: H. C. Brown and P. Heim, J. Am. Chem. Soc., 86, 3566 (1964) and Z. B. Papanastassiou and R. J. Bruni, J. Org. Chem., 29, 2870 (1964).
7. When larger excesses of diborane were employed, a mixture of three components (one of them being (4a) was obtained. Reductions of indoles to indolines have been described: H. Plieninger, H. Bauer, W. Buhler, J. Kurze, and U. Lerck, Ann., 680, 69 (1964).
8. A. P. Phillips and R. Baltzly, J. Am. Chem. Soc., 74, 5231 (1952).

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*Melting points of all the quaternary salts in this series are extremely sensitive to rate of heating