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New Synthetic Approaches To The Benz[*h*]indolo[2,3-*a*]quinolizine Ring System

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In 1955 Potts and Robinson explored the possibility that 2-[2-(3-indolyl)ethyl]isoquinolinium bromide (1) could be converted to a tetrahydrobenz[*h*]indolo-[2,3-*a*]quinolizine (II) by the action of a base in a polar solvent, but they described their results as ambiguous (2). Although members of the benz[*h*]-indolo[2,3-*a*]quinolizine ring system have since been prepared by different routes (3,4,5,6) the failure of I to cyclize to II remained an intriguing problem in view of the several reductive (2,7-12) and oxidative (13) cyclizations which probably involve electrophillic attack of an iminium group on the indole ring (*cf.* III).

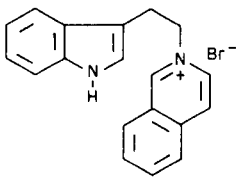
We report herein two new syntheses of 5,6,8,9,-14,14b-hexahydrobenz[*h*]indolo[2,3-*a*]quinolizine (IV) both of which in all likelihood proceed by way of a common dihydroisoquinolinium intermediate (V). The contrast between the behavior of I and the proposed intermediate V can be ascribed in part to the expected greater loss of resonance energy if the isoquinolinium salt (I) were converted to the dihydroisoquinoline in II.

In the first synthesis a direct reaction between tryptophyl bromide (VI) and 3,4-dihydroisoquinoline (VII) slowly gave a crystalline salt that proved to be the hydrobromide of IV.

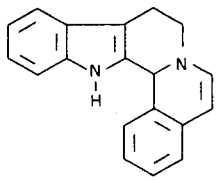
A second synthesis of the hexahydrobenz[*h*]indolo-[2,3-*a*]quinolizine (IV) was accomplished by an oxidative cyclization of 2-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (VIII). The preparation of VIII has been described by others, and mercuric acetate oxidation of VIII in hot dilute acetic acid afforded a base whose analysis, spectral properties and derivatives are in accord with the pentacyclic compound (IV). The hydrobromide of the oxidation product was identical with the salt isolated from the reaction between tryptophyl bromide and 3,4-dihydroisoquinoline.

Dehydrogenation of VIII by mercuric acetate to yield V is expected since Knabe has shown that oxidation of several *N*-substituted tetrahydroisoquinolines by this reagent gave 3,4-dihydroisoquinolines comparable to the hypothetical intermediate V (14). A less likely point of attack at either C_3 or C_4 might lead to the formation in acid solution of the isomeric dehydro derivative (IX) which is the postulated precursor of hexadehydroyohimbane (X) in the lithium aluminum hydride reductive cyclizations of I and related compounds (2,9).

Although the product proposed to have the constitution IV showed an ultraviolet spectrum characteristic of indole derivatives which excluded an indoline system (*cf.* XI) from consideration, and a structure of the yohimbane type was eliminated by direct comparison of a sample of X with our product



I



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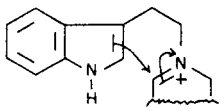
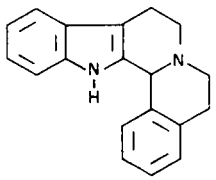
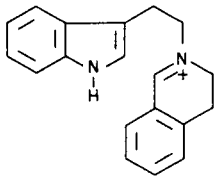


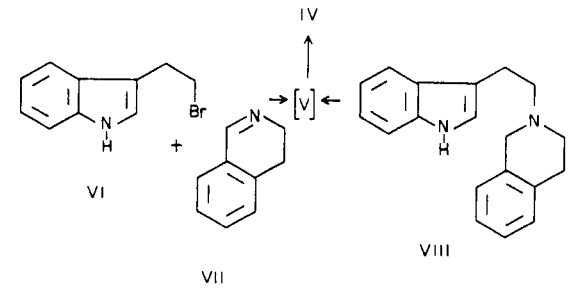
III

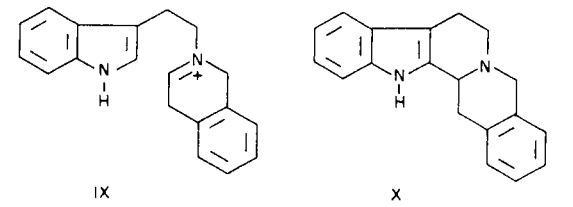


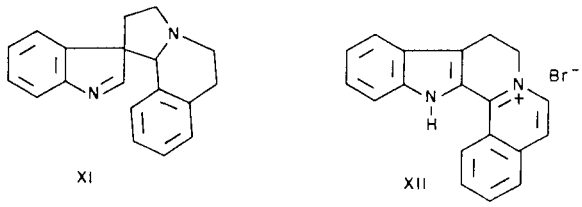
IV

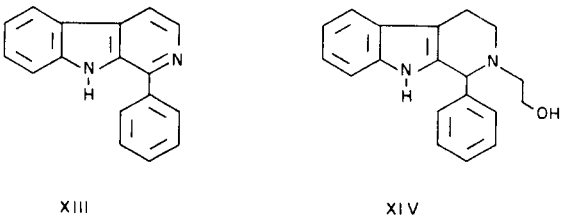


V









(13), further confirmation of structure was sought in an alternative synthesis based on a combination of two previous methods. Ban and Seo reported a one-step condensation between tryptophyl bromide and 1-chloroisoquinoline which gave a salt (XII) with the essential benz[*h*]indolo[2,3-*a*]quinolizine skeleton (5). Sugasawa and Takano had earlier prepared XII by a different route and subsequently reduced XII to IV by sodium borohydride (3). Repetition of the pertinent experiments ultimately afforded a product identical with IV from the other two syntheses. Sugasawa isolated IV as an alcoholate analogous to our solvated product.

A fourth synthetical approach to IV stemmed from 1-phenyl-β-carboline (XIII). Reaction of XIII with chloroethanol gave a salt that was reduced by sodium borohydride to 1-phenyl-2-(2-hydroxyethyl)-1,2,3,4-tetrahydro-β-carboline (XIV). Attempts to cyclize the alcohol (XIV) to IV with sulfuric acid or polyphosphoric acid proved unsuccessful. Bradsher and Litzinger utilized this general procedure to prepare several completely aromatic benz[*h*]indolo[2,3-*a*]-quinolizine salts, but they used ketones in place of the primary alcohol, and in their samples the 1-phenyl ring was substituted by activating alkoxy groups (6).

EXPERIMENTAL (16)

5,6,8,9,14,14b-Hexahydrobenz[*h*]indolo[2,3-*a*]quinolizine (IV). (*a*) By Mercuric Acetate Oxidation of 2-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (VIII).

The procedure of Huffman (9) was used for the preparation of 2-(indolylethyl)-1,2,3,4-tetrahydroisoquinoline (VIII) except tetrahydrofuran was the solvent for the reduction with lithium aluminum hydride, and VIII was obtained in 42% yield. A solution of the base (VIII, 2.4 g.) and mercuric acetate (28 g.) in 5% acetic acid (200 ml.) was heated at reflux temperature for 5 hours. The excess mercuric ion was precipitated by passing in hydrogen sulfide. The mixture was treated with concentrated hydrochloric acid (10 ml.) and filtered through a layer of Celite. The residue was washed with additional dilute acetic acid (100 ml.), and the filtrate and washings were evaporated nearly to dryness then redissolved in 50% ethanol (60 ml.). The *p*H was adjusted to about 6 with sodium bicarbonate, sodium borohydride (2 g.) was added and the mixture was allowed to stand overnight. A yellow crystalline precipitate (0.73 g.) was collected, and recrystallized from aqueous ethanol as colorless crystals, 0.47 g., m.p. 125-127°. A sample dried *in vacuo* over phosphorus pentoxide for 24 hours had a melting point of 166-167°; ultraviolet spectrum (EtOH): λ max 280 mμ (ε, 8,020), λ min 250 mμ (ε, 3,400).

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61; N, 10.21. Found: C, 83.09; H, 6.83; N, 10.48.

Other samples (m.p. 95-98° and 125-127°) gave analytical results that suggested solvation (*cf.* also ref. 3). Found: C, 78.04; H, 7.18; N, 9.16. $C_{19}H_{18}N_2 \cdot H_2O$ requires: C, 78.05; H, 6.89; N, 9.58. $C_{19}H_{18}N_2 \cdot C_2H_6O$ requires: C, 78.22; H, 7.55; N, 8.74.

A methiodide was prepared from IV and had a melting point of 263-264° (lit. (3) m.p. 263-264°).

A hydrobromide of IV, m.p. 246-247°, was prepared.

Anal. Calcd. for $C_{19}H_{19}BrN_2$: C, 64.22; H, 5.39; N, 7.89. Found: C, 64.02; H, 5.35; N, 7.91.

(*b*) From Tryptophyl Bromide and 3,4-Dihydroisoquinoline.

Tryptophyl bromide (1.1 g.) and 3,4-dihydroisoquinoline (17) (0.65 g.) were mixed and the paste was heated until a mild exothermic reaction gave a hard red glass. After 30 minutes on a steam bath, 5% acetic acid (10 ml.) was added, and the mixture was heated 2 hours longer. The aqueous layer was decanted and replaced with 20% sodium hydroxide (5 ml.). The heating was continued another hour, the alkaline solution was decanted and the red oil was washed twice with cold water. The oil was dissolved in hot ethanol, and on cooling and scratching the solution deposited 0.3 g. of fine granular solid, m.p. 126-127° (dec.). The melting point was not raised by recrystallization and the mixture with the compound from *a* was undepressed. The infrared spectra of the two samples were superimposable.

When the reactants were mixed in methanol and allowed to stand, colorless crystals, 0.4 g., m.p. 244-246°, separated after about three weeks in the refrigerator. This product was identical with the hydrobromide from part *a*, and treatment of the salt with dilute sodium hydroxide gave the base IV, m.p. 124-126° (dec.).

(*c*) By Reduction of 8,9-dihydrobenz[*h*]indolo[2,3-*a*]quinolizinium Bromide (V).

By established methods isoquinoline *N*-oxide (18) was converted to 1-chloroisoquinoline (19) which in turn was heated with tryptophyl bromide (20) to afford the salt, m.p. 312-315° (dec.) (lit. (5) m.p. 318-320° (dec.). A solution of V (0.3 g.) in aqueous methanol (30 ml.) was treated with sodium borohydride (0.15 g.). After the initial reaction subsided the reaction mixture which had turned from a deep red solution to an orange suspension was heated for 10 minutes on the steam bath and allowed to stand 1 hour. The pale yellow product,

0.1 g., m.p. 125-126° (dec.) did not depress the melting point on admixture with the oxidation product IV (part *a*), and the infrared spectra were indistinguishable.

1-Phenyl-2-(2-hydroxyethyl)-1,2,3,4-tetrahydro-β-carboline (XIV).

A slurry of 1-phenyl-β-carboline (0.7 g.), m.p. 245-247° (lit. (21) m.p. 246-247°) and 2-chloroethanol (2 ml.) was heated on a steam bath for 24 hours. The red solution was diluted to the point of turbidity with ether and on standing golden crystals (0.5 g.), m.p. 268-269°, slowly separated. The salt (0.4 g.) in methanol (15 ml.) water (2 ml.) was allowed to react with sodium borohydride (0.2 g.). Immediately on adding the borohydride the color of the solution changed from yellow to deep orange and quickly faded to a pale yellow. After 0.5 hour water was added, and there was precipitated a colorless solid (0.3 g.), m.p. 134-135°. Recrystallization from aqueous methanol raised the melting point to 138-139°.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.21; H, 6.93; N, 10.06.

Attempts to prepare IV by heating XIV with 70% sulfuric acid or with polyphosphoric acid led either to formation of high melting products or to recovery of starting material.

REFERENCES

(1) Taken in part from the M.A. Thesis of Y. G. B. (1963).

(2) K. T. Potts and R. Robinson, *J. Chem. Soc.*, 2675 (1955).

(3) S. Sugasawa and S. Takano, *Chem. Pharm. Bull. Tokyo*, 7, 417 (1959).

(4) S. Sugasawa and Y. Deguchi, *ibid.*, 8, 879 (1960); *Chem. Abstr.*, 55, 24747 (1961).

(5) Y. Ban and M. Seo, *Tetrahedron*, 16, 5 (1961).

(6) C. K. Bradsher and E. F. Litzinger, *J. Heterocyclic Chem.*, 1, 168 (1964).

(7) P. L. Julian and A. Magnani, *J. Am. Chem. Soc.*, 71, 3207 (1949).

(8) B. Belleau, *Chem. Ind.* (London), 229 (1955).

(9) J. W. Huffman, *J. Am. Chem. Soc.*, 80, 5193 (1958).

(10) D. R. Liljegren and K. T. Potts, *J. Org. Chem.*, 27, 377 (1962); K. T. Potts and I. D. Nasri, *ibid.*, 29, 3407 (1964).

(11) J. Thesing and W. Festag, *Experientia*, 15, 127 (1959).

(12) E. Wenkert, R. A. Massy-Westropp and R. G. Lewis, *J. Am. Chem. Soc.*, 84, 3752 (1962).

(13) E. Wenkert and J. Kilzer, *J. Org. Chem.*, 27, 2283 (1962); E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, 84, 4914 (1962).

(14) J. Knabe, *Arch. Pharm.*, 292, 461, 652 (1959).

(15) A sample of hexadehydroyohimbane was generously provided by Professor J. W. Huffman.

(16) Melting points were taken on a Mel-temp apparatus (Laboratory Devices, Cambridge, Mass.) and were corrected. Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

(17) W. J. Dale, L. Starr and C. W. Strobel, *J. Org. Chem.*, 26, 2225 (1961).

(18) M. Robinson and B. L. Robinson, *ibid.*, 21, 1337 (1956).

(19) M. Ikehara, *Pharm. Bull.* (Japan), 2, 111 (1954); *Chem. Abstr.*, 50, 1014 (1956).

(20) T. Hoshino and K. Schimandaira, *Ann.*, 520, 25 (1935).

(21) E. Spath and E. Lederer, *Ber.*, 63, 2102 (1930); T. Wieland and E. Neeb, *Ann.*, 600, 161 (1956).

Received October 28, 1966

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