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Synthetic Experiments Related to the Indole Alkaloids V. Mercuric Acetate Oxidation of 2-[2-(3-Indolyl)ethyl]-1,2,3,4-tetrahydroisoquinolines and the Formation of Benz[*a*]indolo[3,2-*h*]quinolizine Derivatives (1)

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Oxidation of 2-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (I) with mercuric acetate gave 5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV) and 8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (VI), as well as starting material. The base (IV) was oxidized with iodine and potassium acetate to VI and on Palladium carbon-maleic acid dehydrogenation yielded 5,6-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]-quinolizin-7-ium iodide (IX), and 14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (X). Heating the iodide (VI) with Palladium-carbon brought about an irreversible rearrangement to VII and both these salts with base yielded the red anhydro base 8,9-dihydrobenz[*a*]indolo[3,2-*h*]quinolizine (VIII). This base was also obtained from IV by oxidation in air.

The corresponding 8,9-dehydroanhydro base (XI), benz[*a*]indolo[3,2-*h*]quinolizine, was readily obtained from X and alkali. The quinolizinium salts (VI), (VII), and (IX), on catalytic, zinc dust and acetic acid, or sodium borohydride reduction, regenerated the base (IV). Selenium degradation of IV gave, among other products, 1-(2-ethylphenyl)-β-carboline. An analogous series of products was obtained with the 6,7-dimethoxy derivative of I. Various other aspects of these and related transformations are described.

In earlier studies on the synthesis of indolo[2,3-*a*]-quinolizine derivatives related to the indole alkaloids by the reductive cyclization of indolylethylisoquinolinium (2a), and pyridinium salts (2b,3) with lithium aluminum hydride, it was shown that the essential intermediate in the cyclization reaction was most likely the iminium salt, $-CH=\overset{+}{N}- \longleftrightarrow -\overset{+}{C}H-N-$, obtained by the addition of a proton to the intermediate enamine generated in the lithium aluminum hydride reduction of the pyridinium salt. Ring closure to the quinolizine system then occurred by nucleophilic attack of the α-position of the indole nucleus on this salt.

The generation of iminium salts from monocyclic and bicyclic tertiary amines with mercuric acetate is a well developed procedure (4) and the oxidation of suitable piperidine and pyrrolidine derivatives has constituted a convenient method for the synthesis of quinoxazolidines (5). This reagent has also been successfully applied in the indole field (6).

In conjuction with efforts to extend the reductive cyclization ring closure to the formation of ββ-disubstituted indolenines (strychnine types), we have also investigated the use of mercuric acetate in generating the iminium salt. This communication describes the results obtained when this oxidation procedure was applied to 2-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinolines (I). This procedure has been utilized recently (6a) to prepare indolo-[2,3-*a*]quinolizine derivatives from the 1-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydropyridines and the method shows considerable potential for these types of syntheses, illustrated by the preparation of Flavopereirine (6a) and *dl*-Eburnamonine (6b). Another application of interest is its use in the formation of a Vincadifformine-type skeleton and Coronaridine (6c).

The oxidation of (I) could yield two different iminium salts: the 1,4-dihydroisoquinolinium salt (III), and the 3,4-dihydroisoquinolinium salt (II). These isomeric salts, upon cyclization, would yield

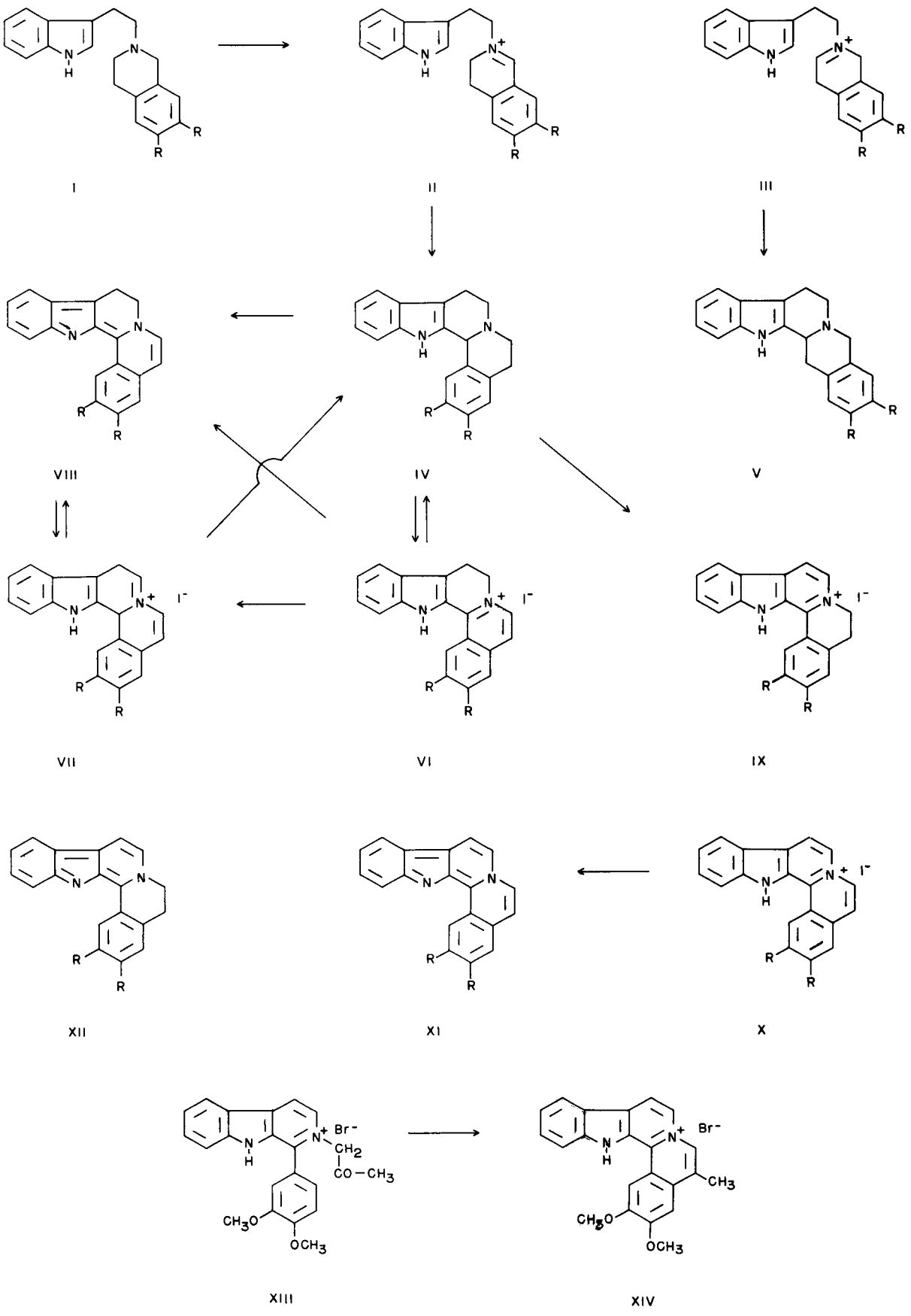
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
XIV
R
I⁻
Br⁻
CH2
CO—CH3
CH3O
OCH3
CH3

TABLE I

Ultraviolet Absorption Data for β-Carboline Derivatives

	λ max (log ε)
β-Carboline (18)	240 (4.60), 285 (4.40), 340 (3.85) mμ
1-(3,4-Dimethoxyphenyl)-β-carboline (17)	217 (4.57), 234 (4.55), 250* (4.35), 265 (4.29), 296 (4.25), 354 (4.02), 361 (4.03) mμ
Yobyrin (19)	237 (4.69), 290 (4.23), 327 (3.65), 338 (3.71), 348 (3.75) mμ
$C_{19}H_{16}N_2$ Selenium base	238 (4.61), 253* (4.38), 284* (4.15), 291 (4.30), 340 (3.76), 353 (3.80) mμ

*Denotes shoulder.

hexadehydroyohimbane (V) and its structural isomer (IV), respectively. It has been shown (7) that in the mercuric acetate oxidation of *N*-substituted tetrahydroisoquinolines, the primary process is the formation of the 1,2-dehydro product before further oxidation at the 3,4-positions takes place, and it would be expected in this case that the oxidative cyclization would lead to the formation of the structural isomer (IV) of hexadehydrohimbane (V). The oxidation of I was found to give only the cyclized base (IV), besides its ring-D oxidation product (VI), and the starting material. The formation of VI by oxidation of the base (IV) in the mercuric acetate oxidation reaction is in agreement with the observations (8,9) that when the piperidine moiety of the quinolizidine system has either unsaturation or is a part of the isoquinoline system, it undergoes aromatization with mercuric acetate.

Thin layer chromatography of compound IV showed it to be homogeneous, although the oxidative cyclization of 1-[2-(3-indolyl)ethyl]piperidine derivatives yielded a mixture of stereoisomers (6a). Elemental analyses and molecular weight data (mass spectra) of the base (IV) established its molecular formula as $C_{19}H_{18}N_2$ and the analytical data for its picrate and methiodide confirmed this formula. The base (IV), upon crystallization from aqueous methanol or ethanol, was found to have an indefinite melting point, depending on the amount of solvent present, and the product, m.p. *ca.* 100°, analyzed for $C_{19}H_{18}N_2 \cdot H_2O$, whereas the melting point of the anhydrous base was 167-169° (dec.). The base (IV) failed to react with Ehrlich's reagent, indicating that both the α and β positions of the indole nucleus were substituted, and the infrared spectrum of the base in chloroform solution showed a strong -NH absorption at 3460 cm^{-1} (ν NH (KBr), 3060-3140 cm^{-1}). The ultraviolet spectrum [λ max (CH_3OH), (log ε): 276 (3.85), 283 (3.87), sh 291 (3.80) mμ] was very similar to that of hexadehydroyohimbane [λ max (CH_3OH), (log ε): 274 (3.79), 284 (3.79), 292 (3.86) mμ] and the n.m.r. spectrum showed a singlet at 4.65 τ (one proton), multiplets at 6.4-7.5 τ (methylene protons) and at 2.1-3.0 τ (aromatic and -NH protons). No proton indicative of an unsubstituted α-indole position was present and, on the basis of this data, the base is best represented as 5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV). The mass spectral fragmentation patterns of the base (IV) and hexadehydroyohimbane were very similar and clearly showed their close relationship. Peaks at m/e 274, 273, 169, 144, 143, and 130 are in accord with well established fragmentation patterns of similar indole systems.

A reaction of particular interest is the transformation undergone by the base (IV) on heating or while being chromatographed on a column of alumina (Woelm, neutral alumina). Oxidation occurred with extreme ease and a red, anhydro base, $C_{19}H_{14}N_2$, was formed. The yield, however, was never in excess of 30%. This red base was always associated with a small quantity of unidentifiable gum, as well as the starting product, and it was not possible to isolate a base in which a corresponding reduction had occurred. The ultraviolet absorption spectrum of the anhydro base showed maxima at 257, 277, 329, and 398 mμ. Its infrared spectrum was devoid of -NH absorption and showed only benzenoid and olefinic type absorptions. The n.m.r. spectrum showed a pair of triplets at 7.08 τ and 5.78 τ (J = 6 cps.), each accounting for two hydrogens, besides the aromatic protons. On this basis, structure VIII, 8,9-dihydrobenz[*a*]indolo[3,2-*h*]quinolizine was assigned to the red base, though of course structure XII cannot be excluded on the basis of this evidence. If XII were indeed the structure, then a certain amount of broadening of the high-field methylene triplet would be expected due to some coupling of the benzylic methylene group with the protons of the aromatic ring. No such effect on this absorption was observed.

This ready oxidation is particularly interesting

in view of the stability of hexadehydroyohimbane under analogous conditions. The C_{14}-b proton of IV, being "benzylic" to two aromatic systems is extremely labile whereas the analogous proton in hexadehydroyohimbane is "benzylic" only to the indole nucleus. Some observations regarding the stereochemistry of the two protons under discussion seem appropriate in relation to this ready oxidation. The presence of the so-called "Bohlmann bands" at 2800-2700 cm^{-1} in the infrared spectra of quinolizidines and the absence of a one-proton signal below 6.0 τ in their n.m.r. spectra have been shown to be indicative of a *trans* relationship between the angular proton and the lone pair of electrons on the bridgehead nitrogen atom (6a,10,11,12). In hexadehydroyohimbane, the angular proton was indicated to be *trans* by the presence of these Bohlmann bands in conjuction with the absence of a one-proton signal below 6.2 τ in the n.m.r. spectrum. In the base (IV) the C_{14}-b proton must be *cis* on the basis of the absence of bands at 2800-2700 cm^{-1} in its infrared spectrum and the appearance of a singlet at 4.65 τ in the n.m.r. spectrum. This ready oxidation of IV may also be due in part to the *cis* configuration of this angular hydrogen atom.

A compound of structure IV has been synthesized (13) by sodium borohydride reduction of a quaternary salt, previously assigned (13,14) structure VI. The differences in the properties of the base (IV), and also the salt assigned structure VI in this present study, with those previously reported required unequivocal proof of the correctness of the structures assigned to the products from these present experiments. The following transformations and interrelationships establish this point.

Oxidation of yohimbine derivatives with potassium acetate and iodine has been found (15,16) to oxidize ring D only. Similar oxidation of compound IV gave the ring-D oxidized product (VI), also isolated from the mercuric acetate oxidation. A comparison of the properties of compound VI with those of the oxidation product derived from hexadehydroyohimbane under comparable conditions excluded the possibility of compound IV being a stereoisomer of hexadehydroyohimbane. Compound VI underwent smooth reduction with a variety of reducing agents: sodium borohydride, Adam's catalyst and two moles of hydrogen, or zinc and acetic acid were equally effective. The only product isolated from these reductions was the initial base (IV) and these experiments indicate that no skeletal rearrangements had occurred in the oxidation reaction.

The 8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (VI), upon treatment with base, afforded as expected the anhydro base 8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizine (VIII). However, hydriodic acid treatment of the anhydro base (VIII) did not cause it to revert to the iodide (VI) but rather to a new salt, tentatively designated as VII. The salt was also obtained from the iodide (VI) on heating with Palladium-charcoal at 250° but it was not found possible to effect the reverse isomerization of VII to VI. The salt (VII) behaved in a similar fashion to its progenitor (VI) on reduction; with sodium borohydride or with Adam's catalyst and two moles of hydrogen it regenerated 5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV). Treatment of the salt (VII) with base afforded the anhydro base (VIII) and these transformations showed that no skeletal rearrangement had occurred in this series of reactions. In the conversion of the salt (VI) into the anhydro base (VIII) with alkali, it was not possible to detect any prior rearrangement to a system such as VII, due to the fast rate of anhydro base formation.

These experiments involving oxidation of ring D were complemented by the study of a series of products in which ring C had been oxidized. Palladium-charcoal oxidation procedures have been used extensively (6a,8) in the yohimbine alkaloid series to effect oxidation of ring C of the β-carboline system and application of this method to 5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV) afforded products which were of particular use as reference products. Two products were obtained from this oxidation: one, in which ring C had been oxidized, was assigned the structure 5,6-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (IX) and the other, in which both rings C and D had been oxidized, was represented as 14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (X). It was possible, at this stage, to relate the product (X) to 3,4-dimethoxy-5-methyl-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium bromide (XIV), recently prepared (17) in an unambiguous fashion by the cyclodehydration of 1-(3,4-dimethoxyphenyl)-2-acetonyl-β-carbolinium bromide (XIII). The ultraviolet absorption spectra of the two products were practically superimposable, thus establishing the presence of identical chromophoric systems. The product (X) was resistant to sodium borohydride reduction, the failure of this type of system to undergo reduction having been noted previously, but of more interest was the effect of alkali on the salt (X). This readily gave the orange-red, anhydro base, benz[*a*]indolo[3,2-*h*]-quinolizine (XI). On treatment with hydriodic acid this anhydro base readily reverted to the salt (X). The infrared spectrum of this anhydro base showed no distinctive peaks other than aromatic-type absorptions and in the visible region of the spectrum there was a shift to longer wave-length in relation to the absorption of the anhydro base assigned structure VIII. In support of this structural assignment, the n.m.r. spectrum of the anhydro base was devoid of methylene absorptions and showed only a complex pattern in the olefinic-aromatic proton region. These data clearly establish the relationship between the anhydro bases and, in turn, the various oxidation products.

The other product from the Palladium-charcoal reaction to which structure IX was assigned was found to absorb two moles of hydrogen in the presence of Adam's catalyst, yielding the original base (IV). This reduction was more sluggish than the

corresponding reduction of a ring-D oxidized product but it could be effected readily with sodium borohydride. The ultraviolet absorption spectrum of IX showed maxima at shorter wave-length in the visible region than product X and was consistent with that of a 1-phenyl-β-carboline nucleus.

Further evidence in support of structure IV was obtained from its behavior on selenium degradation. A crystalline base $C_{19}H_{16}N_2$, m.p. 146-148°, was obtained and its ultraviolet spectrum showed it to be a β-carboline derivative as indicated by the data in Table I. Taken in conjunction with the n.m.r. data, which showed a triplet at τ 9.05 (CH_3), a quartet at τ 7.25 (CH_2), and an NH proton (τ 2.7) and aromatic protons (below τ 1.5), this base is best represented as 1-(2-ethylphenyl)-β-carboline. It was most likely obtained by aromatization and then fission of the C_6-N_b bond of the quinolizine nucleus, a method of fragmentation characteristic of this series (20).

The same series of reactions was also undertaken with 2-[2-(3-indolyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1; R = OCH_3) with analogous results being obtained throughout, and these products are described in the Experimental. The pentacyclic base, 2,3-dimethoxy-5,6,8,9,14,14b-hexahydrobenz-[*a*]indolo[3,2-*h*]quinolizine (IV; R = OCH_3), was found to have the same spectral characteristics, though the melting point was slightly higher, as a product to which this structure was assigned following its synthesis by a long, involved route by Sugasawa and Deguchi (25). The reported physical characteristics of several derivatives were also in agreement with those obtained in this present study.

The above considerations establish beyond doubt the structures of the products obtained in the mercuric acetate oxidation. However, there still remains the clarification of several, at first sight, contradictory reports in the literature. The problem of the melting point discrepancy between 5,6,8,9-14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine obtained in the present study and that obtained earlier by Sugasawa and Takano (13) can be resolved on the basis of the Japanese authors having a solvated product only (1 mole of ethanol). However, the structure of the iodine-potassium acetate oxidation product VI, 8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]-quinolizin-7-ium iodide, had to be questioned when its physical characteristics were not in agreement with those reported for a product previously assigned this structure. In a recent series of articles, Ban and Yeo (14) elaborated a new route to various indole alkaloid derivatives of the Flavopereirine and Serpentine type and, from a reaction in which 2-(3-indolyl)ethyl bromide was heated with 1-chloroisoquinoline, a product was obtained to which structure VI was assigned. These workers established the identity of their quaternary salt by comparison with a product previously assigned this structure by Sugasawa and Takano and it is important to note that the salt obtained by the latter authors gave 5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV) on reduction with sodium borohydride. Repetition of Ban and Yeo's procedures yielded a small quantity of their product in confirmation of their findings except that the product that sublimed from the reaction mixture was not 1-chloroisoquinoline hydrochloride as reported, but rather 1-isoquinolone. Of particular significance is the behavior of their product on sodium borohydride reduction. Reduction yielded not IV but an extremely unstable base that rapidly underwent further oxidation to a system that appeared to be an anhydro base. The ultraviolet absorption spectrum of the reduced product showed absorption maxima at 225, sh 274, 283, 291, 322 mμ (log ϵ 4.07, 3.67, 3.69, 3.62, 2.72) which, except for the band at 322 mμ, is very similar to the ultraviolet spectrum of 5,6-8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV). The same close relationship was observed in their n.m.r. spectra; the reduction product showed multiplets at 6.55-7.07 τ and aromatic protons at 2.85 τ. However, the amount of material available was too small for further structural studies.

EXPERIMENTAL (21)

2-[1,2-Dioxo-2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline.

1,2,3,4-Tetrahydroisoquinoline (20.0 g.) was added slowly to a suspension of 3-indole glyoxalyl chloride (22) (12.4 g.) in methyl ethyl ketone (180 ml.). The temperature of the mixture rose to 40° and, after the addition was complete, the temperature was raised to 50° and maintained there for 30 minutes. The precipitated tetrahydroisoquinoline hydrochloride (5.2 g.) was collected and the filtrate was washed with saturated sodium bicarbonate solution, water and was then dried (sodium sulfate) and concentrated to give a pale yellow, crystalline material. 2-[1,2-Dioxo-2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline crystallized from ethanol as colorless needles, m.p. 187-188°.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 75.0; H, 5.3. Found: C, 74.6; H, 5.2.

2-[2-(3-Indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (I).

2-[1,2-Dioxo-2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (3.5 g.) dissolved in tetrahydrofuran (40 ml.) was added dropwise over 40 minutes to a suspension of lithium aluminum hydride (2.5 g.) in the same solvent (40 ml.). The reaction mixture was heated under reflux for 15 hours and then decomposed with water, basified with dilute sodium hydroxide solution and filtered. The organic solution was dried (magnesium sulfate) and concentrated to a yellow oil (2.7 g.) which solidified. Crystallization from benzene gave the desired product as colorless rhombs, m.p. 123-124°.

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.6; H, 7.3; N, 10.1. Found: C, 82.1; H, 7.2; N, 10.1.

6,7-Dimethoxy-2-[2-(3-indolyl)ethyl]isoquinolium bromide.

A mixture of 2-(3-indolyl)ethyl bromide (23) (0.4 g.) and 6,7-dimethoxyisoquinoline (24) (0.3 g.) in methanol (10 ml.) was refluxed for 18 hours. The solvent was removed under reduced pressure and the oily residue was triturated with acetone. The yellow solid (0.54 g.) crystallized from ethanol-acetone as yellow plates, m.p. 215-218° (dec.) with previous sintering at 211°; infrared (KBr) 3400, 1630, 1610, 1570, 1515, 1490, 1470, 1750, 1430, 1420, 1350, 1340, 1300, 1290, 1275, 1265, 1235, 1210, 1200, 1185, 1180, 1150, 1140, 1020, 995, 985, 925, 870, 840, 810, 790, 765, 750, 700, 610 cm^{-1}.

Anal. Calcd. for $C_{21}H_{21}BrN_2O_2$: C, 61.0; H, 5.1; N, 6.8. Found: C, 61.2; H, 5.1; N, 7.0.

6,7-Dimethoxy-2-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline.

A solution of 6,7-dimethoxy-2-[2-(3-indolyl)ethyl]isoquinolinium bromide (2.0 g.) in methanol (100 ml.) was treated portionwise with

sodium borohydride (3.5 g.) and the mixture refluxed for 2 hours. The solvent was removed under reduced pressure and ether (150 ml.) added. The ether solution was washed with water, dried (sodium sulfate) and concentrated. The oily residue, in benzene solution, was filtered through alumina (60 g., activity IV) and eluted with benzene (300 ml.). Concentration of the solution afforded an oily material (1.6 g.) which crystallized from ether as colorless needles, m.p. 121-122°; infrared ($CHCl_3$) 3250, 2900, 1616, 1465, 1346, 1250, 1110, 1010 cm^{-1}.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 75.0; H, 7.2; N, 8.3. Found: C, 75.2; H, 7.3; N, 8.3.

Mercuric acetate oxidation of 2-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinolines.

(A) 2-[2-(3-Indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (10.0 g.) in aqueous acetic acid (330 ml., 5%) was heated in a nitrogen atmosphere with mercuric acetate (56.0 g.) for 2 hours at 85-90°. The brown reaction mixture was treated with hydrogen sulfide followed by concentrated hydrochloric acid to coagulate the black precipitate, and then filtered. The yellow, aqueous solution was basified with ammonium hydroxide solution and extracted with ether. The ether solution was washed with water, dried (sodium sulfate) and concentrated to a deep-brown, oily residue (A) (2.0 g.). The precipitated, inorganic residue was extracted with hot ethanol in a Soxhlet apparatus for 84 hours. The ethanol solution was concentrated and the residue extracted with aqueous acetic acid (150 ml., 5%). The aqueous solution was basified with ammonium hydroxide and the base was extracted with ether. The ether solution was worked up as before and a gummy residue (B) (2.5 g.) was obtained. The red, aqueous solution was acidified with concentrated hydrochloric acid, cooled in ice, and then treated with solid potassium iodide when a yellow solid (C) separated. The combined basic fractions (A) and (B) were fractionally crystallized from aqueous methanol and 5,6,8,9,14,14b-hexahydrobenz[*a*]indolo-[3,2-*h*]quinolizine (IV) was obtained as the less soluble material (2.7 g.). The mother liquor upon concentration gave a yellowish solid (0.6 g.) which after crystallization from ether had m.p. 122-123°.

It did not depress the melting point of 2-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline. The hexahydroquinolizine base was repeatedly crystallized from methanol and ethanol whence it separated as colorless needles which, after drying *in vacuo*, had m.p. 167-169° (dec.). Prior to complete drying the melting point range was 100-120° with ultimate melting with decomposition at 168-170° (lit. m.p. for solvated product, 97-99°); λ max (CH_3OH), (log ε) 227 (4.30), sh 276 (3.85), 283 (3.87), sh 291 (3.80) mμ; infrared (KBr) 3140, 3050, 2930, 2840, 2760, 2730, 1485, 1470, 1450, 1420, 1360, 1330, 1310, 1300, 1290, 1270, 1235, 1200, 1175, 1160, 1140, 1100, 1055, 1045, 1030, 1005, 985, 940, 920, 900, 870, 840, 790, 740, 570 cm^{-1}; n.m.r. ($CDCl_3$) 7.5-6.4 τ (singlet) and 2.3 τ (unresolved; broad); mass spectral data, mol. wt. 274; m/e 273, 169, 144, 143, 130.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.2; H, 6.6; N, 10.2. Found: C, 83.1; H, 6.8; N, 10.4.

Calcd. for $C_{19}H_{18}N_2 \cdot H_2O$: C, 78.1; H, 6.9; N, 9.6. Found: C, 78.2; H, 6.7; N, 9.6.

The picrate of the base crystallized from ethanol as yellow plates, m.p. 198-200° (dec.).

Anal. Calcd. for $C_{25}H_{21}N_5O_7$: C, 59.6; H, 4.2; N, 13.9. Found: C, 59.8; H, 4.2; N, 13.8.

The methiodide crystallized from methanol-acetone mixture as a colorless, microcrystalline powder, m.p. 245° (dec.) with prior sintering [lit. m.p. 263-264° (dec.)].

Anal. Calcd. for $C_{20}H_{21}IN_2$: C, 57.7; H, 5.0; N, 6.7. Found: C, 57.4; H, 5.2; N, 6.7.

The product (C) upon crystallization from methanol (charcoal) gave golden-yellow plates (2.5 g.) of 8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]-quinolizin-7-ium iodide (VI), m.p. 303-306° (dec.); λ max (CH_3OH), (log ε) 255 (4.02), sh 280 (3.95), 300 (4.00), 380 (4.26) mμ; infrared (KBr) 1590, 1560, 1540, 1455, 1435, 1420, 1380, 1350, 1330, 1295, 1250, 1230, 1140, 1090, 970, 940, 895, 870, 780, 765, 750, 735, 710, 650, 620 cm^{-1}.

Anal. Calcd. for $C_{19}H_{15}IN_2$: C, 57.3; H, 3.8; N, 7.0. Found: C, 57.1; H, 3.95; N, 6.9.

The corresponding bromide, prepared by heating under reflux an aqueous alcoholic solution of the quinolizinium iodide (VI) for 20 hours with silver bromide, crystallized from ethanol as golden-yellow plates, m.p. 305-307° (dec.).

Anal. Calcd. for $C_{19}H_{15}BrN_2$: C, 64.95; H, 4.3; N, 8.0. Found: C, 65.2; H, 4.6; N, 7.9.

(B) A mixture of 6,7-dimethoxy-2-[2-(3-indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (3.0 g.) and mercuric acetate (16.0 g.) in aqueous acetic acid (100 ml. of 5% solution) was heated in a nitrogen atmosphere at 80-85° for 2 hours. The hot reaction mixture was treated with hydrogen sulfide and concentrated hydrochloric acid (20 ml.). The black residue was filtered, washed with hot, aqueous acetic acid (100 ml.) and the yellow, aqueous solution was basified with ammonium hydroxide (*p*H 9-10) and the resultant yellow precipitate was extracted with ether (250 ml.) and then with chloroform (500 ml.). The ether solution was washed with water, dried (sodium sulfate) and concentrated. The brown gummy residue was taken up in chloroform and filtered through a column of alumina (35 g., activity IV) and eluted with chloroform (150 ml.). The chloroform solution upon concentration gave a brown, gummy residue (0.8 g.) which on trituration with ether gave a yellow solid (0.4 g.). Crystallization of the product from a chloroform-ether mixture and finally from methanol gave colorless prisms of 2,3-dimethoxy-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine, m.p. 221-222° (dec.) (lit. (25) m.p. 216-217°; λ max (CH_3OH), (log ε) 225 (4.63), sh 275 (4.02), 283 (4.09), sh 290 (4.03) mμ; infrared (KBr) 3460, 1610, 1515, 1480, 1465, 1450, 1430, 1405, 1365, 1340, 1325, 1305, 1275, 1255, 1230, 1220, 1210, 1190, 1185, 1140, 1115, 1095, 970, 955, 940, 930, 890, 860, 845, 830, 800, 770, 755, 740, 655, 620, 600 cm^{-1}; n.m.r. ($CDCl_3$) 8.0 - 6.5 τ (unresolved multiplet), 6.10 and 6.16 τ (doublet), 4.8 τ (singlet) and 2.2 - 3.5 τ (multiplet).

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.4; H, 6.6; N, 8.4. Found: C, 75.2; H, 6.7; N, 8.4.

The picrate, prepared in methanol, crystallized from acetone as yellow micro-plates, m.p. 219-220° (dec.).

Anal. Calcd. for $C_{27}H_{25}N_5O_9$: C, 57.5; H, 4.5; N, 12.4. Found: C, 57.65; H, 4.7; N, 12.35.

The hydrochloride separated from methanol-ether as colorless needles, m.p. 243-245° (dec.) [lit. (25) m.p. 248° (dec.)].

The chloroform solution from above was washed with water, dried (sodium sulfate) and concentrated to a dark gummy residue which was chromatographed on alumina (40 g., activity IV). Elution with chloroform gave a brown, semi-solid residue. It was rechromatographed on alumina (30 g., activity IV) and eluted with a benzene: chloroform (1:1) mixture. Initial fractions (150 ml.) gave a yellow residue which, upon trituration with methanol, yielded a white solid, m.p. 210-216°, identified as 2,3-dimethoxy-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo-[3,2-*h*]quinolizine. Later fractions (250 ml.) gave a brown, semi-solid residue (0.6 g.) which crystallized from a mixture of benzene-petroleum ether as orange needles, m.p. 209-210°. This was identified as the anhydro base (VIII; R = OCH_3); λ max (CH_3OH), (log ε) 254 (4.21), 266 (4.23), 284 (4.34), 324 (4.08), 350 (4.07), sh 403 (4.26), 415 (4.30) mμ; infrared (KBr) 1610, 1590, 1560, 1510, 1480, 1470, 1450, 1440, 1405, 1330, 1325, 1300, 1285, 1270, 1240, 1220, 1165, 1155, 1145, 1115, 1090, 1025 cm^{-1}; n.m.r. ($CDCl_3$) 7.1 τ (triplet), 6.15 τ (singlet), 5.7 τ (triplet), 3.5-1.5 τ (multiplet).

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.3; H, 5.5; N, 8.5. Found: C, 76.55; H, 5.7; N, 8.5.

Conversion of this anhydro base into its perchlorate gave yellow needles, m.p. 277-278° (dec.), identical in all respects with 8,9-dihydro-2,3-dimethoxy-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium perchlorate prepared below.

Oxidation of 5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV; R = H) with Potassium Acetate and Iodine.

A solution of the quinolizine (0.2 g.) in absolute ethanol (6 ml.) was treated with a solution of iodine (1.0 g.) and potassium acetate (2.1 g.) in absolute ethanol (30 ml.). The mixture was warmed on the steam bath for 5 minutes and then cooled in an ice bath. The deep-brown, crystalline precipitate was filtered and washed with a small amount of cold ethanol and then suspended in hot water and treated with sulfur dioxide. The yellow precipitate (0.2 g.), on crystallization from ethanol (charcoal), gave golden-yellow plates, m.p. 303-306° (dec.), of 8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]-quinolizin-7-ium iodide (VI, R = H).

Isomerization of 8,9-Dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium Iodide (VI) to 9,14b-Dihydrobenz[*a*]indolo[3,2-*h*]quinolizin-7-ium Iodide (VII).

The quinolizinium iodide (VI) (0.2 g.) was intimately mixed with Palladium charcoal (0.2 g., 10% catalyst) and heated at 275-280° for 20 minutes. The reaction mixture was then extracted with methanol in a soxhlet apparatus for 24 hours. Concentration of the methanol solution gave a yellow solid (0.12 g.) which crystallized from methanol as yellow needles, m.p. 282-284° (dec.); λ max (CH_3OH), (log ε) 257 (4.20), 277 (4.41), 330 (4.46), 395 (3.94) mμ.

Anal. Calcd. for $C_{19}H_{15}IN_2$: C, 57.3; H, 3.8; N, 7.0. Found: C, 57.25; H, 4.1; N, 7.3.

When the quinolizinium iodide (VI) (0.12 g.) was heated under reflux in water (10 ml.) with maleic acid (0.35 g.) and Palladium charcoal

(75 mg., 10% catalyst) for 15 hours, the yellow aqueous solution, on cooling, deposited a yellow solid (0.1 g.) which, after crystallization from ethanol, had m.p. 301-304° (dec.). It was identified as the starting material by mixture melting point determination and the superimposability of their infrared spectra.

8,9-Dihydrobenz[*a*]indolo[3,2-*h*]quinolizine. (A) By Thermal Oxidation of 5,6,8,9,14,14b-Hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV).

The quinolizine (IV) (0.34 g.) was heated in an oil bath at 178° for 30 minutes. The resultant, red product was chromatographed on alumina (30 g.). Elution with benzene gave the starting material (0.21 g.), m.p. 166-169° (dec.), identified by mixture melting point determination and infrared data. Elution with chloroform gave a red glass (95 mg.) which crystallized from a benzene-petroleum ether mixture as red plates, m.p. 208-211° (dec.), identical in all respects with the anhydro base obtained below.

(B) From the Action of Base on 9,14b-Dihydrobenz[*a*]indolo[3,2-*h*]-quinolizin-7-ium Iodide (VII).

The quaternary iodide (VII) (0.27 g.) was dissolved in hot water (50 ml.). The yellow aqueous solution, after cooling to room temperature, was basified with 5*N* sodium hydroxide solution. The deep red precipitate that formed was extracted with chloroform, the chloroform extract was washed with water, dried (sodium sulfate) and concentrated to a red, semi-solid residue. This was chromatographed on alumina (30 g., activity IV) and eluted with chloroform, when a deep-red product (0.2 g.) was obtained. It crystallized from benzene-petroleum ether as red plates, m.p. 213-214° (dec.); λ max (CH_3OH), (log ε) 257 (4.07), 277 (4.32), 329 (4.32), 398 (3.91) mμ; infrared (KBr) main bands at 1610, 1560, 1480, 1470, 1450, 1430, 1330, 1285, 1270, 1250, 1220, 1115, 780, 760, 735, 640 cm^{-1}; n.m.r. ($CDCl_3$) 7.1 τ (triplet), 5.8 τ (triplet) and 3.0-1.5 τ (multiplet).

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.4; H, 5.2; N, 10.4. Found: C, 84.2; H, 5.2; N, 10.4.

When a methanol solution of the anhydro base was treated with hydriodic acid, it gave yellow needles, m.p. 283-284° (dec.) of 9,14b-dihydrobenz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (VII).

(C) By Treatment of 8,9-Dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizinium Iodide (VI) with Base.

The quaternary iodide (100 mg.) was dissolved in hot water and the yellow solution was basified, either with ammonium hydroxide or with dilute sodium hydroxide solution and the red solution then extracted with chloroform. The deep-brown, chloroform solution was washed with water, dried (sodium sulfate), and concentrated to a deep-brown gummy residue which was chromatographed over alumina (10 g., activity IV). Elution with chloroform gave a small forerun of a yellow oil, followed by a deep-brown material that was dissolved in methanol and treated with hydriodic acid. Dilution with ether gave a yellow precipitate that crystallized from methanol-ether (charcoal) as yellow needles, m.p. 283-284° (dec.). This was identified by infrared spectral data as 9,14b-dihydrobenz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (VII).

In an alternative procedure the quaternary iodide (VI) (50 mg.) was dissolved in water and then basified with ammonium hydroxide (*p*H 9) while the solution was either hot or cold. The red solution was acidified (*p*H 6) with concentrated hydrochloric acid and treated with solid potassium iodide when a yellow precipitate separated, which after crystallization from methanol (charcoal), had m.p. 293-295° (dec.). It was identified by infrared spectral data and mixture melting point determination as the starting material (VI).

Benz[*a*]indolo[3,2-*h*]quinolizine (XI).

14*H*-Benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (0.2 g.) was dissolved in hot water (50 ml.), filtered and basified with sodium hydroxide solution (5*N*). The brown precipitate was extracted with chloroform and the chloroform solution, upon usual workup, gave a deep red residue which was chromatographed on alumina (15 g.) and eluted with chloroform. The deep red product crystallized from chloroform-petroleum ether mixture as red or orange needles (130 mg.), m.p. 208-210° with sintering at 186°; λ max (CH_3OH), (log ε) 277 (4.31), 300 (4.27), 375 (4.26), 400 (4.21) mμ; infrared (KBr) main bands at 1650, 1605, 1580, 1555, 1475, 1450, 1430, 1380, 1345, 1325, 1280, 1235, 1207, 1185, 1155, 1145, 1108, 1100, 1010, 995, 900, 805, 775, 745, 725, 620 cm^{-1}; n.m.r. ($CDCl_3$) multiplet below 3.0 τ.

Anal. Calcd. for $C_{19}H_{12}N_2$: C, 85.05; H, 4.5; N, 10.4. Found: C, 85.0; H, 4.6; N, 10.3.

The base upon treatment with hydroiodic acid in methanol solution afforded the quinolizinium iodide (X), m.p. 357-359° (dec.), identified by mixture melting point and infrared spectral data.

Oxidation of 5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine (IV) with Palladium Charcoal.

(A) The quinolizine (IV) (0.35 g.) in water (20 ml.) was heated under reflux for 15 hours with maleic acid (0.7 g.) and Palladium charcoal (0.15 g., 10% catalyst). The yellow, aqueous solution was neutralized with potassium bicarbonate and then treated with potassium iodide solution when a yellow precipitate (0.4 g.) separated. Upon crystallization from ethanol, 14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (X) separated as yellow needles, m.p. 355-358° (dec.); λ max (CH_3OH), (log ε) 277 (4.39), 299 (4.33), 375 (4.29), 404 (4.25) mμ; infrared (KBr) main bands at 1615, 1500, 1480, 1450, 1435, 1380, 1340, 1325, 1235, 1220, 1180, 1150, 1110, 810, 790, 765, 750, 735 cm^{-1}.

Anal. Calcd. for $C_{19}H_{13}IN_2$: C, 57.6; H, 3.3; N, 7.1. Found: C, 57.5; H, 3.3; N, 7.0.

The mother liquor, upon concentration, gave orange-yellow plates which crystallized from ethanol, m.p. 305-307° (dec.). This was identified as 5,6-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (IX); λ max (CH_3OH), (log ε) sh 246 (4.16), sh 255 (4.11), 277 (4.06), 331 (4.03), 389 (4.16) mμ; infrared (KBr) main bands at 1615, 1590, 1560, 1525, 1460, 1440, 1425, 1380, 1360, 1300, 1230, 1145, 1100, 900, 870, 800, 785, 765, 755, 740, 710, 630 cm^{-1}.

Anal. Calcd. for $C_{19}H_{15}IN_2$: C, 57.3; H, 3.8; N, 7.0. Found: C, 57.3; H, 4.0; N, 6.9.

(B) The quinolizine (IV) was heated under reflux for 8 hours in water (10 ml.) with maleic acid (0.35 g.) and Palladium-charcoal (75 mg., 5% catalyst). Upon working up as above, a yellow solid (0.18 g.) was obtained which crystallized from ethanol as orange-yellow plates (152 mg.), m.p. 305-307° (dec.), identical with the quinolizinium iodide (IX) by mixture melting point and infrared spectral comparison.

Oxidation of 2,3-Dimethoxy-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo-[3,2-*h*]quinolizine with Palladium Charcoal.

The quinolizine (0.2 g.) in water (4 ml.) was refluxed with maleic acid (0.35 g.) and Palladium charcoal (80 mg., 10% catalyst) for 15 hours. The yellow, aqueous solution was filtered and treated with an excess of solid potassium iodide. The yellow iodide was dissolved in hot water (30 ml.) and perchloric acid added. The yellow precipitate that separated crystallized from methanol and 2,3-dimethoxy-8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium perchlorate was obtained as yellow needles, m.p. 277-278° (dec.); λ max (CH_3OH), (log ε) 254 (4.21), 266 (4.23), 284 (4.34), 324 (4.07), 350 (4.09), sh 403 (4.16), 415 (4.20) mμ; infrared (KBr) 1625, 1600, 1565, 1505, 1495, 1460, 1430, 1405, 1395, 1350, 1320, 1280, 1235, 1190, 1170, 1150, 1095, 1080, 1030, 990, 880, 870, 835, 805, 780, 775, 750, 745, 735, 620 cm^{-1}.

Anal. Calcd. for $C_{21}H_{19}ClN_2O_6$: C, 58.5; H, 4.4; N, 6.5. Found: C, 58.3; H, 4.4; N, 6.7.

Sodium Borohydride Reductions.

(A) 8,9-Dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (VI) (2.5 g.) dissolved in methanol (200 ml.) was treated with sodium borohydride (5.0 g.). The solution was concentrated on the steam bath, diluted with water (400 ml.) and extracted with ether. The ether solution was washed with water, dried (sodium sulfate) and concentrated. The residue crystallized from aqueous methanol as colorless needles (1.7 g.), m.p. 167-169° (dec.) and was identical with the base (IV).

(B) 9,14b-Dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (VII) (0.3 g.) in methanol (25 ml.) was slowly treated with sodium borohydride (0.9 g.), with the solution turning a light brown color. After 15 minutes on the steam bath it was concentrated under reduced pressure and the residue was taken up in water and extracted with chloroform. The chloroform extract was washed with water, dried (sodium sulfate) and concentrated to a red, semi-solid residue (0.18 g.). After chromatography on alumina (12 g., activity IV) and elution with benzene, a pale yellow oil (0.12 g.) which crystallized from benzene-petroleum ether as cream needles, m.p. 165-167° (dec.), was obtained. This was identified as the base (IV) by mixture melting point determination and infrared data.

(C) 5,6-Dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (IX) (0.12 g.), dissolved in aqueous methanol (20 ml.), was treated with sodium borohydride (0.3 g.) in small portions. The yellow solution was concentrated on the steam bath when a yellowish-white, crystalline material started to separate. The reaction mixture was diluted with water (30 ml.) and acidified with concentrated hydrochloric acid. The yellow solution was warmed and then treated with a solution of potassium iodide. The yellow precipitate (0.12 g.) crystallized from methanol (charcoal) and a methanol-ether mixture as fine, colorless needles, m.p. 205-207° with sintering at 202°, and it solidified and remelted with decomposition at 235°. It was identical with the

hydroiodide of the quinolizine base (IV), the identity being established by mixture melting point determination and infrared data.

(D) 14*H*-Benz[*a*]indolo[3,2-*h*]quinolizin-7-ium iodide (X) (80 mg.) in methanol (15 ml.) was treated with sodium borohydride (0.3 g.) with the solution turning a brown color. The solution was warmed on the steam bath for 10 minutes, cooled, and diluted with water. The precipitated red solid was taken up in chloroform. On usual workup, a red, semi-solid residue (61 mg.) was obtained which was suspended in water (25 ml.), and treated with a drop of concentrated hydrochloric acid. The yellow solid that separated was dissolved by warming and the solution was treated with solid potassium iodide. The resulting yellow precipitate crystallized from methanol as cream-yellow needles, m.p. 359-362° (dec.) and was identified as the quinolizinium iodide (X) by mixture melting point determination and infrared spectral data.

Sodium Borohydride Reduction of 2,3-Dimethoxy-8,9-dihydro-14*H*-benz[*a*]indolo[3,2-*h*]quinolizin-7-ium Perchlorate.

The perchlorate (50 mg.) in methanol solution (50 ml.) was treated with sodium borohydride (1.0 g.) and the solution was refluxed for 1 hour. The solvent was removed, the residue diluted with water (50 ml.) and then extracted with ether. The ether solution was worked up in the usual way and the yellow residue filtered through a column of alumina (30 g., activity IV) and eluted with chloroform. The product (18 mg.) crystallized from methanol as colorless plates, m.p. 219-221° (dec.). It was identified as 2,3-dimethoxy-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizine by mixture melting point determination and infrared spectral comparison.

General Method for the Preparation of Quaternary Quinolizinium Chlorides from the Corresponding Iodides.

The quinolizinium iodide (0.2 g.) in water (100 ml.) and ethanol (50 ml.) was heated under reflux for 20 hours with silver chloride (0.6 g.). The solution was filtered and freed from solvent under reduced pressure and the residue crystallized from a methanol-ether mixture.

Catalytic Reduction of the Quinolizinium Salts.

(A) The quinolizinium chloride (VI), m.p. 282-283° (dec.), (30 mg.) in acetic acid (20 ml.) was treated with hydrogen in the presence of pre-reduced platinum oxide (35 mg.) when two moles of hydrogen were absorbed in 50 minutes. The colorless solution was filtered and concentrated under reduced pressure to an oily residue which was dissolved in water, the solution basified with ammonium hydroxide and extracted with ether. The ether solution was worked up in the usual way to give a colorless oil which was chromatographed on alumina and eluted with benzene. The combined product from two such experiments crystallized from petroleum ether as colorless needles, m.p. 163-166° (dec.). This was identified as the quinolizine (IV) by mixture melting point determination and infrared spectral data.

(B) The 5,6-dihydroquinolizinium chloride (IX) (30 mg.), m.p. 273-275° (dec.), was reduced with hydrogen in the presence of pre-reduced platinum oxide (45 mg.) when two moles of hydrogen were absorbed in 2 hours. The pale yellow solution with a deep-green fluorescence was worked up as above. The colorless, oily material thus obtained was crystallized from an ether-petroleum ether mixture and had m.p. 158-160° (dec.). It had an identical infrared spectrum with that of the quinolizine (IV) and the mixture melting point was not depressed. The picrate, m.p. 197-199° (dec.), did not depress the melting point of the quinolizine (IV) picrate.

(C) A solution of the anhydro base (VIII) (20 mg.) in acetic acid or methanol (20 ml.) was stirred with platinum oxide (50-60 mg.) in a hydrogen atmosphere. No absorption of hydrogen was observed in a 4.16 hour period and the starting material was recovered.

Thermal Treatment of the 8,9-Dihydroquinolizinium Iodide (VI).

The quinolizinium iodide (VI) (0.1 g.) was heated at 275-285° for 1 hour. The brown solid, on crystallization from methanol (charcoal), gave a yellow solid, m.p. 292-293° (dec.), having an identical infrared spectrum with that of the starting quinolizinium iodide (VI) and causing no depression in a mixture melting point determination.

Selenium Dehydrogenation of 5,6,8,9,14,14b-Hexahydrobenz[*a*]indolo-[3,2-*h*]quinolizine (IV).

(A) The base (IV) (0.5 g.) was intimately mixed with selenium (1.1 g.) and heated in a nitrogen atmosphere between 225-300° for 25 minutes and maintained at 300° for an additional 5 minutes. The deep brown product was powdered with alumina (activity I) and extracted in a soxhlet apparatus with benzene for 12 hours. The benzene solution was concentrated and the residue dissolved in ether (30 ml.). The ether solution was washed with aqueous phosphoric acid (0.2*M*; 30 ml.), the acid solution backwashed with ether (15 ml.), and the combined ether solutions were washed with water, dried (sodium sulfate) and concentrated to a deep-brown, oily residue with an indolaceous odor. The acid solution was cooled, basified with sodium hydroxide and extracted with ether (100 ml.). The ether solution, on workup in the usual way, gave a gummy residue which was chromatographed on alumina (activity I, 40 g.). Elution with a benzene-ether (2%) mixture gave a small amount of an unidentified yellow solid, m.p. 193-205° (dec.) (λ max (CH_3OH), 311, 291, 246, and 233 mμ) whose picrate crystallized from methanol as yellow needles, m.p. 225° (dec.). Further development of the column produced an oily base whose picrate crystallized from methanol as stout, yellow needles, m.p. 241-243° (dec.), with previous sintering at 237°, and was shown to be the picrate of 1-(2-ethylphenyl)-β-carboline.

Anal. Calcd. for $C_{25}H_{19}N_5O_7$: C, 59.9; H, 3.8; N, 14.0. Found: C, 59.9; H, 4.00; N, 13.7.

(B) In a second experiment, the dehydrogenation was carried out by heating from 220° to 300° in 20 minutes and maintaining the temperature at 300° for 5 minutes. The isolation of the base was carried out as above. The gummy, basic fraction was repeatedly chromatographed on alumina (activity I) from which an oily product (65 mg.) was obtained. This crystallized from hexane as colorless rhombs, m.p. 146-148°, and was identified as 1-(2-ethylphenyl)-β-carboline.

Anal. Calcd. for $C_{19}H_{16}N_2$: N, 10.3. Found: N, 10.3.

The picrate, m.p. 235-239° (dec.), was shown to be identical with the picrate obtained above by mixture melting point determination and infrared spectral comparison.

Reduction of the 8,9-Dihydroquinolizinium Chloride (VI) with Zinc Dust and Acetic Acid.

A mixture of zinc dust (0.25 g.) and the 8,9-dihydroquinolizinium chloride (0.1 g.) in acetic acid (5 ml.) and water (1 ml.) was heated under reflux for 1 hour. The solution was filtered and concentrated under reduced pressure. The residue was dissolved in water (15 ml.) and basified with ammonium hydroxide and the base was extracted with chloroform. The chloroform solution was worked up in the usual way. The brown, semi-solid residue, upon filtration through alumina (8.0 g.) and elution with benzene-ether (2%) mixture (200 ml.), gave a colorless oil (70 mg.) which crystallized from an ether-petroleum ether mixture as yellow needles, m.p. 163-167° (dec.). The product was rechromatographed on alumina (15 g.). Elution with benzene (126 ml.) gave a colorless oil (53 mg.) which crystallized from petroleum ether as colorless needles, m.p. 165-168° (dec.), and was identical with the base (IV). Further elution with benzene-ether (1%) mixture (100 ml.) gave a colorless oil (15 mg.) which, after crystallization from petroleum ether, gave yellow needles, m.p. 166-168° (dec.) of the base (IV).

1-Chloroisoquinoline.

2-Methyl-1-isoquinolone (26) (20.0 g.) was heated to reflux at 150-160° with phosphorous oxychloride (34 ml.) and phosphorous pentachloride (31 g.) for 30 hours. The dark solution was freed from excess phosphorous oxychloride under reduced pressure and the residue poured into water (300 ml.) whence an oil separated. The aqueous mixture was basified with dilute sodium hydroxide solution and extracted with benzene. The benzene solution was washed with water, dried (calcium chloride) and concentrated. The dark, oily residue distilled as a colorless oil, 14.0 g., b.p. 148-172°/15 mm. Steam distillation of this product gave a steam volatile oil mixed with solid material. The distillate was extracted with benzene and, after the usual workup, an oily material was obtained which distilled under reduced pressure to yield 1-chloroisoquinoline, 8.5 g., b.p. 143-145°/15 mm. (lit. (27) b.p. 160-165°/20-30 mm.) as a colorless oil. A second fraction, 3.0 g., b.p. 150-155°/15 mm. was obtained and immediately solidified. It crystallized from methanol as colorless needles, m.p. 89-90°. This was identified as 1,4-dichloroisoquinoline (lit. (28) m.p. 89-90°); infrared ($CHCl_3$) 2990, 1612, 1565, 1485, 1444, 1390, 1365, 1330, 1320, 1295, 1250, 1145, 993, 895 cm^{-1}; n.m.r. (Satd. soln. $CDCl_3$) aromatic protons only.

Anal. Calcd. for $C_9H_5Cl_2N$: C, 54.5; H, 2.5; N, 7.1. Found: C, 54.7; H, 2.7; N, 7.2.

Condensation of 1-Chloroisoquinoline with 2-(3-Indolyl)ethyl Bromide.

A mixture of 1-chloroisoquinoline (990 mg.) and 2-(3-indolyl)ethyl bromide (23) (680 mg.) was heated in a sealed tube in a nitrogen atmosphere for 18 hours during which a colorless solid sublimed to the top of the tube. This was separated mechanically. The black gummy residue was dissolved in methanol and diluted with acetone. The gummy precipitate was filtered and the mother liquor, after concentration, was further diluted with acetone when a yellow, amorphous material (330 mg.) was obtained. This crystallized from ethanol-

acetone as orange plates, m.p. 360° (dec.) with previous darkening at 275°. This was identical with the product prepared by Ban and Yeo; λ max (CH_3OH), (log ε) 233 (4.40); 246 (4.30); sh 275 (3.92); 330 (3.87) and 430 (4.23) mμ; infrared (KBr) 2980, 1624, 1558, 1526, 1480, 1444, 1433, 1384, 1360, 1343, 1328, 1253, 1246, 1235, 1205, 1145, 1135, 1100, 943, 898, 878, 805, 767, 755, 726, 697, 687, 667, 630 cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}BrN_2$: C, 64.95; H, 4.3; N, 8.0; Br, 22.8. Found: C, 64.8; H, 4.2; N, 7.8; Br, 22.75.

The colorless sublimate crystallized from acetone as colorless needles, m.p. 211-212° and was identified as 1-isoquinolone (lit. (29) m.p. 207-208°); infrared (KBr) main bands 3150, 3065, 3010, 2975, 2915, 2885, 2850, 1647, 1632, 1545, 1475, 1342, 1249, 1227, 890, 786 cm^{-1}.

Anal. Calcd. for C_9H_7NO: C, 74.5; H, 4.9; N, 9.65. Found: C, 74.1; H, 4.9; N, 9.7.

The above salt (100 mg.) in ethanol (50 ml.) was treated with sodium borohydride (0.5 g.). The colorless solution was heated under reflux for 1 hour with darkening in color; the solvent was removed, the residue dissolved in water (50 ml.) and extracted with ether. After the usual workup the dark-brown, oily residue was filtered through a column of alumina (10 g., activity IV) in benzene (100 ml.). Evaporation of the solvent left a brown oil, which on trituration with methanol, gave a colorless crystalline product extremely sensitive to oxygen and heat. On recrystallization from aqueous alcohol some decomposition occurred and the product was finally obtained as pale yellow needles, m.p. 132-136° (dec.); λ max (CH_3OH), (log ε) 225 (4.07), sh 274 (3.67), 283 (3.69), 291 (3.62), 322 (2.72) mμ; after standing λ max (CH_3OH), end absorption, 275, 290 mμ; infrared (KBr) main bands 3590, 3430, 3215, 3035, 2905, 2830, 1615, 1485, 1455, 1435, 1357, 1340, 1319, 1275, 1235, 1135, 1085, 928, 737 cm^{-1}; n.m.r. ($CDCl_3$) 6.55 τ (multiplet), 7.07 τ (multiplet), 2.85 τ (aromatic protons). It was not possible to establish the structure of this product.

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