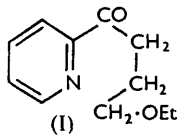
360. *Quinolizines. Part I. Synthesis of Some Indolo*[2,3-a]*quinolizine and Benz*[g]*indolo*[2,3-a]*quinolizine Derivatives.*

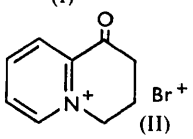
By E. E. Glover and Gurnos Jones.

A general synthesis of 6 : 7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium salts (III) and of 7 : 8-dihydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium salts (VIII) is described. The compound (III; R = H, X = I) has been dehydrogenated to 12*H*-indolo(2,3-*a*)quinolizinium iodide (V).

We describe below a general method by which 6 : 7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium (III) and 7 : 8-dihydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium salts (VIII) can be prepared. Dehydrogenation of the dihydro-compound (III) gives an indolo[2,3-*a*]-quinolizinium salt (V); hydrogenation of pentacyclic compounds of type (VIII) gives derivatives of hexadehydroyohimban (IX).



(I)



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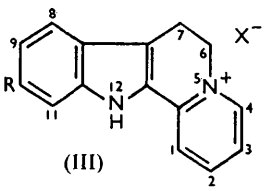

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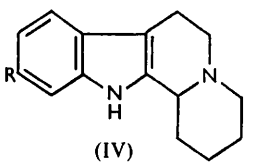

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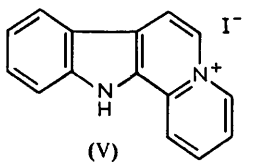
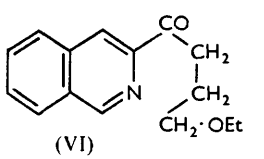
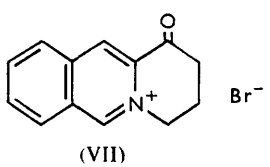


(V)

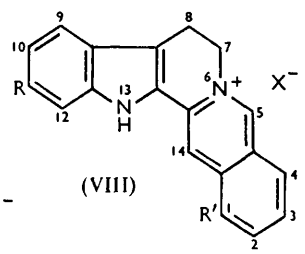
A previous synthesis [1] of the dihydro-compound (III; R = H, X = Br) uses a seven-stage route from 2-2′-pyridylindole. We started from 1 : 2 : 3 : 4-tetrahydro-1-oxoquinolizinium bromide (II), prepared, as briefly reported,[2] from 2-γ-ethoxybutyrylpyridine [3] (I). The ketone (I) was treated with boiling hydrobromic acid, and the intermediate bromo-ketone was cyclized in boiling chloroform, giving the bicyclic ketone (II)



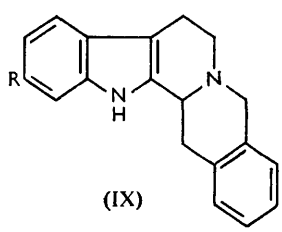
(VI)



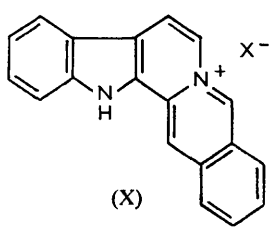
(VII)



(VIII)



(IX)



(X)

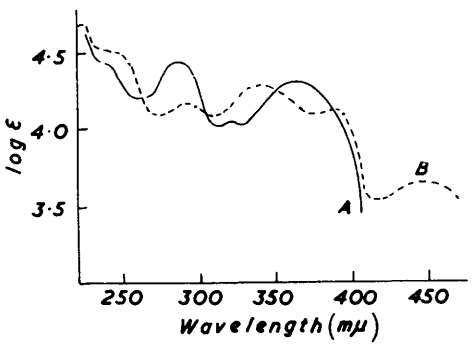
(79%), whose phenylhydrazone was isolated as a water-insoluble iodide; this was cyclized in high yield by anhydrous ethanolic hydrogen chloride to the dihydroindoloquinolizinium salt (III; R = H). Catalytic reduction of this gave 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-octahydro-12*H*-indolo[2,3-*a*]quinolizine (IV; R = H). An attempt to dehydrogenate the dihydro-compound (III; R = H, X = I) with mercuric acetate was unsuccessful; a

[1] Sugasawa, Terashima, and Kanaoka, *Pharm. Bull.* (*Japan*), 1956, **4**, 16.
[2] Glover and Jones, *Chem. and Ind.*, 1956, 1456.
[3] Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 1144.

water-insoluble complex was isolated, containing mercury, from which the dihydro-compound was recovered unchanged. The dehydrogenation was accomplished with acid palladium–charcoal,[4] 12*H*-indolo[2,3-*a*]quinolizinium iodide (V) being isolated. The ultraviolet absorption of this iodide (V) in neutral and in alkaline solution closely paralleled that of sempervirine [5] and of other alkylated indoloquinolizinium compounds,[4,6] of which the compound (V) contains the parent cation (Fig. 1).

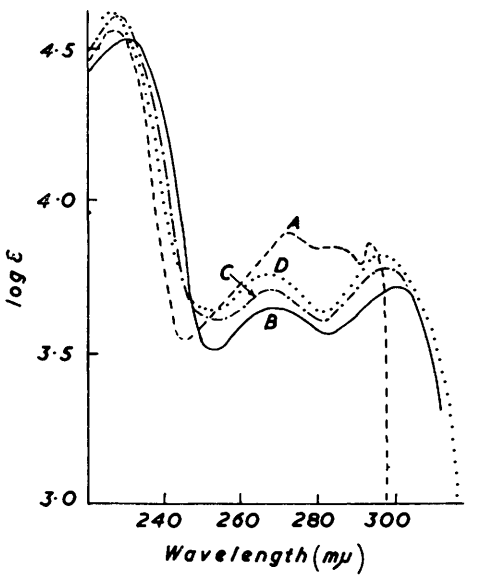
For the synthesis of the pentacyclic compounds the starting material was 3-γ-ethoxybutyryl*iso*quinoline (VI), prepared by the action of 3-ethoxypropylmagnesium bromide on 3-cyano*iso*quinoline. Cyclization gave 1 : 2 : 3 : 4-tetrahydro-1-oxobenzo[*b*]quinolizinium bromide (VII) which was converted into its phenylhydrazone iodide. Indolization then

FIG. 1.



A, 12H-*Indolo*[2,3-a]*quinolizinium iodide in ethanol*; *B*, *indolo*[2,3-a]*quinolizinium iodide in* 0·01N-*alcoholic* KOH.

FIG. 2.



A, 1 : 2 : 3 : 4-*Tetrahydro-5-methoxycarbazole*; [8] *B*, 1 : 2 : 3 : 4-*tetrahydro-7-methoxycarbazole*; [8] *C*, 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*octahydro*-10-*methoxyindolo*[2,3-a]*quinolizine in* EtOH; *D*, 5 : 7 : 8 : 13 : 13*b* : 14-*hexahydro*-11-*methoxy*-13H-*benz*[g]*indolo*[2,3-a]*quinolizine in* MeOH.

gave 7 : 8-dihydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium iodide (VIII; R = R′ = H, X = I), the properties of which were in good agreement with those recorded by Swan [7] for the compound obtained by the action of iodine in acetone on the hexadehydroyohimban (IX; R = H). Attempts to dehydrogenate the dihydro-compound (VIII; R = R′ = H, X = I) have so far failed to give any of the completely aromatic pentacyclic compound (X).

Since one of the objectives of this work was a synthetic route to alstoniline chloride (VIII; R = OMe, R′ = CO_2Me, X = Cl), the *m*-methoxyphenylhydrazones of the ketones (II) and (VII) were prepared and cyclized to the indoles (III; R = OMe, X = I) and (VIII; R = OMe, R′ = H, X = I) respectively. The position of the methoxyl group was proved by catalytic hydrogenation of the dihydro-salts to the hexahydro-compound (IV; R = OMe) and the tetrahydro-compound (IX; R = OMe) respectively. Both these compounds

[4] Cf. Schwyzer, *Helv. Chim. Acta*, 1952, **35**, 867.
[5] Prelog, *ibid.*, 1948, **31**, 588.
[6] Goutarel, Janot, and Perezamador y Barron, *Bull. Soc. chim. France*, 1954, 863.
[7] Swan, *J.*, 1949, 1720.
[8] Chalmers, Openshaw, and Smith, *J.*, 1957, 1115.

showed ultraviolet absorption almost identical with that of 1 : 2 : 3 : 4-tetrahydro-7-methoxycarbazole [8] and different from that of 1 : 2 : 3 : 4-tetrahydro-5-methoxycarbazole [8] (Fig. 2), indicating the presence of a methoxyl group in the 6-position of the indole nucleus. Thus the direction of cyclization of the *m*-methoxyphenylhydrazones is that predicted by Ockenden and Schofield,[9] who found that the introduction of groups which are *ortho-para*-directing in electrophilic substitution, into the 3-position of a phenylhydrazone, led to the preponderance of the 6-substituted indole after cyclization. The ultraviolet absorption of 7 : 8-dihydro-11-methoxy-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium iodide (VIII; R = OMe, R′ = H, X = I) was very similar to that of alstoniline chloride,[10] and the salts of the tetrahydro-compound (IX; R = OMe) were readily oxidized in air to more highly coloured materials, as is reported for the salts of tetrahydroalstoniline.[11]

After completion of this work synthesis of the compounds (III; R = H) and (VIII; R = R′ = H) by a similar route was reported by Jacobs and Fouché.[12]

Experimental

M. p.s were determined on a Kofler block. Ultraviolet absorption was determined for solutions in 95% EtOH unless otherwise stated.

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxoquinolizinium Bromide* (II).—A solution of 2-γ-ethoxybutyrylpyridine [3] (3 g.) in 35% hydrobromic acid (25 ml.) was boiled under reflux for 1 hr., then evaporated to dryness under reduced pressure. The solid residue was dissolved in water (25 ml.) and treated dropwise with aqueous sodium carbonate, the liberated bromo-amine being extracted by small portions of chloroform until the aqueous layer became deep orange-red. The chloroform extracts were dried (Na_2SO_4) and boiled under reflux until the solid bromide separated and could be filtered off. Concentration of the chloroform filtrate gave a further small yield of bromide. Recrystallized from absolute ethanol as colourless needles (2·8 g., 79%) the bromide had m. p. 198° (Found: C, 47·1; H, 4·2. Calc. for $C_9H_{10}ONBr$: C, 47·4; H, 4·4%). The *picrate*, obtained from an aqueous solution of the bromide by addition of aqueous sodium picrate, crystallized from ethanol as yellow needles, m. p. 161—162° (Found: C, 48·0; H, 3·2. $C_{15}H_{12}O_8N_4$ requires C, 47·9; H, 3·2%). The *phenylhydrazone iodide* was prepared in 91% yield by heating a solution of the bromide (II) with a slight excess of phenylhydrazine in glacial acetic acid, diluting the whole with water, and precipitating the product by aqueous sodium iodide. Recrystallized from absolute ethanol as yellow needles, it had m. p. 239° (Found: C, 49·6; H, 4·4. $C_{15}H_{16}N_3I$ requires C, 49·4; H, 4·4%), $\lambda_{max.}$ 2430, 4100 Å ($\log_{10}\varepsilon$ 4·07, 4·48).

The m-*methoxyphenylhydrazone iodide*, prepared as above, crystallized from absolute ethanol as yellow prisms, m. p. 255° (Found: C, 48·3; H, 4·5. $C_{16}H_{18}ON_3I$ requires C, 48·6; H, 4·6%), $\lambda_{max.}$ 2680, 4120 Å ($\log_{10}\varepsilon$ 3·88, 4·51).

6 : 7-*Dihydro*-12H-*indolo*[2,3-a]*quinolizinium Iodide* (III; R = H, X = I).—The phenylhydrazone iodide (2·3 g.) in anhydrous ethanol was saturated with dry hydrogen chloride at 0°. The solution was then boiled under reflux for 2 hr. Evaporation to dryness gave a solid, which was dissolved in water and treated with aqueous sodium iodide. The precipitated *iodide* crystallized from absolute ethanol as yellow needles, m. p. 298° (decomp.) (1·96 g., 89%) (Found: C, 51·8; H, 3·6. $C_{15}H_{13}N_2I$ requires C, 51·75; H, 3·8%), $\lambda_{max.}$ 2520, 3150, 3890 Å ($\log_{10}\varepsilon$ 3·52, 3·79, 3·74). The *picrate*, orange plates (from absolute ethanol), had m. p. 247° (Found: C, 56·35; H, 3·4. $C_{21}H_{15}O_7N_5$ requires C, 56·1; H, 3·4%).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*Octahydroindolo*[2,3-a]*quinolizine* (IV; R = H).—The iodide (III; R = H, X = I) in dry ethanol, over Adams catalyst, was hydrogenated to completion at atmospheric pressure and temperature. Filtration, and evaporation of the filtrate, gave the solid *hydriodide*, recrystallizing from absolute ethanol as plates, m. p. 237—238° (Found: C, 50·5; H, 5·9. $C_{15}H_{19}N_2I$ requires C, 50·9; H, 5·4%). The picrate crystallized from absolute ethanol as yellow needles, m. p. 230° (lit.,[1] m. p. 230—232°). The free base crystallized from light petroleum (b. p. 60—80°) as colourless needles, m. p. 149—150° (lit.,[1] m. p. 150—150·5°).

[9] Ockenden and Schofield, *J.*, 1957, 3175.
[10] Elderfield and Wythe, *J. Org. Chem.*, 1954, **19**, 693.
[11] Hawkins and Elderfield, *ibid.*, 1942, **7**, 573.
[12] Jacobs and Fouché, 16th Congr. Union Pure Appl. Chem., Paris, 1957, Résumés des Comm.. Vol. II, p. 316.

12H-*Indolo*[2,3-a]*quinolizinium Iodide* (V).—(*a*) The iodide (III; R = H, X = I) (0·47 g.), in 5% aqueous acetic acid (50 ml.) with mercuric acetate (1·7 g.), was stirred on the boiling-water bath for 1 hr. After filtration, a sample was diluted and treated with saturated aqueous sodium iodide. The very insoluble precipitate was dissolved in hydrochloric acid and freed from mercury by hydrogen sulphide. The original iodide was then obtained by precipitation with saturated aqueous sodium iodide. Altogether 0·28 g. of starting material was recovered; no trace of dehydrogenated material was found.

(*b*) The dihydro-compound (III; R = H, X = I) (0·15 g.) was finely ground with acid 5% palladium–charcoal [4] (0·3 g.) and rapidly heated to 290° in a Pyrex test-tube and held at this temperature for 5 min. The mixture was cooled and repeatedly extracted with boiling methanol, and the extracts were evaporated; the residue crystallized from absolute ethanol as pale yellow needles (35 mg.), m. p. 304° (decomp.) (Found: C, 52·0; H, 3·1. $C_{15}H_{11}N_2I$ requires C, 52·05; H, 3·2%), $\lambda_{max.}$ in EtOH 2220, 2930, 3430, 3860 Å ($\log_{10}\varepsilon$ 4·69, 4·19, 4·27, 4·13), in 0·01N-alcoholic KOH 2860, 3580, 4360 Å ($\log_{10}\varepsilon$ 4·45, 4·31, 3·56).

6 : 7-*Dihydro*-10-*methoxy*-12H-*indolo*[2,3-a]*quinolizinium Iodide* (III; R = OMe, X = I).—The *m*-methoxyphenylhydrazone of the oxoquinolizinium compound (1·2 g.), when cyclized as described above by anhydrous ethanolic hydrogen chloride (5 hr. at the b. p.), gave the *methoxyindoloquinolizinium iodide* (0·98 g., 83%), crystallizing from absolute ethanol as yellow needles, m. p. 283° (Found: C, 50·95; H, 4·1. $C_{16}H_{16}ON_2I$ requires C, 50·8; H, 4·0%), $\lambda_{max.}$ 2660, 3310, 4240 Å ($\log_{10}\varepsilon$ 3·79, 4·13, 4·28).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*Octahydro*-10-*methoxyindolo*[2,3-a]*quinolizine* (IV; R = OMe).—The methoxyindoloquinolizinium iodide was hydrogenated to completion as described above. The *octahydroindoloquinolizine hydriodide* crystallized from absolute ethanol as pale yellow prisms, m. p. 251—252° (Found: C, 49·3; H, 5·6. $C_{16}H_{21}ON_2I$ requires C, 49·0; H, 5·5%). The *base* (IV; R = OMe) crystallized from aqueous ethanol as colourless prisms, m. p. 201°, $\lambda_{max.}$ 2280, 2690, 2970 Å ($\log_{10}\varepsilon$ 4·58, 3·70, 3·78).

3-*γ*-*Ethoxybutyryl*iso*quinoline* (VI).—3-Cyano*iso*quinoline [13] (2·8 g.), stirred in dry ether (50 ml.) under nitrogen, was treated with the Grignard reagent from 3-ethoxypropyl bromide (4 g.) in dry ether (40 ml.); a yellow complex was formed. Stirring was continued for 1 hr. and the mixture kept overnight at room temperature. The complex was decomposed with ice-cold 2N-hydrochloric acid, and the ethereal layer separated and extracted with further small portions of acid. The acid extracts were combined and basified with aqueous ammonia (*d* 0·88), and the liberated base was extracted with ether. The ethereal extract was dried (Na_2SO_4) and evaporated to dryness. Recrystallization of the solid residue from light petroleum (b. p. 60—80°) gave the *ketone* as colourless prisms, m. p. 74·5° (3·2 g., 72%) (Found: C, 74·35; H, 7·2. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·05%), $\lambda_{max.}$ 2400, 2880, 3120 (infl.), 3250 Å ($\log_{10}\varepsilon$ 4·62, 3·86, 3·61, 3·63).

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxobenzo*[b]*quinolizinium Bromide* (VII).—A solution of the *iso*quinolyl ketone (0·62 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 45 min., then evaporated under reduced pressure. The solid residue was warmed with water and filtered. Treatment of the cooled filtrate with aqueous sodium carbonate and chloroform, as described above, gave a chloroform solution of the bromo-amine which was dried, filtered, and boiled under reflux. The cyclic ketone bromide was rather soluble in chloroform and concentration of the solution to a small volume was necessary before the maximum yield was obtained. Isolated from the chloroform solution, the *bromide* formed colourless plates, m. p. 234° (0·59 g., 83%), unchanged by recrystallization from absolute ethanol, $\lambda_{max.}$ 2570, 3320, 3440 Å ($\log_{10}\varepsilon$ 4·59, 3·73, 3·82). The *picrate*, yellow needles from 95% ethanol, had m. p. 180° (Found: C, 53·3; H, 3·1. $C_{19}H_{14}O_8N_4$ requires C, 53·5; H, 3·3%). The phenylhydrazone bromide crystallized from ethanol as orange-red needles, m. p. 360°. The *phenylhydrazone iodide* crystallized from ethanol as golden needles, m. p. 265—267° (Found: C, 53·0; H, 4·4. $C_{19}H_{18}N_3I,H_2O$ requires C, 52·7; H, 4·65%), $\lambda_{max.}$ 2390, 3980 Å ($\log_{10}\varepsilon$ 4·60, 4·38). The m-*methoxyphenylhydrazone iodide* crystallized from aqueous ethanol as yellow plates, m. p. 262° (decomp.) (Found: C, 53·7; H, 4·2. $C_{20}H_{20}ON_3I$ requires C, 53·9; H, 4·53%), $\lambda_{max.}$ 2400, 3970 Å ($\log_{10}\varepsilon$ 4·60, 4·39).

7 : 8-*Dihydro*-13H-*benz*[g]*indolo*[2,3-a]*quinolizinium Iodide* (VIII; R = R′ = H, X = I).—A solution of the phenylhydrazone bromide (0·34 g.) in anhydrous ethanol (50 ml.) at 0°, was saturated with dry hydrogen chloride, boiled under reflux for 5 hr., then evaporated to dryness

[13] Crowne and Breckenridge, *Canad. J. Chem.*, 1954, **32**, 641.

under reduced pressure. The solid residue was treated in hot water with aqueous sodium iodide giving a yellow precipitate. The indole iodide (0·3 g., 82%) crystallized from methanol in golden-yellow needles, m. p. 334° (decomp.) [Swan [7] gives 333° (decomp.)], $\lambda_{max.}$ 2380, 2525, 2800, 3520 Å (Swan [7] gives 2390, 2520, 2810, 3520 Å).

The iodide (0·25 g.), ground with acid palladium–charcoal [4] (0·5 g.), was rapidly heated in a Pyrex test tube to 330° (bath-temp.). After 10 min. at 330°, the mixture was cooled and extracted with boiling methanol. The solution showed a green fluorescence, but only unchanged starting material was isolated.

7 : 8-*Dihydro*-11-*methoxybenz*[g]*indolo*[2,3-a]*quinolizinium Iodide* (VIII; R = OMe, R′ = H, X = I).—The *m*-methoxyphenylhydrazone iodide (0·38 g.) of the benzoquinolizinium ketone was cyclized under the above conditions with anhydrous ethanolic hydrogen chloride. After recrystallization from methanol, the *indole iodide* formed orange prisms, m. p. 317° (decomp.) (0·32 g., 88%) (Found: C, 56·6; H, 3·9. $C_{20}H_{17}ON_2I$ requires C, 55·1; H, 4·0%), $\lambda_{max.}$ 2410, 3710 Å ($\log_{10}\varepsilon$ 4·56, 4·57).

5 : 7 : 8 : 13 : 13*b* : 14-*Hexahydro*-11-*methoxybenz*[g]*indolo*[2,3-a]*quinolizine* (IX; R = OMe). —The methoxybenzindoloquinolizinium iodide was hydrogenated to completion in methanol over Adams catalyst at atmospheric temperature and pressure. The solution was filtered, and during filtration changed from colourless to yellow. Evaporation gave the *hydriodide*, crystallizing as orange needles, m. p. 304° (decomp.), from aqueous methanol (Found: C, 56·15; H, 4·8. $C_{20}H_{21}ON_2I$ requires C, 55·6; H, 4·9%). The *base* (IX; R = OMe) crystallized from aqueous methanol as buff prisms, m. p. 181—182°, $\lambda_{max.}$ 2270, 2670, 2970 Å ($\log_{10}\varepsilon$ 4·61, 3·76, 3·83) in methanol.

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