2-Methoxy-3-oxo-3H-indole (O-Methylisatin, 34).—A heterogeneous mixture of 7.62 g. (0.030 mole) of **33** (finely powdered and vacuum dried), 3.6 ml. of methyl iodide (0.060 mole), and 25 ml. of anhydrous ether in a 125-ml. erlenmeyer flask (wrapped with aluminum foil) was allowed to stand for 3 days at room temperature in the dark. The mass was extracted with 4 × 20 ml. of dry benzene; an equal volume of petroleum ether (b.p. 90–100°) was added to the combined extracts. The benzene–petroleum ether solution was evaporated (Rinco), and the resulting orange precipitate of 1-methylisatin (**12**) was filtered. Evaporation of the filtrate to dryness (Rinco) on a steam bath gave a liquid which solidified on cooling. One recrystallization of this solid from the minimum amount of benzene led to 1.53 g. (32%) of **34**, m.p. 95–100°. Sublimation of this material at 60–65° at 6 mm. led to pure O-methylisatin (**34**), m.p. 102–104°, lit.[45] m.p. 101–102°, as blood red prisms. Infrared spectrum showed λ_{max}^{KBr} 5.76 μ (C=O).

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38. Found: C, 67.30; H, 4.46.

Isatin 2-Tosylhydrazone (9).—To a warm, stirred solution of 1.00 g. (0.0062 mole) of **34** in 50 ml. of dry benzene was added 1.155 g. (0.0062 mole) of *p*-toluenesulfonylhydrazine. The reaction mixture was heated gently for an additional 30 min., cooled to room temperature, and filtered; the residue was washed with 50 ml. of benzene. Upon drying in air, 1.64 g. (84%) of isatin 2-tosylhydrazone (**9**) was obtained as a chalky orange powder, m.p. 178–184° dec. Two recrystallizations from absolute methanol gave pure **9** as orange-red plates, m.p. 185–187° dec. Infrared spectrum showed λ_{max}^{KBr} 5.83 (C=O) and 6.19 μ (C=N).

Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.14; H, 4.15. Found: C, 57.29; H, 4.43.

Acid-Catalyzed Hydrolysis of Isatin 2-Tosylhydrazone (9) to Isatin 3-Tosylhydrazone (32).—A mixture of 0.180 g. (0.00057 mole) of **9** and 2 drops of concentrated hydrochloric acid in 20 ml. of 50% ethanol was refluxed for 3 hr. The solution was cooled to room temperature, refrigerated for 2 hr., and filtered to give 0.102 g. (57%) of **32**.

Base Decomposition of Isatin 2-Tosylhydrazone (9).—A mixture of 0.500 g. (0.0016 mole) of **9** and a threefold excess of 0.2 *N* potassium hydroxide (24 ml., 0.0048 mole) was stirred at room temperature for 96 hr. Filtration led to 0.505 g. of the potassium salt (**35**). Acidification of the filtrate with 1 *N* hydrochloric acid led to recovery of 0.015 g. of unreacted **9**.

An aqueous solution of the potassium salt was heated at 65–70° for 2 hr. with stirring. The resulting blue-black reaction mass was cooled to room temperature and filtered to yield 0.130 g. (62%) of indigo blue (**38**) as a blue-black powder, m.p. >350° (sublimes), lit.[46] m.p. >300°. The crude indigo sublimed partially as a blue-black powder and partially as a violet crystalline material with a coppery luster. The infrared spectra of both materials proved to be identical with an authentic sample of indigo blue (Eastman): λ_{max}^{KBr} 6.14 μ (C=O). Acidification of the aqueous filtrate with 1 *N* hydrochloric acid led to the recovery of an additional 0.015 g. of unreacted **9**.

When equimolar quantities of sodium ethoxide in ethanol were used (instead of aqueous base) over a 95-hr. period at room temperature, **9** was converted to **38** in only 17% yield.

Treatment of 9 with 1 *N* Sodium Ethoxide and Excess Methyl Iodide.—A solution of 10 ml. of 1 *N* sodium ethoxide (0.01 mole) and 0.50 g. (0.0016 mole) of **9** was allowed to stand at room temperature for 2 days, and then evaporated to dryness in air. Addition of 10 ml. of methyl iodide (0.16 mole) resulted in a deep blood red solution which was allowed to stand at room temperature overnight. Evaporation to dryness in air, followed by copious water washing of the crude red residue gave 0.48 g. (88%) of the dimethyl derivative (**39**) of isatin 2-tosylhydrazone, m.p. 233–235° dec., as brilliant red plates from acetone. Infrared spectrum showed λ_{max}^{KBr} 5.79 μ (C=O).

Anal. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.49; H, 4.99. Found: C, 59.71; H, 5.22.

Isatin 2-Oxime (8).—Treatment of **34** with hydroxylamine hydrochloride at room temperature gave **8** in 90% yield, m.p. 198–200.5° (sublimes), as yellow needles; lit.[47] m.p. 198–200°. Infrared spectrum showed λ_{max}^{KBr} 5.80 μ (C=O).

Attempted Reactions of Isatin 2-Oxime (8). (i) **With Chloramine.**—To a stirred solution of 0.500 g. (0.0031 mole) of **8** in 175 ml. of water and 4 ml. of 1 *N* sodium hydroxide (0.004 mole) at 0° (ice–salt bath) was added 1 ml. of concentrated ammonium hydroxide, followed by the immediate dropwise addition of 21 ml. of 5.25% sodium hypochlorite solution (0.015 mole) over a period of 5 min. The solution was stirred for an additional 30 min. at 0° and then at room temperature for 2 hr. Repeated extraction with large volumes of conventional organic solvents (ether, benzene, and methylene chloride) invariably led to a small amount of a crude, dark yellow-brown residue which could not be identified. Acidification with 0.1 *N* hydrochloric acid, followed by similar extractions, again led to a small amount of crude intractable residue. No starting material could be isolated.

(ii) **With Dilute Base.**—A solution of 0.500 g. (0.0031 mole) of **8** in 20 ml. of water and 4 ml. of 1 *N* sodium hydroxide (0.004 mole) was stirred at room temperature for 3 hr. Acidification with 0.1 *N* hydrochloric acid gave 0.340 g. (68%) of unreacted **8**. The acidic filtrate was extracted with 500 ml. of ether. The ether extracts were dried over anhydrous sodium sulfate, filtered, and upon evaporation to dryness in air led to the recovery of an additional 0.150 g. (30%) of unreacted **8**.

Isatin 2-Hydrazone.—To a solution of 1.00 g. (0.0062 mole) of **34** in 20 ml. of benzene was added 0.36 ml. of 85% hydrazine hydrate (0.0062 mole) in 2 ml. of water with stirring at room temperature. The reaction mixture was stirred an additional 30 min. and filtered to give 0.891 g. (89%) of isatin 2-hydrazone, m.p. 183–186° dec., as dark yellow-brown plates from absolute ethanol. Infrared spectrum showed λ_{max}^{KBr} 5.96 μ (C=O).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.37; N, 26.07. Found: C, 59.81; H, 4.64; N, 25.90.

(45) A. Baeyer and S. Oekonomides, *Ber.*, **15**, 2093 (1882).
(46) U. Weinstein, *J. Am. Chem. Soc.*, **78**, 4010 (1956).
(47) G. Heller, *Ber.*, **49**, 2757 (1916).

A New Route to the 13H-Indolo[2,3-*a*]acridizinium System[1]

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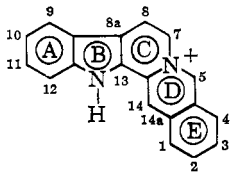
Using bromoacetone instead of chloroacetaldehyde, we have confirmed the observation of Stevens that quaternization of 2-(2′-pyridyl)indoles is accompanied by cyclization on nitrogen, affording indolo[2,1-*a*]-2-azaquinolizinium salts, and also that quaternization of 1-alkyl-2-(2′-pyridyl)indoles affords a 12-alkyl-12H-indolo[2,3-*a*]-quinolizinium system. Extension of the latter method to 1-methyl-2-(3-isoquinolyl)indole has made possible the synthesis of 8,13-dimethyl-13H-indolo[2,3-*a*]acridizinium bromide. The ultraviolet absorption spectrum of the new salt is in agreement with that of the 13H-indolo[2,3-*a*]acridizinium salts of Bradsher and Umans.

The indolo[2,3-*a*]acridizinium nucleus (I) may be regarded as the aromatic parent system of the yohimbine, reserpine, and alstoniline alkaloids.[2] The synthesis of this aromatic system (by dehydrogenation of the 7,8-dihydro derivative) was first claimed by Swan,[3] but the validity of this claim appeared questionable on

(1) This research was supported by U. S. Public Health Service Research Grant No. HE-2170 from the National Heart Institute.

(2) R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 683 (1954).
(3) G. A. Swan, *J. Chem. Soc.*, 2038 (1958).

spectral grounds. In a previous publication from this laboratory[4] the first synthesis, *via* cyclization of quaternary salts derived from 9H-[3,4-*b*]pyridoindole-1-carboxaldehyde, was described. Since no structural proof

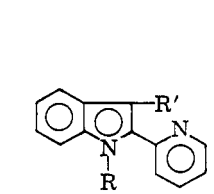


I

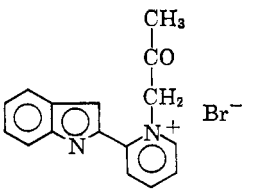
had been obtained, and the properties observed were at variance with those reported by Swan, it seemed desirable to obtain structural evidence through a new and independent synthesis of the indolo[2,3-*a*]acridizinium nucleus.

The synthesis *via* the pyridoindolecarboxaldehyde involved the formation of ring D through establishment of a bond between C-14 and C-14a (I). The present communication describes another synthesis *via* formation of ring C by means of a new bond, between C-8 and C-8a (I).

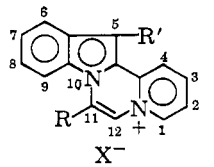
In a model experiment, 2-(2′-pyridyl)indole (II) was refluxed with bromoacetone in acetone solution for 3 days. Instead of the expected quaternary cation (V, R = R′ = H), a cation having 1 mole less of water, and without a carbonyl band in the infrared absorption spectrum, was obtained. At first it seemed probable that the new salt was the desired 7-methyl-12H-indolo-[2,3-*a*]quinolizinium bromide (IX), but the ultraviolet absorption spectrum showed marked differences from



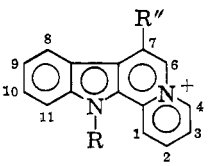
II, R = R′ = H
III, R = H; R′ = CH_3
IV, R = CH_3; R′ = H



V
(not isolated)



VI, R = CH_3; R′ = H; X = Br
VII, R = R′ = CH_3; X = Br
VIII, R = R′ = H; X = Cl



IX, R = H; R″ = CH_3; X = Br
X, R = CH_3; R″ = H; X = I
XI, R = R″ = CH_3; X = Br

that reported earlier for 12-methyl-12H-indolo[2,3-*a*]-quinolizinium iodide (X).[5] Furthermore, the indole NH singlet at 6.03 p.p.m. (measured in dimethyl sulfoxide with tetramethylsilane as an external standard) disappeared completely in the nuclear magnetic resonance spectrum of the cyclized product. This evidence suggested that cyclization had occurred on nitrogen yielding 11-methylindolo[2,1-*a*]-2-azaquinolizinium bromide (VI). Further confirmation that cyclization had not taken place at the carbon atom at position 3 of

(4) C. K. Bradsher and A. J. H. Umans, *J. Org. Chem.*, **28**, 3070 (1963).
(5) K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2024 (1958).

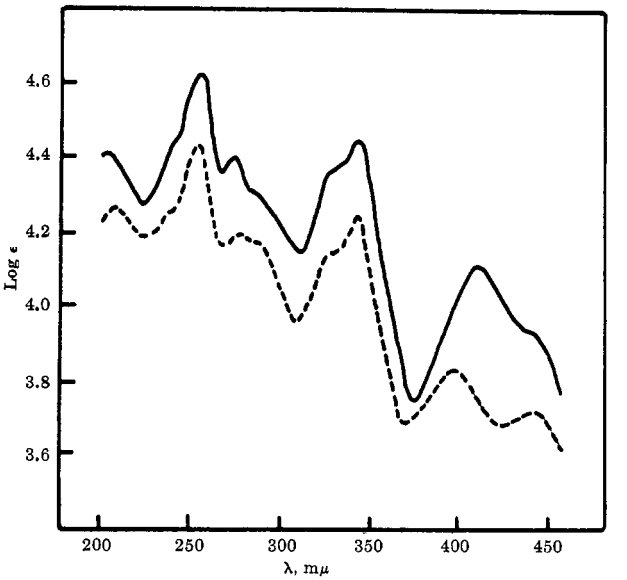
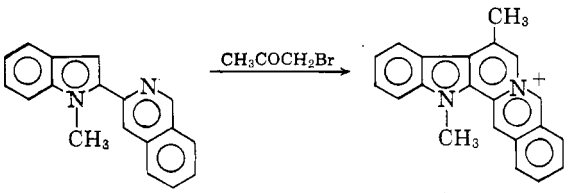


Fig. 1.—Ultraviolet absorption spectra: —, 8,13-dimethyl-13H-indolo[2,3-*a*]acridizinium bromide; - -, 13H-indolo[2,3-*a*]-acridizinium perchlorate.

the indole ring was afforded by the synthesis of 2-(2′-pyridyl)-3-methylindole (III) which on quaternization with bromoacetone yielded a cyclization product (VII) having an ultraviolet absorption spectrum very similar to that of VI.

The desired direction of cyclization could be achieved by use of 1-methyl-2-(2′-pyridyl)indole (IV) as the starting material. Quaternization of (IV) with bromoacetone afforded in 42% yield a salt (XI) having the ultraviolet absorption spectrum to be expected[5] of a 12H-indolo[2,3-*a*]quinolizinium salt.[6]

For the synthesis of the indoloacridizinium system, 1-methyl-2-(3′-isoquinolyl)indole (XII) was synthesized from 3-acetylisoquinoline[7] by the Fischer indole synthesis. When the indole (XII) was refluxed in acetone



XII XIII

with excess bromoacetone, it afforded 8,13-dimethyl-13H-indolo[2,3-*a*]acridizinium bromide (XIII). The ultraviolet absorption spectrum of XV showed a striking similarity to that of the unsubstituted 13H-indolo[2,3-*a*]acridizinium ion of Bradsher and Umans (Fig. 1).

(6) We are indebted to Dr. Gurnos Jones for bringing to our attention an earlier report by Professor T. S. Stevens of Sheffield University [Special Publication No. 3, The Chemical Society, London, 1955, p. 19]. This report in the form of a review was abstracted [*Chem. Abstr.*, **50**, 15551*a* (1956)] only as "A review with 27 references in which the structures of sempervirine and gelsemine are postulated." It is quite clear from reading this review that Professor Stevens discovered that the quaternization of 2-(2′-pyridyl)indole with chloroacetaldehyde leads to indolo[2,1-*a*]-2-azaquinolizinium chloride (VIII), while blocking of the indole nitrogen (by a benzyl group) before quaternization leads to the 12-benzyl-12H-indolo[2,3-*a*]quinolizinium ion.

From the review and from direct correspondence with Professor Stevens it appears that there has been no duplication of effort as regards the compounds reported here. We are, however, happy to acknowledge Professor Stevens' prior development of this route to the 12H-indolo-[2,3-*a*]-quinolizinium system.

(7) F. R. Crowne and J. G. Breckenridge, *Can. J. Chem.*, **32**, 641 (1954).

Experimental

The analyses were done by Dr. Ing A. Schoeller, Kronach, Germany. The melting points were determined in capillary tubes in the Mel-Temp apparatus and are corrected. Ultraviolet absorption spectra were measured in 95% ethanol using 1-cm. matched quartz cells in the Cary Model 14 spectrophotometer. The asterisk (*) is used to denote a shoulder. The nuclear magnetic resonance data were obtained with a Varian A-60 spectrometer.

11-Methylindolo[2,1-*a*]-2-azaquinolizinium Bromide (VI).—Two grams of 2-(2′-pyridyl)indole (II)[8] and 2.8 g. (excess) of bromoacetone were refluxed in 30 ml. of reagent grade acetone for 3 days. The yellow precipitate was collected and recrystallized from methanol–ether: yield 1.1 g. (34%); m.p. 355.5–356.5°; λ_{max} mμ (log ε), 212 (4.41), 253 (4.00), 294 (3.72), and 385 (4.31).

Anal. Calcd. for $C_{16}H_{13}BrN_2 \cdot H_2O$: C, 58.02; H, 4.56; Br, 24.13; N, 8.46. Found: C, 57.95; H, 4.73; Br, 24.22; N, 8.56.

The perchlorate crystallized from ethanol–ether as a fine yellow powder, m.p. 287.5–289.5°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_4$: C, 57.75; H, 3.94; Cl, 10.66; N, 8.42. Found: C, 57.80; H, 3.97; Cl, 10.32; N, 8.65.

Phenylhydrazone of 2-Propionylpyridine.—The phenylhydrazone was formed by refluxing 9.3 g. of phenylhydrazine with 11.6 g. of 2-propionylpyridine in ethanol for 4 hr. No solid separated so the solution was concentrated, and the residue was vacuum distilled. The fraction, b.p. 196–198° (3.5 mm.), turned to a yellow solid, m.p. 129–131°, on standing, yielding 15.8 g. (82%).

Anal. Calcd. for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.86; H, 6.76; N, 18.61.

2-(2′-Pyridyl)-3-methylindole (III).—A mixture of 6.0 g. of the phenylhydrazone of 2-propionylpyridine and 48 g. of polyphosphoric acid was heated for 1 hr. on the steam bath with occasional stirring and then heated at 135° for 10 min.[9] After cooling, 125 ml. of cold water was added and the filtered indole phosphate solution was neutralized with a solution of sodium hydroxide. The precipitated free base was taken up in ethyl acetate, the solution was concentrated, and the residue was crystallized from ethanol–water. Cream-colored crystals were obtained: 2.05 g. (37%); m.p. 100–101°; λ_{max} mμ (log ε), 207 (4.31), 232 (4.20), and 326 (4.31).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.45; H, 5.72; N, 13.60.

5,11-Dimethylindolo[2,1-*a*]-2-azaquinolizinium Bromide (VII).—The indole (III, 100 mg.) and 132 mg. of bromoacetone were refluxed for 3 days in 10 ml. of reagent grade acetone. The yellow precipitate was collected and recrystallized from methanol–ether: yield 71 mg. (43%); m.p. >370°; λ_{max} mμ (log ε), 215 (4.42), 253 (4.05), 283* (3.82), 298 (3.83), 330 (3.93), and 387 (4.24).

Anal. Calcd. for $C_{17}H_{15}BrN_2 \cdot H_2O$: C, 59.14; H, 4.96; N, 8.12. Found: C, 59.27; H, 4.85; N, 7.92.

The perchlorate crystallized from methanol–ether as an orange powder, m.p. >278° dec.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_4$: C, 58.88; H, 4.36; N, 8.08. Found: C, 58.44; H, 4.23; N, 7.98.

1-Methyl-1-phenylhydrazone of 2-Acetylpyridine.—A mixture of 6.1 g. of 1-methyl-1-phenylhydrazine and 5.85 g. of 2-acetylpyridine was allowed to stand for 2 days. The yellow solid first formed redissolved by the end of the interval. The solution was concentrated and the residue was distilled *in vacuo*. The fraction boiling at 230–250° (20 mm.) was used for the preparation of the indole, but a small portion of the orange liquid was redistilled for analysis, b.p. 180° (5 mm.).

Anal. Calcd. for $C_{14}N_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.77; H, 6.72; N, 18.73.

1-Methyl-2-(2′-pyridyl)indole (IV).—The crude 1-methyl-1-phenylhydrazone obtained from 5.85 g. of 2-acetylpyridine was stirred for 1 hr. at 130° with 30 g. of polyphosphoric acid. On cooling, 75 ml. of cold water was added and the filtered indole phosphate solution was neutralized by addition of a solution of sodium hydroxide. The solid free base was taken up in ethyl acetate, the solution was concentrated, and the solid was vacuum distilled. The product was crystallized from petroleum ether (b.p. 30–60°) affording 4.25 g. (41%, based on 2-acetylpyridine) of tan crystals: m.p. 90–91°; λ_{max} mμ (log ε), 204 (4.55), 219 (4.53), and 314 (4.43).

Anal. Calcd. for $C_{14}H_{12}N$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.66; H, 5.76; N, 15.53.

7,12-Dimethyl-12H-indolo[2,3-*a*]quinolizinium Bromide (XI).—Two grams of 1-methyl-2-(2′-pyridyl)indole (IV) in 2.75 g. of bromoacetone in 30 ml. of reagent grade acetone was refluxed for 3 days. The yellow precipitate was collected and recrystallized from methanol–ether: yield 1.3 g. (42%); m.p. >345° dec., λ_{max} mμ (log ε), 201 (4.74), 226 (4.82), 240* (4.80), 248 (4.85), 272* (4.52), 290 (4.50), 327 (4.70), and 395 (4.51).

Anal. Calcd. for $C_{17}H_{15}BrN_2$: C, 62.39; H, 4.62; N, 8.56. Found: C, 62.06; H, 4.49; N, 8.64.

The perchlorate crystallized from methanol–ether as a fine, yellow powder, m.p. >315° dec.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_4$: C, 58.88; H, 4.36; N, 8.08. Found: C, 58.98; H, 4.54; N, 8.23.

1-Methyl-2-(3′-isoquinolyl)indole (XII).—A solution containing 1.4 g. of 3-acetylisoquinoline[7] and 1.0 g. of 1-methyl-1-phenylhydrazine in 100 ml. of benzene was refluxed for 5 hr. under a Dean–Stark water separator. The benzene was then evaporated and 10 g. of polyphosphoric acid was added to the residue. The mixture was heated to 180–190° and that temperature maintained for 5 min.[8] with constant stirring. After cooling, water was added and the solution was neutralized with sodium hydroxide. The solid residue was extracted in a Soxhlet extractor using ethyl acetate. The ethyl acetate was evaporated and the residue placed on an alumina chromatography column in 50% benzene–chloroform solution. The column was eluted with benzene, benzene–chloroform (1:1), and chloroform. Evaporation of the solvent yielded 0.63 g. (30%, based upon acetylquinoline) of crude product, m.p. 116–120°. The analytical sample crystallized from ethanol–water as cream-colored granules: m.p. 121–123°; λ_{max} mμ (log ε), 228 (4.64), 241* (4.48), 279 (4.04), and 319 (4.33).

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.85. Found: C, 83.50; H, 5.65; N, 10.99.

8,13-Dimethyl-13H-indolo[2,3-*a*]acridizinium Bromide (XIII).—The indole (XII, 100 mg.) and 106 mg. of bromoacetone were refluxed for 3 days in 10 ml. of acetone. The yellow precipitate was collected and recrystallized from methanol–ether: yield 85 mg. (58%); m.p. >330° dec.; λ_{max} mμ (log ε), 202 (4.41), 243* (4.46), 255 (4.63), 273 (4.40), 285* (4.31), 332* (4.37), 343 (4.45), 410 (4.11), and 440* (3.93).

(8) S. Sugasawa, M. Terashima, and Y. Kanaoka, *Chem. Pharm. Bull.* (Tokyo), **4**, 16 (1956).

(9) *Cf.* J. W. Huffman, *J. Org. Chem.*, **27**, 503 (1962).