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14H-Indolo[2,3-a]phenanthridizinium Salts (1)

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Four 1-Aryl-9H-[3,4-b]pyridoindoles have been prepared and quaternized with bromoacetone. The resulting salts were cyclized under acidic conditions to afford 5-methyl-14H-indolo[2,3-a]phenanthridizinium perchlorate as well as the 2,3-dimethoxy-, 2,3-methylenedioxy- and 2-methoxy- derivatives.

As a sequel to the first synthesis of fully aromatic indolo[2,3-a]acridizinium salts (1,2), it seemed of interest to undertake the preparation of the isomeric wholly aromatic 14H-indolo[2,3-a]phenanthridizinium or 14H-benz[a]indolo[3,2-h]quinolizinium (3) system (III). Although 8,9-dihydro derivatives of III (R_3 = H) have been described (4,5,6) no attempt to form the aromatic system by dehydrogenation has been reported.

A logical point of departure was 1-phenyl-9H-[3,4-b]pyridoindole (Ia) which can be prepared in fair yield from tryptophan and benzaldehyde (7). Quaternization of the base (Ia) with bromoacetone afforded the 2-acetonyl salt (IIa) which was cyclized in polyphosphoric acid at 150-160°. The low yield (17%) of the 5-methyl-14H-indolo[2,3-a]phenanthridizinium (IIIa) cation isolated (as the perchlorate) is believed to be due to the interference of the indole hydrogen with the achievement of coplanarity by the phenyl ring. A similar phenomenon was encountered earlier (8) in a futile attempt to cyclize 2-acetonyl-1-phenylisoquinoline. The new aromatic system (IIIa) is more reactive than the acridizinium nucleus for an attempt to use the tribromide ion precipitation technique (9) as a means for separation of the product from phosphoric acid solution led to the isolation of a nuclear monobromination product of the new salt.

It was found earlier (10) that the cyclization of a 2-acetonyl-1-phenylisoquinolinium salt occurred easily if an alkoxyl group was present in an activating position of the phenyl ring. Three 1-aryl-9H[3,4-b]-pyridoindoles (I b-d), each having a phenyl ring activated by alkoxyl groups, were prepared from tryptophan and the appropriate aldehyde, and as anticipated, cyclization of the 2-acetonyl quaternary salts (II b-d) occurred much more readily than did the unactivated case (IIa). These activated systems could be cyclized in concentrated hydrochloric acid at 100° for 15 minutes in yields of 68-88%.

EXPERIMENTAL

All analyses not otherwise designated were performed by Ilse Beetz, Kronach, Germany. The melting points were taken with the Mel-Temp apparatus and are corrected. The ultraviolet absorption spectra were measured in 95% ethanol using 1 cm. matched quartz cells in the Cary Model 14 spectrophotometer. Nuclear magnetic resonance data were obtained with the Varian A-60 spectrometer.

2-Acetonyl-1-phenyl-9H-[3,4-b]pyridoindolium Bromide (IIa).

A solution containing 1.91 g. of 1-phenyl-9H-[3,4-b]pyridoindole (Ia) (7) and 2.14 g. (excess) bromoacetone in 100 ml. of reagent grade acetone was refluxed for 24 hours. The solvent was removed under vacuum (aspirator) and the residue crystallized from methanol-ethyl acetate affording 2.83 g. (95%) of yellow microcrystals, m.p. 97-98°, λ max (log ε) 205 (4.48), 263 (4.42), 316 (4.34) and 386 mμ (3.68).

Anal. Calcd. for $C_{20}H_{17}BrN_2O \cdot 1^3/_4H_2O$: C, 58.19; H, 5.00; N, 6.79. Found: C, 58.13; H, 4.73; N, 7.11.

The perchlorate crystallized from methanol-ethyl acetate as light yellow microscopic rhombs, m.p. 199°.

Anal. Calcd. for $C_{20}H_{17}ClN_2O_5$: C, 59.93; H, 4.28; N, 6.99. Found: C, 60.27; H, 4.64; N, 7.06.

5-Methyl-14H-indolo[2,3-a]phenanthridizinium (IIIa) Perchlorate.

A solution containing 1.0 g. of the quaternary salt (IIa) in 50 g. of polyphosphoric acid was stirred for 5 hr. at 150-160°. The reaction mixture was cooled to room temperature and 50 g. of ice water was added to the stirred solution. Digestion of the stirred solution for 2 hours on the steam bath was followed by dropwise addition of 35% perchloric acid to the cooled solution. The precipitate was collected and recrystallized from methanol as yellow needles, yield 0.17 g. (17%), m.p. 307.5-308.5° dec., λ max (log ε) 215 (4.48), 248 sh (4.12), 277 (4.28), 300 (4.26), 379 (4.23), and 405 mμ (4.22).

Anal. Calcd. for $C_{20}H_{15}ClN_2O_4$: C, 62.75; H, 3.95; N, 7.32. Found: C, 62.84; H, 3.66; N, 7.39.

The nuclear magnetic resonance spectrum determined in concentrated sulfuric acid with tetramethylsilane as an external standard showed the methyl group protons as a singlet at τ 6.51.

X-Bromo-5-methyl-14H-indolo[2,3-a]phenanthridizinium Bromide.

The cyclization of 1.0 g. of quaternary salt (IIa) was carried out as in the preparation of IIIa above. After digestion of the reaction mixture, instead of perchloric acid, a solution containing three volumes of 48% hydrobromic acid to one of bromine was added dropwise to the stirred solution. The tribromide salt was collected and washed with cold water, and then converted to the bromide by refluxing for 2 hours in a mixture of methanol and acetone. The mixture was filtered, the filtrate concentrated, and the residue recrystallized from methanol-ethyl acetate, affording 0.49 g. (42%) of yellow microscopic needles, m.p. 327.5° dec., λ max (log ε) 222 (4.50), 237 (4.32), 255 (4.25), 277 (4.22), 297 (4.33), 318 sh (4.00), 379 (4.29), and 400 mμ (4.23).

Anal. Calcd. for $C_{20}H_{15}Br_2N_2$: C, 54.20; H, 3.41; N, 6.32. Found: C, 54.68; H, 3.44; N, 6.45.

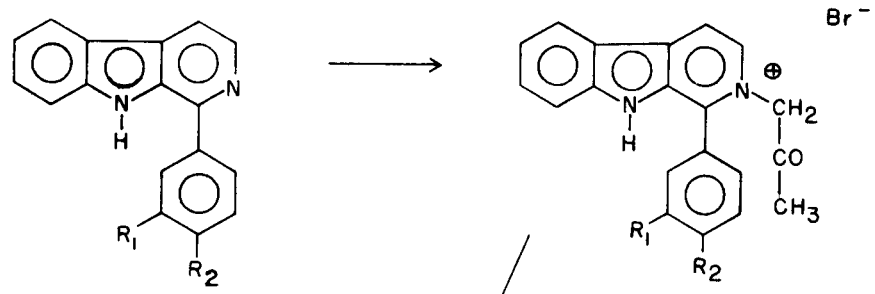
The methyl group of the bromide was found as a singlet at τ 6.62 in the nuclear magnetic resonance spectrum.

The perchlorate crystallized from methanol-ethyl acetate as yellow crystals, m.p. 380.5° dec.

Anal. Calcd. for $C_{20}H_{15}BrClN_2O_4$: C, 51.91; H, 3.26; N, 6.06. Found: C, 51.96; H, 3.15; N, 6.18.

1-(3,4-Dimethoxyphenyl)-9H-[3,4-b]pyridoindole (Ib).

A mixture containing 2.0 g. of tryptophan, 3.27 g. (excess) veratraldehyde, 120 ml. of water, 30 ml. of 95% ethanol and 1 ml. of concentrated sulfuric acid was refluxed for 20 hours. The solution was diluted with water to 250 ml., 30 ml. of glacial acetic acid added and the mixture heated to boiling. To the boiling solution 135 ml. of a boiling 10% solution of potassium dichromate was added rapidly enough to maintain vigorous boiling, and the mixture boiled for exactly two minutes. It was removed from the heating mantle and after exactly one minute



I

a. $R_1 = R_2 = H$

b. $R_1 = R_2 = OCH_3$

c. $R_1 — R_2 = O — CH_2 — O$

d. $R_1 = OCH_3$, $R_2 = H$

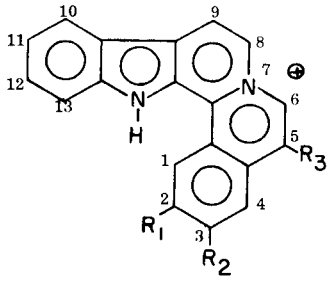
II

a. $R_1 = R_2 = H$

b. $R_1 = R_2 = OCH_3$

c. $R_1 — R_2 = O — CH_2 — O$

d. $R_1 = OCH_3$, $R_2 = H$



III, $R_3 = CH_3$

a. $R_1 = R_2 = H$

b. $R_1 = R_2 = OCH_3$

c. $R_1 — R_2 = O — CH_2 — O$

d. $R_1 = OCH_3$, $R_2 = H$

135 ml. of 10% sodium sulfite was added. The mixture was then cooled and made strongly alkaline with a solution of sodium hydroxide (solid sodium bicarbonate can also be used). The alkaline mixture was extracted with chloroform and the chloroform solution dried over potassium hydroxide. The solid residue remaining after evaporation of the chloroform was dissolved in methanol and converted to the hydrochloride by passing hydrogen chloride into the solution. Ethyl acetate was added and the mixture concentrated. The hydrochloride was recrystallized from methanol-ethyl acetate. The free base was obtained by addition of 10% sodium hydroxide solution to an aqueous solution of the hydrochloride. The free base thus obtained was recrystallized from methanol, affording 0.84 g. (34%) of a colorless microcrystalline powder, m.p. 90-92°, λ max (log ε) 212 (4.57), 234 (4.55), 250 sh (4.35), 265 (4.29), 296 (4.25), 354 sh (4.02), and 361 mμ (4.03).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.60; H, 5.40; N, 9.28.

1-(3,4-Methylenedioxyphenyl)-9H-[3,4-b]pyridoindole (Ic).

The reaction of 2.00 g. of tryptophan with 2.94 g. of piperonal was carried out exactly as described for the congener (Ib) except that 40 ml. of ethanol was used. The free base was recrystallized from methanol-water affording 0.76 g. 32% of colorless microscopic needles, m.p. 104-105°, λ max (log ε) 202 (4.48), 214 (4.47), 224 (4.46), 235 sh (4.44), 250 sh (4.23), 265 (4.17), 297 (4.15), 357 sh (3.92) and 362 mμ (3.93).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.88; H, 4.26; N, 9.81.

1-(3-Methoxyphenyl)-9H-[3,4-b]pyridoindole (Id).

The reaction of 2.00 g. of tryptophane with 2.66 g. of 3-methoxybenzaldehyde was carried out as in the case of the congener (Ib). The free base was crystallized from methanol-water affording 1.20 g. (52%) of colorless microscopic needles, m.p. 130-131°.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C 78.81; H, 5.14; N, 10.21. Found: C, 78.43; H, 5.18; N, 10.08.

2-Acetonyl-1-(3,4-dimethoxyphenyl)-9H-[3,4-b]pyridoindolium Bromide (IIb).

Quaternization of 0.61 g. of 1-(3,4-dimethoxyphenyl)-9H-[3,4-b]-pyridoindole with 0.55 g. of bromoacetone was carried out as in the case of the prototype (Ia). The product crystallized from methanol-ethyl acetate as microscopic clusters of diamond-shaped crystals, m.p. 248.5-249.5°, yield 0.66 g. (75%), λ max (log ε) 207 (4.67), 237 (4.30), 264 (4.44), 314 (4.28) and 384 mμ (3.75).

Anal. Calcd. for $C_{22}H_{21}BrN_2O_3$: C, 59.87; H, 4.80; N, 6.35. Found (11): C, 59.62; H, 4.70; N, 6.42.

The perchlorate crystallized from methanol-ethyl acetate as pale yellow microcrystalline needles, m.p. 227.5-228.5°.

Anal. Calcd. for $C_{22}H_{21}ClN_2O_7 \cdot {}^1/_4H_2O$: C, 56.78; H, 4.66; N, 6.02. Found (11): C, 56.57, 56.50; H, 4.72, 4.61; N, 6.12, 6.34.

2-Acetonyl-1-(3,4-methylenedioxyphenyl)-9H-[3,4-b]pyridoindolium Bromide (IIc).

The quaternization of 1.87 g. of 1-(3,4-methylenedioxyphenyl)-9H-[3,4-b]pyridoindole (Ic) with 1.78 g. of bromoacetone was carried out as in the preparation of IIa. The product crystallized from methanol-ethyl acetate as microscopic yellow prisms, m.p. 166.5-169.5°, yield 2.54 g. (92%).

Anal. Calcd. for $C_{21}H_{17}BrN_2O_3 \cdot {}^3/_4H_2O$: C, 57.48; H, 4.25; N, 6.39. Found: C, 57.57; H, 4.74; N, 6.52.

The perchlorate crystallized from methanol-ethyl acetate as very small light yellow flat parallelogram-shaped crystals, m.p. 160.5-162.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_7$: C, 56.70; H, 3.85; N, 6.30. Found: C, 56.88; H, 4.22; N, 6.35.

2-Acetonyl-1-(3-methoxyphenyl)-9H-[3,4-b]pyridoindolium Bromide (IId).

The quaternization of 1.32 g. of the methoxyphenylpyridoindole (IId) with 1.28 g. of bromoacetone was carried out in the usual way. The product formed light yellow micro crystals from methanol-ethyl acetate, m.p. 180-181°, yield 1.69 g. (86%).

Anal. Calcd. for $C_{21}H_{19}BrN_2O_2 \cdot {}^1/_2H_2O$: C, 60.01; H, 4.80; N, 6.67. Found: C, 59.64; H, 4.74; N, 6.99.

The perchlorate crystallized from methanol-ethyl acetate as a light yellow microcrystalline powder, m.p. 202.5-203.5°.

Anal. Calcd. for $C_{21}H_{19}ClN_2O_6$: C 58.54; H 4.44; N, 6.50. Found: C, 58.51; H, 4.32; N, 6.68.

2,3-Dimethoxy-5-methyl-14H-indolo[2,3-a]phenanthridizinium (IIIb) Perchlorate.

Cyclization of 0.30 g. of 2-acetonyl-1-(3,4-dimethoxyphenyl)-9H-[3,4-b]pyridoindolium bromide (IIb) was carried out in 15 ml. of concentrated hydrochloric acid by heating at steam bath temperature for 15 minutes. Precipitate formation was observed after only 5 minutes heating. The acid was removed in vacuo (aspirator) and the mixed salt crystallized from methanol-ethyl acetate, then dissolved in water, and precipitated as the perchlorate salt by addition of 35% perchloric acid. The perchlorate formed yellow microneedles from acetonitrile-ether, yield 0.21 g. (70%), m.p. 357.5-358.5° dec., λ max (log ε) 215 (4.52), 241 (4.46), 261 (4.38), 297 (4.47), 325 sh (3.95), 378 sh (4.16), 395 (4.40) and 412 mμ (4.61).

Anal. Calcd. for $C_{22}H_{18}ClN_2O_6$: C, 59.66; H, 4.32; N, 6.33. Found: C, 59.50; H, 4.18; N, 6.61.

2,3-Methylenedioxy-5-methyl-14H-indolo[2,3-a]phenanthridizinium (IIIc) Perchlorate.

One gram of the quaternary salt was cyclized in 30 ml. of concentrated hydrochloric acid as in the preparation of (IIIb). The perchlorate crystallized from acetonitrile-ether as a yellow microcrystalline powder, m.p. 354.5° dec., yield 0.69 g. (68%), λ max (log ε) 215 (4.55), 241 (4.43), 260 (4.38), 292 sh (4.43), 296 (4.45), 325 sh (3.90), 380 sh (4.18), 397 (4.40), and 413 mμ (4.62).

Anal. Calcd. for $C_{21}H_{15}ClN_2O_6$: C, 59.09; H, 3.54; N, 6.57. Found: C, 59.34; H, 3.51; N, 6.96.

2-Methoxy-5-methyl-14H-indolo[2,3-a]phenanthridizinium (IIId) Bromide.

Cyclization of 1.0 g. of the quaternary bromide (IId) in 50 ml. of 48% hydrobromic acid was carried out by heating on the steam bath for fifteen minutes, followed by vacuum evaporation of the acid. Crystallization of the resulting salt from methanol-ethyl acetate afforded 0.84 g. (88%) of yellow microneedles, m.p.>400°.

Anal. Calcd. for $C_{21}H_{17}BrN_2O$: C, 64.13; H, 4.36; N, 7.12. Found: C, 63.88; H, 4.40; N, 6.95.

The perchlorate crystallized from methanol as yellow microneedles, m.p. 316.5-317.5° dec.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_5$: C, 61.09; H, 4.15; N, 6.79. Found: C, 60.91; H, 3.99; N, 6.61.

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