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THE SYNTHESIS OF β-CARBOLINE DERIVATIVES—I

A SYNTHESIS OF SOME 12 H-INDOLO[2,3-a]PYRIDOCOLINIUM SALTS, INCLUDING FLAVOPEREIRINE[1]

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Abstract—A new method for synthesizing 6,7-dihydro-12 H-indolo[2,3-a] pyridocolinium bromide in one step from 3-(2-bromoethyl)-indole and 2-halogenopyridine is described. This method was applied to the synthesis of flavopereirine, an alkaloid isolated from *Geissospermum laeve* or *vellosii*. The mechanism of this reaction is discussed.

IN this paper we wish to report in detail a method for the synthesis of β-carboline derivatives, including 6,7-dihydro-12 H-indolo[2,3-a]pyridocolinium salts (I, R = H) and the octahydrocompound (II), both of which constitute the fundamental ring system related to the structures of alstoniline,[2] flavopereirine[3] and other indole alkaloids which have already been synthesized independently by several groups.[4–8]

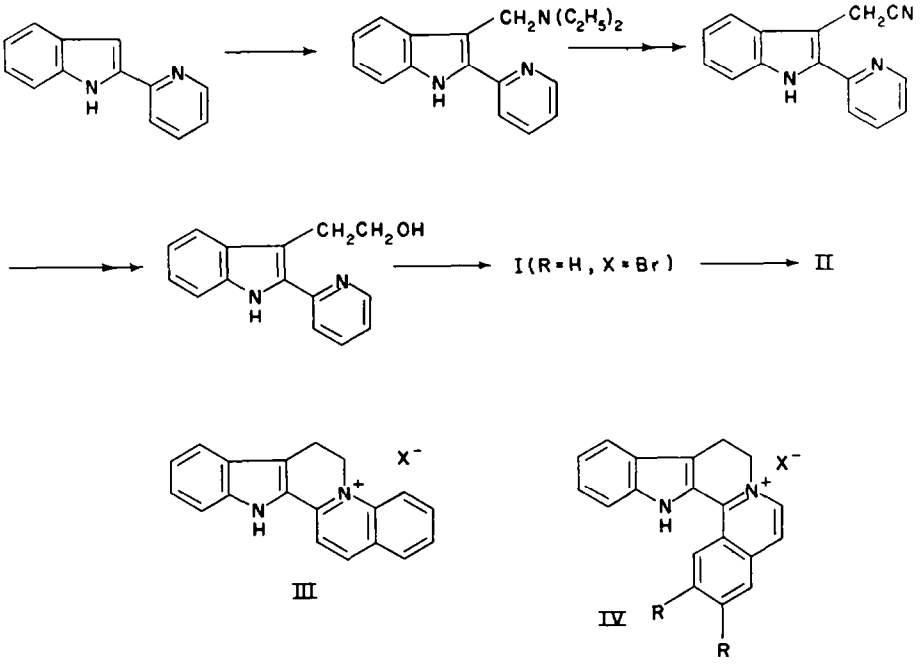
Of these the method of Sugasawa[6] and of Reckhow[5] generalized by Swan[9] may be applicable to the syntheses of various β-carboline derivatives, as shown by the synthesis of the parent compounds I (R = H) and II. The former method was further applied to the syntheses of 6,7-dihydro-12 H-benz[f]-(III),[10] 8,9-dihydro-14 H-benz[h]-(IV, R = H)[10] and 2,3-dimethoxy-8,9-dihydro-14 H-benz[h]-indolo-[2,3-a]pyrido-colinium salts (IV, R = OCH_3);[11] and the latter was extended to include the syntheses of flavocoryline (V, R = C_2H_5),[9] flavopereirine (V, R = H)[9] and sempervirine (VI),[12] etc.

In order to gain some further information concerning the relationship between the stereochemistry and activity of β-carboline derivatives, a general method for the synthesis of these compounds is being investigated. Therefore, as a preliminary, the preparation of 1-[2-(3-indolyl)ethyl]-2(1H)-pyridone (X, R = H) as a key intermediate for the synthesis of II was undertaken.

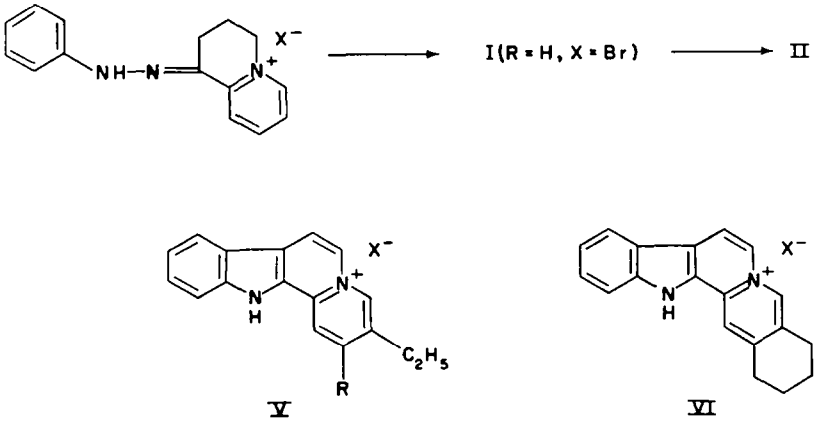
[1] A preliminary communication of a portion of the results now reported has been published. Y. Ban and (Miss) M. Seo, *Chem. & Ind.* 235 (1960).
[2] R. C. Elderfield and S. L. Wythe, *J. Org. Chem.* **19**, 683 (1954).
[3] [a] O. Bejar, R. Goutarel, M. M. Janot and A. Le Hir, *C. R. Acad Sci., Paris* **244**, 2066 (1957); [b] N. A. Huges and H. Rapoport, *J. Amer.Chem. Soc.* **80**, 1604 (1958).
[4] L. H. Groves and G. A. Swan, *J. Chem. Soc.* 650 (1952).
[5] W. A. Reckhow and D. S. Tarbell, *J. Amer. Chem. Soc.* **74**, 4956 (1952).
[6] S. Sugasawa, M. Terashima and Y. Kanaoka, *Pharm. Bull. Japan* **4**, 16 (1956).
[7] R. C. Elderfield, J. M. Lagowski, O. L. McCurdy and S. L. Wythe, *J. Org. Chem.* **23**, 435 (1958).
[8] L. Keufer, *Ann. pharm. Franc.* **8**, 816 (1950); *Chem. Abstr.* **45**, 10246 (1951).
[9] K. B. Prasad and G. A. Swan, *J. Chem. Soc.* 2024 (1958).
[10] S. Sugasawa and S. Takano, *Chem. & Pharm. Bull. Japan* **7**, 417 (1959).
[11] S. Sugasawa and Y. Deguchi, *Chem. & Pharm. Bull. Japan* **8**, 879 (1960).
[12] G. A. Swan, *J. Chem. Soc.* 2038 (1958).

After a number of fruitless experiments, the condensation of 3-(2-bromoethyl)-indole (VII) with 2-chloropyridine to furnish 1-[2-(3-indolyl)-ethyl]-2-chloro-pyridinium bromide (IX, R = H, X = Cl) was performed, as the latter should readily give rise to the desired pyridone on hydrolysis.

(i) Sugasawa's method:

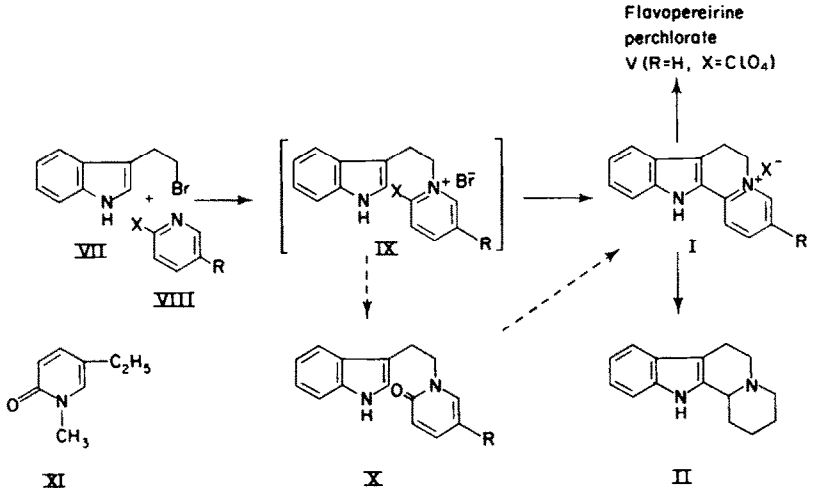


(ii) Swan's method:



The condensation of 3-(2-bromoethyl)-indole (VII) and 2-chloropyridine (VIII, R = H, X = Cl) resulted in a low yield of a yellow crystalline solid. From inspection of its ultra-violet absorption spectrum, which was quite different from the sum of VII and VIII—HBr (R = H, X = Cl), this could not be the expected pyridinium bromide

(IX, R = H, X = Cl), but was thought to be 6,7-dihydro-12 H-indolo[2,3-a]pyridocolinium bromide (I, R = H, X = Br), which had been described by Sugasawa[6] and Swan[9] independently. Its high melting point (325–330° with decomposition) also seems compatible with I rather than with IX (R = H, X = Cl). This view was supported when the reduction of this compound afforded the octahydro-compound (II), which was



identical with a specimen kindly supplied by Prof. Sugasawa. Careful search for the possible intermediate, 1-[2-(3-indolyl)ethyl]-2-chloropyridinium bromide (IX, R = H, X = Cl) was made, but (I, R = H, X = Br) was the sole product isolated and characterized. The one-step synthesis of pyridocolinium salt was thus effected.

Experiments were next conducted to improve the yield of the condensation product and at the same time to acquire insight into the mechanism of this new reaction.

A yield of 31·2 per cent of the pyridocolinium bromide (I, R = H, X = Br) was obtained when a 1:2 molar mixture of VII and 2-chloropyridine was heated on a steam bath for 10 hr. Increasing the molar ratio of VIII (R = H, X = Cl) to VII, e.g. 5 : 1, and using a solvent such as benzene, toluene etc. did not further improve the yield.

When, however, 2-bromopyridine was used in place of 2-chloropyridine the yield of the product rose to 40 per cent, the higher p*Ka* value (0·90)[13] of 2-bromopyridine as compared with that of 2-chloropyridine (0·72)[13] seemed to be responsible. In conformity with this view the more basic 2-iodopyridine (p*Ka* 1·82)[13] furnished the product I (R = H, X = Br) in 54·6 per cent yield.

The ease of quaternization should be in keeping with the increase of p*Ka* value of 2-halogenopyridines, provided the steric requirement of the halogen atom at 2-position does not exert a critical influence upon the quaternization reaction. If so, these findings suggest that this reaction is initiated by the formation of 1-[2-(3-indoly)ethyl]-2-halopyridinium bromide (IX, R = H, X = halogen atom), with the enhanced activity of the halo-atom at 2-position and formation of pyridocolinium bromide (I, R = H, X = Br).

[18] E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods* p. 597. Academic Press, New York (1955).

2-Chloro-5-methoxycarbonylpyridine (VIII, R = $COOCH_3$, X = Cl) is suitable material to justify the above view. The chlorine atom in this compound is rather active, due to the labilizing influence of the electron attracting group at 5-position in addition to an inductive effect of the neighbouring nitrogen. On the other hand, however, the feable basicity of this compound being incapable of forming a stable hydrochloride salt, would render the initiation of the first stage quaternization so difficult as to interfere with the following condensation to form the product I (R = $COOCH_3$, X = Br). Actually, when the condenstaion of this compound with VII was carried out by heating the mixture in a slow current of hydrogen for 20 hours, the pyridocolinium salt (I, R = $COOCH_3$, X = Br) was produced only in 11·1 per cent yield, which result lends support to the above mentioned mechanism. A similar mechanism was also proposed by Wiley *et al.*[14] in the cyclization of 1-phenethyl-2(1H)-pyridone derivatives.

Further speculation on the use of catalysts favouring the formation of electophilic fragments which might promote the rate of this reaction, made us condense 2-bromopyridine with VII in the presence of aluminum chloride. As was expected, the yield of the pyridocolinium bromide (I, R = H, X = Br) was raised to 60 per cent and compared favourably with the yield of 40 per cent without a catalyst. These results are summarized in the Table in the Experimental section.

This reaction was now extended to include the synthesis of flavopereirine, an alkaloid isolated from *Geissospermum laeve* or *vellosii* by Janot[3a] and independently by Rapoport[3b] and synthesized by Swan,[9] Janot[15] and Kaneko.[16] The starting material, 2-chloro-5-ethyl-pyridine was derived from 1-methyl-3-ethyl-6(1H)-pyridone (XI) which had been synthesized by Sugasawa *et al.*,[17] unequivocally establishing its structure. This pyridone was treated with a mixture of phosphoryl chloride and phosphorus pentachloride to give 2-chloro-5-ethyl-pyridine (VIII, R = C_2H_5, X = Cl), having a 2-chloropyridine-like odour. When condensed with 3-(2-bromoethyl)-indole (VII), this base (VIII, R = C_2H_5, X = Cl) gave the corresponding pyridocolinium bromide (I, R = C_2H_5, X = Br), in 31 per cent yield and the ultra-violet absorption was identical with that of the nitrate of the same base described by Swan.[9] Furthermore, following the dehydrogenation procedure given by Swan, the bromide (I, R = C_2H_5, X = Br) afforded flavopereirine perchlorate (V, R = H, X = ClO_4), m.p. 308° (decomp), identical with a sample of the natural alkaloid kindly supplied by Dr. Kaneko.

EXPERIMENTAL

Melting points are not corrected.

6,7-*Dihydro*-12 H-*indolo*[2,3-a]*pyridocolinium bromide* (I, R = H, X = Br)

(a) *Without a catalyst.* A mixture of 448 mg 3-(2-bromoethyl)-indole (VII) and 454 mg 2-chloropyridine was heated on a boiling water bath for 10 hr, the colour of the reaction mixture changed from pale yellow to red after 2 hr and crystals began to appear after 4 hr. On cooling, absolute ether was added to the reaction mixture to remove the starting materials, and 546 mg (81 per cent) of orange solid were obtained, but judging from the light absorption, these were still slightly contaminated with the starting materials. The product, dissolved in 3 ml ethanol was poured onto a column containing activated charcoal. Elution of this column with ethanol afforded a main fraction of yellow crystals, which were recrystallized from ethanol (or methanol–ether) to give 210 mg (31·2 per cent) of yellow

[14] R. H. Wiley, N. R. Smith and L. H. Knabeschuh, *J. Amer. Chem. Soc.* **75**, 4482 (1953).
[15] A. Le Hir, M. M. Janot and D. van Stolk, *Bull. Soc. Chim. Fr.* 551 (1958).
[16] H. Kaneko, *Yakugaku Zasshi* **80**, 1374 (1960).
[17] S. Sugasawa and M. Kirisawa, *Pharm. Bull. Japan* **3**, 190 (1955).

needles, m.p. 325–330°. (Found: C, 59·95; H, 4·36; N, 9·01. $C_{15}H_{13}N_2Br$ requires: C, 59·82; H, 4·35; N, 9·30 per cent). U.V. (95 per cent EtOH) λ_{max} 253 mμ (log E 3·92), 315 mμ (log E 4·14) and 385 mμ (log E 4·16): λ_{min} 239·5 mμ (log E 3·85), 276 mμ (log E 3·44) and 343 mμ (log E 3·89).

In a like manner 2-bromopyridine afforded the same product in a yield of 40 per cent and the purification was easier.

(b) *With aluminum chloride.* To a solution of 448 mg 3-(2-bromoethyl)-indole and 632 mg 2-bromopyridine in 5 ml absolute benzene, 400 mg aluminum chloride was added and the mixture refluxed for 5 hr, with separation of a red amorphous solid from the yellow benzene layer. On cooling, a small amount of water was added, and the yellow-green solid collected by filtration. The aqueous layer of the filtrate was extracted with benzene to remove the starting materials. The solid dissolved in warm water was combined with the aqueous solution of the filtrate, and the whole was saturated with potassium iodide to give 562·4 mg (80·2 per cent) of an orange precipitate. The iodide was shown to be nearly pure, judging from its light absorption, and was converted to the corresponding chloride in the usual way. The latter was recrystallized from ethanol to give 310 mg (60 per cent) of orange yellow needles, m.p. 305° (decomp). When toluene was used as a solvent in this reaction an impurer product was obtained.

TABLE

Molar ratio of VIII to VII	2-Halogeno-pyridine	Solvent	Reaction time (hr)	Temperature (°C)	Yield of I (R=H) (%)
2	2-chloro-	benzene	4	reflux	6
2	2-chloro-	benzene	6	reflux	22 (80)*
2	2-chloro-	—	6	100	28·5 (77·5)*
5	2-chloro-	—	7	100	27·8 (81·2)*
2	2-chloro-	—	10	100	31·2 (81)*
2	2-chloro-	toluene	5	reflux	26·7 (83)*
2	2-bromo-	benzene	10	reflux	40
2	2-bromo-	benzene (with $AlCl_3$)	5	reflux	60
2	2-iodo-	—	10	100	54·6

* The figures in parentheses indicate the yield (%) of the crude product.

1,2,3,4,6,7,12,12b-*Octahydro*-12 H-*indolo*[2,3-a]*pyridocoline* (II)

A solution of 50 mg 6,7-dihydro-12 H-indolo[2,3-a]pyridocolinium bromide (I, R = H, X = Br) in 10 ml 50 per cent ethanol was subjected to hydrogenation over Adam's catalyst at room temp and under atm press, 3 molar equivalents of hydrogen being absorbed in 2½ hr. The light absorption of the reduction solution was in good agreement with that of indole, indicating the absence of the starting material. After filtration of the catalyst and evaporation of the solvent *in vacuo*, there remained a pale yellow residue, which was dissolved in 4 ml water, and the aqueous solution was basified with 10 per cent sodium carbonate. The white precipitate (m.p. 147–148°, 30 mg) collected on a filter, was recrystallized from n-hexane to yield 25·6 mg (68·1 per cent) of white pillars, m.p. 152–153°, which was identical with a sample synthesized by Sugasawa,[6] by mixed m.p. and infra-red absorption comparison. (Found: C, 79·51; H, 7·83; N, 12·65: $C_{15}H_{18}N_2$ requires: C, 79·60; H, 8·02; N, 12·40 per cent). U.V. (95 per cent EtOH) λ_{max} 226 mμ (log E 4·67), 283 mμ (log E 3·88) and 290 mμ (log E 3·80); λ_{min} 247 mμ (log E 3·33) and 288 mμ (log E 3·77).

3-*Methoxycarbonyl*-6,7-*dihydro*-12 H-*indolo*[2,3-a]*pyridocolinium bromide* (I, R = $COOCH_3$, X = Br).

A solution of 2·24 g 3-(2-bromoethyl)-indole (VII) and 3·43 g 2-chloro-5-methoxycarbonylpyridine (VIII, R = $COOCH_3$, X = Cl) in 40 ml toluene, was heated under reflux for 20 hr in a slow current of hydrogen. On cooling, absolute ether was added and the orange precipitate collected, yield 1·3 g (37·7 per cent). This was found to be free from starting materials by its ultra-violet absorption spectrum, and recrystallized from methanol to furnish 400 mg (11·1 per cent) of orange needles, m.p. 269–270°. (Found: C, 56·75; H, 4·23; N, 7·34. $C_{17}H_{15}N_2O_2Br$ requires: C, 56·82; H, 4·17; N, 7·75 per cent). U.V. (95 per cent EtOH) λ_{max} 260 mμ (log E 3·86), 339 mμ (log E 4·14)

and 406 mμ (log E 4·34); λ_{min} 246 mμ (log E 3·86), 285 mμ (log E 3·17) and 357 mμ (log E 4·06). I.R. (Nujol) ν_{max} 1730 cm^{-1} (ester C=O), 3450 cm^{-1}(—NH—), 745 cm^{-1} (out of plane CH-bending vibration of the benzene hydrogens).

A synthesis of flavopereirine

2-Chloro-5-ethylpyridine (VIII, R = C_2H_5, X = Cl). To a mixture of 2·4 g 1-methyl-3-ethyl-6(1H)-pyridone (XI)[17] and 6 g phosphoryl chloride, 3 g phosphorus pentachloride was added, and the whole heated in an oil bath at 160–170° for 10 hr. On cooling, phosphoryl chloride was removed *in vacuo*, and water was added causing the separation of a heavy oily substance. The mixture was then basified with sodium hydroxide and steam distilled to give about 300 ml of distillate, which was extracted exhaustively with ether after being salted out by sodium chloride. The ethereal solution was dried over sodium sulphate and evaporated to give 1·6 g (64·7 per cent) of colourless liquid, b.p. 115°/35 mm (Found: C, 59·07; H, 5·76; N, 9·64. C_7H_8NCl requires: C, 59·36; H, 5·65; N, 9·89 per cent). This is a fairly weak base, dissolving in conc hydrochloric acid, but not in dil acid and water, and does not form picrate.

3-Ethyl-6,7-dihydro-12 H-indolo[2,3-a]*pyridocolinium bromide* (I, R = C_2H_5, X = Br).

A mixture of 448 mg 3-(2-bromoethyl)-indole (VII) and 566 mg 2-chloro-5-ethylpyridine (VIII, R = C_2H_5, X = Cl) was heated in a boiling water bath for 13 hr, giving an orange precipitate. On cooling, absolute ether was added and the orange solid recrystallized from ethanol to give 205·3 mg (31 per cent) of yellow needles, m.p. 320° (decomp). (Found: C, 62·29; H, 5·25. $C_{17}H_{17}N_2Br$ requires: C, 62·00; H, 5·16 per cent). U.V. (a) (95 per cent EtOH) λ_{max} 253 mμ (log E 3·91), 315 mμ (log E 4·16) and 395 mμ (log E 4·14); λ_{min} 243 mμ (log E 3·81), 275 mμ (log E 3·50) and 345 mμ (log E 3·88). (b) (0·015 N–KOH–EtOH) λ_{max} 267 mμ (log E 4·03), 361 mμ (log E 4·10) and 422 mμ (log E 4·21); λ_{min} 249 mμ (log E 3·88), 295 mμ (log E 3·40) and 383 mμ (log E 4·06).

3-Ethyl-12 H-indolo[2,3-a]*pyridocolinium perchlorate* (*Flavopereirine perchlorate*) (V, R = H, X = ClO_4)

According to Swan's procedure[9] the above bromide (I, R = C_2H_5, X = Br) was dehydrogenated with tetrachloro-*o*-benzoquinone to give flavopereirine perchlorate, pale yellow needles, m.p. 308°. (Found: N, 7·88. $C_{17}H_{15}O_4N_2Cl$ requires: N, 8·08 per cent). U.V. (a) (0·015 N–HCl–EtOH) λ_{max} 238 mμ (log E 4·57), 294 mμ (log E 4·22), 350 mμ (log E 4·31) and 389 mμ (log E 4·21). λ_{min} 273 mμ (log E 4·04), 307 mμ (log E 4·08) and 380 mμ (log E 4·17). (b) (0·015 N–KOH–EtOH) λ_{max} 231 mμ (log E 4·39), 236 mμ (log E 4·38), 289 mμ (log E 4·51), 319 mμ (log E 4·09), 365 mμ (log E 4·36), and 450 mμ (log E 3·73). λ_{min} 233 mμ (log E, 4·39), 264 mμ (log E 4·14), 310 mμ (log E 4·06), 328 mμ (log E 4·03) and 418 mμ (log E 3·68).

This was identical with a sample of natural flavopereirine perchlorate kindly supplied by Dr. Kaneko, by a mixed m.p. (308°) and infra-red spectral comparison.

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