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THE SYNTHESIS OF β-CARBOLINE DERIVATIVES—II[1]

A SYNTHESIS OF SOME BENZ-INDOLO[2,3-a]PYRIDOCOLINIUM SALTS, INCLUDING SEMPERVIRINE

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Abstract—A novel synthetic method for β-carboline derivatives, described in the preceding paper, is now applied to the syntheses of 6,7-dihydro-12H-benz[f]indolo[2,3-a]pyridocolinium salt, 8,9-dihydro-14H-benz[h]indolo-[2,3-a]pyridocolinium salt and sempervirine. In the course of synthesis of sempervirine, 2-[2-(3-indolyl)ethyl]-3-chloro-5,6,7,8-tetrahydro-isoquinolinium bromide is obtained as an intermediate, lending strong support for the mechanism previously proposed.

THE preceeding paper[1] described a new method for the syntheses of 6,7-dihydro-12H-indolo[2,3-a]pyridocolinium bromide (I) and its homologs. In the present paper, extension of this method to include the syntheses of β-carboline derivatives containing five rings, such as VII, IX and sempervirine (XIII) is described.

As is well known, Potts and Robinson[2] developed a method for syntheses of pentacyclic hydro-β-carbolines (III, R = H, Me) by reductive cyclization of II(R = H, Me), and this was later applied to the synthesis of alstonilinol by Elderfield.[3] Prior to Robinson's work, Julian and Magnani[4] conducted the reductive rearrangement of a 3-spiro-oxindole (IV, R = Me)[5] to III (R = Me) and were led to consider the method of Robinson, but they confined the application of their method to the rearrangement of IV.

On the other hand, VII and IX were synthesized by Sugasawa[6] and the method applied to the synthesis of 6,7-dihydro-12H-indolo[2,3-a]pyridocolinium bromide (I)[7].

Though Swan (with Prasad)[8] attempted in vain to synthesize these compounds prior to Sugasawa *et al.*, he succeeded in synthesizing sempervirine (XIII),[9] an alkaloid from *Gelsemium sempervirens*, Ait., of which the methochloride had been first synthesized by Woodward and McLamore.[10]

The one-step synthesis of pyridocolinium salts has been successfully applied to the synthesis of these compounds.

The synthesis of 6,7-dihydro-12H-benz[f]indolo[2,3-a]pytidocolinium bromide (VII) has been achieved from a 1:2 molar mixture of 3-(2-bromoethyl)-indole (V) and 2-chloroquinoline (VI) and the pure product, in 15·7 per cent yield, was shown to be

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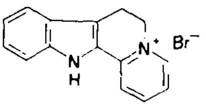
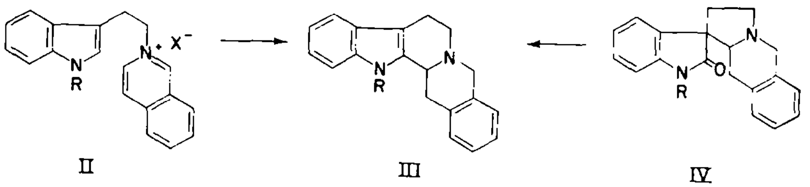
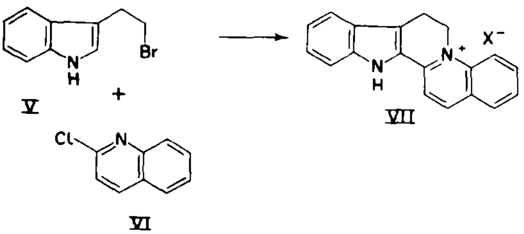
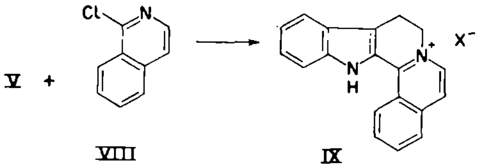
[1] Part I, Y. Ban and M. Seo, *Tetrahedron* **16**, 5 (1961).
[2] K. T. Potts and Sir Robert Robinson, *J. Chem. Soc.* 2675 (1955).
[3] R. C. Elderfield and B. A. Fischer, *J. Org. Chem.* **23**, 949 (1958).
[4] P. L. Julian and A. Magnani, *J. Amer. Chem. Soc.* **71**, 3207 (1949).
[5] B. Belleau, *Chem. & Ind.* 299 (1955); Y. Ban and T. Oishi, *Ibid.* 349 (1960).
[6] S. Sugasawa and S. Takano, *Chem. & Pharm. Bull. Japan* **7**, 417 (1959).
[7] S. Sugasawa, M. Terashima and Y. Kanaoka, *Chem. & Pharm. Bull. Japan* **4**, 16 (1956).
[8] K. B. Prasad and G. A. Swan, *J. Chem. Soc.* 2024 (1958).
[9] G. A. Swan, *J. Chem. Soc.* 2039 (1958).
[10] R. B. Woodward and W. M. McLamore, *J. Amer. Chem. Soc.* **71**, 379 (1949).

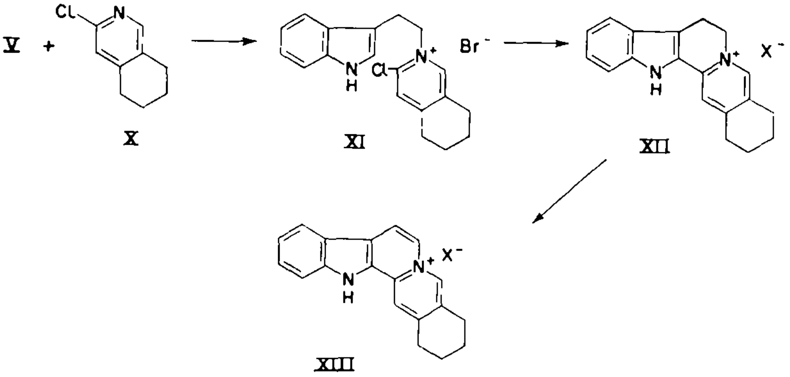


I









identical with 6,7-dihydro-12H-benz[f]indolo[2,3-a]pyridocolinium bromide (VII, m.p. 308–311° (decomp)) synthesized by Sugasawa and Takano.[6]*

Similarly, the condensation of 1-chloroisoquinoline and 3-(2-bromoethyl)-indole (V) afforded in 25 per cent yield, the 8,9-dihydro-14H-benz[h]indolo[2,3,-a]pyridocolinium bromide (IX, m.p. 318–320°(decomp)) identical in all respects with that described by Sugasawa and Takano.[6]*

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* All the necessary data were kindly supplied by Professor S. Sugasawa.

Finally, sempervirine itself was synthesized. From a 1:2 molar mixture of 3-(2-bromoethyl)-indole (V) and 3-chloro-5,6,7,8-tetrahydroisoquinoline (X), a compound was obtained as orange yellow crystals, m.p. 199–200°, in good yield. Contrary to expectation, this compound, deduced by its light absorption (Fig. 1(1)) to be 2-[2-(3-indolyl)ethyl]-3-chloro-5,6,7,8-tetrahydro-isoquinolinium bromide (XI), may be obtained in better yield by heating equimolar mixtures of the stated materials. In conformity with its structure, when treated with $POCl_3$ in xylene, it is converted to 1,2,3,4,7,8-hexahydro-13H-benz[g]indolo[2,3-a]pyridocolinium chloride (XII, X = Cl), the physicochemical properties of which are in good agreement with Swan's description.[9] In several experiments, using aluminium chloride or stannic chloride as a catalyst, the best yield of pure product was 18 per cent. The reason why in this case only the intermediate product was isolated is not clear at present, but if does lend strong support to the view that this type of compound is the intermediate in the one-step formation of pyridocolinium salts. Dehydrogenation of XII(X = Cl) according to Swan using tetrachloro-*o*-benzoquinone, furnishes a product, characterized as 1,2,3,4-tetrahydro-13H-benz[g]indolo[2,3-a]pyridocolinium nitrate (XIII, X = NO_3), the infra-red spectrum of which is completely superimposable on that of sempervirine nitrate kindly supplied by Dr. Kaneko.

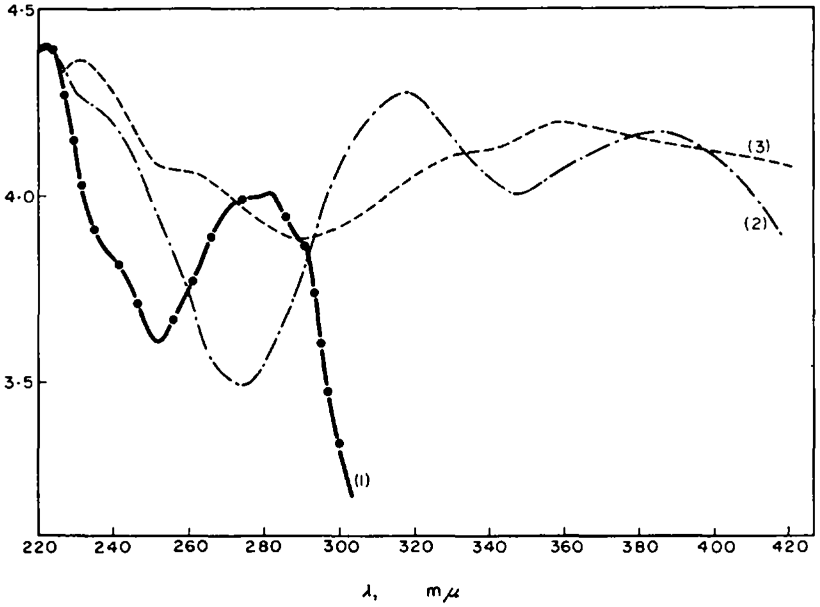

Fig. 1. Ultra-violet absorption spectra

(1) —•—•—•— 2-[2-(3-Indolyl)ethyl]-3-chloro-5,6,7,8-tetrahydro-isoquinolinium bromide (XI) in 95% EtOH.

(2) —.—.—.— 1,2,3,4,7,8-Hexahydro-13H-benz[g]indolo[2,3-a]pyridocolinium chloride (XII, X = Cl) in 95% EtOH.

(3) - - - - - - - - - (XII, X = Cl) in 0·015 N KOH–EtOH.

EXPERIMENTAL

Melting points are not corrected.

6,7-*Dihydro-*12H-*benz*[f]*indolo*[2,3-a]*pyridocolinium bromide* (VII, X = Br).

A mixture of 3-(2-bromoethyl)-indole (274 mg) and 2-chloroquinoline (400 mg) was heated in a current of nitrogen in an oil bath at 100–105° for 17 hr. The separation of a red brown solid was accompanied by the sublimation of 2-chloroquinoline hydrochloride in the upper part of the reaction vessel and the end of the reflux condenser. This was removed manually and 48% recovered. The hard red brown solid attached to the bottom of the flask was pulverized and washed with absolute ether 3 times to remove the starting materials. For further purification this powder (430 mg) was dissolved in water and shaken with ether. To the aqueous layer, which showed an absorption spectrum similar to that of the desired product described by Sugasawa and Takano,[8] a small amount of 48% hydrobromic acid was added and then evaporated *in vacuo* to give 244 mg of the crude product, yield 57%. This was purified twice by chromatography on active charcoal to give 67 mg of the pure product, which was recrystallized from ethanol in red orange needles, m.p. 308–311° (decomp). The infra-red and ultraviolet spectra of this compound are in good agreement with those of VII (X = Br) synthesized by Sugasawa and Takano.[6] The bromide was converted to the corresponding chloride (VII, X = Cl), orange needles, m.p. 270–271° (decomp). (Found: C, 71·63; H, 5·02; N, 8·83. $C_{19}H_{15}N_2Cl$ requires: C, 71·12; H, 4·89; N, 9·13 per cent). U.V. (95 per cent EtOH) λ_{max} 231 mμ (log E 4·35), 251·5 mμ (log E 4·23), 309 mμ (log E 4·24) and 428 mμ (log E 4·28). λ_{min} 246 mμ (log E 4·21), 272 mμ (log E 3·61) and 347 mμ (log E 3·64).

The results of the condensation under various conditions are summarized in Table 1.

8,9-*Dihydro*-14H-*benz*[h]*indolo*[2,3-a]*pyridocolinium bromide* (IX, X = Br).

A mixture of 3-(2-bromoethyl)-indole (672 mg) and 1-chloro-isoquinoline (981 mg) was heated in a current of hydrogen in an oil bath at 105–110° for 18 hr. A precipitate of 1-chloroisoquinoline hydrochloride started to appear after 2 hr. After 1-chloroisoquinoline hydrochloride was removed, absolute ether was added to the mixture to remove the starting materials, affording an orange red powder (850 mg), which was further purified by chromatography on active charcoal. Elution with ethanol gave a fraction (250 mg, 24·7 per cent) which showed the absorption spectrum of the desired product. The latter was recrystallized from ethanol to give orange needles, m.p. 318–320° (decomp). (Found: C, 64·87; H, 4·28; N, 7·77. $C_{19}H_{15}N_2Br$ requires: C, 64·95; H, 4·30; N, 7·97 per cent). U.V. (95 per cent EtOH) λ_{max} 272 mμ (log E 4·03), 331 mμ (log E 3·92) and 432 mμ (log E 4·27). λ_{min} 270 mμ (log E 4·01), 295 mμ (log E 3·48) and 350 mμ (log E 3·57). These physicochemical properties are in good agreement with those of XI (X = Br) synthesized by Sugasawa and Takano.[6]

The results of the condensation under various conditions are summarized in Table 2.

A synthesis of sempervirine nitrate

(i) 2-[2-(3-*indolyl*)*ethyl*]-3-*chloro*-5,6,7,8-*tetrahydroisoquinolinium bromide* (XI). An equimolar mixture of 3-(2-bromoethyl)-indole (2·24 g) and 3-chloro-5,6,7,8-tetrahydroisoquinoline (1·67 g) was dissolved in a small amount of absolute benzene, and the mixture heated on a water bath. A precipitate started to appear after 1 hr, but the mixture was refluxed for 18 hr. On cooling, absolute ether was added, the mixture filtered and thoroughly washed with ether to afford orange yellow crystals, 3·1 g (yield ca. 80 per cent). The filtrate combined with ether-washings was heated for a further several hours to afford an additional crop. The total was recrystallized from ethanol to give 3·2 g (82 per cent) of orange-yellow blades, m.p. 199–200°. (Found: C, 56·64; H, 4·81; N, 6·70. $C_{19}H_{20}N_2ClBr\text{-}0{\cdot}5H_2O$ requires: C, 56·92; H, 5·24; N, 6·99 per cent). U.V. (95 per cent EtOH)

TABLE 1

Molar ratio of VI to V	Solvent	Reaction time (hr)	Temperature (°C)	Yield of (VII) (%)
2	—	8	100	2 (50·7)**
3	toluene	10	reflux	9·8 (53)**
2	—	17	100–105	15·7 (57)**
2	—	15	100	11·2 (52·8)**

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

λ_{max} 223 mμ (log E 4·40), 281 mμ (log E 4·00) and 289 mμ (log E 3·90). λ_{min} 252 mμ (log E 3·61) and 288·5 mμ (log E 3·89).

(ii) 1,2,3,4,7,8-*Hexahydro*-13H-*benz*[g]*indolo*[2,3-a]*pyridocolinium chloride* (XII, X = Cl). To a suspension of 200 mg of the quaternary bromide (XI) in 4 ml xylene was added 0·5 g phosphoryl chloride and the mixture was refluxed on an oil bath for 5 hr. The orange yellow crystals turned into a red gum after 1 hr. After xylene and the excess phosphoryl chloride were evaporated *in vacuo*, a brown powder (250 mg) was obtained which was dissolved in ethanol and treated with active charcoal. Charcoal was removed and the residue recrystallized from ethanol to afford yellow needles, m.p. 305–315°(decomp). Further repeated recrystallizations from ethanol gave yellow needles of m.p. 324° (decomp). (Found: C, 71·02; H, 6·36; N, 8·64. $C_{19}H_{19}N_2Cl{\cdot}0{\cdot}5H_2O$ requires: C, 71·36; H, 6·25; N, 8·76 per cent). U.V. (95 per cent EtOH) λ_{max} 223 mμ(log E 4·40), 318 mμ (log E 4·26) and 385 mμ (log E 4·16). λ_{min} 275 mμ (log E 3·48) and 348 mμ (log E 4·00). These physicochemical properties are in good agreement with Swan's description.[9]

TABLE 2

Molar ration of VIII to V	Solvent	Reaction time (hr)	Temperature (°C)	Yield of (IX) (%)
2	toluene	9	reflux	17·3 (59·5)**
2	benzene	12	reflux	(62)**
2	—	6	100	20·8 (58)**
2	—	15	110	22 (68)**
2	—	18	105–110	25 (72)**

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

Cyclization by aluminium chloride

To an equimolar mixture of the quaternary bromide (XI, 500 mg) and aluminum chloride (232·4 mg), 10 ml absolute xylene was added and the mixture refluxed with stirring on an oil bath at 140–150° for 5 hr. The orange yellow crystals which did not dissolve in the solvent turned into a red brown gum during the reaction. On cooling, water was added and the red brown aqueous layer saturated with solid potassium iodide. The precipitate was collected by filtration (ca. 400 mg) and washed with ethanol, and showed an ultra-violet absorption spectrum of the desired product. Although the ethanol washings were found to be contaminated with starting material, by ultra-violet spectrum, they afforded a very small amount of the desired product after purification from ethanol. The combined iodide was treated with freshly prepared silver chloride in methanol to yield 114 mg of the corresponding chloride, which recrystallized from ethanol in orange yellow needles, m.p. 324° (decomp), yield 71·4 mg (18·01 per cent). By using stannic chloride as a catalyst, the yield was 12·34 per cent.

(iii) 1,2,3,4-*Tetrahydro*-13H-*benz*[g]*indolo*[2,3-a]*pyridocolinium nitrate, sempervirine nitrate* XIII ($X = NO_3$). According to the Swan's procedure,[9] the foregoing chloride (XII, X = Cl; 90·7 mg) was dehydrogenated with tetrachloro-*o*-benzoquinone to give sempervirine nitrate as pale yellow needles, m.p. 267°, yield 38·3 mg. (Found: C, 66·13; H, 5·12; N, 11·66. $C_{19}H_{17}O_3N_3{\cdot}0{\cdot}5H_2O$ requires: C, 66·27; H, 5·23; N, 12·20 per cent). U.V. (95 per cent EtOH) λ_{max} 242 mμ(log E 4·63), 248 mμ(log E 4·65), 297 mμ (log E 4·25), 346 mμ (log E 4·29), and 387 mμ (log E 4·28). λ_{min} 276 mμ (log E 4·02), 309 mμ (log E 4·10) and 372 mμ (log E 4·20). (0·015N KOH-EtOH) λ_{max} 245 mμ (log E 4·46), 289 mμ (log E 4·48), 322 mμ (log E 4·15), 360 mμ (log E 4·32) and 435 mμ (log E 3·75). λ_{min} 237 mμ (log E 4·41), 268 mμ (log E 4·12), 310 mμ (log E 4·05), 333 mμ (log E 4·07) and 425 mμ (log E 3·72).

The infra-red absorption spectrum of the synthetic sample was identical with a sample of sempervirine nitrate of natural origin.

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