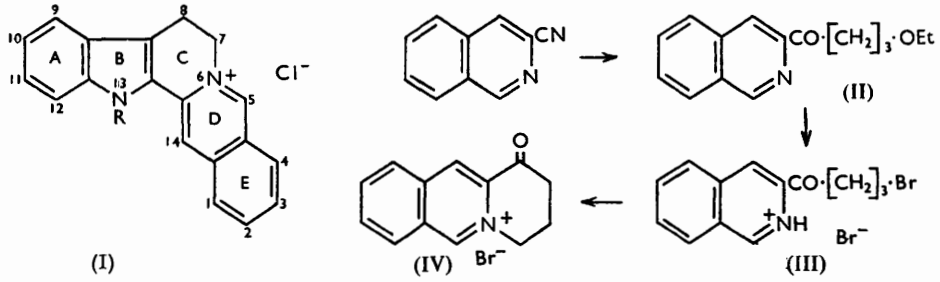
412. *The Constitution of Yohimbine and Related Alkaloids. Part XI.*[1] *A Synthesis of Sempervirine.*

By G. A. Swan.

Syntheses of 7 : 8-dihydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride (I; R = H) and sempervirine (XIII) are described.

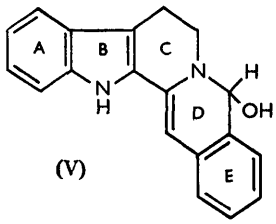
The preceding paper [1] described a general method for the synthesis of compounds containing rings A, B, C, and D, of the yohimbine skeleton. In this paper, the method is extended to the synthesis of compounds containing also ring E and, in particular, of sempervirine (XIII).



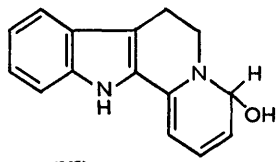
As a preliminary, 7 : 8-dihydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride (I; R = H) was synthesised. Acid hydrolysed the product of the action of 3-ethoxypropylmagnesium bromide on 3-cyano*iso*quinoline to crystalline 3-γ-ethoxybutyryl*iso*quinoline

[1] Prasad and Swan, preceding paper.

(II), showing no band in the 3370 cm.$^{-1}$ region (absence of NH). With hydrobromic–acetic acid this yielded a mixture of 3-γ-bromobutyryl*iso*quinoline hydrobromide (III) and its cyclisation product (IV); the former was converted into the latter by basification.



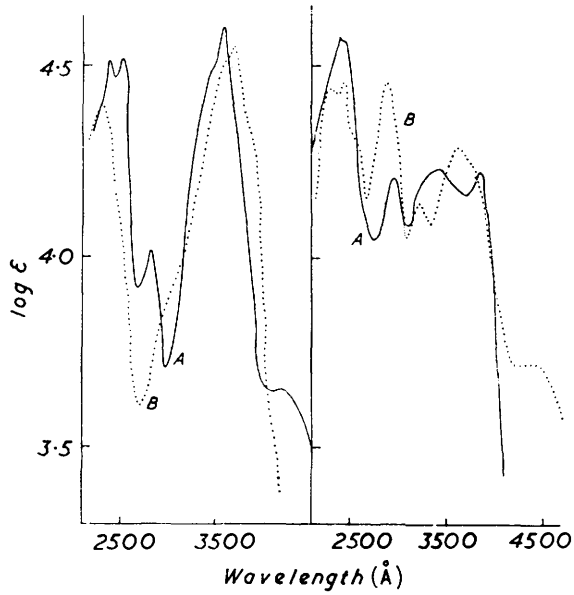
(V)



(VI)

The phenylhydrazone of the ketone (IV) in a Fischer indole reaction yielded 7 : 8-dihydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride (I; R = H), identical with a sample previously prepared by a different method.[2] The structure of the product was further

FIG. 1. FIG. 2.



Absorption spectra of: FIG. 1, 7 : 8-*dihydro*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium chloride*; FIG. 2 1 : 2 : 3 : 4-*tetrahydro*-13H-*benz*[g]*indolo*[a]*pyridocolinium nitrate*: *A, acid or neutral*; *B, alkaline.*

confirmed by the absorption of 2 mols. of hydrogen in the presence of Adams catalyst, with the formation of 5 : 7 : 8 : 13 : 13*b* : 14-hexahydrobenz[*g*]indolo[2 : 3-*a*]pyridocoline, identical with a sample prepared previously.[2]

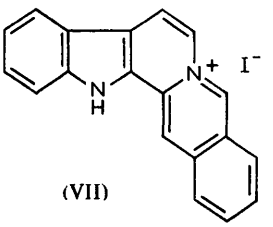
The absorption spectra of the product (I; R = H) in neutral and alkaline solution are shown in Fig. 1. The alkaline spectrum resembled that of 5 : 7 : 8 : 13-tetrahydrobenz-[*g*]indolo[2 : 3-*a*]pyridocoline [previously named 3 : 4-dihydro-7 : 8-benzindolo(2′ : 3′-1 : 2)-pyridocoline *] and this suggested the formation of the *pseudo*-base (V) in alkaline solution; this was confirmed by isolation of this pseudo-base as well as by the fact that the hydrogen atom attached to the indole nitrogen is not concerned with this change in alkaline solution. Thus, a Fischer indole reaction on the 1-methyl-1-phenylhydrazone of

* Owing to a typographical error, $\lambda_{max.}$ for this compound in ethanolic 0·01N-sodium hydroxide was given [2] as 3518 instead of 3718 Å.

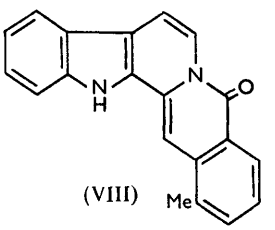
[2] Swan, *J.*, 1949, 1720.

the ketone (IV) gave the *N*-methyl compound (I; R = Me), the spectrum of which resembled that of the methyl-free compound (I; R = H) in both neutral and alkaline solution. This case differs from that of the 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium salts described in the preceding paper, where anhydronium-base formation occurs in alkaline solution, perhaps because the loss of resonance energy associated with the formation of a pseudo-base (VI) becomes less important when the extra benzene ring (E) is present, as in (V).

Attempts to dehydrogenate the product (I; R = H) with tetrachloro-*o*-benzoquinone led to a product, isolated as the iodide, which was probably not obtained pure but was



(VII)



(VIII)

thought to have structure (VII). Its ultraviolet spectrum resembled that of dehydrooxoyobyrine [3] (VIII).

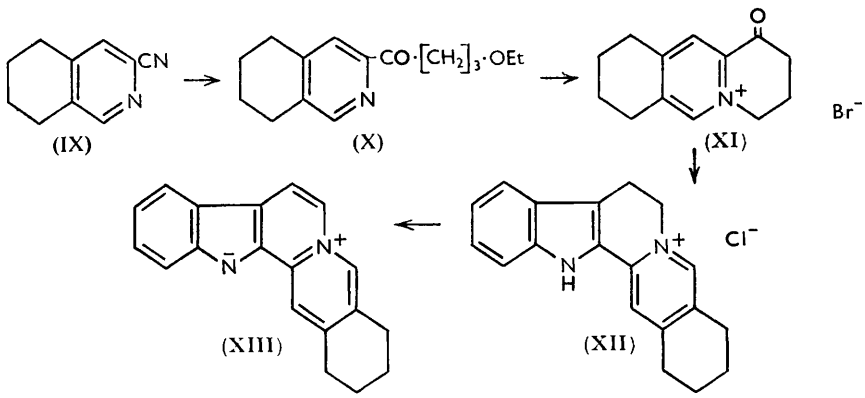
Although it has been reported [4] that Woodward and McLamore's [5] elegant synthesis of the sempervirine methosalts has been extended to the alkaloid itself, the latter work appears not to have been published. There has also been no report that Stevens's work [6] has yet culminated in the synthesis of sempervirine. A synthesis of the alkaloid is, however, now reported.

Although 3-chloro-5 : 6 : 7 : 8-tetrahydro*iso*quinoline is readily obtained from the 3-hydroxy-compound by the action of phosphorus oxychloride,[7] the use of the oxybromide gave mainly 3-bromo*iso*quinoline, instead of its 5 : 6 : 7 : 8-tetrahydro-derivative, which was desired for the preparation of a lithium derivative for reaction with γ-ethoxybutyronitrile to give 3-(γ-ethoxybutyryl)-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (X). It was therefore necessary to prepare the latter by the action of 3-ethoxypropylmagnesium bromide on 3-cyano-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (IX). Stevens [6] (with Bentley) has worked out a method for the synthesis of the nitrile (IX) and, although this work has not yet been published, Dr. Stevens most generously supplied full experimental details. In the final stage of the synthesis, the required nitrile was accompanied by 3-cyano*iso*quinoline and purification was best achieved by repeated crystallisation from light petroleum. On one occasion, when it was attempted to purify the nitrile by chromatography on alumina which had not been specially dried, hydrolysis to the amide occurred.

Although the nitrile (IX) was carefully purified, the product from the Grignard reaction, mainly (X), contained 3-γ-ethoxybutyryl*iso*quinoline (II) and it appeared likely that some dehydrogenation had occurred during the reaction or in the subsequent isolation. However, these two ketones could be separated chromatographically and the pure compound (X) with hydrobromic–acetic acid gave 1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-octahydro-1-oxobenzo[*b*]pyridocolinium bromide (XI); the phenylhydrazone of this readily underwent a Fischer indole reaction, giving 1 : 2 : 3 : 4 : 7 : 8-hexahydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride (XII). The corresponding nitrate has recently been obtained by Wenkert and Roychaudhuri [8] by dehydrogenation of (±)-yohimb-15(20)-ene and its spectroscopic constants are in reasonable agreement with those of our product (XII) and its melting point

[3] Woodward and Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 2409.
[4] Saxton, *Quart. Rev.*, 1956, **10**, 108.
[5] Woodward and McLamore, *J. Amer. Chem. Soc.*, 1949, **71**, 379.
[6] Stevens, *Chem. Soc. Special Publn.* No. 3, 1955, p. 19.
[7] Schlittler and Merian, *Helv. Chim. Acta*, 1947, **30**, 1339.
[8] Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1957, **79**, 1519.

agrees exactly with that of the nitrate derived therefrom. When this chloride was treated with an equimolecular amount of tetrachloro-*o*-benzoquinone in acetic acid and the resulting product was purified by chromatography and converted into a nitrate, it yielded 1 : 2 : 3 : 4-tetrahydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium nitrate, identical with



sempervirine nitrate. The spectra of the product in neutral and alkaline solutions are shown in Fig. 2.

Experimental

Ultraviolet absorptions were measured with a Hilger " Uvispec " spectrophotometer. Those referred to as " alkaline " were made in 0·015N-ethanolic potassium hydroxide and those referred to as " neutral " were in ethanol containing a trace of hydrochloric acid. Unless otherwise stated, " light petroleum " refers to a fraction of b. p. 60—80°, and analytical samples were dried at room temperature in a vacuum-desiccator.

3-*Cyano*iso*quinoline*.—Ethyl *iso*quinoline-3-carboxylate [9] (2·4 g.) when kept in aqueous ammonia (*d* 0·88; 24 ml.) for 2 days at room temperature, with occasional shaking, yielded *iso*quinoline-3-carboxyamide (2·02 g.), m. p. 212—213° (from water) (Found: C, 69·3; H, 4·9; N, 16·0. Calc. for $C_{10}H_8ON_2$: C, 69·75; H, 4·65; N, 16·3%). Case [10] gives m. p. 206° and Teague and Roe [11] give m. p. 213°. This (5 g.) was refluxed for 2 hr. with phosphorus oxychloride (12·5 ml.), the excess of the latter was removed (water-bath/reduced pressure) and the cooled residue was treated with chloroform and dilute sodium hydroxide solution. The chloroform extract was dried (K_2CO_3) and filtered and the solvent was removed. The residual nitrile, recrystallised from benzene–light petroleum (charcoal), yielded plates (2·65 g.), m. p. 124—125° (Found: C, 77·65; H, 3·95. Calc. for $C_{10}H_6N_2$: C, 77·95; H, 3·9%). Crowne and Breckenridge [12] give m. p. 127·5—128°. Light absorption in EtOH: $\lambda_{max.}$ 2310, 2790, 3080, and 3220 Å (log ε 4·76, 3·75, 3·39, and 3·52), $\lambda_{min.}$ 2530 Å (log ε 3·53).

3-*γ-Ethoxybutyryl*iso*quinoline* (II).—The above nitrile (0·64 g.) in ether (50 ml.) when treated with 3-ethoxypropylmagnesium bromide as for the preparation of 2-*γ*-ethoxybutyrylpyridine by method (*a*) of the preceding paper, except that the residue from the chloroform extract was not distilled but recrystallised from benzene–light petroleum (charcoal), gave the *ketone* (0·74 g.) as needles, m. p. 77—78° (Found: C, 74·05; H, 7·15; N, 6·15. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·75%). When this was treated with 2 : 4-dinitrophenylhydrazine in ethanol containing hydrobromic acid, the 2 : 4-dinitrophenylhydrazone bromide, m. p. 198—199°, separated. The latter, in chloroform solution, was treated with dilute sodium carbonate solution, and the residue from the chloroform extract was recrystallised from benzene–light petroleum; it yielded the bright red 2 : 4-*dinitrophenylhydrazone*, m. p. 158—159° (Found: C, 58·3; H, 5·1. $C_{21}H_{21}O_5N_5,0{\cdot}5H_2O$ requires C, 58·35; H, 5·1%).

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxobenzo*[b]*pyridocolinium Bromide* (IV).—The above ketone (0·74 g.) was refluxed for 15 hr. with 48% hydrobromic acid (1·5 ml.) and acetic acid (3 ml.). The

[9] Clemo and Hoggarth, *J.*, 1954, 95.
[10] Case, *J. Org. Chem.*, 1952, **17**, 471.
[11] Teague and Roe, *J. Amer. Chem. Soc.*, 1951, **73**, 688.
[12] Crowne and Breckenridge, *Canad. J. Chem.*, 1954, **32**, 641.

mixture was kept overnight at 0° and the resulting crystals A (0·32 g.; m. p. 160°) were collected and washed with acetone and ether. The filtrate was evaporated to dryness (water-bath/reduced pressure), the residue was dissolved in warm methanol, and the solution was diluted with acetone and allowed to cool. The resulting crystals B (0·47 g.) were washed with ether.

Crystals A, when recrystallised from methanol–acetone, yielded 3-*γ-bromobutyryl*isoquinoline *hydrobromide* (III), needles, m. p. 167° (Found: C, 38·20; H, 4·45. $C_{13}H_{13}ONBr_2,2{\cdot}5H_2O$ requires C, 38·6; H, 4·45%). This (0·1 g.) was shaken with ether and sodium carbonate (30 mg.) in water until all was in solution. The ether extract was dried for a short time (Na_2SO_4) and filtered, the ether was removed, and the residue was kept in chloroform solution for 2 hr. at room temperature. The residue left after removal of the chloroform was recrystallised from methanol–acetone, giving 1 : 2 : 3 : 4-*tetrahydro*-1-*oxobenzo*[b]*pyridocolinium bromide* (IV) as cream-coloured needles, m. p. 243° (Found: C, 56·45; H, 4·3. $C_{15}H_{12}ONBr$ requires C, 56·1; H, 4·3%). The same compound was obtained when crystals B were recrystallised from methanol–acetone (charcoal) and it appeared to be the sole product produced (0·9 g.) when the reaction mixture was evaporated to dryness, instead of being kept overnight in a refrigerator.

When the bromide (1·18 g.) was heated for 2·5 hr. on a water-bath with phenylhydrazine hydrochloride (0·8 g.), crystalline sodium acetate (2·7 g.), and water (38 ml.), and the mixture was cooled and filtered, it yielded the *phenylhydrazone* (1·32 g.), which separated from ethanol as orange-yellow needles, decomp. 285° (Found: C, 61·25; H, 4·7. $C_{19}H_{18}N_3Br$ requires C, 61·95; H, 4·9%). The corresponding *phenylhydrazone iodide* was obtained by adding potassium iodide solution to a hot solution of this bromide and separated from ethanol as orange needles, m. p. 281° (decomp.) (Found: C, 54·8; H, 5·35. $C_{19}H_{18}N_3I,C_2H_6O$ requires C, 54·7; H, 5·2%).

7 : 8-*Dihydro*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium Chloride* (I; R = H).—A mixture of the above phenylhydrazone (1 g.) and ethanol (40 ml.) was saturated with hydrogen chloride at 0°, kept for 2 hr. at room temperature, refluxed for 6 hr. and cooled in a refrigerator; the *chloride* (0·9 g.) separated and crystallised from absolute ethanol as orange-red needles, m. p. 330° (decomp.) (Found: C, 74·2; H, 5·25. $C_{19}H_{15}N_2Cl$ requires C, 74·4; H, 4·9%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2380, 2510, 2810, 3570, and 4180 Å (log ε, 4·52, 4·52, 4·02, 4·60, and 3·66), $\lambda_{min.}$ 2450, 2690, 2990, and 4090 Å (log ε 4·47, 3·91, 3·70, and 3·65); (*b*) alkaline, $\lambda_{max.}$ 2310, 3650 Å (log ε 4·40, 4·55), $\lambda_{min.}$ 2700 Å (log ε 3·60). The nitrate separated from ethanol as orange needles, m. p. 299° (decomp.).

The chloride (26 mg.) in acetic acid (4 ml.) absorbed 4·1 ml. of hydrogen at 18°/760 mm. during 2·25 hr. in the presence of freshly reduced Adams catalyst (23 mg.). The mixture was heated before removal of the catalyst and the filtrate was evaporated to dryness (water-bath/reduced pressure), the residue was basified with aqueous sodium hydroxide and extracted with ether, and the ether was removed from the dried (K_2CO_3) extract. The residue was recrystallised twice from benzene–light petroleum, then from aqueous ethanol, and again from benzene–light petroleum, affording 5 : 7 : 8 : 13 : 13*b*-14-hexahydrobenz[*g*]indolo[2 : 3-*a*]-pyridocoline as colourless needles, m. p. 197° alone or mixed with a specimen prepared by an earlier method.[2]

5 : 7 : 8 : 13 - *Tetrahydro* - 5 - *hydroxybenz*[g]*indolo*[2 : 3 - a]*pyridocoline* (V).—The precipitate formed on addition of dilute sodium hydroxide solution to an aqueous solution of the above chloride was collected, washed with water, and recrystallised from aqueous methanol, affording the brick-red pseudo-*base*, m. p. *ca.* 232° (decomp.) (for analysis dried for 19 hr. at 95°/0·1 mm.) (Found: C, 79·4; H, 5·35. $C_{19}H_{16}ON_2$ requires C, 79·15; H, 5·55%).

7 : 8-*Dihydro*-13-*methyl*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium Chloride* (I; R = Me).—1 : 2 : 3 : 4-Tetrahydro-1-oxobenzo[*b*]pyridocolinium bromide (0·24 g.) was treated with 1-methyl-1-phenylhydrazine (0·13 g.) and crystalline sodium acetate (0·6 g.) in N-hydrochloric acid (1·3 ml.) as described above for the phenylhydrazone. The resulting 1 : 2 : 3 : 4-*tetrahydro*-1-*oxobenzo*[b]*pyridocolinium* 1-*methyl*-1-*phenylhydrazone bromide* (0·2 g.) was recrystallised from ethanol and dried for 6 hr. at 90°/0·1 mm. (Found: C, 63·4; H, 4·9. $C_{20}H_{20}N_3Br$ requires C, 62·8; H, 5·25%). The corresponding iodide separated from ethanol–ether as orange-yellow plates, m. p. 344° (decomp.). The bromide (0·13 g.), in a Fischer indole reaction, yielded 7 : 8-*dihydro*-13-*methyl*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium chloride* (0·11 g.), separating from methanol as deep yellow needles, m. p. 315° (decomp.) (for analysis dried for 5 hr. at 110°/0·1 mm.) (Found: C, 70·85; H, 5·75. $C_{20}H_{17}N_2Cl,H_2O$ requires C, 70·9; H, 5·6%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2400, 2550, 2800, and 3520 Å (log ε 4·54, 4·56, 4·01, and

4·48), $\lambda_{min.}$ 2470, 2700, and 3000 Å (log ε 4·49, 3·93, and 3·75); (*b*) alkaline, $\lambda_{max.}$ 2200, 2310, and 3650 Å (log ε 4·33, 4·33, and 4·51), $\lambda_{min.}$ 2250 and 2750 Å (log ε 4·30 and 3·47).

A solution of the chloride (0·13 g.) and tetrachloro-*o*-benzoquinone (0·2 g.) in acetic acid (3 ml.) was heated on a water-bath for 3 hr., deposition of red needles beginning after a few minutes. The mixture was diluted with ether, and the red solid was collected and shaken with chloroform and N-sodium hydroxide. The chloroform extract was dried (K_2CO_3) and passed through a column of alumina. The residue from the eluate was dissolved in warm dilute hydrochloric acid and methanol, the solution was filtered and treated with one of potassium iodide, the bulk of the methanol was removed by distillation, and the solution then allowed to cool. The resulting precipitate recrystallised from aqueous methanol, affording a small amount of a chocolate-brown powder, m. p. *ca.* 211°, having in EtOH $\lambda_{max.}$ 2900 and 3450 Å (log ε 4·05 and 3·9; *M* assumed to be 400).

3-*Cyano*-5 : 6 : 7 : 8-*tetrahydro*isoquinoline (IX).—This was prepared from 5 : 6 : 7 : 8-tetrahydro-3-hydroxy*iso*quinoline according to the directions supplied by Dr. Stevens. The starting material was prepared by modification of existing methods.[13, 14] Ethyl 5 : 6 : 7 : 8-tetrahydro-3-hydroxy*iso*quinoline-4-carboxylate, after recrystallisation from ethanol and sublimation at 155°/0·1 mm., had m. p. 168° (Found: C, 65·05; H, 7·1. Calc. for $C_{12}H_{15}O_3N$: C, 65·15; H, 6·8%). This ester (7·3 g.) was refluxed for 5 hr. with water (43 ml.) containing sodium hydroxide (5·8 ml.), and the solution was diluted with an equal volume of water, cooled, and treated with acetic acid (18 ml.). The resulting 5 : 6 : 7 : 8-tetrahydro-3-hydroxy*iso*quinoline-4-carboxylic acid, when recrystallised from ethanol, decomposed at 221° (Found: C, 61·65; H, 6·05. Calc. for $C_{10}H_{11}O_3N$: C, 62·05; H, 5·7%), and was decarboxylated at 230°; the resulting 5 : 6 : 7 : 8-tetrahydro-3-hydroxy*iso*quinoline, when recrystallised from ethanol, had m. p. 199° (3·95 g.). Light absorption of 3-cyano-5 : 6 : 7 : 8-tetrahydro*iso*quinoline in EtOH: $\lambda_{max.}$ 2675 Å (log ε 3·44).

Reaction between 5 : 6 : 7 : 8-*Tetrahydro*-3-*hydroxy*isoquinoline *and Phosphorus Oxybromide.*—The hydroxy-compound (1·93 g.) was heated for 18 hr. at 190° in a sealed tube with phosphorus oxybromide (17·5 ml.). The mixture was poured on ice, kept for 1 hr. at room temperature, and filtered and the filtrate was basified with solid sodium carbonate and extracted with ether. The dried (K_2CO_3) extract on distillation yielded an oil (1·8 g.), b. p. 170°/15 mm., a solution of which in ether was extracted repeatedly with a mixture of concentrated hydrochloric acid and water (1 : 1). The acid extract was basified with 40% aqueous sodium hydroxide and extracted with ether; the dried (K_2CO_3) extract on distillation yielded an oil (1·14 g.), b. p. 140°/2 mm., which set to a white solid. When the latter was recrystallised from benzene–light petroleum, then from light petroleum (b. p. 40—60°), sublimed at 55°/0·2 mm., and again crystallised from light petroleum, it yielded 3-bromo*iso*quinoline, as colourless needles, m. p. 61° (Found: C, 51·85; H, 3·0. Calc. for C_9H_6NBr: C, 51·9; H, 2·9%). For this compound Case [10] gives m. p. 63—64°. The material not extractable from ether with hydrochloric acid was recovered and separated from ethanol as white, silky needles, m. p. 144—145°, and appeared to be a *dibromo*isoquinoline (Found: C, 38·0; H, 1·95. $C_9H_5NBr_2$ requires C, 37·6; H, 1·75%).

5 : 6 : 7 : 8-*Tetrahydro*isoquinoline-3-*carboxyamide.*—A solution of the nitrile in light petroleum (b. p. 60—80°) was passed through a column of alumina, which was then eluted successively with light petroleum–benzene, benzene, benzene–ether, and ether; but the solute was still retained by the column. The material was finally removed by methanol, which yielded the *amide*, m. p. 195—196°, as colourless crystals from ethanol, the m. p. being unchanged by sublimation at 100°/0·1 mm. (Found: C, 67·8; H, 6·7. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·8%).

3-γ-*Ethoxybutyryl*-5 : 6 : 7 : 8-*tetrahydro*isoquinoline (X).—A solution of 3-cyano-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (1·1 g.) in ether (25 ml.) was treated with a Grignard reagent prepared from magnesium (0·7 g.), 3-ethoxypropyl bromide (4 g.), and ether (20 ml.) as described under (*a*) for the preparation of 2-γ-ethoxybutyrylpyridine in the preceding paper, the product being a yellow, viscous oil (1·45 g.), b. p. 190° (bath-temp.)/4 mm. The latter was dissolved in a small volume of light petroleum (b. p. 40—60°) and kept in a refrigerator, crystals separating. These were collected, washed with light petroleum (b. p. 40—60°), and recrystallised from the same solvent, affording colourless needles (32 mg.), m. p. 50—58° (Found: C, 71·4; H, 8·35%).

The petroleum solutions containing the remainder of the product were passed through a column of alumina (20 g.), which was then eluted successively with (1) light petroleum (b. p.

[13] Basu and Banerjee, *Annalen*, 1935, **516**, 243.
[14] Swiss P. 253,710.

40—60°), (2) light petroleum–benzene (10 : 1), (3) benzene, and (4) benzene–ethanol (10 : 1). By evaporation of these fractions the following residues were obtained: (1) 0·67 g. of material which, when dissolved in a very small volume of light petroleum (b. p. 40—60°) and kept at 0°, deposited prisms, m. p. 24—25°; (2) 0·17 g., apparently essentially the same as (1); (3) 0·25 g. of material which, when recrystallised from light petroleum (b. p. 40—60°), yielded 3-γ-ethoxybutyryl*iso*quinoline (II), as needles, m. p. 75°, identified by comparison of its infrared spectrum with that of an authentic sample and by analysis (Found: N, 5·9. Calc. for $C_{15}H_{17}O_2N$: N, 5·75%); and (4) a brown oil which, when distilled, gave an oil (0·25 g.), b. p. 150—210° (bath-temp.)/1 mm. Fractions (1) and (2) were combined and distilled, giving a colourless oil (0·6 g.), b. p. 180—190° (bath-temp.)/1 mm., apparently 3-*γ-ethoxybutyryl*-5 : 6 : 7 : 8-*tetrahydro*-iso*quinoline* (X), which showed no band in the 3370 cm.$^{-1}$ region (Found: C, 72·55; H, 8·8; N, 5·7. $C_{15}H_{21}O_2N$ requires C, 72·9; H, 8·5; N, 5·65%).

1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-*Octahydro*-1-*oxobenz*[b]*pyridocolinium Bromide* (XI).—The ketone (X) (0·55 g.) was refluxed for 12·5 hr. in an atmosphere of nitrogen with 48% hydrobromic acid (2 ml.) and acetic acid (4 ml.), and the solution was evaporated to dryness, but the residue failed to crystallise. It was therefore converted, in the usual manner, into the *phenylhydrazone* (0·75 g.), which separated from ethanol–ether as orange crystals, m. p. 285° (decomp.) (Found: C, 60·55; H, 7·0. $C_{19}H_{22}N_3Br,C_2H_6O$ requires C, 60·3; H, 6·7%).

1 : 2 : 3 : 4 : 7 : 8-*Hexahydro*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium Chloride* (XII).—The above phenylhydrazone (0·64 g.) was subjected to a Fischer indole reaction as described previously, and the mixture was concentrated to one-third of its volume and kept at 0°. The resulting solid (0·55 g.) when recrystallised from ethanol gave the orange-yellow *chloride*, m. p. 324° (decomp.) (for analysis dried for 7 hr. at 100°/0·1 mm.) (Found: C, 71·2; H, 6·15. $C_{19}H_{19}N_2Cl,0·5H_2O$ requires C, 71·35; H, 6·25%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2230, 3190, and 3850 Å (log ε 4·37, 4·25, and 4·15), $\lambda_{min.}$ 2750 and 3480 Å (log ε 3·41 and 3·99); (*b*) alkaline, $\lambda_{max.}$ 2320, 2650, 3600, and 4060 Å (log ε 4·41, 3·99, 4·19, and 4·17), $\lambda_{min.}$ 2550, 2900, and 3850 Å (log ε 3·95, 3·38, and 4·15). The nitrate separated from aqueous ethanol as orange needles, m. p. 305—306° (decomp.).

1 : 2 : 3 : 4-*Tetrahydro*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium Nitrate*.—The above chloride (40 mg.) in acetic acid (0·5 ml.) was heated with tetrachloro-*o*-benzoquinone (40 mg.) for 3 hr. on a water-bath and the mixture was diluted with ether. The resulting solid was shaken with chloroform and dilute sodium hydroxide solution, and the chloroform extract was dried (K_2CO_3) and passed through a column of alumina (5 g.), which was then eluted with chloroform, the eluate being collected in 17 equal fractions. The first two fractions yielded a small amount of residue which, in dilute ethanolic solution, gave a greenish-yellow fluorescence; but the residues from the remaining fractions gave a brilliant blue fluorescence. The latter residues (15) were combined and warmed with dilute hydrochloric acid, and the solution was filtered and treated with saturated sodium nitrate solution; a slightly brownish-yellow precipitate (20 mg.) was then formed. This was collected, washed with water, and recrystallised from methanol, giving the *nitrate*, m. p. 267° (decomp.) (Found: C, 65·35; H, 5·15. $C_{19}H_{17}O_3N_3,0·75H_2O$ requires C, 65·4; H, 5·3%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2430, 2480, 2970, 3460, and 3860 Å (log ε 4·58, 4·57, 4·21, 4·23, and 4·22), $\lambda_{min.}$ 2760, 3110, and 3700 Å (log ε 4·04, 4·08, and 4·16); (*b*) alkaline, $\lambda_{max.}$ 2300, 2450, 2890, 3220, 3620, and 4350 Å (log ε 4·44, 4·46, 4·46, 4·14, 4·29, and 3·72), $\lambda_{min.}$ 2370, 2680, 3100, 3330, and 4250 Å (log ε 4·43, 4·15, 4·05, 4·08, and 3·71). The infrared spectrum was almost indistinguishable from that of a sample of sempervirine nitrate of natural origin.

Light absorption of sempervirine methiodide in EtOH: $\lambda_{max.}$ 2420, 2950, 3380, and 3950 Å (log ε 4·53, 4·21, 4·29, and 4·22), $\lambda_{min.}$ 2800, 3100, and 3700 Å (log ε 4·11, 4·06, and 4·07).

Thanks are offered to Dr. T. S. Stevens for his kindness in supplying details of the preparation of 3-cyano-5 : 6 : 7 : 8-tetrahydro*iso*quinoline before publication.

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[*Received, November 18th,* 1957.]