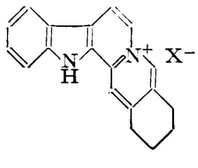
319. *The Constitution of Yohimbine and Related Alkaloids. Part V. Some Attempts to synthesise Sempervirine.*

By G. A. Swan.

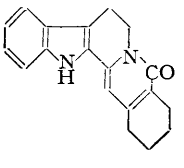
A number of experiments relating to unsuccessful attempts to synthesise sempervirine are recorded.

The synthesis of 3 : 4-dihydro-7 : 8-benzindolo(2′ : 3′-1 : 2)pyridocoline, not identical with sempervirine, was described in Part III (*J.*, 1949, 1720).

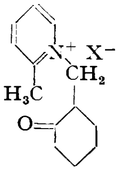
Experiments were then initiated towards the synthesis of (I), which appeared to be the most likely structure for the salts of sempervirine. A short time later, Dr. T. S. Stevens kindly sent the author a copy, before publication, of a communication (Bentley and Stevens, *Nature*, 1949, **164**, 141) in which structure (I) was suggested and supported by experimental evidence. Later, the communications of Woodward and Witkop (*J. Amer. Chem. Soc.*, 1949, **71**, 379), putting forward the same structure and of Woodward and McLamore (*ibid.*, p. 379) describing the synthesis of sempervirine methosalts, came to hand. The synthesis of (I) by a number of possible routes has been investigated; but all proved unpromising and were abandoned, although the positive results obtained are recorded in this paper.



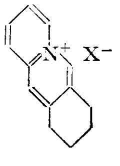
(I.)



(II.)



(III.)



(IV.)

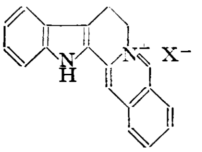
Kon and Nanji (*J.*, 1932, 2426) found that 3 : 4 : 5 : 6-tetrahydrohomophthalic acid (2-carboxy-1-*cyclo*hexenylacetic acid) was unaffected by acetyl chloride even in a sealed tube; but that with acetic anhydride it gave an impure, coloured liquid, believed to consist mainly of the hydroxy-anhydride. Repetition of this work showed that the action of acetyl chloride for 30 minutes on the water-bath gave (in good yield) a pale yellow liquid which appeared to be the anhydride; whilst the action of acetic anhydride gave a small amount of this, together with a neutral compound, $C_{18}H_{20}O_2$, crystallising in colourless needles, m. p. 147—148°, which has not been further investigated. The anhydride was treated with tryptamine, and the acidic product treated first with diazomethane, then with phosphoryl chloride, in the hope of obtaining (II); but the only product isolated formed bright yellow needles, m. p. 262°, and contained chlorine. The neutral *N*-(3′-indolyl-2-ethyl)-3 : 4 : 5 : 6-tetrahydrohomophthalimide simultaneously produced in the reaction between the anhydride and tryptamine also failed to give (II) on treatment with phosphoryl chloride.

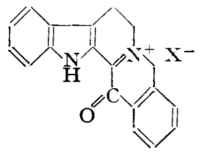
In model experiments, attempts were made to prepare (III; X = I) in the hope that it would undergo cyclisation and dehydrogenation to give (IV). 2-Hydroxymethyl*cyclo*hexanone was prepared essentially by Décombe's method (*Compt. rend.*, 1941, **213**, 579); but its b. p. was found to differ widely from that recorded. Attempts to convert this alcohol into the corresponding bromide and to quaternise this with 2-picoline to give (III) were not promising, nor was a similar approach by the action of paraformaldehyde and hydrochloric acid on *cyclo*hexanone (cf. Sorkin and Hinden, *Helv. Chim. Acta*, 1949, **32**, 63).

By the action of phosphoryl chloride, 3-2′-(chloroacetamido)ethylindole was cyclised to 2-chloromethyl-4 : 5-dihydro-β-carboline hydrochloride, which reacted with potassium cyanide to give 2-cyanomethyl-4 : 5-dihydro-β-carboline; but attempts to dehydrogenate this to 2-cyanomethyl-β-carboline were unsuccessful. The condensation of ethyl cyanoacetate with tryptamine gave 3-2′-(cyanoacetamido)ethylindole; but the cyclisation of this by phosphoryl chloride gave only a very low yield of 2-cyanomethyl-4 : 5-dihydro-β-carboline.

The preparation of 2-keto-1-nitromethyl*cyclo*hexanol is described in the experimental section.

In Part III it was suggested, on the evidence of ultra-violet absorption spectra, that the action of light on a solution of 3 : 4-dihydro-7 : 8-benzindolo(2′ : 3′-1 : 2)pyridocoline involves conversion into a product of the type (V). Edwards and Marion (*J. Amer. Chem. Soc.*, 1949, **71**, 1694) have also described the synthesis of the base [the m. p. of their compound is different from that recorded in Part III, but it depends on the rate of heating], and have isolated the irradiation product, the hydrochloride of which they formulate as (VI; X = Cl), the analytical results being in agreement with the formula $C_{19}H_{15}ON_2Cl,H_2O$. However, we find that when the irradiation product is dried at 100°/1 mm., it analyses as $C_{19}H_{15}N_2Cl$ and appears to be

(V.)




(VI.)

identical with 3 : 4-dihydro-7 : 8-benzindolo(2′ : 3′-1 : 2)pyridicolinium chloride (V; X = Cl), *e.g.*, the behaviour on catalytic hydrogenation is exactly that described for (V; X = Cl) in Part III.

EXPERIMENTAL.

(All m. p.s are uncorrected.)

*The Action of Acetic Anhydride on 2-Carboxy-*1-cyclo*hexenylacetic Acid.*—The acid (Kon and Nanji, *loc. cit.*; Grewe and Mondon, *Chem. Ber.*, 1948, **81**, 279) (0·63 g.) was heated under reflux for 3 hours with acetic anhydride (2 c.c.), and the product distilled at ca. 1 mm., giving (*a*) a moderately viscous yellow oil (0·18 g.; b. p. 150—160°) and (*b*) an extremely viscous yellow gum (0·25 g.; b. p. about 160°). The gum was dissolved in benzene, and the solution diluted with light petroleum. The precipitated solid was recrystallised from benzene–light petroleum (charcoal), giving a *compound* as colourless needles, m. p. 147—148° [Found: C, 80·0, 80·75, 80·55; H, 7·55, 7·95, 7·45%; *M* (Rast), 306. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·45%; *M*, 268].

*The Action of Acetyl Chloride on 2-Carboxy-*1-cyclo*hexenylacetic Acid.*—The acid (2·4 g.) was heated under reflux for 30 minutes with acetyl chloride (10 c.c.) and the product distilled, giving the *anhydride* (1·7 g.) as a moderately viscous, pale yellow oil, b. p. 180—182°/1 mm. (Found: C, 65·4; H, 6·5. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%). This was reconverted into the original acid by being boiled with N-sodium hydroxide solution.

Attempted Condensation of the Anhydride with Tryptamine and Cyclisation of the Product.—A solution of tryptamine (1·46 g.) in pure, dry chloroform (20 c.c.) was added to one of the anhydride (1·62 g.) in chloroform (10 c.c.), and the mixture heated under reflux for 7 hours on the water-bath. The solution was cooled in ice, and extracted three times with 2N-sodium hydroxide solution; the combined alkaline layer was extracted with ether, and then acidified (concentrated hydrochloric acid) with ice-cooling. The precipitated gum was dissolved in chloroform, the extract dried (Na_2SO_4), the solvent removed, the residue dissolved in methanol, and the solution cooled in ice and treated with excess of an ethereal solution of diazomethane. After 2 hours, the solution was evaporated to dryness and the residue kept overnight in a vacuum desiccator, giving a greenish, sticky mass (1·6 g.). This was heated for 35 minutes under reflux in a current of nitrogen with phosphoryl chloride (21 c.c.), the solution evaporated to dryness (water-bath; reduced pressure), and the residue cooled and stirred with water, dilute sodium hydroxide solution being gradually added until the solution was alkaline. The resulting solid was collected, washed with water, dried in a vacuum desiccator, and extracted with chloroform in a Soxhlet apparatus. During the first few minutes of the extraction, a good deal of dark brown material was extracted; this was rejected and the extraction continued. After several hours, the extract was cooled and filtered, and the resulting yellow solid (0·15 g.) washed with chloroform and recrystallised from methanol (charcoal), giving bright yellow needles, which were dried for ½ hour at 100°/1 mm. and then had m. p. 262° (Found: C, 61·65; H, 6·0; N, 7·95%).

From the neutral material produced in the tryptamine condensation N-(3′-*indolyl*-2-*ethyl*)-3 : 4 : 5 : 6-*tetrahydrohomophthalimide* could be isolated. This could also be prepared by heating under reflux for 13 hours a solution in dry benzene (17 c.c.) of tryptamine (0·45 g.) and the anhydride (0·55 g.). After cooling, the sticky solid was collected, washed with benzene, and crystallised from chloroform, methanol, or acetone, giving the imide (0·25 g.) as colourless needles, m. p. 230—231° (Found: C, 74·2; H, 6·7; N, 9·6. $C_{19}H_{20}O_2N_2$ requires C, 74·0; H, 6·5; N, 9·1%).

2-*Hydroxymethyl*cyclo*hexanone.*—A mixture of *cyclo*hexanone (50 c.c.), water (100 c.c.), and potassium carbonate (1 g.) was stirred vigorously at 30—35°, while formalin (75 c.c.; 40%) was added during 1 hour, after which stirring was continued for a further 1 hour. The cooled mixture was extracted with ether, and the extract dried (K_2CO_3) and distilled, giving (*a*) *cyclo*hexanone (27 c.c.); (*b*) a mobile, colourless liquid, b. p. 112—126°/12 mm. (8 g.); and (*c*) a viscous, colourless liquid, b. p. 126—175°/12 mm. (6 g.). Redistilled, the *ketone* (*b*) (6·8 g.) had b. p. 110°/11 mm. (Found: C, 65·8; H, 9·55. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%). [The phenylhydrazone formed pale yellow prisms, m. p. 127—128°, from methanol.]

2-*Chloromethyl*-4 : 5-*dihydro-β-carboline Hydrochloride.*—A mixture of 3-2′-(chloroacetamido)ethylindole (von Braun, Bahn, and Münch, *Ber.*, 1929, **62**, 2766) (0·53 g.), toluene (2·5 c.c.), and phosphoryl chloride (0·75 c.c.) was heated under reflux in a current of nitrogen for 1 hour, cooled, and treated with light petroleum (b. p. 40—60°). The solvents were decanted from the residual gum, which was then treated with warm water. The cooled, aqueous solution was extracted with ether, filtered, basified (ammonia solution), and extracted with ether. The latter ether extract was filtered and stirred with a slight excess of concentrated hydrochloric acid. The ether was decanted from the precipitated yellow solid, which was stirred with acetone, and the product was collected and washed with acetone; it (0·24 g.) then had m. p. 225° (decomp.). Recrystallised from aqueous acetone the *hydrochloride* was obtained as shining, dark, brownish-red prisms, m. p. 230° (decomp.) (Found: C, 56·4; H, 5·5. $C_{12}H_{12}N_2Cl_2$ requires C, 56·45; H, 4·7%).

2-*Cyanomethyl*-4 : 5-*dihydro-β-carboline.*—A solution of the hydrochloride (0·15 g.) in water (1·5 c.c.) was treated with one of potassium cyanide (0·15 g.) in water (0·7 c.c.). After being cooled and stirred, the precipitated gum rapidly solidified and was collected, washed with water, and heated under reflux on the water-bath for 15 minutes with a solution of potassium cyanide (0·25 g.) in water (0·7 c.c.) and ethanol (1 c.c.). Part of the ethanol was removed by distillation, the solution was cooled and the resulting brown solid separated from the black tar. The former was recrystallised from aqueous methanol (the first part to separate being rejected) giving the *base* as a yellowish buff powder (70 mg.), m. p. 202—203° (Found: C, 74·5; H, 5·55. $C_{13}H_{11}N_3$ requires C, 74·65; H, 5·3%).

3-2′-(*Cyanoacetamido*)*ethylindole.*—A mixture of ethyl cyanoacetate (0·33 g.) and tryptamine (0·45 g.) was heated for 2 hours on the water-bath. The product was stirred with dilute hydrochloric acid and cooled, whereupon it solidified; the resulting solid was collected, washed with water, and recrystallised from aqueous methanol (charcoal), giving the *amide* as almost colourless plates (0·49 g.), m. p. 92—93° (Found: C, 68·6; H, 5·9. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·75%).

2-*Keto*-1-*nitromethyl*cyclo*hexanol.*—A mixture of nitromethane (2·7 c.c.) and *cyclo*hexane-1 : 2-dione (Bitz, Davis, and Gadds, *J. Org. Chem.*, 1947, **12**, 122) (6 g.) was cooled in ice and treated with piperidine (0·3 c.c.). After 3 days at room temperature, the mixture was dissolved in chloroform, and the solution washed with dilute hydrochloric acid and sodium hydrogen carbonate solution, and dried (Na_2SO_4). The solvent was removed and the residue treated with light petroleum (b. p. 40—60°) whereupon it crystallised. The solid was collected and washed with light petroleum, and the crude *product* (2 g.; m. p. 88—89°) recrystallised from benzene, giving colourless plates, m. p. 90—91°, b. p. 135—140°/1 mm. (Found : C, 49·0; H, 6·4. $C_7H_{11}O_4N$ requires C, 48·6; H, 6·4%).

The Oxidation Product of 3 : 4-*Dihydro*-7 : 8-*benzindolo* (2′ : 3′-1 : 2)*pyridocoline Hydrochloride.*—This was prepared according to Edwards and Marion's method, and dried for 3½ hours at 100°/1 mm. (Found : C, 74·3; H, 5·4. Calc. for $C_{19}H_{15}N_2Cl$: C, 74·4; H, 4·9%).

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UNIVERSITY OF DURHAM, KING'S COLLEGE,
NEWCASTLE-ON-TYNE, 1.

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