The Constitution of Yohimbine and Related Alkaloids. Part VIII. Synthesis of 3-Ethyl-2-(5-ethyl-2-pyridyl)indole, a Degradation Product of Corynantheine.*

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3-Ethyl-2-(5-ethyl-2-pyridyl)indole (I; R = H) and 5-ethylpyridine-2-carboxylic acid (III; R = H), degradation products of corynantheine, have been synthesised and shown to be identical with the products of natural origin.

The alkaloid corynantheine, on dehydrogenation with selenium, gives two oxygen-free products, alstyrine (coryline) which probably has structure (I; R = Et) (Karrer and Enslin, *Helv. Chim. Acta*, 1949, **32**, 1390), and de-ethylalstyrine (de-ethylcoryline) (I; R = H) (Janot and Goutarel, *Bull. Soc. chim.*, 1951, 588). Ozonolysis of de-ethylalstyrine (Janot and Goutarel, *loc. cit.*) yields the amide (II; R = H) which on acid hydrolysis gives *o*-aminopropiophenone and an ethylpyridinecarboxylic acid which was formulated by Janot and Goutarel (*loc. cit.*) as (III; R = H), because of its decarboxylation to 3-ethylpyridine, although it might conceivably be 3-ethylpyridine-2-carboxylic acid.

The syntheses of 5-ethylpyridine-2-carboxylic acid (III; R = H) and of 3-ethyl-2-(5-ethyl-2-pyridyl)indole were therefore undertaken. Mild oxidation of 5-ethyl-2-styrylpyridine (cf. Clemo and Gourlay, *J.*, 1938, 478, for the oxidation of the 2-styryl derivative of 2 : 4-lutidine) gave 5-ethylpyridine-2-carboxylic acid identical with the acid of natural origin. Decarboxylation of the synthetic acid with copper powder gave 3-ethylpyridine. The ester of (III; R = H), on condensation with ethyl butyrate under Claisen conditions

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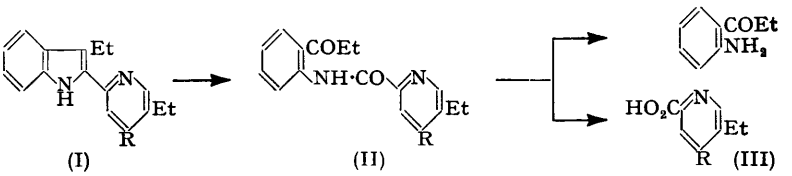
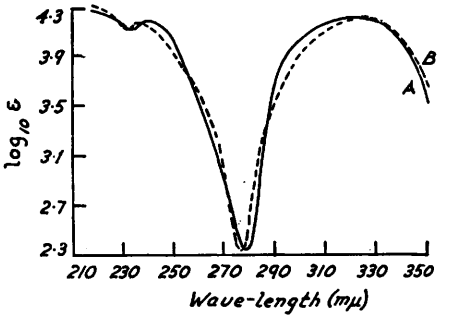
and subsequent hydrolysis, gave 2-butyryl-5-ethylpyridine, the phenylhydrazone of which underwent a Fischer indole reaction to give (I; R = H). This base readily formed a crystalline picrate, styphnate, and hydrochloride; the melting points of our picrate and



hydrochloride, which were determined in capillary tubes, differ from those reported by Janot and Goutarel, but Professor Janot informs us that the values he records were determined on the Maquenne block. From the crude picrate of de-ethylalstyrine of natural origin we have prepared the pure picrate and styphnate which proved to be



Ultra-violet absorption spectra of (*A*) ——— *natural and* (*B*) ----- *synthetic de-ethylalstyrine hydrochloride.*

identical with the corresponding synthetic derivatives. The ultra-violet absorption spectra of the synthetic and natural hydrochlorides showed a great similarity (see Figure) and were characteristic of an indole nucleus conjugated with a pyridine nucleus.

Experimental

Ultra-violet absorption measurements were made in ethanol with a Hilger " Uvispec " spectrophotometer.

5-Ethyl-2-styrylpyridine.—5-Ethyl-2-methylpyridine (Frank, Blegen, Dearborn, Myers, and Woodward, *J. Amer. Chem. Soc.*, 1946, **68**, 1368; purified *via* the picrate, m. p. 164°) (35 g.), freshly distilled benzaldehyde (70 g.), and acetic anhydride (70 g.) were refluxed together for 48 hr. The mixture was made acid to Congo-red with 1 : 1 hydrochloric acid, steam-distilled to remove excess of benzaldehyde, and, while being cooled in ice, basified with 15% sodium hydroxide solution. The dark brown crystals were collected, washed with cold water, and recrystallised from light petroleum (b. p. 40—60°) (charcoal), giving the *styryl* derivative as colourless prisms (35 g.), m. p. 58—59° (Found : C, 86·3; H, 7·2. $C_{15}H_{15}N$ requires C, 86·1; H, 7·2%). The *picrate* separated from ethanol in long, pale yellow needles, m. p. 203—204° (Found : C, 57·4; H, 4·1. $C_{15}H_{15}N,C_6H_3O_7N_3$ requires C, 57·3; H, 4·1%).

5-Ethylpyridine-2-carboxylic Acid (III; R = H).—A solution of the above styryl compound (18 g.) in acetone (180 ml.) was cooled in ice and stirred while finely powdered potassium permanganate (39 g.) was added during 30 min. The manganese dioxide formed was removed by filtration, washed with acetone, and extracted with hot water (3 × 180 ml.). The aqueous filtrate was acidified with dilute hydrochloric acid and kept at room temperature for 1 hr. The precipitated benzoic acid (5·8 g.) was removed, and the filtrate was warmed and stirred while copper carbonate (8 g.) was added. The solution was cooled overnight, and the blue crystalline *copper* salt was collected, washed with water, and dried (Found : C, 53·0; H, 4·6; N, 7·3. $C_{16}H_{16}O_4N_2Cu$ requires C, 52·75; H, 4·4; N, 7·7%), suspended in hot water, and treated with hydrogen sulphide. The copper sulphide was filtered off, and the filtrate rapidly evaporated to dryness on the water-bath under reduced pressure, giving the *acid* (5 g.) as colourless needles, m. p. 101—102° (Found : C, 64·0; H, 6·2; N, 9·6. $C_8H_9O_2N$ requires C, 63·6; H, 6·0; N, 9·3%). The acid (III; R = H) of natural origin had m. p. 100—101° alone or mixed with our synthetic acid.

Decarboxylation of 5-Ethylpyridine-2-carboxylic Acid.—The synthetic acid (10 mg.) was intimately mixed with copper powder (0·6 mg.) and gently heated. The distillate was disolved in ether, and picric acid in ether was added. The picrate (long, yellow needles from methanol) had m. p. 125° not depressed by admixture with authentic 3-ethylpyridine picrate.

Ethyl 5-Ethylpyridine-2-carboxylate.—A solution of the hydrochloride of the acid (III; R = H) (5 g.) in anhydrous ethanol (40 ml.) was cooled in ice, and saturated with dry hydrogen chloride. The solution was gently warmed for 1 hr., then refluxed for 1 hr., and kept at room temperature overnight. The ethanol was removed under reduced pressure, the residue was dissolved in water, basified with saturated sodium carbonate solution, and extracted with ether. The extract was dried (K_2CO_3), the ether removed, and the residue distilled, giving the colourless *ester* (3·5 g.), b. p. 140—142°/16 mm. (Found: C, 67·3; H, 7·4. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%). The *picrate* prepared in ether formed yellow needles, m. p. 107—108° (Found: C, 47·3; H, 3·8. $C_{10}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 47·1; H, 3·9%).

2-Butyryl-5-ethylpyridine.—To a suspension of potassium ethoxide (from potassium, 0·2 g.) in anhydrous benzene (15 ml.) was added the foregoing ester (0·65 g.), followed by ethyl butyrate (1·2 g., 100% excess). The mixture, which immediately became red-brown, was refluxed on the water-bath for 5 hr., cooled in ice-water while hydrochloric acid (2 : 1; 15 ml.) was added, and heated under reflux on the water-bath overnight, then evaporated to dryness under reduced pressure, and the residue was dissolved in water, basified with saturated potassium carbonate solution, and extracted with ether. The extract was dried (K_2CO_3), the solvent removed, and the residue distilled, giving the *ketone* (0·3 g.) as a colourless oil, b. p. 88—91°/2 mm. (Found: C, 74·4; H, 8·6. $C_{11}H_{15}ON$ requires C, 74·6; H, 8·5%). The *picrate* separated from ethanol in yellow plates, m. p. 119—120° (decomp.) (Found: C, 50·4; H, 4·7. $C_{11}H_{15}ON,C_6H_3O_7N_3$ requires C, 50·25; H, 4·4%). The *phenylhydrazone picrate* separated from ethanol in glistening. orange needles, m. p. 178° (decomp.) (Found: C, 56·0; H, 4·8. $C_{17}H_{21}N_3,C_6H_3O_7N_3$ requires C, 55·65; H, 4·7%).

3-Ethyl-2-(5-ethyl-2-pyridyl)indole (I; R = H).—The above ketone (0·438 g.) and freshly distilled phenylhydrazine (0·302 g.) were heated together in a vacuum on the steam-bath for 30 min. The residual mass was dissolved in anhydrous ethanol (20 ml.), cooled in ice, and saturated with dry hydrogen chloride. The solution was kept at room temperature for 1 hr. and refluxed for 2 hr.; ammonium chloride separated and after the whole had been cooled to 0° this was filtered off. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in water, basified with saturated potassium carbonate solution, and extracted with ether. The extract was dried (K_2CO_3), the solvent removed, and the indole (0·2 g.) distilled as a pale yellow, very viscous oil, b. p. (bath-temp.) 160—170°/0·2 mm., which darkened in air. The *hydrochloride* crystallised from methanol in yellow needles, softening at 149°, completely melted by 183° (Found: C, 67·25; H, 7·2. $C_{17}H_{18}N_2,HCl,H_2O$ requires C, 67·0; H, 6·9%). Light absorption: max. at 2380 and 3250 Å (log ε 4·14 and 4·16 respectively), min. at 2330 and 2765 Å (log ε 4·10 and 2·33 respectively). The *picrate* separated from ethanol in small yellow needles, m. p. 177° (decomp.) (Found: C, 57·7; H, 4·7; N, 14·4. $C_{17}H_{18}N_2,C_6H_3O_7N_3$ requires C, 57·6; H, 4·4; N, 14·6%). The *styphnate* formed yellow needles (from ethanol), m. p. 190—191° (Found: C, 55·85; H, 4·6; N, 14·2. $C_{17}H_{18}N_2,C_6H_3O_8N_3$ requires C, 55·8; H, 4·2; N, 14·1%).

Derivatives of De-ethylalstyrine of Natural Origin.—The crude picrate (1 g.) of de-ethylalstyrine was refluxed with potassium hydroxide (0·85 g.) in methanol (15 ml.) for 2 hr. The solution was filtered into a saturated sodium chloride solution (130 ml.). The solution was extracted with ether, the extract was dried (Na_2SO_4), and the ether removed, leaving an oily residue. The picrate separated from acetone or ethanol in yellow crystals, m. p. 177° not depressed on admixture with the synthetic picrate (Found: C, 57·9; H, 4·6%) (Janot and Goutarel, *loc. cit.*, report m. p. 151—152°). The styphnate separated from ethanol in yellow crystals, m. p. 188—189° not depressed on admixture with the synthetic styphnate (Found: C, 55·8; H, 4·4%). The hydrochloride as supplied to us softened at 148° and melted completely by 181° (Janot and Goutarel, *loc. cit.*, report m. p. 148—150°).

Thanks are offered to Professor M.-M. Janot for supplying samples of 5-ethylpyridine-2-carboxylic acid and the hydrochloride and crude picrate of de-ethylalstyrine of natural origin, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. M. A.).

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