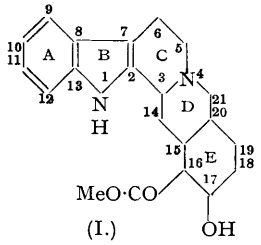
128. *The Constitution of Yohimbine. Part I.*

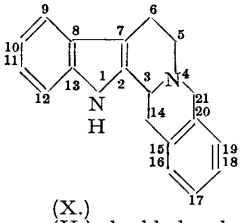
By G. R. CLEMO and G. A. SWAN.

The structure (V) for yobyrine, a selenium dehydrogenation product of yohimbine, has been proved by synthesis. A base having structure (X) has also been synthesised; on dehydrogenation with palladium, this gave (V). The "carboline-blue" colour reaction described by Harvey, Miller, and Robson (*J.*, 1941, 153) is discussed.

THE constitution of the alkaloid yohimbine has been largely elucidated by the work of Barger and Scholz (*Helv. Chim. Acta*, 1933, **16**, 1343; 1935, **18**, 923), Wibaut and van Gastel (*Rec. Trav. chim.*, 1935, **54**, 85), and Hahn and Werner (*Annalen*, 1935, **520**, 123), the probable structure being represented by (I).



(I.)

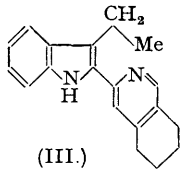


(X.)

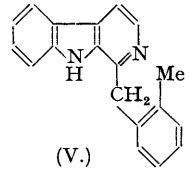
(II.) double bond at C_3–C_{14}

(IV.) " " "

C=O at position 21



(III.)

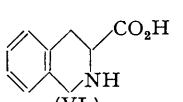


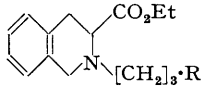
(V.)

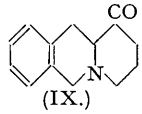
On dehydrogenation with selenium, yohimbine gives rise to yobyrine, $C_{19}H_{16}N_2$, " tetrahydroyobyrine," $C_{19}H_{20}N_2$, and ketoyobyrine, $C_{20}H_{16}ON_2$ (Mendlik and Wibaut, *Rec. Trav. chim.*, 1929, **48**, 191; 1931, **50**, 91; Wibaut and van Gastel, *loc. cit.*; Barger and Scholz, *Helv. Chim. Acta*, 1933, **16**, 1343). The last authors represented the first two of these substances by formulæ (II) and (III) respectively.

Recently an important contribution to the chemistry of the alkaloid has been made (Witkop, *Annalen*, 1943, **554**, 83; Pruckner and Witkop, *ibid.*, p. 127) which has clarified many hitherto unexplained points. Structure (II) for yobyrine is unsatisfactory, as one would not have expected the dehydrogenation to have stopped at this stage. Witkop has suggested the alternative (V), which is in all respects entirely satisfactory (*e.g.*, it explains the salts of yobyrine being colourless, and showing a blue fluorescence in solution, as it is a derivative of β-carboline). Witkop's conclusions are based on degradation and absorption spectra; but we have approached the problem from the synthetic point of view.

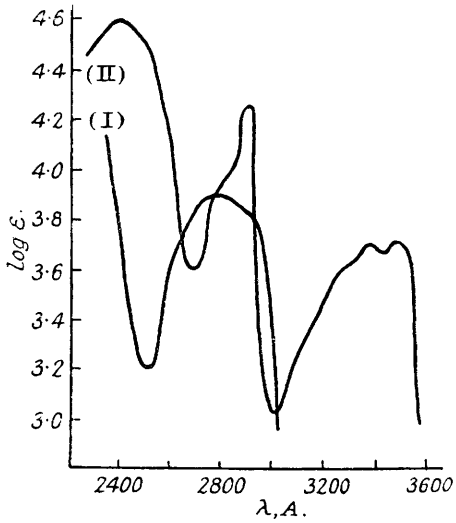
The condensation of phenylalanine with formaldehyde to give 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid (VI) has been described by Pictet and Spengler (*Ber.*, 1911, **44**, 2030). We have condensed the


(VI.)

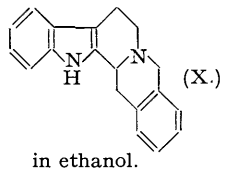

(VII.) R = CN
(VIII.) R = CO_2Et


(IX.)

ethyl ester of this acid with γ-bromopropyl cyanide to give *ethyl* 2-(γ-*cyanopropyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline*-3-*carboxylate* (VII), which was alcoholysed to *ethyl* 2-(γ-*carbethoxypropyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline*-3-*carboxylate* (VIII). By carrying out the Dieckmann reaction on this diester, we obtained 1-*keto*-7 : 8-*benzo*-1 : 2 : 3 : 4 : 6 : 9-*hexahydropyridocoline* (IX), the *phenylhydrazone* of which underwent the Fischer indole reaction, giving 7 : 8-*benzo*-1 : 2-(2′ : 3′-*indolo*)-3 : 4 : 6 : 9-*tetrahydropyridocoline* (X), a colourless, crystalline solid, m. p. 196—197°. A solution of this base in alcohol, or of its hydrochloride in water, contained in a quartz vessel, gave a blue fluorescence when placed in a beam of ultra-violet radiation (this was not observed in a glass vessel). The ultra-violet absorption spectrum is shown in the accompanying figure (Curve I). The

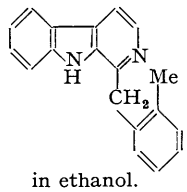


Curve (I)


(X.)

in ethanol.

Curve (II)



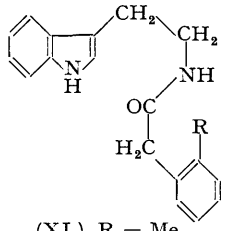
in ethanol.

base (V), gave only a pale yellow colour with *p*-dimethylaminobenzaldehyde in dilute hydrochloric acid in the cold; but, on heating, a pink colour developed, which faded on cooling. This reversible colour change could be repeated indefinitely, and is given by 2 : 3-dimethylindole and by tetrahydroharmine (Perkin and Robinson, *J.*, 1919, **115**, 939).

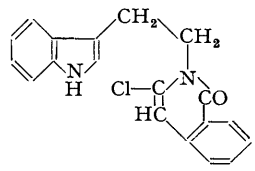
When (X) was heated with palladium black it was converted into a mixture of bases, from which a base ***A*** was isolated. *A* was a colourless, crystalline solid, m. p. 216—217° (corr.), and seemed to correspond to yobyrine. It might conceivably have the structure (II) suggested for yobyrine by Barger and Scholz. However, this was disproved by the following synthesis.

For this, *o*-tolylacetic acid was required. The best method found in the literature for the preparation of this compound is that of Hill, Short, and Stromberg (*J.*, 1937, 937), by the oxidation of *o*-allyltoluene. We found it more convenient to make use of the reaction first described by Arndt and Eistert (*Ber.*, 1935, **68**, 200); and from *o*-toluoyl chloride obtained a 53% yield of the required acid. When this was condensed with 3-(β-aminoethyl)indole (tryptamine), it gave 3-[β-(*o-tolylacetamido*)*ethyl*]*indole* (XI), which, in the presence of phosphoryl chloride, underwent ring closure to give a product which was dehydrogenated in the presence of palladium black, yielding a base *B*, m. p. 216—217° corr.), whose structure is clearly represented by 2-(*o*-

methylbenzyl)-β-*carboline*. Bases *A* and *B* are identical, and no depression of melting point was observed on admixture. A specimen of yobyrine obtained from the alkaloid was not available for comparison; but there is



(XI.) R = Me
(XIII.) R = CO_2H
(XIV.) R = OMe

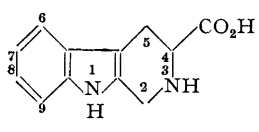


(XII.)

no doubt of the identity of this base (*A* or *B*) with yobyrine. Solutions of the base in alcohol, or of its hydrochloride in water, exhibit a strong blue-violet fluorescence. The melting points of the base, the *picrate*, and the methiodide agree with those recorded for yobyrine; as does the ultra-violet absorption spectrum (Curve II) (cf. Witkop, *loc. cit.*). Moreover, oxidation of our base with selenium dioxide gave a product whose melting point corresponds to that of yobyrone.

We have also carried out preliminary attempts to synthesise the yohimbine ring system by a number of other methods. (1) By condensing ethyl ω-bromo-*o*-toluate with sodium methoxide, followed by hydrolysis, ω-*methoxy*-o-*toluic acid* was obtained. This we had hoped to subject to the Arndt–Eistert reaction to obtain an acid which, when condensed with tryptamine, might yield an amide (XIV) capable of cyclisation to give the yohimbine skeleton. However, attempts to prepare the chloride of this acid failed: under mild conditions, the acid was unattacked, whilst under more vigorous conditions, phthalide resulted. (2) Tryptamine was condensed with homophthalic acid to give *homophthal*-(β-3-*indolylethyl*)*imide*. Attempts to cyclise this with phosphoryl chloride to give (IV), however, resulted in a *compound* which is probably 3-chloro-2-(β-indolylethyl)-1-*iso*quinolone (XII) (cf. Haworth, Perkin, and Pink, *J.*, 1925, **127**, 1709). (3) Tryptamine was condensed with homophthalic anhydride to give a *compound* which is probably an *N*-(β-indolylethyl)homophthalamic acid (XIII). This was esterified by the action of methyl iodide on the silver salt, and then treated with phosphoryl chloride. From the reaction mixture was isolated a product in yield too small to permit of a full investigation; but which may, perhaps, be represented by (IV). (4) Attempts to cyclise 3-*formyl*-2-*benzyl*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline* with phosphoryl chloride or phosphoric oxide have not given any promising results.

Location of the Carbomethoxy Group in the Yohimbine Molecule.—The suggestion, made by Harvey, Miller, and Robson (*loc. cit.*), that the carbomethoxy group is present at position 5 is attractive in so far as this structure might arise from tryptophan. The evidence of these authors is based solely on a colour reaction with concentrated sulphuric acid containing an oxidising agent. A blue colour is first produced and this slowly gives way to an olive-green, which in turn is replaced by a permanent yellow, the final solution possessing a faint green fluorescence. They carried out this test on a series of compounds and concluded that it was indicative of the presence of a β-carboline nucleus, hydrogenated at positions 2, 3, 4 and 5 and carrying a carboxyl group at position 4 (XV). It is, however, significant that out of a list of fourteen derivatives of 2 : 3 : 4 : 5-tetrahydro-β-carboline to which they subjected the test, ten have a carboxyl or carbomethoxy group at position 4, whilst the remaining four did give the test in a transient manner. This evidence seemed to us scarcely sufficient to warrant the generalisation which these authors made, so we have extended the list to include the following derivatives of 2 : 3 : 4 : 5-tetrahydro-β-carboline; the 2-methyl (Hahn and Hansel, *Ber.*, 1938, **71**, 2163), 2-benzyl (Hahn and Ludewig, *Ber.*, 1934, **67**, 2031; Hahn and Hansel, *Ber.*, 1938, **71**, 2192), and 2-(*o*-methylbenzyl) compounds, as well as our base (X). Although in none of these compounds is a carboxyl group present, with each we obtained a series of colour changes similar to those described by Harvey, Miller, and Robson. Moreover, Dewar and King (*Nature*, 1941, **148**, 25) have obtained similar colour transformations with the carboxyl-free yohimbone (this compound, which they designated yohimbol, was subsequently shown by Witkop to be a ketone) and have pointed out that this entirely invalidates the evidence on which the suggested alternative formula rests. Our results are in accord with this; and Witkop has shown that the results of his work on the Oppenauer dehydrogenation of yohimbine are best explained by a structure in which the hydroxyl group is in the β-position to the carboxyl group, as in (I).



(XV.)

Harvey, Miller, and Robson have suggested that the blue pigment formed in the above colour test reaction may be 4 : 5-dihydro-β-carboline-4-carboxylic acid. This seems to us unlikely; another possibility is that the colour may be due to a semiquinone (cf. Weiss, *J.*, 1942, 245).

Further work in this field is in hand.

Experimental

dl-N-*Benzoylphenylalanine*.—The azlactone of α-benzamidocinnamic acid (20 g.)(Erlenmeyer, *Annalen*, 1893, **275**, 1) was suspended in 95% alcohol (300 c.c.) and heated to 75°. Sodium amalgam (100 g., 4%) was added and the mixture stirred for 1½ hours; a similar portion of amalgam was then added, and stirring continued for a further 2½ hours. The liquid was filtered hot, the bulk of the alcohol distilled off (water-bath), and the residue dissolved in water and acid-

ified with hydrochloric acid. The resulting solid was collected and dissolved in hot alcohol, and the solution filtered and diluted with an equal volume of hot water; on cooling, the product separated (13·5 g., m. p. 182°).

Ethyl 1 : 2 : 3 : 4-*Tetrahydro*iso*quinoline*-3-*carboxylate*.—A mixture of the above (10 g.) and concentrated hydrochloric acid (50 c.c.) was heated in a sealed bulb in the water-bath for 30 hours. Benzoic acid was removed from the reaction product by steam-distillation, and the residue evaporated to dryness under reduced pressure (water-bath). The resulting solid was dissolved in a hot mixture of water (100 c.c.) and ammonia (10 c.c., *d* 0·88), the solution filtered, excess of ammonia removed by concentration under reduced pressure (water-bath), and the resulting solution added to one of copper acetate (4 g.) in hot water (60 c.c.). After having been kept overnight in the refrigerator, the precipitated copper salt was collected, washed with cold water, suspended in boiling water (200 c.c.), and decomposed by hydrogen sulphide. The copper sulphide was filtered off from the hot solution and extracted with boiling water; the combined filtrate and washings were evaporated to dryness under reduced pressure (water-bath). The residue was suspended in concentrated hydrochloric acid (50 c.c.) and methylal (10 c.c.) was added. After having been kept overnight at room temperature, the mixture was heated for 24 hours on the water-bath and evaporated to complete dryness under reduced pressure (water-bath), the last traces of water being removed by adding a little absolute alcohol and then distilling it off. Absolute alcohol (40 c.c.) was added to the resulting solid, and the cooled mixture saturated with dry hydrogen chloride and refluxed for 3 hours (water-bath). Alcohol was then removed (water-bath), the residue dissolved in a small volume of cold water, and the solution saturated with sodium carbonate and extracted with ether. Ether was removed from the dried (K_2CO_3) extract, and the residue distilled, the fraction, b. p. 110—130°/1 mm. (1·4 g.), being collected. The *ester* is a colourless liquid, b. p. 120°/1 mm. (Found: C, 70·2; H, 7·7. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3%). The *picrate* separated from alcohol as yellow crystals, m. p. 204° (Found: C, 50·3; H, 4·2. $C_{12}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 50·0; H, 4·2%). The picrolonate separated from alcohol as clusters of yellow needles, m. p. 212—213°.

Ethyl 2-(γ-*Cyanopropyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline*-3-*carboxylate* (VII).—A mixture of the above ester (4 g.), γ-bromopropyl cyanide (3 g.) (Derick and Hess, *J. Amer. Chem. Soc.*, 1918, **40**, 547) and anhydrous potassium carbonate (1·45 g.) was heated, with occasional stirring, for 5 hours in the water-bath. After cooling, water (30 c.c.) was added, the mixture extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue fractionated at 1 mm., giving: (i) 1 g., b. p. below 140°; (ii) 2·3 g., b. p. 150—190°. On redistillation, the latter gave the *cyanide* as a yellow, viscous liquid, b. p. 170°/1 mm. (Found: C, 70·55; H, 7·7. $C_{16}H_{20}O_2N_2$ requires C, 70·6; H, 7·3%).

Ethyl 2-(γ-*Carbethoxypropyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline*-3-*carboxylate* (VIII).—A solution of the above cyanide (2·3 g.) in absolute alcohol (14 c.c.) was cooled in ice and saturated with dry hydrogen chloride. The resulting solution was refluxed for 7 hours (water-bath) and evaporated to dryness under reduced pressure (water-bath), and the residue was dissolved in cold water, basified (sodium carbonate), and extracted with ether. The ether was removed from the dried (K_2CO_3) extract and the residue distilled, giving the *diester* as a pale yellow, viscous liquid (1·6 g., b. p. 170°/1 mm.) (Found: C, 68·0; H, 8·05. $C_{18}H_{25}O_4N$ requires C, 67·7; H, 7·85%).

1-*Keto*-7 : 8-*benzo*-1 : 2 : 3 : 4 : 6 : 9-*hexahydropyridocoline* (IX).—The above diester (1 g.) in toluene (2 c.c.) was added in the cold to powdered potassium (0·33 g.) under toluene (8 c.c.); the flask containing the mixture was plunged into a boiling water-bath and shaken for 2 minutes, after which it was left there for 1½ hours. After cooling, the excess of potassium was destroyed by the addition first of a few drops of alcohol, then of a few drops of water, after which concentrated hydrochloric acid (25 c.c.) was added, and the mixture heated in the water-bath for 3 hours. The liquid was then evaporated to dryness under reduced pressure (water-bath), the residue dissolved in water, basified (sodium carbonate) and extracted with ether. Ether was removed from the dried (K_2CO_3) extract, and the residue distilled as an orange-coloured oil which partly crystallised on cooling (0·28 g., b. p. 140°/1 mm.). This was stirred with a small volume of dry ether, and the yellow crystalline solid collected and washed with a little ether (0·14 g., m. p. 98° after softening at 88°); when recrystallised from light petroleum (b. p. 60—80°) this gave the *ketone* as orange-coloured plates, m. p. 99—100° (Found: C, 77·7; H, 7·4. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·45%). The *oxime* was prepared by refluxing a solution of the ketone, hydroxylamine hydrochloride, and anhydrous sodium acetate in methanol for 2 hours (water-bath), distilling off the methanol, adding water to the residue, collecting the resulting solid, and washing with water; from methanol (charcoal) it separated in colourless prisms, m. p. 207—208° (Found: C, 72·45; H, 7·6. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4%). When calcium carbonate was used instead of sodium acetate, the oxime *hydrochloride* was obtained; this separated from alcohol in colourless prisms, m. p. 221° (Found: C, 62·1; H, 6·5. $C_{13}H_{17}ON_2Cl$ requires C, 61·8; H, 6·7%). The *phenylhydrazone* was prepared by heating a solution of the ether-washed ketone (0·14 g.) in absolute alcohol (2 c.c.) with phenylhydrazine (0·2 g.) for 2 hours on the water-bath, concentrating the solution, keeping it in the refrigerator, and collecting the resulting solid; when recrystallised from methanol, this afforded yellow prisms, m. p. 92°, softening at 80° (0·17 g.) (Found: C, 73·9; H, 7·8. $C_{19}H_{21}N_3,CH_3OH$ requires C, 74·3; H, 7·75%).

7 : 8-*Benzo*-1 : 2-(2′ : 3′-*indolo*)-3 : 4 : 6 : 9-*tetrahydropyridocoline* (X).—The above phenylhydrazone (0·13 g.) was dissolved by warming in absolute alcohol [4 c.c.), the solution cooled in ice, and saturated with dry hydrogen chloride. After having been kept for 1 hour at room temperature the solution was refluxed for 1½ hours (water-bath), the alcohol distilled off (water-bath), the residue cooled, and water added. The resulting yellow solid [60 mg., m. p. 298° (decomp.)] was collected, washed with water, and shaken with ether and dilute sodium hydroxide solution until all was dissolved. The ether layer was separated, dried (K_2CO_3), and the ether removed, when a solid (50 mg., m. p. 188—191°) remained. When recrystallised from methanol–water (charcoal) this afforded the *base* (X) as colourless needles, m. p. 196—197° (Found: C, 83·4; H, 6·6; N, 9·9. $C_{19}H_{18}N_2$ requires C, 83·2; H, 6·6; N, 10·2%). The picrate, prepared in alcoholic solution, separated from acetone–water as orange-yellow felted needles, m. p. 173—174°.

This base (20 mg.) was heated with palladium black (20 mg.) (Willstätter and Waldschmidt-Leitz, *Ber.*, 1921, **54**, 123) for 30 minutes at 225°/12 mm., when the greater part of the organic material sublimed. The product was dissolved in hot methanol, the solution boiled with charcoal, filtered, concentrated, and water added; on cooling, colourless needles, m. p. 216—217° (corr.), separated (Base *A*).

o-*Tolylacetic Acid*.—A solution of *o*-toluoyl chloride (1·5 g.) (Davies and Perkin, *J.*, 1922, **121**, 2207) in dry ether (10 c.c.) was added gradually with stirring to one of diazomethane (1·5 g.) in ether (80 c.c.) at 5°. After the mixture had been kept overnight at room temperature, the ether was removed under reduced pressure (finally at 30°). A solution of the residual, oily diazoketone in dioxan (10 c.c.) was added during 15 minutes to a stirred suspension of silver oxide (0·4 g.) in a solution of sodium carbonate (0·8 g.) and sodium thiosulphate (0·5 g.) in water (30 c.c.) at 55—60°. The temperature was kept at 55—60° for a further 1 hour and finally raised to 95° for 1 hour. Charcoal was then added to the diluted solution which was filtered hot. The cooled filtrate was acidified (dilute nitric acid), extracted with chloroform, the extract dried (Na_2SO_4), the chloroform removed, and the residue crystallised from water (charcoal), giving the acid as colourless plates, m. p. 88° (0·75 g.) (Found: C, 72·5; H, 6·35. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·65%).

3-[β-(o-*Tolylacetamido*)*ethyl*]*indole* (XI).—An intimate mixture of the above acid (0·52 g.) and 3-(β-aminoethyl)indole (0·52 g.) (Majima and Hoshino, *Ber.*, 1925, **58**, 2042) was heated for 30 minutes at 180—190°. After cooling, the residue was dissolved in hot methanol, and the solution boiled with charcoal, filtered, and cooled in ice; water was added dropwise with stirring until the solution just became turbid, when the *amide* soon separated as colourless plates, m. p. 99° (0·58 g.) (Found: C, 78·15; H, 6·85. $C_{19}H_{20}ON_2$ requires C, 78·10; H, 6·85%).

2-(o-*Methylbenzyl*)-β-*carboline* (V) *and* 2-(o-*Methylbenzyl*)-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline*.—The above amide (0·42 g.) was refluxed in dry benzene (20 c.c.) with phosphoryl chloride (0·9 c.c.) for 1 hour (water-bath), the benzene removed under reduced pressure (water-bath), and the residue boiled with dilute acetic acid; the resulting extract was filtered hot, cooled in ice, and basified with ammonia. The pale yellow precipitate (0·35 g.) was separated, washed with water, and dried as rapidly as possible in a vacuum desiccator. No attempt was made to purify this 2-(o-methylbenzyl)-4 : 5-dihydro-β-carboline, the crude material being used in the following experiments: (*a*) The base (50 mg.) was heated with palladium black (25 mg.) for 30 minutes at 180—190°/12 mm.; the product, worked up as described for the previous dehydrogenation, gave 2-(o-*methylbenzyl*)-β-*carboline* (Base *B*) (25 mg.) as colourless felted needles, m. p. 216—217° (corr.) after recrystallisation first from methanol–water, then from benzene (Found: C, 84·1; H, 6·05; N, 9·65. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·9; N, 10·3%). No depression of m. p. was observed on admixture with Base *A*. For yobyrine, Mendlik and Wibaut gave m. p. 217° (corr.). The *picrate*, prepared in alcoholic solution, separated from acetone–water as bright yellow crystals, m. p. 240° (decomp.) (Found: C, 60·0; H, 3·85. $C_{19}H_{16}N_2,C_6H_3O_7N_3$ requires C, 59·9; H, 3·8%). For yobyrine picrate, Witkop gave m. p. 239° (decomp.). When a solution of base *B* in dry acetone containing methyl iodide was kept, the methiodide separated as very pale yellow plates, m. p. 296° (decomp.). For yobyrine methiodide, Witkop gave m. p. 295°. When base *B* (90 mg.) in xylene (6 c.c.) was refluxed with freshly prepared selenium dioxide (90 mg.) for 2 hours, the solution decanted from the selenium, the xylene removed under reduced pressure (water-bath), and the residue distilled at 2 mm., an oil was obtained, which rapidly solidified, the *product* separating from methanol (charcoal) as yellow leaflets, m. p. 185° (Found: C, 79·85; H, 5·1. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%). For yobyrone, Witkop gave m. p. 185°.

(*b*) A solution of the above dihydro base (0·3 g.) in absolute alcohol (15 c.c.) was refluxed on the water-bath while sodium (1·15 g.) was added during 15 minutes. After all the sodium had dissolved, the solution was diluted with water (15 c.c.) and the alcohol distilled off under reduced pressure (water-bath). The cooled solution was extracted with ether, the extract dried (K_2CO_3), the ether removed, the residue dissolved in methanol, and dry hydrogen chloride passed into the solution. On adding ether, a solid separated; this was collected, washed with ether [0·12 g., m. p. 260° (decomp.)] and treated with dilute sodium hydroxide solution; the product was extracted with ether, the extract dried (K_2CO_3) and the ether removed. The residue was recrystallised twice from methanol–water, giving colourless, rectangular tablets, m. p. 92—94° (Found: C, 77·75; H, 7·8. $C_{19}H_{20}N_2,H_2O$ requires C, 77·55; H, 7·5%). This is probably 2-(o-*methylbenzyl*)-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline*.

2-*Benzyl*-β-*carboline*.—2-Benzyl-2 : 3 : 4 : 5-tetrahydro-β-carboline was prepared by the method of Hahn and Hansel (*loc. cit.*) and from it we obtained a *picrate* separating from methanol–water as yellow needles, turning orange-coloured on drying on the water-bath, m. p. 215° (Found: C, 58·25; H, 4·4. $C_{18}H_{18}N_2,C_6H_3O_7N_3$ requires C, 58·65; H, 4·3%). The above authors gave m. p. 180° for the picrate. On heating with palladium black (20 mg.) for 30 minutes at 170—180° (12 mm.), this base (50 mg.) gave 2-*benzyl*-β-*carboline* as colourless leaflets, m. p. 177—178°, from methanol–water (30 mg.) (Found: C, 82·95; H, 5·55. $C_{18}H_{14}N_2$ requires C, 83·75; H, 5·45%). The solution of this base in alcohol–water or in dilute hydrochloric acid exhibited a blue-violet fluorescence. The *picrate*, prepared in alcoholic solution, separated from acetone–alcohol as bright yellow prisms, m. p. 235° (decomp.) (Found: C, 59·1; H, 3·5. $C_{18}H_{14}N_2,C_6H_3O_7N_3$ requires C, 59·15; H, 3·5%). The same base was also obtained by similarly dehydrogenating 2-benzyl-4 : 5-dihydro-β-carboline, prepared by the method of Hahn and Ludewig (*loc. cit.*).

ω-*Methoxy*-o-*toluic Acid*.—Ethyl ω-bromo-o-toluate (18 g.) (Davies and Perkin, *loc. cit.*) was added gradually, with shaking, to a solution of sodium (1·8 g.) in methanol (90 c.c.), cooled in ice. After the mixture had been refluxed for 2 hours, the precipitated sodium bromide was filtered off, the methanol removed (water-bath), and the residue cooled, diluted with water, and extracted with ether. Ether was removed from the dried (Na_2SO_4) extract, and the residue distilled. The distillate (9·7 g., b. p. 240—250°/760 mm.) was refluxed for 2 hours on the water-bath with a mixture of 95% alcohol (45 c.c.) and 40% sodium hydroxide solution (18 c.c.), the bulk of the alcohol distilled off (water-bath), and the residue diluted with water, cooled and acidified with concentrated hydrochloric acid. The *acid* (7·75 g., m. p. 92—93°) was collected, washed with water, dried, and recrystallised from benzene, giving colourless needles, m. p. 94° (Found: C, 65·15; H, 5·95. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%).

Homophthal-(β-3-*indolylethyl*)*imide*.—(i) A mixture of 3-(β-aminoethyl)indole (80 mg.) and homophthalic acid (90 mg.) (*Org. Synth.*, **22**, 61) was heated at 180° for 3 hours, and the residue recrystallised first from dilute acetic acid (charcoal) then from benzene, and finally from alcohol, giving the *compound* as very pale pinkish-yellow needles, m. p. 205°, softening at 198° (Found: C, 74·6; H, 5·3. $C_{19}H_{16}O_2N_2$ requires C, 75·0; H, 5·3%). (ii) Hot benzene solutions of 3-(β-aminoethyl)indole (0·19 g.) and o-carbomethoxyphenylacetic acid (0·3 g.) (Wegscheider and Glogau, *Sitzungsber. Akad. Wien*, 1903, **112**, 2B, 782) were mixed and, after cooling, ether was added. The precipitated salt (0·3 g., m. p. 158—160°) was collected, washed with benzene, and heated for 30 minutes at 185°. The product (0·2 g.) was as in (i).

Attempted Cyclisation of Homophthal-(β-3-*indolylethyl*)*imide*.—(i) The imide was recovered unchanged after refluxing in benzene solution with phosphoryl chloride. (ii) The imide (0·12 g.) was refluxed for 2 hours in toluene (2 c.c.) with phosphoryl chloride (0·3 c.c.). The solvent was removed under reduced pressure and the residue crystallised first from alcohol, and then from acetic acid, giving dark red crystals, m. p. 265°, of a *compound*, probably 3-chloro-2-(β-indolylethyl)-1-*iso*quinolone (XII) (Found: C, 70·1; H, 4·75. $C_{19}H_{15}ON_2Cl$ requires C, 70·7; H, 4·65%). Some unchanged imide was also recovered.

Condensation of 3-(β-*Aminoethyl*)*indole with Homophthalic Anhydride and Attempted Cyclisation of the Product*.—The base (1 g.) and anhydride (1 g.) (Dieckmann, *Ber.*, 1914, **47**, 1432) were refluxed together in dry benzene (15 c.c.) for 3 hours. Dilute sodium hydroxide was added, the benzene layer separated, and the aqueous layer extracted with ether. The aqueous layer was then acidified (concentrated hydrochloric acid) and the resulting gum was washed with water, dissolved in dilute ammonia, and the excess of ammonia removed by evaporation on the water-bath. The filtered solution was added to a solution of silver nitrate (0·8 g.) in water and the precipitated silver salt (1·45 g.) was collected, washed with water and dried in a vacuum desiccator. It was suspended in dry ether (20 c.c.) and refluxed for 12 hours with methyl iodide (5 c.c.). The ether was removed from the filtered solution and the residue refluxed for 1 hour in dry benzene with phosphoryl chloride (water-bath), the benzene distilled off (water-bath), and the residue warmed with water, then cooled and filtered. The filtrate was basified (sodium hydroxide) and the resulting precipitate collected and recrystallised twice from alcohol (charcoal), giving pale yellow needles of a *compound*, m. p. 299° (10 mg.) (Found: C, 78·2; H, 4·9. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%). This may be (IV); it is insoluble in dilute hydrochloric acid.

3-*Formyl*-2-*benzyl*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline*.—2-Benzyl-2 : 3 : 4 : 5-tetrahydro-β-carboline (0·5 g.) was heated with anhydrous formic acid (0·2 g.) for 4 hours at 185°. When cold, the mass was stirred with alcohol, and the resulting solid (0·45 g., m. p. 208—210°) recrystallised from alcohol, affording colourless crystals of 3-*formyl*-2-*benzyl*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline*, m. p. 211—212° (Found: C, 78·7; H, 6·4. $C_{19}H_{18}ON_2$ requires C, 78·5; H, 6·2%).

We thank the University of Durham for the award of an I.C.I. Fellowship to one of us (G. A. S.).

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[*Received, December* 31*st*, 1945.]