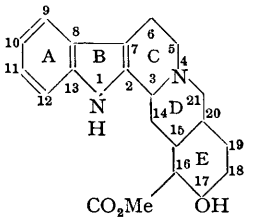
110. *The Constitution of Yohimbine. Part II.*

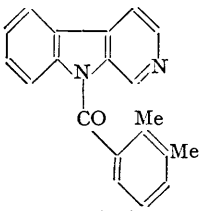
By G. R. Clemo and G. A. Swan.

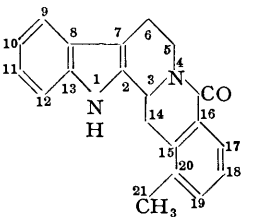
The structure (II) suggested by Witkop for ketoyobyrine is disproved by synthesis. A synthesis of ketoyobyrine is described; this compound probably has structure (V), the only slight doubt being with regard to the double bond at C_5–C_6 and the single bond at C_3–C_{14}. This is regarded as being strong evidence for the location of the carbomethoxy-group at C_{16} in the yohimbine molecule.

On dehydrogenation with selenium for 30 minutes at 300°, the alkaloid yohimbine gives rise to the basic compounds yobyrine and " tetrahydroyobyrine ", together with a smaller amount of ketoyobyrine, $C_{20}H_{16}ON_2$ (for references, see Part I, Clemo and Swan, *J.*, 1946, 617). The work described in Part I not only proved synthetically the constitution of yobyrine to be 2-(α-methylbenzyl)-β-carboline; but also demonstrated the possibility of formation of this compound from the ring-structure of yohimbine (probably I) by dehydrogenation, involving fission at the C_{21}–N_4 bond to enable ring C to aromatise. The synthesis of yobyrine (by a method almost identical with one of those mentioned above) has since been described by Julian, Karpel, Magnani, and Meyer (*J. Amer. Chem. Soc.*, 1948, **70**, 180), who have also synthesised " tetrahydroyobyrine ", which is formed by fission at the C_5–N_4 bond, enabling ring D to aromatise. The present communication deals with the structure of ketoyobyrine, which is of considerable importance, since it contains the carbonyl group derived from the carbomethoxy-group of the alkaloid; and hence the establishment of its structure can be taken as evidence for the location of the latter group.

Ketoyobyrine has been described as a bright yellow, crystalline solid, m. p. 330°, insoluble in dilute aqueous acids and alkalis. It is soluble in concentrated sulphuric acid, giving a red


(I.)


(II.)

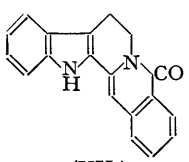

(III.)

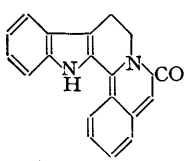
(IV.) As III, but double bond at C_3–C_{14}. (V.) As III, but double bond at C_5–C_6.
(VI.) As III, but double bonds at C_3–C_{14} and C_5–C_6.

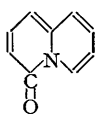
solution, but is reprecipitated on addition of water. It is slightly soluble in glacial acetic acid and in alcohol, giving yellow solutions, exhibiting a characteristic bluish-green fluorescence. By fission of ketoyobyrine with potassium hydroxide in amyl alcohol, Barger and Scholz (*Helv. Chim. Acta*, **1933**, **16**, 1343) obtained β-carboline and 2 : 3-dimethylbenzoic acid. As Mendlik and Wibaut (*Rec. Trav. chim.*, **1931**, **50**, 91) reported that dehydrogenation of diacetylyohimbine gave rise to yobyrine and " tetrahydroyobyrine ", but no ketoyobyrine, Barger and Scholz suggested that in the latter compound the carbonyl residue of the yohimbine carbomethoxy-group has become attached to N_1. Later, Witkop (*Annalen*, **1943**, **554**, 83) suggested structure (II) for ketoyobyrine. Clearly, these suggestions fail to explain the absence of basic properties in the compound; and, moreover, Raymond-Hamet (*Compt. rend.*, **1945**, **221**, 387) has pointed out the great difference in the ultra-violet absorption spectra of harman and ketoyobyrine. The condensation of β-carboline with 2 : 3-dimethylbenzoyl chloride, giving 1-(2 : 3-*dimethylbenzoyl*)-β-*carboline* (II), has now been carried out; the product was a colourless, crystalline solid, m. p. 151—153°, with the expected basic properties, and giving a blue fluorescence in acid solution.

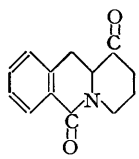
A possible mode of formation of ketoyobyrine might be as follows. During the selenium dehydrogenation, bond C_{21}–N_4 is known to break in some yohimbine molecules; and this is usually followed by aromatisation of rings C and E, the hydroxyl and carbomethoxy-substituents being lost, and hence the main product here is yobyrine. But if, after the C_{21}–N_4 bond has broken, free rotation about the C_{14}–C_{15} bond should bring the carbomethoxy-group into the vicinity of N_4 before aromatisation of ring C had occurred, then cyclisation might occur to give structure (III), in which the atoms are given the same numbers as in (I), *e.g.*, the CH_3 group of (III) is derived from C_{21} of (I); (III) might then lose two or four hydrogen atoms with the formation of (IV), (V), or (VI). Either structure (IV) or (V) would appear possible for ketoyobyrine, and would explain the absence of basic properties.

In Part I were described preliminary experiments towards the synthesis of such a ring system. Condensation of tryptamine with homophthalic anhydride, esterification, and

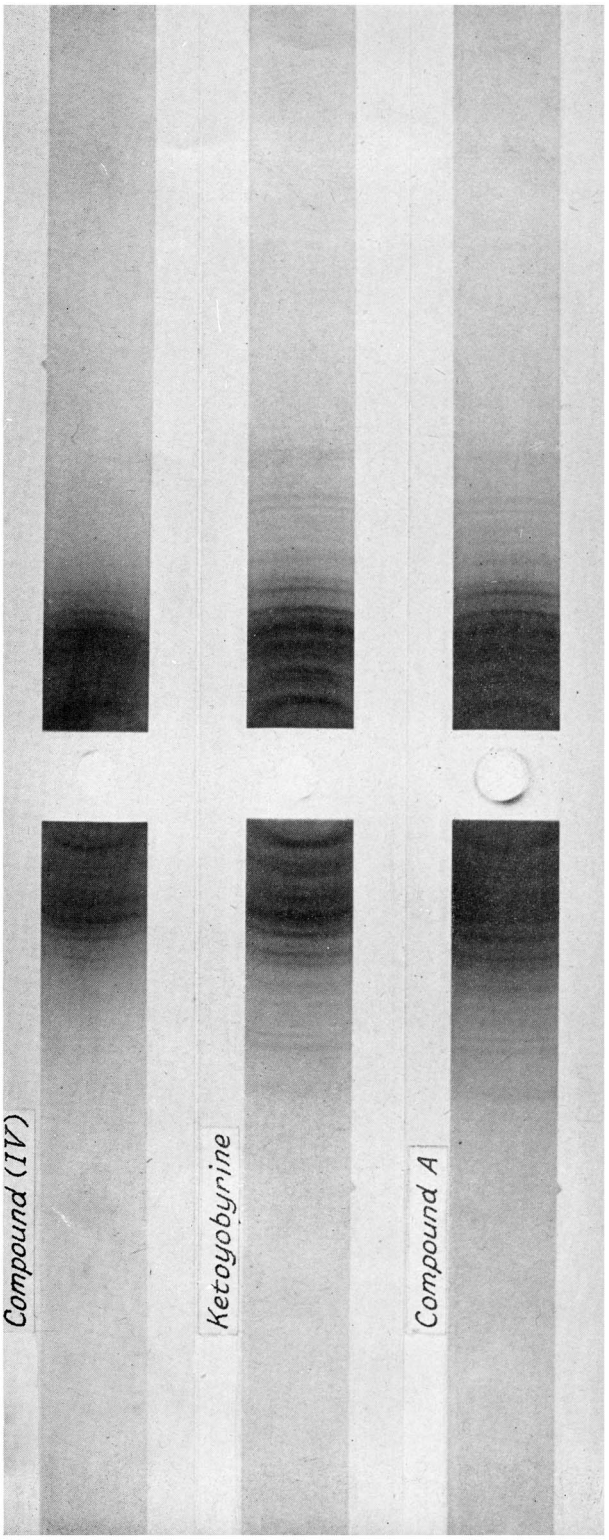

(VII.)


(VIII.)


(IX.)


(X.)

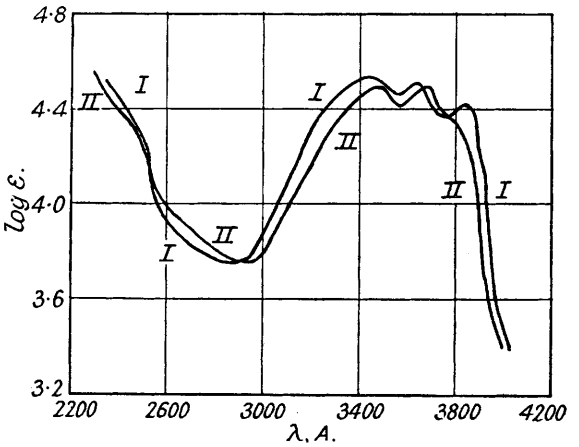
cyclisation of the product, led to formation of a trace of a pale yellow, crystalline compound, m. p. 299° (decomp.), which it was suggested might be 6-keto-7 : 8-benzo-1 : 2-(2′ : 3′-indolo)-3 : 4-dihydropyridocoline (VII). Recently, Schlittler and Allemann (*Helv. Chim. Acta*, **1948**, **31**, 128) have repeated this work and improved the yield obtained. In the experimental section of this paper are described conditions for still further improving the yield, and, moreover, the intermediate *methyl* N-(β-*indolylethyl*)*homophthalamate* was obtained as a crystalline solid (in contrast to the Swiss workers, who obtained only an oil). There was also the possibility that the condensation and cyclisation might have given rise to (VIII) instead of (VII) and, although this seemed unlikely in view of the pale yellow colour of the product (cf. oxyprotoberberine and oxy*iso*protoberberine; Haworth, Perkin, and Pink, *J.*, **1925**, **127**, 1709), further evidence on



[*To face p.* 489.

this point was sought. Attempts to carry out a quantitative catalytic hydrogenation were unsatisfactory, on account of the low solubility of the material in glacial acetic acid and alcohol; but the indication was that hydrogen uptake was very slow in the presence of platinum at room temperature and pressure. However, evidence in favour of structure (VII) was found in the fission with potassium hydroxide in amyl alcohol, which gave rise to *o*-toluic acid (in almost quantitative yield equivalent to the material decomposed) and a small amount of β-carboline.

The ultra-violet absorption spectra of (VII) and of ketoyobyrine in ethanol are shown in Curves I and II, respectively, and these bear a striking resemblance. But equally striking is the difference in the appearance of solution of these two compounds in the same solvent, the former being almost colourless, with a blue fluorescence, while the latter is yellow with a bluish-green fluorescence. (VII) is soluble in concentrated sulphuric acid, giving a yellow solution. However, it was found that when a solution of (VII) in xylene was boiled with Raney nickel and then allowed to cool, it deposited bright yellow crystals of a *compound* which appeared to be isomeric with (VII), but which differed from it in the appearance, colour, and optical properties of the crystals, in the appearance of the solution, which was yellow with a green fluorescence, and in giving a red solution in concentrated sulphuric acid.



Curve (I). *Compound (VII).*
Curve (II). *Compounds (IV), A, and ketoyobyrine.*

The synthesis of (IV) was then carried out. For this, 6-methylhomophthalic acid was required. This had previously been obtained by Mercer and Robertson (*J.*, 1936, 292) by condensation of *o*-toluoyl chloride with malonic ester, followed by reductive hydrolysis to give *o*-tolylpropionic acid, cyclisation of the chloride of which gave the methylindanone, which was converted into the homophthalic acid *via* the oximino-derivative. Repetition of this synthesis gave satisfactory yields except for the reductive hydrolysis, which was found to yield mainly *o*-toluic acid; and it was found preferable to prepare *o*-tolylpropionic acid from *o*-xylyl bromide, by condensation with malonic ester, followed by hydrolysis and decarboxylation. 6-Methylhomophthalic anhydride was condensed with tryptamine, and the product esterified with diazomethane giving *methyl* N-(β-*indolylethyl*)-6-*methylhomophthalamate*; this was cyclised with phosphoryl chloride, giving 6-*keto*-7 : 8-[1′ : 2′-(3′-*methylbenzo*)]-1 : 2-(2′ : 3′-*indolo*)-3 : 4-*dihydropyridocoline* (IV), a pale yellow crystalline solid, m. p. *ca.* 320° (decomp.), giving in alcoholic solution (2 mg./100 c.c.) an almost colourless solution with a blue fluorescence, and soluble in concentrated sulphuric acid to give a yellow solution, but whose ultra-violet absorption spectrum was indistinguishable from that of ketoyobyrine (Curve II). When (IV) was boiled in xylene solution with Raney nickel, it was converted into a bright yellow crystalline *compound A*, indistinguishable from ketoyobyrine in the crystalline state (under the microscope) or in solution (ultra-violet absorption spectrum, colour, and fluorescence) and in the colour of its solution in concentrated sulphuric acid. Mr. H. E. Blayden kindly arranged to photograph the *X*-ray diffraction patterns by the powder method in the Northern Coke Research Committee's Laboratory, Department of Physical Chemistry, King's College, Newcastle-upon-Tyne, and the results are shown on the accompanying Plate. The photographs from A and ketoyobyrine are indistinguishable; that of (IV) is very similar, but the outer lines are here absent, and some of

the others are of slightly different intensity. The samples were examined after the *X*-ray analysis and appeared to be unchanged by the treatment. The melting points of these materials appeared to be of little value for identification, as they varied with the rate of heating and were accompanied by decomposition and sublimation; however, the values determined for the synthetic and the degradative material were both *ca.* 322°, and admixture appeared not to cause depression.

From the above synthesis, the structure of (IV) appears well established. There remains to consider in what way A differs from this, and why the ultra-violet absorption spectra of these two compounds are identical. The reactions most likely to occur during the Raney nickel treatment are either (*a*) a dehydrogenation, in which case A would presumably have structure (VI), which would be $C_{20}H_{14}ON_2$, as compared with $C_{20}H_{16}ON_2$ previously reported for ketoyobyrine, or (*b*) an isomerisation such as that encountered in the conversion of strychnine and brucine into their *neo*-isomerides by Chakravarti and Robinson (*J.*, 1947, 78), in which case A would be $C_{20}H_{16}ON_2$ and might be represented by structure (V) 6-*keto*-7 : 8-[1′ : 2′-(3′-*methylbenzo*)]-1 : 2-(2′ : 3′-*indolo*)-9 : 10-*dihydropyridocoline*. The analytical figures for $C_{20}H_{14}ON_2$ and $C_{20}H_{16}ON_2$ scarcely differ sufficiently to enable decisive conclusions to be drawn; but if (*a*) is correct, then it should be possible to obtain A from (IV) by the action of oxidising agents. So far, no success has been achieved in this direction (*e.g.*, with iodine and potassium acetate in alcohol, with chromium trioxide in glacial acetic acid, or with platinum and oxygen in acetic acid).

As to the ultra-violet absorption spectra, it appears that the curves obtained really refer to the structure (IV), isomerisation of A to (IV) occurring very rapidly under the influence of ultra-violet light. Thus, a dilute alcoholic solution of A or of ketoyobyrine was stable for weeks in the dark; but when it was allowed to stand even in diffused daylight, the yellow colour and blue-green fluorescence disappeared in a day or so and a blue fluorescence developed, and evaporation of the solution led to the recovery of a pale yellow crystalline material, apparently identical with (IV) (*e.g.*, its solution in concentrated sulphuric acid was yellow). On the basis of (*a*) above, the light reaction must involve a hydrogenation of A at the expense of the solvent alcohol; but it was found that this change occurs also in glacial acetic acid, which is not reducing in properties. Attempts to carry out a quantitative catalytic hydrogenation of ketoyobyrine were unsuccessful on account of its low solubility in acetic acid and alcohol; hydrogenation with platinum under pressure led to extensive hydrogenation, as shown by the high solubility of the product in organic solvents.

Thus assumption (*b*) above is supported. It may seem surprising that A and ketoyobyrine (both obtained under dehydrogenating conditions) should have structure (V) rather than (VI); but it must be borne in mind that the ring system of 4 (or 6)-ketopyridocoline (IX) does not constitute an aromatic system, and very little is known about its chemistry, although Clemo, Morgan, and Raper (*J.*, 1936, 1025) have described a yellow crystalline compound, whose solutions exhibit an intense green fluorescence, formulated as 4-keto-1-carbethoxy-3-(2′-pyridyl)-pyridocoline. To settle this matter finally, it is intended to investigate the ozonolysis of ketoyobyrine and related substances, and to attempt the synthesis of model compounds, including those having the ring-structure of (IX). It is noteworthy that recent work by Goutarel and Janot and Prelog (*Experientia*, 1948, **4**, 24) and by Prelog (*Helv. Chim. Acta*, 1948, **31**, 588) suggests that the alkaloid sempervirine has structure (VII) with CH_2 in place of CO.

Meanwhile, this slight doubt does not invalidate the implication of this work to the structure of yohimbine itself—namely, that it confirms the location of the carbomethoxy-group at C_{16}, and hence (indirectly) structure (I) for the alkaloid, since there is much evidence that the carbomethoxy- and the hydroxyl group are attached to adjacent carbon atoms.

While the above work was in progress, preliminary experiments on other possible routes to the synthesis of compounds of similar ring structure to the above were begun. These are briefly recorded below. (1) Attempts to condense tryptamine with *o*-nitrophenylpyruvic acid or *o*-nitrobenzaldehyde were unsuccessful. (2) By carrying out a Claisen condensation between *o*-tolunitrile and ethyl oxalate, o-*cyanophenylpyruvic acid* was obtained; but attempts to condense this with tryptamine were unsuccessful. (3) Ethyl ω-bromo-*o*-toluate was condensed with ethyl malonate, and the product hydrolysed to o-*carboxybenzylmalonic acid*. This is a possible intermediate for the synthesis of (X), from the phenylhydrazone of which (III) might be obtained by the Fischer indole synthesis.

Further work attempting to clarify still further the chemistry of yohimbine and related alkaloids is in progress.

Experimental.

1-(2 : 3-*Dimethylbenzoyl*)-β-*carboline* (II).—*o*-3-Xylidine, purified through its acetyl derivative (Cocker, *J.*, 1946, 38), was converted into 2 : 3-dimethylbenzoyl chloride (Brunner, Hofer, and Stein, *Sitzungsber. Akad. Wiss. Wien*, 1934, IIB, **142**, 302).

A mixture of β-carboline (Harvey, Miller, and Robson, *J.*, 1941, 158) (50 mg.) and 2 : 3-dimethylbenzoyl chloride (160 mg.) was heated for 2½ hours at 180°. After cooling, water and dilute sodium hydroxide solution were added; the resulting oil solidified after being stirred with the addition of a drop or two of ether. The *carboline* (II) was collected, washed with water, and recrystallised twice from methanol–water (charcoal) and twice from benzene–light petroleum (b. p. 60—80°), affording long, thin, colourless prisms, m. p. 151—153° (60 mg.) (Found: C, 79·9; H, 5·45. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·35%). This was soluble in dilute hydrochloric acid, being reprecipitated by dilute sodium hydroxide solution.

N-(β-*Indolylethyl*)*homophthalamic Acid*.—A warm solution of tryptamine (1·15 g.) in pure, dry chloroform (25 c.c.) was added to one of homophthalic anhydride (1·15 g.) in chloroform (25 c.c.), and the mixture heated under reflux for 2 hours, during which the acid crystallised out in practically pure condition. After cooling, the product (2 g., m. p. 144°) was collected and washed with chloroform (Found: C, 70·4; H, 5·6. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·8; H, 5·6%). Methylation in the way described by Schlittler and Allemann (*loc. cit.*) afforded the *methyl* ester as an oil which rapidly set to a solid, m. p. 99—101°; from benzene–light petroleum (b. p. 60—80°) this separated as colourless needles, m. p. 106°, after drying at 80°/1 mm. (Found: C, 71·8; H, 6·25. $C_{20}H_{20}O_3N_2$ requires C, 71·45; H, 5·95%).

6-*Keto*-7 : 8-*benzo*-1 : 2-(2′ : 3′-*indolo*)-3 : 4-*dihydropyridocoline* (VII).—The above crystalline methyl ester (0·7 g.) was cyclised as described by Schlittler and Allemann (*loc. cit.*) except that the reaction was carried out in an atmosphere of pure, dry nitrogen. After removal of phosphoryl chloride, the residue was treated with water, the resulting red solid collected, washed with water, dissolved in 95% ethanol (250 c.c.), and the solution boiled with charcoal, filtered, concentrated, and allowed to cool; the *compound* (VII) (0·31 g., m. p. 299°) which separated, recrystallised from ethanol, formed pale yellow needles, m. p. 299° (Found: C, 79·8; H, 4·9. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%). Light absorption in ethanol: $\lambda_{max.}$ 3430, 3640 A., log ε 4·54, 4·52; $\lambda_{min.}$ 2890, 3560 A., log ε 3·75, 4·47.

6-*Keto*-7 : 8-*benzo*-1 : 2-(2′-3′-*indolo*)-9 : 10-*dihydropyridocoline*.—A solution of the above compound (32 mg.) in dry xylene (15 c.c.) was heated under reflux for 13 hours with a small amount of Raney nickel (washed first with absolute alcohol, then several times with xylene). The experiment was carried out in the absence of strong illumination. The hot solution was filtered, and on cooling, clusters of bright yellow needles separated. The *pyridocoline* (29 mg.) was filtered off, washed with benzene, and recrystallised from absolute alcohol, giving bright yellow crystals which were dried at 80°/1 mm.; m. p. *ca.* 295—310°, depending on rate of heating (Found: C, 79·9; H, 5·35. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%).

Fission of (VII). This compound (0·15 g.) was refluxed for 11 hours with amyl alcohol (3 c.c.) and potassium hydroxide (0·15 g.) (bath temp., 180—185°). After cooling, the mass was extracted with water (20 c.c.), some undecomposed material (50 mg., m. p. 297°, decomp.) being recovered by filtration. The solution was extracted with ether, and the extract washed several times with dilute sodium hydroxide solution, then with dilute hydrochloric acid (extract A), the remaining ethereal amyl-alcoholic solution being referred to as solution B. The combined alkaline solution and washings were acidified (hydrochloric acid), extracted with ether (aqueous solution = C), the extract dried (Na_2SO_4), and the ether removed, leaving a brownish solid (40 mg., m. p. 97—100°). This was boiled in benzene solution with charcoal, filtered, the benzene removed, and the residue recrystallised from light petroleum (b. p. 60—80°), giving colourless needles, m. p. 103—104° (Found: C, 71·0; H, 6·1. Calc. for $C_8H_8O_2$: C, 70·6; H, 5·9%); mixed m. p. with *o*-toluic acid 103—105°.

Extract A (above) was basified (sodium hydroxide solution), extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue recrystallised twice from benzene–light petroleum (b. p. 60—80°), affording a small amount of colourless crystals, m. p. 197—198° (sintering at 191°) (mixed with β-carboline, prepared by method of Harvey, Miller, and Robson, *loc. cit.*, m. p. 197—198°, sintering at 191°), soluble in dilute hydrochloric acid to give a colourless solution with a blue fluorescence.

Solution B (above) was evaporated to dryness (water-bath/reduced pressure), giving a further 10 mg. of undecomposed material.

Solution C (above) was neutralised with sodium hydrogen carbonate, and extracted with ether; but the extract left no residue on evaporation.

β-o-*Tolylpropionic Acid*.—Technical *o*-xylene was brominated as described by Atkinson and Thorpe (*J.*, 1907, **91**, 1695), and the once-distilled monobromo-compound (b. p. 215—218°) used for the following preparation. Ethyl malonate (9·1 g.) was added to a warm solution of sodium (1·3 g.) in absolute alcohol (30 c.c.), ω-bromo-*o*-xylene (10 g.) was added during 20 minutes, and the mixture refluxed for a further 100 minutes. The bulk of the alcohol was removed by distillation, the residue cooled, treated with water, extracted with ether, the extract dried (Na_2SO_4), the ether removed, and the residue distilled, the fraction of b. p. 165—180°/11 mm. (6·3 g.) being collected. This was heated in an open flask for 3 hours on the water-bath with a solution of potassium hydroxide (5·5 g.) in water (5·5 c.c.), the water lost by evaporation being replaced from time to time. After cooling, the solution was acidified (hydrochloric acid), extracted with ether, the extract dried ($CaCl_2$), the ether removed, and the residue heated for 30 minutes at 160°, and then distilled, giving β-*o*-tolylpropionic acid (3·1 g.), b. p. 160—170°/12 mm., m. p. 91—102°, which was then recrystallised from alcohol–water.

Methyl N-(β-*Indolylethyl*)-6-*methylhomophthalamate*.—A solution of tryptamine (0·34 g.) in warm chloroform (8·5 c.c.) was added to one of 6-methylhomophthalic anhydride (0·37 g.) in chloroform (7·5 c.c.). The mixture was heated under reflux for 5 hours, cooled in ice, and extracted with cold dilute sodium hydroxide solution. The yellow extract was extracted with ether, and acidified (hydrochloric acid) in the cold. The precipitated oil was taken up in chloroform, the extract dried (Na_2SO_4), the solvent removed, and the resulting gum left overnight in a vacuum desiccator. It was then dissolved

in a little methanol, and the solution cooled in ice and treated with excess of an ethereal solution of diazomethane. After 30 minutes, the solution was evaporated to dryness (water-bath), and the residue kept in a vacuum desiccator. The resulting gum, on being stirred with a little ether, solidified. The product (0·5 g., m. p. 127—130°) was collected, washed with a little ether, dried in a vacuum desiccator, and the bulk used in the following cyclisation. A portion was recrystallised three times from benzene containing a little light petroleum (b. p. 60—80°) and afforded the *methyl* ester as large tablets, m. p. 139—140° (Found: C, 71·6; H, 6·05. $C_{21}H_{22}O_3N_2$ requires C, 72·0; H, 6·3%).

6-*Keto*-7 : 8-[1′ : 2′-(3′-*methylbenzo*)]-1 : 2-(2′ : 3′-*indolo*)-3 : 4-*dihydropyridocoline* (IV).—The above ester (0·44 g.) was refluxed with phosphoryl chloride (7 c.c.) for 50 minutes in an atmosphere of nitrogen, and the *product* (0·16 g.) isolated as in the preparation of (VII). It separated from alcohol as pale yellow plates or needles, m. p. *ca.* 320° (decomp.), depending on rate of heating (Found: C, 79·15; H, 5·55; C, 79·40; H, 4·95. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·3%). Light absorption in ethanol: $\lambda_{max.}$ 3470, 3670, 3850 A., log ε 4·5, 4·5, 4·42; $\lambda_{min.}$ 2920, 3570, 3770 A., log ε 3·75, 4·42, 4·36.

6-*Keto*-7 : 8-[1′ : 2′-(3′-*methylbenzo*)]-1 : 2-(2′ : 3′-*indolo*)-9 : 10-*dihydropyridocoline* (V).—A solution of (IV) (30 mg.) in xylene (20 c.c.) was heated under reflux for 11 hours with Raney nickel. On cooling, the filtered solution deposited clusters of bright yellow needles (24 mg.). Recrystallisation of the *product* from absolute alcohol (charcoal) afforded bright yellow prisms, m. p. *ca.* 322° (decomp.), depending on rate of heating (Found: C, 78·8; H, 5·4. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·3%).

o-*Cyanophenylpyruvic Acid.*—Potassium *tert.*-butoxide, from potassium (1 g.) and dry *tert.*-butanol (30 c.c.), was heated for 15 minutes at 150°/15 mm., and then cooled. Dry benzene (20 c.c.), ethyl oxalate (1·7 c.c.), and *o*-tolunitrile (1·5 c.c.) were added, the mixture heated for 2 hours on the water-bath, cooled, and water then added. The dark-red aqueous layer was separated, the benzene layer extracted with dilute sodium hydroxide solution, and the combined alkaline solutions extracted with ether, and acidified (hydrochloric acid) with cooling. The product was extracted with chloroform, the extract dried (Na_2SO_4), the solvent removed, the residue stirred with a little benzene, and the resulting solid collected, washed with benzene and dried, giving the *acid*, 0·45 g., m. p. 160° (decomp.). A solution of this in ethyl acetate was boiled with charcoal, filtered, and diluted with an equal volume of hot benzene. On cooling, clusters of pale yellow needles, m. p. 160° (decomp.), separated (Found: C, 63·7; H, 4·0. $C_{10}H_7O_3N$ requires C, 63·5; H, 3·7%).

Attempted Condensation of the Above Acid with Tryptamine.—Attempts to condense the pyruvic acid with tryptamine hydrochloride in aqueous or aqueous–alcoholic solutions led to recovery of tryptamine as the only basic product. When a solution of the acid (60 mg.) in alcohol (2 c.c.) was heated with one of tryptamine hydrochloride (70 mg.) in alcohol (3 c.c.) for 2 days on the water-bath, the bulk of the alcohol distilled off, dilute sodium hydroxide solution added to the residue, the mixture extracted with ether, and the extract kept overnight with a little dilute hydrochloric acid, a pale yellow solid separated. This was collected, washed with ether, and shaken with dilute sodium hydroxide solution and ether; the ethereal layer was dried (K_2CO_3), the ether removed, and the residue recrystallised from benzene–light petroleum (b. p. 60—80°). A very small amount of pale yellow crystals, m. p. 240—245°, was obtained. They were basic, and when added to concentrated sulphuric acid containing a trace of sodium nitrite, they slowly gave an olive-green colour.

Ethyl o-*Carbethoxybenzylmalonate.*—The solution obtained by adding ethyl malonate (7·2 c.c.) to a warm one of sodium (1·1 g.) in absolute alcohol (50 c.c.) was added gradually with shaking to a hot solution of ethyl ω-bromo-*o*-toluate (Davies and Perkin, *J.*, 1922, **121**, 2207) (11·8 g.) in alcohol (10 c.c.). After 30 minutes' heating on the water-bath, the bulk of the alcohol was distilled off, the residue treated with water (solution was alkaline), extracted with ether, the extract dried (Na_2SO_4), the ether removed, and the residue distilled, the fraction, b. p. 165—168°/1 mm. (7·35 g.), of the *ethyl* ester being collected (Found: C, 63·2; H, 6·7. $C_{17}H_{22}O_6$ requires C, 63·3; H, 6·8%).

o-*Carboxybenzylmalonic Acid.*—A solution of the above ester (0·48 g.) in 95% alcohol (1·8 c.c.) was heated under reflux for 2 hours on the water-bath with 40% aqueous potassium hydroxide (1·8 c.c.). After distilling off the bulk of the alcohol, the residue was dissolved in water, acidified (hydrochloric acid), extracted with ether, the extract dried (Na_2SO_4), the ether removed, and the residue rubbed with a little benzene, whereupon it crystallised. The solid (0·19 g.) was collected, dissolved in ethyl acetate, the solution boiled with charcoal, filtered, concentrated, and diluted with hot benzene. On cooling, the *acid* separated as colourless needles, m. p. *ca.* 180—190° (decomp.), depending on rate of heating (Found: C, 55·85; H, 4·4. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%).

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

[*Received, May 29th,* 1948.]