Synthetical Experiments related to the Indole Alkaloids.

By K. T. Potts and Sir Robert Robinson.

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Homophthalaldehyde has been isolated and characterised. It condenses with a tryptamine salt to give (indolylethyl)*iso*quinolinium salts which, following an indication by Julian and Magnani, are reduced by lithium aluminium hydride, with spontaneous cyclisation, to bases possessing the ring-system of yohimbine.

By using two better established methods a dimethoxy compound (IX) containing the yohimbine ring-system (ring E aromatic) has been synthesised with a view to the eventual study of possible opening of ring E.

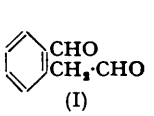
Some incidental experiments with furan derivatives are mentioned. The opening of the furan ring in various indole derivatives never led to the isolation of pure products.

In continuation of experiments on the condensation of indole derivatives with dicarbonyl compounds (cf. Robinson and Saxton, *J.*, 1953, 2596) we proposed the use of homophthalaldehyde which, combined with tryptamine, presented a number of interesting possibilities.

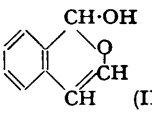
The preparation of homophthalaldehyde (Blount and Robinson, *J.*, 1933, 555) has been re-investigated since the aldehyde had never been isolated, or characterised by derivatives other than *iso*benzopyrylium ferrichloride. The dialdehyde was obtained as a colourless oil which polymerised on storage but could be regenerated by distillation.

Even a freshly distilled specimen was a mixture of the forms (I) and (II) and showed infrared bands as follows: 2·94 (associated OH), 3·52 (CH_2), 5·81 (aliphatic CHO), 5·92 (aromatic CHO), 6·24 (conjugated C:C), 8·32—8·33 μ (C:C·O·C), and 13·2 μ (*o*-disubstituted benzene).

An attempt to make the 2 : 4-dinitrophenylhydrazone in the usual manner in alcoholic sulphuric acid gave 2-(2 : 4-dinitroanilino)*iso*quinolinium hydrogen sulphate (III) instead of the expected bis-2 : 4-dinitrophenylhydrazone.



(I)



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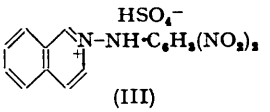


(III)

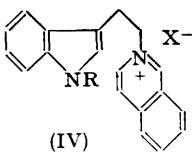
The generality of this type of reaction was established by condensation of homophthalaldehyde with methylamine, ethylenediamine, aniline, and 2-phenylethylamine to the respective *N*-substituted *iso*quinolinium salts.

With tryptamine a 2-(2-3'-indolylethyl)*iso*quinolinium salt (IV; R = H) was produced,

and 1-methyltryptamine gave the analogue (IV; R = Me). These salts were characterised by ultraviolet absorption spectra and by an infrared band at 6·2 μ (C:N), as well as by indole colour reactions. An alternative synthesis of (IV; R = H) was effected by condensation of 2-3′-indolylethyl bromide with *iso*quinoline in benzene (cf. Haworth and Perkin, *J.*, 1925, 1434).

In view of the reactivity of the carbinol-amine ("*iso*quinolinanol") derived from 2-methyl*iso*quinolinium salts (cf. Robinson and Robinson, *J.*, 1914, **105**, 1456) it was expected that a salt (IV; R = H) would yield the base (V) in dissociating solvents and under the influence of bases. We were at first under the impression that this cyclisation could be brought about, but the outcome of later work was ambiguous and the matter will be further investigated.

As the structure (V) does not contain the yohimbine skeleton, we have in the first place examined the possibilities of a device suggested by the work of Julian and Magnani (*J. Amer. Chem. Soc.*, 1949, **71**, 3207). Indeed these authors were led by their results to contemplate the feasibility of the process described herein and their priority in this respect is fully acknowledged. Our reading of this part of their memoir was much belated.



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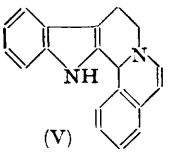

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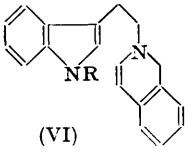

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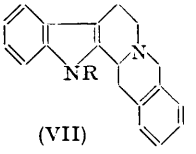
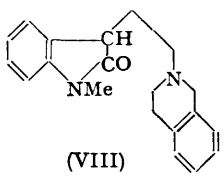
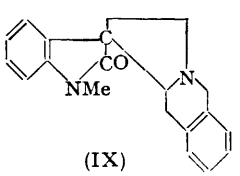


(VII)

The actual work described by Julian and Magnani concerned the reduction of an oxindole derivative by means of lithium aluminium hydride with eventual formation of the base (VII; R = Me) through the postulated intermediate (VI; R = Me). The transformation of (VI) into (VII) was considered to be spontaneous, but this is hardly likely and the reaction occurred in a solution that contained active anions and cations. Belleau recently (*Chem. and Ind.*, 1955, 229; cf. Potts, D.Phil thesis, Oxford, 1954) has made it very probable that Julian and Magnani's process was much more complex than was thought and that it proceeds in the stages shown. Dehydrogenation must also occur in the preparation of (IX) from dihydro-*N*-methylfuranoindole and tetrahydro*iso*quinoline hydrobromide, which could be generators of (VIII) (Julian, Magnani, Pikl, and Karpel, *J. Amer. Chem. Soc.*, 1948, **70**, 174). Presumably the conversion of (VIII) into (IX) proceeds



(VIII)



(IX)

(VII; R = Me)

by way of a dihydro*iso*quinoline and then by a step analogous to that taken by (VI) in its change to (VII). Thus the formation of (VII; R = Me) from (IX) involves an intramolecular rearrangement and does not necessarily go *via* (VI; R = Me), so that Julian and Magnani's prognostication that (VI) should be transformed into (VII) was based on an erroneous interpretation of their experiments. It was nevertheless perfectly correct. Belleau (*loc. cit.*) has also deduced that (VI) should yield (VII) and mentions a preliminary chromatographic observation in support.

Cationoid reactivity of $C{=}C^*{\cdot}NR_2$ at the atom C* is readily explicable if acids are available in the system because of the conversion into $CH{\cdot}C^*{=}NR_2^+$. However, the same effect can theoretically be achieved by complexes which can accept electrons, that is, the so-called Lewis acids could have the same effect as a proton source. The conditions under which this type of reaction occurs and the limits of its applicability require further investigation.

In the present case the reduction of the chloride (IV; R = H, X = Cl) with lithium aluminium hydride gave the base (VII; R = H), probably by way of (VI) and the related

iminium cation as explained above. The reaction also succeeded with the analogue (IV; R = Me).

The infrared and ultraviolet absorption spectra of the product (VII; R = H) were identical with those of an authentic specimen kindly provided by Professor G. R. Clemo, though the m. p. of our product was always several degrees lower than his reported m. p.; the spectra of the methyl analogue were also those characteristic of the ring system. No colour was obtained with Ehrlich's reagent. Schmid and Karrer's work (*Helv. Chim. Acta*, 1949, **32**, 960) suggests that the reduction of the *iso*quinolinium salts (IV) to dihydro-*iso*quinoline bases (VI) can be regarded as a normal event.

The tryptamine used in this and other researches in this laboratory has been synthesised for several years by what may be called the " gramine methiodide " method. In view of other reports of the synthesis of tryptamine which have appeared recently (Thesing and Schülde, *Ber.*, 1952, **85**, 324; Henbest, Jones, and Smith, *J.*, 1953, 3796) our method is reported only in so far as it differs from the others (see p. 2679). Our method of preparation of gramine methiodide gave an analytically pure specimen (cf. Geismann and Armen, *J. Amer. Chem. Soc.*, 1952, **74**, 3916) and the correlation of its properties with those reported in the literature is the subject of another communication (K. T. P.).

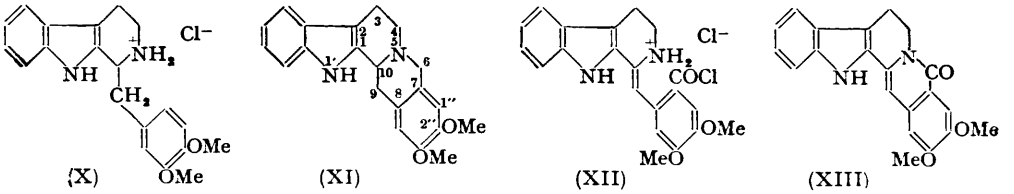
An improvement of the *iso*quinoline method of synthesis of the yohimbine ring system would be one that could employ tryptamine and a substituted *iso*quinoline instead of an indolylethyl bromide and an *iso*quinoline on the one hand, or a substituted homophthalaldehyde and tryptamine on the other.

Such a process is in course of investigation but pending the outcome of this study we have used two well-known methods for the synthesis of 3 : 4 : 6 : 9-tetrahydro-2'' : 3''-dimethoxy-7 : 8-benzoindolo(2' : 3'-1 : 2)pyridocoline (XI). The base is required as a model in attempts to imitate in the laboratory the Woodward fission of an aromatic ring E which is the characteristic step in his scheme for the biogenesis of strychnine (*Nature*, 1948, **162**, 155).

The first method was an application of that of Hahn and his collaborators (*Annalen*, 1935, **520**, 123; *Ber.*, 1938, **71**, 2193). The description given by these authors was not detailed and a supplementary account is now submitted. Tryptamine hydrochloride was condensed with 3 : 4-dimethoxyphenylpyruvic acid in aqueous solution by heating them on the boiling water-bath for several days and 1-(3 : 4-dimethoxybenzyl)-1 : 1 : 3 : 4-tetrahydro-β-carboline hydrochloride (X) was obtained directly. Ring-closure to the pentacyclic base (XI) was effected in excellent yield by refluxing with aqueous formaldehyde (cf. Swan, *J.*, 1950, 1534).

The second method is similar to that used by Späth and Lederer (*Ber.*, 1930, **63**, 120, 2102) for the synthesis of harmaline by cyclisation of the acetyl derivatives of 6-methoxytryptamine. This Bischler–Napieralski type of reaction has been much used in the indole series (Clemo and Swan, *J.*, 1946, 617; 1949, 687; Julian, Karpel, Magnani, and Meyer, *J. Amer. Chem. Soc.*, 1948, **70**, 180, 2834; Schlittler and Allemann, *Helv. Chim. Acta*, 1948, **31**, 128). 4 : 5-Dimethoxyhomophthalic anhydride was obtained in nearly quantitative yield from the corresponding acid (Perkin and Robinson, *J.*, 1907, **91**, 1081) and acetyl chloride; a poor yield was obtained when acetic anhydride was used (cf. Robinson and Young, *J.*, 1935, 1414). Tryptamine was condensed with 4 : 5-dimethoxyhomophthalic acid to give *N*-(2-3'-indolylethyl)-4 : 5-dimethoxyhomophthalimide which, after hydrolysis by alkali, gave 2-carboxy-4 : 5-dimethoxyphenyl-*N*-(2-3'-indolylethyl)acetamide (cf. Scholz, *Helv. Chim. Acta*, 1935, **18**, 923); this acid was obtained directly by the condensation of tryptamine and 4 : 5-dimethoxyhomophthalic anhydride. Esterification of the acid with diazomethane gave the methyl ester in excellent yield and, when this ester was heated under reflux with phosphoryl chloride, alone or in toluene, a compound which appears to be 1-(2-chlorocarbonyl-4 : 5-dimethoxybenzylidene)-1 : 2 : 3 : 4-tetrahydro-β-carboline hydrochloride (XII) was obtained. The same substance was formed when 2-carboxy-*N*-(2-3'-indolylethyl)-4 : 5-dimethoxyphenylacetamide was treated with phosphoryl chloride. It separated from methanol as orange needles and had the composition, $C_{21}H_{20}N_2O_3Cl_2$; ionic chlorine was found to be present and the absence of a free α-position in the indole nucleus was shown by its failure to give a colour with Ehrlich's reagent or with vanillin

and hydrochloric acid. Its solutions in organic solvents had a greenish fluorescence and its ultraviolet absorption was consistent with extensive conjugation in the molecule (max. at 4300 Å). The infrared spectrum showed bands at 3·03 (>NH), 6·15 (C:C), 6·23 (benzene ring), and 6·25 μ (conjugated ·COCl). Treatment of this salt (XII) with sodium hydroxide



(X) (XI) (XII) (XIII)

solution gave the cyclised lactam (XIII). The spectrum of this was nearly identical with that of 3 : 4-dihydro-6-oxo-7 : 8-benzoindolo(2′ : 3′-1 : 2)pyridocoline prepared by Clemo and Swan (*loc. cit.*). An infrared band at 6·3 μ can be attributed to the cyclic amide group. This appears to be one of the few instances in which the intermediate product in such a cyclisation has been isolated. The product soon crystallised from the reaction mixture and it is probable that this separation prevented the reaction from proceeding to completion. It is conceivable that the red, crystalline material obtained by Clemo and Swan (*loc. cit.*) on treatment of *N*-(2-3′-indolylethyl)homophthalimide with phosphoryl chloride in toluene may have a similar structure.

On reduction with lithium aluminium hydride in tetrahydrofuran solution (cf. Ehrlich, *J. Amer. Chem. Soc.*, 1948, **70**, 2286; Clemo *et al.*, *Nature*, 1948, **162**, 296) the lactam (XIII) gave an excellent yield of the dihydrobenzoindolopyridocoline (XI with a 9 : 10-double bond). The ultraviolet absorption spectrum of this compound showed a small change to longer wavelength after the material had been in solution for several hours, probably owing to migration of the 9 : 10-double bond. Hydrogenation in the presence of Adams catalyst in acetic acid at room temperature and pressure gave the tetrahydro-compound (XI), identical with the specimen prepared by the first method.

The use to be made of the base (XI) depends on the outcome of experiments with simpler substances and, of these, 2 : 3-dihydroxynaphthalene, 6 : 7-dihydroxytetralin, and 1 : 2 : 3 : 4-tetrahydro-6 : 7-dihydroxy*iso*quinoline, and their methyl ethers are the preferred models.

The opportunity is now taken to describe some experiments with furan derivatives, the ring-fision of which might produce reactive groupings that could facilitate syntheses in the indole group. In general this approach has been disappointing, especially with pendent furyl residues in indole derivatives. The desired substances can naturally be synthesised but are either unchanged by acid reagents or, if reactive, are converted into intractable materials. The Experimental section should be consulted for details but attention may be drawn to the fact that, although the product of the bromination of furfuraldehyde diacetate in methanol, namely, 2 : 5-dimethoxy-2 : 5-dihydrofurfuraldehyde diacetate, has been obtained as a crystalline solid, about 25% of the product remained as an oil and this may contain stereoisomerides. No smooth ring-fission of any one of the 2-furyl derivatives described could be realised.

Experimental

Ultraviolet absorption spectra are for MeOH solutions.

Homophthalaldehyde (I ⇌ II).—*trans*-Indane-1 : 2-diol (4·5 g.) (Porter and Suter, *J. Amer. Chem. Soc.*, 1935, **57**, 2025) in dry benzene (100 c.c.) was gradually treated with lead tetra-acetate (13·4 g.) during 5 min., the solution being kept just boiling and occasionally shaken. After boiling for a few minutes the mixture was cooled and filtered, and the clear solution concentrated to a small volume under reduced pressure on the steam-bath. Ether (*ca.* 150 c.c.) was added and the solution shaken with saturated sodium hydrogen carbonate solution, washed with water, and dried (Na_2SO_4). The *aldehyde* was obtained as a mobile oil with an aromatic, benzaldehyde-like odour (2·7 g., 60%), b. p. 93°/0·4 mm., n_D^{18} 1·5680 (Found : C, 72·9; H, 5·6%; *M*, 196. $C_9H_8O_2$ requires C, 72·9; H, 5·4%; *M*, 148). Light absorption : $\lambda_{max.}$ 2600 (log ε 3·03), $\lambda_{inflex.}$ 2875 (log ε 2·22), $\lambda_{min.}$ 2300 Å (log ε 2·38). The aldehyde reduced an ammoniacal

silver solution and gave a positive Schiff reaction after a few minutes. When it was heated on the steam-bath with aqueous ammonia, *iso*quinoline was quickly produced [picrate (from water), m. p. and mixed m. p. 225°].

The aldehyde is oxidised to phthalic acid by acid permanganate on the steam-bath.

A solution of potassium borohydride (1·1 g.) in water (20 c.c.) was added, slowly and with shaking, to one of homophthalaldehyde (2·8 g.) in 75% ethanol (15 c.c.). The solution immediately became orange-coloured, and straw-yellow on addition of further quantities of the reagent. After 30 minutes' refluxing, excess of the hydride was decomposed by dilute sulphuric acid. The solution was continuously extracted with ether for 8 hr. and, after drying (Na_2SO_4) and evaporation of the ether extract, 2-2′-hydroxyethylbenzyl alcohol was obtained as a colourless oil, b. p. 130°/0·5 mm. (Anderson and Holliman, *J.*, 1950, 1037, report b. p. 194—196°/15 mm.). The diphenylurethane, white needles from benzene, had m. p. 133—134° (*idem*, *loc. cit.*, give m. p. 133—133·5°).

With alcoholic 2 : 4-dinitrophenylhydrazine containing a small amount of sulphuric acid the aldehyde gave a light orange, crystalline precipitate which, recrystallised from ethanol (charcoal), afforded 2-(2 : 4-*dinitroanilino*)iso*quinolinium hydrogen sulphate* (III) as pale cream needles, m. p. 235° (Found : C, 44·2, 44·2; H, 3·2, 3·1; N, 13·7, 13·7. $C_{15}H_{12}O_8N_4S$ requires C, 44·1; H, 3·0; N, 13·7%). Light absorption : $\lambda_{max.}$ 2300, 3050, 3250 (log ε 4·59, 4·14, 41·5); $\lambda_{min.}$ 2800, 3150 Å (log ε 4·96, 4·12).

3-2′-*Dimethylaminoethylindole Methiodide* (*Gramine Methiodide*).—A solution of gramine (130 g.; Kuhn and Stein, *Ber.*, 1937, **70**, 567) in absolute alcohol (1 l.) was cooled to 0° and methyl iodide (104 c.c.) added during an hour with stirring at about 0°. Dry ether was added until a slight cloudiness appeared and the mixture then kept overnight in the refrigerator. The crystalline *methiodide* (223 g., 94%) which had separated was collected and dried in a vacuum-desiccator. It had m. p. 162—163° (Found : C, 45·9, 45·6; H, 5·7, 5·4; N, 9·3, 8·5. $C_{12}H_{17}N_2I$ requires C, 45·6; H, 5·4; N, 8·9%). Light absorption : $\lambda_{max.}$ 2700, 2800 (log ε 3·61, 3·61), $\lambda_{min.}$ 2450, 2750 Å (log ε 3·25, 3·59).

3-*Indolylacetonitrile*.—A solution of recrystallised sodium cyanide (100 g.) in water (2 l.) was heated to incipient boiling and gramine methiodide (220 g.) added as quickly as possible. The mixture was heated on a vigorously boiling water-bath for 25 min., with stirring. After cooling, the oil which had separated was isolated by means of chloroform. During this operation some 3-indolylacetamide, m. p. 149—150° (Baker and Happold, *Biochem. J.*, 1940, **34**, 657, record m. p. 150—151°) separated and was removed. The pale yellow, viscous oil was distilled as rapidly as possible using a short-path still and 3-indolylacetonitrile (67·4 g., 70%) was obtained as a nearly colourless, viscous oil, b. p. 159—160°/0·2 mm. Majima and Hoshino (*Ber.*, 1925, **58**, 2042) record b. p. 160°/0·2 mm. The nitrile crystallised in an ice–salt mixture but was always partly liquid at room temperature (Henbest, Jones, and Smith, *J.*, 1953, 3796, record m. p. 36—36·5°). The picrate separated from alcohol as orange needles, m. p. 128° (Majima and Hoshino, *loc. cit.*, give m. p. 127—128°).

3-*Indolylacetic Acid*.—3-Indolylacetamide (2 g.) was hydrolysed with an excess of boiling 8% sodium hydroxide solution (2—3 hr.). The acid crystallised from water as almost colourless plates, m. p. 165°, alone or mixed with an authentic specimen (Found : C, 68·2; H, 5·1. Calc. for $C_{10}H_9O_2N$: C, 68·6; H, 5·2%). The picrate was obtained as clusters of brick-red needles, m. p. 178°. Majima and Hoshino, *loc. cit.*, record m. p. 164·5—165° for the acid and 178° for the picrate.

Condensation of Tryptamine with Homophthalaldehyde.—Solutions of tryptamine (4·8 g.) in acetic acid (30 c.c.) and of homophthalaldehyde (4·4 g.) in acetic acid (10 c.c.) were mixed and then heated on the steam-bath for 4 hr., the orange yellow colour gradually deepening. The solvent was removed under reduced pressure on the steam-bath, and portions of the oily residual 2-(2-3′-indolylethyl)*iso*quinoline treated with a slight excess of the appropriate acid affording the following salts (IV; R = H) : *picrate* (from methanol; charcoal), bronze plates, m. p. 208° (Found : C, 59·7; H, 4·0; N, 14·1. $C_{25}H_{19}O_7N_5$ requires C, 59·9; H, 3·8; N, 14·0%); *perchlorate* (from methanol; charcoal), lemon-coloured blades, m. p. 223° (Found : C, 61·5; H, 4·3; N, 7·5; Cl, 9·5. $C_{19}H_{17}O_4N_2Cl$ requires C, 61·2; H, 4·6; N, 7·5; Cl, 9·5%); *iodide*, canary-yellow needles (from methanol; charcoal), m. p. 245° (Found : C, 56·6; H, 4·3; N, 6·9; I, 31·6. $C_{19}H_{17}N_2I$ requires C, 57·0; H, 4·3; N, 7·0; I, 31·7%) [light absorption : $\lambda_{max.}$ 2250, 2800, 3400 (log ε 4·62, 3·98, 3·75), $\lambda_{min.}$ 2500, 3100 Å (log ε 3·72, 3·51)]; *chloride* (from wet acetone; charcoal), yellow needles, m. p. 128° (Found : C, 70·2, 69·9; H, 5·9, 6·3; N, 8·4. $C_{19}H_{17}N_2Cl,H_2O$ requires C, 69·8; H, 5·9; N, 8·6%).

In a run in which tryptamine (1·3 g.) in acetic acid (10 c.c.) and homophthalaldehyde (1·3 g.)

in acetic acid (10 c.c.) were condensed together on the steam-bath for 4 hr. and the product isolated as the chloride, the yield was 2·2 g. (88%), m. p. 122°, raised to 128° on crystallisation.

Condensation of 1-*Methyltryptamine with Homophthalaldehyde.*—A mixture of 1-methyltryptamine (1·7 g.) (prepared by the method of Potts and Saxton, *J.*, 1954, 2641) and homophthalaldehyde (1·5 g.) in acetic acid (20 c.c.) was heated on the steam-bath for 1 hr. The condensation product was again converted into a series of salts of (IV; R = Me), all crystallising from methanol (charcoal): 2-(2-1′-*Methyl*-3′-*indolylethyl*iso*quinolinium iodide*, golden needles, m. p. 229° (Found: C, 58·1; H, 4·7; N, 6·4. $C_{20}H_{19}N_2I$ requires C, 58·0; H, 4·6; N, 6·8%); *picrate*, pale yellow nodules, m. p. 234° (Found: C, 60·8; H, 4·4; N, 14·0. $C_{26}H_{21}O_7N_5$ requires C, 60·6; H, 4·1; N, 13·6%); *perchlorate*, lemon-yellow plates, m. p. 191° (Found: C, 62·0; H, 5·1; N, 7·6. $C_{20}H_{19}O_4N_2Cl$ requires C, 62·1; H, 5·0; N, 7·2%); *chloride*, yellow, hygroscopic needles, m. p. 192° (Found: C, 67·4; H, 7·0. $C_{20}H_{19}N_2Cl,2{\cdot}5CH_3{\cdot}OH$ requires C, 67·1; H, 7·2%).

Condensation of 2-3′-*Indolylethyl Bromide and* iso*Quinoline.*—A mixture of 2-3′-indolylethyl bromide (0·5 g.; Hoshino and Shimodaira, *Annalen*, 1935, **520**, 25), *iso*quinoline (0·3 g.), and dry benzene (9 c.c.) was kept for 24 hr. and then evaporated under reduced pressure on the steam-bath. A concentrated solution of potassium iodide was added to the gummy residue, and the supernatant liquid decanted from the oil which separated. When rubbed with acetone, the product crystallised as yellow needles, m. p. 244°. Recrystallisation from methanol (charcoal) raised the m. p. to 245°, alone or mixed with 2-(2-3′-indolylethyl)*iso*quinolinium iodide prepared as above using homophthalaldehyde. An alcoholic solution of the iodide, treated with alcoholic picric acid, gave a picrate which crystallised from methanol as orange columns, m. p. and mixed m. p. 207°. The corresponding perchlorate crystallised from methanol as lemon-yellow blades, m. p. and mixed m. p. 223°. When acetic acid was used as the medium for the condensation, the product was obtained in an impure state in lower yield.

Condensation of 2-3′-*Indolylethyl Bromide and* 6 : 7-*Dimethoxy*iso*quinoline.*—Solutions of 2-3′-indolylethyl bromide (0·9 g.) in benzene (7 c.c.) and of 6 : 7-dimethoxy*iso*quinoline (0·8 g.) in benzene (5 c.c.) were mixed and kept at room temperature for several weeks, the bromide (0·5 g., 32%, m. p. 197°) gradually crystallising. 2-(2-3′-*Indolylethyl*)-6 : 7-*dimethoxy*iso*quinolinium bromide* crystallised from methanol–ether (charcoal) as irregular, fawn-coloured prisms, m. p. 219° (decomp.) (Found: C, 60·1, 60·2; H, 5·3, 5·5. $C_{21}H_{21}O_2N_2Br,0{\cdot}5CH_3{\cdot}OH$ requires C, 60·1; H, 5·4%), which with aqueous potassium iodide gave the *iodide* which crystallised from water (charcoal) as irregular prisms, m. p. 246—247° (decomp.) (Found: C, 54·5; H, 4·8; N, 6·4. $C_{21}H_{21}O_2N_2I$ requires C, 54·8; H, 4·6; N, 6·1%). Attempted reduction of this salt by lithium aluminium hydride did not succeed but we have reason to believe that it might work with the chloride. The corresponding *picrate* crystallised from methanol (charcoal) as brown blades, m. p. 180° (Found: C, 50·6, 50·2; H, 3·6, 3·7; N, 14·4, 13·8. $C_{33}H_{26}O_{16}N_8$ requires C, 50·2; H, 3·3; N, 14·2%).

Condensation of 2-*Phenylethylamine with Homophthalaldehyde.*—A solution of 2-phenylethylamine (1·0 g.) and homophthalaldehyde (1·2 g.) in acetic acid (20 c.c.) was heated on the steam-bath for 2 hr. 2-2′-Phenylethyl*iso*quinolinium salts were obtained from the product as follows: *picrate* (from methanol), yellow, hexagonal rods, m. p. 160° (Found: C, 59·5; H, 3·8. $C_{23}H_{18}O_7N_4$ requires C, 59·7; H, 3·9%); *perchlorate* (from methanol; charcoal), colourless, rectangular rods, m. p. 167° (Found: C, 61·6; H, 4·9. $C_{17}H_{16}O_4NCl$ requires C, 61·2; H, 4·8%); *iodide*, pale yellow, irregular prisms, m. p. 179° (from acetone–ether; charcoal) (Found: C, 56·8; H, 4·7. $C_{17}H_{16}NI$ requires C, 56·5; H, 4·5%) [light absorption: $\lambda_{max.}$ 2300, 2700, 2800, 3350 (log ε 4·58, 3·60, 3·59, 3·60), $\lambda_{min.}$ 2550, 3000 Å (log ε 3·56, 3·12)].

Condensation of Aniline with Homophthalaldehyde.—Aniline (0·9 g.) was added to homophthalaldehyde (1·4 g.) in acetic acid (10 c.c.). The solution became orange-yellow and was heated on the steam-bath for 5 min., then excess of acetic acid was removed under reduced pressure and alcoholic picric acid added to the oily residue. An immediate crystalline precipitate of 2-phenyl*iso*quinolinium picrate was obtained which crystallised from methanol as yellow needles, m. p. 126° (Schöpf, Hartmann, and Koch, *Ber.*, 1936, **69**, 2768, report m. p. 125—127°) (Found: C, 57·8; H, 3·6. Calc. for $C_{21}H_{14}O_7N_4$: C, 58·1; H, 3·3%). The condensation was also effected without use of any solvent but with no advantage.

Condensation of Ethylenediamine with Homophthaldehyde.—Solutions of aqueous ethylenediamine (0·9 g. of 70%) in acetic acid (5 c.c.) and of homophthalaldehyde (2·5 g.) in acetic acid (10 c.c.) were mixed and heated on the steam-bath for 30 min. The condensation product was characterised as in previous cases by formation of the following derivatives:

Ethylenebis-2-iso*quinolinium dipicrate* (from a large volume of glacial acetic acid), yellow

needles, m. p. 264° (decomp.) (Found : C, 52·2; H, 3·1; N, 15·4. $C_{32}H_{22}O_{14}N_8$ requires C, 51·8; H, 3·0; N, 15·1%); *diperchlorate* (from water; charcoal), white, hexagonal plates, m. p. 296° (decomp.) (Found : C, 49·4; H, 3·7; N, 5·7. $C_{20}H_{18}O_8N_2Cl_2$ requires C, 49·5; H, 3·7; N, 5·8%); *di-iodide* (from water; charcoal), orange cubes, m. p. 287° (decomp.) (Found : C, 44·7; H, 3·6; N, 5·2. $C_{20}H_{18}N_2I_2$ requires C, 44·5; H, 3·4; N, 5·2%) [light absorption : $\lambda_{max.}$ 2400, 2800, 3400 (log ε 4·66, 3·91, 3·94), $\lambda_{min.}$ 2650, 3000 Å (log ε 3·85, 3·53)]; *dichloride* (from methanol–ether), white, irregular prisms, m. p. 282° (decomp.) (Found : C, 61·2, 61·2; H, 5·6, 5·6. $C_{20}H_{18}N_2Cl_2,2H_2O$ requires C, 61·1; H, 5·6%).

Condensation of Methylamine with Homophthalaldehyde.—A solution of methylamine (1·5 g. of 20% aqueous solution) in acetic acid (15 c.c.) was mixed with one of homophthalaldehyde (1·3 g.) in acetic acid (10 c.c.) and heated on the steam-bath for 30 min. 2-*Methyl*iso*quinolinium picrate* was obtained as needles (from methanol), m. p. 170° (Found : C, 51·9; H, 3·5; N, 14·9. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·3; N, 15·1%). The *perchlorate* (from water), formed irregular prisms, m. p. 177° (Found : C, 49·5; H, 4·0; N, 5·4. $C_{10}H_{10}O_4NCl$ requires C, 49·3; H, 4·1; N, 5·8%).

3 : 4 : 6 : 9-*Tetrahydro*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (VII; R = H).—Finely powdered 2-(2-3′-indolylethyl)*iso*quinolinium chloride (1 g.) was added in small portions during 5 min. to a suspension of lithium aluminium hydride (0·5 g.) in ether (100 c.c.). After 2 hr. at the room temperature the excess of the hydride was decomposed by careful addition of water. On addition of dilute hydrochloric acid a gum separated which solidified in contact with methanol. The *hydrochloride* crystallised from methanol (charcoal) as colourless columns, m. p. 208—209° (decomp.) (Found : C, 73·5; H, 6·3; N, 8·8. $C_{19}H_{19}N_2Cl$ requires C, 73·4; H, 6·2; N, 9·0%). Light absorption : $\lambda_{max.}$ 2250, 2700, 2890 (log ε 4·54, 4·00, 3·86), $\lambda_{min.}$ 2400, 2850 Å (log ε 3·54, 3·85). The colourless solution in 80% sulphuric acid became light green on the addition of ferric chloride. The free base crystallised from methanol (charcoal) as white needles, m. p. 188—189° (decomp.) with darkening and previous sintering (Clemo and Swan, *J.*, 1946, 617, report m. p. 196—197°) (Found : C, 83·0; H, 6·6; N, 10·1. Calc. for $C_{19}H_{18}N_2$: C, 83·2; H, 6·6; N, 10·2%). Light absorption : $\lambda_{max.}$ 2800 (log ε 4·3), $\lambda_{min.}$ 2480 Å (log ε 3·64). The *picrate* crystallised from aqueous acetone as pale yellow needles, m. p. 173° with previous sintering (*idem*, *loc. cit.*, gave m. p. 173—174°) (Found : C, 59·5; H, 4·3; N, 14·4. $C_{25}H_{21}O_7N_5$ requires C, 59·6; H, 4·2; N, 13·9%). The *methiodide*, prepared in hot acetone, crystallised from methanol–ether as white, irregular prisms, m. p. 178—179° (Found : C, 57·9, 57·5; H, 5·9, 5·8; N, 6·6. $C_{20}H_{21}N_2I,0{\cdot}5C_3H_6O$ requires C, 57·9; H, 5·4; N, 6·3%). Confirmation of the presence of acetone of crystallisation was obtained by means of the sodium nitroprusside–alkali and the *m*-dinitrobenzene–alkali colour reaction.

3 : 4 : 6 : 9-*Tetrahydro*-1′-*methyl*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (VII; R = Me).—2-(2-1′-Methyl-3′-indolylethyl)*iso*quinolinium chloride (1·0 g.) was added to a suspension of lithium aluminium hydride (0·5 g.) in ether (150 c.c.). After 2 hr. at the room temperature, most of the ether was removed and the excess of lithium aluminium hydride decomposed by the addition of water and dilute hydrochloric acid. The gum which separated was collected and dissolved in water; addition of sodium hydroxide solution gave the required base which was isolated by means of ether as an oil which did not crystallise. It distilled at 170—180° (bath)/0·01 mm. (Julian and Magnani, *loc. cit.*, report m. p. 135°) (Found : C, 82·5; H, 7·4; N, 9·8. Calc. for $C_{20}H_{20}N_2$: C, 83·2; H, 7·0; N, 9·7%). Light absorption : $\lambda_{max.}$ 2250, 2900 (log ε 4·42, 3·76), $\lambda_{min.}$ 2550 Å (log ε 3·46). The main absorption bands in the infrared spectrum occur at 3·45, 6·16, 6·64, 7·30, and 13·45—13·6 μ. The picrate separated from methanol as small, reddish yellow needles, m. p. 208—209° (decomp.) [*idem*, *loc. cit.*, give m. p. 209° (decomp.)].

Reduction of 2-(2-3′-*Indolylethyl*)iso*quinolinium Chloride with Potassium Borohydride.*—This chloride (0·5 g.) in water (10 c.c.) was treated with a solution of potassium borohydride (0·2 g.) in 50% methanol (6 c.c.). The solution was refluxed for 10 min. and then the excess of hydride was decomposed by dilute hydrochloric acid. The solution was concentrated and the gum which was obtained afforded a small amount of 3 : 4 : 6 : 9-tetrahydro-7 : 8-benzoindolo(2′ : 3′-1 : 2)pyridocoline hydrochloride, m. p. 287—288° (decomp.) alone or mixed with the salt reported above.

1 : 2 : 3 : 4-*Tetrahydro*-2-(2-3′-*indolylethyl*)iso*quinoline.*—*N*-(2-3′-Indolylethyl)homophthalimide (200 mg.; Clemo and Swan, *J.*, 1946, 617) was added to a solution of lithium aluminium hydride (100 mg.) in ether (50 c.c.) and the mixture was refluxed for 3 hr. with stirring under nitrogen. The excess of lithium aluminium hydride was decomposed with water, dilute hydrochloric acid added, and the ethereal layer separated. Unchanged imide was recovered from this ether solution. The aqueous layer was basified and a small amount of an

oil extracted with ether. This afforded an orange *picrate*, m. p. *ca.* 135°. It crystallised from aqueous acetone as orange, fern-like aggregates, m. p. 171° (Found : C, 59·6; H, 4·6. $C_{25}H_{23}O_7N_5$ requires C, 59·4; H, 4·6%). The infrared spectrum showed no band in the carbonyl region. Ring-closure during the reduction is excluded since the substance shows a strong Ehrlich reaction, a reddish-purple coloration.

1-(3 : 4-*Dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline Hydrochloride* (X).—A solution of tryptamine hydrochloride (3·4 g.) in water (50 c.c.) was mixed with 3 : 4-dimethoxyphenylpyruvic acid (3·9 g.; *Org. Synth.*, Coll. Vol. II, pp. 55, 335) dissolved in a mixture of warm ethanol (40 c.c.) and water (400 c.c.), and the red solution was then heated on the steam-bath for 72 hr. The solution was evaporated to dryness under reduced pressure, the residue dissolved in hot methanol (charcoal), the solution concentrated, and the hydrochloride (X) (3·7 g., 66%; m. p. 234—235°) precipitated by ether. It crystallised from methanol–ether as needles, m. p. 236° (Hahn, Schales, Bärwald, and Werner, *Annalen*, 1935, **520**, 109, reported m. p. 230°) (Found : C, 66·6; H, 6·5; N, 7·4. Calc. for $C_{20}H_{23}O_2N_2Cl$: C, 66·9; H, 6·5; N, 7·8%). The base obtained from this salt crystallised from ether–light petroleum as needles, m. p. 91°, or from water as long, white needles, m. p. 98° (Hahn and Hansel, *Ber.*, 1938, **71**, 2192, report m. p. 98°). An alcoholic solution of the tetrahydro-β-carboline showed a pale blue fluorescence in ultraviolet light, quenched by the addition of acid. The addition of ferric chloride to the colourless solution in 80% sulphuric acid gave a dull green colour which was moderately stable. With chromic acid it gave a transient purple colour which quickly became green. Light absorption : $\lambda_{max.}$ 2250, 2800 (log ε 4·49, 4·04), $\lambda_{min.}$ 2450 Å (log ε 3·52).

3 : 4 : 6 : 9-*Tetrahydro*-2″ : 3″-*dimethoxy*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (XI).—The above β-carboline hydrochloride (2·9 g.), 40% aqueous formaldehyde (60 c.c.), and water (400 c.c.) were refluxed together for 6 hr. (a) *Isolation as the hydrochloride.* The solution was evaporated to dryness under reduced pressure and the residue dissolved in boiling methanol, the solution decolorised (charcoal), and the hydrochloride, m. p. 263°, precipitated by the addition of ether. It crystallised from methanol–ether as white plates, m. p. 276°, and decomposed just above the m. p. (*idem, loc. cit.*, give m. p. 254—255° after sintering at 250°) (Found : C, 68·3; H, 6·3; N, 6·8; Cl, 10·3. Calc. for $C_{21}H_{23}O_2N_2Cl$: C, 68·0; H, 6·3; N, 7·5; Cl, 9·6%). (b) *Isolation as the base.* The concentrated solution was made alkaline with sodium hydroxide, and the precipitated product (2·6 g., *ca.* 90%; m. p. 285°) collected and washed well with water. The base crystallised from aqueous acetone as fern-like aggregates of colourless needles, m. p. 294—295° (*idem, loc. cit.*, give m. p. 249—250°) (Found : C, 75·3; H, 6·5; N, 8·4. Calc. for $C_{21}H_{22}O_2N_2$: C, 75·4; H, 6·6; N, 8·4%). Light absorption : $\lambda_{max.}$ 2250, 2800 (log ε 4·48, 4·08), $\lambda_{min.}$ 2500 Å (log ε 3·69). The picrate crystallised from aqueous acetone as yellow needles, darkening at 175° and decomposing at about 180° (*idem, loc. cit.*, give m. p. 173—174°) (Found : C, 57·8; H, 5·1. Calc. for $C_{27}H_{25}O_9N_5,0{\cdot}5C_3H_6O$: C, 57·8; H, 4·8%).

4 : 5-*Dimethoxyhomophthalic Anhydride.*—4 : 5-Dimethoxyhomophthalic acid (5·0 g.) and acetyl chloride (35 c.c.) were refluxed together for 2 hr. All the acid had gone into solution after 90 min. and 4 : 5-*dimethoxyhomophthalic anhydride* crystallised on cooling. The excess of acetyl chloride and acetic acid was removed by evaporation and the anhydride crystallised from benzene (charcoal) as felted, cream needles (4·6 g.), m. p. 175°. It retained traces of solvent very tenaciously and was sublimed at *ca.* 170—180° (bath)/0·03 mm. and so obtained as white needles, m. p. 175° (Found : C, 60·0; H, 4·6. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

N-(2-3′-*Indolylethyl*)4 : 5-*dimethoxyhomophthalimide.*—An intimate mixture of tryptamine (1·6 g.) and 4 : 5-dimethoxyhomophthalic acid (2·4 g.) was heated at 180° for 2 hr.; the dark brown melt was then extracted with hot methanol (charcoal). The *imide* (2·9 g., 81%) crystallised from methanol as light brown needles, m. p. 195°, and, after sublimation at 180—200° (bath)/0·01 mm. and crystallisation from methanol, it was obtained as pale cream needles, m. p. 199° (Found : C, 69·3; H, 5·6. $C_{21}H_{20}O_4N_2$ requires C, 69·2; H, 5·5%). It gave a yellow solution in concentrated sulphuric acid and an orange-red solution in concentrated nitric acid. Its alkaline solution had a brilliant green fluorescence in ultraviolet light. With Ehrlich's reagent it gave a red colour on heating; the colour disappeared on cooling; this colour change could be repeated indefinitely.

2-*Carboxy*-4 : 5-*dimethoxyphenyl*-N-(2-3′-*indolylethyl*)*acetamide.*—(a) *From* 4 : 5-*dimethoxyhomophthalic anhydride.* A solution of tryptamine (1·6 g.) and 4 : 5-dimethoxyhomophthalic anhydride (2·2 g.) in benzene (75 c.c.) was refluxed for 9 hr. Crystals, together with some oil, separated after 30 min.; after cooling, all the separated material crystallised. 2-*Carboxy*-4 : 5-*dimethoxyphenyl*-N-(2-3′-*indolyethyl*)*acetamide* (3·7 g., 96%; m. p. 185°) crystallised from

methanol as white cubes, m. p. 185·5° (Found : C, 65·9; H, 5·9; N, 7·4. $C_{21}H_{22}O_5N_2$ requires C, 65·9; H, 5·8; N, 7·3%). It was soluble in the common organic solvents, and in concentrated sulphuric acid it developed an orange-red colour changing to yellow and then reddish-brown on warming; with concentrated nitric acid it gave a yellow solution. A positive Ehrlich test was obtained on warming; the colour disappeared on cooling. When chloroform was used as the solvent in the condensation the yield was 76%. Light absorption : $\lambda_{max.}$ 2250, 2650 (log ε 4·64, 4·06), $\lambda_{min.}$ 2400 Å (log ε 3·75).

(b) *By the hydrolysis of* N-(2-3′-*indolylethyl*)-4 : 5-*dimethoxyhomophthalimide*. A solution of the imide (1·3 g.) in 2N-sodium hydroxide (25 c.c.) was heated on the steam-bath for 12 hr. The hot alkaline solution was decolorised with charcoal, cooled, and acidified with concentrated hydrochloric acid, and the flocculent, fawn precipitate (1·1 g., 80%) collected. After several crystallisations from methanol it separated as white cubes, m. p. 184—185°, alone or mixed with a specimen prepared by method (a).

N-(2-3′-*Indolylethyl*)-2-*methoxycarbonyl*-4 : 5-*dimethoxyphenylacetamide*.—The foregoing acid (0·38 g.) and an excess of ethereal diazomethane containing a little methanol were left for 2 hr. at room temperature, the solvent was removed, the residue dissolved in methanol, and the solution filtered from a small amount of solid. The addition of water to the concentrated solution precipitated the *ester* (0·36 g., 90%) which crystallised from aqueous methanol (charcoal) as cream needles, m. p. 170° (Found : C, 66·8; H, 6·3; N, 7·0. $C_{22}H_{24}O_5N_2$ requires C, 66·7; H, 6·1; N, 7·1%). With Ehrlich's reagent it gave a red colour on heating, and on cooling the colour faded.

1-(2-*Chlorocarbonyl*-4 : 5-*dimethoxybenzylidene*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline Hydrochloride* (XII).—A mixture of the above ester (0·4 g.), phosphoryl chloride (5 c.c.), and toluene (5 c.c.) was refluxed for 2 hr. After 90 min., orange yellow crystals separated and these were collected (0·34 g., 84%; m. p. 271°) after cooling. A further, small quantity of material was obtained from the mother-liquor by evaporation to dryness and extraction of the residue with chloroform. The *hydrochloride* crystallised from methanol (charcoal) as orange needles, m. p. 273° (Found : C, 60·0, 60·1; H, 5·0, 4·7; N, 6·6; Cl, 17·4. $C_{21}H_{20}O_3N_2Cl_2$ requires C, 60·2; H, 4·8; N, 6·7; Cl, 16·9%). Its solution in organic solvents exhibited a light green fluorescence in ultraviolet light and the yellow solution in concentrated sulphuric acid also had a green fluorescence. No colour was obtained with Ehrlich's reagent or with vanillin and hydrochloric acid. Light absorption : $\lambda_{max.}$ 2350, 2650, 3200, 3600, 4300 (log ε 4·28, 4·57, 4·78, 4·57, 3·93), $\lambda_{min.}$ 2300, 2450, 2850, 3400, 4000 Å (log ε 4·27, 4·26, 4·13, 4·53, 3·79).

3 : 4-*Dihydro*-2″ : 3″-*dimethoxy*-6-*oxo*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (XIII).—The above acid chloride hydrochloride (100 mg.), dissolved in water (50 c.c.) containing a little alcohol, was treated with 10% sodium hydroxide solution (*ca.* 5 c.c.). The colour of the solution immediately disappeared and a product separated. The mixture was gently heated on the steam-bath for 5 min., then cooled, and the solid collected (85 mg.; m. p. 288°). The *lactam* crystallised from aqueous methanol (charcoal) as lemon-yellow needles, m. p. 292° (Found : C, 73·2; H, 5·6; N, 7·6. $C_{21}H_{18}O_3N_2$ requires C, 72·8; H, 5·2; N, 8·1%). Its colourless solution in methanol showed a blue fluorescence which was intensified in ultraviolet light. With concentrated sulphuric acid it gave a bright yellow solution, with concentrated nitric acid a dull orange-red colour, and with chromic acid it gave a transient yellow green changing to dull red in a few minutes. It was insoluble in hot concentrated hydrochloric acid and in hot sodium hydroxide solution. Light absorption : $\lambda_{max.}$ 2300, 2550, 3450, 3650, 3800 (log ε 4·73, 4·70, 4·62, 4·63, 4·54), $\lambda_{min.}$ 2250, 2400, 2950, 3550, 3750 Å (log ε 4·52, 4·54, 3·87, 4·57, 4·47).

3 : 4-*Dihydro*-2″ : 3″-*dimethoxy*-7 : 8-*benzoindolo*(2′ : 3′-1 : 2)*pyridocoline* (as XI, but $\Delta^{9:10}$).—The above, pure lactam (260 mg.) in tetrahydrofuran (30 c.c.) was added to a slurry of lithium aluminium hydride (200 mg.) in ether (10 c.c.), and the yellow solution refluxed for 3 hr. with stirring under nitrogen. Excess of the hydride was decomposed with water, the solution acidified with hydrochloric acid, and the tetrahydrofuran distilled from the steam-bath under reduced pressure. The mother-liquor, after cooling, deposited fine, canary-yellow needles (250 mg., 90%), m. p. 230° with frothing. 3 : 4-*Dihydro*-2″ : 3″-*dimethoxy*-7 : 8-*benzoindolo*-(2′ : 3′-1 : 2)*pyridocoline hydrochloride* crystallised from water as brilliant, yellow needles, m. p. *ca.* 240—245° with frothing (Found : C, 62·8; H, 5·9; N, 6·9; Cl, 8·9. $C_{21}H_{21}O_2N_2Cl,2H_2O$ requires C, 62·3; H, 6·2; N, 6·9; Cl, 8·8%). Light absorption : $\lambda_{max.}$ 2650, 3200, 3600 (log ε 5·47, 5·58, 5·56), $\lambda_{min.}$ 2400, 2800, 3350 Å (log ε 5·16, 5·08, 5·44). A solution of the hydrochloride (200 mg.) in water was made alkaline with sodium hydroxide solution, and the precipitated *base* [150 mg.; m. p. 224—225° (decomp.)] collected. It crystallised from aqueous acetone as irregular, bright yellow prisms, decomposing at *ca.* 227° with previous shrinking and

darkening from about 200° (Found : C, 76·2; H, 6·7; N, 8·6. $C_{21}H_{20}O_2N_2$ requires C, 75·9; H, 6·1; N, 8·4%). Light absorption : $\lambda_{max.}$ 2300, 3100, 3600 (log ε 4·06, 3·94, 4·07), $\lambda_{min.}$ 2800, 3300 Å (log ε 3·58, 3·86). After 4·5 hr. in solution : $\lambda_{max.}$ 2250, 2650, 3100, 3450, 3600, 4000 (log ε 4·16, 4·45, 4·45, 4·38, 4·38, 3·79), $\lambda_{min.}$ 2400, 2800, 3250, 3500, 3900 Å (log ε 3·95, 3·97, 4·31, 4·33, 3·75).

3 : 4 : 6 : 9-*Tetrahydro*-2'' : 3''-*dimethoxy*-7 : 8-*benzoindolo*(2' : 3'-1 : 2)*pyridocoline* (XI).—A mixture of the above, purified base (30 mg.), Adams catalyst (10 mg.), and acetic acid (10 c.c.) was shaken under hydrogen at room temperature and pressure. The theoretical volume of hydrogen was absorbed in about 10 min. and, after filtration, the solution was evaporated to dryness under reduced pressure. The residue was treated with water and sodium hydroxide solution. The precipitated base (m. p. 283—285°) crystallised from aqueous acetone as colourless needles, m. p. 294°, identical with the specimen prepared by the alternative method.

Action of Phosphoryl Chloride on 2-*Carboxy*-4 : 5-*dimethoxyphenyl*-N-(2'-3'-*indolylethyl*)*acetamide*.—A solution of the above homophthalamic acid (100 mg.) and phosphoryl chloride (2 c.c.) in toluene (5 c.c.) was refluxed for 40 min. A small amount of the product crystallised and, after evaporation to dryness (reduced pressure), the residue was dissolved in boiling methanol (charcoal). After concentration of the solution to a small volume, the product crystallised as orange needles, m. p. 262°. After several crystallisations from methanol the m. p. was raised to 273—274° alone or when mixed with 1-(2-chlorocarbonyl-4 : 5-dimethoxybenzylidene)-1 : 2 : 3 : 4-tetrahydro-β-carboline hydrochloride. The addition of sodium hydroxide solution to an aqueous solution of this product gave the corresponding lactam, lemon needles (from methanol), m. p. 290° (291—292° on admixture with an authentic specimen). Slightly impure lactam was isolated direct from the cyclisation by addition of alkali to the crude residue obtained on evaporation of the excess of phosphoryl chloride and solvent.

3-2'-(*Furfurylideneamino*)*ethylindole*.—Furfuraldehyde (6·0 g.) and tryptamine (10 g.) were mixed and stirred. With evolution of heat, the contents of the flask set solid within a minute. 3-2'-(*Furfurylideneamino*)*ethylindole* crystallised from aqueous alcohol (charcoal) as buff-coloured plates (13·5 g., 93%), m. p. 135° (Found : C, 76·0; H, 6·1; N, 11·7. $C_{15}H_{14}ON_2$ requires C, 75·6; H, 5·9; N, 11·8%). Absorption bands occur at 2·9 (NH) and 6·06 μ (C:N). When a solution of picric acid in ether was added to an ethereal solution of the base tryptamine picrate separated (Found : C, 49·7; H, 3·4. Calc. for $C_{16}H_{15}O_7N_5$: C, 49·4; H, 3·8%).

3-2'-(*Furfurylamino*)*ethylindole*.—3-2'-(Furfurylideneamino)ethylindole (5·0 g.), platinum dioxide (0·4 g., *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 463), and methanol (150 c.c.) were shaken together under hydrogen. The catalyst was reduced in 5 min. (80 c.c. of hydrogen) and hydrogen (520 c.c., 1 mol.) was absorbed in a further 50 min. The product was obtained as a nearly colourless, very viscous oil (4·3 g., 86%), b. p. 168°/0·06 mm. The *base* slowly crystallised and then separated from light petroleum as white needles, m. p. 56—57° (Found : C, 74·9; H, 7·2; N, 11·5. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7%). The *picrate*, prepared in alcohol, crystallised from benzene as irregular, orange prisms, m. p. 161° (Found : C, 54·0; H, 4·2; N, 15·0. $C_{21}H_{19}O_8N_5$ requires C, 53·7; H, 4·1; N, 14·9%). The *hydrochloride* crystallised from acetone–ether as irregular, cream prisms, m. p. 168° (Found : C, 65·0; H, 6·4; N, 10·0; Cl, 12·7. $C_{15}H_{17}ON_2Cl$ requires C, 65·2; H, 6·2; N, 10·1; Cl, 12·7%).

3-2'-(N-*Acetyl*-N-*furfurylamino*)*ethylindole*.—A mixture of 3-2'-(furfurylamino)ethylindole (5·0 g.) and acetic anhydride (6·4 g.) was refluxed for 15 min. and the solution poured on ice and neutralised with sodium carbonate. The *acetyl* derivative (5·8 g.) crystallised from aqueous acetone as irregular, white prisms, m. p. 102·5° (Found : C, 72·6; H, 6·6; N, 10·1. $C_{17}H_{18}O_2N_2$ requires C, 72·3; H, 6·4; N, 9·9%).

Attempted fission of the furan nucleus of this base by means of aqueous alcoholic hydrochloric acid and alcoholic hydrogen chloride was unsuccessful. Boiling glacial acetic acid brought about no change and boiling 50% hydrobromic acid in glacial acetic acid gave a tar.

N-*Furfurylidene*-2-*phenylethylamine*.—When furfuraldehyde (9·6 g.) was added to 2-phenylethylamine (12·1 g.) evolution of heat occurred and the mixture became red. After 15 minutes' heating on the steam-bath the *product* was isolated by means of ether and obtained (16·5 g., 83%) as a colourless oil, b. p. 94°/0·06 mm., n_D^{17} 1·6795, m. p. 33—34° (prisms from light petroleum) (Found : C, 78·5; H, 6·6; N, 7·4. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%).

N-*Furfuryl*-2-*phenylethylamine*.—*N*-Furfurylidene-2-phenylethylamine (2·0 g.) was hydrogenated in the presence of Adams catalyst (0·1 g.) in methanol (30 c.c.). Reduction of the catalyst occurred in 5 min. (20 c.c. absorbed) and the reduction stopped after 250 c.c. of hydrogen had been absorbed. N-*Furfuryl*-2-*phenylethylamine* (1·6 g., 80%) had b. p. 107°/0·06 mm., n_D^{17} 1·5500 (Found : C, 77·8; H, 7·6; N, 7·1. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%).

The *picrate*, prepared in alcohol, crystallised from water as irregular, yellow prisms, m. p. 133° (Found : C, 53·2; H, 3·9; N, 12·8. $C_{19}H_{18}O_8N_4$ requires C, 53·0; H, 4·2; N, 13·0%), and the 3 : 5-*dinitrobenzoate* from acetone as cream cubes, m. p. 165° (Found : C, 58·2; H, 4·8. $C_{20}H_{19}O_7N_3$ requires C, 58·1; H, 4·6%).

Furfurylideneacetophenone.—This was prepared by Drake and Gilbert's method (*J. Amer. Chem. Soc.*, 1930, **52**, 4966; cf. Semmler, *Ber.*, 1906, **39**, 729). The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as deep red rosettes, m. p. 161—162°, with previous shrinking (Found : C, 60·0, 60·2; H, 3·8, 4·0; N, 15·1. $C_{19}H_{14}O_5N_4$ requires C, 60·3; H, 3·7; N, 14·8%).

β-2′-*Furylpropiophenone.*—Furfurylideneacetophenone (5·0 g.) in methanol (50 c.c.) was hydrogenated in the presence of Raney nickel at atmospheric pressure and room temperature. Absorption of hydrogen (660 c.c., 10% excess) was complete in 15 min. β-2′-Furylpropiophenone (4·7 g., 94%) was obtained as a colourless oil, b. p. 92°/0·01 mm., n_D^{19} 1·5701, m. p. 36° (plates from light petroleum) (Found : C, 77·8; H, 6·2. Calc. for $C_{13}H_{12}O_2$: C, 78·0; H, 6·1%). Plattner *et al.* (*Helv. Chim. Acta*, 1935, **18**, 935) carried out the hydrogenation at 70° and found that 1·5 mols. of hydrogen were absorbed. They stated that their compound was impure but they obtained it crystalline (m. p. 37—37·5°). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as red needles, m. p. 144° (Found : C, 59·7; H, 4·2; N, 14·7. $C_{19}H_{16}O_5N_4$ requires C, 60·0; H, 4·2; N, 14·7%).

2-3′-*Phenylpropylfuran.*—β-2′-Furylpropiophenone (5·0 g.), diethylene glycol (30 c.c.), hydrazine hydrate (3 c.c. of 90%), and potassium hydroxide (3 g.) were refluxed together. After 90 min. the temperature was raised slowly to 200° and kept at 190—200° for 4 hr. 2-3′-Phenylpropylfuran was isolated by known methods as a mobile oil, b. p. 75—76°/0·01 mm., n_D^{17} 1·5318 (Plattner *et al.*, *loc. cit.*, give b. p. 134°/10 mm., n_D^{20} 1·5332; Semmler, *Ber.*, 1906, **39**, 729, reports b. p. 135°/10 mm., n_D 1·529) (Found : C, 83·6; H, 7·7. Calc. for $C_{13}H_{14}O$: C, 83·9; H, 7·6%). Light absorption : $\lambda_{max.}$ 2100, 2180 (log ε 4·01, 4·12), $\lambda_{min.}$ 2140 Å (log ε 3·98).

Oxidation of 2-3′-*Phenylpropylfuran by Means of Bromine in Methanol.*—A solution of bromine (0·5 c.c.) in methanol (10 c.c.) was added during 20 min. to a solution of the furan (1·8 g.) and fused potassium acetate (4·0 g.) in methanol (25 c.c.) with vigorous stirring at *ca.* 0°. The product was a pale yellow oil (1·2 g.), b. p. 96—100°/0·1 mm., n_D^{19} 1·5298 (Found : C, 77·5; H, 7·8. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%). Light absorption : $\lambda_{max.}$ 2140, 2550, 2650 (log ε 2·90, 2·76, 2·80), $\lambda_{min.}$ 2080, 2300, 2600 Å (log ε 2·75, 2·50, 2·70). This substance is possibly 2-*methoxy*-5-3′-*phenylpropylfuran.*

2-n-*Butylfuran.*—A mixture of 2-butyrylfuran (20·0 g.) (Gilman and Galloway, *J. Amer. Chem. Soc.*, 1933, **55**, 4197), diethylene glycol (240 c.c.), hydrazine hydrate (40 c.c. of 90%), and potassium hydroxide (43 g.) was refluxed for 2 hr. The temperature was raised slowly to 190—200°, the volatile fractions being collected. After 4 hr. at this temperature, the mixture was cooled, the distillate added to it, and the whole diluted with water. The 2-*n*-butylfuran was isolated by ether and obtained as a colourless, mobile oil with a pleasant odour (12 g., 67%), b. p. 140°, n_D^{25} 1·4460 (Gilman and Galloway, *loc. cit.*, give b. p. 137—138°, n_D^{25} 1·4460). Light absorption : $\lambda_{max.}$ 2120, 2250 (log ε 3·75, 3·88), $\lambda_{min.}$ 2160 Å (log ε 3·66).

2-*Butyl*-2 : 5-*dihydro*-2 : 5-*dimethoxyfuran.*—2-*n*-Butylfuran (1·2 g.) and fused potassium acetate (4·0 g.) in methanol (25 c.c.) were treated with bromine (0·5 c.c.) in methanol (10 c.c.) during 20 min. with stirring and cooling to about 0°. The *product* was a pale yellow, mobile oil with a pleasant, pear-like odour, b. p. 90—92°/14 mm., n_D^{20} 1·4510 (Found : C, 65·4; H, 9·3. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%). Light absorption : $\lambda_{max.}$ 2120, 2200, 2600 (log ε 3·41, 3·38, 3·41), $\lambda_{min.}$ 2100, 2160, 2400 Å (log ε 3·34, 3·31, 3·28). 2 : 5-Dihydro-2 : 5-dimethoxysylvan was prepared by bromine–methanol oxidation of sylvan (Clauson-Kaas and Limborg, *Acta Chem. Scand.*, 1947, **1**, 619), and had b. p. 79°/68 mm., n_D^{20} 1·4289 (Found : C, 58·2; H, 8·4. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·4%). Light absorption : $\lambda_{max.}$ 2080, 2140 (log ε 2·97, 2·96), $\lambda_{min.}$ 2100 Å (log ε 2·90).

2 : 5-*Dihydro*-2 : 5-*dimethoxyfurfuraldehyde Diacetate.*—Furfuraldehyde diacetate (39·8 g.) (Gilman and Wright, *Iowa State Coll. J. Sci.*, 1929, **4**, No. 1, 35) and fused potassium acetate (40·0 g.) were dissolved in methanol (300 c.c.) and a solution of bromine (10 c.c.) in methanol (200 c.c.) added during 40 min. at 19—20° with stirring. The greater part of the methanol was then removed under reduced pressure and a large volume of ether was added. The filtered solution was washed with a saturated solution of potassium hydrogen carbonate and with water and dried. The product distilled as a colourless, very viscous oil (20 g.), b. p. 122—130°/1·5 mm. (Clauson-Kaas and Fakstorp, *Acta Chem. Scand.*, 1947, **1**, 415, report b. p. 122—126°/1 mm.). On standing about 75% of the oil crystallised and the substance crystallised from methanol as prisms, m. p. 113° (Found : C, 51·2; H, 6·3. Calc. for $C_{11}H_{16}O_7$: C, 50·8; H, 6·2%). Light

absorption: $\lambda_{max.}$ 2060, 2180, 2500, 2550, 2950 (log ε 2·93, 2·87, 2·70, 2·70, 2·34), $\lambda_{min.}$ 2120, 2350, 2850 Å (log ε 3·61, 2·50, 2·26).

2 : 5-*Dihydro*-5-*methoxyfurfuraldehyde Diacetate*.—2 : 5-Dihydro-2 : 5-dimethoxyfurfuraldehyde diacetate (20·0 g.) in methanol (50 c.c.) was hydrogenated at room temperature and pressure in the presence of Raney nickel. The reduction stopped (*ca.* 6 hr.) after the theoretical volume of hydrogen (1870 c.c.) had been absorbed. 2 : 5-Dihydro-5-methoxyfurfuraldehyde diacetate was obtained as a colourless, mobile oil (14·0 g., 80%), b. p. 82—87°/0·06 mm., n_D^{23} 1·4508 (Found: C, 51·9, 51·8; H, 6·1, 6·2. $C_{10}H_{14}O_6$ requires C, 52·2; H, 6·1%). Light absorption: $\lambda_{max.}$ 2100, 2160, 2550, 2700 (log ε 3·54, 3·59, 2·89, 2·96), $\lambda_{min.}$ 2120, 2450, 2600 Å (log ε 3·48, 2·06, 2·80). On further catalytic reduction tetrahydrofurfuraldehyde diacetate was obtained as a mobile oil with a pleasant fruit-like odour, b. p. 124—126°/27 mm., n_D^{20} 1·4370 (Scheibler, Sotscheck, and Friese, *Ber.*, 1924, **57**, 1443, report b. p. 133°, $n_D^{20\cdot3}$ 1·4405) (Found: C, 53·1; H, 7·1. Calc. for $C_9H_{14}O_5$: C, 53·4; H, 7·0%); this showed no ultraviolet absorption.

Tetrahydrofurfuraldehyde, prepared from its acetate by hydrolysis with boiling dilute sulphuric acid, had b. p. 136—138°, n_D^{20} 1·4475 (Brenner, Coats, Robertson, and Allan, *J.*, 1949. S 25, give b. p. 145°/760 mm., n_D^{20} 1·4473). Its 2 : 4-dinitrophenylhydrazone separated from alcohol as orange needles, m. p. 133° (*idem*, *loc. cit.*, give m. p. 134°). The *dimedone derivative* was prepared in aqueous alcohol and crystallised from water as blades, m. p. 148°. For analysis it was sublimed at 117°/0·5 mm. (Found: C, 69·3; H, 8·8. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%).

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