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THE SYNTHESIS, REARRANGEMENT AND CERTAIN REACTIONS OF 1-(3,4-DIHYDROXYBENZYL)-1,2,3,4-TETRAHYDRO-β-CARBOLINE AND ITS 9-METHYL ANALOGUE

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Abstract—1-(3,4-Dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline (I; R = H) and 1-(3,4-dihydroxybenzyl)-9-methyl-1,2,3,4-tetrahydro-β-carboline (I; R = Me) have been synthesized by conventional methods, and the former has been converted into 5,7,8,13,13b,14-hexahydro-2,3-dihydroxybenz[g]-indolo[2,3-a]pyridocoline (II; R = H). On treatment with strong acid the 9-methylcarboline undergoes a remarkable rearrangement to give an isomeric product in high yield. The structure of this product has been established as IV(R = Me). 1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline undergoes a similar rearrangement to give IV(R = H) as a minor product, together with coloured products of undetermined structure. A mechanism for these rearrangements is suggested, and their possible biogenetic significance is mentioned.

IN THE Barger-Hahn-Robinson[1] proposals for the biogenesis of the yohimbine-type alkaloids and their extension to the strychnine-type alkaloids by Woodward,[2] 1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline (I; R = H) was suggested as a key intermediate. It was therefore of interest to synthesize this compound, which was required in another connection[3] for oxidation studies. Condensation of tryptamine hydrochloride with 3,4-dihydroxyphenylpyruvic acid in boiling water gave this carboline directly. The pyruvic acid was best prepared by the acid hydrolysis of rigorously purified β-3,4-diacetoxyphenyl-α-acetamidoacrylic acid under carefully controlled conditions; use of the impure acid led to an appreciable reduction in yield. 2-Phenyl-4-(3,4-diacetoxybenzylidene)-oxazolone could also be hydrolysed to 3,4-dihydroxyphenylpyruvic acid, but in this case the reaction was slow, and a pure product was isolated less easily. In contrast to the ease of formation of the carboline (I; R = H), the synthesis of its 9-methyl analogue (I; R = Me) proved to be surprisingly difficult, and the required product could not be isolated from the reaction of 1-methyltryptamine hydrochloride with 3,4-dihydroxyphenylpyruvic acid at temperatures of 100° and above. However, condensation took place very slowly at room temperature giving 1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-9-methyl-β-carboline-1-carboxylic acid, which could be quantitatively decarboxylated to the carboline (I, R = Me) by brief acid treatment. The amino-acid was obtained in a maximum yield of 45% after 8 weeks, and at 35° this reaction rate was approximately doubled. Above this temperature non-crystalline products were formed. This inactivity of

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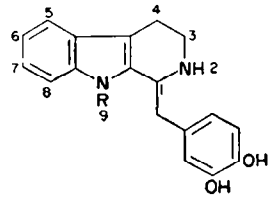
[1a] G. Barger, *Proc. of. Int. Congress of Chemistry, Madrid* 1934; [b] G. Hahn and H. Ludewig, *Chem. Ber.* **67**, 2031 (1934); [c] G. Hahn and H. Werner, *Liebigs Ann.* **520**, 123 (1935); [d] G. Hahn and A. Hansel, *Chem. Ber.* **71**, 2192 (1938); [e] R. Robinson, *Structural Relations of Natural Products* Oxford University Press (1955).

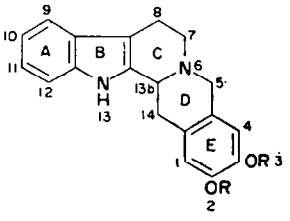
[2] R. B. Woodward, *Nature, Lond.* **162**, 155 (1948); *Angew. Chem.* **68**, 13 (1956).

[3] J. Harley-Mason and W. R. Waterfield, *Chem. & Ind.* 1478 (1960).

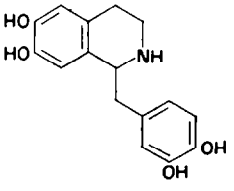
1-methyltryptamine appears to be general. During the present work we found that it did not react at room temperature with α-ketoglutaric, acid 3,4-dimethoxyphenylpyruvic acid, or 3,4-dimethoxyphenylacetaldehyde, whereas tryptamine gave products with all three, and other workers[4] report reduced yields when 1-methyltryptamine was substituted for tryptamine in similar reactions.



I



II



III

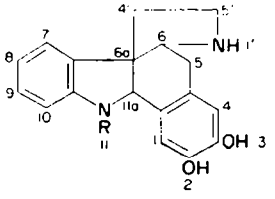
The Mannich condensation of 1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline with formaldehyde was next investigated. Theoretically, two products might arise from this reaction, resulting from the coupling of the formaldehyde with the available positions *ortho* and *para* to the hydroxyl groups. However, only one product was obtained and this was shown to be 5,7,8,13,13b,14-hexahydro-2,3-dihydroxybenz[g]indolo-[2,3-a]pyridocoline (II; R = H) by the direct comparison of its derivatives with those of the compound obtained by demethylation of the corresponding dimethoxypyridocoline (II; R = Me) of known[1d] structure. Thus the condensation takes place exclusively at the *para* position and the product so formed is the intermediate postulated by Robinson[5] as a possible yohimbine precursor. The condensation of formaldehyde with tetrahydropapaveroline (III) which contains a similar reacting system, is reported[6] to give a mixture of both possible products. In all other reports of the condensation of formaldehyde with *ortho* dihydroxy- or dimethoxyphenyl groups in the above manner, the coupling is exclusively at the *para* position,[1e] and the case of tetrahydropapaveroline must be considered anomalous.

Since the demethylation of the pyridocoline (II, R = Me) was smoothly effected by 48% hydrobromic acid, it appeared likely that an alternative route to the carbolines (I) was available through similar demethylation of their O-methyl derivatives. However, on boiling 1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline with 48% hydrobromic acid, a bright yellow product separated from the reaction mixture which had none of the properties characteristic of a tetrahydrocarboline. Subsequently it was found that a similar yellow substance could be obtained by boiling the dihydroxy-compound (I; R = H) itself with concentrated hydrochloric acid or with 10 N-sulphuric acid. After this part of the work was completed, Kanaoka[7] reported the preparation of 1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline from 1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline "as usual by means of 48% HBr" but gave no details of the properties of his product. On the basis of our findings, there is little doubt that he obtained a mixture of rearrangement products (see below).

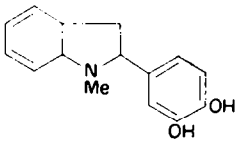
Treatment of 1-(3,4-dimethoxybenzyl)-9-methyl-1,2,3,4-tetrahydro-β-carboline

[4] L. H. Groves and G. A. Swan, *J. Chem. Soc.* 650 (1952).
[5] R. Robinson, *Proc. Roy. Soc.* **205**(A), 15 (1951).
[6] E. Späth and E. Kruta, *Monatsh* **50**, 341 (1928); *Chem. Ber.* **62**, 1024 (1929).
[7] Y. Kanaoka, *Chem. and Pharm. Bull. Japan* 7, 597 (1959).

with boiling 48% hydrobromic acid, or of the dihydroxymethylcarboline (I; R = Me) or its 1-carboxylic acid with refluxing concentrated hydrochloric acid also effected rearrangement, with the formation of two easily separable products. The minor product was a deep yellow dihydrohalide which rapidly decomposed on basification. In dilute aqueous acid it exhibited a long-wave absorption maximum at 402 mμ. It was not further investigated. The major product has been identified as 5,6,6a,11a-tetrahydro-2,3-dihydroxy-11-methylbenz[a]pyrrolidino[2,3-d]carbazole (IV; R = Me). This structure has been assigned to the product on the basis of the following evidence.



IV



V

The product was a di-acid base, giving stable, well-crystallized salts, and having p*Ka* values of 2·7 and 8·5 in aqueous solution. These values are consistent with an aromatic [N(a)] amino group and an aliphatic [N(b)] amino group respectively, and are virtually identical with those of desacetyl aspidospermine[8] which contains a similar dibasic system. The free base was itself unstable, but analysed satisfactorily as an isomer of the methyl carboline (I, R = Me). It formed a colourless, acid-soluble, triacetyl derivative, confirming the presence of a basic N-methyl group. With acid ferric chloride solution the product and all its derivatives gave an intense red colour. This colour is characteristic of dihydroindoles; for example, it is given by strychnidine and its derivatives.[9] A red colour was also given with ceric sulphate solution, and in this case the solution became yellow on standing. This behaviour is stated to be typical of N-alkyl indolines.[10]

Further evidence for the presence of an indoline system in the rearranged material was obtained by the synthesis of 1-methyl-2-(3,4-dihydroxyphenyl)-indoline (V) as a model system. Acetoveratrone-*as*-methylphenylhydrazone readily underwent Fischer cyclization on treatment with polyphosphoric acid, which has been used with success on similar hydrazones,[11] to give 1-methyl-2-(3,4-dimethoxyphenyl)-indole in good yield. This was reduced with zinc dust and hydrochloric acid, and the resulting product demethylated with 48% hydrobromic acid, to give the required indoline. The UV spectra of this indoline and its diacetyl derivative were very similar to those of the rearranged material and its triacetyl derivative. In 0·1 N hydrochloric acid both the indoline and our product underwent a similar hypsochromic shift, caused by the protonation of the indoline nitrogen atom. According to Hodson and Smith[12] and Battersby and Hodson,[13] such protonation indicates that the two nitrogen atoms in

[8] A. J. Everett, H. T. Openshaw and G. F. Smith, *J. Chem. Soc.* 1120 (1957).

[9] H. L. Holmes in R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol I; p. 376. Academic Press, New York (1949).

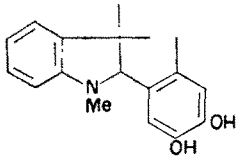
[10] A. R. Battersby and H. F. Hodson, *Quart. Rev.* **14**, 77 (1960).

[11] H. M. Kissman, D. W. Farnsworth and B. Witkop, *J. Amer. Chem. Soc.* **74**, 3948 (1952); J. M. Bruce, *J. Chem. Soc.* 360 (1960).

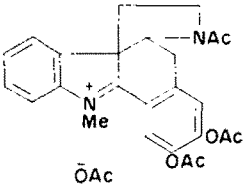
[12] H. F. Hodson and G. F. Smith, *J. Chem. Soc.* 1877 (1957).

[13] A. R. Battersby and H. F. Hodson, *J. Chem. Soc.* 736 (1960).

the rearranged material are separated by three or more carbon atoms, since the indoline nitrogen atom of hexahydro-β-carbolines and of folicanthine and related alkaloids is not protonated in 0·1N hydrochloric acid, owing to the field effect of the second, closely placed, positively charged nitrogen atom. Thus the observed protonation in our product is in agreement with the proposed structure.



VI



VII

The evidence so far presented suggests the presence of the grouping (VI), in which the catechol ring is joined directly to two carbon atoms, whereas in 1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline it is joined to one only. This necessitates the formation of a fifth ring during the rearrangement, since the oxidation state of the system remains unchanged. Methylation of the product with diazomethane, followed by permanganate degradation, gave *m*-hemipinic acid, its amide, and its N-methylimide. Treatment of these products with methylamine allowed the isolation of N-methyl-*m*-hemipinimide in substantial yield and no traces of veratic acid or hemipinic acid were observed. The N-methylimide was used for characterization since it was readily distinguishable from N-methylhemipinimide, and its UV spectrum was known.[14] This result not only confirms that the catechol ring is joined at two places to the remainder of carbon skeleton of the rearranged material, but also indicates that the postulated orientation (as in VI) of this ring is correct.

It will be observed that the product (IV; R = Me) contains one proton (at the indoline α-position) bonded to a carbon atom whose immediate neighbours do not bear protons. This proton should give rise to an isolated single, sharp peak in the nuclear magnetic resonance spectrum of the product, since it cannot participate in spin-spin coupling. Although solubility considerations precluded the use of the free base in a proton magnetic resonance investigation, we were able to obtain a satisfactory spectrum of its triacetyl derivative. A pronounced feature of this spectrum was a single peak having a τ value[15] of 6·0 which we attribute to the isolated proton, since the equivalent proton of 1-methyl-2-(3,4-diacetoxyphenyl)-indoline appeared as a quartet* of similar chemical shift (τ = 5·7).

Final confirmation of the presence of the proton at the indoline α-position was provided by the mercuric acetate oxidation of the triacetyl derivative of the product (IV; R = Me). Mercuric acetate was chosen for this oxidation since the extensive work of Leonard[17] has shown that it provides an effective and selective method for the

* Erroneously described in our preliminary communication[16] on this subject.

[14] H. R. Arthur and Y. L. Ng, *J. Chem. Soc.* 3094 (1959).

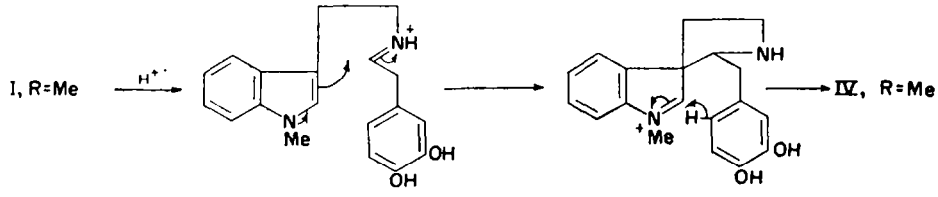
[15] G. V. D. Tiers, *J. Phys. Chem.* **62**, 1151 (1958).

[16] J. Harley-Mason and W. R. Waterfield, *Chem. & Ind.* 1477 (1960).

[17] N. J. Leonard and W. K. Musker, *J. Amer. Chem. Soc.* **81**, 5631 (1959) and preceding papers in this series.

dehydrogenation of tertiary amines to immonium salts, and Ban *et al.*[18] have shown that N-acyl and N-methyl groups are not attacked by this reagent. An orange product was obtained from this reaction, for which the quaternary acetate structure (VII) is proposed. This material was not obtained analytically pure, and its structure is based on the following observations. It was unstable in alkaline solution and it gave no indoline colour tests. It exhibited a long-wavelength light absorption maximum in 95% ethanol at 459 mμ which was shifted to 390 mμ in 0·1 N hydrochloric acid. Acid hydrolysis gave a phenolic product exhibiting similar maxima. This absorption is characteristic of a highly conjugated system and indicates that during the dehydrogenation the two benzene rings are brought into conjugation by the removal of the proton at the indoline α-position. This oxidation thus provides clear chemical evidence that the rearranged material does not contain an α,α-disubstituted indoline grouping, and that the catechol ring must be attached at the indoline α-position.

Additional evidence in favour of the structure IV (R = Me) may be obtained from consideration of the mechanism of the rearrangement which we envisage as follows. Protonation at the indole α-position of the carboline (I; R=Me) leads to a reversal of the Mannich reaction by which the carboline was originally prepared, with the formation of the intermediate VIII.



VIII IX

This ring cleavage is supported by the observation[19] that acid treatment can induce epimerization at C_1 in the yohimbine-type alkaloids, which has been explained by an identical mechanism.[20] The intermediate VIII then cyclizes at the indole β-position to give the indoleninium salt IX. This preference for β-condensation is probably brought about by the highly acidic conditions necessary for the rearrangement, since it gives rise to a more basic product. We have already mentioned[16] the possibility of an equilibrium between α-type (I) and β-type (IV) product at this stage in similar reactions.

The last stage of the rearrangement then involves the reaction of the highly anionoid catechol 4-position with the protonated indolenine as shown. The success of the rearrangement therefore depends upon the very strong nucleophilic properties of this final attacking group. The 4-position of catechol dimethylether is insufficiently activated for this reaction, since 1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline does not rearrange in boiling concentrated hydrochloric acid. We were also unable to condense 1-methyltryptamine with catechol in boiling 48% hydrobromic acid, hence the attacking group must be held close to the indolenine system for combination to take place. Finally, if rearrangement is to occur in analogous systems it is

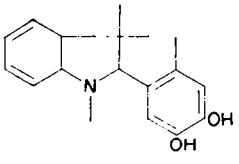
[18] Y. Ban, O. Yonemitsu and M. Terashima, *Chem. and Pharm. Bull., Japan* **8**, 183 (1960).

[19] H. B. Macphillamy, L. Dorfman, C. F. Huebner, E. Schlittler, and A. F. St. André, *J. Amer. Chem. Soc.* **77**, 1071 (1955); E. Wenkert and L. H. Liu, *Experientia* **11**, 302 (1955).

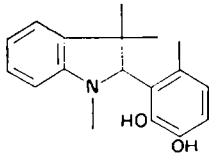
[20] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).

obvious that the structure of the product must be sterically possible. Thus the extra methylene bridge in the pyridocoline (II; R = Me), which is absent in the carbolines (I), prevents rearrangement during demethylation.

The rearrangement of 1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline (I; R = H) in boiling 48% hydrobromic acid proved to be more complex than that of the 9-methyl analogue discussed above, and three distinct products were formed during this reaction. In the present paper we report only the structure of the minor product. This was isolated in 10% yield from the reaction mixture after removal of the bright yellow material previously mentioned. The minor product was a di-acid base, isomeric with the starting carboline, and gave characteristic indoline colour tests. Its UV spectrum was similar to that of 1-methyl-2-(3,4-dihydroxyphenyl)-indoline and showed the same hypsochromic shift in acid solution. It formed a non-basic, colourless, tetra-acetyl derivative, which gave no colour with ferric chloride solution. The UV spectrum of this derivative strongly resembled those of diaboline[21] and spermostrychnine,[22] both of which contain an N-acetylindoline system as sole chromophore. Methylation of the base, followed by permanganate degradation, yielded *m*-hemipinic acid and its imide. This evidence establishes the structure of the product as IV (R = H), by analogy with the observations presented to substantiate the structure of the 9-methyl compound (VI; R = Me). The bright yellow material which constitutes the bulk of the rearrangement products was found to be a mixture of two dihydrobromides, which were present in approximately equal amounts. The separation and purification of these components have not been undertaken, but preliminary experiments have shown that mild acetylation of the mixture yields products which are separable by column chromatography. This separation is not described in the experimental section as the results are not yet conclusive. More definite evidence has been obtained by methylation and subsequent permanganate oxidation of the mixture. In contrast to the two preceding degradations, both *m*-hemipinic acid and hemipinic acid were isolated in this case. This result suggests that the two components contain the groups X and XI respectively, but further work is required to establish complete structures.



X



XI

On the basis of the earlier biogenetic hypotheses,[2] these rearrangements are of interest in that they represent a direct transformation from a yohimbine-type to a strychnine-type precursor. However, it must be noted that there is now considerable doubt[23] whether compounds such as I and II having aromatic E rings are really biosynthetic intermediates, and any conclusion must await further tracer experiments *in vivo*.

[21] F. E. Bader, E. Schlittler and H. Schwarz, *Helv. Chim. Acta* **36**, 1256 (1953).
[22] F. A. L. Anet and R. Robinson, *J. Chem. Soc.* 2253 (1955).
[23] E. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.* **81**, 1474 (1959); E. Wenkert, *Experientia* **15**, 165 (1959); *J. Amer. Chem. Soc.* **84**, 98 (1962); R. Thomas, *Tetrahedron Letters* 544 (1961); E. Leete, S. Ghosal and P. N. Edwards, *J. Amer. Chem. Soc.* **84**, 1068 (1962).

EXPERIMENTAL

Melting and boiling points are not corrected. Specimens for analysis were dried over phosphorous pentoxide at a pressure of 1 mm Hg or less. Paper chromatography was carried out by the ascending method on Whatman No. 1 paper except where otherwise stated. All new compounds described gave consistent IR spectra.

3,4-Dihydroxyphenylpyruvic acid

(a) Freshly recrystallized 3,4-diacetoxyphenyl-α-acetamidoacrylic acid[24] (10 g) was refluxed with N HCl (200 ml) under nitrogen for 3 hr. The mixture was cooled, extracted with ethyl acetate (8 × 100 ml), and the combined extracts dried. Evaporation of the solvent under red. press. of nitrogen, followed by removal of traces of acetic acid under high vacuum gave 3,4-dihydroxyphenylpyruvic acid (5·75 g, 95%) as an almost white solid m.p. 182–183°. Recrystallization from a small volume of water gave the pure product, m.p. 188–189°, lit,[25] 192–193°. (Found: C, 54·9; H, 4·1. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·0%).

(b) 2-Phenyl-4-(3,4-diacetoxybenzylidene)-oxazolone[26] (3·5 g) was refluxed with N HCl (150 ml) for 3 hr. The solution was then cooled rapidly, extracted with benzene (5 × 50 ml) to remove benzoic acid, and concentrated to 50 ml. The concentrate was kept at 0° overnight and the by-product identified as 3,4-dihydroxy-α-benzamidoacrylic acid[27] (1·3 g) which separated was filtered off. The filtrate was worked up as in (a) to give the crude pyruvic acid, m.p. 179–182° (0·93 g, 45%).

1-(3,4-Dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline (I; R = H)

Tryptamine hydrochloride (2·5 g) and 3,4-dihydroxyphenylpyruvic acid (2·5 g) in water (200 ml) were refluxed for 12 hr under nitrogen. The mixture was concentrated to 40 ml and the solid which separated was filtered off. The filtrate was concentrated to 20 ml when more product was obtained on cooling to 0°. Recrystallization of the combined products from ethanol gave *1-(3,4-dihydroxybenzyl)-1,2,3,4-tetra-β-carboline-hydrochloride* (3·4 g) as colourless prisms, m.p. 226–227°. Prolonged drying at 120° failed to remove the last traces of water from this compound; the material thus dried became slightly hygroscopic. (Found: C, 64·5; H, 6·2; N, 8·4. $C_{18}H_{19}O_2N_2Cl$ requires: C, 65·4; H, 5·8; N, 8·5%).

The hydrochloride (0·3 g) was dissolved in boiling water (50 ml), and the free base was liberated by addition of a slight excess of sodium bicarbonate solution to the cooled mixture. Sublimation at 240–245°/10^{-4} mm gave pure *1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline*, m.p. 256–257°. (Found: C, 73·45; H, 6·05; N, 9·5. $C_{18}H_{18}O_2N_2$ requires: C, 73·45; H, 6·2; N, 9·5%). Acetylation with acetic anhydride gave the triacetyl derivative, which crystallized from ethyl acetate as the monohydrate, m.p. 112°. (Found: C, 65·4; H, 6·1; N, 6·2. $C_{24}H_{24}O_5N_2 \cdot H_2O$ requires: C, 65·7; H, 6·4; N, 6·0%). Prolonged drying at 95° gave the anhydrous compound. (Found: C, 68·4; H, 6·0; N, 6·7. $C_{24}H_{24}O_5N_2$ requires: C, 68·6; H, 5·75; N, 6·7%).

1-(3,4-Dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline-1 carboxylic acid

Tryptamine hydrochloride (0·29 g) and 3,4-dihydroxyphenylpyruvic acid (0·3 g) were each dissolved in warm water (7 ml), and the cooled solutions were combined. After standing 2 weeks at room temp the mixture was filtered and the solid product washed with boiling ethanol, leaving the *amino-acid* (0·345 g, 65%) as a white granular solid, m.p. 269° (dec). (Found: C, 66·8; H, 5·2; N, 8·4. $C_{19}H_{18}N_2O_4$ requires: C, 67·4; H, 5·4; N, 8·3%).

1-(3,4-Dihydroxybenzyl)-1,2,3,4-tetrahydro-9-methyl-β-carboline-1-carboxylic acid

1-Methyltryptamine hydrochloride (5·0 g) and 3,4-dihydroxyphenylpyruvic acid (4·8 g) were dissolved in water (200 ml) and kept at room temp under an atmosphere of nitrogen. After 6 weeks the solid (2·6 g) which had separated was filtered off and the green filtrate was concentrated to 50 ml. After keeping at room temp for a further 2 weeks more product was obtained. The two solid fractions were combined and washed with boiling ethanol to give the *amino-acid* (3·5 g, 44%), m.p. 238° (dec). (Found: C, 67·7; H, 6·0; N, 8·0. $C_{20}H_{20}O_4N_2$ requires: C, 68·2; H, 5·7; N, 7·95%). Subsequent preparations were carried out at 35° and gave the amino-acid in 50–55% yield after 3 weeks.

[24] C. R. Harington and S. S. Randall, *Biochem. J.* 1028 (1931).
[25] G. Billek, *Monatsh.* **92**, 343 (1961).
[26] V. Deulofeu and G. Mendivelzua, *Z. physiol. Chem.* 219 (1933).
[27] C. Funk, *J. Chem. Soc.* 554 (1911).

1-(3,4-*Dihydroxybenzyl*)-1,2,3,4-*tetrahydro-9-methyl-β-carboline* (I; R = Me)

1-(3,4-Dihydroxybenzyl)-1,2,3,4-tetrahydro-9-methyl-β-carboline-1-carboxylic acid (0·6 g) was refluxed with NHCl (50 ml) for 45 min. The solution was filtered hot and concentrated to 20 ml under red. press. After standing overnight at 0°, the product (0·55 g, 91%) which had separated was filtered off and crystallized from ethanol. The 1-(3,4-*dihydroxybenzyl*)-1,2,3,4-*tetrahydro-9-methyl-β-carboline hydrochloride*, m.p. 233–234°, softening 160–170°, which separated from this solvent contained one molecule of ethanol of crystallization. (Found: C, 64·4; H, 6·7; N, 7·1. $C_{19}H_{21}O_2N_2$ Cl, C_2H_6O *requires* C, 64·5; H, 7·0; N, 7·2%). The hydrochloride (0·015 g) was dissolved in hot water (30 ml), and the free base was liberated by addition of a slight excess of sodium bicarbonate solution to the cooled mixture. Crystallization from ethyl acetate gave colourless prisms, m.p. 227°, slowly turning brown when exposed to air. (Found: C, 73·65; H, 6·7; N, 9·1. $C_{19}H_{21}O_2N_2$ *requires*: C, 74·0 H, 6·6; N, 9·1%). Acetylation with acetic anhydride in pyridine gave the *triacetyl derivative*, prisms from ethyl acetate, m.p. 185°. (Found: C, 69·1; H, 5·6; N, 6·5. $C_{25}H_{26}O_5N_2$ requires: C, 69·1; H, 6·0; N, 6·45%).

1-(3,4-*Dimethoxybenzyl*)-1,2,3,4-*tetrahydro-9-methyl-β-carboline hydrochloride*

1-Methyltryptamine hydrochloride (2·1 g) and 3,4-dimethoxyphenylpyruvic acid[28] (2·2 g) were refluxed with water (80 ml) for 15 hr. A brown oil separated from the reaction mixture. The oil was dissolved in methanol, and ether added until a faint cloudiness was observed. A small amount of solid separated from this solution at −30° during 10 days. Recrystallization gave the required *carboline hydrochloride* (0·05 g 2·5%), m.p. 225–226° as its hemihydrate. (Found: C, 66·0; H, 7·0; N, 7·4. $C_{21}H_{25}O_2N_2Cl$, $\frac{1}{2}H_2O$ requires: C, 66·0; H, 6·9; N, 7·3%).

1-(3,4-*Dimethoxybenzyl*)-1,2,3,4-*tetrahydro-β-carboline hydrochloride* (cf. references 29, 30)

Tryptamine hydrochloride (10·5 g) and 3,4-dimethoxyphenylpyruvic acid (12 g) were refluxed with water for 36 hr. The solution was concentrated to 40 ml and cooled to 0°. The carboline hydrochloride which separated was filtered off and washed with hot ethanol to give a product, m.p. 236° (11·6 g, 67%). (Found: C, 67·3; H, 6·6; N, 8·2. Calc. for $C_{20}H_{23}O_2N_2Cl$: C, 66·9; H, 6·5; N, 7·8%).

5,7,8,13,13b,14-*Hexahydro*-2,3-*dimethoxybenz*[g]*indolo*[2,3-a]*pyridocoline* (II; R = Me)
(cf. references 30,1*d*).

1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride (1·0 g) was dissolved in water (75 ml) and 40% aqueous formalin solution (2 ml) was added. After 3 weeks the pyridocoline hydrochloride (0·62 g, 59%) which had separated was filtered off and crystallized from methanol as colourless leaflets, m.p. 255–256°; lit[1d] 254–255°, lit[30] 276°. Formalin (20 ml) was added to the aqueous filtrate and the solution boiled for 8 hr. Evaporation of the solvent and crystallization of the residue from methanol gave more product (0·275 g, 26%) m.p. 255–256°. The free base crystallized from chloroform as fine colourless needles, m.p. 248–250°; lit[1d] 249–250°, lit[30] 294–295°.

5,7,8,13,13b,14-*Hexahydro*-2,3-*dihydroxybenz*[g]*indolo*[2,3-a]*pyridocoline*. (II; R = H)

(a) *By demethylation.* The foregoing dimethoxypyridocoline hydrochloride (0·25 g) was refluxed with 48% hydrobromic acid (40 ml) for 2 hr. The reactant quickly dissolved and the product crystallized as colourless prisms during the course of the reaction. After cooling, the *dihydroxypyridocoline hydrobromide* was filtered off and recrystallized from methanol, m.p. 281·5–282°. (Found: C, 59·4; H, 5·5; N, 7·2. $C_{19}H_{19}O_2N_2Br$ requires: C, 58·9, H, 5·0; N, 7·2%). The product ran on paper as one spot, R_F 0·66, in n-butanol : acetic acid : water :: 12 : 3 : 5 v/v, detected by spraying with 1% aqueous ferric chloride solution. The hydrobromide (0·3 g) was dissolved in boiling water (50 ml), the solution cooled to 50° and a slight excess of ammonia added. The liberated *free base* (230 mg 95%) was filtered off and crystallized from ethanol containing a trace of ammonia as small, colourless, leaflets, m.p. 245–246°. A sample for analysis was dried at 100° and then allowed to equilibrate in moist air at room temp to give the hemihydrate. (Found: C, 72·6; H, 6·4; N, 8·9. $C_{19}H_{19}O_2N_2$, $\frac{1}{2}H_2O$ requires C, 72·35; H, 6·1; N, 8·9%).

The free base (0·1 g) was dissolved in hot ethanol (5 ml) and 5 drops of conc hydrochloric acid were

[28] H. R. Snyder, J. S. Buck and W. S. Ide, *Org. Synth.* Coll. Vol. II, 333.
[29] G. Hahn, L. Barwäld, O. Schales and H. Werner, *Liebigs Ann.* **520**, 107 (1935).
[30] K. T. Potts and R. Robinson, *J. Chem. Soc.* 2676 (1955).

added. The *pyridocoline hydrochloride* (0·1 g 92%) crystallized on cooling, as prisms, m.p. 282–284°. Recrystallization from methanol raised the m.p. to 284–285°. (Found: C, 66·4; H, 6·2; N, 8·2. $C_{19}H_{19}O_2N_2Cl$ requires: C, 66·6; H, 5·6; N, 8·2%).

The hydrobromide (0·09 g) was dissolved in pyridine (5 ml) and acetic anhydride (0·3 ml) was added. After 15 hr the solvent was evaporated under red. press. at 40° and the residue treated with N NH_4OH (10 ml) and extracted with ethyl acetate (30 ml). The extract was washed successively with N NH_4OH (10 ml) and water (20 ml), and dried (Na_2SO_4). The *diacetyl derivative* (0·055 g, 61%) crystallized on concentration of this solution as fine needles, m.p. 220°. (Found: C, 70·8; H, 5·8; N, 7·2. $C_{23}H_{22}O_4N_2$ requires: C, 70·6; H, 5·9; N, 7·2%).

(b) *By formaldehyde condensation.* 1-(3,4-Dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride (1·0 g) was dissolved in water (100 ml) and 40% aq. formalin (2·0 ml) was added. After 3 weeks the dihydroxypyridocoline hydrochloride (0·55 g, 54%) was filtered off and crystallized from methanol as colourless prisms, m.p. 284–285°. The product was chromatographically pure (R_F 0·66) and free from the starting carboline (R_F 0·77 in the above solvent system) which was recovered in 40% yield from the aqueous mother liquors. The hydrochloride was converted into the diacetyl derivative as described for the hydrobromide in method (a).

The respective samples of the hydrobromide and the diacetyl derivative prepared by methods (a) and (b) had identical IR and UV spectra, and suffered no depression of m.p. on mixing or on co-crystallization.

The rearrangement of 1-(3,4-*dihydroxybenzyl*)-1,2,3,4-*tetrahydro*-9-*methyl*-β-*carboline* (I; R = Me)

(a) 1-(3,4-Dihydroxybenzyl)-1,2,3,4-tetrahydro-9-methyl-β-carboline hydrochloride (3 g) was refluxed with conc hydrochloric acid (400 ml) under nitrogen for 3 hr. The acid was evaporated and the residue extracted continuously with methanol for 15 hr, leaving a yellow insoluble substance (0·6 g), m.p. 290–310°, λ_{max} (0·1 N HCl) 402, 290, and 245 mμ, which was not further investigated. Evaporation of the methanolic extract and crystallization of the residue from ethanol gave 5,6,6a,11a-*tetrahydro*-2,3-*dihydroxy*-11-*methylbenz*[a]*pyrrolidino*[2,3-d]-*carbazole* (IV; R=Me) *dihydrochloride* (2·3 g, 76%) as small, lustrous plates, m.p. 271–272°. (Found: C, 58·1; H, 5·6; N, 7·25; Cl, 18·4 $C_{19}H_{22}O_2N_2Cl_2$, $\frac{1}{2}H_2O$ requires: C, 58·45; H, 5·9; N, 7·2; Cl, 18·2%); λ_{max}(0·1 N HCl)284 and 234 mμ (ϵ_{max} 4,730 and 8,000), λ_{min} 263 and 225 mμ (ϵ_{min} 2,320 and 7,650). Titration with 0·2 N-aq. KOH gave p*Ka* values of 2·7 and 8·5, equiv. 194; required equiv. 195.

The *free base* (IV; R = Me) was precipitated from an aq. solution of the dihydrochloride by sodium bicarbonate solution, and was crystallized in low yield from aq. ethanol as colourless microleaflets, m.p. 252°. (Found: C, 73·8; H, 6·7; N, 8·85; $C_{19}H_{20}O_2N_2$ requires: C, 74·0; H, 6·6; N, 9·1%); λ_{max} (EtOH)291 and 255 mμ (ϵ_{max} 7,850 and 11,800), λ_{min} 275 and 242 mμ (ϵ_{min} 5,700 and 10,150).

IV(R = Me) gave a bright red colour with a 1% solution of ferric chloride in N HCl, and an orange-red colour with 0·5% aq. ceric sulphate.

(b) 1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydro-9-methyl-β-carboline-1-carboxylic acid (0·2 g) was refluxed for 1 hr with freshly distilled 48% hydrobromic acid. Pale yellow leaflets of the *dihydrobromide* (0·13 g, 48%) separated from the solution on cooling. Recrystallization from ethanol–ether gave almost colourless leaflets, m.p. 286–287°. (Found: C, 48·9; H, 5·2; N, 5·9; Br, 34·1. $C_{19}H_{22}O_2N_2Br_2$ requires: C, 48·5; H, 4·7; N, 6·0; Br, 34·0%).

(c) 1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydro-9-methyl-β-carboline hydrochloride (0·025 g) was refluxed for 45 min with freshly distilled 48% hydrobromic acid. The dihydrobromide separated from the reaction mixture, and was identified by comparison with an authentic sample prepared by method (b).

Acetylation of IV (R = Me)

The above dihydrochloride (0·3 g) was dissolved in pyridine (5 ml) and acetic anhydride (1 ml) was added. The mixture was kept at 20° for 14 hr and the solvent removed under red. press. at 40°. The residue was dissolved in ethyl acetate (90 ml), and the soltuion washed successively with N NH_4OH (2 × 30 ml) and water (2 × 30 ml), and dried (Na_2SO_4). On concentration of the ethyl acetate to a small volume, the colourless *triacetyl derivative* (0·11 g, 33%) separated and was recrystallized from ethyl acetate as leaflets, m.p. 223° or from aq. ethanol as needles m.p. 226°. (Found: C, 68·0; H, 5·9; N, 6·6. $C_{25}H_{26}O_5N_2$ requires: C, 69·1; H, 6·0; N, 6·45%); λ_{max} (EtOH) 301 and 253 mμ (ϵ_{max} 3,840 and 11,800), λ_{min} 287 and 236 mμ (ϵ_{min} 3,340 and 7,100). The triacetyl derivative dissolved readily in N HCl. The NMR spectrum of this compound in chloroform solution was obtained at

40 Mc/s using a Varian Associates V.4300B spectrometer. Chemical shifts were measured relative to chloroform (τ = 2·76) used as an internal reference.

Acetoveratrone as-methylphenylhydrazone

Acetoveratrone (5 g) in ethanol (20 ml) was added to a solution of *as*-methylphenylhydrazine (4 g) and sodium acetate (4 g) in 10% aqueous acetic acid. This mixture was kept at 100° for 30 min when a dark yellow oil separated. The oil solidified on cooling to 0° and was crystallized from ethanol, giving *acetoveratrone* as-*methylphenylhydrazone* (6·1 g, 82%) as fine needles, m.p. 94°. (Found: C, 71·3; H, 6·5; N, 9·7%. $C_{17}H_{20}O_2N_2$ requires: C, 71·8; H, 7·1; N, 9·85%).

1-*Methyl*-2-(3,4-*dimethoxyphenyl*)-*indole*

Acetoveratrone *as*-methylphenylhydrazone (2·5 g) was slowly heated, with stirring, in polyphosphoric acid (7 g) to 150°. The cooled mixture was mixed with water (20 ml) and extracted with ether (5 × 40 ml). Evaporation of the ether from the combined extracts gave a brown oil (1·4 g, 53%) which solidified on keeping overnight at 0°. Crystallization from ethanol followed by sublimation at 60°/10^{-4} mm gave 1-*methyl*-2-(3,4-*dimethoxyphenyl*)-*indole* m.p. 99–100·5°. (Found: C, 76·4; H, 6·3; N, 5·3. $C_{17}H_{17}O_2N$ requires: C, 76·4; H, 6·4; N, 5·2%).

1-*Methyl*-2-(3,4-*dimethoxyphenyl*)-*indoline*

Conc hydrochloric acid (40 ml) was added dropwise to a refluxing mixture of 1-methyl-2-(3,4-dimethoxyphenyl)-indole (1·5 g) and zinc dust (10 g) in ethanol (60 ml) during 6 hr. The mixture was refluxed for a further 12 hr, and evaporated to dryness. The residue was dissolved in water (50 ml) and made strongly alkaline with sodium hydroxide solution, and extracted with ether (5 × 50 ml). Evaporation of the ether gave a brown solid which was extracted with boiling 2 N HCl (100 ml). Basification and ether extraction yielded a pale brown gum which slowly crystallized. Recrystallization from ethanol gave 1-*methyl*-2-(3,4-*dimethoxyphenyl*)-*indoline* as colourless cubes, m.p. 109°. (Found: C, 75·8; H, 6·9; N, 5·2. $C_{17}H_{19}O_2N_2$ requires: C, 75·8; H, 7·1; N, 5·2%).

1-*Methyl*-2-(3,4-*dihydroxyphenyl*)-*indoline*

1-Methyl-2-(3,4-dimethoxyphenyl)-indoline (0·45 g) was refluxed with 48% HBr (50 ml) for 75 min. and the solution concentrated to a small volume. Water (50 ml) and an excess of solid sodium bicarbonate were added, and the oil thus liberated was extracted with ether (3 × 30 ml). Evaporation of the ether gave a pale brown gum which crystallized from benzene (10 ml) as pale brown needles, m.p. 175°. Sublimation at 165°/10^{-1} mm gave colourless 1-*methyl*-2-(3,4-*dihydroxyphenylindoline*, m.p. 177°. (Found: C, 74·7; H, 6·2; N, 5·8. $C_{15}H_{15}O_2N$ requires: C, 74·7; H, 6·3; N, 5·8%); λ_{max} (EtOH) 287 and 254 mμ (ϵ_{max} 5,730 and 10,750), λ_{min} 278 and 242 mμ (ϵ_{min} 5,510 and 9,700); λ_{max} (0·1 N HCl) 280 and 230 mμ (ϵ_{max} 3,570 and 7,580); λ_{min} 255 and 225 mμ (ϵ_{min} 1,200 and 7,430).

The dihydroxyindoline (0·04 g) was dissolved in pyridine (1 ml) and acetic anhydride (0·1 g) was added. The mixture was kept at 20° for 15 hr and the solvent evaporated under red. press. at 40° The residue was dissolved in ethyl acetate (25 ml) and washed successively with dil ammonia (2 × 10 ml) and water 3 × 15 ml). Evaporation of the ethyl acetate gave a gum which distilled at 160–170° (bath)/10^{-3} mm yielding the *diacetyl derivative* as a colourless gum. (Found: C, 69·85; H, 5·9. $C_{19}H_{19}O_4N$ requires: C, 70·1; H, 5·9%); λ_{max} (EtOH) 298 and 250 mμ (ϵ_{max} 3,860 and 9,220), λ_{min} 281 and 233 mμ (ϵ_{min} 3,340 and 7,450).

Permanganate oxidation of the di-O-methyl derivative of IV (R = Me)

The dihydrochloride (0·55 g) was suspended in methanol (15 ml) and cooled to −30°. Distilled diazomethane (ca. 0·75 g) in ether (50 ml) was added and the mixture allowed to stand at −30° for 24 hr at 0° for 24 hr and at 20° for 12 hr. The solvent was evaporated and the residue dissolved in chloroform (20 ml) and treated with more diazomethane (ca. 0·5 g) in ether (40 ml) at 0° for 24 hr. Evaporation to dryness, followed by solution in chloroform (50 ml) and washing with 0·5 N NaOH aq.(4 × 25 ml) and water (2 × 25 ml) gave the methylated product (0·295 g) as a brown gum which solidified on trituration with ether. The product ran on paper pretreated with 0·1M-sodium borate solution as a single spot, R_F 0·91 in n-BuOH sat. with water, giving a bright red colour when sprayed with acid ferric chloride, and was free from starting material, R_F 0·25 in this system.

The crude methylated product was suspended in a solution of potassium carbonate (0·3 g) in water (20 ml). 5% Aqueous potassium permanganate solution (65 ml) was added, in small portions,

to this solution while its temp was maintained at 20° for 1 hr and 100° (reflux) for 2 hr, when the pink colour no longer faded. The precipitated manganese dioxide was filtered off and washed thoroughly with boiling water. The excess permanganate in the combined filtrate and washings was reduced with sulphur dioxide. 10% Aqueous sodium hydroxide (5 ml) was added, and the mixture washed with ethyl acetate (4 × 50 ml), then acidified to pH 1 with conc hydrochloric acid, and evaporated to dryness. The pale yellow residue was extracted continuously with ether for 8 hr, and the extract evaporated to give a brown gum which was dissolved in water (20 ml) and treated with a slight excess of aqueous calcium acetate. The precipitated calcium oxalate was filtered off, and the filtrate charcoaled and evaporated to dryness. The residual gum was examined by paper chromatography in the two solvent systems n-BuOH : AcOH : H_2O: : 4 : 1 : 5 (A) and n-BuOH : EtOH : NH_3: : 40 : 10: 2 v/v sat. with water[31] (B). Three constituents were identified by co-chromatography with authentic specimens as *m*-hemipinic acid,[32] R_F (A) 0·64, lit[31] 0·67, R_F (B) 0·17, giving a buff spot with ferric chloride solution and a yellow spot with bromothymol blue at pH 9; *m*-hemipinimide,[33] R_F (A) 0·82, R_F (B) 0·78, fluorescing yellow-green in UV light; and N-methyl-*m*-hemipinimide,[34] R_F (A) 0·88, R_F (B) 0·86, lit[31] 0·85, fluorescing yellow in UV light.

The gum was divided into two equal portions. Attempted isolation of *m*-hemipinic acid from one portion was not successful. The other portion was evaporated to dryness 3 times with 40% aq. methylamine (2 ml), and then heated to 190° during 30 min. A gas was evolved at 175–180° and at 185° the gum solidified and began to sublime as colourless needles, m.p. 245–248°. The temp was raised to 230° for 5 min, and the mixture cooled. 9 mg of the sublimate were resublimed at 200°/10^{-3} mm to give a low yield of N-methyl-*m*-hemipinimide, m.p. 268–270°. The remainder was extracted with chloroform (50 ml). Evaporation of the chloroform gave a pale brown solid which was refluxed with ethanol (40 ml) and charcoal (10 mg), and filtered. The filtrate was concentrated to 10 ml and kept at 0° for 15 hr. Needles of N-methyl-*m*-hemipinimide (12·5 mg) m.p. 268–269°, separated from the solution and were sublimed at 160°/10^{-3} mm to give the pure product m.p. 269–270°, undepressed on admixture with an authentic specimen. (Found: C, 60·0; H, 5·1. Calc. for $C_{11}H_{11}O_4N$: C, 59·7; H, 5·0%); λ_{max} (EtOH) 347, 296 and 247 mμ (ϵ_{max} 1,780, 2,150 and 47,700), λ_{min} 311, 277 and 220 mμ (ϵ_{min} 1,300, 1,500 and 6,810).

Mercuric acetate oxidation

Mercuric acetate (35 mg) in 10% aq. acetic acid (5 ml) was added to a solution of the triacetyl derivative of IV (R = Me; 11 mg) in 95% aq, ethanol (5 ml), and the mixture was refluxed for 5 hr. Water (5 ml) was added and most of the ethanol distilled off. The residual aq. solution was lyophilized to give an orange powder which was extracted into chloroform. The concentrated extract was applied to acid-washed Whatman 3MM paper and chromatographed in n-BuOH : AcOH : H_2O : : 12 : 3: 5 v/v. The orange strip, R_F 0·56 was cut out and extracted with 95% aq. ethanol containing 0·1% acetic acid. Evaporation of the extract yielded an orange solid (9 mg) which dissolved readily in 0·1 N HCl to give a pale yellow solution containing no mercuric salts. λ_{max} (EtOH) 459, 307 (shoulder), 285 and 255 mμ, λ_{min} 337, 273 and 238 mμ; λ_{max} (0·1N HCl) 390, 340 (shoulder) and 252 mμ, λ_{min} 283 and 227 mμ.

The rearrangement of 1-(3,4-*dihydroxybenzyl*)-1,2,3,4-*tetrahydro-β-carboline* (I; R=H)

(a) 1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride (10 g) was refluxed under nitrogen with freshly distilled 48% hydrobromic acid for 90 min. A clear yellow solution was obtained after 15 min, thereafter a yellow microcrystalline material (9·6 g), m.p. 360° separated from the boiling solvent. After cooling, this was filtered off, and the filtrate concentrated to 20 ml. The pale yellow amorphous solid which precipitated was collected and extracted into boiling methanol. Concentration of the methanol yielded colourless prisms, m.p. 284–285°, of 5,6,6a,11a-*tetrahydro*-2,3-*dihydroxybenz*[a]*pyrrolidino*[2,3-d]*carbazole* (IV, R=H) *dihydrobromide* (1·3 g, 10%; Found: C, 45·5, 45·1; H, 5·3, 4·9; N, 5·6; Br, 33·7; $C_{18}H_{20}O_2N_2Br_2$, H_2O requires: C, 45·6; H, 4·7; N, 5·9; Br, 33·7%); λ_{max} (EtOH/NH_3) 291, 250 and 244 mμ (ϵ_{max} 7,400, 11,900 and 12,050), λ_{min} 271, 248 and 230 mμ (ϵ_{min} 3,860, 11,780 and 10,800); λ_{max} (0·1 N-HCl) 283 and 232 mμ (ϵ_{max} 3,400 and 6,380),

[31] M. J. Vernengo, A. S. Cerezo, G. A. Iaccobucci and V. Deulofeu, *Liebigs Ann.* **610**, 173 (1957).
[32] B. D. W. Luff, W. H. Perkin and R. Robinson, *J. Chem. Soc.* 1131 (1910).
[33] W. H. Perkin, *J. Chem. Soc.* 815 (1916).
[34] H. R. Arthur, W. H. Hin and Y. L. Ng, *J. Chem. Soc.* 1840 (1959).

λ_{min} 256 and 225 mμ (ϵ_{min} 940 and 6,200). IV(R = H) gave a red colour, rapidly changing to blue-green, with a 1% solution of ferric chloride in N-hydrochloric acid; and a pink colour, slowly changing to blue-green, with 0·5% aq. ceric sulphate.

The above mentioned yellow material did not give satisfactory carbon and hydrogen analyses. Other evidence indicated that it was the salt of a di-acid base. (Found: N, 6·6; equiv. 224; p*Ka* 3·6 and 8·3. $C_{18}H_{20}O_2N_2Br_2$ (for example) requires: N, 6·6%; equiv. 228); λ_{max} (H_2O) 245, 268, 241 and 219 mμ, λ_{min} 307, 252 and 237 mμ. Paper chromatography in n-BuOH : AcOH : H_2O : : 12 : 3: 5 v/v separated it into two yellow components, R_F 0·38 and R_F 0·60.

(b) 1-(3,4-Dihydroxybenzyl)-1,2,34-tetrahydro-β-carboline hydrochloride (0·04 g) was refluxed with 48% hydrobromic acid (5 ml) for 90 min. After cooling, the yellow crystalline product (0·03 g) was filtered off and identified with the yellow substance prepared by method (a).

(c) 1-(3,4-Dihydroxybenzyl)-1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (0·05 g) was refluxed with conc hydrochloric acid (10 ml) for 6 hr. The solution was evaporated to dryness, and the residue washed with methanol, leaving a bright yellow product (0·045 g) similar to that obtained by method (a).

Acetylation of IV (R = H)

The dihydrobromide (0·2 g) of IV (R = H) was dissolved in pyridine (3 ml) and acetic anhydride (3 ml) was added. The mixture was kept at 20° for 36 hr and evaporated under red. press. at 40°. The residue was dissolved in ethyl acetate (50 ml) and the solution washed successively with 0·5 N NaOH (2 × 15 ml), 0·5 N HCl (2 × 15 ml) and water (2 × 15 ml) and water (2 × 15 ml), and dried (Na_2SO_4). Evaporation of the solvent gave the hydrated *tetra-acetyl derivative* (0·11 g, 57%) as a colourless gum which crystallized from ethyl acetate–hexane at 30°, and recrystallized from aqueous ethanol as small, feathery needles, m.p. 186·5–188°. (Found: C, 64·9; H, 5·9; N, 5·8. $C_{36}H_{36}O_6N_2$, H_2O requires: C, 65·0; H, 5·9; N, 5·9%); λ_{max} (EtOH) 286 and 250 mμ (ϵ_{max} 2,660 and 13,580), λ_{min} 283 and 233 mμ (ϵ_{min} 2,480 and 9,230). Prolonged drying at 100° failed to produce an anhydrous sample.

Permanganate oxidation of the di-O-methyl derivative of IV (R = H)

The dihydrobromide (0·45 g) in methanol (20 ml) was methylated with diazomethane similarly to the above mentioned N-methyl compound. The crude di-O-methyl derivative (0·290 mg, 85%) so obtained was oxidised with alkaline permanganate and worked up as before to give a gummy product (0·045 g) which was shown by paper chromatography to contain *m*-hemipinic acid and its imide. Treatment of this gum with methylamine gave pure N-methyl-*m*-hemipinimide (4·5 mg), needles from methanol, m.p. 268–270°, undepressed on admixture with an authentic specimen. The UV spectrum of this sample was identical with those obtained previously.

Methylation and permanganate oxidation of the yellow product formed by rearrangement of 1-(3,4-*dihydroxybenzyl*)-1,2,3,4-*tetrahydro-β-carboline* (with Mr. K. G. Yates).

Treatment of the yellow dihydrobromide (2·0 g) with diazomethane as described above gave a crude methylated product (1·62 g) which was oxidised with alkaline permanganate. Working up the oxidation mixture as before gave a pale brown gum (0·62 g) which was shown by paper chromatography to contain *m*-hemipinic acid and *m*-hemipinimide among other constituents. The gum was treated with methylamine, slowly heated to 200°, and the product extracted with benzene. Evaporation of the benzene gave a brown solid (0·205 g) which sublimed at 160°/10^{-4} mm to give a pale yellow powder (0·12 g). Fractional sublimation of this product yielded two components.

(a) Sublimed at 85°/10^{-4} mm. This material (0·052 g) crystallized from ethanol (charcoal) as white needles, m.p. 155–156°. (Found: C, 60·25; H, 5·4; N, 6·4. Calc. for $C_{11}H_{11}O_4N$: C, 59·7; H, 5·0; N, 6·3%), and was identified as N-methylhemipinimide by comparison with an authentic specimen prepared according to Arthur and Ng.[14] These authors give λ_{max} 337 and 232 mμ (ϵ_{max} 5,130 and 339) for this compound, whereas our sample had λ_{max} (EtOH) 337 and 232 mμ (ϵ_{max} 4,330 and 31,200), λ_{min} 273 mμ (ϵ_{min} 1,110).

(b) Sublimed at 140–145°/10^{-5} mm. This product (0·038 g) was washed with hot ethanol giving a white powder m.p. 255–260°, which was identified as N-methyl-*m*-hemipinimide by comparison with an authentic specimen.

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