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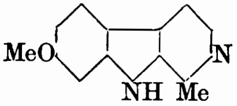
I.—*Harmine and Harmaline. Part IX. A Synthesis of Harmaline.*

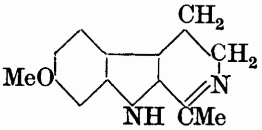
By Richard Helmuth Fred Manske, William Henry Perkin, jun., and Robert Robinson.

In earlier parts of this series of papers several syntheses of derivatives or degradation products of the *harmala* alkaloids have been recorded and the evidence afforded by the syntheses of *apo*harmine (Part VII; Lawson, Perkin, and Robinson, J., 1924, **125**, 626), norharman (Part V; Kermack, Perkin, and Robinson, J., 1921, **119**, 1619), harman (Part IV; Perkin and Robinson, J., 1919, **115**, 968), and *N*-methyltetrahydronorharmine (Part VI; Kermack, Perkin, and Robinson, J., 1922, **121**, 1890) amply suffices to determine the constitution of harmine (I). Some details of the structure proposed for harmaline (II), however, awaited confirmation by a synthetical method and for this reason, in planning the present investigation, although harmine and harmaline are interconvertible, we decided to attempt the synthesis of harmaline in the first place and, furthermore, we hoped to employ a series of reactions such that a successful outcome of the work would have a real bearing on the constitutional problem. After numerous attempts in other directions, only one of which is mentioned in this communication, the synthesis of harmaline has been effected and in such a manner (see below) as strongly to support the adoption of the expression (II) and to exclude (III) as a representation of the constitution of this base. Apart from (II), the synthesis is consistent only with the formula (IV), and we take this opportunity of pointing out that the reactions of harmaline may be satisfactorily interpreted on the hypothesis that (II) and (IV) are tautomerides, the crystallised base being probably (II). It has already been shown (Part VIII; Nishikawa, Perkin, and Robinson, J., 1924, **125**, 657) that methylharmaline and acetylharmaline are

N-substituted derivatives of (IV) and therefore the nucleus exhibits little disinclination to assume this configuration, which probably

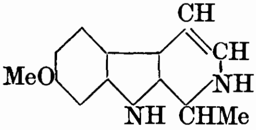
(I.)

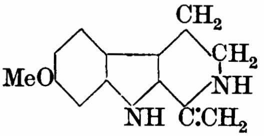




(II.)

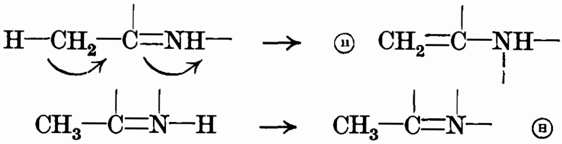
(III.)





(IV.)

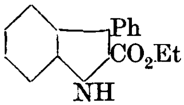
comes into play in the characteristic reactions of harmaline with diazonium salts and with benzaldehyde. On the other hand, the tertiary basic character required by formula (II) is exhibited towards methyl iodide and other alkylating agents and all analogies (compare, for example, the salt formation of ethyl β-aminocrotonate, 1-benzylidene-*N*-methyltetrahydro*iso*quinoline, *iso*papaverine, methylenedihydroquinolines, and of other anhydronium bases) indicate that the double bond in a salt of harmaline is invariably in the position illustrated in (II). We do not conceive the interchange between (II) and (IV) as a direct one but rather as a process dependent on the presence of hydrogen ions, the decomposition of a kation in two directions being responsible for any equilibrium which may be established. The electronic changes and fission involved are represented in the annexed scheme.



$$H{-}CH_2{-}\overset{|}{C}{=}NH{-} \rightarrow \textcircled{H}\ CH_2{=}\overset{|}{C}{-}\underset{|}{N}H{-}$$

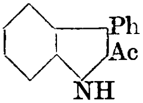
$$CH_3{-}\overset{|}{C}{=}\overset{|}{N}{-}H \rightarrow CH_3{-}\overset{|}{C}{=}\overset{|}{N}{-}\ \textcircled{H}$$

Turning to the detail of the synthetical work, the feasibility of our plan in main outline was clearly indicated when we found in a favourable case that E. Fischer's synthesis of indole derivatives could be applied to the monophenylhydrazone of an α-diketone, a member of a class of substances which are very readily accessible in great variety through the Japp–Klingemann reaction (*Ber.*, 1888, **21**, 549; *Annalen*, 1888, **247**, 218). The advantages of this procedure are manifold; indole derivatives can be prepared which are difficult or impossible to obtain in other ways, but apart from this, the Japp–Klingemann reaction gives excellent yields and the stage of reduction of the diazonium salt to a hydrazine is eliminated. Ethyl α-acetyl-β-phenylpropionate condenses directly with benzenediazonium chloride in alkaline-alcoholic solution with extrusion of the acetyl group, and the product, after hydrolysis and treatment with alcoholic hydrogen chloride, yields *ethyl 3-phenylindole-2-carboxylate* (V). On the other hand, an alkaline solution of sodium α-acetyl-β-phenylpropionate and benzenediazonium chloride affords, with extrusion of the carboxyl group, *α-phenylbutane-βγ-dione β-phenylhydrazone* (VI). Boiling concentrated hydrochloric acid induces indole cyclisation of this substance to *2-acetyl-3-phenylindole* (VIII), which yields 3-phenylindole on fusion with sodium hydroxide.



(V.)

(VI.)



(VII.)

The method was then extended to the preparation of a 2-acetyl-3-β-aminoethylindole derivative and, as appeared in the sequel, we fortunately selected the phthaloyl residue for the protection of the amino-group. Ethyl δ-phthalimido-α-acetylvalerate,

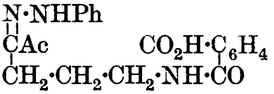
$$C_6H_4(CO)_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHAc{\cdot}CO_2Et$$

(Gabriel, *Ber.*, 1909, **42**, 1242), was hydrolysed by cold aqueous-alcoholic sodium hydroxide with the formation of the salt

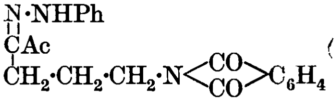
$$CO_2Na{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHAc{\cdot}CO_2Na,$$

and this coupled in the alkaline solution with benzenediazonium chloride, losing the carboxyl group and yielding, after acidification, *ζ-o-carboxybenzamidohexane-βγ-dione γ-phenylhydrazone* (VIII). This phthalamic acid was easily converted into the corresponding phthalimide (IX) by means of acetic anhydride.

(VIII.)



$$\begin{array}{ll} \mathrm{N{\cdot}NHPh} & \\ \| & \\ \mathrm{CAc} & \mathrm{CO_2H{\cdot}C_6H_4} \\ | & \qquad\quad | \\ \mathrm{CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}CO} & \end{array}$$



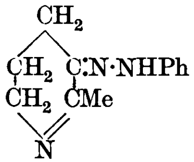
$$\begin{array}{l} \mathrm{N{\cdot}NHPh} \\ \| \\ \mathrm{CAc} \\ | \\ \mathrm{CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}N}{<}^{\mathrm{CO}}_{\mathrm{CO}}{>}\mathrm{C_6H_4} \end{array}$$

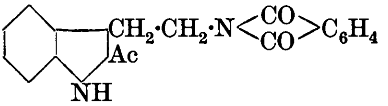
(IX.)

At this stage, serious difficulty was encountered in the course of attempts to induce the indole transformation of these phenylhydrazones. The compound (VIII) exhibits a marked tendency to split off phthalic acid with formation of a remarkable tetrahydropicoline derivative (X). This substance is a strong, stable base forming intensely yellow salts and it is best prepared from the phthalamic acid derivative by the action of hydrogen chloride in hot acetic acid solution; further representatives of this series have been similarly obtained and are described in the experimental section. An interesting property of the base is its stability to acids and so far as we are aware it cannot be converted into an indole derivative under the influence of acids or reagents such as zinc chloride. In the light of the theory of the mechanism of the Fischer indole synthesis (Robinson and Robinson, J., 1918, **113**, 639; 1924, **125**, 827), this means that the substance does not occur in the phase containing the group $\mathrm{NHPh{\cdot}NH{\cdot}\overset{|}{C}{=}\overset{|}{C}{-}}$, and it is not unreasonable to attribute this circumstance to the plastic, semi-aromatic character of the system $\mathrm{NHPh{\cdot}N{:}C{\cdot}C{:}N{-}}$. In such assemblages there is a reduction of unsaturated character and a stability factor which operates against the transfer of the unsaturation to any external group in a tautomeric process.

Further evidence that the hydrazone complex has been modified in character by the associated imino-centre is supplied by the resistance which the base exhibits to hydrolysis. The formation of (X) from (VIII) is doubtless facilitated by, or is even entirely due to, the formation of an intermediate product containing the group $\mathrm{{\cdot}CMe(OH){\cdot}\overset{|}{N}{\cdot}CO{-}}$, and if the nitrogen of the amide group carried no hydrogen atom this preliminary ring closure would, of course, be avoided. Actually it was found possible to obtain the corresponding indole derivative (XI) from (IX) by the use of boiling alcoholic hydrochloric acid, and no other reagent, in our experience, is able to bring about the transformation.

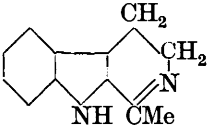
(X.)





(XI.)

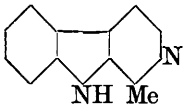
(XII.)

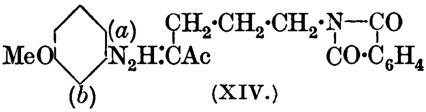


In order to obtain *harmalan*, the name by which we propose to designate *des*methoxyharmaline (since *des*methoxyharmine is termed harman), it was necessary to remove the phthaloyl group from (XI) by hydrolysis, and in this connexion a method was devised which is likely to prove generally serviceable in synthetical investigations involving the use of phthalimide derivatives. The action of hydrazine hydrate in hot alcoholic solution on (XI), followed by treatment of the product with hydrochloric acid, yields, quite smoothly, phthalhydrazide, $C_6H_4(CO)_2(NH)_2$, which is insoluble, and a solution of harmalan hydrochloride. Ing and Manske (compare J., 1926, 2348) have shown that the process is generally applicable as the final stage in Gabriel's synthesis of amines.

Harmalan (XII) crystallises with $10H_2O$ and on oxidation with chromic acid yields harman (aribine, loturine) (XIII).

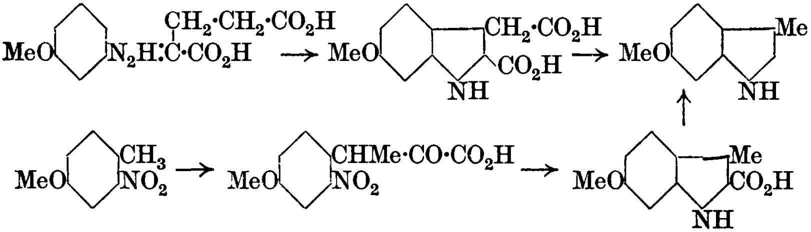
(XIII.)



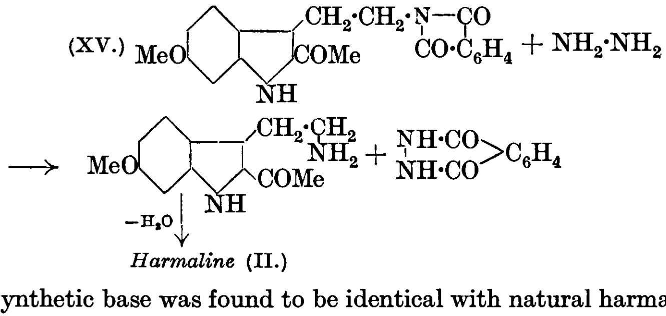


(XIV.)

Replacing benzenediazonium chloride by *m*-methoxybenzenediazonium chloride in the above series of reactions, we obtained a methoxy-derivative of the phthalamic acid (VIII) and then by dehydration the phthalimide derivative (XIV). In this substance, the indole ring might be closed in either of the positions (*a*) and (*b*), but Kermack, Perkin, and Robinson (J., 1921, **119**, 1614) have realised the following scheme, proving not only that closure in position (*a*) is favoured, but also that the reaction involves no alteration in the orientation of the substituents in the benzene ring.



It was found very difficult to transform the hydrazone (XIV) into an indole derivative, but ultimately the change was brought about with the help of *n*-butyl-alcoholic hydrogen chloride. The product (XV) was then converted into harmaline (II) by the hydrazine method as illustrated below.



(XV.)

Harmaline (II.)

The synthetic base was found to be identical with natural harmaline in all respects; the less pure residues were oxidised to harmine, indistinguishable from a specimen derived from *Peganum harmala*.

Although this memoir does not quite complete the account of our investigations in the group of the *harmala* alkaloids, we feel that the present opportunity should be taken in order to pay a tribute of appreciation to the pioneer worker in this field of chemistry. Our researches owe much to the difficult experimental investigations of Otto Fischer which preceded them.

EXPERIMENTAL.

γ-Phthalimidobutyronitrile, $C_6H_4(CO)_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$.—In the course of our earlier experiments considerable quantities of this nitrile were prepared with the object of attempting the reduction of the substance to γ-phthalimidobutaldehyde. The latter stage was not accomplished satisfactorily, but the direct replacement of bromine by the cyano-group in γ-bromopropylphthalimide was effected by the use of anhydrous methyl-alcoholic sodium cyanide. This transformation was attempted by Gabriel (*Ber.*, 1889, **22**, 3337) without success and it is certain that the following conditions cannot be greatly varied. Anhydrous hydrogen cyanide (7 c.c.) and sodium iodide (0·5 g.) were added to a solution of sodium methoxide (from 3 g. of sodium) in dry methyl alcohol (50 c.c.); the sodium cyanide was precipitated in a finely-divided condition. After the introduction of γ-bromopropylphthalimide (27 g.), the mixture was refluxed for 2 hours and most of the alcohol removed by distillation. The product, isolated after the addition of water, crystallised from alcohol (20 c.c.) (charcoal) in rhombohedra (yield, 12—16 g.). This pale brown material is sufficiently pure for many purposes and one recrystallisation from alcohol gives the pure nitrile, m. p. 81°. The substance has been previously obtained by Gabriel (*Ber.*, 1889, **22**, 3337) from potassium phthalimide and γ-bromobutyronitrile.

3-*Phenylindole*-2-*carboxylic Acid* (formula as V).—The phenylhydrazone of phenylpyruvic acid (Wislicenus, *Ber.*, 1887, **20**, 593) may be conveniently prepared by the following application of the Japp-Klingemann reaction. A solution of sodium hydroxide (12 g.) in water (30 c.c.) was added to one of ethyl α-acetyl-β-phenylpropionate (22 g.) in alcohol (150 c.c.) and, without delay, a solution of benzenediazonium chloride (from 9·3 g. of aniline and 50 c.c. of concentrated hydrochloric acid) was introduced, causing the precipitation of a heavy brown oil. A few minutes later the product was precipitated by the addition of water, washed by decantation, and, as it did not solidify, was at once hydrolysed by means of alcoholic sodium hydroxide on the steam-bath. The acid obtained on acidification was crystallised from aqueous alcohol, yielding 20 g. of a product, m. p. 160° (Wislicenus, *loc. cit.*, gives m. p. 161°).

A solution of the hydrazone (26 g.) in alcohol (75 c.c.) was rapidly saturated with hydrogen chloride and then refluxed for ½ hour; ammonium chloride separated. The resinous mass obtained on the addition of water afforded, on solution in hot alcohol and cooling, about 2 g. of *ethyl* 3-*phenylindole*-2-*carboxylate* (V). This ester crystallised from alcohol in colourless rhombohedra, m. p. 137—138° (Found: C, 76·8; H, 5·8; N, 5·3. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%). The alcoholic mother-liquor, after the separation of the ester, was made strongly alkaline by means of sodium hydroxide and heated on the steam-bath for an hour. Water then precipitated some 3-phenylindole, identified by its m. p. (87°) and by colour reactions, whilst the alkaline filtrate from this, on acidification, gave 3-*phenylindole*-2-*carboxylic acid*, which was dried (10 g.) and crystallised from benzene. The colourless clusters of needles, m. p. 186° (Found: C, 75·3; H, 4·7; N, 5·8. $C_{15}H_{11}O_2N$ requires C, 75·9; H, 4·6; N, 5·9%), lose carbon dioxide, on heating, with formation of 3-phenylindole.

α-Phenylbutane-βγ-dione β-*Phenylhydrazone* (VI).—A solution of sodium hydroxide (9 g.) in water (25 c.c.) was added to ethyl α-acetyl-β-phenylpropionate (44 g.) in alcohol (50 c.c.). Shortly after the formation of a semi-solid gelatinous mass, water (500 c.c.) was added and the mixture stirred until only a small amount of oil remained unacted upon. This was removed by passing the liquid through a wet filter and a solution of benzenediazonium chloride (from 18 g. of aniline, 13 g. of sodium nitrite, and 50 c.c. of concentrated hydrochloric acid) was introduced. The addition of crystallised sodium acetate (100 g.) caused the rapid precipitation of the phenylhydrazone, which was carried to the surface by the liberated carbon dioxide and was collected, washed with water, aqueous sodium carbonate, and then again with water (yield after drying, 42—44 g.). The substance, which may be distilled in small quantities undecomposed under diminished pressure, crystallises from alcohol or benzene in glistening, pale yellow plates, m. p. 108°, and is readily soluble in chloroform (Found: C, 75·5; H, 6·3; N, 11·2. $C_{16}H_{16}ON_2$ requires C, 76·2; H, 6·3; N, 11·1%).

α-Phenylbutane-βγ-dione β-m-*nitrophenylhydrazone* and β-2:5-*dimethoxyphenylhydrazone* were obtained in the same way as the preceding compound, the appropriate derivative being substituted for aniline. The former is sparingly soluble in acetic acid, from which it separates in yellow needles, m. p. 146° (Found: C, 64·9; H, 5·1; N, 14·5. $C_{16}H_{15}O_3N_3$ requires C, 64·6; H, 5·0; N, 14·1%). The latter crystallises from alcohol in greenish-yellow needles, m. p. 107° (Found: C, 69·5; H, 6·5; N, 9·2. $C_{18}H_{20}O_3N_2$ requires C, 69·2; H, 6·4; N, 9·0%). In both cases, the yield was 80% of that theoretically possible.

2-Acetyl-3-phenylindole (VII).—α-Phenylbutane-βγ-dione β-phenylhydrazone (25·2 g.) was added in one portion to boiling hydrochloric acid (75 c.c.; *d* 1·16), and the mixture then boiled for 15 minutes. The oil precipitated on the addition of a large volume of water was washed by decantation and soon crystallised (dried, 23 g.). The substance was crystallised from alcohol and then from benzene, being obtained in stout, pale yellow prisms, m. p. 151° (Found: C, 81·4; H, 5·8; N, 6·1. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%). The crude product may also be conveniently purified by distillation under diminished pressure. On fusion with sodium hydroxide and a little water for a few minutes at a high temperature, 3-phenylindole was obtained; it was identified by the m. p. (87°) of a mixture and by comparison with an authentic specimen.

Ethyl δ-Phthalimido-α-acetylvalerate.—This ester has been described by Gabriel (*loc. cit.*). Since relatively large quantities of it were required, we have studied the optimum conditions for the preparation. After sodium (24 g.) had been dissolved in anhydrous alcohol (300 c.c.), ethyl acetoacetate (140 g.) and γ-bromopropylphthalimide (268 g.) (Gabriel and Weiner, *Ber.*, 1888, **21**, 2671; compare Ing and Manske, this vol., p. 2348) were successively introduced and the mixture was refluxed for 2 hours. The greater part of the alcohol was then removed by distillation and the residue added to water (2000 c.c.). The oil crystallised and was collected, washed with much cold water and dried. The yield was uniformly 300—310 g. and in this form the substance is sufficiently pure to be employed for the purposes mentioned below. A specimen crystallised from benzene–light petroleum had m. p. 64° (Gabriel, *loc. cit.*, gives 65°) (Found: C, 64·8; H, 6·0; N, 4·3. Calc. for $C_{17}H_{19}O_5N$: C, 64·4; H, 6·0; N, 4·4%).

ζ-o-Carboxybenzamidohexane-βγ-dione γ-Phenylhydrazone (VIII).—A solution of sodium hydroxide (25 g.) in water (100 c.c.) was added to one of ethyl δ-phthalimido-α-acetylvalerate (95 g.) in alcohol (100 c.c.), the temperature being kept below 10°. After 5 hours, cold water (1000 c.c.) was added and on the following day the solution was shaken with a little animal charcoal and filtered, and crystallised sodium acetate (200 g.) was dissolved in it. The liquid was then mechanically agitated during the introduction of a solution of benzenediazonium chloride prepared from aniline (28 g.), concentrated hydrochloric acid (150 c.c.), and sodium nitrite (21 g.) dissolved in water (50 c.c.). A brown, pasty mass was immediately formed and carried to the surface by the liberated carbon dioxide. Stirring was continued for an hour and after the solution had been rendered strongly acid by means of hydrochloric acid the pale brown precipitate was collected and washed with water. The crude product was dissolved as far as possible in aqueous sodium hydroxide (1000 c.c. of 4%) and was reprecipitated after the solution had been treated with charcoal and filtered (dried, 90—95 g.). After crystallisation from acetone, almost colourless needles, melting with loss of water at 156—157°, were obtained (Found: C, 65·4; H, 6·1; N, 11·3. $C_{20}H_{21}O_4N_3$ requires C, 65·4; H, 5·7; N, 11·4%). This acid is sparingly soluble in most organic solvents in the cold.

ζ-Phthalimidohexane-βγ-dione γ-Phenylhydrazone (IX).—The acid just described was at first converted into an anhydro-derivative by heating it at 180° under diminished pressure (yield, 10—20%). The following procedure is much more satisfactory, the yield being 70% of that theoretically possible. Carboxybenzamidohexanedione phenylhydrazone (37 g.) was added to an equal weight of boiling, freshly-distilled acetic anhydride, and the source of heat removed. When the exothermic reaction ceased, the mixture was boiled for 5 minutes, allowed to cool to 80°, and 95% alcohol (40 c.c.) then added. Crystallisation was induced by inoculation and after cooling in ice-water the solid was collected and washed with alcohol until the filtrate was colourless (dried, 24—28 g.). This material, m. p. 168—170°, is pure enough for most purposes. The substance crystallises from acetic acid in pale yellow needles, m. p. 172° (Found: C, 68·7; H, 5·7; N, 11·5. $C_{20}H_{19}O_3N_3$ requires C, 68·8; H, 5·4; N, 12·0%). It is but sparingly soluble in hot acetic acid and extremely sparingly soluble in boiling alcohol.

5-*Keto*-6-*methyl*-2 : 3 : 4 : 5-*tetrahydropyridine* 5-*Phenylhydrazone* (X).—A stream of dry hydrogen chloride was led during 10 minutes through a boiling solution of carboxybenzamidohexanedione phenylhydrazone (37 g.) in acetic acid (75 c.c.). The hydrochloride which separated on cooling was collected and washed with cold acetic acid (dried, 20 g.). The corresponding base, set free by means of aqueous sodium hydroxide, crystallised from benzene in pale yellow, almost rectangular prisms, m. p. 134—135°, which effloresce on exposure to air and even then contain benzene (Found: C, 74·9; H, 7·7; N, 17·7. $C_{12}H_{15}N_3,\frac{1}{2}C_6H_6$ requires C, 75·0; H, 7·5; N, 17·5%); it is readily soluble in alcohol, moderately readily soluble in benzene, and sparingly soluble in light petroleum. The *hydrochloride* is sparingly soluble in water and crystallises in brilliant yellow leaflets, m. p. 286° (decomp.) (Found: C, 61·7; H, 7·1; N, 17·6; Cl, 14·7. $C_{12}H_{15}N_3,HCl$ requires C, 60·6; H, 6·8; N, 17·7; Cl, 14·9%). The solutions of this salt and of other salts of the base and of the analogues described below are bright yellow and unaffected by nitrous acid. Addition of zinc dust to an acid solution causes decoloration and a diazotisable amine is produced. The filtrate from the original preparation contained phthalic acid but no ammonium salt. Owing to the unusual difficulty experienced in getting satisfactory or consistent results in the estimation of carbon, two further examples of the reaction were investigated and the combined evidence as to the composition of these curious bases is decisive.

*ζ-*o*-Carboxybenzamidohexane-βγ-dione γ-*m*-Chlorophenylhydrazone* (formula as VIII).—This substance was obtained in the same way as the corresponding phenylhydrazone on substituting *m*-chloroaniline for aniline. The crude product was purified by reprecipitation from a solution in dilute aqueous sodium hydroxide, and the substance separated from acetone and then from alcohol as a pale yellow, crystalline powder, m. p. 210° (decomp.) (Found: C, 60·4; H, 5·2; N, 10·5; Cl, 8·5. $C_{20}H_{20}O_4N_3Cl$ requires C, 59·7; H, 5·0; N, 10·4; Cl, 8·8%). This acid is sparingly soluble in most organic solvents.

5-*Keto*-6-*methyl*-2 : 3 : 4 : 5-*tetrahydropyridine* 5-m-*Chlorophenylhydrazone* (formula as X).—Carboxybenzamidohexanedione chlorophenylhydrazone (10 g.), dissolved in boiling acetic acid (20 c.c.), was submitted to the action of a stream of hydrogen chloride for 5 minutes, the resulting hydrochloride crystallising, even from the hot solution. The related base, isolated from an aqueous solution which had been treated with charcoal (yield, 5 g.), crystallised from benzene in yellow prisms, m. p. 161° (Found: N, 17·7; Cl, 14·6. $C_{12}H_{14}N_3Cl$ requires N, 17·8; Cl, 15·1%). The *hydrochloride* separates from boiling aqueous solutions in glistening, yellow leaflets.

5-*Keto*-6-*phenyl*-2 : 3 : 4 : 5-*tetrahydropyridine* 5-*Phenylhydrazone* (formula as X).—In the preparation of this substance no serious attempt was made to purify the intermediates. The condensation of ethyl benzoylacetate (39 g.) and γ-bromopropylphthalimide (52 g.) in the presence of alcoholic sodium ethoxide gave 74 g. of an oily product which was hydrolysed by means of aqueous-alcoholic sodium hydroxide and subsequently coupled with benzenediazonium chloride as in the type example. The yield of resinous hydrazone acid was 60 g. A stream of hydrogen chloride was passed into a solution of one-third of this product in its own weight of boiling acetic acid for 10 minutes. On cooling, a certain amount of the hydrochloride separated, but it was found advantageous to add water (200 c.c.), boil (charcoal), and concentrate the filtered solution to about 75 c.c. On cooling, there was a copious separation of a pale yellow, crystalline *hydrochloride*, which was collected, washed, and then decomposed with aqueous sodium hydroxide. The base (5 g.) crystallised from benzene–methyl alcohol in yellow, prismatic needles, m. p. 146—147° (Found: C, 78·2; H, 6·9; N, 15·2. $C_{17}H_{17}N_3$ requires C, 77·6; H, 6·5; N, 15·9%).

2-*Acetyl*-3-β-*phthalimidoethylindole* (XI).—The indole cyclisation of phthalimidohexanedione phenylhydrazone does not give quite satisfactory yields under any conditions which we have employed, but the following procedure affords uniform results. A stream of dry hydrogen chloride was passed through a suspension of the hydrazone (17·5 g.) in boiling alcohol (150 c.c.) (reflux) for 45 minutes. Most of the alcohol was removed by distillation and the residue repeatedly washed with hot water. The aqueous extract contained ammonium chloride. The brown tar was dried (17 g.) and refluxed with acetone (400 c.c.) and animal charcoal (2 g.) for about 2 hours; the solution was then filtered and concentrated to a small volume. On keeping for several days, the residual pale brown syrup became semi-solid—the change may be hastened by inoculation. The crystals were collected, washed with cold acetone, and dried (2·5—3 g.; m. p. 206—210°). The substance is very sparingly soluble in boiling acetone or alcohol and crystallises from acetic acid in small, colourless, rhombic prisms, m. p. 214° (Found: C, 72·5; H, 5·0; N, 8·4. $C_{20}H_{16}O_3N_2$ requires C, 72·3; H, 4·8; N, 8·4%). The combined mother-liquors from four such preparations were worked up for harman (see below).

Harmalan (XII).—A mixture of acetylphthalimidoethylindole with its own weight of hydrazine hydrate and ten times its weight of alcohol was boiled for 20 minutes and the resulting clear solution, acidified with hydrochloric acid, was boiled for a further 20 minutes and filtered through a layer of charcoal. An excess of sodium hydroxide was added to the pale yellow, strongly fluorescent filtrate, and, after cooling, the semi-crystalline base was collected, washed, and dried (weight about $\frac{1}{2}$ of the phthalimido-derivative taken). Harmalan crystallises best from water or from 10% alcohol in very pale yellow needles and after two recrystallisations has m. p. 182—183°, if previously dried for several hours at 75°. This product lost 48·9% at 100° in a vacuum (Found in anhydrous material: C, 78·1; H, 6·6; N, 14·8. $C_{12}H_{12}N_2,10H_2O$ requires H_2O, 49·4%. $C_{12}H_{12}N_2$ requires C, 78·3; H, 6·5; N, 15·2%). Solutions of salts of harmalan are pale yellow and exhibit a blue fluorescence, which is intensified on the addition of alcohol. The solution in concentrated sulphuric acid is non-fluorescent.

Harman (XIII).—Harmalan chromate is a sparingly soluble, brown powder and on boiling with dilute sulphuric acid some harman is produced, although the yield is poor. Harman has been prepared in this way from pure harmalan, but a larger quantity became available from residues. The mother-liquors obtained in the preparation of acetylphthalimidoethylindole were freed from acetone on the steam-bath and the tar was extracted with boiling alcohol (150 c.c.). After several days, the alcohol was decanted, the resin mixed with hydrazine hydrate (25 g.) and refluxed for 1 hour with alcohol (100 c.c.), and the resulting solution diluted with water (500 c.c.), filtered (charcoal), and acidified. The precipitated phthalhydrazide was removed (charcoal again), and the pale brown filtrate rendered strongly alkaline by the addition of sodium hydroxide. The precipitated base (about 7 g.) was collected, dissolved in dilute sulphuric acid, and a slight excess of sodium dichromate added to the solution, which was then boiled for several hours. The sparingly soluble chromate gradually disappeared as oxidation proceeded. The liquid was rendered alkaline by means of sodium hydroxide and filtered hot, and the residue extracted thrice with boiling water. The combined filtrate and extracts deposited, on cooling, sand-coloured needles, m. p. 210—215° (about 1·0 g.). One crystallisation from 5% alcohol raised the m. p. to 237°, which is the m. p. of harman (Hopkins and Cole, *J. Physiol.*, 1903, **29**, 451, give 238° as the m. p. of the base, $C_{12}H_{10}N_2$, subsequently shown to be harman; compare also Perkin and Robinson, J., 1919, **115**, 967, and Späth, *Monatsh.*, 1919, **40**, 351, who give 238° and 237—238°, respectively) (Found: N, 15·0. Calc. for $C_{12}H_{10}N_2$: N, 15·3%). The base exhibited the characteristic properties of harman, in particular the bluish-violet fluorescence of the aqueous solutions of its salts.

*ζ-*o*-Carboxybenzamidohexane-βγ-dione β-*m*-Methoxyphenylhydrazone* (formula as VIII).—A solution of sodium δ-*o*-carboxybenzamido-α-acetylvalerate, obtained exactly as described above from ethyl δ-phthalimido-α-acetylvalerate (95 g.), in which crystallised sodium acetate (200 g.) had been dissolved was stirred, and a solution of *m*-methoxybenzenediazonium chloride (from 37 g. of *m*-anisidine, 150 c.c. of concentrated hydrochloric acid, and 21 g. of sodium nitrite) gradually introduced. The precipitated brown semi-solid hydrazone adhered to the sides of the vessel and was washed by decantation and dried (95—100 g.). The substance was employed in this form for the next stage. It may be purified by solution in aqueous sodium carbonate (charcoal) and reprecipitation; crystallised from much ethyl acetate and again from alcohol, it then forms orange-yellow plates, m. p. 208° (decomp.) (Found: C, 63·8; H, 5·9; N, 10·6. $C_{21}H_{23}O_3N_3$ requires C, 63·5; H, 5·8; N, 10·6%).

*ζ-Phthalimidohexane-βγ-dione γ-*m*-Methoxyphenylhydrazone* (XIV).—The above hydrazone acid (crude product, 40 g.) was added to boiling acetic anhydride (40 g.) and the solution was boiled for

5 minutes and then allowed to cool to about 80°. Alcohol (40 c.c.) was added and, on cooling and keeping, the mixture deposited a mass of crystals which were collected, washed with alcohol, and dried (28 g.; m. p. 163—165°). The substance crystallises from acetic acid in orange prisms, m. p. 167—168° (Found: C, 66·1; H, 5·6; N, 11·3. $C_{21}H_{21}O_4N_3$ requires C, 66·5; H, 5·5; N, 11·1%), and is readily soluble in chloroform.

6-*Methoxy*-2-*acetyl*-3-β-*phthalimidoethylindole* (XV).—After numerous unsuccessful attempts to prepare this indole derivative, it was found that the following procedure gave results which were at least as good as those obtained in the simpler case. A stream of hydrogen chloride was passed through a boiling solution of phthalimidohexanedione *m*-methoxyphenylhydrazone (18 g.) in *n*-butyl alcohol (150 c.c.) for 15 minutes. The solvent was then removed by distillation under diminished pressure and the brown, resinous residue was freed from impurities volatile in a current of steam. The heavy oil was repeatedly washed with hot water, dried at 100°, and treated with animal charcoal in boiling acetone solution (600 c.c.) for several hours. The filtered liquid, concentrated to a small volume, deposited the indole in the course of a few hours in almost colourless crystals (2·4 g.; m. p. 214°). The substance crystallises from acetic acid in colourless prisms, m. p. 218° (Found: C, 69·1; H, 5·2; N, 7·7. $C_{21}H_{18}O_4N_2$ requires C, 69·6; H, 5·0; N, 7·7%). Further small quantities of the substance may be obtained from the mother-liquor by renewed solution in acetone, treatment with charcoal, and concentration to a small volume.

Harmaline (II).—The removal of the phthalic residue from methoxyacetylphthalimidoethylindole was effected by the action of hydrazine as described in the section dealing with the preparation of harmalan. Harmaline, precipitated by the addition of sodium hydroxide to the acid solution, was obtained in 90% yield. Crystallisation from methyl alcohol with the aid of charcoal gave the pure base which, alone or intimately mixed with a specimen of the alkaloid derived from *Peganum harmala*, melted at 239—240° (Found in the synthetic specimen: C, 73·1; H, 7·0; N, 12·7. Calc. for $C_{13}H_{14}ON_2$: C, 72·9; H, 6·5; N, 13·1%). Comparison of the crystalline forms and fluorescent properties confirmed the identity of the specimens and nothing was observed which could differentiate them. The synthetic base was acetylated (O. Fischer, *Ber.*, 1897, **30**, 2484) and the acetyl derivative, after two crystallisations from alcohol, had m. p. 204°, alone or mixed with an authentic specimen from natural harmaline. It displayed the characteristic colour changes on heating in alcoholic aqueous hydrochloric acid solution.

Harmine (I).—In the course of the work, partly in preliminary experiments, but chiefly by working up the mother-liquors from the indole derivative preparation with hydrazine hydrate, several grams of impure and uncrystallisable harmaline were accumulated. This material was oxidised by means of chromic acid in boiling dilute sulphuric acid solution and the resulting harmine could then be crystallised from methyl alcohol with the aid of charcoal. The pale yellow needles (Found : N, 13·2. Calc. for $C_{13}H_{12}ON_2$: N, 13·3%) had m. p. 256—258°, alone or mixed with an authentic specimen of harmine, and careful comparison with the natural base also showed that the specimens were identical.

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