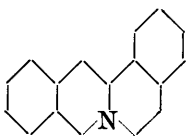
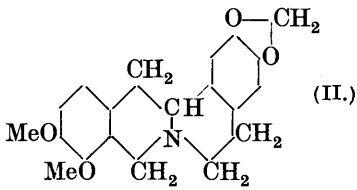
IX.—*Synthetical Experiments in the* iso*Quinoline Group. Part VI. A Synthesis of Derivatives of Paraberine.**

By Ray Campbell, Robert Downs Haworth, and William Henry Perkin, jun.

The careful investigation of the alkaloids of the palmatine, berberine, corydaline type has not only demonstrated their *iso*quinoline structure, but has also shown that they are all built up on the same curious "angular" skeleton (I), a point which is made clear when the formula of berberine or, still better, of tetrahydroberberine (II) is written alongside.

(I.)





(II.)

Furthermore, the alkaloids cryptopine, protopine, and β-homochelidonine, although containing a ten-membered ring, are readily

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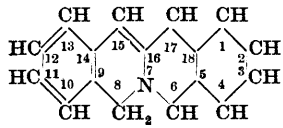
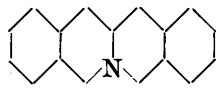
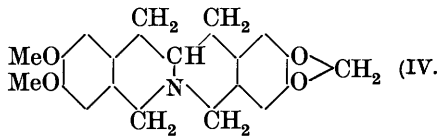


should be named "*paraberine*."

converted into quaternary salts, such as *iso*cryptopine chloride, which again are derived from the skeleton (I). It is not clear why this particular angular structure should be selected as the basis of so many of the naturally occurring alkaloids, unless indeed it be that substances of this type are particularly amenable to synthesis. In order to obtain evidence on this point, it appeared to us that it would be of interest to synthesise an alkaloid of the paraberine type containing in the place of (I) the " linear " skeleton (III) and to compare the ease of formation and general properties of such a substance with those of the alkaloids met with in nature.

(III.) 

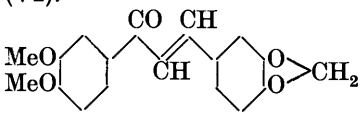


(IV.)

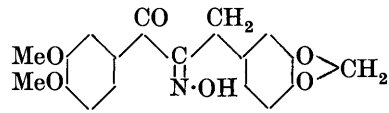
It will be seen from the experimental section of this communication that, although we were ultimately successful in constructing an alkaloid (IV) derived from the skeleton (III), the smallness of the yields at several stages made the completion of the synthesis a particularly difficult one. It is quite clear to us that substances of the angular type (I) are much more readily synthesised, under the conditions we have employed in this series of researches, than those of the linear type (III), and this fact may have some bearing on the occurrence of the angular type in nature. In attempting to synthesise (IV), the most obvious starting point was 6 : 7-dimethoxy-4-dihydro*iso*quinolone, $C_6H_2(OMe)_2\langle\begin{matrix}CO\text{---}CH_2\\CH_2\cdot NH\end{matrix}$, but we were unable to obtain this substance either from ω-aminoacetoveratrone, $(MeO)_2C_6H_3\cdot CO\cdot CH_2\cdot NH_2$, by the action of formalin or from the *N*-formyl derivative of the base by treatment with phosphorus oxychloride. Moreover, *N*-phenacetyl-ω-aminoacetoveratrone (Robinson, J., 1909, **95**, 2167), on treatment with phosphorus oxychloride, yielded not the *iso*quinoline derivative but 5-veratryl-2-benzyloxazole (m. p. 86°), which Robinson had obtained from the phenacetyl derivative by the action of sulphuric acid. This failure to close the *iso*quinoline ring seems to indicate that it is the carbonyl group in ω-aminoacetoveratrone which inhibits ring formation, because when this group is replaced by $>CH_2$ or $>CH\cdot OH$ *iso*quinoline derivatives may be readily obtained (Pictet and Gams, *Ber.*, 1909, **42**, 2943; Decker, *Annalen*, 1913, **395**, 299). After many other unsuccessful attempts, we ultimately succeeded, with the aid of the following scheme, in synthesising 2 : 3-*methylenedioxy*-11 : 12-*dimethoxy*-6 : 15 : 16 : 17-*tetrahydroparaberine* (IV).

3 : 4-Dimethoxyphenyl 3 : 4-methylenedioxystyryl ketone (V),

prepared from acetoveratrone and piperonal by Bargellini and Monti's method (*Gazzetta*, 1914, **44**, ii, 25), was reduced by hydrogen in the presence of colloidal palladium to 3 : 4-*dimethoxyphenyl* 3 : 4-*methylenedioxy*-β-*phenylethyl ketone*, which, on treatment with methyl nitrite and sodium ethoxide, yielded the iso*nitroso*-derivative (VI).



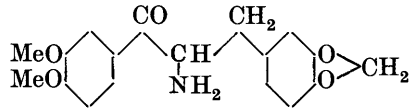
(V.)



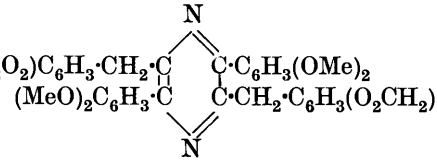
(VI.)

The reduction of this *iso*nitroso-derivative to 3 : 4-*dimethoxyphenyl* 3 : 4-*methylenedioxy*-β-*phenyl*-α-*aminoethyl ketone* (VII) proved to be a troublesome operation. When alkaline reducing agents were employed, the pyrazine derivative (VIII) was produced as the result of condensation between two molecules of the base (VII) followed by spontaneous oxidation. Eventually the amine (VII) was obtained by reducing the *iso*nitroso-derivative (VI) with stannous chloride, but in order to obtain even approximately good yields the conditions described on p. 38 must be exactly followed.

(VII.)

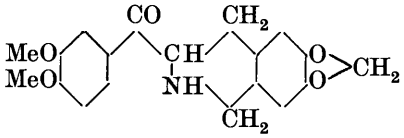


(VIII.)

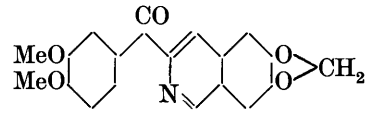


The amine (VII) condenses readily with formalin and hydrochloric acid to give 6 : 7-*methylenedioxy*-3-(3′ : 4′-*dimethoxybenzoyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (IX), the *hydrochloride*, *oxime*, *picrate*, and *benzoyl* derivative of which have been prepared. When the base (IX) is oxidised with iodine, it is converted into 6 : 7-*methylenedioxy*-3-(3′ : 4′-*dimethoxybenzoyl*)iso*quinoline* (X), which is closely related to papaveraldine in structure and properties. It is a weak tertiary base yielding pale yellow salts which are slowly dissociated by water. On fusion with potassium hydroxide, it is decomposed and veratric acid has been isolated from the product, but the basic residue could not be identified, as it was no doubt destroyed during the fusion owing to disruption of the methylenedioxy-group. The formation of veratric acid is, however, welcome confirmation of the validity of the structures (IX) and (X) and it is evident that when the amine (VII) is condensed with formalin it

is again the >CO group which inhibits ring closure with the veratryl nucleus.

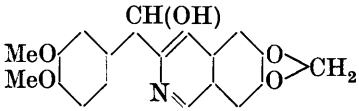


(IX.)

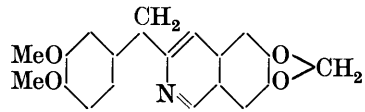


(X.)

The base (X), on reduction with zinc dust and acetic acid, yields 6 : 7-*methylenedioxy*-3-(α-*hydroxy*-3′ : 4′-*dimethoxybenzyl*)iso*quinoline* (XI), a secondary alcohol which shows reactions similar to those of papaverinol. When treated with hydrobromic acid and zinc dust (compare Buck, Perkin, and Stevens, J., 1925, **127**, 1471), it yielded an oily base the crystalline picrate of which gave analytical figures agreeing with those required for the *picrate* of 6 : 7-*methylenedioxy*-3-(3′ : 4′-*dimethoxybenzyl*)iso*quinoline* (XII), but owing to the small amount of material at our disposal we were unable to isolate the base in a pure state.



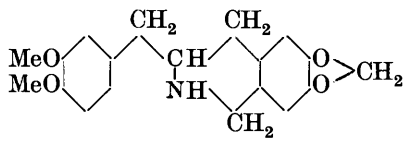
(XI.)



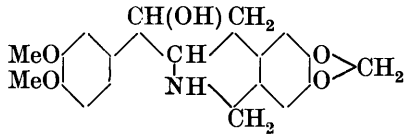
(XII.)

The reduction of the substances (IX), (X), and (XI) to 6 : 7-*methylenedioxy*-3-(3′ : 4′-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (XIII) proved to be a very difficult operation. Reducing agents such as sodium amalgam, zinc and sulphuric acid, as well as electrolytic reduction in the cold, led to the formation of amorphous bases. Since an exactly similar series of substances was obtained from papaveraldine and papaverinol under the same conditions, we are of the opinion that these amorphous bases are of the type (XIV).

(XIII.)



(XIV.)

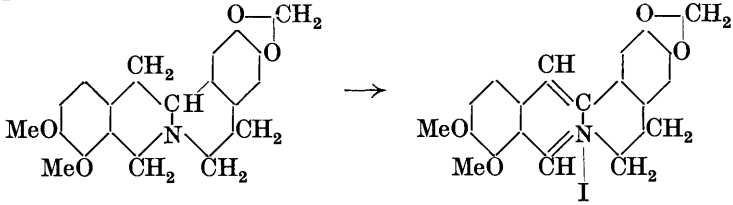


Freund and Beck (*Ber.*, 1904, **37**, 3321) obtained an amorphous base, which they named "*iso*tetrahydropapaverine," by the electrolytic reduction of papaveraldine in hot dilute sulphuric acid,

but Pyman (J., 1909, **95**, 1610) showed that their base is identical with tetrahydropapaverine prepared by reducing papaverine with tin and hydrochloric acid. We have confirmed the identity of the two preparations by a careful comparison of the hydrochlorides, hydriodides, and nitrosoamines. When we applied the conditions employed by Freund and Beck to the electrolysis of the substance (X), we obtained the base (XIII) corresponding with tetrahydropapaverine. It is remarkable that this also is amorphous, but it yields a well-crystallised *hydrochloride*, *hydriodide*, and *nitrosoamine*.

The base (XIII) is converted into 2 : 3-*methylenedioxy*-11 : 12-*dimethoxy*-6 : 15 : 16 : 17-*tetrahydroparaberine* (IV) by the action of formalin and hydrochloric acid, but the yield is extremely small and modifications of the process did not lead to any improvement. This experience appears to indicate that the system of rings (III) is produced only with difficulty and when compared with the ease of formation of substances of the tetrahydroberberine type under the same conditions clearly emphasises the greater tendency towards angular ring formation (I) (compare Lellmann and Schmidt, *Ber.*, 1887, **20**, 3154; von Braun, *ibid.*, 1922, **55**, 1710; Mayer and Schnecko, *ibid.*, 1923, **56**, 1408).

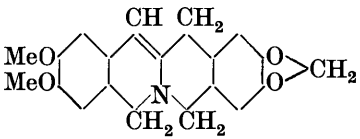
In spite of the poor yield we have been able to examine the properties of the base (IV) in some important directions. It was to be expected that, owing to analogy in constitution, the base (IV) would exhibit properties closely allied to those of tetrahydroberberine and still more to those of tetrahydro-ψ-berberine (Haworth, Perkin, and Rankin, J., 1924, **125**, 1696). The latter two are characterised by the facility with which they crystallise as well as by the sparing solubility of their salts. But the most striking characteristic is their behaviour on oxidation with iodine, when they yield quaternary salts such as berberinium iodide or ψ-berberinium iodide (*loc. cit.*, p. 1698) which are not decomposed by alkali with separation of a base.



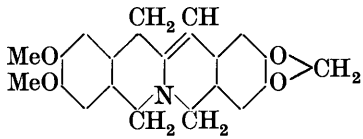
I

2 : 3-Methylenedioxy-11 : 12-dimethoxy-6 : 15 : 16 : 17-tetrahydroparaberine (IV; m. p. 222°) resembles tetrahydroberberine (m. p. 168°) and tetrahydro-ψ-berberine (m. p. 177°) in being rather sparingly soluble and yielding sparingly soluble, beautifully crystalline salts. The *methiodide* (m. p. 268°), like tetrahydroberberine

methiodide (m. p. 251°) and tetrahydro-ψ-berberine methiodide (m. p. 260°), exhibits remarkable stability to boiling alcoholic potassium hydroxide. On the other hand, when it is treated with iodine, base (IV) does not undergo a change corresponding with the conversion of tetrahydro-berberine or -ψ-berberine into the quaternary berberinium salts. The product consists mainly of a bright yellow, crystalline *hydriodide*, $C_{20}H_{19}O_4N,HI$, from which the corresponding *hydrochloride* is obtained by the action of silver chloride, and the latter, in contact with ammonia, is immediately decomposed with separation of an amorphous base, $C_{20}H_{19}O_4N$, which is clearly a 2 : 3-*methylenedioxy*-11 : 12-*dimethoxydihydroparaberine* (6 : 17 or 6 : 15) having one or other of the constitutional formulæ (XV and XVI).



(XV.)



(XVI.)

The reason for this difference in behaviour is difficult to understand, since the formula of base (IV) contains the grouping which is responsible for the formation of berberinium salts in the berberine series.

EXPERIMENTAL.

3 : 4-*Dimethoxyphenyl* 3 : 4-*Methylenedioxy*-β-*phenylethyl Ketone*.—3 : 4-Dimethoxyphenyl 3 : 4-methylenedioxystyryl ketone (V) was obtained in quantitative yield from piperonal and acetoveratrone under the conditions described by Bargellini and Monti (*loc. cit.*), but in reducing large quantities of this substance the following method is more suitable than that of the above-mentioned investigators. The styryl ketone (50 g.), glacial acetic acid (500 c.c.), 3% palladium chloride (15 c.c.), and gum arabic (0·5 g. in a little water) were introduced into a flask, connected to the hydrogen supply and immersed in a water-bath at 50—60°. The flask was fitted with a vigorously acting air-tight mechanical stirrer, the air displaced, and the mixture stirred, when a rapid absorption of hydrogen took place for 2 hours. The hot, colourless solution was filtered, most of the solvent removed, with the aid of a column, under diminished pressure, and methyl alcohol added, when the residue set to a mass of white crystals (41 g.); these crystallised from methyl alcohol in white, woolly needles, m. p. 102—103° (B. and M., *loc. cit.*, give 98—100°). The *oxime*, prepared by boiling the phenylethyl ketone with potassium acetate and hydroxylamine hydrochloride in alcoholic solution, crystallised from aqueous alcohol in slender needles, m. p.

119—121°. The iso*nitroso*-derivative (VI) was obtained by adding the phenylethyl ketone (10 g.) to boiling alcohol (200 c.c.) in which sodium (2·5 g.) had been dissolved. The hot solution was treated with a stream of dry methyl nitrite (Slater, J., 1920, **117**, 587), cooled, completely saturated with methyl nitrite, and kept in a stoppered flask for 12 hours at the room temperature, when a small amount of solid separated. Most of the alcohol was removed under diminished pressure, the residue diluted with water, and impurities extracted with benzene. Air was drawn through the aqueous layer, which was then rendered slightly acid with acetic acid, the precipitate collected,* dried (8 g.), and crystallised from aqueous acetic acid, separating in colourless needles, m. p. 137° (Found : C, 62·9; H, 5·1; N, 4·3. $C_{18}H_{17}O_6N$ requires C, 62·9; H, 5·0; N, 4·1%). This *iso*nitroso-derivative is soluble in alcohol, chloroform, or ethyl acetate, slightly soluble in ether, and sparingly soluble in water or petroleum. An attempt to reduce it with zinc dust and acetic acid at 60° led to the regeneration of the phenylethyl ketone (m. p. 102—103°).

3 : 4-*Dimethoxyphenyl* 3 : 4-*Methylenedioxy*-β-*phenyl*-α-*aminoethyl Ketone* (VII).—Anhydrous stannous chloride (56 g.) dissolved in absolute alcohol (300 c.c.) was saturated with dry hydrogen chloride at −10°, the finely powdered *iso*nitroso-derivative (40 g.) added, and the solution again saturated with hydrogen chloride at −10°. After remaining over-night, the crystalline *stannichloride* of the base (VII) which had separated was collected, dissolved in water, decomposed with hydrogen sulphide, filtered, and the filtrate concentrated until the hydrochloride separated as an oil which rapidly hardened. This (40 g.) was crystallised from a mixture of alcohol and ether, separating in slender, colourless needles, m. p. 218—219° (decomp.) (Found : C, 59·5; H, 5·5. $C_{18}H_{18}O_5N,HCl$ requires C, 59·9; H, 5·5%). This *hydrochloride* is sparingly soluble in cold alcohol, but dissolves readily in water or warm alcohol. The *picrate* was prepared in alcoholic solution and crystallised from alcohol in yellow needles, m. p. 213° (Found : C, 51·7; H, 4·1. $C_{24}H_{22}O_{12}N_4$ requires C, 51·6; H, 3·9%). When sodium hydroxide is added to the aqueous solution of the hydrochloride, a turbid solution is first produced and after some time a brown, sticky solid separates which is evidently produced by the base undergoing condensation and oxidation to the pyrazine (VIII).

The *pyrazine* (VIII) is best prepared by stirring a solution of the *iso*nitroso-derivative (VI) in sodium hydroxide with zinc dust

* The mother-liquors contain a little *iso*nitroso-compound together with some veratric acid, evidently produced by the hydrolysis of some of the *iso*nitroso-derivative.

for 3 hours at the room temperature. The sticky solid which separates is extracted with chloroform, dried, the solvent removed, and the syrup crystallised from a mixture of alcohol and chloroform, when pale yellow needles, m. p. 205°, are obtained (Found : C, 69·0; H, 5·2. $C_{36}H_{32}O_8N_2$ requires C, 69·6; H, 5·2%). This *pyrazine* is insoluble in alkali and is a weak base dissolving in concentrated hydrochloric acid, from which it is precipitated by dilution with water.

6 : 7 - *Methylenedioxy*-3 - (3′ : 4′-*dimethoxybenzoyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (IX).—A solution of the hydrochloride of the amine (VII) (2 g.) in methyl alcohol (25 c.c.) and 40% formalin (5 c.c.) was decomposed with sodium bicarbonate, boiled for 20 minutes, diluted with water, and the reddish-brown condensation product collected, washed free from formalin, and digested on the steam-bath with 20% hydrochloric acid. The mass dissolved and in a few minutes the hydrochloride of the base (IX) began to separate, the quantity increasing during 20 minutes. The mixture was cooled, the hydrochloride collected, washed with water, and recrystallised from very dilute hydrochloric acid. It was then dissolved in water and the base liberated by the addition of ammonia, collected, and crystallised from ethyl alcohol, from which it separates in rosettes of almost colourless needles, m. p. 137° (Found : C, 67·2; H, 5·7. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·5%). The *base* (IX) is readily soluble in chloroform, acetone, hot alcohol, or hot benzene, and sparingly soluble in ether, petroleum, cold alcohol, or cold benzene. It dissolves in concentrated sulphuric acid to a pale yellow solution, which becomes blood-red on the addition of a crystal of potassium nitrate. The *hydrochloride* crystallises from very dilute hydrochloric acid in slender needles containing water of crystallisation, which is lost at 115—120°. The hydrated salt is very soluble in alcohol and the addition of ether to an alcoholic solution precipitates the anhydrous hydrochloride in fine needles, m. p. 232—234° (decomp.), which are now insoluble in alcohol. The hydrated salt dried at 120° lost 9·7% H_2O; $C_{19}H_{20}O_5NCl,2H_2O$ requires H_2O, 8·7% (Found : C, 60·0; H, 5·5. $C_{19}H_{20}O_5NCl$ requires C, 60·4; H, 5·3%). The *benzoyl* derivative, obtained by the action of benzoyl chloride and sodium hydroxide on a solution of the hydrochloride, crystallises from alcohol in long, slender needles, m. p. 187—188° (Found : C, 69·7; H, 5·2. $C_{26}H_{23}O_6N$ requires C, 70·1; H, 5·2%). The *picrate*, prepared from an alcoholic solution of the hydrochloride, crystallises from alcohol in yellow needles containing solvent of crystallisation, m. p. 157—158° (decomp.) (Found : C, 50·9; H, 4·5. $C_{25}H_{22}O_{12}N_4,H_2O$ r quires C, 50·9; H, 4·1%). The *oxime* was obtained by heating the hydro-

chloride with hydroxylamine hydrochloride for 1 hour in pyridine solution. The mixture was diluted with water and saturated with carbon dioxide; the oxime then slowly separated in needles, m. p. 205—209° (decomp.).

6 : 7-*Methylenedioxy*-3-(3′ : 4′-*dimethoxybenzoyl*)iso*quinoline* (X).—The base (IX) (2 g.) was dissolved in ethyl alcohol (50 c.c.) containing potassium acetate (2 g.) and the solution boiled for ½ hour during the gradual addition of a 2% alcoholic solution of iodine (200 c.c.). On cooling, a mass of crystals separated which were collected, washed with sulphurous acid, water, and alcohol and crystallised from 50% alcoholic glacial acetic acid, separating in colourless needles, m. p. 222° (Found : C, 67·1; H, 4·5. $C_{19}H_{15}O_5N$ requires C, 67·6; H, 4·4%). This substance (X) is sparingly soluble in alcohol, but readily soluble in glacial acetic acid or chloroform. It is insoluble in water, but dissolves in warm dilute hydrochloric acid to a yellow solution, from which the free base separates on cooling. The *sulphate* crystallises from 20% sulphuric acid in pale yellow plates which slowly dissociate on washing with water. The *oxime* was obtained by boiling an alcoholic solution of the base (X) with hydroxylamine hydrochloride and potassium acetate for 8 hours. The solid was collected and washed with water, when the oxime remained as slender, colourless needles, m. p. 234—236° (decomp.). The base (X) (1 g.) was fused at 180° with potassium hydroxide (10 g.) and a little water. After 5 minutes the brown mass was dissolved in water, the black solution saturated with carbon dioxide, and the brown, amorphous precipitate collected. The filtrate was acidified, extracted with chloroform, the extract dried, and the solvent removed, when a brown solid remained. This was warmed with sodium bicarbonate solution, filtered, the filtrate acidified, the solid collected and crystallised from hot water containing animal charcoal, when needles, m. p. 178°, were obtained which were identified as veratric acid.

6 : 7 - *Methylenedioxy* - 3 - (α - *hydroxy* - 3′ : 4′ - *dimethoxybenzyl*)iso*quinoline* (XI).—The substance (X) (2 g.) dissolved in glacial acetic acid (20 c.c.) was heated on a water-bath during the gradual addition of zinc dust (0·4 g.). After 4 hours, the solution was filtered, the filtrate diluted with water, allowed to remain for some time, and the small precipitate of unchanged (X) removed. The filtrate was saturated with hydrogen sulphide, the zinc sulphide removed, the filtrate concentrated and made alkaline with concentrated ammonia, when a sticky solid separated which gradually hardened. This was collected, and crystallised from alcohol in colourless needles, m. p. 153° (Found : C, 67·4; H, 5·1. $C_{19}H_{17}O_5N$ requires C, 67·3; H, 5·0%). This base (XI) is insoluble in water, sparingly soluble

in cold alcohol, but readily soluble in hot alcohol, acetone, or chloroform. It dissolves in concentrated sulphuric acid to a magenta-coloured solution, which becomes deep green on the addition of a crystal of potassium nitrate. The *picrate* separated as an oil which rapidly hardened when an alcoholic solution of the base (XI) was treated with picric acid. It crystallises from much alcohol in yellow needles which darken at 183° and melt at 195° (decomp.) (Found : C, 53·1 ; H, 3·7. $C_{25}H_{20}O_{12}N_4$ requires C, 52·8 ; H, 3·5%).

6 : 7-*Methylenedioxy*-3-(3′ : 4′-*dimethoxybenzyl*)iso*quinoline* (XII).—The base (XI) (0·5 g.) was allowed to remain for 12 hours in glacial acetic acid (5 c.c.) saturated with hydrogen bromide. The solution was then heated to 30°, stirred, and excess of zinc dust added slowly during 3 hours. After filtration, the solution was diluted with water (50 c.c.), made alkaline with ammonia, extracted with chloroform, the extract dried and concentrated, when a thick syrup was obtained which did not crystallise. The *picrate* was prepared in alcoholic solution and crystallised from much alcohol in yellow needles, m. p. 206—207° (Found : C, 53·9 ; H, 3·7. $C_{25}H_{20}O_{11}N_4$ requires C, 54·3 ; H, 3·6%). All attempts to decompose the picrate by digesting with ammonia or sodium hydroxide were unsuccessful.

6 : 7-*Methylenedioxy*-3-(3′ : 4′-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (XIII).—The substance (X) (4 g.) was suspended in 10% sulphuric acid (200 c.c.) and placed in an enamelled metal can, which constituted the cathode compartment of an electrolytic cell. The solution was heated to 90—95° and subjected to a current of 10 amperes, when the suspended sulphate gradually dissolved to a yellow solution which became colourless after 2 hours. The hot solution was filtered, made alkaline with strong ammonia, and extracted with chloroform ; a red syrup remained on removing the solvent. This was extracted with boiling dilute hydrochloric acid, the solution filtered, and the filtrate treated with solid potassium iodide, when a sticky *hydriodide* separated which gradually hardened on cooling. This separated from alcohol, in which it was sparingly soluble, in small crystals, m. p. 226° (decomp.) (Found : C, 50·2 ; H, 5·0. $C_{19}H_{21}O_4N$,HI requires C, 50·1 ; H, 4·8%). The *hydrochloride*, obtained by digesting an aqueous solution of the hydriodide with silver chloride, crystallised from alcohol in small needles, m. p. 220—222° (decomp.). The *nitrosoamine* separated, on the addition of sodium nitrite to a solution of the hydrochloride, as an oil which hardened, and crystallised from alcohol in short needles, m. p. 128° (Found : C, 63·8 ; H, 5·7. $C_{19}H_{20}O_5N_2$ requires C, 64·0 ; H, 5·6%).

2 : 3-*Methylenedioxy*-11 : 12-*dimethoxy*-6 : 15 : 16 : 17-*tetrahydroparaberine* (IV).—The hydriodide of the base (XIII) (2 g.), dissolved

in methyl alcohol (10 c.c.), was decomposed with sodium bicarbonate and boiled for a few minutes with 40% formalin solution (10 c.c.). The mixture was cooled, diluted with water, sodium chloride added, and the solution decanted from the semi-solid mass which had separated. The latter was well washed with water, digested with concentrated hydrochloric acid (10 c.c.) on the steam-bath for a few minutes, diluted with water, and made alkaline with ammonia; an oil then separated which rapidly hardened. This was collected, triturated with methyl alcohol (15 c.c.), and the insoluble, colourless base (IV) (0·3 g.) collected and crystallised from benzene, from which it separated in small, colourless prisms, m. p. 221—222° (Found: C, 70·8; H, 6·4. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2%). The base (IV) is insoluble in water, sparingly soluble in ether, petroleum, or cold alcohol, moderately easily soluble in warm alcohol or benzene, and readily soluble in chloroform. The *hydrochloride* crystallises from water, in which it is fairly soluble, in small, colourless needles, m. p. 236—238°. The *picrate*, prepared in alcoholic solution, crystallises from alcohol in yellow nodules, m. p. 199—201° (decomp.) (Found: C, 54·5; H, 4·3. $C_{26}H_{24}O_{11}N_4$ requires C, 54·9; H, 4·2%). The *methiodide* was prepared by boiling a benzene solution of the base (IV) with an excess of methyl iodide for 1 hour, the solvent removed, and the residue crystallised from methyl alcohol, separating in large prisms, m. p. 268° (Found: C, 52·2; H, 5·2. $C_{21}H_{24}O_4NI$ requires C, 52·4; H, 5·0%). This methiodide was boiled with a large excess of 25% methyl-alcoholic potassium hydroxide for 6 hours, but, on cooling, crystals of the unchanged methiodide separated and no other substance could be isolated from the product. The methiodide was digested for 3 hours with an aqueous suspension of silver chloride and filtered, when the *methochloride* separated as a gelatinous precipitate, m. p. 260° (decomp.), from the filtrate. The methochloride was recovered after boiling for 6 hours with 25% methyl-alcoholic potassium hydroxide.

2 : 3-*Methylenedioxy*-11 : 12-*dimethoxy*-6 : 17 or -6 : 15-*dihydroparaberine* (XV or XVI).—The base (IV) (1 g.), dissolved in alcohol (20 c.c.) containing potassium acetate (1 g.), was treated with a 1% alcoholic solution of iodine (200 c.c.). After boiling for ½ hour, the mixture was cooled, and the crystalline periodide was collected and converted, by the action of sulphurous acid, into the bright yellow hydriodide; this was collected, boiled with water and the solution filtered hot. The residue consisted of a high-melting, orange-coloured hydriodide, the yield of which was too small to allow of detailed investigation. A small quantity, however, was converted into the hydrochloride by means of silver chloride, and this

gave an immediate precipitate with ammonia, showing that it was not a quaternary salt. The filtrate, on cooling, deposited pale yellow needles, m. p. 225—226° (Found: C, 51·5; H, 4·4. $C_{20}H_{19}O_4N$,HI requires C, 51·6; H, 4·3%). This *hydriodide* is sparingly soluble in cold water or cold alcohol, but moderately soluble in the warm solvents. The *hydrochloride* was obtained by digesting an aqueous solution of the hydriodide with silver chloride and separated from a little water in bright yellow needles which melted at 120° with loss of water of crystallisation. On drying at 120°, it lost 11·5% H_2O (Found: C, 63·3; H, 5·5. $C_{20}H_{19}O_4N$,HCl,$\frac{1}{2}H_2O$ requires C, 62·9; H, 5·5%). The *base* (XV or XVI) was obtained as a pale yellow, amorphous, gelatinous precipitate by the addition of ammonia to an aqueous solution of the hydrochloride, and was collected and dried. It was soluble in the usual organic solvents with the exception of petroleum, but it could not be obtained in the crystalline state. The addition of petroleum (b. p. 40—60°) to the dry ethereal solution precipitated the base as a pale yellow, amorphous powder melting indefinitely between 180° and 190° (Found: C, 70·9; H, 5·7. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·6%).

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