CCCCXXXVIII.—*Preliminary Synthetical Experiments in the Morphine Group. Part I.*

By Robert Robinson and Shigehiko Sugasawa.

In the course of a lecture delivered before this Society in November, 1925, it was suggested by one of us that the blocked hydroaromatic structure of the alkaloids of the morphine–thebaine–sinomenine

group has its biogenesis in a union of the two aromatic nuclei of a base of the laudanosine type.

Such a process is analogous to the formation of a terpene from isoprene or of vinylacetylene from acetylene, and one of the nuclei must become reduced.

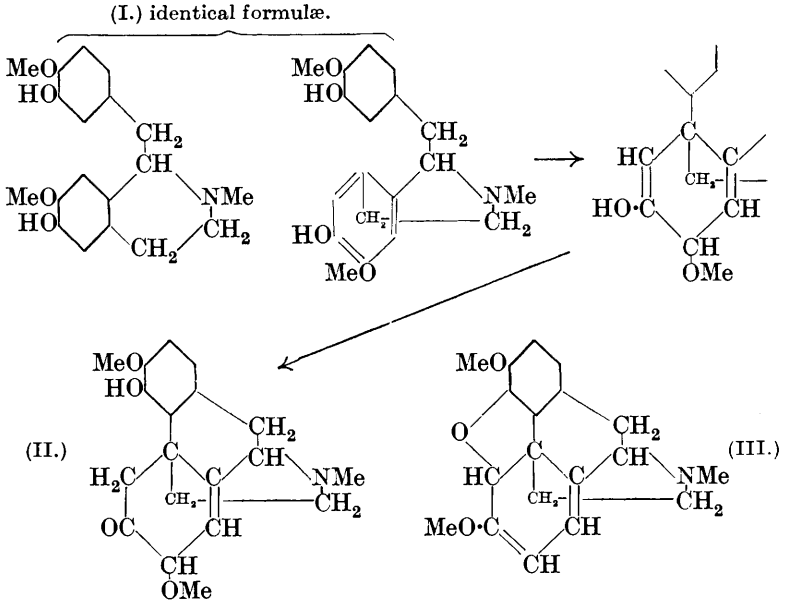
Analogies in the aromatic series are not available, but the pyrogenic formation of diphenyl is probably best envisaged as proceeding by the stages :

$$C_6H_6 + C_6H_6 \longrightarrow C_6H_5{\cdot}C_6H_7 \longrightarrow C_6H_5{\cdot}C_6H_5 + H_2.$$

If the union of the two nuclei of a base of the laudanosine type occurs in such a position that loss of hydrogen with re-formation of a true aromatic nucleus is feasible, then an aporphine alkaloid results.

If, on the other hand, addition of the one nucleus to the other occurs at a position already bearing a substituent, then loss of hydrogen is impossible without migration and a member of the morphine group is obtained.

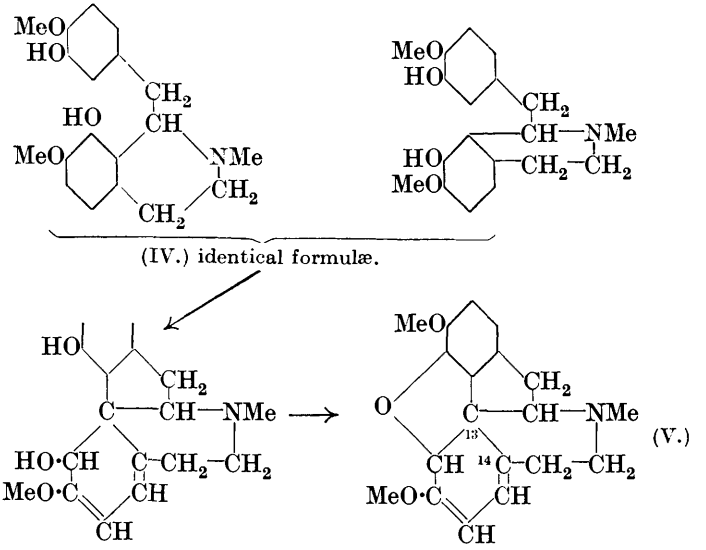
It is hardly necessary to illustrate these views in the case of glaucine or other member of the aromatic sub-group, but the phytosynthesis of sinomenine (II) from a hypothetical protosinomenine (I) is one of the simplest cases in the second category.



It will be observed that the orientation of substituents in the benzene rings of protosinomenine is identical in the two halves of the molecule, so that the postulated protosinomenine could arise from two molecules of a 3-hydroxy-4-methoxyphenylalanine.

Thebaine (III) is constituted differently and on the straightforward view is derivable from one molecule of 3-hydroxy-4-methoxyphenylalanine and one molecule of 2-hydroxy-3-methoxyphenylalanine.

A more attractive hypothesis is that which postulates the synthesis by way of a protothebaine (IV) from initial materials having the same orientation as those required for protosinomenine. The variation depends on the occurrence of tetrahydro*iso*quinoline ring closure in different directions. For protosinomenine, the substituted phenylacetaldehyde must attack a hydroxyphenylethylamine in the *p*-position to hydroxyl; for protothebaine, in the *o*-position to hydroxyl.



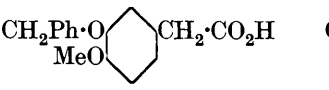
The transposition of substituents attached to C–13 and C–14 in (V) furnishes thebaine (III) and the assumption of such a change is theoretically plausible.

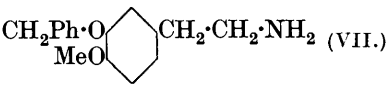
We have considered the possibility that formulæ of the type (V) might actually represent the bases of the morphine group, but the weight of evidence is opposed to such a view. It would be necessary in almost all cases to assume a preliminary migration to the Gulland–Robinson constitutions in order to furnish satisfactory explanations

of the reactions leading to degradation products. The recent experiments of Schöpf and Hirsch (*Annalen*, 1931, **489**, 224) on the formation of thebainone and metathebainone from thebaine and codeinone also provide evidence in favour of the formula (III) for thebaine, since (V) is the closer to metathebainone, and it is this latter substance that Schöpf and Hirsch regard as the secondary product in the action of hydrochloric acid and reducing agents on thebaine.

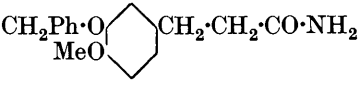
It will be understood that we make no claim to have located the stages at which *O*-methylation and *N*-methylation occur and that, equally, the formation of the oxide ring (or diaryl ether group) may also be early or late in the biosynthesis; the assumptions made in the text are purely a matter of convenience. These speculations in the field of natural alkaloidal synthesis supply the explanation of the lines on which we have chosen to develop our experimental work. It is strongly held that the only promising route to an ultimate synthesis of morphine and its congeners is by a path already laid down by Nature. Therefore we proposed the examination of suitable diaryl ethers and bases of the laudanosine type, especially such as contain free phenolic hydroxyl groups.

The present communication describes the preparation of some intermediates by methods which are detailed in the experimental section. *O*-Benzyl*iso*vanillin was the starting point in the attempt to synthesise protosinomenine. 3-Benzyloxy-4-methoxyphenylacetic acid (VI) was obtained in the usual way through the arylpyruvic acid, and β-(3-benzyloxy-4-methoxyphenyl)ethylamine (VII) was accessible by way of the arylidene-ω-nitrostyrene. The alternative method failed, since the Hofmann reaction could not be applied to *O*-benzyldihydrohesperetinamide (VIII).

(VI.) 



(VII.)

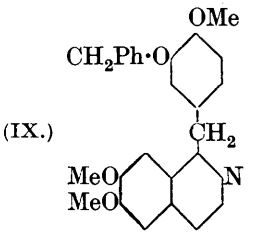


(VIII.)

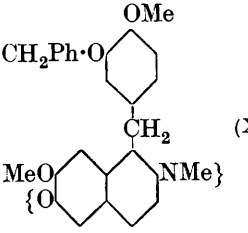
The Bischler–Napieralski condensation of the amide from (VI) and (VII) had no satisfactory outcome. In order to simplify the synthetical work we next attempted to take advantage of the observations of Decker and Eichler (*Annalen*, 1913, **395**, 377) that the *N*-alkylpapaverinium hydroxides may be caused to lose the elements of methyl alcohol, the methyl group being derived from the methoxyl in position 6.

The appropriate papaverine analogue has the constitution (IX)

and this we have synthesised by a method developed by Mannich and Walther (*Arch. Pharm.*, 1927, **265**, 1) for another case.



(IX.)



(X.)

The methosulphate of (IX) yields the phenol-betaine (X) on being heated with aqueous barium hydroxide. The final stage is the transformation of (X) into protosinomenine by reduction and debenzylation, and this has been accomplished but unfortunately the product has not yet been induced to crystallise.

EXPERIMENTAL.

O-Benzylisovanillin.—An improvement of the prescription of Lovecy, Robinson, and Sugasawa (J., 1930, 817)* consists in replacing the potassium hydroxide employed by potassium carbonate. A mixture of *iso*vanillin (15 g.), benzyl chloride (13 g.), finely powdered potassium carbonate (7 g.), and absolute methyl alcohol (30 c.c.) was refluxed for 5 hours. The filtered solution was concentrated somewhat and kept in the ice-chest; the nearly colourless crystals that separated were collected, washed with dilute sodium hydroxide solution and with water, and dried. The mother-liquor was steam-distilled, and the residue extracted with ether, yielding, after removal of the solvent, a brownish oil which crystallised when kept at 0°; this material was drained, washed with methyl alcohol, and dried (total yield, 22 g. or 90%).

2-Phenyl-4-(3'-benzyloxy-4'-methoxybenzylidene)oxazolone.—The product obtained by heating benzyl*iso*vanillin (4·8 g.), hippuric acid (3·6 g.), fused sodium acetate (2·0 g.), and acetic anhydride (10 c.c.) at 100° for 1½ hours was mixed with alcohol, and the yellow solid collected and washed with much boiling water. The substance crystallised from acetic acid in yellow prismatic needles (5·5 g.), m. p. 155° (Found: C, 74·5; H, 5·0; N, 3·9. $C_{24}H_{19}O_4N$ requires C, 74·8; H, 4·9; N, 3·6%). The substance is sparingly soluble in hot alcohol.

3-Benzyloxy-4-methoxyphenylpyruvic Acid.—The above phenylarylideneoxazolone (10 g.) was hydrolysed by refluxing with aqueous sodium hydroxide (100 c.c. of 10%) for 4 hours; evolution of

* In the preparation of *iso*vanillin the hydrobromic acid should be 37% and not 43% as stated in this memoir.

ammonia then no longer occurred. When the cooled solution was saturated with sulphur dioxide, a pasty mass was first precipitated and later benzoic acid. Separation by decantation was feasible and when the first precipitate was washed with hot dilute hydrochloric acid it became more definitely crystalline and consisted of the pyruvic acid derivative. The filtrate from benzoic acid was acidified with hydrochloric acid, heated to expel the bulk of the sulphur dioxide, and then cooled and kept. The colourless flocculent material was collected and crystallised from aqueous alcohol and then from acetic acid, forming prisms, m. p. 160—161° (Found: C, 68·2; H, 5·6. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). This *acid* is very readily soluble in hot alcohol or acetic acid.

3-*Benzyloxy*-4-*methoxyphenylacetic Acid* (VI).—Perhydrol (5 c.c.) was added dropwise and with shaking to a solution of the benzyloxymethoxyphenylpyruvic acid (5 g.) in aqueous potassium hydroxide (75 c.c. of 2%). Next day, the filtered solution was acidified and the precipitated acid crystallised from acetic acid. This material had m. p. 105—110° after drying in a vacuum over sulphuric acid (Found: loss at 70°, 3·2. $C_{16}H_{16}O_4,H_2O$ requires $\frac{1}{2}H_2O$, 3·1%. Found in material dried at 70°: C, 68·4; H, 6·0. $C_{16}H_{16}O_4,\frac{1}{2}H_2O$ requires C, 68·4; H, 6·0%). Dried at 100° and crystallised from benzene, the *acid* was obtained in nearly colourless prisms, m. p. 125°.

ω-*Nitro*-3-*benzyloxy*-4-*methoxystyrene*.—The condensation of benzyl*iso*vanillin with nitromethane was attempted under various conditions, potassium hydroxide in aqueous, methyl or ethyl alcoholic solution, methylamine hydrochloride, methylamine and ammonium acetate (compare Rao, *Helv. Chim. Acta*, 1929, **11**, 518) being employed as catalyst. The last method yielded a product which appeared to consist of the nitro-alcohol,

$$CH_2Ph{\cdot}O{\cdot}C_6H_3(OMe){\cdot}CH(OH){\cdot}CH_2{\cdot}NO_2,$$

because the action of hot alcoholic sulphuric acid changed it into the nitrostyrene.

Ultimately methylamine carbonate (compare Knoevenagel, *Ber.*, 1904, **37**, 4502) was found to be the most effective reagent for the purpose.

A mixture of benzyl*iso*vanillin (2·5 g.), nitromethane (0·7 g.), methylamine hydrochloride (0·1 g.), sodium carbonate (0·1 g.), and alcohol (5 c.c.) was kept for 4—5 days, and the product collected and washed with alcohol and water (yield, 2·5 g.).

The substance crystallised from alcohol–acetone in yellow scales, m. p. 127—128° (Found: C, 67·4; H, 5·3; N, 5·1. $C_{16}H_{15}O_4N$ requires C, 67·4; H, 5·3; N, 4·9%); it is readily soluble in acetone, benzene or ethyl acetate, sparingly soluble in alcohol and ether.

β-(3-*Benzyloxy*-4-*methoxyphenyl*)*ethylamine* (VII).—The reduction of the foregoing benzyloxymethoxy-ω-nitrostyrene was accomplished at a lead cathode by means of a current of 6·5—7 amps. The anode chamber contained 20% sulphuric acid, and a soluton of benzyloxymethoxy-ω-nitrostyrene (5 g.) in alcohol (100 c.c.), acetic acid (100 c.c.), and 30% hydrochloric acid (40 c.c.) was placed in the cathode chamber. The temperature varied in different experiments between the limits 25° and 45° and the yield of base averaged 60% of the theoretical.

During the reduction the solution was mechanically stirred and after 2—4 hours the solid had passed into solution; the reduction was then continued for a further 2 hours. The liquid was concentrated under diminished pressure, the residue taken up in water and extracted, first with ethyl acetate and then with ether. The base was then liberated by the addition of sodium hydroxide, and isolated by means of ether. It crystallised on keeping in the ice-chest. The *hydrogen oxalate* separated from alcohol as a sandy crystalline powder, m. p. 161° (Found: C, 62·4; H, 6·2; N, 4·3. $C_{18}H_{21}O_6N$ requires C, 62·3; H, 6·0; N, 4·0%). The *hydrochloride* crystallised from alcohol in slender colourless needles, m. p. 166° after softening at 162° (Found: N, 4·8; Cl, 12·4. $C_{16}H_{20}O_2NCl$ requires N, 4·8; Cl, 12·1%).

O-*Benzyldihydrohesperetinamide* (VIII).—In the preparation of derivatives of this series it was found preferable to delay the entry of the benzyl group as indicated below. However, the process employing *O*-benzyl*iso*vanillin as the starting point has also been investigated.

O-Benzylhesperetic acid was obtained by the malonic acid–pyridine–piperidine method, but the related styrene derivative was always a by-product. The acid crystallised from alcohol in prisms, m. p. 179—180° (Found: C, 71·7; H, 5·7. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%). On reduction in the usual manner, O-*benzyldihydrohesperetic acid* was obtained. This also separated from alcohol in colourless prisms, m. p. 121—122° (Found: C, 71·4; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%). The direct esterification of this acid always afforded some methyl homo*iso*vanillate.

Hesperetic acid was obtained in excellent yield by heating a mixture of *iso*vanillin (25 g.), malonic acid (25 g.), pyridine (100 c.c.), and piperidine (1 c.c.) at 100° for 2—3 hours and then refluxing it for 30 minutes. In this case the styrene derivative was not obtained and the crude product, m. p. 224—225°, could be employed for the next stage.

Hesperetic acid was reduced in aqueous-alkaline solution at 80° by means of 3% sodium amalgam, and the dihydro-acid (10 g.,

m. p. 146°) esterified by refluxing with 5% methyl-alcoholic hydrogen chloride (50 c.c.) for 5 hours. The ester crystallised from methyl alcohol in prisms, m. p. 94° (yield, 10 g.). A mixture of this substance (10 g.), benzyl chloride (6 g.), powdered potassium carbonate (3·3 g.), and methyl alcohol (20 c.c.) was refluxed for several hours, and the product isolated. *Methyl* O-*benzyldihydrohesperetate* crystallised from methyl alcohol in elongated prisms, m. p. 64° (Found: C, 71·9; H, 6·6. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%).

The clear solution obtained from this ester (12 g.), aqueous ammonia (120 c.c., *d* 0·88), and pyridine (*ca.* 250 c.c.) was saturated with ammonia at 0° and kept for 48 hours. The filtered liquid was concentrated under diminished pressure and then added to an excess of dilute hydrochloric acid, a white flocculent mass thus being precipitated. This was collected, dried, and extracted with boiling light petroleum in order to remove unchanged ester. After the latter had been worked up again in the same way, the total yield of *amide* amounted to 8 g. The substance crystallised from acetone–benzene in colourless needles, m. p. 142° (Found: C, 71·5; H, 6·6; N, 4·9. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7; N, 4·9%).

O-*Benzylhomo*isovanillo-β-(3-*benzyloxy*-4-*methoxyphenyl*)*ethylamide*.—Phosphorus pentachloride (1·5 g.) was added to *O*-benzylhomo*iso*vanillic acid (2 g.), mixed with chloroform (10 c.c.), and the whole kept for 12 hours with occasional shaking. The solvent and phosphoryl chloride were removed in a vacuum, the residual acid chloride taken up in ether, and the solution vigorously shaken with one of β-(3-benzyloxy-4-methoxyphenyl)ethylamine (2 g.) in ether mixed with aqueous 0·5*N*-sodium hydroxide (20 c.c.). The product separated as a voluminous white mass of crystals. After 30 minutes' shaking, the ether was removed, and the solid collected and washed with dilute acid and alkali (starting materials recovered from both extracts); it was crystallised from methyl alcohol, twice from benzene and finally from ethyl acetate, forming clusters of colourless needles, m. p. 118° (Found: C, 74·7; H, 6·3; N, 2·8. $C_{32}H_{33}O_5N$ requires C, 75·2; H, 6·5; N, 2·8%). Cyclisation of this *amide* was attempted under a variety of conditions without success.

O-*Benzylhomo*isovanillo-β-*methoxy*-β-*veratrylethylamide*, $C_7H_7{\cdot}O{\cdot}C_6H_3(OMe){\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH(OMe){\cdot}C_6H_3(OMe)_2$.—ω-Nitro-3:4-dimethoxystyrene was prepared by the method used by Tanaka and Midzuno (*J. Pharm. Soc. Japan*, 1929, **49**, 255) for the corresponding piperonyl derivative; the yield was good. A solution of veratraldehyde (33 g.) and nitromethane (13 g.) in alcohol (100 c.c.) was cooled in ice-water, and potassium hydroxide (18 g.) in methyl alcohol (50 c.c.) gradually added with shaking. After 2 hours at the room temperature the white crystalline

precipitate was collected, dissolved in water, and added to dilute hydrochloric acid (3000 c.c.). The yellow precipitate was collected; it crystallised from acetone in leaflets, m. p. 140°. Addition of the elements of methyl alcohol and reduction of the product were accomplished by the methods of Mannich and Walther (*loc. cit.*). The veratryl derivatives have also been made in a different way by Rosenmund (*Ber.*, 1913, **46**, 1048) and by Rosenmund, Nothnagel, and Riesenfeldt (*Ber.*, 1927, **60**, 392).

Phosphorus pentachloride (8 g.) was added to a mixture of anhydrous *O*-benzylhomo*iso*vanillic acid (10 g.) and chloroform (50 c.c.), and the mixture kept for 12 hours. On removal of the solvent an oil remained and this slowly crystallised. The chloride was, however, dissolved in chloroform (30 c.c.) and added drop by drop to a mixture of methoxyaminoethylveratrole (10 g.) dissolved in ether and aqueous sodium hydroxide (100 c.c. of 5%) with continuous vigorous agitation. The resultant *amide* separated, and was collected after 2 hours; it crystallised from ethyl acetate in aggregates of colourless needles, m. p. 124° (Found: C, 70·0; H, 6·7; N, 3·0. $C_{27}H_{31}O_6N$ requires C, 69·7; H, 6·7; N, 3·0%). The filtrate from the crude amide furnished a further quantity by concentration in a current of air and extraction with ethyl acetate; the total yield was 13 g. The substance is fairly readily soluble in most organic solvents but is rather sparingly soluble in ether and very sparingly soluble in light petroleum.

1-(3′-*Benzyloxy*-4′-*methoxy*)*benzyl*-6 : 7-*dimethoxy*isoquinoline (IX). —A mixture of the amide (10 g.) described in the foregoing section, toluene (50 c.c.), and phosphoryl chloride (30 g.) was gently boiled (oil-bath) under reflux for 1 hour, cooled, and an excess of light petroleum added. The solvent was decanted, and the residue was washed with benzene, taken up in alcohol, and added to aqueous sodium hydroxide. The rather sticky base was collected, dried, and extracted in a Soxhlet apparatus with benzene. The benzene solution was washed with aqueous sodium hydroxide, dried, and concentrated, and light petroleum added to produce a turbidity. The *base* then crystallised slowly at 0° and, recrystallised from benzene–light petroleum, formed colourless slender needles, m. p. 112—113° (Found: C, 74·9; H, 6·1; N, 3·4. $C_{26}H_{25}O_4N$ requires C, 75·2; H, 6·0; N, 3·4%). The base is readily soluble in benzene and sparingly soluble in ether.

The *picrate* crystallised from much alcohol in slender yellow plates, m. p. 192° (Found: N, 8·4. $C_{32}H_{28}O_{11}N_3$ requires N, 8·7%).

1-(3′-*Hydroxy*-4′-*methoxy*)*benzyl*-6 : 7-*dimethoxy*isoquinoline (3′-*Des*-O-*methylpapaverine*).—The alkaline filtrate from the crude base mentioned in the last section was concentrated under diminished

pressure, and sufficient potassium bicarbonate added to neutralise the free caustic alkali. On keeping, a flocculent material separated, which crystallised from benzene in colourless needles, m. p. 181—182° (Found : C, 70·1; H, 6·0; N, 4·3; MeO, 28·4. $C_{19}H_{19}O_4N$ requires C, 70·2; H, 5·8; N, 4·3; 3MeO, 28·6%).

Anhydro-1-(3′-*benzyloxy*-4′-*methoxy*)*benzyl*-6-*hydroxy*-7-*methoxy*-iso*quinoline Methohydroxide* (X).—Benzyloxytrimethoxybenzyl*iso*-quinoline (3 g.) was added to dry benzene (15 c.c.) and pure methyl sulphate (1 g.), and the mixture refluxed for 1 hour; the methosulphate, m. p. 181—182°, separated and was sufficiently pure for the next step. The derivative crystallised from water with solvent and melted over the range 135—145°. The *methiodide*, obtained by double decomposition, crystallised from aqueous methyl alcohol in pale yellow needles, m. p. 230—231° (Found : I, 22·8. $C_{27}H_{28}O_4NI$ requires I, 22·3%).

A solution of barium hydroxide (3 g.) in water (50 c.c.) was gradually added to one of the methosulphate (1 g.) in water (100 c.c.) which had been boiled for some time in a hydrogen atmosphere; the boiling was continued for 10 hours. The solution was filtered hot, and barium removed from the filtrate by means of a current of carbon dioxide and filtration. On keeping, the clear greenish-yellow liquid deposited the *phenol-betaine* as yellow prisms (yield, 0·3 g.). The substance is very sparingly soluble in water and alcohol and almost insoluble in other neutral organic solvents; it was recrystallised from much aqueous alcohol, forming prisms, m. p. 239—240° (Found : C, 74·6; H, 6·2; N, 3·4. $C_{26}H_{25}O_4N$ requires C, 75·2; H, 6·0; N, 3·4%). Treated with hydrochloric acid, this phenol-betaine is immediately converted into the methochloride, m. p. 242°, which, dissolved in 90% alcohol, absorbs two molecular proportions of hydrogen in the presence of platinum oxide (Adams, *J. Amer. Chem. Soc.*, 1928, **50**, 2260). The product was a gum which was debenzylated by means of a hot mixture of acetic and hydrochloric acids. This process also succeeded, but again the product could not be crystallised. The benzoyl derivative of the protosinomenine was also uncrystallisable.

These substances are still being investigated.

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