198. *Strychnine and Brucine. Part XLII. Constitution of the* neo-*Series of Bases and their Oxidation Products.*

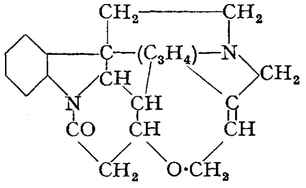
By L. H. Briggs, H. T. Openshaw, and Sir Robert Robinson.

An alternative strychnine (brucine and colubrine) formula is feasible in which N(b) is joined to position 4 of the tetrahydrocarbazole nucleus, instead of to position 3 as hitherto postulated. An advantage is gained in that the new possible structure contains a β-collidine skeleton in addition to those of carbazole and tryptamine. In addition a biogenetic relation to cinchonine can be perceived.

The obstacles to consideration of this modification of the formulæ were the formation and properties of methoxymethyl*chano*dihydrostrychnone and these have not yet been removed by a reinterpretation of the chemistry of the *neo*-series of bases.

The action of *p*-nitrobenzenediazonium chloride on *neo*strychnine and methoxymethyldihydro*neo*strychnine results in the formation of derivatives that are devoid of basic properties. They are undoubtedly *p*-nitrophenylhydrazones of keto-amides containing :N(b)·CO·. The consequences are discussed and it is concluded that a change of view in regard to the skeleton of the alkaloids could only be entertained after acceptance of one of two alternative theories of the structure of the oxidation products of the *neo*-bases. It is now found that the reduction of methyl*neo*strychnidinium chloride by means of sodium amalgam does not afford methyl*chano*dihydro*neo*strychnidine *des*-base-A, m. p. 143°, but instead methyldihydrostrychnidinium-A chloride. The *des*-base-A, m. p. 143°, is therefore, in all probability, methyl*chano*dihydrostrychnidine. The constitutions of the series of Hofmann elimination products on this basis are indicated.

Unambiguous experimental proofs are now available covering the whole periphery of the strychnine molecule and what is certainly known * is formulated in the expression I.



(I.)

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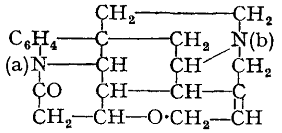
* The hydrogen atom shown attached to the α-position of the indole nucleus is included because evidence has been obtained that one of the so-called "colourless" benzylidene derivatives is a benzyl-α-pyridone. This work will shortly be submitted for publication.

It is also known that strychnine contains $\colon N(b)-CH<^{C}_{C}$ because ψ-strychnine (hydroxystrychnine) (Warnat, *Helv. Chim. Acta*, 1931, **14**, 997; Blount and Robinson, *J.*, 1932, 2305; 1934, 595; Leuchs, *Ber.*, 1937, **70**, 1543 and later papers) is a tertiary alcohol. If in addition to this condition, we also exclude 4-rings there remain eight structures most conveniently symbolised after noting that quadrivalent C_3H_4 is (a)$\cdot CH_2\cdot CH$(b)$\cdot CH\colon$(c, c) or (α, α)$\colon CH\cdot CH_2\cdot CH\colon$(β, β); the possibilities $\cdot CH_2\cdot CH_2\cdot C\vdots$ and $\cdot CH_2-\overset{\cdot\cdot}{C}-CH_2\cdot$ could not give $\cdot N$(b)$\cdot CH\colon$. The eight structures are therefore :

(A) written in full is II, the constitution hitherto preferred, and (G) is III which we consider a good alternative. The other six structures offer no advantages and can be discussed along lines analogous to those of the sequel. The cyclic ether ring is seven-membered in (A) and (G), eight-membered in (C), (D), and (E) and nine-membered in (B), (F), and (H).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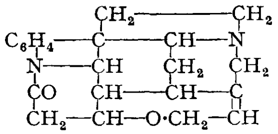
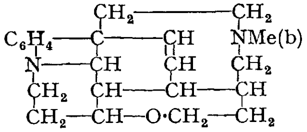

(III.)


(IV.)

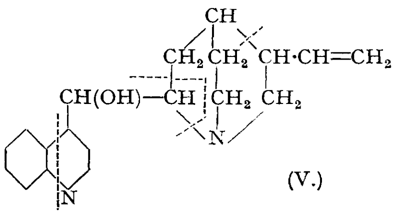
It may be noted that the *des*-base-D (Achmatowicz and Robinson, *J.*, 1934, 581) must on either basis have the structure IV.

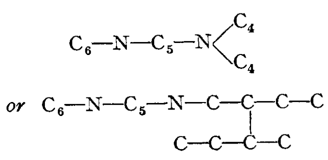
This *des*-base, on catalytic reduction in acid solution furnishes no dihydro-base but a methyldihydrostrychnidinium-D salt and a much smaller proportion of a methyldihydrostrychnidinium-A salt, by a kind of reversed Emde process. When a model of IV is constructed it is found that N(b) lies almost equidistant from the two carbon atoms of the double bond, and structures based on II and III are made with equal ease on the model and are both strainless. This fact led to a discussion as long ago as 1936 of the correctness of the assignment of the structure type-II to the A-series and type-III to the D-series. A transposed allocation was an obvious possibility and was seen to possess advantages.

The idea was, however, abandoned on account of our inability to explain the formation and properties of methoxymethyl*chano*dihydrostrychnone on the basis of III for strychnine.

Reference to earlier memoirs (Clemo, Perkin, and Robinson, *J.*, 1927, 1589; Gulland, Perkin, and Robinson, *ibid.*, p. 1627; Perkin and Robinson, *J.*, 1929, 964; Achmatowicz, Perkin,* and Robinson, *J.*, 1932, 486; Achmatowicz, Clemo, Perkin,* and Robinson, *ibid.*, p. 775; Perkin,* Robinson, and Smith, *ibid.*, p. 1239; *idem*, *J.*, 1934, 574; Achmatowicz and Robinson, *ibid.*, p. 581; Briggs and Robinson, *ibid.*, p. 590; Reynolds and Robinson, *ibid.*, p. 592; Robinson, *ibid.*, p. 1490; Reynolds and Robinson, *J.*, 1935, 935; Achmatowicz and Robinson, *ibid.*, p. 1291; Achmatowicz, Lewi, and Robinson, *ibid.*, p. 1685; Achmatowicz, *J.*, 1938, 1472) may be made for an account of these matters and it will be appreciated that the difficulty was a very real one. Our further studies have narrowed the structural possibilities in the *neo*-series but have not made the acceptance of III easier. This matter is discussed in the sequel. On certain other grounds III† has notable advantages which may be mentioned in explanation of our interest in this alternative. Alkaline degradation of strychnine or certain derivatives (*e.g.*, methylstrychnine, strychninolone) furnishes various substances among which indole, 3-ethylindole, tryptamine, carbazole, β-collidine (4-methyl-3-ethylpyridine), and a base $C_{10}H_{11}N$ (Clemo) have been recognised (Kotake, *Proc. Imp. Acad. Tokyo*, 1936, **12**, 99; Kotake, Mori, and Mitsuwa, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 129; Clemo, *J.*, 1936, 1695; Clemo and Metcalfe, *J.*, 1937, 1518). The formula III contains the β-collidine skeleton but II requires a migration before it can provide it.

We are impressed by the fact that III exhibits a close structural relation to cinchonine, the molecule of which (V) may be dissected into units, in general agreement with an early theory (Robinson, *J.*, 1917, **111**, 876), as illustrated.


(V.)



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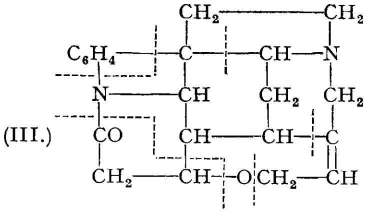
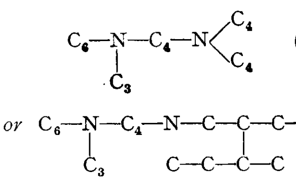
* Posthumous memoirs.

† We have occasionally discussed this possibility with other chemists. It was raised at a meeting of the Alembic Club (Oxford University, 1942) and by Dr. R. B. Woodward of Harvard University in the summer of 1945.

The dissection of III is similar :



(III.)

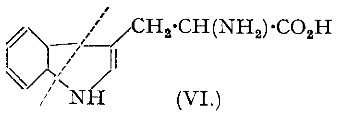


(III.)

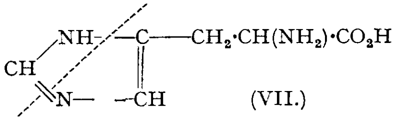
or

(II or III.)

Thus in cinchonine we have a lysine progenitor (*proto*lysine) and in strychnine a *proto*-ornithine, *plus* a triose. In this connexion it should be recalled that we have already recognised a *proto*-ornithine progenitor in tryptophan (VI) and histidine (VII) as well as in the solanaceous alkaloids. These hypotheses apply only to phytochemical syntheses, not to bacterial metabolisms.



(VI.)



(VII.)

The enlargement of a pyrrolidine to a pyridine ring is conceivable in an alkaline degradation at an elevated temperature, but it appears less probable that such a change would occur in the biogenesis of the alkaloid. However this may be, we are unwilling to abandon the recognition of the significant degree of coincidence indicated above and, if II is valid, we suggest that the intramolecular change necessary has indeed occurred at some stage of the synthesis. The relation of *des*-base-D to dihydrostrychnidines-A and -D shows that the ring-system can be transformed under some circumstances. As illustrated above the dimethylhexane chain equates strychnine (II or III) with cinchonine and its use would imply a mere alteration in the order of coupling of the units from that contemplated in 1917.

Constitution of the neo-*Bases*.—In order to provide a direct interpretation of the results of oxidation processes, Leuchs and Berger (*Ber.*, 1935, **68**, 290) suggested that the relation of double bond to N(b) in the *neo*-series is not that of an allylamine but of a vinylamine. In commenting on this Reynolds and Robinson (1935, *loc. cit.*) admitted the feasibility of the hypothesis but considered that the evidence was insufficient to justify a preference for one of the two possible views.

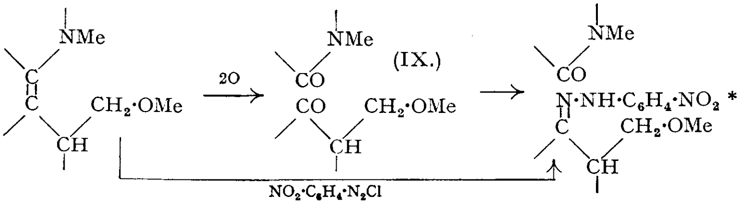
We have now found a diagnostic reaction which is decisive in favour of the vinylamine structure.

The *neo*-bases couple with diazonium salts in dilute aqueous acid solution and the precipitated yellow products are neutral and exhibit the properties of arylhydrazones. Evidently $\colon N(b)\cdot$ becomes $\colon N(b)\cdot CO\cdot$ and the process, dependent on the reactivity of the hetero-enoid system, $\colon N(b)\cdot\dot{C}{=}\dot{C}\cdot$, is most simply represented as follows :

$$\colon N\cdot\dot{C}{=}\dot{C}\cdot \longrightarrow \colon N\cdot\dot{C}(OH)\cdot\dot{C}\cdot N_2\phi \longrightarrow \colon N{-}\dot{C}O\ \dot{C}\colon N_2H\phi.$$

Whatever the mechanism of the reaction it must take a course analogous to that of the characteristic oxidation of the *neo*-bases which in several cases has been shown to result in the addition of two oxygen atoms, with the formation of keto-amides. Thus Briggs and Robinson (*loc. cit.*) oxidised methoxymethyldihydro*neo*strychnine (VIII) to the neutral ketone methoxymethyl*chano*dihydrostrychnone (IX) in almost quantitative yield by means of perbenzoic acid.

The *p*-nitrophenylhydrazone of IX is identical with the product obtained by coupling VIII with *p*-nitrobenzenediazonium chloride.



(VIII.) (IX.) *

The methyl-ψ-strychnidine of Clemo, Perkin, and Robinson (*loc. cit.*) was later shown to be *neo*strychnidine (Achmatowicz, Perkin, and Robinson, *J.*, 1932, 486) ; its oxidation by permanganate to strychnidone is doubtless fully analogous and the same applies to brucidone (Gulland, Perkin, and Robinson, *loc. cit.*). The substance termed diketo*neo*strychnine (Kotake and Yokoyama, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 321) obtained by oxidation of *neo*strychnine with permanganate represents another example It is better termed

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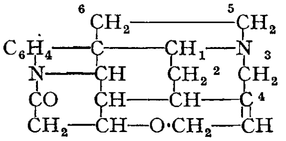
* These formulæ are based on interpretations already advanced and have no significance beyond illustration of the text.

strychnone * (it is not derived by the conversion $2CH_2 \longrightarrow 2CO$, but by addition of 2O). We find that its *p*-nitrophenylhydrazone may also be obtained by the action of *p*-nitrobenzenediazonium chloride on *neo*strychnine. It may be noted that the *neo*-bases have also been oxidised so as to add two hydroxyl groups or one oxygen atom to the molecule; the constitution of these products is under investigation. We have described the above scheme as the simplest available and it is directly applicable to the appropriate derivatives of II, but not to those of III. Nevertheless it is clearly necessary to consider less obvious alternatives before we can reject III on these grounds, in view of its advantages in the other directions already indicated. A vinylamine group including N(b) in III could have three positions; the double bond moving to C_1C_2, C_3C_4, or C_5C_6.



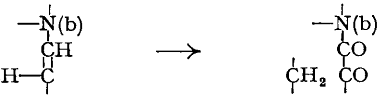
(III.)

The positions C_1C_2 and C_5C_6 require that the oxidation products of the *neo*-bases should be aldehydes.

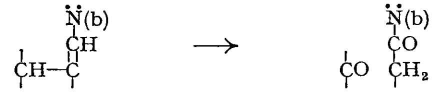
Although these substances are obtained by permanganate oxidations and have never been oxidised to acids by addition of an oxygen atom, it is just possible that the aldehyde group is sterically protected to a sufficient extent. Reynolds and Robinson (*loc. cit.*) considered the possibility that methoxymethyl*chano*dihydrostrychnone is an aldehyde because of the reactivity of the substance, its power of reducing ammoniacal silver solution, and the fact that the corresponding strychnane (but not the strychnone) affords a molecule of acetic acid in the Kuhn–Roth process. They decided against the aldehyde hypothesis because the strychnone was found to be stable to mercuric oxide in a boiling alcoholic suspension. Perhaps this experiment was inconclusive and the matter is at present being further studied.

The oxidation of a group $\colon N(b){\cdot}CH{=}\dot{C}{\cdot}$ at C_3C_4 and C_5C_6 could give $\colon N(b){\cdot}CHO\ CO\colon$; the question therefore arises as to whether it is conceivable that the oxidation products are substituted formamides. The answer is that the *N*-formyl group has not yet been detected. In submitting methoxymethyl*chano*dihydrostrychnone to the Clemmensen reaction, whereby the corresponding strychnane was formed, Reynolds and Robinson (*loc. cit.*) heated the substance with a large excess of concentrated hydrochloric acid for 29 hours. Again, an *N*(b)-formyl derivative is known in formylmethoxytetrahydrostrychnidine-B (Perkin and Robinson, *J.*, 1929, 992) and this is hydrolysed to a secondary amine by boiling sulphuric acid (10% by vol.) in 1 hour although it was found to be unchanged after attempted fission by alcoholic sodium ethoxide at 100°. This substance evolves carbon monoxide on heating but none could be obtained in this way, or on heating with concentrated sulphuric acid, from methoxymethyl*chano*dihydrostrychnone. When this substance is treated with phenylmagnesium bromide and the product decomposed, there is no evidence of the formation of benzaldehyde. If a formamide grouping is present, it must be endowed with quite remarkable stability.

The only other loophole that we can devise is illustrated in the scheme :



The inherent probability of such a transformation is not great, but it must be taken into consideration. Such an α-keto-amide group is contained in diketonucidine, dihydrostrychninone, strychninonic acid, and brucinonic acid. In all these cases the action of barium peroxide in the presence of barium hydroxide effects facile decomposition and barium carbonate is precipitated. That does not occur in a similar fashion with strychnone or methoxymethyl*chano*dihydrostrychnone. Moreover the *p*-nitrophenylhydrazones of these substances exhibit colour reactions which are almost exactly the same as those of the corresponding derivatives of simple ketones. Under the same conditions the *p*-nitrophenylhydrazones of the undoubted α-keto-amides listed show quite different intense colour reactions, which appear to be characteristic for this class of compounds. An apparently alternative scheme is :



This might be acceptable for the direct oxidation processes, but it is inapplicable to the formation of the nitrophenylhydrazones by diazo-coupling. The same remark holds for certain other possibilities and it must be recognised that the ketonic (or aldehydic) carbonyl is derived from the carbon atom in the β-position to N(b).

Reviewing these alternatives we do not favour the indirect mechanisms for the oxidations and it seems that the strychnones are unlikely to prove to be formamides. Hence the double bond in the *neo*-series is not thought to be in positions C_3C_4 and C_5C_6 of III. The acceptance of III with the *neo*-unsaturation at C_1C_2 is therefore dependent on the eventual recognition of the strychnones as aldehydes.†

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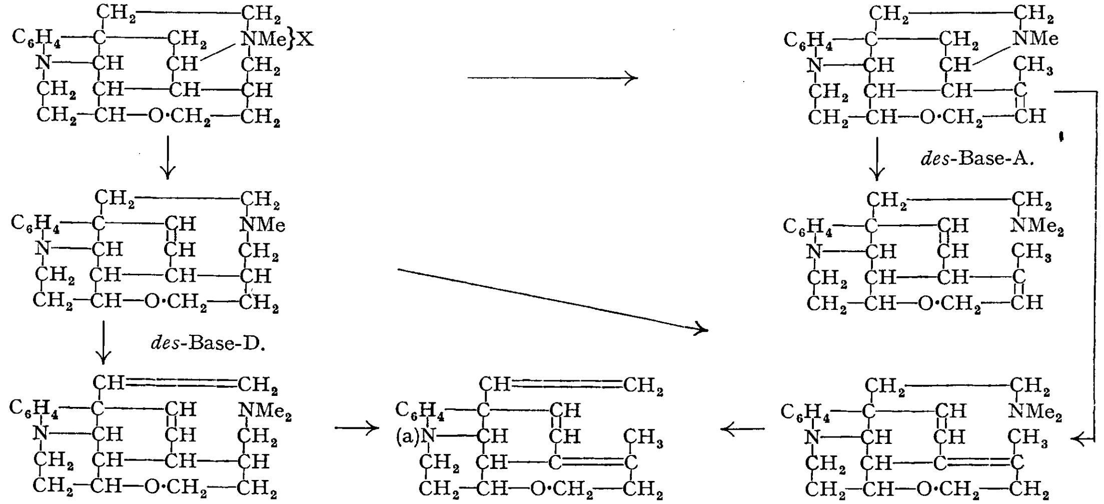
* Our use of the term "strychnone" dates from 1937 (strychnidone still earlier) and we deprecate its employment in a different connexion (Leuchs and Räck, *Ber.*, 1940, **73**, 731), especially for the substance $C_{21}H_{20}O_3N_2$ which is not a ketone.

† The C_1C_2 position is, however, highly improbable for stereochemical reasons.

The vinylamine character of the *neo*-bases has certain other consequences. The allyloid hypothesis, formerly invoked in explanation of the ready reconstitution of quaternary salts from methoxymethyldihydro*neo*strychnidine by the action of acids $(\colon\text{NMe(b) CH}_2\text{(OMe)}\cdot \longrightarrow \colon\overset{+}{\text{N}}\text{Me}\cdot\text{CH}_2\cdot)$ and the contrast with the difficulty experienced in effecting the same change with the dihydro-derivative, must now be abandoned. In its place we may postulate: (*a*) the presence of free base in the acid solutions of the *neo*-derivative, or (*b*) the formation of a butadienoid intermediate and subsequent ring-closure $[\colon\text{N(b)}\cdot\dot{\text{C}}\colon\dot{\text{C}}\text{—}\dot{\text{C}}\text{H—CH}_2\cdot\text{OMe} \longrightarrow \colon\text{N(b)}\cdot\dot{\text{C}}\colon\dot{\text{C}}\cdot\dot{\text{C}}\colon\text{CH}_2 \longrightarrow \colon\underline{\overset{+}{\text{N}}\text{(b)}\cdot\dot{\text{C}}\text{H}\cdot\dot{\text{C}}\colon\dot{\text{C}}\text{—CH}_2}]$. In connexion with (*a*) it has been frequently observed that *neo*strychnine is a much weaker base than strychnine. This is in accord with anticipation unless the hetero-enoid system functions so as to develop a quaternary salt $(\colon\text{N}\cdot\dot{\text{C}}{=}\dot{\text{C}}\cdot \longrightarrow \colon\overset{+}{\text{N}}{=}\dot{\text{C}}\text{—}\dot{\text{C}}\text{H}\cdot)$, an unlikely event in view of the bridgehead double bond that would be formed. No alteration of the current view of the position of methoxylating fission is desirable and the only observation inconsistent with the *neo*-bases theory outlined above is that methyl*neo*strychnidinium chloride affords methyl*chano*dihydro*neo*strychnidine (*des*-base-A) on reduction with sodium amalgam (Perkin, Robinson, and Smith, *J.*, 1932, 1239). The specimen used was available and found to be wrongly labelled; the *neo* having been added to the name. The authentic material yields no *des*-base-A on reduction, but is converted into methyldihydrostrychnidinium-A chloride. It is therefore probable that *des*-base-A is methyl*chano*dihydrostrychnidine. The reduction of *neo*strychnine to dihydrostrychnine already afforded a proof that the skeleton is unaltered in the passage to the *neo*-series. The present observation is confirmatory. Naturally the allylamine hypothesis still applies to the reductive fission.

The course of the Hofmann process is best represented as shown below and it will be seen that III for strychnine could have been used and would give the same products at the first stage in the D-series and at the second stage in the A-series.

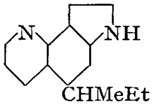


The two lower double bonds in the last formula, which represents one possibility for *des*-*aza*strychnidine-a or -b, can move into two positions nearer to N(a). Admittedly the *des*-base-A series could be formulated in a different way at the second stage but the representation given is the simplest and is in good agreement with the facts.

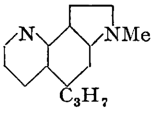
Changes in the nomenclature of the two second stage *des*-bases from *des*-base-A may well await confirmation of the structure proposed for *des*-base-A, experiments in relation to which are in progress.

It may be added that the constitutions of vomipyrine indicated by III for strychnine are X and XI (cf. Wieland and Horner, *Annalen*, 1937, **528**, 73). In XI both propyl and *iso*propyl groups are possible.

(X.)



(XI.)



Our view of the present status of the structure III has been fully explained. A formula for vomicine on this basis cannot be excluded, and since a part of the skeleton II is transformed to that of III in the degradation of strychnine to β-collidine a similar change of the ring system is conceivable during the formation of vomipyrine (vomicine based on II).

In order to avoid misunderstanding we add the following summary of conclusions.

(1) The *neo*-bases are vinylamine derivatives.

(2) The structure III exhibits a more direct relation with cinchonine than II, and a more direct explanation of the formation of β-collidine on degradation.

(3) The available evidence bearing on the problem is insufficient and a decision cannot yet be made with confidence.*

EXPERIMENTAL.

p-*Nitrophenylhydrazone of Strychnone.*—*neo*Strychnine (2·0 g.) was dissolved in hot N-hydrochloric acid (100 c.c.) and alcohol added as the solution was cooled so as to prevent the crystallisation of the hydrochloride. Crushed ice and a solution of diazotised *p*-nitroaniline (2 g.) were added with mechanical stirring. A yellow precipitate separated and after an hour this was collected, washed, and dried in a vacuum over sulphuric acid (2·6 g.). The product was not easily crystallised and behaved like a mixture of stereoisomerides. In preliminary trials some crystals were obtained and these were used to seed a concentrated solution in acetone which was allowed to evaporate slowly in the refrigerator. A crust of yellow prisms separated and the substance was recrystallized in a similar manner, m. p. 269—271° (decomp.) (Found : C, 64·6; H, 5·6; N, 14·1. Calc. for $C_{27}H_{27}O_5N_5$: C, 64·7; H, 5·4; N, 14·0%). A specimen prepared from strychnone (Kotake *et al.*, *loc. cit.*) had the same properties, m. p., and mixed m. p. The addition of potassium hydroxide to a dilute alcoholic solution produces a bright cherry-red coloration with bluish nuance in thin layers; the coloration in acetone is very slightly bluer. The same coloration was noted in the case of the *p*-nitrophenylhydrazone of 4-methoxy*cyclo*hexanone but the *p*-nitrophenylhydrazones of diketonucidine, strychninonic acid, and dihydrostrychninone gave quite distinct results. In all these cases the colour was purplish-violet.

p-*Nitrophenylhydrazone of Methoxymethyl*chano*dihydrostrychnone.*—(A) It suffices to triturate methoxymethyl*chano*dihydrostrychnone (1·0 g.) and *p*-nitrophenylhydrazine (0·6 g.) in cold acetic acid (10 c.c.). After 24 hours, water (5 c.c.) was added and the solid collected. The product was twice crystallised from acetone as yellow prisms which shrank at 263° and decomposed at 266° to a red liquid (Found : C, 63·5; H, 6·0; N, 12·9. Calc. for $C_{29}H_{33}O_6N_5$: C, 63·6; H, 6·0; N, 12·8%). (B) *p*-Nitroaniline (7 g.) was dissolved by heating in concentrated hydrochloric acid (20 c.c.) and water (20 c.c.). Water (200 c.c.) and crushed ice were added and, with stirring, sodium nitrite (3·6 g.) in a little water. The diazo-solution measured 375 c.c. and 100 c.c. was added to a solution of methoxymethyldihydro*neo*strychnine (5 g.) in N-hydrochloric acid (50 c.c.). The yellow precipitate was very quickly formed and was collected after ten minutes, washed, and dried. It became crystalline on trituration with a little cold acetic acid but a considerable amount (stereoisomeride ?) remained in the solution. The solid was crystallised twice from acetone and formed yellow, elongated prisms which showed the same behaviour on heating, alone or mixed, as the specimen made as described in (A) (Found : C, 63·4; H, 6·1%).

The coloration in alcohol and in acetone on the addition of potassium hydroxide was indistinguishable from that exhibited by the *p*-nitrophenylhydrazone of strychnone.

Reduction of neo*Strychnidine Methosulphate by Means of Sodium Amalgam.*—*neo*Strychnidine (5·0 g.) was dissolved in boiling benzene (100 c.c.) and distilled methyl sulphate (15 c.c.) added and the whole refluxed for 6 hours. The salt was dissolved in water (250 c.c.) and the aqueous solution separated and rendered slightly alkaline. It was filtered from a small amount of unchanged base, heated on the steam-bath, and treated with sodium amalgam (200 g. of 3%) with passage of a stream of carbon dioxide. After 8 hours the solution was diluted, filtered, and acidified to Congo-red with hydrochloric acid. It was then evaporated to dryness and the residue exhausted with boiling alcohol. The alcoholic solution was evaporated, the residual quaternary salt dissolved in water, and the iodide precipitated by addition of excess sodium iodide. This salt crystallised from water in arrow-shaped prisms, decomp. 340—350°, and was converted by means of silver chloride into dihydrostrychnidine-A methochloride which was identified by comparison with an authentic specimen and by conversion into methoxymethyltetrahydrostrychnidine; leaflets from xylene, m. p. 223°, alone or mixed with an authentic specimen (cf. Oxford, Perkin, and Robinson, *J.*, 1927, 2401).

One of us (H. T. O.) acknowledges gratefully the assistance of a Senior Demyship of Magdalen College, Oxford, and of a Senior Research award (D.S.I.R.).

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[*Received, February 27th,* 1946.]