328. *Strychnine and Brucine. Part XX. Some Derivatives of Pseudostrychnine. Comments on a Recent Memoir of H. Leuchs—Über Strychnos-Alkaloide, LXVIII.*

By B. K. Blount and Robert Robinson.

Owing to the kindness of Dr. K. Warnat and Dr. M. Guggenheim, and to the generosity of the firm of Hoffmann–La Roche of Basle, to all of whom we are greatly indebted, we have been able to examine further the derivatives of pseudostrychnine. This base was isolated by Warnat (*Helv. Chim. Acta*, 1931, **14**, 99) and shown to have the formula $C_{21}H_{22}O_3N_2$ or $C_{21}H_{24}O_3N_2$; it furnished neutral salts

($B,HCl,2H_2O$; B,HNO_3) and a *N*-nitroso-derivative insoluble in dilute acids.

Crystallisation of the pure base from methyl or ethyl alcohol afforded methyl or ethyl derivatives, which were at once hydrolysed by cold dilute mineral acids with formation of pseudostrychnine salts and the respective alcohol. All these properties suggested to us that pseudostrychnine ($C_{21}H_{22}O_3N_2$ in this event) is hydroxystrychnine and contains a group :C(OH)·N:; the alkyl derivatives would then be ethers, :C(OR)·N:, and the nitrosoamine would be :CO NO·N:. This hypothesis is strongly supported by near analogies such as the carbinol-bases, cotarnine and berberine, but, unlike these bases, pseudostrychnine does not form anhydro-salts containing the group :C=N:}X. Even the *ferrichloride* and *perchlorate* are of the form $C_{21}H_{23}O_3N_2\}X$.

Nevertheless pseudostrychnine has been found to be readily reducible in acid solution and the product is strychnine; thus there is little doubt that it is, in fact, hydroxystrychnine and that the hydroxyl is situated on a carbon atom contiguous to N(*b*). It is almost certainly a tertiary alcohol, because the group :N·CH(OH)· can usually be oxidised to :N·CO· with facility and we have found that pseudostrychnine is relatively stable, for example, towards alkaline ferricyanide.

Pseudostrychnine methyl ether forms a normal *methiodide*, from which a des-*base* is readily obtained :

$$:CH\cdot\dot{C}(OMe)\cdot NMe:\}OH \longrightarrow :C{=}\dot{C}(OMe)\ NMe: + H_2O$$

In this substance the methoxyl is much more resistant to hydrolysis than it is in *O*-methylpseudostrychnine, but the action of hot dilute hydrochloric acid brought about the reaction with formation of a well-characterised base termed N-*methyl*chano*pseudostrychnine*.*

It is quite likely that the series of reactions leading to the production of this base involve wandering of the double bond of strychnine by the stages :

$$HO\{:NMe\cdot C(OMe)\cdot CH\cdot C:CH \longrightarrow :NMe\ \ C(OMe):CH\cdot C:CH\cdot$$
$$\longrightarrow :NMe\ CO\cdot CH:C\cdot CH_2.$$

The most significant property of *N*-methyl*chano*pseudostrychnine is that it forms a *dibenzylidene* derivative with considerable ease.

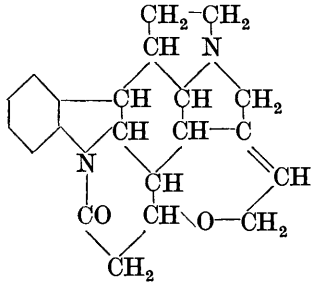
One reactive CH_2 group is known to be present in strychnine

* The prefix *chano-*, from the Greek word meaning " chasm," is used to indicate the process, real or imaginary, of opening a cyclic structure by isomeric change. It is the converse of *cyclo* as employed in the expression *cyclo*citral but not, as in *cyclo*hexane, where loss of 2H is implied. This prefix has been found to be very useful in the nomenclature of a series of bases derived from strychnidine by ring-opening.

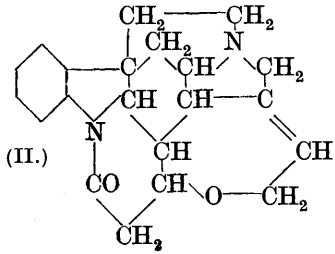
(Perkin and Robinson, J., 1929, 997), and the group responsible in this case is :N(*a*)CO·CH_2:; probably, therefore, one of the benzylidene residues is in the position occupied in benzylidenestrychnine, and this view is supported by the similar Otto reactions of the latter base and of the new dibenzylidene compound.

The second reactive CH_2 must be under the influence of a carbonyl occupying the site of the *t*-alcoholic group of pseudostrychnine. In other words, pseudostrychnine probably contains the group $-CH_2$·C(OH)·N(*b*):. The loophole is that the dibenzylidene derivative may contain :N(*a*)·CO·C:CHPh and :NMe(*b*) CO·CH:C·C:CHPh. We do not consider the latter hypothesis (compare, however, benzylidenepiperitone; Read and Smith, J., 1921, **119**, 784) in view of the pale yellow colour of the substance, but it will be experimentally tested.

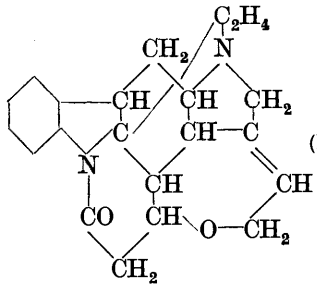
(I.)



(II.)



(III.)



In the meantime the strong indication, if not proof, is that strychnine contains N(*b*)·CH·CH_2. H. Leuchs (*Ber.*, 1932, **65**, 1230) advocates a slight modification (I) of the strychnine formula (II) of Menon and Robinson (this vol., p. 780), and one of us must now state, in justice to his collaborator, that this formula (I) was that which was preferred by K. N. Menon and employed by him in a Thesis for the Doctorate submitted in 1931 to the University of London. It was modified because, despite Leuchs's arguments to the contrary, strychnine does not behave like a dihydroindole (or even hexahydrocarbazole) convertible by loss of 2H into a true indole. Therefore one of the carbon atoms, α or β, in the indole

nucleus (5-, or 6- in Leuchs's scheme of numbering) must be attached by a carbon chain to N(*b*). The particular development of this idea adopted in formula (II) was selected (i) because it gives a tryptophan nucleus and beyond this a continuous block of carbon atoms, and (ii) because the arrangement is strainless. There is no insuperable objection to attachment of the side-chain to the α-position as in (III) and if the group C_2H_4 is interpreted as ·CHMe· rather than ·CH_2·CH_2· the remarkable possibility emerges that the strychnine skeleton may embody that of harmine.

Certainly great weight must be attached to the observation (Leuchs, *loc. cit.*) that dioxonucidin is very readily monobrominated; this undoubtedly indicates that the β-carbon of the indole nucleus bears a hydrogen atom and therefore formula (III) best expresses the whole of the known chemical behaviour of strychnine and its derivatives.

EXPERIMENTAL.

Pseudostrychnine perchlorate crystallised from hot H_2O, in which it is sparingly sol., in long, colourless, hexagonal prismatic needles, which blackened above 240° but did not melt at 300° (Found: C, 55·9; H, 5·1. $C_{21}H_{23}O_7N_2Cl$ requires C, 56·0; H, 5·1%). The *ferrichloride* crystallised from AcOH in orange-red plates, m.p. 234—235° (decomp.) after darkening. It is readily sol. in H_2O, EtOH, and Me_2CO, sparingly in AcOH and HCl aq. (Found: C, 45·9; H, 4·3. $C_{21}H_{23}O_3N_2Cl_4Fe$ requires C, 45·9; H, 4·2%).

Reduction of Pseudostrychnine with Formation of Strychnine.—To pseudostrychnine hydrochloride (0·5 g.), dissolved in hot 2*N*-HCl (25 c.c.), Zn dust (1 g.) was added during 15 mins. A colourless cryst. solid soon separated and after 30 mins.' heating on the steam-bath sufficient hot H_2O was added to give a clear solution, followed by a slight excess of sat. Na_2CO_3 aq. After cooling, the solid was collected and dried, and the org. material separated from the Zn residues by means of hot $CHCl_3$. The $CHCl_3$ extract was concentrated, EtOH added, and the evaporation continued until crystn. occurred. On cooling, nearly pure strychnine (0·29 g., 74%), m.p. 264—266°, separated, and a further quantity was obtained from the mother-liquor. After recrystn. from EtOH the substance melted at 270—271°, alone or mixed with natural strychnine (Found: C, 75·0; H, 6·6. Calc. for $C_{21}H_{22}O_2N_2$: C, 75·4; H, 6·6%). The recorded m. p.'s for strychnine vary widely (268° to 290°): the value given above was obtained by slow heating. M. p. and mixed m. p. determinations were always carried out simultaneously to avoid errors through variation in the rate of heating. Benzylidenestrychnine, prepared from this reduction product by the method of Perkin and Robinson (J., 1929, 997), melted at 235—237°, alone or mixed with an authentic specimen. The Otto reactions given by both specimens were also identical.

Attempted Ferricyanide Oxidation of Pseudostrychnine.—A solution of pseudostrychnine (0·17 g.) in boiling EtOH (5 c.c.) was treated successively with K_3FeCy_6 (0·33 g.) in H_2O (5 c.c.) and with KOH (0·3 g.) in H_2O (1 c.c.). After boiling for 15 mins., the mixture was cooled, and the brown solid collected. It was sol. in dil. acids, and separated on being made alkaline in a cryst. condition, m.p. 253—255° (decomp.). It evidently consisted of some-

what impure pseudostrychnine, and was further identified by conversion into the methyl ether by crystn. from MeOH.

O-*Methylpseudostrychnine Methiodide.*—*O*-Methylpseudostrychnine (4 g.) was dissolved in freshly distilled MeI (20 c.c.) and kept at about 40° for 3 days; the mixture then became a jelly. As much as possible of the MeI was removed by distillation from the steam-bath, the horny residue dissolved in MeOH (50 c.c.), and the solution concentrated to half vol. The *methiodide*, colourless woolly needles, was collected after cooling and washed with MeOH and Et_2O (yield, 4·6 g. or 83%). The m. p., which depends greatly on the rate of heating, was 213° (decomp.) on moderately rapid heating. The compound was recrystallised from MeOH, in which it was sparingly sol. (Found : C, 54·4; H, 5·4. $C_{23}H_{27}O_3N_2I$ requires C, 54·4; H, 5·3%).

des-N : O-*Dimethylpseudostrychnininium Hydroxide.*—KOH (1 g.) in H_2O (2 c.c.) and then boiling H_2O (40 c.c.) were added to a boiling solution of *O*-methylpseudostrychnine methiodide (2 g.) in MeOH (20 c.c.). The colourless gum crystallised when stirred with a little hot MeOH. The crystals were collected at 0°, washed with a little ice-cold MeOH (yield, 0·84 g. or 56%; m. p. 168—172°), and thrice crystallised from EtOH; m. p. 174—175° (decomp.) after slight browning (Found : C, 73·1; H, 6·8; N, 7·5; MeO, 7·6; NMe, 8·2. $C_{23}H_{26}O_3N_2$ requires C, 73·0; H, 6·7; N, 7·4; MeO, 8·2; NMe, 7·7%).

A mixture of the des-*base* (0·1 g.), MeOH (1 c.c.), Ph·CHO (2 drops), and 40% KOH aq. (1 drop) was refluxed for 1½ hrs. The product was collected at 0° and recrystallised from EtOH. It sintered at *ca.* 135° and was converted at 145° into a gum, which liquefied at about 180° (Found : C, 75·6; H, 6·7%).

In a second expt. (double quantities) the mixture was refluxed for 19 hrs., cooled, and kept at 0° for 1 hr. Yellow crystals separated, m. p. 190—193° after sintering at about 180°. The mother-liquor, kept over-night in the ice-chest, gave a second crop of crystals, m. p. 145—150°. The first crop, recryst. twice from MeOH, formed long, thin, yellow plates, m. p. 189—193° after sintering at 180° (Found : C, 76·1; H, 6·4; OMe, 6·5%); the substance gave a blue Otto reaction. The second crop was also twice recrystallised from MeOH, forming long, thin, very pale yellow prisms, m. p. 153° (Found : C, 75·8; H, 6·7; N, 6·0; OMe, 9·1; NMe, 6·8%). It gave *no* Otto reaction. The nature of these substances is not at all clear to us.

N-*Methyl*chano*pseudostrychnine.*—This compound was formed in a pure condition when a solution of the *des*-base of dimethylpseudostrychnininium hydroxide in excess of dil. HCl was heated at 100° for 2 hrs. For preparative purposes, however, it was unnecessary to isolate the intermediate stage.

O-Methylpseudostrychnine methiodide (2 g.) was treated as in the last prep. and the gummy *des*-base, from which the mother-liquor had been decanted, was dissolved in 2*N*-HCl (20 c.c.) and heated on the steam-bath for 2 hrs. After cooling, NH_3 was added; the solution then became yellow-green, bluish-green, and finally, at the point at which the product separated, pure blue. The *base* was crystallised from EtOH (0·76 g., or 53%, m. p. 266—268°) and then twice from MeOH, giving well-formed quadrilateral prisms, m. p. 270—271° (decomp.) (Found : C, 72·0; H, 6·7; N, 7·7; MeO, 0·0; NMe, 8·3. $C_{22}H_{24}O_3N_2$ requires C, 72·5; H, 6·6; N, 7·7; NMe, 8·0%).

The sparingly sol. *perchlorate* crystallised from H_2O in thin, four-sided plates, which blackened at 250° and exploded at 295° (Found : C, 57·0; H, 5·5; N, 6·1. $C_{22}H_{25}O_7N_2Cl$ requires C, 56·9; H, 5·4; N, 6·0%).

Dibenzylidene - N - *methyl*chano*pseudostrychnine.* — *N* - Methyl*chano*pseudo-

strychnine (80 mg.) was dissolved in hot EtOH (1·5 c.c.), Ph·CHO (3 drops) and 40% KOH aq. (1 drop) were added, and the mixture was heated for 80 mins. on the steam-bath, during which the *dibenzylidene* derivative separated in long yellow prisms. It crystallised from *iso*amyl alcohol in small lemon-yellow prisms, m. p. 284—285° (decomp.) with previous darkening (moderately rapid heating). It is sparingly sol. in neutral org. solvents and gives a pure blue Otto reaction (Found: C, 80·0; H, 6·1; N, 5·3. $C_{36}H_{32}O_3N_2$ requires C, 80·0; H, 5·9; N, 5·2%).

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