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BY-PRODUCTS OF THE PERMANGANATE OXIDATION OF STRYCHNINE

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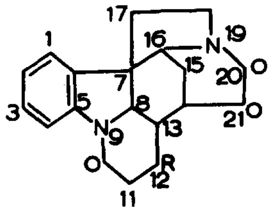
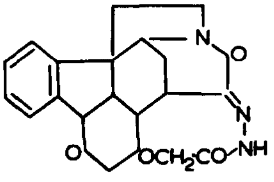
Abstract—Hydroxydihydrostrychninone-A (I; R = OH) and hydroxycuninecarboxylic acid (III) have been identified among the oxidation products of strychnine. Several examples of the effect of a $C_{(21)}$ hydroxyl group in facilitating elimination of OR groups from $C_{(12)}$ have been noted.

IN preparing strychninonic acid (I; R = $O{\cdot}CH_2{\cdot}CO_2H$) by the oxidation of strychnine with permanganate, Leuchs and Schwaebel[1] obtained a small quantity of a neutral compound shown later[2] to have the formula $C_{19}H_{18}O_4N_2$. We have shown, by the preparation of derivatives, the presence of a hydroxyl and a carbonyl group in this compound, suggesting that it is hydroxydihydrostrychninone-A (I; R = H). This formula was confirmed when it was found that the compound could be obtained from strychninonic acid by degradation of the acid side-chain. The sequence of reaction was essentially that employed by Leuchs and his collaborators[3] with brucinonic acid. Strychninonic acid was converted by hydrazine hydrate into the hydrazinium salt of its hydrazone. The product was contaminated by the hydrazinium salt of the azine, and could not be satisfactorily purified at this stage. Consequently it was converted into the ethyl ester and thence into strychninonic hydrazide hydrazone. The attempt to prepare this compound directly by the reaction of methyl strychninonate with hydrazine hydrate gave only a small yield of the desired product, accompanied by a compound $C_{21}H_{22}O_5N_4$, which was probably a hydrate of the cyclisation product (II) of strychninonic hydrazide. Strychninonic hydrazide hydrazone was treated with 2 moles of nitrous acid to obtain strychninonic azide. The azide when boiled in water decomposed to give a small amount of hydroxydihydrostrychninone-A (I; R = OH).



I



II

This compound could not be prepared by the Hofmann degradation of strychninonamide.

Oxidation of hydroxydihydrostrychninone-A with hydrogen peroxide in formic

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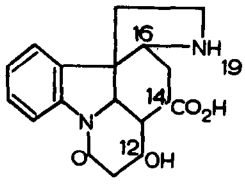
[1] Leuchs and Schwaebel *Ber.* **46**, 3693 (1913).

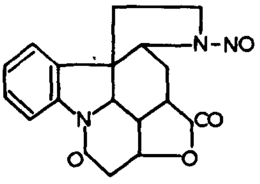
[2] Holmes, Openshaw, and Robinson *J. Chem. Soc.* 908 (1946).

[3] Leuchs and Schneider *Ber.* **59**, 267 (1926); Leuchs and Gladkorn *Ber.* **56**, 1780 (1923); Leuchs and Kanao *Ber.* **57**, 1318 (1924).

acid[4] or barium hydroxide solution[5] gave 12-hydroxycunine-14-carboxylic acid (III), isolated as a hydrochloride, $C_{18}H_{21}O_4N_2Cl,H_2O$, or a perchlorate.



III



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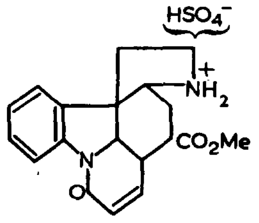


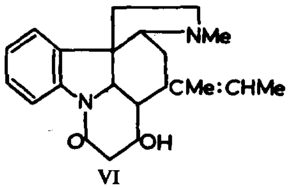
V

The hydrochloride proved to be identical with the compound obtained by Leuchs and Schwaebel[1] by treating an amorphous product from the permanganate oxidation of strychnine with methanol and concentrated hydrochloric acid. The nitroso-derivative of the acid (III) formed the lactone (IV), and the N-benzoyl derivative of the acid was partially lactonised, on crystallisation from aqueous acetic acid. The formation of these lactones indicates a *cis* configuration of the hydrogen atoms at C(12) and C(14).[6]

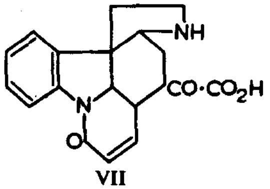
12-Hydroxycunine-14-carboxylic acid perchlorate was esterified in methanol containing a small amount of concentrated sulphuric acid to methyl dehydrocunine-carboxylate hydrogen sulphate, for which the most probable formula is (V).

Because these derivatives of cunine were obtained in small overall yield, the preparation of 12-hydroxy-14-(2-but-2-enyl)-19-methylcunine(VI) as a possible starting material for further degradations was investigated. This compound was believed to be the chief constituent of the mixture of products obtained by the Emde reduction of strychnine methosulphate.[7] The reduction of methylstrychnine by sodium in liquid ammonia[8] followed by treatment of the product with acid, afforded the compound (VI), but in very low yield.

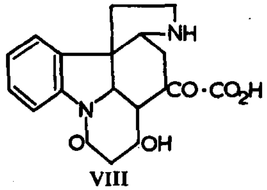
When hydroxydihydrostrychninone-A was heated with strong hydrochloric acid it was hydrolysed to an amino-acid which differed from the hydrolysis product (VII) of strychninone-A, and probably had the structure (VIII). It thus resembles



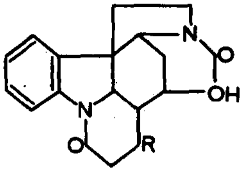
VI



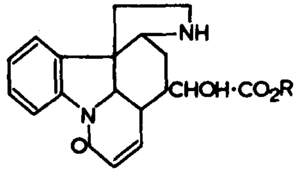
VII



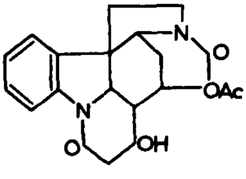
VIII



IX



X



XI

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[4] Prelog and Kocor *Helv. Chim. Acta* 31, 237 (1948).

[5] Leuchs and Kröhnke *Ber.* 65, 980 (1932); 66, 252 (1933).

[6] Holmes *The Alkaloids* Vol. II. p. 517. Ed. Manske and Holmes, Academic Press (1952).

[7] Perkin, Robinson, and Smith *J. Chem. Soc.* 1239 (1932); 574 (1934); Reynolds and Robinson *J. Chem. Soc.* 592 (1934).

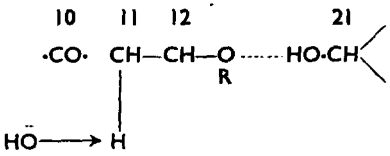
[8] Clemo and King *J. Chem. Soc.* 1661 (1948).

strychninonic acid, which is hydrolysed to a "monohydrate" and a "dihydrate," without significant elimination of glycollic acid.[9] On the other hand, its reduction product,[2] hydroxydihydrostrychninolone-A (IX: R = OH), like strychninolic acid (IX; R = O·CH$_2$·CO$_2$H), eliminated the C$_{(12)}$ oxygen atom when heated in strong hydrochloric acid, forming the amino acid (X: R = H)[10] and when warmed in dilute alkali,[11] forming strychninolone-C.[12] In the latter instance strychninolone-A was almost certainly the primary product, but under the conditions of the experiment isomerised to strychninolone-C.

The base-catalysed elimination of water from hydroxydihydrostrychninolone-A may be reversible, for the compound, $C_{19}H_{20}O_4N_2$, isolated in low yield as a by-product of the alkaline cleavage of strychninolic acid to strychninolone-A[13] and of the base-catalysed isomerisation of strychninolone-A to strychninolone-B,[12] appears to be identical with it.

A further example of the facility with which compounds related to strychninolic acid eliminate a C$_{(12)}$ oxygen function was given by the reaction of ethyl strychninolate (IX; R = O·CH·CO$_2$Er) with hydrazine hydrate to afford a mixture of isomeric hydrazinodihydrostrychninolones-A, (IX; R = NHNH$_2$) instead of the expected hydrazide (IX; R = O·CH$_2$·CONHNH$_2$). These compounds are probably isomeric at C$_{(12)}$, being formed by addition of hydrazine to strychninolone-A; such addition to strychninolone-C proceeds much more slowly. Two isomeric aminodihydrostrychninolones have been prepared by analogous reactions between strychninolone- and ammonia.[12]

The base-catalysed fission of glycollic acid from strychninolic acid has been discussed by Woodward[14] in terms of a "push-pull" mechanism, the release of the negative glycollate ion being facilitated by hydrogen bonding from the hydroxyl group at C$_{(21)}$ as shown. It is assumed that the cage-like structure of strychnine makes it sterically impossible for a solvent molecule to approach closely enough to form such a hydrogen bond. Hence such a mechanism is possible in strychninolic acid, but not in strychninonic acid. However, this hypothesis, though attractive in principle, does not apply so aptly to acid-catalysed eliminations.



It seems possible, from an examination of molecular models, that steric compression of the C$_{(12)}$ oxygen atom by the C$_{(21)}$ hydroxyl group may explain these results. Such interference may also explain the formation from hydroxydihydrostrychninolone-A under mild conditions of a *monoacetate*. This was shown to be the C$_{(21)}$ acetoxy compound (XI), the isomeric C$_{(12)}$ monoacetate (IX: R = OAc) being

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[9] Leuchs and Reich *Ber.* **43**, 2420 (1910).

[10] Leuchs, Diels, and Dornow *Ber.* **68**, 106 (1935); Leuchs and Dornow *ibid.* p. 1786.

[11] Leuchs and Schneider *Ber.* **42**, 2494 (1909).

[12] Leuchs and Bendixsohn *Ber.* **52**, 1443 (1919).

[13] Leuchs and Schwaebel *Ber.* **47**, 1553 (1914).

[14] Woodward, quoted in ref. 6.

[15] Kotake and Mitsuwa *Bull. Chem. Soc. Japan* **11**, 231 (1936).

obtained by hydrogenation of the acetate of hydroxydihydrostrychninone-A (I; R = OAc).

EXPERIMENTAL

(Melting points are uncorrected. Where not specified, concentrations of solutions used in the determination of specific rotation were about 0·5%.)

Strychninonic acid hydrazone. Strychninonic acid (0·48 g) was refluxed for 3 hours with hydrazine hydrate (0·28 c.c.) and absolute ethanol (6 c.c.), and the mixture then cooled in ice. The thick precipitate (0·42 g), m.p. 210–212°, was shown by analysis to be a mixture of the hydrazinium salts of the hydrazone and the azine (Found: C, 58·1; H, 5·9; N, 18·1. A mixture of 65% $C_{21}H_{26}O_5N_6$ and 35% $C_{42}H_{48}O_{10}N_{10}$ requires C, 58·1; H, 5·8; N, 18·1%).

Strychninonic hydrazide hydrazone. The mixture of the hydrazinium salts of the hydrazone and the azine (1 g) was triturated with 12% ethanolic hydrogen chloride (10 c.c.) and allowed to stand for 5 hours at room temperature. It was then poured into an ice-cold 7% solution of potassium hydrogen bicarbonate (70 c.c.), and the mixture extracted with chloroform (4 × 10 c.c.). The dried extract on evaporation gave ethyl strychninonate hydrazone as an uncrystallisable yellow oil. The ester was boiled with hydrazine hydrate (0·25 c.c.) in absolute ethanol (7 c.c.) for 20 min. The solution was concentrated, and the residue crystallised twice from ethanol to give *strychninonic hydrazide hydrazone*, sintering at 160°, decomp. 180–190° (Found: C, 58·2; H, 5·9; N, 19·4. $C_{21}H_{24}O_4N_6,\frac{1}{2}H_2O$ requires C, 58·2; H, 5·8; N, 19·4%). The filtrate, on concentration and scratching, deposited another crop of crystals, sintering at 160°, decomp. 222–230° of *hydrazide hydrazone* (Found: C, 57·9; H, 5·9; N, 19·3%) probably containing different proportions of isomerides (cf. ref. 3).

An alternative method was to reflux methyl strychninonate (0·85 g) with hydrazine hydrate (0·8 c.c.) in ethanol (15 c.c.) for 2 hours. Concentration to 10 c.c. gave impure hydrazide hydrazone (0·22 g). The filtrate on further concentration yielded a *compound* (possibly II) crystallising from ethanol as white needles, m.p. 226–228° (Found: C, 61·4; H, 5·7; N, 13·8. $C_{21}H_{22}O_5N_4$ requires C, 61·4; H, 5·4; N, 13·6%).

Strychninonic hydrazide hydrazone gave a deep red, rather then the usual blue or purple colour, in the Otto test.

Hydroxydihydrostrychninone-A (I; R = OH). Strychninonic hydrazide hydrazone (0·46 g) in 1 N hydrochloric acid (2·2 c.c.) at 0° was treated with sodium nitrite (0·15 g) dissolved in a little water. After standing for 45 min at 5–15°, the precipitate of azide was removed and heated in water (40 c.c.) at 100° for 45 min. The mixture was then made alkaline with potassium hydrogen carbonate and extracted with chloroform. The sticky residue from the chloroform dissolved in concentrated hydrochloric acid to a deep crimson solution, from which a yellow solid separated on dilution with water. It was crystallised from methanol; the first crop, a curdy yellow *solid*, decomp. 235–245°, gave a crimson colour in hydrochloric acid (Found: C, 59·2; H, 5·6; N, 16·6. $C_{21}H_{24}O_5N_5$ requires C, 59·1; H, 5·7; N, 16·4%). The filtrate was treated with charcoal and concentrated; on cooling, tiny, white needles of hydroxydihydrostrychninone-A separated, sintering at 317°, m.p. 327–328°, undepressed by admixture with material from the oxidation of strychnine.

The yield from this reaction was unfavourable, and all further experiments on hydroxyhydrostrychninone-A were carried out with material from the oxidation of strychnine.[1,2] The compound (and many related compounds) showed widely varying melting-points, depending on the solvent from which it had been crystallised. Thus it crystallised from water in needles, m.p. 330–334°, $[\alpha]^{20}_{D}$, —16° (c. 0·37 in acetic acid), —74° (c. 1·01 in pyridine, λ^{EtOH}_{max}, 2500 Å; log ε_{max}, 4·1, while it separated from concentrated hydrochloric acid on dilution with water in microscopic prisms, m.p. 350–354°, $[\alpha]^{20}_{D}$, —17° (c. 0·36 in acetic acid), —73° (c. 0·74 in pyridine) (Found: C, 67·3; H, 5·5; N, 8·3. Calc. for $C_{19}H_{18}O_4N_2$: C, 67·4; H, 5·4; N, 8·3%). It crystallised from methanol in small needles, m.p. 328–330°, and from ethanol in needles, m.p. 330–332°, showing the same optical rotation and giving the same results on analysis as the forms above.

The *p*-nitrophenylhydrazone crystallised from aqueous acetic acid as microscopic, yellow rods, m.p. 299–300° (Found: C, 62·8; H, 4·9; N, 14·4. $C_{25}H_{23}O_5N_5$ requires C, 63·3; H, 5·0; N, 14·8%). It gave a deep magenta coloration in alcoholic sodium hydroxide.

The *semicarbazone* crystallised from aqueous methanol in minute needles, sintering at 210°, decomp. 230–232°, $[\alpha]^{21}_{D}$, 340° (c. 0·44 in acetic acid), $[\alpha]^{17}_{D}$, 344° (c. 0·554 in acetic acid) (Found: C, 60·6; H, 5·4; N, 17·2. $C_{20}H_{21}O_4N_5$ requires C, 60·7; H, 5·4; N, 17·7%).

The oxime, after two crystallisations from methanol, was obtained as needles, m.p. 297–302° (frothy decomp.), $[\alpha]^{20}_{D}$, —6° (c. 0·31 in acetic acid) (Found: C, 64·6; H, 5·4; N, 11·4. $C_{19}H_{19}O_4N_3$ requires C, 64·7; H, 5·4; N, 11·9%).

The *acetate* (I; R = OAc), prepared by heating a suspension of hydroxydihydrostrychninone-A in acetic anhydride containing one drop of 60% perchloric acid for 1 hour at 100°. It separated on cooling the mixture as microscopic rhombs, blackening at 250°, m.p. 265–266°, $[\alpha]^{16}_{D}$, 38°, 36° (acetic acid) (Found: C, 65·6,66·1, 65·8; H, 5·2, 6·0, 5·3; N, 7·7. $C_{21}H_{20}O_5N_2$ requires C, 66·3; H, 5·3; N, 7·4%). The acetate prepared with pyridine-acetyl chloride darkened at 236°, m.p. 241–242°. Acetylation by boiling acetic anhydride gave large crystals sintering at 235°, m.p. 238–241°. Any of these different forms crystallised from ethanol in needles, m.p. 230–237°. All forms gave the same analytical results and had the same optical rotation.

The *benzoate* (I; R = OBz) crystallised from alcohol in minute needles, m.p. 224–226°, $[\alpha]^{18}_{D}$, +140° (c. 0·45 in acetic acid) (Found: C, 70·5, 70·8; H, 5·1, 5·4. $C_{26}H_{22}O_5N_2$ requires C, 70·6; H, 5·0%) and was precipitated from pyridine solution by ethanol as an amorphous solid, m.p. 235–238°, $[\alpha]^{18}_{D}$, 143° (c. 0·66 in acetic acid) (Found: C, 70·8; H, 5·1%).

Strychninonamide (I; R = O·CH$_2$·CONH$_2$). Strychninonic acid (0·8 g) in chloroform (10 c.c.) was refluxed with thionyl chloride (1 c.c.) for 1 hour. The residue after evaporation under reduced pressure was shaken with concentrated ammonium hydroxide (5 c.c.), and gave *strychninonamide* (0·5 g), sintering and darkening at 280°, m.p. 295–296°, $[\alpha]^{19}_{D}$, +53° (c. 0·67 in acetic acid) (Found: C, 63·8; H, 5·3; N, 10·2. $C_{21}H_{21}O_5N_3$ requires C, 63·8; H, 5·4; N, 10·6%). The amide crystallised from water as white, microscopic rhombs, m.p. 260–262°, $[\alpha]^{19}_{D}$, +58° (c. 0·29 in acetic acid) (Found: C, 63·2; H, 5·3; N, 11·0%).

In an attempted repetition of this preparation, using strychninonic acid (5 g) and thionyl chloride (7 c.c.) in chloroform (50 c.c.), a *neutral* isomer of strychninonic acid was obtained, sintering at 210°, m.p. 253–258°. After two recrystallisations from methanol it was obtained as long needles, sintering at 220°, m.p. 238–245°, $[\alpha]_D^{19}$, $-81°$ (*c.* 0·37 in acetic acid), λ_{max}^{EtOH} 2500 Å, log ε_{max} 4·1 (Found in air-dried material: C, 61·5, 61·3, 60·8; H, 5·8, 4·9, 5·7; N, 6·9, 6·9, 6·9; loss at 130°/1 mm: 3·5. $C_{21}H_{20}O_6N_2,\frac{3}{4}H_2O$ requires C, 61·5; H, 5·3; N, 6·7; H_2O, 3·3%. Found in material dried at 130°/10 mm: C, 64·1; H, 5·3; N, 7·1; M, cryoscopic in camphor, 536. $C_{21}H_{20}O_6N_2$ requires C, 63·7; H, 5·0; N, 7·1%; M, 396). The solid gave a positive Otto reaction, and was insoluble in dilute mineral acid and sodium carbonate solution.

Its p-*nitrophenylhydrazone* crystallised from aqueous acetic acid as microscopic, yellow prisms, m.p. 240–242° (Found: C, 59·8; H, 5·5; N, 12·6. $C_{27}H_{25}O_7N_5{\cdot}H_2O$ requires C, 59·0; H, 4·9; N, 12·7%). It was insoluble in dilute sodium hydroxide and on addition of ethanol to the mixture a deep magenta colour appeared. The formation of this derivative excludes the hydroxylactone possibility, and the substance would appear to be the hydrate of an anhydro-strychninonic acid.

The isomeric p-*nitrophenylhydrazone of strychninonic acid* crystallised from acetic acid in microscopic yellow rods, sintering at 216°, m.p. 219–221° (Found in material dried at 120° in vacuum: C, 58·7; H, 5·1. $C_{27}H_{25}O_7N_5H_2O$ requires C, 59·0; H, 4·9%). It gave a light-red colour with ammonium hydroxide, and a deep magenta solution with dilute sodium hydroxide.

12-*Hydroxycunine*-14-*carboxylic acid* (III). (a) *From the permanganate oxidation of strychnine*. The compound, prepared according to Leuchs and Schwaebel,[1] crystallised from a small quantity of water (charcoal) as glistening, white rods, m.p. 297–298°, $[\alpha]_D^{18}$, $-46°$ (*c.* 0·52 in 8% aqueous ammonia) (Found: loss at 100°/0·1 mm, 4·6. Calc. for $C_{18}H_{21}O_4N_2Cl{\cdot}H_2O$: H_2O, 4·7. Found: C, 59·2, 59·8; H, 5·8, 5·2; Cl, 9·7. $C_{18}H_{21}O_4N_2Cl$ requires C, 59·3; H, 5·8; Cl, 9·8%).

The compound gave a faint, evanescent coloration in the Otto test.

(b) *From the oxidation of hydroxydihydrostrychninone-A with hydrogen peroxide and barium hydroxide*. Hydroxydihydrostrychninone-A (2·5 g) suspended in 5% barium hydroxide (60 c.c.) and perhydrol (1·7 c.c.) was heated on the steam-bath for 15 min with occasional shaking. The cooled mixture was made faintly acid with dilute sulphuric acid and filtered. Next day a small amount of brownish precipitate was removed, and 60% perchloric acid (4·4 c.c.) added gradually to the filtrate. After some brown gums had separated, hydroxycuninecarboxylic acid perchlorate was obtained; after two crystallisations from water it blackened at 255°, m.p. 262–263°, $[\alpha]_D^{18}$, $-42°$ (*c.* 0·53 in 8% aqueous ammonia) (Found: C, 50·7; H, 5·0. $C_{18}H_{21}O_8N_2Cl$ requires C, 50·4; H, 4·9%). The perchlorate was identical with that obtained by treating a hot solution of Leuchs and Schwaebel's hydrochloride with sodium perchlorate.

Methyl-11-*dehydrocunine*-14-*carboxylate* (V). Hydroxycuninecarboxylic acid perchlorate (0·25 g) was refluxed for 1½ hours in methanol (5 c.c.) containing concentrated sulphuric acid (0·08 c.c.). The mixture on cooling to $-10°$ deposited microscopic rhombs (0·19 g) of the *methyl ester hydrogen sulphate*, softening at 190°, decomp. 237°, $[\alpha]_D^{23}$, $+30°$ (*c.* 1·28 in water) (Found: C, 54·2; H, 5·1; S, 7·1; MeO, 6·6. $C_{19}H_{20}O_3N_2,H_2SO_4$ requires C, 54·0; H, 5·3; S, 7·6; MeO, 7·3%). It gave no perceptible colour in the Otto test.

18-*Nitroso*-12-*hydroxycunine*-14-*carboxylic acid*. N-Hydrochloric acid (4 c.c.) was added with shaking to a solution of hydroxycuninecarboxylic acid hydrochloride

(0·32 g) and sodium nitrite (0·06 g) dissolved in 0·25 N sodium hydroxide (13 c.c.). After 5 min the faintly yellowish *nitroso acid* was removed. It softened above 50°, and melted between 150° and 180° (Found: C, 60·3; H, 5·4; N, 11·8. $C_{18}H_{19}O_5N_3$ requires C, 60·5; H, 5·4; N, 11·8%). It was soluble in cold sodium carbonate solution. When crystallised from aqueous acetic acid, it changed to the nitrosolactone (IV) sintering at 247°, m.p. 255–257° (Found: C, 63·2; H, 5·3. $C_{18}H_{17}O_4N_3$ requires C, 63·7; H, 5·0%). The lactone was insoluble in cold dilute alkali, but dissolved on warming. It gave a deep purple colour in the Otto reaction.

18-*Benzoyl*-12-*hydroxycunine*-14-*carboxylic acid.* Hydroxycuninecarboxylic acid perchlorate (0·38 g) in N-sodium hydroxide (2·5 c.c.) was treated with benzoyl chloride (0·09 c.c.). After shaking for 30 min, the solution was decanted from a small amount of gum and acidified. The flocculent white precipitate crystallised from aqueous acetic acid as a mixture of *lactone* and *acid*, m.p. 170–180°, with previous sintering (Found: C, 70·8; H, 5·1; N, 6·5; acid equivalent, 597, 600. A mixture of 72% $C_{25}H_{24}O_5N_2$ –28% $C_{25}H_{22}O_4N_2$ requires C, 70·3; H, 5·5; N, 6·6%; acid equivalent 600). The solid was partially soluble in cold sodium carbonate solution, but dissolved completely on warming. It gave a deep blue colour in the Otto test.

12-*Hydroxy*-14-(2′-*but*-2-*enyl*)-19-*methylcunine* (VI). Sodium (2·1 g) was added during 20 min to a stirred suspension of finely-ground methylstrychnine (3·7 g) in liquid ammonia (200 c.c.). Methanol (10 c.c.) was added, and the ammonia allowed to evaporate. The aqueous solution of the residue gave on acidification a gum, which dissolved almost completely in hot 20% hydrochloric acid. The base separating when this solution was made alkaline was taken up in benzene and chromatographed on alumina, giving 12-hydroxy-14-(2′-but-2′-enyl)-19-methylcunine as a first fraction: after six crystallisations from light petroleum (b.p. 40–60°), rods, m.p. 122–125° (0·1 g) were obtained (Found: C, 75·4; H, 8·1; C-Me, 11·1; NMe, 5·7. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 7·9; 2C-Me, 15·3; NMe, 8·2%).

The perchlorate, crystallised twice from water, was obtained in tiny spherulites, darkening at 250°, m.p. 264–166° (decomp.) (Found: C, 58·4; H, 6·7; N, 6·9; Cl, 7·2. $C_{22}H_{29}O_6N_2Cl$ requires C, 58·3; H, 6·5; N, 6·2; Cl, 7·8%).

12-*Hydroxy*-14-*hydroxyoxalylcunine* (VIII). Hydroxydihydrostrychninone-A (0·7 g), when heated with concentrated hydrochloric acid (3 c.c.) on the steam-bath for 30 min; afforded, on cooling, the *amino-acid hydrochloride*, softening and darkening above 250°, decomp, about 310°, unaltered by recrystallisation from water, $[\alpha]_D^{18}$, +14° (*c.* 0·50 in water), λ_{max}^{EtOH} 2500 Å, log ε_{max} 4·1 (Found in air-dried material: C, 55·8; H, 5·8; Cl, 8·9. $C_{19}H_{21}O_5N_2Cl,H_2O$ requires C, 55·5; H, 5·6; Cl, 8·6%. Found in material dried at 130°/10 mm: C, 57·6; H, 5·8; Cl, 9·8. $C_{19}H_{21}O_5N_2Cl$ requires C, 58·1; H, 5·4; Cl, 9·0%). It gave no coloration in the Otto test. When crystallised twice from methanol, the amino-acid hydrochloride formed the *methyl ester*, decomp, 270° (Found in material dried at 130°/10 mm: C, 59·1; H, 5·8; Cl, 7·9; MeO, 6·6. $C_{20}H_{23}O_5N_2Cl$ requires C, 59·0; H, 5·7; Cl 8·7; MeO, 7·6%). The ester gave a brownish Otto reaction.

Strychninone-A. The directions of Holmes, Openshaw, and Robinson[3] were followed, except that it was found necessary to warm the reaction mixture for 1 hour on the steam-bath. The crude strychninone-A in benzene was chromatographed on alumina, from which it was eluted by chloroform, giving a white solid sintering at 220°, m.p. 237–247°, $[\alpha]_D^{25}$, −143° (*c.* 3·73 in acetic acid) (Found: C, 71·0; H, 5·0. Calc.

for $C_{19}H_{18}O_3N_2$: C, 71·2; H, 5·0%). When strychninone-A was crystallised from ethanol, it first separated in micaceous plates, sintering at 220°, m.p. 240–246° (Found: C, 68·3; H, 6·1; N, 7·8, loss at 130°/mm, 10·5. Calc. for $C_{19}H_{18}O_3N_2$, C_2H_6O: C, 68·8; H, 6·1; N, 7·7; loss, 12·6%) and as a later crop of tufts of tiny needles, sintering at 228°, m.p. 246–249° (Found: C, 68·0; H, 6·1; N, 8·0%) (cf. ref. 2). The *semicarbazone* crystallised from the aqueous reaction mixture as pale yellow, microscopic rods, foamy decomp. 208–209°, $[\alpha]_D^{16}$, +148° (*c.* 1·07 in acetic acid) (Found: C, 60·1; H, 5·1; N, 17·6. $C_{20}H_{19}O_3N_5,H_2O$ requires C, 60·7; H, 5·4; N, 17·7%). The *oxime* softened at 215°, m.p. 224–228° (Found: C, 64·7; H, 5·5; N, 11·5. $C_{19}H_{17}O_3N_3,H_2O$ requires C, 64·7; H, 5·4; N, 11·9%). The *p-nitrophenylhydrazone* crystallised from aqueous acetic acid as microscopic, yellow rods, sintering at 242°, m.p. 250–253° (Found in material dried at 120°/0·1 mm: C, 66·0; H, 5·1; N, 15·4. $C_{25}H_{21}O_4N_5$ requires C, 65·9; H, 5·2; N, 15·4%).

11-*Dehydro*-14-*hydroxyoxalylcunine* (VII). Strychninone-A (0·1 g) in concentrated hydrochloric acid (1 c.c.) was heated to 100° for 1 hour. The dirty brown solid separating from the mixture on cooling was dissolved in water (2 c.c.) and filtered. Dilution with acetone precipitated a tar; the residual solution on evaporation yielded 11-*dehydro*-14-*hydroxyoxalylcunine* softening at 290°, decomp. 232–337° (Found: C, 58·2; H, 5·3; Cl, 9·7. $C_{19}H_{19}O_4N_2Cl,H_2O$ requires C, 58·1; H, 5·4; Cl, 9·0%). λ_{max}^{EtOH} 2500 Å, log ε_{max} 4·1. It gave a feeble Otto reaction.

Chlorodihydrostrychninone-A (I; R = Cl). A suspension of hydroxydihydrostrychninone-A (2 g) in dry chloroform (30 c.c.) and thionyl chloride (2 c.c.) was shaken occasionally for two days. The solution was then washed with water and dilute ammonia, dried, boiled with Fuller's earth, and concentrated. Several crops of sticky solids were obtained which on recrystallisation from chloroform gave a white solid (0·17 g), m.p. 225–226° (Found: C, 63·9; H, 5·1; Cl, 9·9. $C_{19}H_{17}O_3N_2Cl$ requires C, 63·9; H, 4·8; Cl, 9·9% as well as larger amounts (0·77 g) melting between 220° and 224°). Attempts to dehydrohalogenate this compound with pyridine to form strychninone-A were fruitless.

Hydroxydihydrostrychninolone-A (IX: R = OH). Hydroxydihydrostrychninone-A (6·75 g) in acetic acid (100 c.c.) was hydrogenated in the presence of platinum oxide (0·65 g) to give hydroxydihydrostrychninolone-A[2] (0·65 g), m.p. 300–301°, $[\alpha]_D^{20}$, +26° (acetic acid) (Found: C, 66·9; H, 6·0. Calc. for $C_{19}H_{20}O_4N_2$: C, 67·0; H, 5·9%). It crystallised from methanol in needles, m.p. 260–270°, $[\alpha]_D^{20}$, +26° (acetic acid) (Found: C, 66·4, 66·5; H, 5·7, 6·0%; no loss at 100°/0·1 mm), and from water in tiny, felted needles, m.p. 270–280° (Found: C, 67·2; H, 6·0%).

Oxidation of hydroxydihydrostrychninolone-A to hydroxydihydrostrychninone-A. Chromic anhydride (0·13 g) in water (0·5 c.c.) and acetic acid (12 c.c.) was added with shaking to a suspension of hydroxydihydrostrychninolone-A (0·68 g) in acetic acid (100 c.c.). After two days the solution was concentrated under reduced pressure, diluted with water, and extracted with chloroform (6 × 15 c.c.). The chloroform solution was washed with dilute ammonia and concentrated to 10 c.c. to give a first crop of a mixture of compounds. Further concentration gave a crop of hydroxydihydrostrychninone-A, m.p. 319–325°; after two precipitations from concentrated hydrochloric acid solution by water the m.p. was 348–350°, undepressed by admixture with authentic material (Found: C, 67·1; H, 5·4. Calc. for $C_{19}H_{18}O_4N_2$: C, 67·4; H, 5·4%).

Strychninolone-C. (*a*) *From hydroxydihydrostrychninolone-A.* Hydroxydihydrostrychninolone-A (0·97 g) in N-sodium hydroxide (3·6 c.c.) was heated on the steam-bath for 90 min. The solid (0·72 g) which separated was taken up in benzene and chromatographed on alumina. Elution with carbon tetrachloride-alcohol gave strychninolone-C,[12] sintering at 237°, m.p. 246–249° without foaming, $[\alpha]_{D}^{23}$, $-177°$ (*c.* 0·73 in acetic acid) (Found: C, 70·5; H, 5·8; N, 8·9. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·8; H, 5·6; N, 8·7%). (*b*) *From strychninolone-A.* The following method was more convenient than those already reported.[12,15] Crude strychninolone-A (0·65 g) in 4% sodium hydroxide solution (5 c.c.) was digested for 6 hours on the steam-bath.

The crude strychninolone-C was purified by passing it in chloroform (20 c.c.) through a short column of activated alumina, which was then washed with more chloroform (20 c.c.). The combined percolates gave strychninolone-C (0·48 g), m.p. 254–250°.

11-*Dehydro*-14-*methoxycarbonylhydroxymethylcunine* (X; R = Me)—(*a*) *From hydroxydihydrostrychninolone-A.* Hydroxydihydrostrychninolone-A (0·5 g) in concentrated hydrochloric acid (5 c.c.) was heated on the steam-bath for 40 min. The solution was evaporated to dryness, the residue taken up in water and neutralised to pH7, and again evaporated to dryness. The residue was extracted with hot methanol. The solid separating from the solution was recrystallised twice from methanol, giving needles of the methyl ester hydrochloride,[10] sintering at 297°, m.p. 301–303°, $[\alpha]_{D}^{27}$, $+9°$ (*c.* 0·16 in water) (Found: C, 61·0; H, 6·0; Cl, 9·3; MeO, 7·4. Calc. for $C_{20}H_{22}O_4N_2Cl$: C, 61·5; H, 5·9; Cl, 9·1; MeO, 7·9%).

The *nitrosamine* formed from the methyl ester had m.p. 215–217° (Found: C, 62·0; H, 5·6; N, 10·6. $C_{20}H_{21}O_5N_3$ requires C, 62·7; H, 5·5; N, 11·0%).

(b) *From strychninolic acid.* The acid (1 g) was heated in concentrated hydrochloric acid (7 c.c.) on the steam-bath for 1 hour. The syrup obtained on evaporation of the solution was refluxed with methanol (10 c.c.) and hydrochloric acid (0·2 c.c.) for several hours to give the ester hydrochloride (0·1 g). After one crystallisation from water the tiny needles had m.p. 301–303°, $[\alpha]_{D}^{20}$, $+8°$ (*c.* 0·36 in water) (Found: C, 61·9; H, 5·8%).

Ethyl strychninolate (IX; R = OCH_2CO_2Et). Strychninolic acid (1 g) was shaken in 5% ethanolic hydrogen chloride (20 c.c.) at 0° and the mixture allowed to attain the room temperature. After 25 min the solution was neutralised with ice-cold 5% potassium hydrogen carbonate solution, and extracted with chloroform (4 × 10 c.c.). The residue from the chloroform crystallised from ethanol as microscopic prisms of *ethyl strychninolate* softening at 157°, m.p. 161–163°, $[\alpha]_{D}^{17}$, $+27°$ (*c.* 0·77 in acetic acid) (Found: C, 64·0; H, 6·5; EtO, 10·1. $C_{23}H_{26}O_6N_2$ requires C, 64·8; H, 6·2; EtO, 10·5%).

Hydrazinodihydrostrychninolone-A (IX; R=$NHNH_2$)—(*a*) *From ethyl strychninolate.* Ethyl strychninolate (4·0 g) and hydrazine hydrate (1·6 c.c.) in ethanol (20 c.c.) were heated for 5 min on the water-bath and the solution than evaporated to dryness. On adding ethanol (16 c.c.) to the yellow syrup, a white crystalline solid was obtained; concentration of the filtrate gave further amounts. The gummy solid (3·0 g) was digested twice with ethanol (30 c.c.) leaving microscopic rods, sintering at 220°, m.p. 228–230°, $[\alpha]_{D}^{20}$, $-88°$ (*c.* 0·69 in acetic acid) (Found: C, 64·2, 64·9; H, 6·2, 6·4; N, 16·3, 15·1. $C_{19}H_{22}O_3N_4$ requires C, 64·4; H, 6·3; N, 15·8%).

Hydrazino dihydrostrychninolone-A was soluble in dilute hydrochloric acid and sparingly soluble in hot water. It gave a deep red colour in the Otto test.

Final concentration of the original filtrate and of the filtrates from the digestion left a white solid which, after digestion with ethanol (10 c.c.), gave an impure *isomeric hydrazinodihydrostrychninolone*-A sintering at 280°, decomp. 283–286° (Found: C, 63·2, 63·5; H, 6·1, 6·2; N, 14·9, 16·2%). These hydrazinodihydrostrychninolones on repeated crystallisation from ethanol deteriorated to brown gums.

(*b*) *From strychninolone-A.* Strychninolone-A (0·8 g) was heated on the water-bath with hydrazine hydrate (0·3 c.c.) in absolute ethanol (4 c.c.). It rapidly dissolved, then microscopic white prisms (0·49 g) separated, decomp. 222–230°, $[\alpha]_D^{20}$, −100° (*c.* 0·79 in acetic acid) (Found: C, 64·1; H, 7·0; N, 15·8%). The difference in specific rotation of the material prepared from ethyl strychninolate is probably due to difference in the proportions of isomerides.

Action of hydrazine on strychninolone-C. Strychninolone-C (0·7 g), heated in ethanol (4 c.c.) containing hydrazine hydrate (0·3 c.c.) for six hours on the steam-bath, went very slowly into solution. Next day, round, white nodules of a mixture (0·55 g) of *hydrazinodihydrostrychninolone-C* and strychninolone-C, sintering at 170°, decomp. 185–200°, were collected (Found: C, 65·8; H, 6·3; N, 14·7. A mixture of 80% $C_{19}H_{22}O_3N_4$ and 20% $C_{19}H_{18}O_3N_2$ requires C, 65·6; H, 6·3; N, 14·5%). The material was partially soluble in dilute hydrochloric acid, and gave a red Otto reaction.

$C_{(21)}$*Monoacetate of hydroxydihydrostrychninolone-A* (XI). Obtained by treatment of hydroxydihydrostrychninolone-A with acetic anhydride-sodium acetate at 100°, the *acetate* crystallised from methanol in microscopic prisms, m.p. 234–236°, $[\alpha]_D^{22}$, −24° (*c.* 1·07 in acetic acid) (Found: C, 65·6, 65·6; H, 5·8, 5·8; Ac, 13·6. $C_{21}H_{22}O_5N_2$ requires C, 65·9; H, 5·7; Ac, 11·2%).

$C_{(12)}$-*Monoacetate of hydroxydihydrostrychninolone-A* (IX; R = OAc). Hydroxydihydrostrychninone-A acetate (1·0 g) in acetic acid (80 c.c.) with platinum oxide (0·02 g) was hydrogenated to give the $C_{(12)}$-*monoacetate* (0·9 g), m.p. 235–239°, obtained after two recrystallisations from methanol as needles, sintering at 205°, m.p. 215–217°, $[\alpha]_D^{20}$, +91° (*c.* 0·91 in acetic acid) (Found: C, 65·7; H, 5·7. $C_{21}H_{22}O_5N_2$ requires C, 65·9; H, 5·7%).

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