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STUDIES ON STRYCHNINE DERIVATIVES AND CONVERSION INTO BRUCINE

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Abstract—Several new derivatives of strychnine substituted at positions C_2 and C_3 of the aromatic ring have been prepared in order to convert strychnine into brucine. This goal was attained by means of a double oxidation process with Fremy salt (potassium nitrosodisulphonate) on strychnic acid and 2-hydroxy-strychnine, and final methylation of 2,3-dihydroxystrychnine into brucine.

THE two well known alkaloids strychnine (I) and brucine (II), have been extensively investigated[1] and the former has been synthesized[2] but no interconversion has been yet described. We wish to report several approaches which led to the synthesis of brucine from strychnine. The problem was to introduce two OH groups at the 2,3-positions of the aromatic nucleus without interfering with the other parts of the molecule, a goal which was ultimately attained by direct oxidation.

2-Nitrostrychnine (III)[3,4] was converted in high yields by new methods to pure 2-aminostrychnine (IV).[3,4] Acetylation afforded 2-acetamidostrychnine (V),[5] the NMR spectrum of which displayed the expected Me signal at δ 2·11; this compound could also be obtained in excellent yields by reducting III directly with zinc and acetic anhydride in acetic acid solution.

When the nitrate salt of V was treated at 0–5° with sulphuric acid in aqueous or in acetic acid solution, 2-amino-3-nitro-(VI) or respectively 2-acetamido-3-nitro-strychnine (VII)[5] was formed. That the nitro group entered the C_3 position was shown by the NMR spectrum of the acetamido derivative which displayed at low field two singlets at δ 8·66 and 8·82 for the C_1 and C_4 aromatic protons.

2-N-dimethyl-amino-3-nitrostrychnine (VIII) was prepared by treating VI with a solution of formaldehyde and formic acid and obtained as a bright red crystalline product which was characterized as the hydrochloride. The NMR spectrum of this compound displayed a singlet at δ 2·83 accounting for 6 protons ($2 \times CH_3$) and two one proton singlets at δ 6·84 and 8·36 for C_1—H and C_4—H.

Experiments were then undertaken to prepare 2-hydroxy-3-nitrostrychnine (IX) from the 2-amino-3-nitro derivative. To this end diazotisation of the amino group was performed and treated in several ways, but the expected product could not be obtained. However, in order to explore the reaction sequence, several decomposition methods were studied. With cuprous chloride, 2-chloro-3-nitrostrychnine (X) was obtained and fully characterized, it possessed the appropriate spectroscopic data (singlets at δ 7·32 and 8·66), whereas if the reaction was performed in methanol solution and copper bronze was added, high yields of 3-nitrostrychnine (XI)[5] were obtained following complete reduction of the diazonium salt. Decomposition in the

presence of sodium hypophosphite afforded 3-aminostrychnine (XII),[5] in which reduction of the 3-nitro to the corresponding 3-amino derivative had taken place. The product was characterized as its acetamide which was identical with the product obtained from the reduction of 3-nitrostrychnine (XI).

When 2-amino-3-nitrostrychnine (VI) was treated with zinc powder and hydrochloric acid the double salt of zinc chloride and 2,3-diaminostrychnine was formed, which was decomposed with gaseous hydrogen sulphide yielding 2,3-diaminostrychnine (XIII) as a grey powder. The IR spectrum of this compound indicated the disappearance of the nitro band originally present in the starting material at 1360 and 1560 cm^{-1}. Upon acetylation with acetic anhydride the 2,3-diacetamido derivative was formed and fully characterized, strong peak at 1700 cm^{-1}, and NMR signals at δ 2·15 for 6 protons and at 7·42 (s), 8·08 (s) for one aromatic proton each. An alternative and probably better route for the formation of this diacetamido derivative was by treating the 2-amino-3-nitro compound directly with zinc and acetic acid in the presence of acetic anhydride.

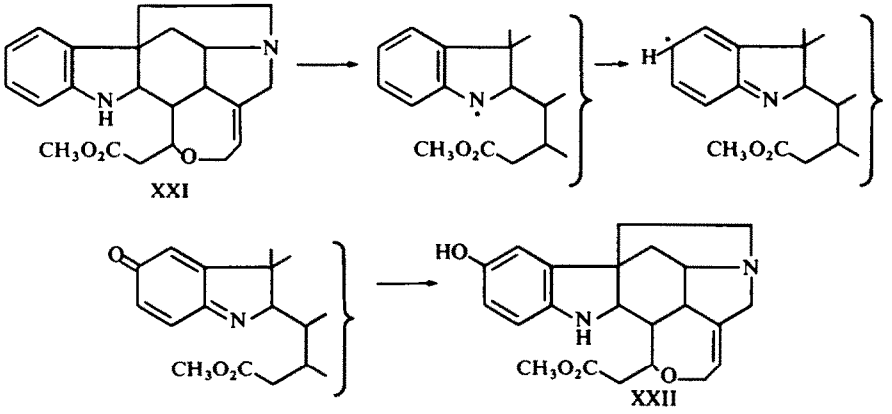
Repeated attempts to oxidize the *o*-diamino derivative in aqueous acid solution with various oxidizing agents produced only wine red colored solution. When using for example ferric chloride, the red solution which was formed was treated with tartaric acid and the iron complex formed extracted with chloroform. Evaporation of the solvent gave a crude red powder which could not be further purified. The IR spectrum of this residue, bands at ν^{KBr} 3350 cm^{-1} indicated the probable formation of an *o*-quinone-imine. On the other hand, attempts to hydrolyse the 2-hydroxy-3-nitrososstrychnine (XIV; brucinoquinone mono-oxime) to brucinoquinone[6] by treating the product either with excess formaldehyde or with copper oxide in hydrochloric acid, were unsuccessful.

At this stage, an alternative sequence of reactions aiming at the preparation of 2-methoxy-3-hydroxystrychnine was undertaken. The first step involved the conversion of 2-aminostrychnine (IV) to the 2-hydroxy derivative (XV)[7] through an improved method. Following diazotisation, the salt was gradually added to a hot concentrated sulphuric acid solution (180°). The reaction was completed within 10 min with high yields of 2-hydroxystrychnine. 2-Methoxystrychnine (β-colubrine; XVI)[1] was then easily prepared with diazomethane and identified by comparison with an authentic sample. The methylation reaction could also be performed with dimethyl sulphate if reacted on the N-oxide of 2-hydroxystrychnine. Reduction with sodium hydrosulphite yielded again β-colubrine. It is noteworthy that during the high temperature decomposition of the diazonium salt, together with the expected product, small quantities of 2,3-dihydroxystrychnine (XVII), probably formed by spontaneous air oxidation, were detected by the methylation reaction which produced brucine (II) in the reaction mixture. Decomposition of the above diazonium salt with 2N H_2SO_4 at 110° afforded generally a mixture consisting of 2-hydroxystrychnine N-oxide and strychnine which were formed by an oxidation-reduction reaction. When Caro acid was added during the decomposition reaction, higher yields of the dihydroxy derivative (XVII) were obtained, however, most of the compound underwent destruction.

Functionalisation of position 3 in this series, was performed by the following sequence. The nitrate salt of 2-methoxystrychnine was treated with sulphuric acid at −5° for 2 hr yielding the yellow 2-methoxy-3-nitrostrychnine (XVIII). This

compound showed in the NMR spectrum, in addition to the three proton signal of the MeO group at δ 3·96, two singlets for one proton each at δ 6·95 and 8·46 due to C_1—H and C_4—H, indicating unequivocally that the nitro group occupies the C_3 position. The nitro group was then reduced in good yields with sodium hydrosulphite to the white 2-methoxy-3-amino compound (XIX). The presence of the amino group was indicated by the appropriate bands in the IR spectrum, ν^{KBr} 3500 and 1635 cm^{-1}. Attempts to convert the 3-amino group to the corresponding 2-methoxy-3-hydroxy derivative (XX) using the Sandmeyer reaction afforded untractable mixtures.

In order to reduce the number of steps leading to 2-hydroxystrychnine, a direct hydroxylation procedure using Fremy salt (potassium nitrosodisulphonate) was investigated. As expected, when reacted with strychnine no reaction took place. Fremy salt reacts first by the abstraction of an H atom from a OH group then by combination of a second mole of the reagent with the phenolic radical.[8] In the present case, the initiation of the reaction was obtained at the dihydroindol nitrogen by the opening of the lactam group to yield the corresponding strychnic acid, which generates with the reagent a radical at the *para* position. The intermediate complex formed with the second mole of reagent is then decomposed and a 2-quinone-imine is obtained disclosed by the formation of wine red colored solution.



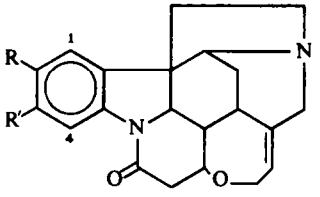
The reaction was first carried out on the methyl ester of strychnic acid (XXI)[9] in order to avoid recyclization of the lactam. Upon addition of sodium hydrosulphite to the reaction mixture, methyl-2-hydroxystrychnate was formed (XXII).

When the same procedure was performed on strychnic acid in carefully controlled neutral pH and the quinone-imine treated with sodium hydrosulphite in acidic conditions, concomitant cyclization of the lactam took place to yield 2-hydroxystrychnine (XV) in about 50% yield. Methylation with diazomethane afforded β-colubrine (XVI).

For the introduction of a second OH group in 2-hydroxystrychnine it was expected that the phenolic OH group would provide good initiation for a reaction with the same reagent by repeating the procedure; the lactam moiety being linked at the *para* position to the OH group, *ortho* reaction should take place. Indeed, treating 2-hydroxystrychnine with an additional quantity of Fremy salt, produced the red *o*-quinone which was directly reduced in the reaction mixture with sodium hydrosulphite to the 2,3-dihydroxy derivative (XVII). The whole reaction was carried

out in acidic conditions in order to avoid opening of the lactam which due to the formation of the *o*-quinone seems to be prone to such an opening resulting in water soluble substances. Upon neutralization of the solution with ammonium hydroxide to pH 7–7·5 the product precipitated as a white powder. Methylation of the crude product yielded a mixture of β-colubrine (XVI) and brucine (II) as shown on a chromatoplate. Chromatography on neutral alumina and elution with a solvent mixture of hexane–chloroform 9:1 afforded fractions containing first β-colubrine followed by pure brucine. Both were identified with authentic samples.

The conversion of strychnine to brucine with reactions which do not interfere with the stereochemistry of the molecule, provide thereby proof for the same stereochemistry in the two naturally occurring substances.



I: R = R' = H
II: R = R' = OMe
III: R = NO_2; R' = H
IV: R = NH_2; R' = H
V: R = MeCONH—; R' = H
VI: R = NH_2; R' = NO_2
VII: R = MeCONH; R' = NO_2
VIII: R = Me_2N—; R = NO_2
IX: R = OH; R' = NO_2
X: R = Cl; R' = NO_2
XI: R = H; R' = NO_2
XII: R = H; R' = NH_2
XIII: R = R' = NH_2
XIIIa: R = R' = NHCOMe
XIV: R = OH; R' = NO
XV: R = OH; R' = H
XVI: R = OMe; R' = H
XVII: R = R' = OH
XVIII: R = OMe; R' = NO_2
XIX: R = OMe; R' = NH_2
XX: R = OMe; R' = OH

EXPERIMENTAL

M.ps were taken on a Fisher–Johns apparatus and are uncorrected. UV absorption spectra were done on a Cary 14 spectrophotometer. IR spectra were recorded on a Perkin–Elmer Infracord model 137 spectrophotometer equipped with a NaCl prism and were determined in $CHCl_3$ soln of 5–10% concentration. NMR spectra were recorded on a Varian A-60 spectrometer, for 5–10% solns in $CDCl_3$, containing TMS as internal standard. TLC was done on chromatoplates of silica gel G (Merck) and spots were developed with iodoplateate. In the chromatography, alumina refers to neutral alumina (Woelm), activity III. The mol wts, whenever given were determined by mass spectrometry on an Atlas CH4 instrument.

2-Aminostrychnine[4]

(a) 2-Nitrostrychnine[4] (60 mg) was dissolved in CH_2Cl_2 (300 ml) and EtOH 90% (2 l) and NH_4Cl aq (24 g in 120 ml) was added. The mixture was stirred and warmed, Zn powder (112 g) added and then heated to reflux for 2 hr. The soln was filtered, acidified with 10% H_2SO_4 (300 ml), and the organic solvents were evaporated. Addition of NH_4OH to the hot aqueous soln precipitated 2-aminostrychnine (47 g), m.p. 278°.

(b) 2-Nitrostrychnine (100 g) was suspended in hot water and dissolved with 10% HCl (500 ml) at about pH 3–4, and $Na_2S_2O_4$ (100 g) was then introduced in small portions while stirring. Within a few min the yellow color disappeared indicating the end of the reaction, H_2SO_4 (350 ml) was added and the soln heated to reflux for 3 hr, filtered and while hot NH_4OH was added to pH 8; the 2-aminostrychnine precipitated as a white crystalline substance (75 g), m.p. 276–278°.

The N-*oxide* was prepared by gentle heating of 2-aminostrychnine (5 g) in H_2O_2 30% (25 ml) up to 80° until a clear soln was obtained. The soln was then poured onto ice (50 g) and the ppt collected and washed with cold isopropanol (4·6 g).

2-Acetamido-strychnine[5]

(a) A soln of the 2-amino-derivative (10 g) was heated to 50° for 3 hr in water (250 ml) and AcOH (5 ml) with Ac_2O (3 ml) and a 25% NaOAc aq (100 ml). The reaction mixture was cooled and neutralized with 10% NaOH aq whereupon a pure white crystalline product (8 g) was obtained; recrystallisation from MeOH, m.p. 183–184°.

(b) 2-Aminostrychnine (10 g) was heated under reflux for 30 min in Ac_2O (3·5 ml) and AcOH (5 ml), with Zn powder (0·1 g). The reaction mixture was poured on ice (250 g), the pH adjusted to 7·5 with NH_4OH whereupon the acetamido-strychnine precipitated as a white powder (9·7 g), m.p. 189–190°.

2-Acetamido-strychnine from 2-nitrostrychnine

A mixture of 2-nitrostrychnine (15 g) and Zn powder (21 g) was slowly added with stirring to Ac_2O (6 ml) in AcOH (75 ml), an exothermic reaction developed and the temp was kept at 80° by cooling. The mixture was then heated under reflux for 2 hr with stirring, filtered hot, and the residue washed with AcOH (2 × 20 ml). Ice (500 g) was added and the soln brought to pH 7·5–8 with NH_4OH whereupon the product precipitated; it was filtered off and washed with water and acetone (16 g); recrystallized from MeOH, m.p. 190° and *sulphate* m.p. 145–148°.

The *nitrate*[5] was prepared by suspending the compound (20 g) in water (20 ml) at 55°, and 3N HNO_3 was added to pH 5·3 and stirred until complete soln. Then NH_4NO_3 (50 g) was added and the mixture kept at the same temp for an additional hr. The soln was stored at 5° for 24 hr, and the salt collected washed with sat NH_4NO_3 aq, water and acetone, yield 85%.

2-Acetamido-3-nitrostrychnine

2-Acetamido-strychnine nitrate (20 g) was dissolved in AcOH (45 ml) and conc H_2SO_4 (15 ml) at 10° by stirring for 1 hr. Ice was added followed by NH_4OH to pH 7·5, and the ppt was filtered off and washed with cold water. It was crystallized as its *acetate* from benzene–$CHCl_3$ (1:1), m.p. 175–177° (yield 75%). (Found: C, 58·01; H, 5·51; N, 11·52. $C_{25}H_{27}O_7N_4$ requires: C, 57·26; H, 5·52; N, 11·45%).

2-Amino-3-nitrostrychnine[5]

To a soln of conc H_2SO_4 (45 ml) in water (65 ml) cooled at 0–5°, 2-acetamido-strychnine nitrate (20 g) was gradually added with efficient stirring. After 48 hr at 10° the soln was poured on ice (300 g) and NH_4OH introduced to pH 8. The ppt was filtered off, dissolved in 2N H_2SO_4 (170 ml) and refluxed for 2 hr. Then NH_4OH was carefully added to pH 3; after cooling 2-amino-3-nitrostrychnine sulphate crystallized (yield 90%). This product was dissolved in boiling conc HCl and the soln poured into slight excess of NH_4OH. The 2-amino-3-nitrostrychnine was filtered off and washed with water and alcohol (yield 97%), m.p. 170° dec; *sulphate*; red-orange needles, m.p. 270° dec.

2-Dimethylamino-3-nitrostrychnine

The above compound as its sulphate (22 g) was dissolved in formaldehyde 30% (30 ml) and formic acid (240 ml) and the soln heated to reflux for 2 hr. After cooling neutralized with NH_4OH aq and the product extracted with $CHCl_3$. The organic layer was separated, washed with water and dried over Na_2SO_4. The residue after evaporation of the solvent was selectively extracted with benzene and chromatographed on alumina. Elution with pet. ether–$CHCl_3$ (9:1) afforded a brilliant red solid (10 g). The hydrochloride was prepared by dissolving the product in 4N isopropanolic HCl soln and evaporating the solvent, recrystallized from EtOH, m.p. 165°, yield 45% (Found: C, 60·02; H, 6·50; N, 11·39; Cl, 7·32. $C_{23}H_{26}O_4N_4$. HCl; requires: C, 60·10; H, 5·93; N, 12·21; Cl, 7·51%).

2-Chloro-3-nitrostrychnine

2-Amino-3-nitrostrychnine sulphate (20 g) in 10% H_2SO_4 (500 ml) was diazotized with 5% of $NaNO_2$ aq (60 ml) at 50°. Urea was then added in order to destroy excess of the nitrite. The diazonium was poured dropwise with stirring into a soln of Cu_2Cl_2 in conc HCl (8 g in 225 ml) warmed at 50° and the soln heated at 90° for 30 min. After pouring onto ice, NH_4OH was added to pH 9–10, and the mixture was extracted with $CHCl_3$, the organic layer was washed, decolorized, dried over Na_2SO_4 and evaporated

(13 g). The product crystallized from dimethyl formamide and further purified by chromatography on alumina eluting with a solvent mixture of pet ether–$CHCl_3$ 1:9 (7 g), m.p. 280° dec, $[\alpha]_D$ −118° (*c* 2·0 $CHCl_3$). (Found: C, 61·25; H, 4·72; N, 9·84; Cl, 8·67. $C_{21}H_{20}O_4N_3Cl$ requires: C, 60·94; H, 4·87; N, 10·15; Cl, 8·57%).

3-Nitrostrychnine[5]

To a soln of 2-amino-3-nitrostrychnine (20g) in MeOH (600 ml) and conc H_2SO_4 (15 ml) at 50°, $NaNO_2$ (3·9 g) powder was added in portions. The diazonium soln was decomposed by adding dropwise to conc H_2SO_4 (80 ml); copper bronze dust (0·1 g) was introduced with efficient stirring and the mixture heated to reflux for 2·5 hr. After cooling the soln was diluted with water (600 ml) and the alcohol evaporated, decolorized and while boiling NH_4OH added to pH 7–8. The cooled soln was extracted with $CHCl_3$ and the solvent evaporated. The residue was chromatographed on alumina eluting with $CHCl_3$. The product (13·5 g) crystallized from dimethylformamide, m.p. 280–282° dec. (Found: C, 66·8; H, 5·70; N, 10·85. $C_{21}H_{21}N_3O_4$ requires: C, 66·48; H, 5·58; N, 11·08%).

3-Aminostrychnine[5]

(a) This was obtained from 3-nitrostrychnine by reduction with Zn powder and HCl or $Na_2S_2O_4$ as described above. Crystallized from dimethylformamide, decomposition point 310–315°. (Found: C, 72·54; H, 6·53; N, 12·51. $C_{21}H_{23}N_3O_2$ requires: C, 72·18; H, 6·63; N, 12·03%).

(b) A soln of the diazonium salt of 2-amino-3-nitrostrychnine (20 g) in 2·5 N H_2SO_4 (600 ml) was added to a soln of NaH_2PO_2 (120 g) in water (800 ml) warmed at 50°. The soln was heated to 90° for 1 hr and then poured on a slight excess of NH_4OH. The mixture was extracted with $CHCl_3$, dried and evaporated (yield 95%).

3-Acetamido-strychnine

This was prepared by acetylation in Ac_2O and pyridine overnight. After decomposition of the anhydride with ice water, and neutralized with NH_4OH, the product was extracted with $CHCl_3$; crystallized from alcohol m.p. 265°.

2,3-Diaminostrychnine

(a) To a hot soln of 2-amino-3-nitrostrychnine (5 g) in 3N HCl (150 ml), Zn powder (20 g) was added and the mixture heated under reflux for 2 hr. The soln was filtered and cooled to 5° whereupon the double salt precipitated. It was collected, dissolved in warm water (200 ml) and H_2S gas was passed until all the ZnS had separated. After filtration NH_4OH was added to pH 8 when 2,3-diaminostrychnine precipitated (3 g) dec >300°.

(b) To 2-amino-3-nitrostrychnine (30 g) in CH_2Cl_2 (100 ml) and EtOH 95% (650 ml) Zn dust was slowly added (50 g) with efficient stirring. The mixture was heated under reflux until decolorization took place. The soln was filtered on celite, water added (100 ml) and the organic solvent was evaporated. NH_4OH was added to pH 7 and the product which separated (27 g) was collected; the double salt decomposition was done as above.

2,3-Diacetamido-strychnine

(a) An intimate mixture of 2-amino-3-nitrostrychnine sulphate (30 g) and Zn dust (40 g) was added in portions to AcOH (150 ml) and Ac_2O (38 ml) with efficient stirring, and carefully heated to 60° when an exothermic reaction took place. When this reaction subsided the reaction mixture was heated under reflux for one additional hr. After filtration through celite, the soln was poured on ice (60 g) and then NH_4OH was introduced to pH 5–6, when the product precipitated as its acetate, white crystals, (yield 70%), m.p. 213–215° $[\alpha]_D$ −60° (*c* 1·0 EtOH). (Found: C, 62·96; H, 7·02; N, 11·43. $C_{25}H_{28}N_4O_4 \cdot CH_3CO_2H$ requires: C, 63·76; H, 6·34; N, 11·02%).

(b) The same compound was also obtained by acetylation of 2,3-diaminostrychnine in Ac_2O and pyridine.

Strychnic acid[9]

Strychnine (20 g) dissolved in 5% NaOEt (400 ml) was stirred and heated under reflux for 1½ hr. The reaction mixture was poured onto ice and cold water added to 1·8 l, AcOH was introduced to reach a pH 7–7·5 when the compound precipitated (17·5 g); m.p. 272–275°; ν_{max}^{KBr} 3333–2857 (for carboxylic OH), 1603, 1558 and 750 cm^{-1}.

The *methyl ester* was prepared from the above acid (7 g) in MeOH–$CHCl_3$ (1:1, 50 ml) with ethereal diazomethane for 24 hr at room temp. The residue (7·5 g) was chromatographed on alumina. Elution with hexane–$CHCl_3$ (3:7) yielded methyl strychnate; recrystallized from acetone–water, m.p. 200°, $\nu_{max}^{CHCl_3}$ 2941, 1751, 1230 and 1205 cm^{-1}. (Found: C, 71·52; H, 7·05; N, 7·36. $C_{22}H_{26}N_2O_3$ requires: C, 72·11; H, 7·15; N, 7·65%).

Methyl 2-hydroxystrychnate

Methyl strychnate (1 g) in acetone (250 ml) was stirred in the dark with potassium nitrosodisulphonate (Fremy salt; 2·68 g) in KH_2PO_4 (200 ml) for 48 hr at room temp. To the wine red soln, $Na_2S_2O_4$ (1 g) was added in order to convert the quinone to the hydroxyl group, then NH_4OH was introduced and the mixture was extracted with $CHCl_3$. Evaporation of the solvent yielded the product (0·64 g), m.p. 300° dec; λ_{max}^{EtOH} 265 mμ (ε 16,800); λ_{max}^{EtOH} (KOH) 285 mμ (ε 19,250); ν_{max}^{KBr} 3592–3330, 2941, 1613, 1587, 1410 and 1205 cm^{-1}. (Found: C, 68·76; H, 6·91; N, 7·69. $C_{22}H_{26}O_4N_2$ requires: C, 69·09; H, 6·85; N, 7·33%).

Methyl 2-methoxystrychnate

The above compound (1 g) in $CHCl_3$–MeOH (1:1) was treated with ethereal diazomethane for 24 hr at room temp. Evaporation of the solvents afforded the product which was chromatographed on a column of alumina and eluted with hexane–$CHCl_3$ (3:7), m.p. 300° dec.

2-Hydroxystrychnine[7] *prepared with Fremy salt*

Strychnic acid (1 g) in acetone soln (250 ml) was stirred as above with potassium nitroso-disulphonate in the same buffer soln which was adjusted to pH 7. To the red soln, $Na_2S_2O_4$ (1 g) was added when it became light yellow, the acetone was evaporated under reduced press, then NH_4OH was added to pH 8 and the soln extracted with $CHCl_3$. Evaporation of the solvent afforded 2-hydroxystrychnine (0·60 g). The product crystallized from dimethylformamide water, m.p. above 300° dec; λ_{max}^{EtOH} 265 mμ (ε 14,000), λ_{max}^{EtOH} (KOH) 285 mμ (ε 15,000); ν_{max}^{KBr} 3350, 1618, 1613, 1405 and 1299 cm^{-1}.

On a chromatoplate, one red spot was obtained by spraying with a diazonium salt soln. The product was fully characterized by its conversion in MeOH–$CHCl_3$ soln into 2-methoxystrychnine (β-colubrin) with diazomethane in ether. The reaction mixture was chromatographed over alumina with hexane–$CHCl_3$ (3:7). The compound emerged as white crystals. By comparison with an authentic sample, a mixture m.p. was underpressed, same IR spectrum throughout the whole range; identical NMR spectra.

2-Acetoxystrychnine

2-Hydroxystrychnine (1·3 g) was acetylated with Ac_2O (10 ml) in dry pyridine (10 ml) by the usual procedure. The product was extracted with $CHCl_3$ and after evaporation the residue was chromatographed on alumina. Elution with $CHCl_3$–hexane (3:7) afforded the product in pure and crystalline form; m.p. 242–245°; $\nu_{max}^{CHCl_3}$ 1754, 1274–1220, 1205 and 1198 cm^{-1}

2-Hydroxystrychnine from 2-aminostrychnine[7]

2-Aminostrychnine (10 g) was dissolved in 30% H_2SO_4 (50 ml) heated to 40° and diazotized with 20% $NaNO_2$ (10 ml). The excess $NaNO_2$ was destroyed with urea. The diazonium soln was then added (5 min) to a stirred mixture of conc H_2SO_4 (70 ml), water (30 ml) and Na_2SO_4 (70 g) heated to 170–180°, while simultaneously conc H_2SO_4 (60 ml) was carefully introduced in order to maintain the temp above 150°. After 10 min the reaction mixture was diluted with hot water (250 ml) and then slowly poured into NH_4OH aq (500 ml). A ppt was formed which was filtered off and washed with water. The crude compound (8·1 g) was a mixture of 2-hydroxystrychnine, 2-hydroxystrychnine N-oxide and some 2,3-dihydroxystrychnine.

The mixture was suspended in boiling water and an equal quantity of $Na_2S_2O_4$ was added. After cooling 2-hydroxystrychnine precipitated (8 g) which was identified with the compound described above. By methylation of the reaction product with diazomethane, and chromatography of the mixture, β-colubrine was obtained in a total yield of 75–80% and brucine in a 1% yield. However, by adding dropwise H_2SO_5 during the decomposition of the diazonium salt, yields of 40% β-colubrine and 7–8% brucine were obtained.

The N-*oxide* could be prepared by dissolving 2-hydroxystrychnine (1 g) in H_2O_2 30% (7 ml) at 80° then pouring the clear soln onto ice. The ppt was collected and washed with cold water (1·1 g) dec above 300°; ν_{max}^{KBr} 3350, 1620, 1615, 1400, 1300 and 955 (for N → O) cm^{-1}.

2-Methoxystrychnine N-oxide

2-Hydroxystrychnine N-oxide (1 g) suspended in boiling MeOH (20 ml) was methylated with Me_2SO_4 (3·5 ml) and methanolic KOH 20% (10 ml), during 24 hr. The mixture was acidified with H_2SO_4 10%, heated for 30 min and made basic with NH_4OH. The ppt was collected (70% yield).

The product was identified by reduction with $Na_2S_2O_4$ affording 2-methoxystrychnine, m.p. 222°, $[\alpha]_D$ −156° (*c*, 0·5 $CHCl_3$), compared with an authentic sample and found identical.

2-Methoxy-3-nitrostrychnine

2-Methoxystrychnine nitrate (1 g) was dissolved in 70% H_2SO_4 (5 ml) at −5° and stirred for 2 hr. Ice was added followed by NH_4OH to pH 7–8, the product was collected (0·8 g); m.p. 250° dec; $\nu_{max}^{CHCl_3}$ 1603, 1538, 1465, 1390, 1360, 1342, 1260 and 1030 cm^{-1}.

2-Methoxy-3-aminostrychnine

2-Methoxy-3-nitrostrychnine (1 g) was dissolved in hot dil HCl to pH 5 and $Na_2S_2O_4$ (1 g) was added when the soln became colorless; by addition of NH_4OH to pH 7 the ppt was filtered off and washed with cold water (yield 85%), m.p. dec above 300°; ν_{max}^{KBr} 3500 and 1635 cm^{-1}. (Found: C, 69·19; H, 6·71; N, 10·58. $C_{22}H_{25}O_3N_3$ requires: C, 69·63; H, 6·64; N, 11·08%).

Brucine

(a) *Preparation of 2,3-dihydroxystrychnine.* 2-Hydroxystrychnine (1 g) in AcOH (5 ml) was stirred in a flask protected from light together with a soln of Fremy salt (2·7 g) in water (100 ml) for 48 hr at room temp. The wine red colored soln showed absorptions at λ_{max} 310 and 450 mμ for the *o*-quinone (brucinoquinone) which was formed. At the end of the reaction 2N $HClO_4$ was added to ppt the inorganic salts which were discarded. $Na_2S_2O_4$ (1 g) was then added and the soln filtered from free sulphur. The soln was adjusted with NH_4OH to pH 7–7·5 and a grey ppt (0·5 g) was collected. On a chromatoplate developed with a solvent mixture of EtOAc–benzene–diethylamine (7:2:1) two spots could be disclosed following spraying with a soln of diazonium salt. The UV of the mixture λ_{max}^{MeOH} 265 and 305 mμ; λ_{max}^{MeOH} (KOH) 305 and 450 mμ; strong phenolic bands in the IR.

(b) The mixture (0·5 g) dissolved in $CHCl_3$–MeOH (1:1; 200 ml) was treated with ethereal diazomethane (60 ml) for 48 hr at 5°. The product after evaporation of the solvent was chromatographed on a column of alumina. By elution with hexane–$CHCl_3$ 7:3 first emerged the β-*colubrin* (0·2 g) followed by *brucine* (0·25 g). The two compounds were identified by comparison with authentic samples.

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