Some New Derivatives of Strychnine.

ABDUL MALIK AND NIGHAT AFZA

H.E.J. Postgraduate Institute of Chemistry, University of Karachi, Karachi-32, Pakistan.

(Received 7th October, 1980)

Summary: In the context of studies in the correlation of structure and activity, a number of new derivatives of strychnine with substitution in the benzene ring have been prepared. NMR studies revealed that the electrophilic substitution in strychnine takes place at C-2.

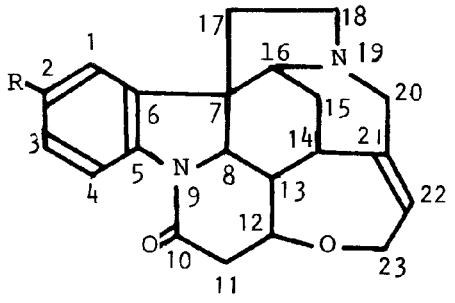
Strychnine is the most important of the Strychnos alkaloids,[1-9] and finds its principal use in medicine as a tonic owing to its bitter taste and local action upon the digestive organs[10-15] In certain forms of paralysis it may also be used because of the stimulating action upon the central nervous system. The major use of strychnine, however, is as a vermin killer[10-15]

Siddiqui and co-workers have observed[16-17] that the introduction of certain electronegative groups in the aromatic ring has potentiating effect on the physiological activity of various indole alkaloids. For instance, the pharmacological investigation of the antiarrythmic activity of nitroajmaline and bromoajmaline revealed that these are more than twice as active as ajmaline[18]. Siddiqui et al. have reported 3 position isomers of mononitroreserpine[19] among which 12-and 1-nitroreserpine have shown similar hypotensive activity as that of reserpine whereas their sedative action is less than one eighth and one third as compared with reserpine, and they possess none of its side effects[19]. Profiting from these findings, it appeared of interest to extend this study to another indole alkaloid-strychnine-in order to prepare interesting new derivatives, some of which might prove useful therapeutic agents.

Electrophilic substitution reactions in strychnine had so far yielded nitro[20], amino[20], chloro[21] and bromo derivatives[22] the substitution in each case taking place at position para to the aromatic nitrogen atom. Apart from that, various position isomers of strychnine sulphonic acid have also been reported[23-24] As a result of present work, the following new derivatives have been prepared with the introduction of various groups in the aromatic ring of strychnine.

2-Nitrosostrychnine I; 2-formylstrychnine III; 2-hydroxymethylstrychnine. IV; 2-acetylstrychnine V; 2-hydroxyethylstrychnine VI; 2-allylstrychnine VII; 2-benzylstrychnine. VIII and 2-isopropylstrychnine IX.

The nitrosation of strychnine was carried out by treatment of strychnine nitrite with 10% hydrochloric acid In this method the 1:1 molar proportion of nitrous acid and strychnine is assured and an excess of nitrous acid avoided. 2-nitrosostrychnine formed light yellow needles which melted at 298°C (yield 54%). On reduction with iron and hydrochloric acid, it furnished 2-amino strychnine, m.p. 275-76°. Formyl strychnine was obtained by Vilsmaier formylation of strychnine as colourless prismatic plates, m.p. 296-7°C (yield 60%). Its selective reduction with sodium borohydride afforded 2-hydroxymethyl strychnine, colourless prismatic rods, m.p. 256°C. Friedal Crafts acylation of strychnine with acetyl chloride in the presence of anhydrous aluminium chloride yielded 2-acetyl strychnine as cream coloured prismatic plates, m.p. 308-10° (yield 52%). It could be reduced with sodium borohydride to 2-hydroxyethyl strychnine, the acetyl group being reduced during the process. Other alkylated derivatives were obtained by Friedal Crafts alkylation of strychnine with respective alkyl halides in the presence of anhydrous aluminium



trihalides as catalyst. 2-allyl strychnine formed light yellow needles, m.p. 262°C (yield 45%); 2-benzyl strychnine, colourless neeldes, m.p. 273°C (yield 30%) and 2-isopropyl strychnine, colourless needles, m.p. 278°C (yield 25%).

The electrophilic substitution in the aromatic ring of strychnine may be expected to take place at position 2 and 4. NMR spectral studies of the substitution products indicated that the groups have entered at position 2. For example, the aromatic region of the NMR spectrum of nitrosostrychnine shows a doublet at δ 6.95 (J 9 C/s) and may be assigned to H-4 which has a higher electron density, shows ortho coupling with H-3 and a small para coupling with H-1 (j 0.5 c/s) visible unhas a higher electron density, shows ortho coupling with H-3 and a small para coupling with H-1 (J 0.5 c/s) visible under high resolution only. The signal H-3 is a distorted quartet at δ 8.1 which is shifted downfield due to the electron withdrawing nature of the nitroso group at C-2. It shows ortho coupling with H-4 (J 9 c/s) and meta coupling with H-1 (J. 2.5 c/s). The H-1 signal is again a doublet at δ 8.35 showing meta coupling with H-3 (J 2.5 c/s) and para coupling with H-4 (J 0.5 c/s) visible under high resolution only. All other substitution products showed similar NMR pattern in the aromatic region.

Experimental

All melting points were recorded in glass capillary tubes and are uncorrected. NMR spectra were recorded on Jeol PMX 60 instrument at 60 MHz, using deuterated chloroform as solvent and TMS as internal reference. The mass spectra were taken on VG Micromass 12 at 70 electron volt and 3.5 kV accelarating voltage. The IR and UV spectra were recorded on UNICAM SP-200 G and SP-800 spectrophotometers.

2-Nitrosostrychnine: Strychnine nitrite (1 gm, 0.0025 mole) was dissolved in methanol (10 ml), the solution was diluted with water (10 ml), cooled and treated with 4N hydrochloric acid (20 ml). The resulting solution gradually turned orange red. Right at this stage, it was basified with ammonia and the resulting precipitate extracted out with ethyl acetate. The ethyl acetate layer was washed, dried (anhyd. Na_2SO_4) and triturated with ether and petroleum ether. The darkish insoluble residue thereby obtained was filtered off and the clear filtrate was freed of the solvent in vacuo. The residue crystallized out on rubbing with methanol as light yellow needles, m.p. 298°C (yield 0.54 gm). In the IR spectrum 2-nitrosostrychnine shows absorption peaks at 1670 cm^{-1} (amide CO), 1610 cm^{-1} (C=C) and 1500 cm^{-1} (C-NO). (Found: C, 69.36; H, 5.82; N, 11.35% and M^+ peak at 363. Calculated for $C_{21}H_{21}N_3O_3$: C, 69, 42%; H, 5.78%; N, 11.57%, mol. wt. 363).

The reduction of 2-nitroso strychnine. 2-amino strychnine.

2-nitroso strychnine (1 gm., 0.0027 mole) was dissolved in dilute hydrochloric acid (N/2, 20 ml) and iron powder (1 gm) was added on to the solution. Kept at room temperature for 30 minutes with occasional shaking, the excess of iron was filtered, the filtrate was cooled, basified with ammonia and extracted out with ethyl acetate. The ethyl acetate extract was washed, dried over anhydrous sodium sulphate, triturated with ether and petroleum ether, and the resulting precipitate was filtered and washed with ethyl acetate. This process was repeated once more, whereby an almost colourless solution was finally obtained. The solution was freed of the solvent in vacuo, and the residue taken up in methanol from which 2-amino strychnine crystallized out as colourless needles, m.p. 275-76°C (lit.[20] m.p. 275-78°).

2-Formyl strychnine:

Vilsmeier's complex was prepared by adding 0.466 ml (0.003 mole) of phosphorus oxychloride to 0.662 ml (0.00533 mole) of N-methyl formanilide at 0°C and the mixture was kept at the same temperature for 45 minutes. To it was added a solution of 1 gm strychnine (0.003 mole) in pure o-dichloro benzene. The reaction mixture was refluxed for 1 hour when its colour changed to dark brown. It was poured in crushed ice and shaken with ethyl acetate. The ethyl acetate layer was extracted with 30% acetic acid and the acidic extract was combined with the aqueous layer. It was then basified with dilute ammonia in the cold and extracted with ethyl acetate. The ethyl acetate extract was washed, dried (anhyd. Na_2SO_4) and concentrated, whereby 2-formyl strychnine crystallized out in the cold as colourless prismatic plates, m.p. 296-97° (Yield 0.6 gm). It showed IR

absorptions at 2750 cm^{-1} (C-H stretching of aldehydes), 1690 cm^{-1} (CO stretching of aldehyde), 1666 cm^{-1} (amide carbonyl) and 1605 cm^{-1} (C=C). The aromatic aldehydic group was also confirmed by NMR peak at δ 9.8 (1H, singlet). (Found: C, 72.85; H, 6.00; N, 7.59% and M^+ peak at 362. $C_{22}H_{22}N_2O_3$ requires: C, 72.93; H, 6.07; N, 7.73% and mol. wt. 362).

2-hydroxymethyl strychnine:

To a solution of 2-formyl strychnine (200 mg., 0.00054 mole) in ethanol (10 ml) was added an aqueous soluton of sodium borohydride (0.4 gm. in 10 ml) and the mixture stirred overnight at room temperature. The excess of borohydride was decomposed by the addition of acetic acid (10%) and the solvent was removed under reduced pressure. The resulting colourless powder crystallized out from methanolic benzene as prismatic rods, m.p. 256°C. It showed IR absorptions at 3400 cm^{-1} (OH), 1670 cm^{-1} (amide CO) and 1610 cm^{-1} (C=C). NMR spectrum showed 2H singlet at δ 4.3 for methylene protons in the grouping $-CH_2OH$, and a broad proton hump at δ 4.5 represents OH group (exchangeable proton with D_2O). (Found: C, 72.45; H, 6.52; N, 7.71% and M^+ peak at 364. Calculated for $C_{22}H_{24}N_2O_3$; C, 72.52; H, 6.59; N, 7.69% and mol. wt. 364).

2-acetyl strychnine.

2 gm (0.015 mole) aluminium chloride was suspended in CS_2 and to it was added in the cold 10 ml of acetyl chloride, whereby a clear solution was obtained. To it was then added a solution of 1 gm (0.003 mole) of strychnine in CS_2 and a little chloroform. The reaction mixture was heated under reflux on the water bath for about 2 hours, whereby the initially viscous yellow layer turned into a brown semisolid mass. The reaction mixture was treated with dilute HCl in the cold and shaken with ethyl acetate to remove CS_2. The acidic layer was basified with a strong solution of ammonia and extracted exhaustively with ethyl acetate. The ethyl acetate extract was washed, dried (anhyd. Na_2SO_4) and concentrated in vacuo. On cooling in the ice chest, 2-acetyl strychnine crystallized out as cream coloured prismatic plates, m.p. 308-10°C (Yield 0.52 gm). Its IR spectrum showed absorptions at 1685 cm^{-1} (aromatic ketone), 1666 cm^{-1} (amide carbonyl) and 1610 cm^{-1} (C=C). The NMR showed a 3H singlet at δ 2.31 for aromatic acetyl group. (Found: C, 73.52%; H, 6.41%; N, 7.52% and M^+ peak at 376. $C_{23}H_{24}N_2O_3$ requires: C, 73.4%; H, 6.38%; N, 7.44% and mol. wt. 376).

2-hydroxy ethyl strychnine:

This compound was prepared from 2-acetyl strychnine in exactly the same manner as described for 2-hydroxymethyl strychnine. It afforded colourless rectangular plates from methanol, m.p. 270°, IR peaks at 34000 cm^{-1} (OH), 1666 cm^{-1} (amide carbonyl) and 1610 cm^{-1} (C=C). The NMR spectrum showed one H distorted quartet at δ 4.85 for methine proton of secondary alcohol, shifted further downfield due to phenyl group. The methyl group gives a distorted doublet at δ 1.2 and OH group comes as a broad hump at δ 4.2 (exchangeable proton with D_2O). (Found: C, 73.1% H, 5.91; N, 7.36% and M^+ peak at 378. Calculated for $C_{23}H_{26}N_2O_3$: C, 73.01; H, 5.87; N, 7.40% and mol. wt. 378).

2-allyl strychnine:

1 gm (0.003 mole) strychnine was dissolved in freshly distilled nitrobenzene (8 ml) and added 2 ml of pure allyl bromide. The solution was cooled in ice and slowly treated with pure anhydrous $AlBr_3$ (1.65 gm) in small portions keeping the temperature below 30°. The mixture was refluxed with constant stirring for 3 hours till the colour changed to deep brown. It was poured in crushed ice and the product recovered exactly as described for 2-acetyl strychnine. 2-allyl strychnine crystallized out from methanol as light yellow needles m.p. 262°C (Yield 0.35 gm). The IR spectrum showed absorptions at 1670 cm^{-1} (amide carbonyl), 1640 cm^{-1} (C=C of allyl group) and 1615 cm^{-1} (C=C at Δ^{21}). The NMR spectrum showed C-22 olefinic proton as a triplet at δ 4.8 and characteristic peaks of aromatic allylic group (2 H doublet at δ 2.97; 1 H multiplet at δ 5.92 and 2 H doublet at δ 5.54). (Found: C, 76.89; H, 6.68; N, 7.51% and M^+ peak at 374. $C_{24}H_{26}N_2O_2$ requires; C, 77; H, 6.95; N, 7.48% and mol. wt. 374).

2-benzyl strychnine:

1 gm (0.003 mole) strychnine was dissolved in nitrobenzene (8 ml) added 2 ml of benzyl chloride and treated with anhydrous aluminium chloride in exactly the same manner as described for 2-allyl strychnine. The product was recovered from the reaction mixture through preparative thick layer chromatography using silica gel G plates and solvent system chloroform: acetone: diethyl amine (5:4:1). It formed colourless needles from methanol, m.p. 273° (Yield 0.30 gm). The presence of benzylic group was confirmed by NMR spectrum (2 H singlet for CH_2 group at δ 3.81 and 5 H singlet for aromatic protons at δ 7.2). (Found C, 79.10%; H, 6.72%; N, 6.54% and M^+ peak at 424. Calculated for $C_{28}H_{28}N_2O_2$: C, 79.24; H, 6.60; N, 6.60% and mol. wt. 424).

2-isopropyl strychnine:

It was prepared in the same manner as allyl strychnine through isopropyl bromide using anhydrous aluminium bromide as catalyst. The product was separated from the reaction mixture through preparative thick layer chromatography (silica gel G plates, solvent system chloroform: acetone: diethyl amine 5:4:1). It crystallized out from methanol as colourless needles, m.p. 278° (Yield 0.25 gm). The presence of isopropyl group was confirmed through NMR spectrum (1H heptet for CH group at δ 3.4 and 6H doublet for methyl groups at δ 1.2). (Found: C, 76.47; H, 7.51; N, 7.40%; and M^+ peak at 376. $C_{24}H_{28}N_2O_2$ requires: C, 76.59; H, N, 7.44%; and mol. wt. 376).

Acknowledgement

The authors wish to express their sincere thanks to Professor Salimuzzaman Siddiqui, FRS., for his interest in this work. One of us (Nighat Afza) wishes to express her gratitude to Hamdard Foundation for providing research fellowship during this work.

References

1. V. Regnault, *Annalen*, **26**, 17 (1938).
2. R. Robinson, *Annual Report of Biochemistry*, 1935, **4**, 512 (Bibl.)
3. H. Leuchs and H. Beyer, *Ber.*, **68**, 290 (1935).
4. G.R. Clemo, *J. Chem. Soc.*, 1936, 1695.
5. L.H. Briggs, H.T. Openshaw and R. Robinson, *J. Chem. Soc.*, 1946, 903.
6. R.N. Chakravarti and R. Robinson, *Nature*, **160**, 18 (1947).
7. R.B. Woodward, *Nature*, **162** 155 (1948).
8. R.B. Woodeward, *Experientia Supplement II*, 1955, 213; *Tetrahedron*, 1963, **19** 247.
9. K. Nagarajan, C. Weismann, H. Schmid, and P Karrer, *Helv. Chem. Acta* **46**, **1212 (1963).**
10. C. Lambruschini, *Rev. Soc. Argent. biol.*, **14**, 353 (1938).
11. J. Travell, *J. Pharm. exp. Ther.*, **69**, 21 (1940).
12. R. Weigmann, *Arch. exp. Path. Pharm.*, **196**, 521 (1940).
13. Raymond Hamet., *Bull. Sci. pharmacol.*, **48**, 306 (1941).
14. R.A. Woodbury and B.E. Abreu, *J. Pharm. exp. Ther.*, **78**, 321 (1943).
15. G. Coppee and M.H. Coppe – Bolly, *Arch. intern. physiol.*, **51**, 97 (1941).
16. S. Siddiqui, S.A. Warsi, M. Allauddin and V.U. Ahmad, *Pak. J. Sci. Ind. Res.*, **2**, 86 (1959).
17. S. Siddiqui and V.U. Ahmad, *Proc. Pakistan Acad. Sci., 5, 1, (1968).*
18. Private communication from E. Merck, Darmstadt, West. Germany.
19. S. Siddiqui and M. Attaullah Khan, *Pak. J. Sci. Ind. Res.*, **18**, 199 (1975).
20. H. Leuchs and F. Krohnke, *Ber.*, **62**, 2176 (1929).
21. H. Leuchs and K. Steinborn, *Ber*, **71**, 1579 (1938).
22. H. Leuchs and D. Ritter, *Ber.* **52**, 1585 (1919).
23. H. Leuchs and W. Schneider, *Ber.*, **41**, 4393-6 (1909).
24. H. Leuchs and W. Schneider, *Ber.*, **42**, 2681-5 (1909).