

ON THE IDENTITY OF STRYCHNICINE

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Abstract—Evidence is presented for the probable identity of strychnicine, a *Strychnos* alkaloid isolated by Boorsma in 1902 but no longer available, with vomicine (4-hydroxy-*N*-methyl-*sec*-pseudostrychnine). A product obtained in 1966 by Hifny Saber *et al.* and identified by them as strychnicine is different from Boorsma's compound and its nature remains uncertain.

BOORSMA¹ isolated an alkaloid strychnicine from the leaves of *Strychnos ignatii* Berg (*S. tieute* Lesch) and *S. nux-vomica* L. The alkaloid crystallized in ethanol as colourless, tasteless needles, decomposing above 240°, its salts, on the other hand, were very bitter and its tartrate was much less soluble in cold water than were the tartrates of strychnine and brucine. With conc. H_2SO_4 , $\text{H}_2\text{SO}_4\text{-K}_2\text{Cr}_2\text{O}_7$, and conc. HNO_3 no strong colorations were observed. Na_2CO_3 , even in excess, precipitated the alkaloid almost completely. Strychnicine had little pharmacodynamic activity, 5 mg of the hydrochloride injected into a guinea-pig had no effect, but in a frog the same dose caused symptoms of intoxication.

More importantly, however, Boorsma¹ described the following specific colour test for strychnicine: when NaOH solution was added to a weakly acid solution of the base a white precipitate formed which redissolved, the solution gradually turned orange and addition of HCl at this stage or earlier gave rise to a violet-purple colour. $\text{Ba}(\text{OH})_2$ could be used instead of NaOH, but the final colour did not develop when Na_2CO_3 was employed. Strychnine and brucine did not give this colour test, and 0.2 mg strychnicine in a mixture with 10 mg strychnine and 10 mg brucine was readily detected.

Nothing more was published on strychnicine until Hifny Saber *et al.*² reported the isolation from the seeds of *S. nux-vomica* of a base crystallizing in dilute ethanol as needles, m.p. 240–242°, which afforded the specific colour test just described.

We have subjected 9 of the alkaloids known to occur in *S. nux-vomica* and 6 closely related alkaloids to Boorsma's colour test for strychnicine and have found that only one alkaloid gave a positive result, namely vomicine (4-hydroxy-*N*-methyl-*sec*-pseudostrychnine) (see Table 1). The other bases with a 4-hydroxy substituent gave negative results. These findings suggest that Boorsma's strychnicine could well have been vomicine.

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¹ BOORSMA, W. G. (1902) *Meded. 's Lands Plantentuin (Batavia)* **52**, 11, (1902) *Bull. Inst. Bot. Butenzorg* **14** (Pharmacologie I), 3, LOTSY, J. P. (1905) *Rec. Trav. Bot. Neerl.* **1**, 1.

² HIFNY SABER, A., ZAKI, A. Y. and ABD-EL-WAHAB, S. M. (1966) *Egypt. Pharm. Bull.* **48**, 203.

The *N*-methyl-*sec*-pseudo base vomicine is readily obtained from the leaves of *S. nux-vomica*, where bases of the *N*-methyl-*sec*-pseudo and pseudo series tend to occur in large amounts,⁵ and this fits in well with Boorsma's original isolation of strychnicine from the leaves. Vomicle crystallizes in ethanol as needles, it has m p 281–282° (decomp), but Boorsma's much lower figure could simply indicate that his product was less pure and that the conditions of taking the m p (decomposition point) were different. Vomicle is tasteless, while its salts are bitter, its tartrate is poorly soluble in water,⁶ the free base gives weak colours with H₂SO₄–K₂Cr₂O₇ and HNO₃ and has little pharmacodynamic activity (LD₅₀ for mice 74.2 mg/kg).⁷ The similarity of these properties with those reported for strychnicine is evident.

TABLE 1 STRYCHNINE TEST*

Compound†	5% NaOH	After adding HCl	3% Ba(OH) ₂	After adding HCl
4-Hydroxystrychnine ³	Precipitate	Colourless soln	Precipitate	Colourless soln
4-Hydroxy-3-methoxy-strychnine	Reddish purple soln	Colourless soln	Reddish purple soln	Pale straw-coloured soln
Vomicle	Pale orange-pink soln	Violet soln	Straw-coloured soln	Violet soln
21,22- <i>a</i> -Epoxyvomicle ⁴	Pinkish purple soln + pptate	Very pale violet soln‡	Pale orange-yellow soln	Very pale violet soln‡
21,22- <i>a</i> -Epoxy-14-hydroxyvomicle ⁴	Pale orange soln	Colourless soln	Straw-coloured soln	Colourless soln

* A small amount of the alkaloid was dissolved in 2–3 drops 10% HCl, 4 drops 5% NaOH or 10 drops 3% Ba(OH)₂ were then added. Finally, 3–4 drops conc. HCl were added.

† All the other compounds tested gave, after adding the conc. HCl, a final colourless solution: strychnine, β-colubrine, brucine, pseudostrychnine, pseudobrucine, icajine, novacine, 21,22-*a*-epoxynovacine, 21,22-*a*-epoxy-14-hydroxyicajine,⁴ and strychnine chloromethobromide.

‡ According to the MS the 21,22-*a*-epoxyvomicle contained about 10% vomicle—hence the weakly positive strychnine test.

While the grounds for identifying Boorsma's strychnicine with vomicle are reasonably convincing, the nature of the product identified by Hifny Saber *et al.* as strychnicine is not clear. The product is apparently not vomicle, which these workers isolated and identified, and its evidently highly polar nature (TLC) suggests that it is more likely to be either a *N*-oxide or a quaternary base artefact,⁸ i.e. either 4-hydroxystrychnine *N*-oxide or 4-hydroxystrychnine chloromethobromide. Neither of these two compounds is known, but it seems improbable that either of them would give the specific colour reaction since 4-hydroxystrychnine itself does not.

Enquiries indicate that samples of the two strychnicines are no longer available, so that the considerations put forward in the present note regarding the identification of Boorsma's strychnicine must stand on their own merits.

³ SANDBERG, F., ROOS, K., RYRBERG, K. J. and KRISTIANSON, K. (1968) *Tetrahedron Letters* 6217, (1969) *Acta Pharm. Suec.* 6, 103.

⁴ BISSET, N. G. (1968) Ph.D. Thesis, University of London, pp. 57, 83, 88 and 96.

⁵ ŠTEFČOVIČ, P., DUBRAVKOVA, L. and TORTO, F. G. (1968) *Planta Med.* 16, 143; MAIER, W. and GROGER, D. (1968) *Pharm. Zentralhalle* 107, 883; CHATTERJEFF, A. and BASA, S. C. (1967) *J. Ind. Chem. Soc.* 44, 663; QUIRIN, M., LÉVY, J. and LE MEN, J. (1965) *Ann. Pharm. Fr.* 23, 93.

⁶ MARTIN, W. F., BENTLEY, H. R., HENRY, J. A. and SPRING, F. S. (1952) *J. Chem. Soc.* 3603.

⁷ SANDBERG, F. and KRISTIANSON, K. (1970) *Acta Pharm. Suec.* 7, 329.

⁸ PHILLIPSON, J. D. and BISSET, N. G. (1972) *Phytochemistry* 11, 2547.