

191. *Strychnine and Brucine. Part LIII.* Compounds of Phenols and Certain Strychnine Derivatives.*

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Methylstrychnine combines with many phenols, especially polyhydric phenols, to give crystalline complexes which are not methylstrychninium salts. Such salts can however also be prepared and the two classes are readily distinguished from one another by characteristic colour reactions.

Benzylstrychnine and *N(b)*-hydroxystrychnine afford similar complexes.

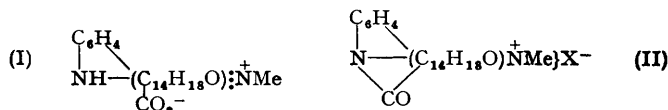
It is suggested that formation of these compounds provides the best known method for the isolation of polyhydric phenols from mixtures such as are obtained, for example, by the alkali-fusion of many natural products. The pure phenol may be recovered from the complex by treatment with hydrochloric acid and extraction with ether.

COMPOUNDS of methylstrychnine which are usually, but not invariably, derived from one molecule each of base and phenol, separate in beautifully crystalline forms when saturated aqueous solutions of the components are mixed. The crystals contain varying amounts of water of crystallisation (methylstrychnine-phloroglucinol is anhydrous) and have unsatisfactory melting points. Identification would be best effected by comparison of the crystals by well-established procedures. When heated under 0.2 mm. pressure, some of the complexes, for example, methylstrychnine-resorcinol, decompose. The phenol is

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volatilised and the residue has the melting point of methylstrychnine. The method of mixed melting points is useless in this series.

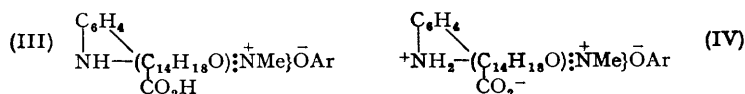
It is known that methylstrychnine (I) is a betaine converted by an acid HX into a methylstrychninium salt (II). Because (I) is an aniline derivative with a free *p*-position



it exhibits colour reactions of which the most convenient is the oxidative coupling by ferric chloride. This produces orange-red to carmine bisphenoquinimmonium salts. The acylated aniline derivative (II) shows no such behaviour but it does exhibit the Otto reaction which fails in the case of (I).

To our surprise methylstrychnine-resorcinol (and other similar complexes) exhibited the reactions of (I) and not those of (II). The behaviour on heating in a vacuum is also a proof that the substance is not the methylstrychninium resorcinol salt.

The most probable view of the constitution of these complexes is that they are indeed salts, but not lactams, and they may be formulated like (III) or (IV).



In solution the molecules cannot all be in the form (IV) because the nucleus of the substituted aniline salts is unreactive.

It is noteworthy that, whereas simple acids such as benzoic acid do not furnish well-crystallised complexes, phenolic acids, for example, salicylic and *p*-hydroxybenzoic acids, do so. The colour reactions show that the products are methylstrychnine complexes. For comparison with methylstrychnine-resorcinol, it was sought to obtain the true methylstrychninium resorcinol salt by interaction of methylstrychninium chloride and sodium resorcinolate. A new compound was isolated and this gave the colour reactions of resorcinol and of the methylstrychninium salts but not those of methylstrychnine. Analysis showed that the substance was derived from two molecules of resorcinol and one of the methylstrychninium hydroxide.

Attempts to prepare this type of salt were made in several other cases but the products were uncrystallisable gums.

Benzylstrychnine gave complexes similar to those made from methylstrychnine but its use offers no advantages. *N*(*b*)-Hydroxystrychnine (the betaine from strychnine *N*-oxide, through strychnic acid *N*-oxide), however, furnished some good complexes. It suffers from the disadvantage of sparing solubility, even in hot water. Strychnine *N*-oxide formed a complex with quinol, but not with other polyhydric phenols.

A tendency to form complexes with phenols has been noted with various *Cinchona* alkaloids (cf. Rossignol and Riboulleau, *Compt. rend.*, 1939, 207, 495).

EXPERIMENTAL

Methylstrychnine.—This compound, made according to the procedure of Clemo, Perkin, and Robinson (*J.*, 1927, 1624), had m. p. 303—304° (decomp.). Treatment of a hot concentrated aqueous solution with hydrochloric acid gave, on cooling, a felted mat of white needles of strychninium methochloride, m. p. 295—296° (Found: C, 62.9; H, 6.7. Calc. for $\text{C}_{22}\text{H}_{26}\text{O}_2\text{N}_2\text{Cl}$: C, 62.7; H, 6.9%). Kotake and Mitsuwa (*Annalen*, 1933, 505, 208) prepared this salt from the methiodide, and report m. p. 288—290°. It is much more readily soluble in water than methylstrychnine. *Methylstrychninium perchlorate* is sparingly soluble in water, from which it crystallizes in long needles, m. p. 309—310° (decomp.) (Found: C, 58.7; H, 5.7; N, 6.2; Cl, 8.0. $\text{C}_{22}\text{H}_{26}\text{O}_6\text{N}_2\text{Cl}$ requires C, 58.8; H, 5.6; N, 6.2; Cl, 7.9%).

Complexes of Phenols with Methylstrychnine.—The complexes recorded in the table were made

by mixing aqueous solutions of methylstrychnine and the phenol. In some cases [marked (s)] hot saturated solutions were mixed, because of the greater solubility of the complexes.

Phenol	M. p. of complex	Formula	Required, %			Found, %		
			C	H	N	C	H	N
Pyrogallol	214—215°	$C_{28}H_{32}O_6N_2 \cdot 3H_2O$	61.5	7.0	—	61.6	6.9	—
Phloroglucinol	281—283	$C_{28}H_{32}O_6N_2$	68.3	6.6	—	68.8	6.8	—
Resorcinol	246—248	$C_{28}H_{32}O_5N_2 \cdot 1.5H_2O$	66.7	7.0	—	{ 66.5 66.4	{ 7.1 7.1	{ — —
Quinol	227—229	$C_{28}H_{32}O_5N_2 \cdot 2H_2O$	65.7	7.1	—	66.1	6.9	—
<i>p</i> -Hydroxybenzaldehyde	213—216	$C_{29}H_{32}O_5N_2 \cdot 2H_2O$	66.4	6.9	—	66.7	7.1	—
Catechol (s)	229	$C_{28}H_{32}O_5N_2 \cdot 3.5H_2O$	62.4	7.3	—	62.6	7.2	—
<i>p</i> -Hydroxybenzoic acid (s)	207—209	$C_{29}H_{32}O_6N_2 \cdot 2H_2O$	64.5	6.7	—	64.8	6.9	—
<i>p</i> -Methoxyphenol (s)	200	$C_{36}H_{41}O_7N_2 \cdot 3H_2O$	64.7	7.2	4.2	64.3	7.3	4.3
Salicylic acid (s)	192	$C_{29}H_{32}O_6N_2 \cdot 0.5H_2O$	67.9	6.5	—	68.3	6.3	—
Guaiacol (s)	308	$C_{29}H_{34}O_5N_2 \cdot 5.5H_2O$	59.1	7.7	4.8	59.3	7.4	5.1
Protocatechuic acid (s)	204—205	$C_{29}H_{32}O_7N_2 \cdot 3H_2O$	60.7	6.7	4.9	60.5	7.0	4.9

The following phenols failed to give satisfactory derivatives; phenol, *o*- and *m*-aminophenol, *m*-cresol, *p*-chlorophenol, gentisic acid, gallic acid.

When the following complexes were made by mixing hot concentrated solutions, and then cooling, the m. p.s were: resorcinol–methylstrychnine, 251°; pyrogallol–methylstrychnine, 220—221°; phloroglucinol–methylstrychnine, 276—279°; quinol–methylstrychnine, 237—238°. The divergences from the previously observed m. p.s may be due to the different method of preparation and different content of water of crystallisation, as shown in the analysis for the *resorcinol–methylstrychnine* complex (Found: C, 65.9; H, 7.1. $C_{28}H_{32}O_5N_2 \cdot 2H_2O$ requires C, 65.7; H, 7.1%).

Our experience suggests that the water of crystallisation in many of the complexes may be clathrate and it is certainly unusually subject to variation with the conditions of preparation. We have therefore calculated the water contents on the basis of determinations of carbon, which we regard as the most accurate, and wish expressly to avoid the suggestion of precise ratios of solvent of crystallisation.

It was noted that when the m. p. of resorcinol-, quinol-, or phloroglucinol–methylstrychnine (but not pyrogallol–methylstrychnine) was taken in a capillary continuously exhausted to a pressure of 0.2 mm. it was the same as that of methylstrychnine, indicating dissociation and sublimation of the phenol. The recovery was never satisfactory and this thermal decomposition cannot be recommended as a practical method of preparation.

Methylstrychninium Resorcinol Salt.—Resorcinol (0.3 g.) in water (4 c.c.) containing *N*-sodium hydroxide (3 c.c.) was added with shaking to a solution of strychnine methosulphate (1.0 g.) in water (5 c.c.). White plates crystallised from the cloudy solution; after recrystallisation from water these melted at 169—171° without decomposition to a clear liquid (Found, in air-dried material: C, 64.8; H, 7.2. $C_{34}H_{36}O_6N_2 \cdot 3.5H_2O$ requires C, 64.6; H, 6.9. Found, in material dried at 90°/10 mm.: C, 70.7; H, 6.7; N, 4.6. $C_{34}H_{36}O_6N_2 \cdot 0.5H_2O$ requires C, 70.7; H, 6.5; N, 4.9%). The Otto test using 60% sulphuric acid gave a brownish-purple colour; the ferric chloride reaction was a pale purple, like that for resorcinol itself.

Benzylstrychnine (cf. Achmatowicz, Clemo, Perkin, and Robinson, *J.*, 1932, 767).—Strychnine (34 g.) and benzyl chloride (12 c.c.) were triturated together, and after 1 day the mass was boiled with water (300 c.c.) and filtered from a small amount of unchanged strychnine. The slightly gummy needles of benzylstrychninium chloride were recrystallised twice from water (charcoal) and once from methanol. The large rhombs obtained melted at 283—284° (Found: C, 69.8, 70.0; H, 6.3, 6.3; N, 5.8. Calc. for $C_{28}H_{29}O_2N_2Cl \cdot H_2O$: C, 70.2; H, 6.5; N, 5.8%). Treatment of a hot aqueous solution of the salt (10 g.) with aqueous potassium hydroxide (15 c.c. of 50%) gave a yellow oil which solidified on shaking and heating. The crude benzylstrychnine was purified by recrystallisation from water (charcoal) from which it separated as a mat of long needles. The m. p. was unsharp, above 220°; it was very sensitive to the rate of heating and was not raised by repeated recrystallisation of the substance from water (Found: C, 57.1; H, 8.2; N, 4.6. Calc. for $C_{28}H_{30}O_3N_2 \cdot 8H_2O$: C, 57.3; H, 7.9; N, 4.8%).

Benzylstrychninium perchlorate, made by the action of perchloric acid on aqueous solutions of benzylstrychninium chloride or benzylstrychnine, had m. p. 301° (decomp.) and was very sparingly soluble in water. Consistent analytical results were not obtained for this compound, probably owing to explosive decomposition during combustion (Found: C, 63.6; H, 5.7. $C_{28}H_{29}O_6N_2Cl$ requires C, 64.1; H, 5.6%).

Complexes of Phenols with Benzylstrychnine.—These complexes are shown in the following table.

Phenol	M. p. of complex	Formula	Required, %			Found, %		
			C	H	N	C	H	N
Phloroglucinol.....	225—230°	C ₃₄ H ₃₆ O ₆ N ₂ ·8·5H ₂ O	56·6	7·4	3·9	56·9	7·7	4·0
Catechol	201	C ₃₄ H ₃₆ O ₅ N ₂ ·2·5H ₂ O	68·3	6·9	—	68·1	6·7	—
Gallic acid	182	C ₃₅ H ₃₆ O ₅ N ₂ ·2·5H ₂ O	63·9	6·3	—	63·9	6·5	—
Salicylic acid	213	C ₃₅ H ₃₆ O ₆ N ₂ ·2H ₂ O	68·2	6·5	4·5	68·2	6·5	4·7
<i>p</i> -Chlorophenol	191	C ₃₅ H ₃₆ O ₄ N ₂ Cl ₁ ·8·5H ₂ O	57·1	7·1	3·8	57·2	7·4	4·2
Pyrogallol	195	C ₃₄ H ₃₆ O ₆ N ₂ ·2H ₂ O	67·5	6·7	4·6	67·0	6·7	4·8

The mother-liquor from the salicylic acid–benzylstrychnine, m. p. 213°, slowly deposited another crystalline *complex*, having m. p. 190° and the composition 2 benzylstrychnine + 1 salicylic acid + 15 H₂O (Found: 58·9; H, 7·4; N, 4·4. C₆₃H₆₆O₉N₄·15H₂O requires C, 58·5; H, 7·5; N, 4·3%).

The following phenols failed to give satisfactory derivatives and in many cases benzylstrychnine of varying m. p. was recovered: phenol, resorcinol, quinol, *o*- and *m*-aminophenol, *m*-cresol, gentisic acid, guaiacol, protocatechuic acid, *p*-methoxyphenol, *p*-hydroxybenzoic acid.

N(b)-Hydroxystrychnine.—The following procedure is simpler than that of Oesterlin (*Ber.*, 1943, 73, 229). Strychnine *N*-oxide (Bailey and Robinson, *J.*, 1948, 703) (25 g.) in a solution of potassium hydroxide (13 g.) in water (250 c.c.) was heated on the steam-bath with occasional shaking for 3 hours. Next day, the cooled solution was acidified with glacial acetic acid (about 22 c.c.). The *N(b)*-hydroxystrychnic acid was collected and digested with hot ethanol (150 c.c.) which converted the mush into a white powder (13·6 g.), decomp. 215—216° (Found, in air-dried material: C, 64·5; H, 6·9. Calc. for C₂₁H₂₄O₄N₂·1·25H₂O: C, 64·5; H, 6·8. Found, in material dried at 130°/15 mm. for 3 hours: C, 66·3; H, 6·6; N, 7·0. Calc. for C₂₁H₂₄O₄N₂·0·7H₂O: C, 66·3; H, 6·6; N, 7·4%). Its solubility in hot alcohol and water was extremely small; from a hot solution of the latter it was recovered on cooling in ice in poor yield, m. p. 206—207° (Found: C, 64·9; H, 6·8%). It gave colour reactions (see below) indicative of a free –N(a)H– group.

When the hot aqueous suspension was heated with hydrochloric acid, it dissolved, and then almost immediately strychnine *N*-oxide hydrochloride crystallised from the solution in prisms, darkening above 230° and decomposing at about 325° (Pictet and Mattisson, *Ber.*, 1905, 38, 2785, report needles, darkening above 250° and not melted at 310°). When a suspension of the salt was treated with sulphur dioxide, boiled, and made alkaline, strychnine (m. p. and mixed m. p.) was precipitated.

Strychnine *N*-oxide or *N(b)*-hydroxystrychnine, when heated with dilute perchloric acid, gave *N*-hydroxystrychninium perchlorate, very sparingly soluble in water, from which it crystallised in white needles, m. p. ca. 280° (decomp.) (Found: C, 54·0; H, 5·0; Cl, 7·3. C₂₁H₂₃O₇N₂Cl₁H₂O requires C, 53·8; H, 5·4; Cl, 7·6%).

Complexes of Phenols with N(b)-Hydroxystrychnine.—Because of the slight solubility of *N(b)*-hydroxystrychnine in water, the complexes were made by dissolving the appropriate phenol in a hot saturated solution of the betaine. On cooling, the *complex* crystallised out as a mat of soft, woolly needles. Details are given in the following Table.

Phenol	M. p. of complex	Formula	Required, %		Found, %	
			C	H	C	H
Resorcinol	211—212°	C ₂₇ H ₃₀ O ₆ N ₂ ·1·5H ₂ O	64·1	6·6	64·1	6·7
Phloroglucinol	220—221	C ₂₇ H ₃₀ O ₇ N ₂ ·H ₂ O	63·3	6·3	63·6	6·6
Quinol	209—210	C ₂₇ H ₃₀ O ₆ N ₂ ·H ₂ O	65·3	6·5	65·0	6·7
Catechol	165—166	C ₂₇ H ₃₀ O ₆ N ₂	67·8	6·3	67·9	6·3
Phenol	199—200	C ₂₇ H ₃₀ O ₅ N ₂ ·1·5H ₂ O	66·2	6·8	65·8	6·7
Pyrogallol	about 170	C ₂₇ H ₃₀ O ₇ N ₂ ·2·5H ₂ O	60·2	6·5	60·0	6·6

Reaction of Strychnine N-Oxide with Phenols.—Addition of quinol to a hot aqueous solution of strychnine *N*-oxide gave, on cooling, tufts of rhombs, m. p. 191°, of a molecular *complex* (Found: C, 62·8; H, 6·9; N, 5·7. C₂₇H₂₈O₅N₂·3H₂O requires C, 63·1; H, 6·7; N, 5·5%). In the Otto test with 60% sulphuric acid, this compound gave a transitory purple colour, instantly decolourized to a yellow, contrasting with the normal Otto test for strychnine *N*-oxide.

With the following phenols, strychnine *N*-oxide gave only gums: resorcinol, phloroglucinol, pyrogallol, catechol, protocatechuic acid, *p*-hydroxybenzoic acid, salicylic acid, *p*-methoxyphenol, gentisic acid, gallic acid.

Colour Reactions.—(a) *With ferric chloride.* Addition of one drop of ferric chloride solution to a suspension of the phenol complex (about 5 mg.) in water (1 c.c.) resulted in colours characteristic of the phenol or strychnine derivative, probably dependent on their relative reducing powers. The following complexes gave the same red colour as methylstrychnine: resorcinol-methylstrychnine; phloroglucinol-methylstrychnine, phloroglucinol-benzylstrychnine, resorcinol-*N(b)*-hydroxystrychnine, phloroglucinol-*N(b)*-hydroxystrychnine; *p*-chlorophenol-benzylstrychnine, *p*-hydroxybenzaldehyde-methylstrychnine, *p*-hydroxybenzoic acid-methylstrychnine, phenol-*N*-oxystrychnic acid. These colours, like those from methylstrychnine and other compounds having an opened lactam ring, change on storage for several hours through purple and port-wine colour to green; the red colour from strychnidine does not change.

The following complexes gave colours characteristic of the phenols: pyrogallol-methylstrychnine, -benzylstrychnine, and -*N(b)*-hydroxystrychnine (brown); quinol-methylstrychnine and -*N(b)*-hydroxystrychnine (pale gold); *p*-methoxyphenol-methylstrychnine (purple); salicylic acid-methylstrychnine (intense purple); guaiacol-methylstrychnine (yellow); protocatechuic acid-methylstrychnine (intense green); gallic acid-benzylstrychnine (green); catechol-methylstrychnine, -benzylstrychnine, and -*N(b)*-hydroxystrychnine (intense green). These colours did not change on storage

(b) *Otto test.* In the usual Otto test, one drop of potassium dichromate solution is added to a solution of about 10 mg. of substance in 1 c.c. of 60% sulphuric acid. Strychnidine and compounds with an opened lactam ring, such as methylstrychnine or *N(b)*-hydroxystrychnine give a permanent red; the same colour is given by most derivatives of phenols with methylstrychnine, benzylstrychnine, and *N(b)*-hydroxystrychnine. With the derivatives of certain phenols (salicylic acid, *p*-hydroxybenzoic acid, protocatechuic acid, *p*-chlorophenol, *p*-hydroxybenzaldehyde, phenol) this colour does not change; with derivatives of other phenols the colour changes, in a time varying from a few seconds to several hours, to one characteristic of the phenol. The final colours given by complexes of the following phenols are: catechol, black-green; quinol, faint green; resorcinol, madeira; pyrogallol, brown; *p*-methoxyphenol, pale yellow; guaiacol, deep purple; gallic acid, pale brown; phloroglucinol, pale brown.

In 96% sulphuric acid, strychnidine and methylstrychnine give no colour in the Otto test. No colour was given with complexes containing gallic acid, *p*-hydroxybenzoic acid, or protocatechuic acid; other complexes give colours ranging from reddish-brown to green, determined apparently by the phenol present.

Strychnine and most compounds containing a closed lactam ring give in either 60% or 96% sulphuric acid a transient series of colours, changing from purple to red and finally to yellow. With compounds containing a phenolic component (*e.g.*, the methylstrychninium resorcinol salt) the colours are slightly brownish, but the change is still quite recognisable. In no case did any of the molecular complexes give a result of this kind.

(c) *Persulphate test.* Potassium persulphate (about 50 mg.) added to a suspension of a compound containing the *N(a)H* group, such as methylstrychnine (10 mg.), in water (1 c.c.) gives on warming a deep red or black colour. Most complexes of methylstrychnine, benzylstrychnine, or *N(b)*-hydroxystrychnine with phenols behave in the same way. Strychnine gives no colour; neither does the methylstrychninium resorcinol salt. Strychnidine gives, very slowly, the red colour resulting with other oxidizing agents; this test furnishes a method for distinguishing between compounds with a reduced and a hydrolysed lactam ring, such as are typified by tetrahydrostrychnine and strychnidine.

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