

Studies on the Reaction of Benzoyl Peroxide with *NN*-Disubstituted Aromatic Amines and Related Compounds. Part VI.¹ Some Attempts to Effect *o*-Hydroxylation in the Strychnine Series

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Attempts to protect the carboxy-group of strychnic acid so as to allow hydroxylation in the 4-position by means of dibenzoyl peroxide were unsuccessful. The Wieland–Gumlich aldehyde methyl ether (5) and its 12-epimer reacted with dibenzoyl peroxide to yield the corresponding *N*_b-oxides. 11-Isonitroso-*N*-methyl-sec-pseudostrychnine was prepared, but we were unable to convert it into a compound analogous to the Wieland–Gumlich aldehyde.

4-Hydroxystrychnine (2)† has been isolated from *Strychnos icaja* Baill.³ Vomicine (4)⁴ contains a hydroxy-group at position 4; and a number of alkaloids from *Aspidosperma* species contain a hydroxy-, methoxy-, or acetoxy-group in a corresponding position. As *N*-methylaniline undergoes *o*-hydroxylation with dibenzoyl peroxide,⁵ we attempted to use a similar reaction as a step in the conversion of strychnine (1) into 4-hydroxystrychnine, or of *N*-methyl-sec-pseudostrychnine (3) into vomicine.

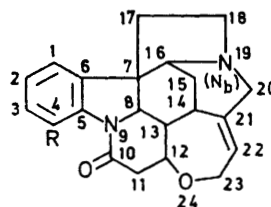
The conversion of strychnine into *N*-methyl-sec-pseudostrychnine⁶ via pseudostrychnine⁷ as described by Blount and Robinson⁶ gave an overall yield of ca. 15%. However, by treatment of pseudostrychnine with dimethyl sulphate, followed by decomposition of the intermediate salt without isolation, as described in the brucine series,⁸ we obtained an overall yield of 33%.

For *o*-hydroxylation with dibenzoyl peroxide it is necessary to have *N*_a secondary, so the possibility of blocking the carboxy-group of strychnic acid⁹ was explored. Strychnic acid did not react with diazomethane in ether, or with dihydropyran in the presence of acid.

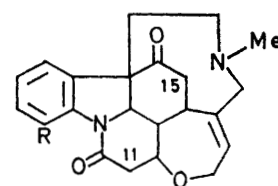
Oxford, Perkin, and Robinson¹⁰ have described a mixed anhydride of strychnic and benzoic acids, which was stable to cold alkali. We failed to isolate this, by either of the methods described (*i.e.* using sodium hydroxide or sodium hydrogen carbonate), although we tried using various molecular proportions of reactants, and hence obtained various final pH values of the reaction mixture. According to the conditions, varying amounts of strychnine, strychnic acid, benzoic acid, and benzoic anhydride were obtained. Evidently the mixed anhydride was being converted too rapidly into strychnine in the pH range 7–11 to be of use to us.

We then investigated the possibility of protecting the secondary amino-group of strychnic acid with some

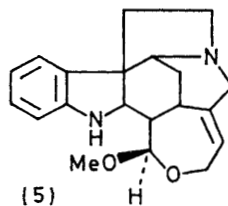
group (*e.g.* phenacylsulphonyl¹¹ or pivaloyloxy-methyl¹²), to give a product in which the carboxy-group could be protected or modified, followed by removal of



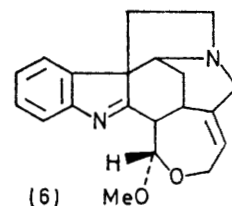
(1) R = H
(2) R = OH



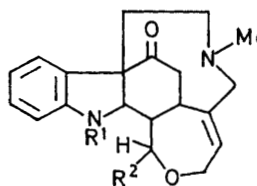
(3) R = H
(4) R = OH



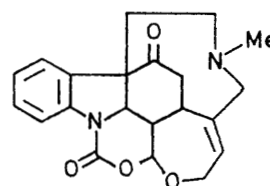
(5)



(6)



(7) R¹ = H, R² = OMe
(8) R¹ = CO·CO₂Me, R² = Cl
(9) R¹ = CO·CN, R² = Cl
(10) R¹ = H, R² = CN



(11)

the *N*-protecting group under mild conditions. Treatment of strychnic acid in pyridine with phenacylsulphonyl chloride yielded strychnine. Treatment of

† The numbering of the strychnine molecule used in this paper is that suggested in ref. 2a rather than that used in ref. 2b.

¹ Part V, G. A. Swan, *J. Chem. Soc. (C)*, 1971, 2880.

² (a) R. B. Woodward and W. J. Brehm, *J. Amer. Chem. Soc.*, 1948, **70**, 2107; (b) J. R. Hymon, H. Schmid, P. Karrer, A. Boller, E. Els, P. Fahrni, and A. Fürst, *Helv. Chim. Acta*, 1969, **52**, 1564.

³ F. Sandberg, K. Roos, K. J. Ryrberg, and K. Kriestiansson, *Tetrahedron Letters*, 1968, 6217.

⁴ G. F. Smith, in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1965, vol. VIII, p. 647.

⁵ R. B. Roy and G. A. Swan, *J. Chem. Soc. (C)*, 1968, 80.

⁶ B. K. Blount and R. Robinson, *J. Chem. Soc.*, 1932, 2305.

⁷ A. S. Bailey and Sir Robert Robinson, *J. Chem. Soc.*, 1948, 703.

⁸ H. Leuchs and H. G. Boit, *Ber.*, 1940, **73**, 885.

⁹ M. Oesterlin, G.P. 839,798/1952 (*Chem. Abs.*, 1956, **50**, 4242).

¹⁰ A. E. Oxford, W. G. Perkin, jun., and R. Robinson, *J. Chem. Soc.*, 1927, 2389.

¹¹ J. B. Hendrickson and R. Bergeron, *Tetrahedron Letters*, 1970, 345.

¹² M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, 1967, **89**, 5439.

strychnine acid with chloromethyl pivalate in *NN*-dimethylformamide in the presence of potassium carbonate afforded a solid, which showed i.r. absorption bands at 1669 and 1750 cm^{-1} ; but when this was washed with ether it yielded strychnine.

Another possibility was to use tetrahydrostrychnine, but in our hands the electrolytic reduction of strychnine¹³ afforded much more strychnidine than tetrahydrostrychnine; and reduction of strychnine acid with excess of lithium aluminium hydride in tetrahydrofuran yielded a product which was shown by t.l.c. to contain at least seven compounds.

The reaction of the Wieland–Gumlich aldehyde (WGA) methyl ether (5)^{2b} with dibenzoyl peroxide in the presence of 2*N*-sodium hydroxide gave no phenolic product, but a compound which was formulated as the WGA N_b -oxide methyl ether, rather than the isomeric N_a -hydroxy-compound. This compound was more soluble in water than was the WGA methyl ether, and only slightly soluble in chloroform; its behaviour on t.l.c. resembled that of strychnine *N*-oxide. Its i.r., u.v., and n.m.r. spectra were very similar to those of the starting material, although an additional peak in the i.r. spectrum at 1130 cm^{-1} was attributed to N–O stretching, the N–H stretching band at 3385 cm^{-1} being retained. The u.v. spectrum was unchanged after addition of alkali; and integration of the n.m.r. spectrum showed that four aromatic protons were still present in the molecule. A broad singlet at τ 5.1 was attributed to the N_a -proton. The signal at τ 4.2 due to the olefinic proton at C-22 in the WGA methyl ether was shifted to τ 3.9 in the spectrum of the N_b -oxide. The mass spectrum of the latter showed a molecular ion peak of low intensity at m/e 340, and an intense peak corresponding to ($M^+ - 16$) (cf. ref. 14). In the mass spectrum of strychnine *N*-oxide,⁷ the intensity of the molecular ion peak is approximately one tenth that of the ($M^+ - 16$) peak. The same product was obtained even with an excess of dibenzoyl peroxide, or in the absence of sodium hydroxide, and also by treatment of the WGA methyl ether with hydrogen peroxide. It could be reduced back to the former with iron(II) sulphate in the presence of alkali.

Schmid, Karrer, and their collaborators,^{2b} in attempting to formylate N_a of the WGA methyl ether, observed steric hindrance from the equatorial methoxy-group at position 12. However, they found that 12-*epi*-WGA methyl ether, in which the methoxy-group is in the axial position, reacted readily with formic acid at 20° to give the N_a -formyl derivative, so we investigated the reaction of this epimer with dibenzoyl peroxide in the presence of sodium hydroxide. However, the main product was 12-*epi*-WGA N_b -oxide methyl ether, although a small quantity of another compound, contaminated with starting material, was isolated; and this was probably 8,9-dehydro-12-*epi*-WGA methyl ether (6). Similar re-

actions in the absence of sodium hydroxide, or in boiling chloroform, again yielded the N_b -oxide.

We then attempted to prepare compound (7). *N*-Methyl-sec-pseudostrychnine (pK_a 6.1) is a weaker base than strychnine (pK_a 7.4), owing to interaction of the carbonyl group with N_b . This interaction might therefore reduce the tendency towards *N*-oxide formation in compound (7).

Under mild conditions *N*-methyl-sec-pseudostrychnine reacts with benzaldehyde to form the 11-benzylidene derivative, and under more vigorous conditions it yields the 11,15-dibenzylidene compound.¹⁵ When we treated *N*-methyl-sec-pseudostrychnine with isopentyl nitrite, as described for the conversion of strychnine into its 11-hydroxyimino-derivative,^{2b} we obtained 11-hydroxyimino-*N*-methyl-sec-pseudostrychnine in 5% yield. However, by using ethyl nitrite, we obtained the product in 69% yield. The fact that nitrosation had occurred at the 11- rather than at the 15-position was seen by comparison of the three u.v. spectra detailed below.

11-Hydroxyimino- <i>N</i> -methyl-sec-pseudostrychnine	234(15,900), 294(5500), 320(6000)
11-Hydroxyiminostrychnine ^{2b}	234(17,400), 290(6000), 314(7300)
Cyclohexane-1,2-dione monooxime ¹⁶	241(2100), 304(600), 345(200)

Treatment of the hydrochloride of this 11-hydroxyimino-compound with thionyl chloride yielded a product which was shown by t.l.c. to contain at least four compounds. We failed to separate this completely by column chromatography, but we obtained one fraction, the mass spectrum of which showed a molecular ion peak at m/e 366, and the i.r. spectrum of which showed a carbonyl stretching absorption at 1715 cm^{-1} . This may be the cyclic urethane (11), but the amount obtained did not allow further investigation. Another fraction, which showed a molecular ion peak at m/e 444 and carbonyl stretching absorptions at 1730 and 1645 cm^{-1} , may have structure (8).

When the reaction with thionyl chloride was carried out in the presence of pyridine, a mixture of compounds was obtained, among which were two (M^+ 411 and 349, respectively) possibly having structures (9) and (10).

Thus the reaction of 11-hydroxyimino-*N*-methyl-sec-pseudostrychnine with thionyl chloride is complex. Similar by-products have been obtained (although in much lower yields) in the corresponding reaction of 11-hydroxyiminostrychnine, especially in the presence of pyridine.^{2b} The stable form of 11-hydroxyiminostrychnine is that which allows hydrogen-bonding between the hydrogen atom of the hydroxyimino-group and the lactam carbonyl group; presumably in the presence of pyridine some isomerisation occurs. It appears that in 11-hydroxyimino-*N*-methyl-sec-pseudostrychnine both geometrical isomers are present (cf. the

¹⁵ H. Leuchs, H. Grunow, and K. Tessmar, *Ber.*, 1937, **70**, 1701.

¹⁶ T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, 1946, **11**, 771.

¹³ B. M. G. Zwicker and R. J. Robinson, *J. Amer. Chem. Soc.*, 1942, **64**, 790.

¹⁴ T. A. Bryce and J. R. Maxwell, *Chem. Comm.*, 1965, 206.

problems encountered in the case of 11-hydroxyimino-vomicine¹⁷).

EXPERIMENTAL

General directions are given in Part II.⁵ N.m.r. spectra were measured for solutions in deuteriochloroform (tetramethylsilane as internal standard) with a Perkin-Elmer R10 spectrometer at 60 MHz. U.v. spectra were measured for solutions in ethanol. Plates for t.l.c. were spread with Merck aluminium oxide G type E. Neutral alumina for column chromatography was prepared by storing B.D.H. aluminium oxide over ethyl acetate, then drying it at 100°. Hopkin and Williams M.F.C. silica gel was also used.

Preparation of N-Methyl-sec-pseudostrychnine (3).—Pseudostrychnine, m.p. 236–237° (decomp.), had ν_{\max} 3400 (OH str.) and 1671 (8-lactam CO str.) cm^{-1} . A sample (3 g) was added in small portions to stirred, freshly purified dimethyl sulphate (22 ml) at 90°. After 15 min barium carbonate (20 g) was added, followed by dimethyl sulphate (22 ml) and water (20 ml), and the mixture was heated until the oil had disappeared. It was then cooled and filtered. The filtrate was basified (NH_4OH) and extracted with chloroform. The extract was evaporated to dryness, and the residual solid (2.1 g) was chromatographed on neutral alumina. Elution with benzene–chloroform (1:1) gave N-methyl-sec-pseudostrychnine, m.p. 265–267° (from ethanol) (1.8 g), ν_{\max} 1663 cm^{-1} , M^+ 364 ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3$), identical with a specimen prepared by Blount and Robinson's method.⁸

WGA N_b-Oxide Methyl Ether.—(a) A solution of dibenzoyl peroxide (0.22 g, 0.93 mmol) in benzene (4 ml) was added slowly to a stirred mixture of the WGA methyl ether (0.3 g, 0.93 mmol), benzene (5 ml), and 2N-sodium hydroxide (5 ml) at 5°. The mixture was stirred overnight at room temperature, after which it was free from peroxide. The organic layer afforded unchanged WGA methyl ether. The aqueous layer was saturated with carbon dioxide, but as no precipitate was formed, it was extracted with chloroform. The dried (Na_2SO_4) extract on evaporation gave the WGA N_b-oxide methyl ether (0.21 g, 68%), m.p. 181–183° (from aqueous ethanol) (Found: C, 70.1; H, 7.0; N, 8.2. $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ requires C, 70.5; H, 7.05; N, 8.25%).

(b) A solution of the WGA methyl ether (0.12 g) in a mixture of water (1.5 ml) and hydrogen peroxide (30%; 0.5 ml) was heated on a water-bath for 15 min, after which a piece of platinum foil was added, and the heating was continued for a further 5 min. The solution was evaporated to half its original volume, then cooled to 0°; a solid (0.05 g) separated which was identical (t.l.c.) with the foregoing N-oxide [chloroform–methanol (15:1), R_F 0.37].

A solution of this N-oxide (0.2 g) in water (10 ml) containing sodium hydroxide (0.2 g) was shaken at 50° with crystalline iron(II) sulphate (0.26 g), then filtered. Extraction of the filtrate with chloroform yielded the WGA methyl ether, m.p. 229–231° (from benzene) (0.15 g).

12-epi-WGA N_b-Oxide Methyl Ether.—This was obtained from 12-epi-WGA methyl ether as in (a) above, and had m.p. 169–171° (decomp.), ν_{\max} 1145 cm^{-1} . The benzene

layer yielded a small quantity of a solid which on t.l.c. [chloroform–methanol (34:1)] showed two spots, R_F 0.70 and 0.37. The former corresponded to unchanged 12-epi-WGA methyl ether. The mass spectrum of the mixture showed molecular ion peaks at m/e 324 ($\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$) and 322 ($\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$).

11-Hydroxyimino-N-methyl-sec-pseudostrychnine.—A mixture of sulphuric acid (5.2 ml), ethanol (4.2 ml), and water (40 ml) was slowly added to a solution of sodium nitrite (12.4 g) in water (45 ml) containing ethanol (4.2 ml). The resulting gases were passed into a flask containing N-methyl-sec-pseudostrychnine (1.5 g) and ethanol (18 ml) under a condenser cooled with solid carbon dioxide. Simultaneously, a solution of sodium (0.6 g) in ethanol (21 ml) was slowly dropped into the flask. The mixture was boiled for 3 h then cooled and filtered to give N-methyl-sec-pseudostrychnine (0.08 g). The filtrate was evaporated to a syrup. A solution of the latter in water (10 ml), after neutralisation to pH 7 with acetic acid, was extracted with chloroform. Removal of chloroform from the dried (Na_2SO_4) extract afforded a solid (1.3 g), which was chromatographed on silica. Elution with benzene–chloroform (1:1) gave N-methyl-sec-pseudostrychnine (0.09 g). Elution with chloroform–methanol (10:1) afforded the product, m.p. 210° (from chloroform–ethanol) (1.1 g, 69%) (Found: C, 67.3; H, 5.9; N, 10.5%; M^+ , 393. $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_4$ requires C, 67.4; H, 5.95; N, 10.7%; M , 393); ν_{\max} 3220 and 1665 cm^{-1} .

Reaction of 11-Hydroxyimino-N-methyl-sec-pseudostrychnine with Thionyl Chloride.—(a) A mixture of 11-hydroxyimino-N-methyl-sec-pseudostrychnine hydrochloride (0.3 g) and thionyl chloride (4 ml) was stirred at room temperature for 15.5 h, and the excess of thionyl chloride was then removed under reduced pressure. A solution of the residue (0.3 g) in water (5 ml) was basified (NaHCO_3) and extracted with chloroform. The extract yielded a solid (0.24 g) which on t.l.c. showed the presence of at least four components, and was chromatographed on alumina. Elution with benzene–chloroform (3:1) gave a solid (0.12 g), m.p. 215–220°, M^+ 366, ν_{\max} 1715 cm^{-1} . Elution with chloroform yielded a solid (0.08 g), m.p. 190° (decomp.), ν_{\max} 1730 and 1645 cm^{-1} , seen from the mass spectrum to contain chlorine (M^+ 444 and 446, owing to the isotope).

(b) A similar mixture to which pyridine (1 ml) had been added was stirred for 23 h and worked up as before. Elution with benzene gave a solid (0.028 g), m.p. 118° (decomp.); ν_{\max} 1730 and 1650 cm^{-1} ; M^+ 411 (containing Cl), 401, and 349. Elution with benzene–chloroform (3:1) yielded a solid (0.039 g), m.p. 150–155° (decomp.), M^+ 411 (containing Cl) and 401. Later fractions showed also molecular ions at m/e 476 and 437.

We thank Mr. P. Kelly for the mass spectrometry and the S.R.C. for a research studentship (to J. D. W.).

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¹⁷ H. Wieland and G. Varvoglis, *Annalen*, 1933, **507**, 82.