A TASTELESS DERIVATIVE OF CHLORAMPHENICOL

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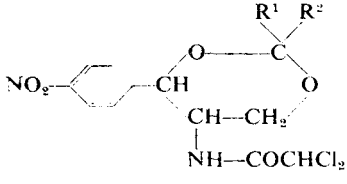
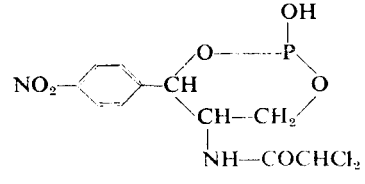
Although chloramphenicol has the advantage over both penicillin and streptomycin of being effective by mouth, this property is partly nullified by its extremely bitter taste. Recent work has shown, however, that certain derivatives of chloramphenicol, such as esters,[1] and heterocyclic derivatives of the type (I)[2], whilst retaining the antibiotic activity, no longer possess the bitter taste. It therefore appeared probable that cyclic esters such as the phosphite (II) would possess similar properties.



R^1, R^2 = H, Alk, Ar or ArAlk

(I)



(II)

The preparation of cyclic phosphites of certain aliphatic diols has been described by Lucas, Mitchell and Scully,[3] who treated the diols with phosphorus trichloride in methylene dichloride or chloroform, followed by careful hydrolysis of the product. By slightly modifying the experimental details, and using methylene dichloride as the solvent, a crystalline chloramphenicol phosphite was obtained by the author, although in poor yield. When chloroform was used, only an uncrystallisable gummy product was obtained. A slightly improved yield resulted by the use of ethylene dichloride, whilst the addition of pyridine to the reaction mixture again gave a gum. In the original experiments, freshly distilled phosphorus trichloride was used, but it was later found that this precaution was unnecessary. Phosphorus tribromide could be used instead of the trichloride, but the yield was diminished. The use of white phosphorus and iodine (i.e. phosphorus tri-iodide) yielded only a tarry gum. Several attempts were made to increase the yield by modifying the method; for example, in some cases, the phosphorus trichloride was added in 2 equal portions at a 24-hour interval, but with no improvement in the yield.

Chloramphenicol phosphite is a tasteless white solid which separates from a warm concentrated solution in ethylene dichloride as prismatic needles, but if crystallised by concentration *in vacuo* at room temperature, separates as a microcrystalline powder. It is very sparingly soluble (<0·1 per cent.) in hot water, the suspension being neutral to litmus. The solubility in ethanol is approximately 0·5 per cent.

Preliminary pharmacological results indicate that the *in vitro* activity of chloramphenicol phosphite against *Streptococcus pyogenes* is somewhat less than that of chloramphenicol itself, the minimal inhibitory concentrations in μg./ml. at 24 hours being >10 and 2·5 respectively. However, an *in vivo* test on mice infected with *Str. pyogenes* reveals no significant difference between chloramphenicol and its phosphite when administered orally at a dose of 0·2 g./kg. one hour after intraperitoneal inoculation with *Str. pyogenes.*

TABLE I

ANTIBACTERIAL ACTIVITY AGAINST *Str. pyogenes in vivo.*

Samples administered orally to groups of 10 mice 1 hour after infecting inoculation

Drug	Dose in g./kg.	Number of survivors at days			
		1	2	3	7
Chloramphenicol	1.0	10	10	9	9
	0.2	10	7	3	3
Chloramphenicol phosphite	1.0	10	8	6	6
	0.2	10	7	5	4
Untreated controls	—	0	–	–	–

It was originally proposed to extend this work to the preparation of related cyclic esters, such as the sulphite and carbonate, and in fact the sulphite was actually prepared, when an American patent[4] covering the preparation of the sulphite and carbonate appeared.

EXPERIMENTAL

A mixture of chloramphenicol (5 g., 1 mol.), phosphorus trichloride (2·13 g., 1 mol.) and dry redistilled ethylene dichloride (150 ml.) was gently refluxed for 104 hours. After a few hours, crystals began to separate. The mixture was then cooled, filtered, washed with ethylene dichloride and dried. (Evaporation of the filtrate gave a gummy uncrystallisable residue.) The product (2·2 g.) was hydrolysed by treatment with wet ether (50 ml.), with occasional shaking. After leaving overnight, the ether was removed *in vacuo* at room temperature, the residue dissolved in hot dry ethylene dichloride (*ca.* 700 ml.), filtered, and the filtrate concentrated *in vacuo* at room temperature to 200 ml., giving 1·4 g. of chloramphenicol phosphite. Found: C, 35·55; H, 3·3; N, 7·6; Cl, 19·45; P, 8·5. $C_{11}H_{11}O_6N_2PCl_2$ requires: C, 35·8; H, 3·0; N, 7·6; Cl, 19·2; P, 8·4 per cent.). The melting point varied with the rate of heating; when heated very slowly, the product melted at 214° to 215° C. with decomposition, but when heated more rapidly, the melting point rose to 220° to 222° C. with decomposition.

SUMMARY

1. Chloramphenicol phosphite, a tasteless crystalline solid, has been prepared by the action of either phosphorus trichloride or phosphorus tribromide on a solution of chloramphenicol in either methylene dichloride or ethylene dichloride, followed by mild hydrolysis of the product.

2. There is no significant difference between the *in vivo* antibiotic activity of chloramphenicol and of its phosphite.

I wish to thank Dr. H. O. J. Collier for the pharmacological results, and the Directors of Messrs. Allen and Hanburys, Ltd., for permission to publish this note.

REFERENCES

1. Belgian Patent 503,657. Parke, Davis and Co.
2. South African Patent 12,670. Parke, Davis and Co.
3. Lucas, Mitchell and Scully, *J. Amer. chem. Soc.*, 1950, **72**, 5491.
4. U.S. Patent 2,587,641. Parke, Davis and Co.