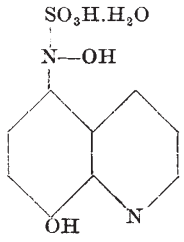
Antitubercular Activity of some 8-Hydroxyquinoline Derivatives

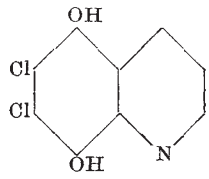
THE well-known antiseptic properties of 8-hydroxyquinoline, and particularly experiments on the use of this compound as an antitubercular agent[1], led one of us (T. U.) to prepare a few derivatives of 8-hydroxyquinoline, in order to examine their activity against *Mycobacterium tuberculosis*.

One of the products tested, *T* 28, proved to be particularly interesting due to its activity both *in vitro* and *in vivo* and to its low toxicity. The product was prepared by the action of sodium hydrogen sulphite on 5-nitroso-8-hydroxyquinoline. It proved to be monohydrate of N-sulpho-N-[5-quinolyl-8-hydroxy]-hydroxylamine (I), so far unknown in the literature.

A detailed description of the method of preparation and the proof of the structure will be reported elsewhere[2]. On boiling with concentrated hydrochloric acid, (I) was hydrolysed and, surprisingly enough, chlorinated, to yield the hydrochloride of 6.7-dichloro-5.8-dihydroxyquinoline (II).



I



II

The substance (II) also possesses strong antitubercular action *in vitro*, but experiments *in vivo* have not been carried out because of its high toxicity.

The other 8-hydroxyquinoline derivatives tested were: 5-amino-(III)- and 5.7-diamino-(IV)-quinoline. They were prepared in a new way—by reduction with sodium hydrosulphite of 5-nitroso- and 5.7-dinitro-8-hydroxyquinoline respectively. 5-Sulpho-8-hydroxyquinoline (sodium salt) (V) and 8-hydroxyquinoline sulphate (VI) were also tested and used as a standard.

The bacteriostatic concentrations were determined *in vitro* in Youmans's medium against six strains of saprophytic mycobacteria. Limits obtained for different strains are shown in Table 1.

Table 1

Substance	*T* 28 (I)	(II)	(III)	(IV)	(V)	(VI)
Bacteriostatic concentrations (mgm. per 100 ml.)	5–30	2	2·5–5	2·5–15	125–250	2·5–5

Table 2 shows the toxicity to rats of substances (I)–(V).

Table 2. LETHAL DOSE (GM. PER KGM. BODY-WEIGHT)

Substance	Intravenous injection	Subcutaneous injection	*per os*
T 28 (I)	1·0	1·5	*c.* 3·0
(II)	0·02	—	—
(III)	0·06	0·11	*c.* 0·5
(IV)	0·02	0·03	0·5
(V)	1·2	2·0	*c.* 5·0

The experiments carried out with Langendorf's rat's heart preparation showed that *T* 28 has no influence on the heart and coronary flow when 0·1 ml. of 5 per cent solution was administered. When given intravenously to a rabbit in doses of 50 mgm. per kgm. body-weight it caused only a small and temporary increase of the blood pressure. An injection of 50 mgm. per kgm. body-weight produced a fall of the sugar level by *c.* 20 per cent, lasting for 4 hr. Also only a very insignificant influence was observed on the peristaltic concentrations of the isolated rabbit's small intestine in a 0·1 per cent solution. No hæmolysis of rabbit red cells *in vitro* was observed.

Experiments *in vivo* were carried out by using guinea pigs (*c.* 500 gm.) inoculated intraperitoneally with 0·1 mgm. of *Mycobacterium tuberculosis* ($H_{37}Rv$ strain). The results are shown in Table 3.

Table 3

	No. of animals	Daily dose (mgm. per animal, subcut.)	Mortality (per cent)	Average tuber. index	Average survival time (days)
Streptomycin	20	8	10	57	84·4
T 28	20	10	40	64	76·1
Control	20	—	90	100	47·2

Treatment with *T* 28 and streptomycin started one week after inoculation.

The animals were treated for 42 days. They were then observed for a further 36 days; all survivors were killed, and the extent of tuberculous involvement was noted and rated.

Experiments on the clinical use of *T* 28 are being commenced.

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[1] McElroy, *Lancet*, 1408 (1910). Bidault, Urbain, *C.R. Soc. Biol.*, **99**, 461 (1928). Albert, A., Rubbo, S. D., Goldacre, J. R., and Balfour, B. G., *Brit. J. Exp. Path.*, **28**, 2579 (1948). Binswanger, L. A., Erlenmeyer, H., Sorkin, E., and Suter, E., *Helv.*, **31**, 1975 (1948).

[2] *Roczniki Chemii* (Warsaw) (to be published).

Preparation of the Optical Forms of Tris-Acetylacetone Cobalt III

IN an earlier communication[1], a number of experiments were described leading to the conclusion that the activities of enantiomeric ions could be changed to a different extent by the addition of an electrolyte containing an optically active anion or cation. In order to demonstrate the general applicability of this principle, we have sought to resolve a typical non-electrolytic complex salt without salt-forming groups. The peripheral atoms in the tris-acetylacetone cobalt III complex probably carry a slight negative charge, and hence negative or anionic asymmetrical fields are associated with the antipodal forms. The maximum differential interaction in solution is to be