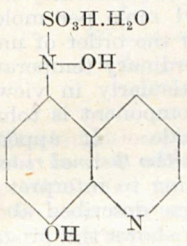
## Antitubercular Activity of some 8-Hydroxyquinoline Derivatives

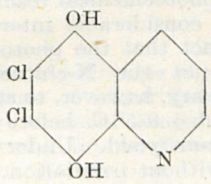
THE well-known antiseptic properties of 8-hydroxyquinoline, and particularly experiments on the use of this compound as an antitubercular agent[1], led one of us (T. U.) to prepare a few derivatives of 8-hydroxyquinoline, in order to examine their activity against *Mycobacterium tuberculosis*.

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