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THE SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF 4-CHLORO-2,6-BIS (2-HYDROXY-∝-TOLYL) PHENOL

A.A. MOSHFEGH Ph.D., A. AZARIPOUR Ph.D., H. MOT-TAGHIAN, AND G.H. HAKIMELAHI, Ph.D.

From the Departments of Chemistry, Microbiology, and Surgery, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran.

ABSTRACT

The synthesis of the title compound is described. This compound was found to be active (3c) against a number of pathogenic microorganisms *in vitro*. It is a non-absorbable antibacterial topically and its pharmacologic studies revealed that it is a non-toxic agent with a wide range of safety. It proved to be effective in the prevention and treatment of *pseudomonas*-wound infections in volunteer patients.

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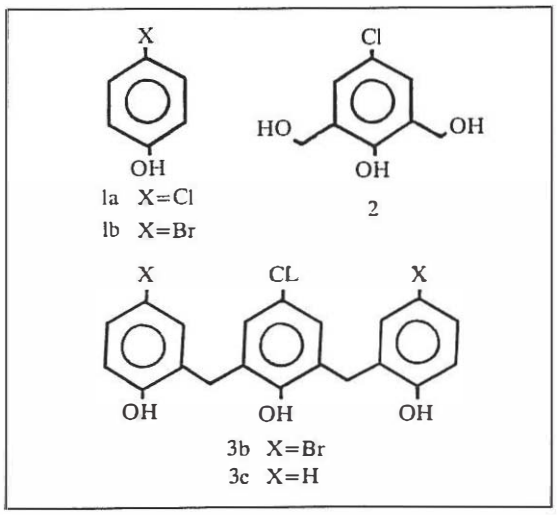
INTRODUCTION

A significant feature common to several classes of antibiotics is the presence of functional groups in a suitable spatial arrangement for chelate formation with metal ions of enzymes.[1] Examples include phloroglucides[2] (i.e.trisaspidinol). aranciamycin,[3] cryptosporin[4] and terramycin.[5] These compounds show varying degrees of activity against gram-positive bacteria as well as other microorganisms. In the previous papers,[6-9] we described the synthesis of models and structural analogues possessing functional similarity capable of chelate formation. Most of the reported compounds[6-9] exhibit interesting antibacterial activity in vitro. The biological properties of those compounds might well be linked to the presence of functional groups suitably positioned to chelate with metal ions of enzymes and perhaps to the ease with which these molecules are transported across membranes. Our studies on the structure-activity relationship of the reported[6-9] compounds suggested that the presence of halogen atoms is essential for biological activity. The homohalogenated and hetero-halogenated phloroglucide analogues[6,7] as well as their cyclic analogues[8,9] were found to exhibit good-to-excellent antimicrobial activities *in vitro*. We now report the synthesis of 4-chloro-2,6-bis (2-hydroxy-∝-tolyl) phenol, which successfully passed clinical trials in some patients.

CHEMISTRY

P-chlorophenol (1a) was converted to 4-chloro-2,6-bis (hydroxymethyl) phenol (2) by means of CH_2O/NaOH (50%).[6] Acid catalyzed condensation of 2 with p-bromophenol (1b) gave 4-chloro-2,6-bis (5-bromo-2-hydroxy-∝-tolyl)phenol (3b, 70%). Debromination of 3b with Zn/KOH[7] afforded bioactive compound 3c (80%). Since 3c is a combination of three phenolic rings we named its ointment, tricycline ointment for simplicity.



Biological Activity

Compound 3C was tested for activity against *S.aureus, E.coli, C. albicans,* and *Ps. aeruginosa.* It shows minimal inhibitory concentration against *S. aureus* 1.5 μg/ml, *C. albicans* 10 μg/ml, *Ps. aeruginosa* 0.3 μg/ml, and *E.coli* >100 μg/ml.

The pharmacologic effects of compound 3c were studied and the findings were: LD_{50}, 200 mg/kg in rats and mice when the drug was administered IM or IP and 25 mg/kg when given IV. After staining with hematoxylin-eosin (H & E) the histologic appearance of the visceral organs of control and tested groups of rats receiving the drug IM (25, 50, 100 or 150mg/kg) for 10 days, and the other groups who received it topically for 30 days, showed no discernible abnormality. There were no CVS or CNS physiological changes in mice given compond 3c, IM, up to 150 mg/kg. The drug was devoid of analgesic action. The difference in MIC and LD_{50} of compound 3c might reveal a wide range of safety forthe drug.

EXPERIMENTAL

General Procedure. See ref. 10.

4-Chloro-2,6-bis (hydroxymethyl) phenol (2). Formaldehyde (38%, 90 ml) was added to an aqueous solution of NaOH (25%, 50 ml) containing P-chlorophenol (la, 12.8 g, 0.1 mol) and methanol (25 ml). The reaction mixture was shaken at 60-80° for lh and then was allowed to stand at room temperature for 24 h. A mixture of water (50 ml) and acetic acid (15 ml) was added. The reaction mixture was stirred for 4 h at 25° to give a yellow precipitate. Filtration gave 14 g (80%) of 2 . Sublimation (153°/.01 Torr) gave pure product, m.p. 166-168° . MS 188 (Cl-clusters) M001 . Anal. Calc. for $C_8H_9ClO_3$ (188.15): C 50.74, H 4.66, Cl 18.79; found: C 50.92, H 4.77, Cl 18.83.

4-Chloro-2,6-bis (5-bromo-2,hydroxy-∝-tolyl) phenol (3b). To a solution of compounds 2 (14g, 0.07 mol) and lb (0.45mol) in methanol (150 ml) was added conc. HCl (30 ml). The reaction mixture was left at room temperature for 12 h. The solution was evaporated and the residue was suspended in boiling water to dissolve unreacted materials. The precipitate was filtered off, washed with H_2O, and dried to give 25.9g (80%) of 3b, m.p. 250° . MS for $C_{20}H_{15}Br_2ClO_3$ 499 (Cl, Br-clusters)M^+.

4-Chloro-2,6-bis (2-hydroxy-∝-tolyl) phenol (3c). To an aqueous solution of 40% KOH containing compound 3b (0.01 mol) was added Zn-dust (5g). The mixture was refluxed for 5h. Acidification with HCl (20% aqueous solution) afforded 3c as a white precipitate (85%), m.p. 188-190° . Sublimation (177°/0.01 Torr). MS 340 (Cl-clusters) M^+ . Anal. Calc. for $C_{20}H_{17}ClO_3$ (340.79): C 70.48, H 5.02, Cl 10.40; found: C 70.34, H 5.06, Cl 10.60 .

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