Soluble Polymers for Substitute of Biopolymers in Natural Compounds, I
Replacement of the Oligosaccharide Chain in Cinerubin A by Polyoxyethylene

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The glycosidic component of cinerubin A, an anthracycline antibiotic, has been replaced by a polyoxyethylene (POE) chain. The resulting POE-bound \( \varepsilon \)-pyrromycinone was readily soluble in water and exhibited full biological activity.

The attachment of biological molecules to soluble polymers has recently attracted great attention [1–3]. The general idea of this concept is to modify or alter the pharmacological properties of biological active compounds in a specific way. The most ambitious effort in the use of soluble polymers, however, represents the replacement of biopolymers, e.g. the protein component in chromoproteides, by a synthetic polymer by retention of the biological function. For example, Bayer and Holzbach tried to mimic the ‘surrounding’ of the heme group in hemoglobin by covalent binding of the prosthetic group to a polyoxyethylene bound tripeptide [4]. Whereas it is difficult to simulate adequately the unique three-dimensional structure of a protein – and consequently its impact upon the biological function of the active group – by a randomly coiling chain molecule, the substitution of polysaccharides, which exhibit similar conformational properties as synthetic polymers, appeared to us more promising.

As prototype for the realization of this concept we chose cinerubin A, a glycosidic anthracycline antibiotic with antimitotic activity, whose aglycone, \( \varepsilon \)-pyrromycinone 3 (depicted as \( R \) in compound 1 and 2), is linked to a trisaccharide chain via a glycosidic bond [5]. The subject at hand was to replace the oligosaccharide chain of compound 1 by a polyoxyethylene (POE) chain (compound 2). POE was chosen because it is known for its strong solubilizing power in organic solvents as well as in water [6]. Additionally, it can be attached to functional groups by polymerization of ethylene oxide. To this end, \( \varepsilon \)-pyrromycinone was reacted with ethylene oxide to yield compound 2. The average degree of polymerization was \( n \approx 45 \). The modified cinerubin A was readily soluble in water and organic solvents, whereas \( \varepsilon \)-pyrromycinone itself shows very low solubility and no biological activity. Plate diffusion tests showed identical biological activity of compounds 1 and 2 over a broad dose scale [7].

Thus, for the first time to our knowledge, an oligosaccharide chain in a natural compound could be replaced by a synthetic polymer without loss of biological activity. Obviously, the hydrophilic POE chain is perfectly suited to mimic the physico-chemical properties of the oligosaccharide chain. The modification of other biological molecules along these lines is presently under investigation.

Experimental

General procedure: To a mixture of 22 mg (50 \( \mu \)mole) \( \varepsilon \)-pyrromycinone and 400 \( \mu \)l ethylene oxide in 1 ml \( p \)-dioxane 5 \( \mu \)l of boron trifluoride etherate was added at +4 °C. The reaction mixture was shaken at 20 °C for 5 days in a sealed tube.

Compound 2 is a dark red solid, m.p. 32 °C, which is soluble in water and a series of organic solvents. Thin layer chromatography in mixtures of MeOH/CHCl3 showed complete conversion.

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