Carbohydrate Research, 65 (1978) C1–C2

Preliminary communication

Synthesis of 2-deoxy-L-fucopyranosyl-ϵ-pyrromycinone and 2-deoxy-D-*erythro*-pentopyranosyl-daunomycinone, -carminomycinone, and -ϵ-pyrromycinone

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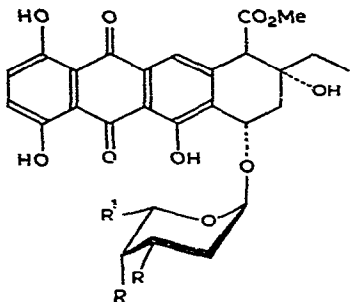
(Received December 10th, 1977; accepted for publication, May 31st, 1978)

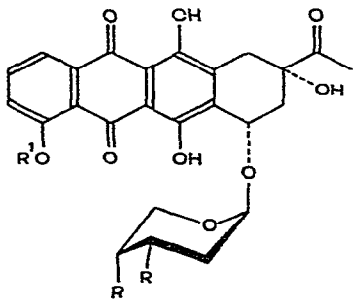
The anthracycline antibiotics are powerful antineoplastic agents. However, their use is curtailed by their dose-related cardiotoxicity, which limits the total dose that can be given to a patient, and the duration of the treatment. Analogs that show enhanced potency, or diminished toxicity, or both, could have clinical importance. This paper describes the synthesis of oxygen analogs of the anthracycline antibiotics ϵ-pyrromycin, daunorubicin, and carminomycin.

Recently, we described the synthesis of a number of glycosides of ϵ-rhodomycinon of which the most active were the 2-deoxy-L-fucopyranosyl (2,6-dideoxy-L-*lyxo*-hexopyranosyl) and 2-deoxy-D-*erythro*-pentopyranosyl derivatives[1]. This prompted us to prepare 2-deoxy-L-fucopyranosyl-ϵ-pyrromycinone (**2**) and 2-deoxy-D-*erythro*-pentopyranosyl-ϵ-pyrromycinone, -daunomycinone, and -carminomycinone (**4**, **6**, and **8**) and their di-*O*-acetyl derivatives (**1** and **3**, and **5** and **7**, respectively) for screening.

The procedure for the preparation of the protected glycosides (**1**, **3**, **5**, and **7**) may be exemplified by the synthesis of 3,4-di-*O*-acetyl-2-deoxy-L-fucopyranosyl-ϵ-pyrromycinone (**1**), as follows. ϵ-Pyrromycinone (1 molar equivalent) and 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl bromide (di-*O*-acetyl-2-deoxy-L-fucosyl bromide)[2] (1 molar equivalent) in anhydrous tetrahydrofuran were refluxed for 1 h with molecular sieve 3A under Koenigs–Knorr conditions, using a mercuric bromide–mercuric cyanide catalyst[3]. The mixture was then treated with another equivalent of the glycosyl halide, and refluxed overnight. The solids and mercury compounds were filtered off, and the solvent was evaporated. Column chromatography on silica gel developed with ether separated the sugar components that had not reacted with the aglycon from the desired glycoside, which was eluted with chloroform, and crystallized from 95% ethanol. The other protected glycosides were prepared in exactly the same way from the appropriate aglycon and di-*O*-acetyl-2-deoxy-D-*erythro*-pentopyranosyl chloride[4]. The resulting acetylated glycosides were obtained in ~80% yield (based on the aglycon); m.p. **1**, 144–147°; of **3**, 122–124°; of **5**, 106–110°; and of **7**, 125–126°.



1 R = OAc, R^1 = Me
2 R = OH, R^1 = Me
3 R = OAc, R^1 = H
4 R = OH, R^1 = H



5 R = OAc, R^1 = Me
6 R = OH, R^1 = Me
7 R = OAc, R^1 = H
8 R = OH, R^1 = H

Deacetylation, as exemplified by the preparation of glycoside **2**, was achieved by treating the protected glycoside **1** with an excess of sodium methoxide in absolute methanol for 20 min at room temperature. The purple solution was poured into a separatory funnel containing a solution of sodium hydrogensulfate, and the desired glycoside was extracted with chloroform. Evaporation of the solvent, followed by crystallization from 95% ethanol, afforded pure 2-deoxy-L-fucopyranosyl-ε-pyrromycinone (**2**). The other glycosides (**4**, **6**, and **8**) were prepared in the same way from their acetates (**3**, **5**, and **7**). In all cases, the deacetylation proceeded quantitatively; m.p. of **2**, 230–233°; of **4**, 217–220°; of **6**, 188–190°; and of **8**, 214–218°.

All compounds prepared gave the correct elemental analyses, and their structures were confirmed by their n.m.r. spectra. The latter showed the expected number of phenolic protons in the offset region, suggesting that the glycosidic linkage was either through the secondary or the tertiary hydroxyl group of the aglycon, but the second possibility was excluded, because this hydroxyl group is highly hindered and would not be expected to participate in the reaction to any appreciable extent.

ACKNOWLEDGMENTS

The authors express their gratitude to Bristol Laboratories, a division of Bristol–Myers Co., for financial support and for samples of carminomycin and ε-pyrromycinone, and to the National Cancer Institute for a sample of daunomycinone.

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