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Note

Synthesis of 7-(tetrahydropyran-2-yl)- and 7-(4-acetoxytetrahydropyran-2-yl)-ε-rhodomycinone and 7-(tetrahydropyran-2-yl)-ε-pyrromycinone

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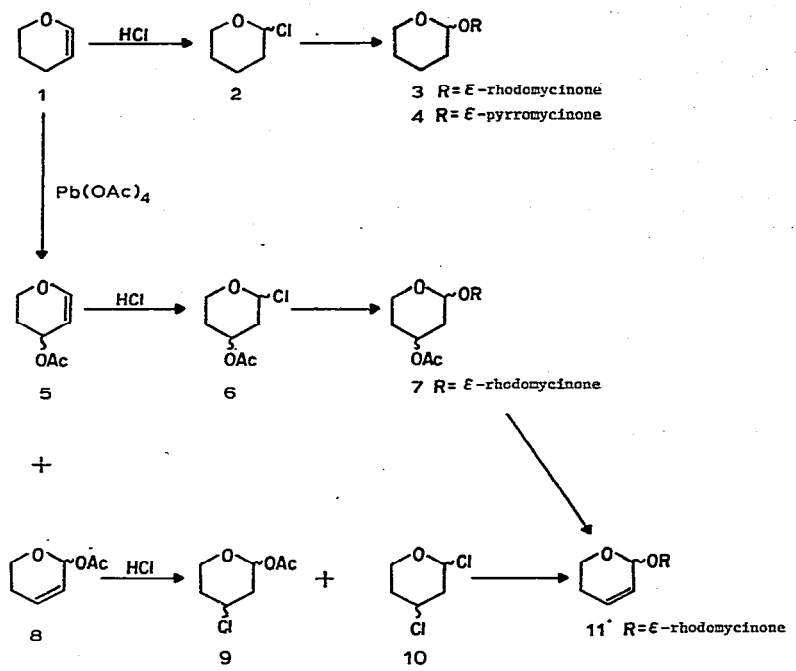
Continuing our work on the synthesis of analogs of anthracycline antibiotics[1,2], we describe here the synthesis of 7-(tetrahydropyran-2-yl)-ε-rhodomycinone (**3**) and -ε-pyrromycinone (**4**), as well as 7-(4-acetoxytetrahydropyran-2-yl)-ε-rhodomycinone (**7**).

All of the compounds were prepared from a common starting-material, 2,3-dihydro-4*H*-pyran (**1**). To prepare the 7-tetrahydropyran-2-yl derivatives **3** (of ε-rhodomycinone) and **4** (of ε-pyrromycinone), compound **1** was treated with HCl, and the resulting 2-chlorotetrahydropyran (**2**) was allowed to react with the chosen anthracyclinone by the usual Koenigs–Knorr method[3]. The glycosides were then separated from the unreacted sugars by chromatography on silica gel.

When compound **1** was treated with lead tetraacetate, it afforded a mixture of the 2- and 4-acetoxy derivatives (**5** and **8**). These were treated with HCl, without separation, affording a three-component mixture of 4-acetoxy-2-chlorotetrahydropyran (**6**), 2-acetoxy-4-chlorotetrahydropyran (**9**), and 2,4-dichlorotetrahydropyran (**10**). On treatment with ε-rhodomycinone under Koenigs–Knorr conditions, this mixture afforded the desired 7-(4-acetoxytetrahydropyran-2-yl)-ε-rhodomycinone (**7**) and an elimination product, namely, 7-(3,4-dihydropyran-2-yl)-ε-rhodomycinone (**11**). The two compounds could be readily separated by column chromatography, and were identified by n.m.r. spectroscopy.

EXPERIMENTAL

General. — Melting points were determined with a Kofler block and are uncorrected. N.m.r. spectra were recorded with Varian T-60 and EM-360 spectrometers, using tetramethylsilane as the internal standard, and $CDCl_3$ as the solvent. Thin-layer chromatography was performed on Eastman Kodak 13181 silica gel plates. Chromatographic columns were packed with Sargent–Welch SC 14608 silica gel (60–200 mesh). Microanalyses were performed in the Department of Chemistry and Chemical



Engineering Microanalysis Laboratory by Mrs. S. Brotherton. Compound **1** was purchased from Aldrich Chemical Co., 940 West Saint Paul Avenue, Milwaukee, WI.

2-Chlorotetrahydropyran (**2**). — Compound **1** (2 g) was dissolved in dry, thiophene-free benzene (15 mL), and HCl was bubbled into the solution for 5 min. The excess of HCl was removed under vacuum, and the resulting solution of **2** was used, without purification, for the preparation of the anthracycline analogs.

7-(Tetrahydropyran-2-yl)-ε-rhodomycinone (**3**). — The foregoing solution of **2** in benzene was added portionwise to a stirred suspension of ε-rhodomycinone (200 mg), mercuric bromide (500 mg), mercuric cyanide (30 mg), and finely ground, 3A molecular sieves (3 g) in tetrahydrofuran (40 mL). The reaction at room temperature was monitored by t.l.c., which showed that all of the **2** had reacted with the aglycon in ~5 min. Addition of more **2** was continued until all of the aglycon had been used up; the mixture was then filtered through Celite, the residue was washed well with chloroform, and the filtrates were combined, and evaporated to a red syrup under diminished pressure. The syrup was dissolved in chloroform (150 mL), and the solution washed with 2M potassium iodide (2 × 150 mL) to remove mercuric salts, dried (anhydrous sodium sulfate), and evaporated under diminished pressure to a syrup that was dissolved in chloroform (10 mL) and the solution applied to a column (2 × 80 cm) of silica gel that was eluted with chloroform. The first fractions contained some unreacted pyran derivatives and a trace of the glycoside; the subsequent fractions contained the desired glycoside, followed by the aglycon. The middle fractions were evaporated under diminished pressure, and the residue triturated with ether.

The resulting crystals were filtered off, washed with ether, and dried; m.p. 206–209°.

Anal. Calc. for $C_{27}H_{28}O_{10} \cdot 0.5\ H_2O$: C, 62.18; H, 5.60. Found: C, 62.48; H, 5.20.

7-(Tetrahydropyran-2-yl)-ε-pyrromycinone (**4**). — A solution of compound **2** in benzene was similarly added to a suspension of ε-pyrromycinone (70 mg), mercuric bromide (400 mg), mercuric cyanide (25 mg), and finely ground, 3A molecular sieves (3 g) in tetrahydrofuran (35 mL). T.l.c. indicated that the reaction was complete within 30 min; the mixture was then treated as for **3**. The crystals that separated out were filtered off, washed with ether, and dried; m.p. 200–207°.

Anal. Calc. for $C_{27}H_{28}O_{10} \cdot 0.5\ H_2O$: C, 62.18; H, 5.60. Found: C, 61.75; H, 5.39.

4-Acetoxy-2,3-dihydro-4H-pyran and 2-acetoxy-5,6-dihydro-2H-pyran (**5** *and* **8**). — To a solution of compound **1** (20 g) in dry, thiophene-free benzene (50 mL) was added lead tetraacetate (96 g, in 1-g portions), and the mixture was stirred continuously in a water bath at 30°. During the addition, the lead acetate formed was removed by filtration, and washed with benzene, and the benzene washings were combined with the main solution. The process was halted when unreacted crystals of lead tetraacetate could be detected in the mixture. The benzene was then evaporated under diminished pressure, and the residue fractionally distilled in a 15-cm, Vigreux column at 0.05 mm Hg. The isomeric dihydropyranyl acetates were collected at 38–40° (2.0 mL) and 40° (2.6 mL) (lit.[4] b.p. of **5** and **8** at 8 mm Hg, 69–71° and 72–73°, respectively).

7-(4-Acetoxytetrahydropyran-2-yl)-ε-rhodomycinone (**7**) *and 7-(5,6-dihydropyran-2-yl)-ε-rhodomycinone* (**11**). — The lower boiling fraction of the dihydropyranyl acetate mixture was dissolved in benzene (50 mL), and anhydrous HCl was bubbled through the solution for 15 min. The benzene was then evaporated under diminished pressure, and the syrupy residue was treated with toluene to remove traces of HCl. The resulting halide was added to a suspension of ε-rhodomycinone (1 g), finely ground 3A molecular sieves (5 g), mercuric cyanide (60 mg), and mercuric bromide (820 mg) in tetrahydrofuran (50 mL). The mixture was stirred continuously for 2 h; t.l.c. then showed the reaction to be complete, and the mixture was filtered through Celite, the residue was washed well with chloroform, and the filtrate and washing were combined, and evaporated to a red syrup under diminished pressure. A solution of the syrup in chloroform (200 mL) was washed with 2M potassium iodide solution (3 × 200 mL) to remove any mercuric salts, dried (anhydrous sodium sulfate), and evaporated to dryness under diminished pressure, and a solution of the resulting product in chloroform (15 mL) was applied to a column (2 × 80 cm) of silica gel, and eluted with chloroform. The first eluate was yellow, and contained unreacted sugars; the second was red, and contained a mixture of glycosides **7** and **11**; and unreacted aglycon remained on the column. Separation of the middle fraction by rechromatography afforded, from the faster band, compound **7**, which was filtered off, washed with ether, and dried; m.p. 198–204°.

Anal. Calc. for $C_{29}H_{30}O_{12}$: C, 61.04; H, 5.31. Found: C, 61.12; H, 4.89.

The slower fractions yielded compound **11**, which was filtered off, washed with ether, and dried; m.p. 177–185°.

Anal. Calc. for $C_{27}H_{26}O_{10}$: C, 63.52; H, 5.13. Found: C, 63.15; H, 5.17.

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