in 20 mL of pyridine. The reaction mixture was kept at 3 °C for 24 h, during which the crystalline product precipitated. The crystals were isolated by filtration, washed thoroughly with petroleum ether, dried, and recrystallized from $CHCl_3$ to give 0.42 g (53%): mp 203–206 °C (dec); NMR (Me_2SO-d_6) δ 2.40 (s, 3 H, $-CH_3$), 6.12 (s, 2 H, $-CH_2$), 7.63–8.34 (m, 5 H, H-4, H-5, H-6, H-7, and H-8, aromatic), 9.14–9.34 (m, 2 H, H-1, H-3, aromatic). Anal. ($C_{16}H_{12}O_5S$) C, H, S.

2-[[(*p*-Toluenesulfonyl)oxy]methyl]anthraquinone (7). A solution of **3** (1.12 g, 4.70 mmol) and *p*-toluenesulfonyl chloride (1.07 g, 5.64 mmol) in 30 mL of pyridine was kept at 3 °C for 24 h. The resulting crystalline material was collected by filtration, washed with water, EtOH, and Et_2O, dried, and recrystallized from $CHCl_3$–DMF to yield 1.24 g (67%) of pale yellow fine needles: mp 203–204 °C; NMR (Me_2SO-d_6) δ 2.30 (s, 3 H, $-CH_3$), 6.12 (s, 2 H, 2-CH_2), 7.10 (d, 2 H, H_a tolyl ring), 7.50 (d, 2 H, H_b tolyl ring), 7.80–8.40 (m, 5 H, H-4, H-5, H-6, H-7, H-8, aromatic), 9.20–9.41 (m, 2 H, H-1, H-3, aromatic). Anal. ($C_{21}H_{16}O_5S$) C, H, S.

2-(Methoxymethyl)anthraquinone (8). 2-(Chloromethyl)-anthraquinone (**2**; 4.4 g, 17.4 mmol) in 250 mL of MeOH was refluxed for 18 days. The solution was concentrated, and the crystalline product was isolated by filtration and recrystallized from DMF to yield 1.94 g (44%): mp 132–134 °C (lit.[25] 134 °C); NMR ($CDCl_3$) δ 2.48 (s, 3 H, OCH_3), 4.60 (s, 2 H, 2-CH_2), 7.52–7.94 (m, 3 H, H-1, H-3, and H-4, aromatic), 8.08–8.40 (m, 4 H, H-5, H-6, H-7, and H-8, aromatic).

Polarography. First half-wave reduction potentials were measured in 0.05 M phosphate buffer prepared in water–EtOH (1:1, v/v), pH 7.0, by differential pulse polarography using a PAR 174A polarographic analyzer. The values were obtained in volts vs. a saturated calomel reference electrode using 0.1 M KCl as the supporting electrolyte.

Acknowledgment. This work was supported in part by U.S. Public Health Service Grants CA-02817 and CA-16359 from the National Cancer Institute, a grant from the Bristol-Myers Co., National Institutes of Health Postdoctoral Fellowship CA-06365 (B.A.T.), and Grant ACS-IN-31-T-5 from the American Cancer Society.

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8-Hydroxyanthracyclinones from ε-Rhodomycinone

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Received May 23, 1980

ε-Rhodomycinone was converted into 8,9-dehydro-ζ-rhodomycinone, which gave a cis diol with osmium tetroxide and a pair of epimeric epoxides with *m*-chloroperbenzoic acid. Acid-catalyzed opening of the epoxides gave the corresponding trans diols. In contrast, acid treatment of the trimethyl ethers of these epoxides gave predominantly a lactone and an η-rhodomycinone derivative, with only small amounts of the diols. None of the new rhodomycinones were active against *Bacillus subtilis*, but 8,9-dehydro-ζ-rhodomycinone was active in the induction of lytic phage in *Escherichia coli*.

Beginning with Brockmann's pioneering studies,[1] research on anthracyclines has developed into a major field. Anthracyclines containing the aglycons aklavinone, ε-pyrromycinone, adriamycinone, carminomycinone, or daunomycinone combined with sugars such as daunosamine, rhodosamine, 2-deoxy-L-fucose, rhodinose, and cinerulose have shown significant antitumor activity.[2] The clinical importance of doxorubicin (adriamycin) has stimulated recent investigations into the preparation of semisynthetic anthracyclinones and anthracyclines.[3]

The production of anthracyclines by *Streptomyces* species is usually accompanied by inactive aglycons. One of these aglycons, ε-rhodomycinone (**1**; Scheme I), was made available to us by Bristol Laboratories for the purpose of preparing modified anthracyclinones.

This paper describes the successful replacement of the 7α-hydroxyl group in **1** by 8α- and 8β-hydroxyl groups to obtain products which represent potentially useful intermediates to novel 8-glycosylated anthracycline analogues. The preparation of compounds of this type by total synthesis was reported recently by other workers.[4]

The 7α-hydroxy group of ε-rhodomycinone was readily removed by catalytic hydrogenolysis to give the known ζ-rhodomycinone (**2**).[5] Treatment of **2** with *p*-toluenesulfonic acid then afforded the 8,9-olefin **4**. Catalytic hydrogenation of **4** gave 9-deoxy-ζ-rhodomycinone **3**. When **4** was treated with osmium tetroxide, a good yield of the cis diol, 8α-hydroxy-ζ-rhodomycinone (**9**), was obtained.

Treatment of the 8,9-olefin **4** with *m*-chloroperbenzoic acid gave a mixture of the α-epoxide **5** (45%) and β-epoxide **7** (30%), plus other substances that were not identified. This mixture was readily separated by chromatography on silica gel. Stereochemistry of the epoxides was assigned according to transformations described below and from their NMR spectra (see Experimental Section). Each epoxide afforded the corresponding trans diol (**10** and **12**) upon treatment with 70% perchloric acid in acetone. In contrast to these results, opening of the corresponding epoxide trimethyl ethers, **6** and **8**, with perchloric acid in acetone afforded little of the corresponding diols. The α-epoxide **6** gave a small amount of the desired trans diol **11**, but the predominant product was γ-lactone **14**. The formation of **14** established the stereochemistry of epoxides **5** and **6**. We were unable to find conditions for opening epoxide **6** that did not afford mainly the lactone. Moreover, we were not able to convert the lactone into **11**.

(1) Brockmann, H. "Anthracyclinone und Anthracycline", in "Progress in the Chemistry of Organic Natural Products", Zechmeister, L., Ed.; Springer-Verlag, Berlin, Heidelberg, and New York, 1963.
(2) Remers, W. "The Chemistry of Antitumor Antibiotics"; Wiley-Interscience: New York, 1979; Vol. 1, p 66.
(3) (a) Arcamone, F.; Penco, S.; Vigevani, S.; Redaelli, S.; Franchi, G.; Di Marco, A.; Casazza, A. M.; Dasdia, T.; Formelli, F.; Necco, A.; Soranzo, C. *J. Med. Chem.* **1975**, *18*, 703. (b) Israel, M.; Tinter, S. K.; Lazarius, H. Proceedings of the 11th International Cancer Congress, Florence, Italy, October 20–26, 1974. (c) Tong, G. L.; Wie, H. Y.; Smith, T. H.; Henry, D. W. *J. Med. Chem.* **1979**, *22*, 912.
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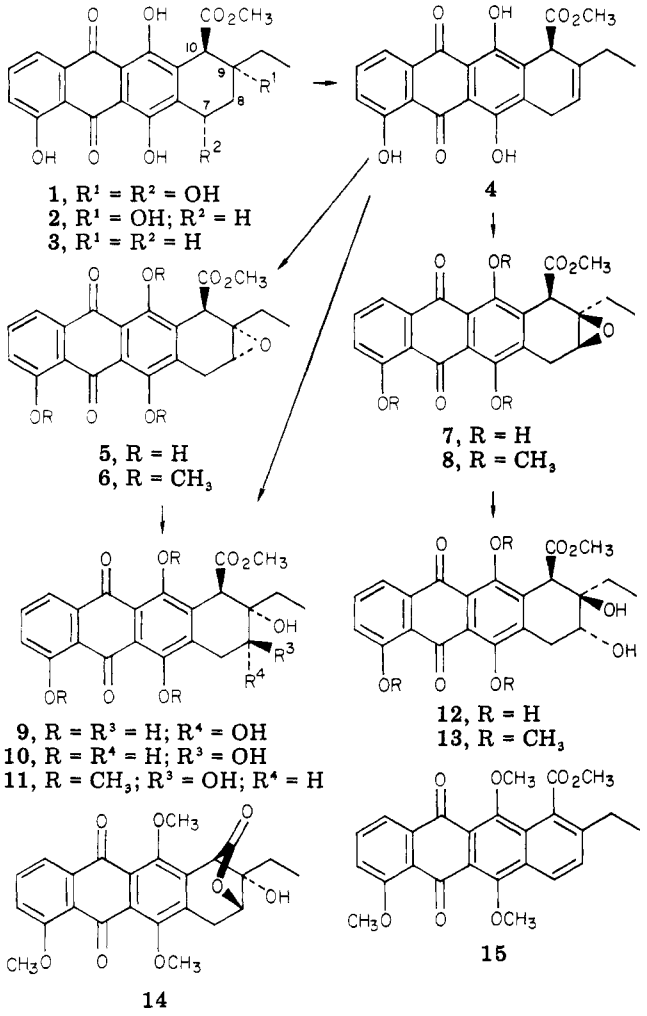
0022-2623/80/1823-1242$01.00/0

Table I. Phage Induction Activities[a]

compd	induction of λ phage of *E. coli*, ratio of plaques in treated culture to those in control[b] dose, μg/mL: 50	25	12.5	6.2	3.1	1.6	0.8
1	2.9T	1.8	1.5				
3	2.4	1.8	1.2	1.3	1.0		
4	13.4	9.3	6.0	2.8			
5	3.0	2.0	1.1	1.4	1.2		
7	2.9	1.9	1.5	1.3	1.2		
daunorubicin				11.1T	11.9	5.3	3.1
carminomycin				7.0	6.2	3.0	2.2

[a] Conducted at Bristol Laboratories, Syracuse, NY. [b] For a detailed description of the procedure, see K. E. Price, R. E. Buch, and J. Lein, *Appl. Microbiol.*, 12, 428 (1964). T means toxic to culture; blank space means not tested at this dose.

Scheme I



Acid-catalyzed opening of methylated β-epoxide 8 also was surprising in that the predominant product was η-rhodomycinone trimethyl ether (15). Only a small amount of the desired diol 13 was obtained under a variety of conditions. The facile formation of 15 supports the assigned stereochemistry of epoxide 8 because the resulting diol 13 is set up for trans elimination of water at the 9 and 10 positions. It is interesting to compare the difference in types of products obtained between epoxides 5 and 7 and their trimethyl ethers 6 and 8. The predominance of diol products from 5 and 7 suggests that they are formed initially and precipitate before they can undergo further reactions. However, the more soluble diols formed from 6 and 8 are readily converted into the lactone 14 and aromatic system 15. Alternatively, the lactone formation might be facilitated by the presence of the 11-*O*-methyl group in compound 11. It is known that the 10-carbomethoxy group of certain rhodomycinones is very unreactive because of interaction with the 11-hydroxyl group,[6] but this interaction is absent in 11.

Biological Activity. Table I shows the abilities of ε-rhodomycinone and certain of our new anthracyclinones to activate lytic phage in *Escherichia coli*, relative to the corresponding activities of daunorubicin and carminomycin. This assay is useful as an indicator of potential antitumor activity. To be considered active in it, a compound should show a ratio of test to control sample plaque counts of 3.0 or greater. Compound 4, 8,9-dehydro-ζ-rhodomycinone, is active in this assay and compound 5, the 8α,9α-epoxide, is barely active. However, both are much less potent than daunorubicin and carminomycin. None of the anthracyclinones was against *Bacillus subtilis* in a disk-plate assay at pH 8, whereas daunorubicin and carminomycin were active at concentrations as low as 0.8 μg/mL.[7]

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-33 spectrophotometer as KBr pellets. Nuclear magnetic resonance spectra were recorded on Varian EM-360L and T-60 spectrometers using tetramethylsilane as the internal standard. R_f values were determined on 0.2-mm-thick Kieselgel 60 F-254 on 5 × 20 cm plates. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. Analytical results were within ±0.4% of theoretical values.

ζ-Rhodomycinone (2). A solution of 1 (1.0 g, 2.3 mmol) in 150 mL of tetrahydrofuran was treated with 0.3 g of 10% palladium on carbon and shaken with hydrogen for 8 h. The mixture was filtered and the filtrate was concentrated. Chromatography of the residue on a silica gel column with chloroform as solvent gave 0.96 g (89%) of 2 as red solid: mp 272–274 °C (lit.[5] mp 274–275 °C); R_f 0.39 (benzene–ethyl acetate, 4:1).

8,9-Dehydro-ζ-rhodomycinone (4). A mixture of 2 (500 mg, 1.21 mmol) and *p*-toluenesulfonic acid monohydrate (250 mg, 1.31 mmol) in 50 mL of toluene was heated under reflux for 16 h, while water was removed with a Dean–Stark trap. The mixture was concentrated and the residue was chromatographed on a silica gel column with a benzene–ethyl acetate mixture (1:3) used as solvent. This procedure gave 400 mg (84%) of 4 as a red solid: mp 169–171 °C after recrystallization from benzene; IR 1730 cm^{-1} (ester); NMR ($CDCl_3$) showed the 8-vinyl proton as a multiplet at δ 5.9; R_f 0.89 (benzene–ethyl acetate, 4:1). Anal. ($C_{22}H_{18}O_7$) C, H.

9-Deoxy-ζ-rhodomycinone (3). A mixture of 4 (205 mg), 10% palladium on carbon (200 mg), and 25 mL of tetrahydrofuran was shaken with hydrogen at 1 atmosphere pressure for 24 h, filtered, and concentrated. Chromatography of the residue on silica gel with a 3:1 benzene–hexane system gave 94.4 mg (47%) of 3 as red crystals, mp 210–212 °C. Recrystallization from benzene–

(6) Smith, T. H.; Fujiwara, A. J.; Henry, D. W. *J. Med. Chem.* **1978**, *21*, 280.

(7) Conducted at Bristol Laboratories, Syracuse, NY, according to the procedure of Bauer, A. W.; Sheris, J. C.; Turek, M. *Am. J. Clin. Pathol.* **1966**, *45*, 493.

hexane gave the analytical sample: mp 217–218 °C; IR 1730 cm^{-1} (ester); NMR showed no vinyl hydrogen at δ 5.9; R_f 0.73 (benzene–ethyl acetate, 4:1). Anal. ($C_{22}H_{20}O_7$) C, H.

8α-Hydroxy-ζ-rhodomycinone (9). A mixture of **4** (124 mg, 0.31 mmol), osmium tetroxide (160 mg, 0.63 mmol), and pyridine (1 mL) in 250 mL of ether was stirred in the dark for 42 h, filtered, washed with 50 mL of ether, and air-dried. The osmate was dissolved in 5 mL of pyridine and treated with a solution of 0.33 g of sodium bisulfite in 5 mL of water. The mixture was stirred for 1 h and then extracted with 80 mL of chloroform in 5 portions. These extracts were combined, washed with 20 mL of water, and dried. Evaporation of the chloroform in a stream of nitrogen gave 120 mg (89%) of **9** as red solid: mp 256–258 °C; IR 3560 (OH), 1730 cm^{-1} (ester); R_f 0.36 (benzene–ethyl acetate, 1:1). Anal. ($C_{22}H_{20}O_9$) C, H.

8,9-Dehydro-ζ-rhodomycinone 8,9-α-Epoxide (5) and 8,9-Dehydro-9-*epi*-ζ-rhodomycinone 8,9-β-Epoxide (7). A stirred ice-cooled solution of **4** (300 mg, 0.72 mmol) in 8 mL of dichloromethane was treated dropwise with *m*-chloroperbenzoic acid (300 mg, 1.65 mmol) in 5 mL of dichloromethane. After 12 h at 25 °C, the mixture was extracted with 10% sodium bicarbonate solution, dried over magnesium sulfate, and concentrated. The residue was separated by preparative layer chromatography on silica gel with a benzene–ethyl acetate mixture (4:1) as solvent. Concentration of eluate from the first red band gave 166 mg (53%) of **5** as red solid: mp 213–215 °C; IR 1730 (ester), 1230 cm^{-1} (epoxide); NMR ($CDCl_3$) δ 1.6–2.3 (m, 5, CH_2CH_3, 7-H's, 8-H), 4.81 (s, 1, 10-H); R_f 0.79 (benzene–ethyl acetate, 4:1). Anal. ($C_{22}H_{18}O_8$) C, H.

Concentration of eluate from the third red band gave 115 mg (37%) of **7** as a red solid: mp 214–216 °C; IR 1730 (ester), 1270 cm^{-1} (epoxide); NMR ($CDCl_3$) δ 1.6 (m, 1, 8-H), 1.7–2.3 (m, 4, CH_2CH_3, 7-Hz), 4.23 (s, 1, 10-H); R_f 0.71 (benzene–ethyl acetate, 4:1). Anal. ($C_{22}H_{18}O_8$) C, H.

The second red band eluted gave a small amount of a mixture of compounds. It was not further resolved.

8β-Hydroxy-ζ-rhodomycinone (10). A mixture of **5** (85 mg, 0.21 mmol), 80 mL of acetone, and 5 mL of 70% perchloric acid was kept at 5 °C for 6 days. The precipitate that formed was collected, washed with acetone, and dried in the air to give 48 mg (54%) of **10** as red solid: mp 280–282 °C; IR 3420 (OH), 1735 cm^{-1} (ester); the sample was not sufficiently soluble to allow determination of its NMR spectrum; R_f 0.53 (benzene–ethyl acetate, 4:1). Anal. ($C_{22}H_{20}O_9$) C, H.

8α-Hydroxy-9-*epi*-ζ-rhodomycinone (12). A mixture of **7** (82 mg, 0.20 mmol), 80 mL of acetone, and 5 mL of 70% perchloric acid was kept at 5 °C for 12 days. The precipitate that formed was collected, washed with acetone, and dried in air to give 33 mg (38%) of **12** as red solid: mp 293–295 °C; IR 3430 (OH), 1750 cm^{-1} (ester); MS, *m/e* 428 (M^+), 410 ($M^+ - H_2O$), 396 ($M^+ - CH_3OH$). This sample was too insoluble for purification or determination of its NMR spectrum. However, it gave a tetraacetate upon stirring with acetic anhydride in pyridine for 16 h. This tetraacetate was a yellow solid: mp 175–177 °C; IR 3460 (OH), 1790, 1760 (acetate), 1740 cm^{-1} (ester); R_f 0.30 (benzene–ethyl acetate, 1:1). Anal. ($C_{30}H_{28}O_{13}$) C, H.

8,9-Dehydro-4,6,11-tri-*O*-methyl-ζ-rhodomycinone 8,9-Epoxide (6). A solution of **5** (50 mg, 0.12 mmol) in 25 mL of acetone was treated with potassium carbonate (110 mg, 0.79 mmol) and dimethyl sulfate (0.15 mL, 1.58 mmol). The mixture was stirred at 50 °C for 30 h, cooled, filtered, and concentrated. Preparative-layer chromatography of the oily residue on silica gel with 1:1 benzene–ethyl acetate as solvent gave 38 mg (67%) of **6** as yellow solid: mp 110–111 °C; IR 1740 cm^{-1} (ester); NMR ($CDCl_3$) showed O-CH_3 groups at δ 3.75, 3.90, 3.93, and 3.96; R_f 0.64 (benzene–ethyl acetate, 1:1). Anal. ($C_{25}H_{24}O_8$) C, H.

8,9-Dehydro-9-*epi*-4,6,11-tri-*O*-methyl-ζ-rhodomycinone 8,9-Epoxide (8). This compound was prepared by the method described for **12**. From 80 mg of **7** was obtained 72 mg (82%) of **8** as a yellow solid: mp 88–90 °C after recrystallization from benzene–petroleum ether; IR 1735 cm^{-1} (ester); NMR ($CDCl_3$) showed O-CH_3 groups at δ 3.75, 3.88, 3.95, and 4.00; R_f 0.72 (benzene–ethyl acetate, 1:1). Anal. ($C_{25}H_{24}O_8$) C, H.

8β-Hydroxy-4,6,11-tri-*O*-methyl-ζ-rhodomycinone (11) and 15-Demethoxy-8-hydroxy-4,6,11-tri-*O*-methyl-ζ-rhodomycinone 8,15-Lactone (14). A mixture of **6** (132 mg, 0.29 mmol), 15 mL of acetone, and 1 mL of 70% perchloric acid was kept at 5 °C for 64 h, neutralized with 10% sodium bicarbonate solution, and partly concentrated. The residual aqueous solution was extracted with 30 mL of chloroform, and this extract was dried and concentrated. Preparative-layer chromatography of the oil residue on silica gel with 1:1 benzene–ethyl acetate as solvent gave two major yellow bands. The one of lower R_f contained 20 mg (15%) of **11**: mp 180–181 °C; IR 3480 (OH), 1730 cm^{-1} (ester); NMR ($CDCl_3$) showed O-CH_3 groups at δ 3.75, 3.89, 3.96, and 4.00; R_f 0.19 (benzene–ethyl acetate, 1:1). Anal. ($C_{25}H_{26}O_9$) C, H. The yellow band of higher R_f contained 63 mg (49%) of **14**: mp 140–142 °C; IR 3450 (OH), 1780 cm^{-1} (γ-lactone); NMR ($CDCl_3$) showed three O-CH_3 on aromatic nuclei at δ 3.97–4.00, but no methyl ester at δ 3.75; R_f 0.44 (benzene–ethyl acetate, 1:1). Anal. ($C_{24}H_{22}O_8$) C, H.

8α-Hydroxy-9-*epi*-4,6,11-tri-*O*-methyl-ζ-rhodomycinone (13) and 4,6,11-Tri-*O*-methyl-η-rhodomycinone (15). These compounds were prepared by the procedure used for **11** and **14**. From 88 mg of **8** was obtained in the yellow band 17 mg (18%) of **13**: mp 175–178 °C; IR 3500 (OH), 1730 cm^{-1} (ester); NMR ($CDCl_3$) showed O-CH_3 groups at δ 3.75, 3.87, 3.97, and 4.00; R_f 0.42 (benzene–ethyl acetate, 1:1). Anal. ($C_{25}H_{26}O_9$) C, H. A pink band of higher R_f gave 23 mg (27%) of **15** with mp 155–156 °C, undepressed upon admixture with a sample prepared by methylation of η-rhodomycinone. The infrared spectra and R_f values on chromatography of these two samples were identical.

For the alternative sample of **15**, a mixture of η-rhodomycinone[1] (20 mg), potassium carbonate (50 mg), and 10 mL of acetone was stirred for 0.5 h and treated with methyl iodide (0.5 mL). The mixture was heated at reflux for 3 h and another 0.5 mL of methyl iodide was added. After an additional 3 h, the mixture was filtered and concentrated. Chromatography of the residue on a silica gel column with 9:1 benzene–ethyl acetate as solvent gave as the major product 15 mg (68%) of **15** as a yellow solid: mp 155–156 °C; R_f 0.71 (benzene–ethyl acetate, 1:1). Anal. ($C_{25}H_{22}O_7$) C, H.

Acknowledgment. This investigation was supported by a grant from Bristol Laboratories. We thank Dr. W. T. Bradner for the biological assays and Dr. T. W. Doyle for samples of ε-rhodomycinone and certain NMR spectra.