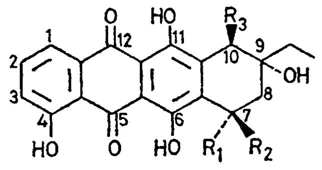
Total Synthesis of Rhodomycin Aglycones

By ANDREW S. KENDE* and YUH-GENG TSAY
(*Department of Chemistry, University of Rochester, Rochester, New York* 14627)

Summary The tetracyclic ketone (VIa), readily available from 1,4,5-trimethoxyanthraquinone, has been converted by C-9 vinylation and subsequent transformations into the four rhodomycin aglycones (I)—(IV).

RHODOMYCINONES (I)—(V) are the principal aglycones of the aminoglycoside antibiotics of the rhodomycin group,[1] which include mycetins A, B, and C.[2] We now report the first total synthesis of the racemic rhodomycinones (I)—(IV) by methods which could prove useful for the construction of similar aglycones in the citromycin[3] and isorhodomycin[4] series.

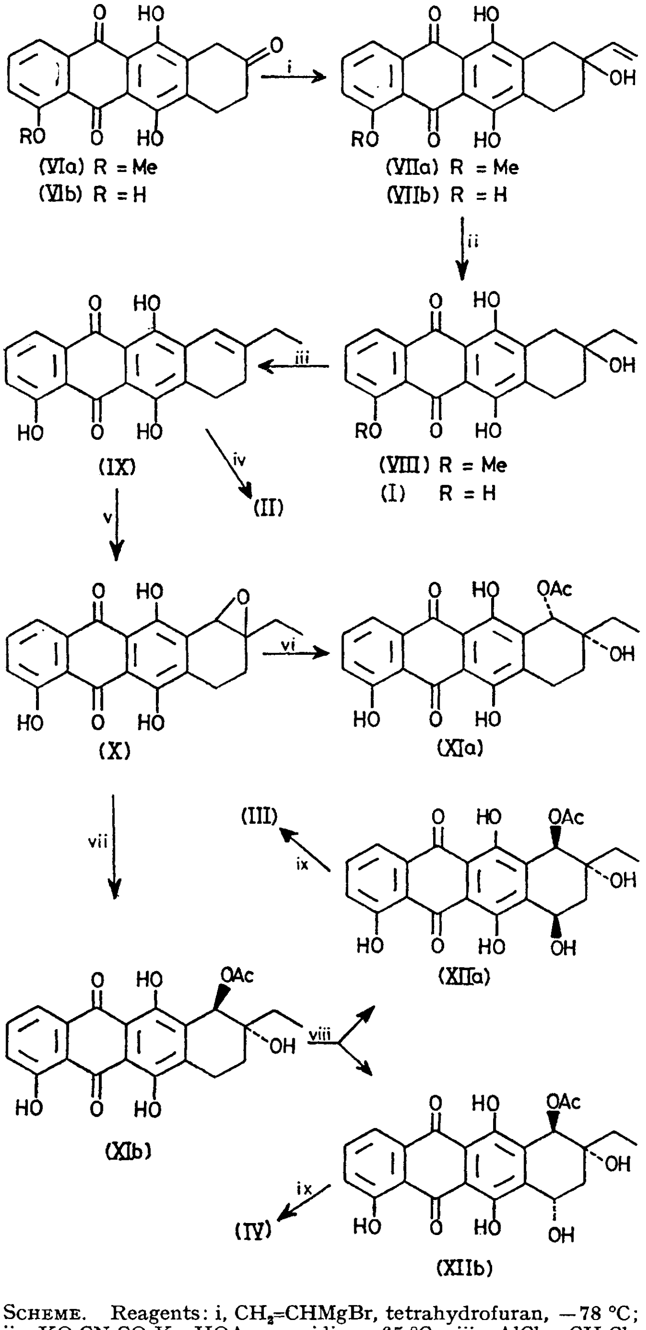


(I)	$R^1 = R^2 = R^3 = H$	10-deoxy-γ-rhodomycinone
(II)	$R^1 = R^2 = H, R^3 = OH$	γ-rhodomycinone
(III)	$R^1 = H, R^2 = R^3 = OH$	α-rhodomycinone
(IV)	$R^1 = R^3 = OH, R^2 = H$	β-rhodomycinone
(V)	$R^1 = OH, R^2 = H, R^3 = CO_2Me$	ε-rhodomycinone

Conversion of 1,4,5-trimethoxyanthraquinone into the crystalline tetracyclic ketone (VIa) in 25% yield over three steps has recently been reported.[5] Demethylation of the ketone (VIa) ($AlCl_3$ in CH_2Cl_2, room temp.) produced the ketone (VIb) (90%, m.p. 263—266 °C). Although the reaction of this ketone with EtMgBr led mainly to enolization, reaction with $CH_2{=}CHMgBr$ was normal, giving the vinyl carbinol (VIIb) (50%), which on di-imide† reduction gave 96% of the red, crystalline (±)-10-deoxy-γ-rhodomycinone (I), m.p. 203—204 °C.‡

Similarly, the ketone (VIa) could be converted by way of the vinyl carbinol (VIIa) (m.p. 205—206 °C) into the alcohol (VIII), m.p. 209—210 °C, in 73% overall yield. Aluminium chloride effected both demethylation and dehydration to give 72% of the olefin (IX), m.p. 180—183 °C, δ ($CDCl_3$) 6·73 (s, 10-H). Stereospecific *trans*-hydroxylation[6] converted (IX) in 70% yield into (±)-γ-rhodomycinone (II), m.p. 254—257 °C (decomp.), spectroscopically identical to the natural material.[7]

Attempts to introduce oxygen at C-7 by homolytic bromination[5] of (II) led to oxidation at C-10. Therefore the olefin (IX) was transformed to the crystalline epoxide (X), m.p. 209—210 °C in 76% yield. Acetic acid at 85 °C cleaved (X) stereospecifically to give predominantly the 10-acetate (XIa) of (±)-epi-γ-rhodomycinone, R_f 0·38,



SCHEME. Reagents: i, $CH_2{=}CHMgBr$, tetrahydrofuran, −78 °C; ii, $KO_2CN_2CO_2K$, HOAc, pyridine, 65 °C; iii, $AlCl_3$, CH_2Cl_2, 25 °C; iv, *o*-sulphobenzoic anhydride, see ref. 6, 30% H_2O_2, acetone, 25 °C; v, *m*-chloroperbenzoic acid, CH_2Cl_2, 25 °C; vi, HOAc, 85 °C; vii, HOAc–NaOAc, 85 °C; viii, Br_2, CCl_4, *hν*, then $AgOCOCF_3$, Me_2SO; ix, 0·5N NaOH, EtOH, room temp.

---

† Hydrogenation of carbinols (VII) over Pd or Pt catalysts gave complex mixtures unsuitable for further transformations.

‡ Mass spectra, t.l.c. properties, and n.m.r. spectra of synthetic (I) were identical to those reported by Brockmann and Niemeyer, see ref. 1.

ν ($CHCl_3$) 1716 cm^{-1}.§ In contrast, a mixture of acetic acid and 2—4% sodium acetate at 85 °C gave both (XIa) and (±)-γ-rhodomycinone-10-acetate (XIb), R_f 0·31, ν ($CHCl_3$) 1738 cm^{-1}, in the ratio 1 : 9.§ The acetate (XIb) was brominated, and the very labile C-7 bromination product was treated with silver trifluoroacetate and then hydrolysed to afford a 1 : 1 mixture of C-7 alcohols (50% yield), readily separable by preparative t.l.c. into (±)-α-rhodomycinone-10-acetate (XIIa), δ ($CDCl_3$) 5·28 (7-H, $\nu_{\frac{1}{2}}$ 16 Hz), and (±)-β-rhodomycinone-10-acetate (XIIb), δ ($CDCl_3$) 5·28 (7-H, $\nu_{\frac{1}{2}}$ 7 Hz). Hydrolysis of (XIIa) and (XIIb) yielded, respectively, (±)-α-rhodomycinone (III) and (±)-β-rhodomycinone (IV), having mass spectrometric and chromatographic properties indistinguishable from the values recorded by Brockmann and Niemeyer.[7]

We thank the National Institutes of Health, U.S.P.H.S., the Hoffmann-La Roche Company, and the Pennwalt Corporation for financial support, and Miss S. Barclay and Mr. J. Schneider for technical assistance.

(*Received, 13th December* 1976; *Com.* 1354.)

---

§ These R_f values refer to 0·5 mm silica gel 60 F-254 t.l.c. plates (Brinkmann), employing 3% MeOH in CH_2Cl_2. The ester C=O shifts may reflect intramolecular H-bonding in the *cis* acetate (XIa), *cf.* H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1957, 1965.

[1] H. Brockmann, *Fortschr. Chem. org. Naturstoffe*, 1963, **21**, 121; H. Brockmann and J. Niemeyer, *Chem. Ber.*, 1967, **100**, 3578.
[2] G. Z. Yakubov, N. O. Blinov, L. N. Sergeeva, O. I. Artamonova, and A. S. Khokhlov, *Antibiotiki*, 1965, **10**, 771.
[3] H. Brockmann and J. Niemeyer, *Chem. Ber.*, 1968, **101**, 1341.
[4] H. Brockmann, J. Niemeyer, and W. Rode, *Chem. Ber.*, 1965, **98**, 3145.
[5] A. S. Kende, Y. Tsay, and J. E. Mills, *J. Amer. Chem. Soc.*, 1976, **98**, 1967.
[6] J. M. Bachhawat and N. K. Mathur, *Tetrahedron Letters*, 1971, 691.
[7] J. Niemeyer, Dissertation, 'Isolierung und Strukturermittlung von Zwölf Neuen Anthracyclinone,' Univ. Göttingen, 1966. We thank Professor Brockmann for providing us with this dissertation and copies of unpublished spectra.