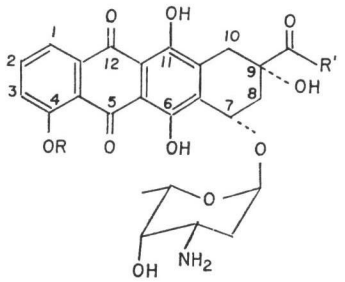
THE SYNTHESIS OF ϵ-RHODOMYCINONE- AND CARMINOMYCIN-11-METHYL ETHERS

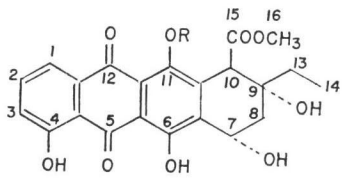
Sir:

In recent years, the anthracycline antibiotics adriamycin (**1a**) and daunomycin (**1b**) have been shown to be clinically effective anti-tumor agents. Carminomycin (**1c**), isolated from *Actinomadura carminata* in the Soviet Union,[1] has a similar antitumor spectrum to adriamycin but with less cardiotoxic potential.[2] Since daunomycin is the 4-methyl ether of carminomycin, we were interested in preparing the 6- and/or 11-methyl ether of carminomycin in order to determine structure-activity relationships in this series.

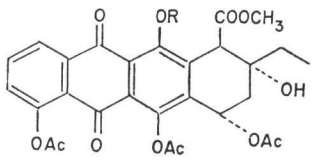
Direct methylation of the phenolic functions of **1c** was expected to give a mixture of products, and in fact the N-trifluoroacetyl derivative of **1c** on methylation with methyl iodide and potassium carbonate gave a complex mixture which was difficult to separate. A similar result was obtained when diazomethane was reacted with ϵ-rhodomycinone (**2a**), an anthracyclinone with the same aromatic oxidation pattern as carminomycin. Attention was therefore directed to the known ϵ-rhodomycinone-4,6,-7,11-tetraacetate[3] (**3a**), and it was found that after 64 hours at 22°C in an acetone-pH 7.5 phosphate buffer mixture (4: 3), hydrolysis of only one of the aromatic acetates occurred. Since the aromatic region of the pmr spectrum of the hydrolysis product was characteristic for a C_4 acetate (Table 1), the product, mp 245~247°C, was either the 4,6,7-triacetate (**3b**) or the isomeric 4,7,11-triacetate. Methylation of this phenol (excess of methyl iodide in dry acetone with a 10% excess of potassium carbonate under reflux for 6.5 hours) afforded a mono-methyl ether (**3c** or its C_6 isomer). Removal of the remaining acetyl groups (5% aqueous sodium bicarbonate-acetone 1: 1 stirred 4 hours at 22°C) gave ϵ-rhodomycinone-11-methyl ether (**2b**), mp 181~183°C. Found: C, 61.42; H, 4.84%. Calcd. for $C_{23}H_{22}O_9 \cdot 0.5H_2O$: C, 61.19; H, 4.84%. That this was the product, and not the isomeric 6-methyl ether, was shown by IR and UV spectral comparisons with other anthraquinones. The in-



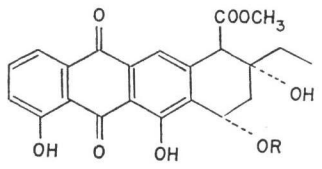
1a, R = CH_3, R' = CH_2OH
1b, R = R' = CH_3
1c, R = H, R' = CH_3



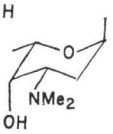
2a, R = H
2b, R = CH_3

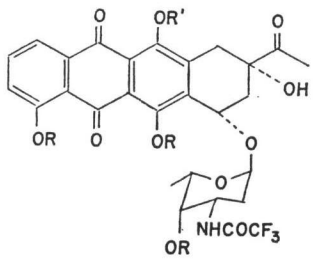


3a, R = Ac
3b, R = H
3c, R = CH_3



4a, R = H
4b, R =





5a, R = R' = H
5b, R = R' = Ac
5c, R = Ac, R' = H

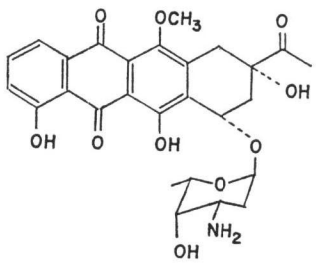


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Table 1. ^{1}H-NMR chemical shifts of selected protons.*

Compound	Position						
	1	2	3	7	10	OCH_3	Phenolic OH
2a	7.76——7.54(m)		7.24(dd)	5.32(s)	4.26(s)		13.05(s) 12.33(s) 11.48(s)
3a	8.07(dd)	7.71(t)	7.36(dd)	6.48(b)	4.22(b)		
3b	8.21(dd)	7.74(t)	7.38(dd)	6.38(b)	4.37(s)		13.50(s)
3c	8.10(dd)	7.72(t)	7.35(dd)	6.44(b)	4.37(s)	3.93(s)	
2b	7.80——7.53(m)		7.18(dd)	5.33(b)	4.20(s)	3.80(s)	13.06(s) 11.73(s)
5a	7.83——7.60(m)		7.24(dd)	5.16(s)	3.07(AB)		13.03(s) 12.48(s) 11.60(b)
5b	8.12(dd)	7.76(t)	7.41(dd)	5.20(b)	3.12(b)		
5c	8.20(dd)	7.74(t)	7.38(dd)	5.16(b)	3.17(AB)		13.20(s)
6	7.90——7.60(m)		7.26(dd)	5.30(b)	3.21(AB)	3.91(s)	not observed

* All spectra were recorded at 100 MHz in $CDCl_3$ and chemical shifts are reported in ppm from tetramethylsilane as internal standard. s=singlet, t=triplet, dd=doublet of doublets, AB=AB quartet, b=broad signal, m=multiplet.

Table 2. ^{13}C-NMR chemical shifts.*

Carbon No.	**2a** (in DMSO-d_6)	**2b** (in $CDCl_3$)	Carbon No.	**2a** (in DMSO-D_6)	**2b** (in $CDCl_3$)
1	119.5	119.7	10	51.8	52.3
2	137.7	137.2	10a	132.9	135.0
3	125.0	123.5	11	156.7	157.8
4	162.1	161.7	11a	111.0	122.0
4a	115.8	115.0	12	185.9	180.0
5	190.1	191.9	12a	139.3	140.3
5a	110.9	113.9	13	32.7	32.5
6	156.6	153.4	14	7.1	6.8
6a	134.7	134.3	15	171.3	171.2
7	61.2	62.4	16	52.6	52.2
8	35.0	34.0	OCH_3	—	61.3
9	71.5	71.4			

* In ppm downfield from tetramethylsilane; assignments were based on comparison with known compounds such as those described by DOYLE *et al.*[7]

frared spectra of **2b** (both as KBr disc and in chloroform solution) showed absorptions for both non-bonded (1670 cm^{-1}) and hydrogen-bonded (1620 cm^{-1}) quinone carbonyl groups which is typical of a 1,8-dihydroxyanthraquinone and not that expected for a 1,5-dihydroxyanthraquinone (which would show only a single carbonyl absorption).[4] Similarly, aklavinone (**4a**) gives absorption bands at 1674 and 1623 cm^{-1},[5] while ε-rhodomycinone (**2a**) shows only bonded quinone absorption at 1615 cm^{-1}. The UV-visible spectrum of **2b** was also very similar to that of the 1,8-dihydroxyanthraquinone aklavin (**4b**), showing a single absorption maximum in the visible region at 448 nm which moved to 525 nm on addition of sodium hydroxide. Finally, the quinone carbonyl resonances in the ^{13}C nmr spectrum of **2b** were at 191.9 and 180.0 ppm (Table 2) indicating that one of these carbonyls is bis-hydrogen bonded (the downfield one) and the other is non-bonded.[6]

A similar sequence of reactions was then carried out on N-trifluoroacetyl carminomycin (**5a**, prepared from **1c** and trifluoroacetic anhyd-

ride in dichloromethane at 22°C followed by chromatography over silica gel using ethyl acetate). Acetylation (with an excess of pyridine-acetic anhydride 1:1 for 2.5 hours at 22°C followed by addition to water) gave the 4,6,11,4′-tetraacetate (**5b**) as an off-white solid of mp 214~266°C. Found: C, 54.58; H, 4.54; N, 1.91%. Calcd. for $C_{36}H_{34}F_3NO_{15}\cdot H_2O$: C, 54.34; H, 4.56; N, 1.76%. Hydrolysis of **5b** (acetone-5% aqueous sodium bicarbonate, 3:5 for 1.5 hours at 22°C followed by acidification and extraction into chloroform) provided the 4,6,4′-triacetate (**5c**) as an orange solid of mp 245~247°C. Found: C, 55.51; H, 4.39; N, 1.90%. Calcd. for $C_{34}H_{32}F_3NO_{14}$: C, 55.59; H, 4.45; N, 1.99%.

Methylation of **5c** (anhydrous potassium carbonate in acetone at reflux with an excess of methyl iodide added at 0.5, 3, 6 and 10 hours, with a reflux period of 16 hours following the final addition) gave a methyl ether which was not purified. It was hydrolysed (tetrahydrofuran −0.1 N sodium hydroxide 2:5 for 1 hour at 22°C) and the product was purified by HPLC on C_{18}/Porasil B using methanol −0.1 M sodium acetate buffered to pH 4.0 (55:45) as the liquid phase. This provided **6** as a red solid of mp 185~186°C (from ether). Found: C, 60.26; H, 5.93; N, 2.39%. Calcd. for $C_{27}H_{29}NO_{10}\cdot 0.5H_2O$: C, 60.44; H, 5.64; N, 2.61%. The infrared absorption spectrum of **6** was similar to those of **2b** and **4a**, showing maxima due to both hydrogen-bonded and nonbonded quinone carbonyl groups. The UV-visible spectrum of **6** was very similar to those of **2b** and **4b**, confirming that it was the 11-methyl ether as shown. When tested against L-1210 leukemic mice, **6** had a maximum T/C value of 136 at 16 mg/kg whereas carminomycin (**1c**, used as the control) had a value of 157 at 0.8 mg/kg. A more detailed comparison between **1c** and **6** both *in vitro* and *in vivo* will be the subject of a further communication.

Summary

The conversion of ε-rhodomycinone to its 11-methyl ether *via* selective hydrolysis of the 4,6,7,11-tetraacetate is described. This series of reactions was used as a model for the conversion of carminomycin to its 11-methyl ether. The anti-tumor activity of the latter compound was less than that of both carminomycin and its 4-methyl ether (daunomycin).

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References

1) GAUZE, G. F.; M. A. SVESHNIKOVA, R. S. UKHOLINA, G. V. GAVRILINA, V. A. FILICHEVA & E. G. GLADKIKH: Production of antitumor antibiotic carminomycin by *Actinomadura carminata* sp. nov. Antibiotiki 18: 675~678, 1973
2) CROOKE, S. T.: A review of carminomycin, a new anthracycline developed in the USSR. J. Medicine 8: 295~316, 1977
3) BROCKMANN, H. & H. BROCKMANN, Jr.: ε-Rhodomycinon. Chem. Ber. 94: 2681~2694, 1961
4) BLOOM, H.; L. H. BRIGGS & B. CLEVERLEY: Physical properties of anthraquinones and its derivatives. 1. Infrared spectra. J. Chem. Soc. 1959: 178~185, 1959
5) GORDON, J. J.; L. M. JACKMAN, W. D. OLLIS & I. O. SUTHERLAND: Aklavinone. Tetrahed. Lett. 1960: 28~34, 1960
6) COX, R. H.; F. CHURCHILL, R. J. COLE & J. W. DORNER: Carbon-13 nuclear magnetic resonance studies of the structure and biosynthesis of versiconal acetate. J. Am. Chem. Soc. 99: 3159~3161, 1977
7) DOYLE, T. W.; D. E. NETTLETON, R. E. GRULICH, D. M. BALITZ, D. L. JOHNSON & A. L. VULCANO: Antitumor agents from the bohemic acid complex. (submitted to J. Am. Chem. Soc.)