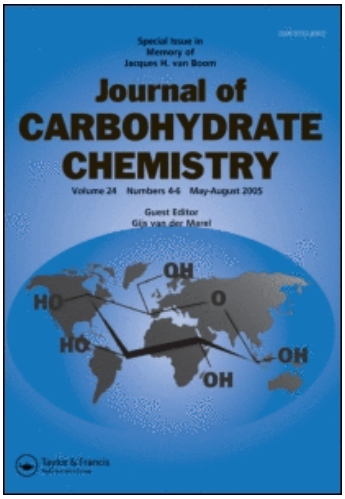

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SYNTHESIS AND STRUCTURE ELUCIDATION OF p-METHOXYBENZOYL DERIVATIVES OF RHODOMYCINS[1]

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ABSTRACT

It was determined that ß-rhodomycin-II (rhodomycin A) (**1**), ß-rhodomycin-I (rhodomycin B, betaclamycin T) (**2**) and γ-rhodomycin-I (iremycin) (**3**) may regioselectively be acylated at OH-4' of the sugar (rhodosamine) moiety(ies), using a two-phase (chloroform/water) solvent system and sodium bicarbonate as a base. This report exemplarily describes the synthesis of the corresponding p-methoxybenzoate esters of **1**, **2**, and **3**, i. e. derivatives **4-7**, and highlights the structure elucidation of isomers **5a** and **5b**.

INTRODUCTION

Anthracycline antibiotics play a major role in the effective treatment of a number of neoplastic diseases and present one of the most investigated classes of antitumor agents.[2] Of all chemotherapeutic agents used today, doxorubicin (adriamycin) has the widest spectrum of antitumor activity. It is used with a high degree of efficacy in many human cancers and is probably the most utilized antitumor drug world-wide.[3] However, the clinical use of doxorubicin is restricted due to its cumulative dose-limiting

cardiotoxicity. Moreover, the clinical efficacy of adriamycin is limited by the emergence of tumor-drug resistance, resulting in significant treatment failure.[4] Therefore, there is a pressing need to provide new anthracycline derivatives which show no cross-resistance to adriamycin and are distinguished by a new spectrum of action and lower toxicity. The discovery of new cancer therapeutic agents with curative potential for slowly proliferating solid tumors is of especially high priority.[5]

In order to gain access to new anthracycline compounds, we have concentrated on the derivatization of rhodomycins, a class of anthracyclines first described by Brockmann and co-workers (for an early review see Brockmann[6]). A number of rhodomycin-type anthracyclines have since been discovered and evaluated with respect to a certain structure-activity relationship (for a review see Oki[2]). However, to our knowledge, only one such rhodomycin-type drug, called rodorubicin, has thus far entered clinical trials.[7]

We have primarily focused on ß-rhodomycin-II (**1**)[8], formerly termed rhodomycin A[9], as drug of choice. **1** can readily be converted into ß-rhodomycin-I (**2**)[8] and γ-rhodomycin-I (**3**)[8] by acid hydrolysis and hydrogenolysis, respectively, and their structure-activity relationship has recently been discussed.[10] We have found that all three drugs, **1**, **2**, and **3**, can most readily and regioselectively be acylated at OH-4' of the sugar (rhodosamine) moiety(ies), leaving the OH-groups of the aglycones, ß-rhodomycinone (ß-RMN) and γ-rhodomycinone (γ-RMN), respectively, unaffected.[11]

Here we report on the synthesis and structure elucidation of the corresponding 4'-O-(p-methoxybenzoyl) derivatives.

RESULTS AND DISCUSSION

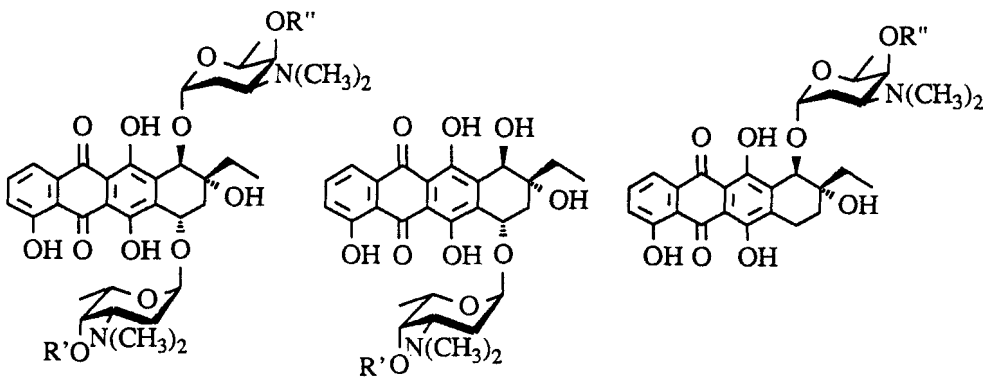
ß-rhodomycin-II (**1**) has turned out to be an interesting key compound as it can readily be converted:

a) by acid hydrolysis[8] into 7-*O*-α-L-rhodosaminyl-ß-rhodomycinone (7-RN-ß-RMN) (**2**) [also known as rhodomycin B,[12] ß-rhodomycin-I[8] or betaclamycin T[13]] or into the corresponding aglycone, ß-rhodomycinone (ß-RMN)[14];
or b) by hydrogenolysis[8] into 10-*O*-α-L-rhodosaminyl-γ-rhodomycinone (10-RN-γ-RMN) (**3**), [also termed γ-rhodomycin-I[8] or iremycin[15]].

Ihn et al.[15] reported that iremycin (**3**), by treatment with acetic anhydride in pyridine, could be converted into the corresponding tetraacetate. To our knowledge, no efforts have thus far been undertaken with respect to the regioselective *O*-acylation of these drugs.

We have found that **1**, **2**, and **3** may regioselectively be acylated at OH-4' of the

sugar (rhodosamine) moiety(ies), using a two-phase (chloroform/water) solvent system and sodium bicarbonate as a base.[11]



1	5a	5b	4	2	7	3	6	(compd.) / residue
H	H	pMBz	pMBz	-	-	H	pMBz	R"
H	pMBz	H	pMBz	H	pMBz	-	-	R'

Under these conditions reaction of **1** with, for example, p-methoxybenzoyl chloride (2.2 equiv.) yielded the disubstituted derivative **4** in good yield. Reaction with 1 equiv. of p-methoxybenzoyl chloride provided, along with disubstituted derivative **4** as well as residual starting compound **1**, the corresponding monosubstituted derivatives **5a** and **5b** in a molar ratio of about 2:3, deduced from ^{1}H NMR data. Both isomers were separated by column chromatography on silica gel, and their structures unequivocally assigned by hydrogenolytic conversion to the corresponding γ-rhodomycinone derivatives **3** and **6**, respectively. **6** was alternatively synthesized from **1** via hydrogenolysis[8] and subsequent p-methoxybenzoylation, thus allowing confirmation of the structure of isomer **5b**. The structure of isomer **5a** was independently confirmed via acid hydrolysis of **5a**, leading to derivative **7**, which could alternatively be synthesized from **2**. Efforts to directly convert the disubstituted derivative **4** into **7** by way of acid hydrolysis were unsuccessful, and similarly **5b** could not be hydrolyzed to compound **2**.[16] Thus it was obvious that p-methoxybenzoylation of the rhodosamine unit strongly stabilized the glycosidic bond. On the other hand, p-methoxybenzoylation of the rhodosamine unit attached to *C-10* of the aglycone did not prevent hydrogenolysis to the corresponding γ-rhodomycinone derivative. Thus both **4** and **5b** could be converted into **6**, although only at low yield.

Table 1. ^{1}H NMR Data of Selected Protons of the Rhodosamine Units of 1-7

compound no.	protons							
	H-1'	H-1"	H-4'	H-4"	H-5'	H-5"	H-6'	H-6"
1	5.48	5.45	3.68	3.68	4.06	3.90	1.30	1.36
2	5.51	-	3.70	-	4.07	-	1.41	-
3	-	5.41	-	3.70	-	3.95	-	1.36
4	5.65	5.65	5.48	5.46	4.25	4.11	1.21	1.16
5a	5.64	5.46	5.48	3.64	4.25	3.92	1.21	1.35
5b	5.50	5.64	3.70	5.45	4.05	4.11	1.40	1.16
6	-	5.58	-	5.49	-	4.16	-	1.18
7	5.67	-	5.50	-	4.28	-	1.22	-

All ^{1}H NMR data are in agreement with the proposed structures. Phenolic OH-groups of the aglycone were assigned according to Vigevani et al..[17]

As can be seen from selected ^{1}H NMR data of compounds **1-7** (Table 1), the introduction of a p-methoxybenzoyl group at OH-4' or OH-4" of the rhodosamine unit resulted in downfield shifts of 0.15-0.2 ppm for H-1' or H-1", of ca. 1.8 ppm for H-4' and H-4", of ca. 0.2 ppm for H-5' or H-5", and in upfield shifts of ca. 0.18 ppm for H-6' or H-6".[18]

From the optical rotation data of compounds **1-7**, summarized in Table 2, it can be seen that introduction of a p-methoxybenzoyl group into the rhodomycin molecules resulted in a large decrease of the $[\alpha]_D^{25}$ values by approximately 250 -350°, while introduction of a rhodosamine unit increased the $[\alpha]_D^{25}$ values by approximately 100 - 200°.

The R_F values of compounds **1-7**, detected in four different solvent systems (Table 3), are also summarized in Table 2. As may be expected, the introduction of a p-methoxybenzoyl group into the rhodomycins **1**, **2**, and **3** dramatically increases the R_F

TABLE 2. R_F and $[\alpha]_D^{25}$ Values of Compounds 1-7

	R_F values				$[\alpha]_D^{25}$
	solvent systems			$CHCl_3/CH_3OH$	
	A	B	C	(3/1)	
1	0.29	0.01	0.13	0.12	+453°
2	0.55	0.12	0.37	0.33	+283°
3	0.58	0.12	0.39	0.31	+260°
4	0.88	0.45	0.79	0.99	-76°
5a	0.70	0.13	0.49	0.60	+79°
5b	0.61	0.12	0.39	0.49	+154°
6	0.88	0.47	0.79	0.97	-52°
7	0.88	0.42	0.79	0.97	-17°

TABLE 3. Solvent Systems Used for TLC Assays

solvent system composition (%) (v/v)	**A**	**B**	**C**
Chloroform	70	89	77
Methanol	18	7.4	14
Acetic acid	8.5	3	7
Water	3.5	0.6	2

values, concomitant with an increase in the lipophilicity of the compounds. As various factors such as lipophilicity,[19,20] DNA-binding [19] and molecular size[21] of anthracyclines may influence their cytotoxicity, rhodomycins **1-7** may be useful for the establishment of a certain structure-activity relationship. It has been reported that the rhodosamine moiety at *C-7* is important to antimicrobial and antitumor activity. Thus **3**, in contrast to **2**, proved inactive in various test systems, whereas **1** was of moderate activity.[10]

Our newly synthesized p-methoxybenzoyl derivatives, along with other *O*-acyl analogues,[11] may prove useful as inhibitors of tumor growth in vitro and in vivo.

EXPERIMENTAL

General Procedures. Melting points were determined with a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz or 400 MHz with a Bruker AC-300 or a Bruker AM-400 NMR spectrometer, respectively, using deuterated chloroform as solvent and tetramethylsilane as internal standard.[18] Reactions were monitored by thin layer chromatography on silica gel 60 plates F 254 (Merck), and spots were determined by their inherent color or by ultraviolet light. Preparative chromatography was performed on silica gel 60 (Merck, 0.040-0.063 mm).

After column chromatography the fractions containing the desired product(s) were neutralized by the addition of a saturated aqueous solution of sodium bicarbonate, and the products were extracted with chloroform, thus providing the anthracyclines as free base, each. Evaporations were conducted *in vacuo*. Specific rotations were determined with a Perkin Elmer Polarimeter-241 in concentrated acetic acid as solvent of choice. Hydrogenations were performed in the presence of 10% palladium on charcoal (Riedel-de Haen). Celite 545, used as filter aid, was from Roth.

7,10-Di-*O*-(4-*O*-p-Methoxybenzoyl-α-L-rhodosaminyl)-ß-rhodomycinone (4). To a stirred solution of ß-rhodomycin-II (**1**) (700 mg, 1.0 mmol) in a mixture of chloroform (500 mL) and aqueous saturated sodium bicarbonate (50 mL), a solution of p-methoxybenzoyl chloride (4-anisoyl chloride) (380 mg, 2.23 mmol) in chloroform (50 mL) was added, and the mixture was stirred at room temperature in the dark for 16 h. The organic phase was then separated off and concentrated to dryness. The crude product was purified by column chromatography (solvent system B) to give, after neutralization by sodium bicarbonate and extraction into chloroform, 824 mg (85%) of compound **4** as an amorphous solid: mp 174-176 °C, $[\alpha]_D^{25}$ -76° (c 0.1, acetic acid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, 3H, $J_{Me,H-13}$ = 7.2 Hz, Me-14), 1.16 (d, 3H, $J_{5",Me-6"}$ = 6.5 Hz, Me-6"), 1.21 (d, 3H, $J_{5',Me-6'}$ = 6.5 Hz, Me-6'), 2.21 (s, 12H, $(NMe_2)_2$), 2.53 (bd, 1H, $J_{2',3'}$ = 12 Hz, H-3'), 2.68 (bd, 1H, $J_{2",3"}$ = 12 Hz, H-3"), 3.86 and 3.87 (s, 3H, OMe, each), 3.70 (s, 1H, OH-9), 4.11 (q, 1H, $J_{5",Me-6"}$= 6.5 Hz, H-5"), 4.25 (q, 1H, $J_{5',Me-6'}$= 6.5 Hz, H-5'), 5.46 (bs, 1H, H-4"), 5.48 (bs, 1H, H-4'), 5.06 (s, 1H, H-10), 5.22 (m, 1H, H-7), 5.65 (bs, 2H, H-1', H-1"), 6.91 and 6.93 (d, 2H, $J_{a,b}$ = 9 Hz, Ph-b, each), 7.33 (dd, 1H, $J_{1,3}$= 1 Hz, $J_{2,3}$ = 8 Hz, H-3), 7.73 (t, 1H, $J_{1,2}$= $J_{2,3}$ = 8 Hz, H-2), 7.92 (dd, 1H, $J_{1,2}$ = 8 Hz, $J_{1,3}$= 1 Hz, H-1), 8.03 and 8.05 (d, 2H, $J_{a,b}$ = 9 Hz, Ph-a, each), 12.16 (bs, 1H, OH-4), 12.94 (bs, 1H, OH-6), 13.97 (bs, 1H, OH-11).

7-*O*-(4-*O*-p-Methoxybenzoyl-α-L-rhodosaminyl)--10-*O*-α-L-rhodosaminyl-ß-rhodomycinone (5a) and **10-*O*-(4-*O*-p-Methoxybenzoyl-α-L-rhodosaminyl)-7-*O*-α-L-rhodosaminyl-ß-rhodomycinone (5b).** ß-Rhodomycin-II (**1**) (210 mg, 0.30 mmol) and 1

equiv. of 4-anisoyl chloride (51 mg, 0.30 mmol) were brought to reaction and worked up as described for the preparation of **4**. The product mixture was first separated by column chromatography, using a mixture of toluene/methanol (3:1) as solvent system, which separated disubstituted derivative **4**, 117 mg (47%) yield, from the isomeric mixture of **5a** and **5b**. The mixture was separated by repeated column chromatography using solvent mixture B as mobile phase, yielding **5a** and **5b** each as an amorphous mass. **5a**: mp 169-172 °C; $[\alpha]_D^{25}$ +79° (c 0.1, acetic acid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3H, $J_{Me,H-13}$ = 7.3 Hz, Me-14), 1.21 (d, 3H, $J_{5',Me-6'}$= 6.5 Hz, Me-6'), 1.35 (d, 3H, $J_{5'',Me-6''}$= 6.6 Hz, Me-6"), 2.20 (s, 12H, $(NMe_2)_2$), 2.56 (bd, 1H, $J_{2',3'}$= 12 Hz, H-3'), 3.64 (bs, 2H, OH-9 and H-4"), 3.87 (s, 3H, OMe), 3.92 (q, 1H, $J_{5'',Me-6''}$= 6.5 Hz, H-5"), 4.25 (q, 1H, $J_{5',Me-6'}$= 6.5 Hz, H-5'), 5.03 (s, 1H, H-10), 5.20 (m, 1H, H-7), 5.46 (bd, 1H, $J_{1'',2''}$= 3 Hz, H-1"), 5.48 (bs, 1H, H-4'), 5.64 (bd, 1H, $J_{1',2'}$ = 3 Hz, H-1'), 6.93 (d, 2H, $J_{a,b}$ = 8.8 Hz, Ph-b), 7.32 (d, 1H, $J_{2,3}$ = 8 Hz, H-3), 7.72 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 8 Hz, H-2), 7.91 (d, 1H, $J_{1,2}$= 8 Hz, H-1), 8.05 (d, 2H, $J_{a,b}$ = 8.8 Hz, Ph-a), 12.16 (bs, 1H, OH-4), 12.90 (bs, 1H, OH-6), 13.72 (bs, 1H, OH-11).

5b: mp 175-178 °C; $[\alpha]_D^{25}$ +154° (c 0.1, acetic acid); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, $J_{Me,H-13}$ = 7.4 Hz, Me-14), 1.16 (d, 3H, $J_{5'',Me-6''}$= 6.5 Hz, Me-6"), 1.40 (d, 3H, $J_{5',Me-6'}$ = 6.5 Hz, Me-6'), 2.20 and 2.22 (s, 6H, NMe_2, each), 2.68 (bd, 1H, $J_{2'',3''}$= 12 Hz, H-3"), 3.70 (bs, 2H, OH-9 and H-4'), 3.85 (s, 3H, OMe), 4.05 (q, 1H, $J_{5',Me-6'}$ = 6.5 Hz, H-5'), 4.11 (q, 1H, $J_{5'',Me-6''}$= 6.5 Hz, H-5"), 5.05 (s, 1H, H-10), 5.17 (m, 1H, H-7), 5.45 (bs, 1H, H-4"), 5.50 (bs, 1H, H-1'), 5.64 (bd, 1H, $J_{1'',2''}$ = 3 Hz, H-1"), 6.91 (d, 2H, $J_{a,b}$ = 9 Hz, Ph-b), 7.32 (dd, 1H, $J_{1,3}$ = 1.1 Hz, $J_{2,3}$ = 8 Hz, H-3), 7.72 (t, 1H, $J_{1,2}$= $J_{2,3}$= 8 Hz, H-2), 7.91 (dd, 1H, $J_{1,2}$ = 7.5 Hz, $J_{1,3}$= 1.1 Hz, H-1), 8.03 (d, 2H, $J_{a,b}$= 9 Hz, Ph-a), 12.15 (bs, 1H, OH-4), 12.89 (bs, 1H, OH-6), 13.79 (bs, 1H, OH-11).

10-*O*-(4-*O*-p-Methoxybenzoyl-α-L-rhodosaminyl)-γ-rhodomycinone (6).

a) Preparation of 6 from 3. Iremycin (**3**) (100 mg, 0.19 mmol) and 4-anisoyl chloride (33 mg, 0.19 mmol) were reacted and worked up as described for compound **4**. Purification by column chromatography over silica gel, using solvent system B, gave compound **6** as an amorphous solid in 89% yield (113 mg): mp 144-146 °C, $[\alpha]_D^{25}$ -52 ° (c 0.1, acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, 3H, $J_{Me,H-13}$ = 7.5 Hz, Me-14), 1.18 (d, 3H, $J_{5'',Me-6''}$= 6.5 Hz, Me-6"), 2.23 (s, 6H, NMe_2), 2.74 (bd, 1H, $J_{2'',3''}$= 12 Hz, H-3"), 3.86 (s, 3H, OMe), 4.16 (q, 1H, $J_{5'',6''}$ = 6 Hz, H-5"), 5.02 (s, 1H, H-10), 5.49 (bs, 1H, H-4"), 5.58 (bd, 1H, $J_{1'',2''}$= 3 Hz, H-1"), 6.91 (d, 2H, $J_{a,b}$ = 9 Hz, Ph-b), 7.31 (dd, 1H, $J_{1,3}$= 1 Hz, $J_{2,3}$ = 8.5 Hz, H-3), 7.70 (t, 1H, $J_{1,2}$ = $J_{2,3}$= 8.5 Hz, H-2), 7.90 (dd, 1H, $J_{1,2}$ = 8.5 Hz, $J_{1,3}$= 1 Hz, H-1), 8.04 (d, 2H, $J_{a,b}$= 9 Hz, Ph-a), 12.24 (bs, 1H, OH-4), 12.75 (bs, 1H, OH-6), 13.93 (bs, 1H, OH-11).

b) Preparation of 6 from 4. A solution of compound **4** (48 mg, 0.05 mmol) in acetic acid (50 mL) was hydrogenated in the presence of palladium on charcoal (48 mg) for 1 h. The mixture was then filtered over celite and the solvent evaporated. The residue was partitioned between chloroform and an aqueous solution of trisodium phosphate (20%, w/v). The product was extracted with chloroform and purified by column chromatography over silica gel in solvent system B, providing compound **6** as an amorphous solid in 18% yield (6 mg).

c) Preparation of 6 from 5b. A solution of isomer **5b** (25 mg, 0.03 mmol) in acetic acid (30 mL) was hydrogenated in the presence of palladium on charcoal (25 mg) for 1 h. The mixture was worked up and repeatedly chromatographed in solvent system B, yielding 11 mg (55%) of compound **6**.

7-*O*-(4-*O*-p-Methoxybenzoyl-α-L-rhodosaminyl)-ß-rhodomycinone (7).

a) Preparation of 7 from 2. ß-Rhodomycin-I (**2**) (40 mg, 0.07 mmol) and 1 equiv. of anisoyl chloride (12 mg, 0.07 mmol) were reacted and worked up as described for compound **4**. Purification by column chromatography over silica gel, using solvent system B, gave compound **7** as an amorphous solid in 86% yield (41 mg): mp 169-171 °C, $[\alpha]_D^{25}$ -17° (c 0.1, acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t,3H, $J_{Me,H-13}$ = 7.4 Hz, Me-14), 1.22 (d, 1H, $J_{5',Me-6'}$= 6.5 Hz, Me-6'), 2.21 (s, 6H, NMe_2), 2.47 (bd, 1H, $J_{2',3'}$ = 12 Hz, H-3'), 3.87 (s, 3H, OMe), 4.08 (s, 1H, OH-9), 4.28 (q, 1H, $J_{5',Me-6'}$= 7 Hz, H-5'), 4.93 (s, 1H, H-10), 5.19 (m, 1H, H-7), 5.50 (bs, 1H, H-4'), 5.67 (bd, 1H, H-1'), 6.94 (d, 2H, $J_{a,b}$ = 9 Hz, Ph-b), 7.34 (dd, 1H, $J_{1,3}$= 1 Hz, $J_{2,3}$= 8.4 Hz, H-3), 7.73 (t, 1H, $J_{1,2}$= $J_{2,3}$= 8.4 Hz, H-2), 7.90 (dd, 1H, $J_{1,3}$= 1 Hz, $J_{2,3}$= 8.4 Hz, H-1), 8.06 (d, 2H, $J_{a,b}$= 9 Hz, Ph-a).

b) Preparation of 7 from 5a. A solution of compound **5a** (15 mg = 0.018 mmol) in dichloromethane (1.5 mL) was acidified by the addition of trifluoroacetic acid (15 µL) and stirred for 65 h in the dark. The acid was then neutralized by the addition of a saturated aqueous solution of sodium bicarbonate, and the aqueous phase was repeatedly extracted with dichloromethane. The product was purified by column chromatography over silica gel, using solvent system B, yielding 9 mg (74 %) of **7** as an amorphous solid.

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