SEMISYNTHETIC COUMERMYCINS. II

PREPARATION AND PROPERTIES OF 3-(SUBSTITUTED BENZAMIDO)-4-HYDROXY-8-METHYL-7-[3-O-(5-METHYL-2-PYRROLYLCARBONYL)NOVIOSYLOXY]COUMARINS

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A series of 29 derivatives was obtained from the ditetrahydropyranyl ether of coumermycin A_1 by treatment with 3- and 3,5-substituted 4-acetoxy and 4-methoxy benzoyl chlorides. Many of the required acids were hitherto unknown and three were obtained from novobiocin by published procedures. Although all of the semisynthetic coumermycins so obtained were potent antibiotics, they showed significant differences in activity depending on the nature of the substituents in the benzamido portion of the molecules.

Coumermycin A_1 is an antibiotic first isolated by KAWAGUCHI *et al.*[8]; its structure was elucidated independently by KAWAGUCHI *et al.*[9] and by BERGER *et al.*[2] who also reported a total synthesis.

With a view toward compounds related to both coumermycin and novobiocin[13] we synthesized compounds I (Fig. 1) from 3-(substituted benzamido)-4-benzyloxy-7-hydroxy-8-methylcoumarin (II, Fig. 2) N-acylated with the appropriate acyl chloride *via* reaction with 2-acetoxy-3-O-(5-methyl-2-pyrrolylcarbonyl)-4-O-methyl-5,5-dimethyl-L-lyxosyl chloride (IIIb, Fig. 3) by a method analogous to the glycoside synthesis described by VATERLAUS *et al.*[15]. When compound Ia (Fig. 1) was found to possess biological properties similar to novobiocin, and a practical

Fig. 1

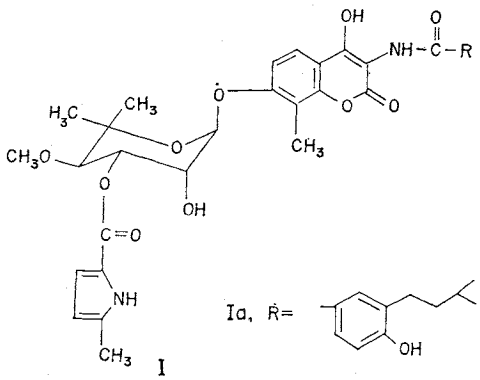


Fig. 2

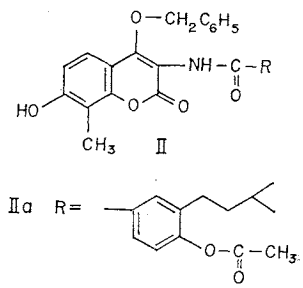


Fig. 3

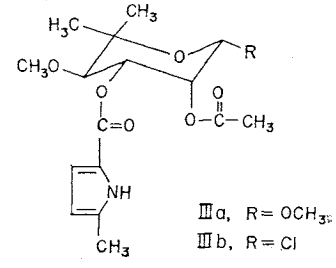
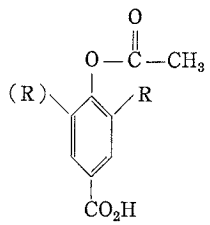
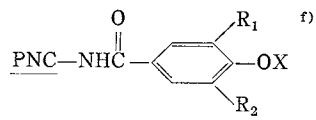


Table 1. Precursor acids for coumermycin derivatives



R	Method	m. p. ℃	Formula	Calculated		Found	
				% C	% H	% C	% H
CH_3	C	152~153	$C_{10}H_{10}O_4$	61.85	5.19	61.88	5.26
$CH_2CH=CH_2$	B	117~119	$C_{12}H_{12}O_4$	65.44	5.49	65.09	5.39
i-C_3H_7	C	155	$C_{12}H_{14}O_4$	64.85	6.35	64.93	6.28
n-C_4H_9	A	115	$C_{13}H_{16}O_4$	66.08	6.83	66.19	6.53
$CH(CH_3)CH=CH_2$	B	137~138	$C_{13}H_{14}O_4$	66.65	6.02	66.59	6.08
$CH=C(CH_3)_2$	B	139~140	$C_{13}H_{14}O_4$	66.65	6.02	66.38	6.13
t-C_4H_9	C	182~183	$C_{13}H_{16}O_4$	66.08	6.83	65.85	6.66
$COCH_2CH_2CH_3$	A	113	$C_{13}H_{14}O_5$	62.39	5.64	62.27	5.77
$C(CH_3)=C(CH_3)_2$	B	153~155	$C_{14}H_{16}O_4$	67.73	6.50	67.50	6.86
n-C_6H_{13}	A	105	$C_{15}H_{20}O_4$	68.16	7.63	68.51	7.43
cyclohexyl	C	212~214	$C_{15}H_{18}O_4$	68.65	6.92	68.72	6.83
3,5-dimethyl	C	192~195	$C_{11}H_{12}O_4$	63.45	5.81	63.43	5.83
3,5-diallyl	B	138	$C_{15}H_{16}O_4$	69.21	6.20	69.40	6.45
3,5-diisopropyl	C	201~203	$C_{15}H_{20}O_4$	68.16	7.63	68.00	7.72
$CH(C_6H_5)CH=CH_2$	B	122~128	$C_{15}H_{16}O_4$	72.06	5.44	72.65	5.20

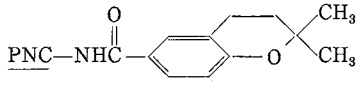
Table 2. Semisynthetic coumermycin derivatives [e]



Compound No.	R_1	R_2	X	Dec. pt. ℃	Calc.		Found	
					C	H	C	H
1	H	CH_3	$COCH_3$	204	61.44	5.46	61.80	5.83
2	H	CH_3	H	170	61.73	5.50	61.42	5.52
3	H	$CH_2CH=CH_2$	H	191	62.96	5.59	63.18	5.90
4	H	$CH_2CH=CH_2$	CH_2	119	63.43	5.78	63.48	5.60
5	H	n-C_3H_7 [c]	CH_3	133	63.24	6.07	63.99	6.55
6	H	n-C_3H_7 [c]	H	157	62.76	5.89	62.88	6.53
7	H	i-C_3H_7	H	169	62.76	5.89	62.52	5.76
8	H	n-C_4H_9	H	156	63.24	6.07	62.99	5.75
9	H	$CH(CH_3)CH=CH_2$	H	129	63.43	5.78	63.37	6.01
10	H	$CH(CH_3)CH_2CH_3$ [c]	H	182	63.24	6.07	63.52	6.36
11	H	$CH=C(CH_3)_2$	H	170	63.43	5.78	63.18	6.13
12	H	$CH_2CH(CH_3)_2$ [c]	H	127	63.24	6.07	63.05	6.37
13 [a]	H	t-C_4H_9	H	186	62.39	6.13	62.14	6.17

(to be continued)

Table 2. (continued)

Compound No.	R_1	R_2	X	Dec. pt. °C	Calc. C	Calc. H	Found C	Found H
14	H	$COCH_2CH_2CH_3$	H	125	61.94	5.64	61.97	6.05
15 [a]	H	n-C_5H_{11}	H	180	62.86	6.30	62.60	5.95
16	H	$C(CH_3)=C(CH_3)_2$	H	158	63.90	5.96	63.85	6.21
17 [a]	H	$CH(CH_3)CH(CH_3)_2$ [c]	H	165	62.86	6.30	62.88	6.40
18 [a]	H	$CH_2CH=C(CH_3)_2$ [d]	$COCH_3$	137	62.71	5.96	62.82	6.06
19 [a]	H	$CH_2CH=C(CH_3)_2$ [d]	H	139	63.05	6.03	63.35	5.74
20 [a]	H	$CH_2CH_2CH(CH_3)_2$ [d]	H	178	62.87	6.30	63.01	6.25
21 [a]	H	n-C_6H_{13}	H	154	63.32	6.46	63.25	6.41
22 [a]	H	cyclohexyl	H	210	63.50	6.19	63.68	7.14
23	CH_3	CH_3	H	198	62.26	5.70	62.43	5.76
24 [a]	$CH_2CH=CH_2$	$CH_2CH=CH_2$	H	152	63.69	5.92	63.80	5.85
25	n-C_3H_7	n-C_3H_7 [c]	H	178	61.73	6.58	61.93	6.20
26	i-C_3H_7	i-C_3H_7	H	166	64.15	6.40	63.80	6.67
27	H	$C(C_6H_5)=CHCH_3$	H	166	65.47	5.63	65.62	5.84
28	H	$CH(C_6H_5)CH_2CH_3$ [c]	H	145	66.10	5.82	65.87	6.08
29				219	63.90	5.96	63.76	5.99

a) Hemihydrate. b) Dihydrate.
c) Obtained by catalytic reduction of the olefinic substituent on the preceding compound.
d) The precursor acids were obtained from novobiocin by degradation.[13]
e) Structures were confirmed by infrared and nmr spectra.
f) See ref.[10]

method for its production became available in our laboratories[10], we prepared a series of substituted 4-acetoxy-benzoic acid chlorides which attacked the amido linkages in ditetrahydropyranyl coumermycin A_1 to yield compounds of the type I (Fig. 1).

The requisite benzoic acids were prepared by FRIEDEL-CRAFTS acylation of alkyl *p*-hydroxy benzoates (Method A), by CLAISEN rearrangement of substituted allyl ethers of alkyl *p*-hydroxy benzoates (Method B), by FRIES rearrangement of *o*-substituted phenol acetates or benzoates followed by oxidation of the resulting ketones (Method C), or by degradation of novobiocin or dihydronovobiocin[14](Table 1).

The antibiotics, prepared as in the preceding paper[10], were chromatographed on silica gel, on cellulose thin-layer plates, and on paper strips; bioautographs, chemical sprays, and UV scanning were used to demonstrate homogeneity, and infrared and nmr spectra to confirm purity and structure. Some physical data are listed In Table 2.

Antibiotic spectra were obtained by serial dilution *in vitro*, and oral CD_{50}'s were determined in mice infected with *Staph. aureus* (SMITH).

Biology*

Some of the biological properties of these semisynthetic coumermycins are listed

* Microbiological details on these and other semisynthetic coumermycins will be reported elsewhere.

in Table 3. *Staphylococcus aureus* SMITH made resistant to novobiocin is also somewhat resistant to these antibiotics, as is a coumermycin-resistant strain. Activity *in vitro* is reduced in 3-acyl, 4-methoxy, and drastically, in the 3,5-dialkyl compounds. Acetylation of the 4-hydroxyl group has little effect on activity. All compounds were serum bound in varying degrees.

Maximum activity *in vitro* against *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes* was shown by the 4-hydroxy-benzamido derivatives containing butyl, pentyl, hexyl, and cyclohexyl substituents in the 3-position. A partial correlation was found between the distribution coefficient for ether-aqueous buffer, pH 5, and *in vitro* MIC's.

Table 3. Minimum inhibitory concentrations and oral CD_{50}'s of semisynthetic coumermycin derivatives

Compound No.	*Diplococcus pneumoniae* +5% serum	*Streptococcus pyogenes*	*Staphylococcus aureus*				*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	CD_{50} *vs. S. aureus* Smith mg/kg (mice)
			Smith	Smith +50% serum	Novobiocin resistant	Coumermycin resistant			
1	3.1	1.6	0.13	25	12.5	1.6	25		4.5
2	3.1	0.8	0.06	6.2	6.2	1.6	12.5	12.5	11
3	1.6	0.4	0.03	12.5	0.8	0.2	50		3.5
4	100	0.25	0.05	>50	6.2	1.0	>100		11
5	100	1.0	>0.1	>50	12.5	>1	12.5		>100
6	6.2	0.25	0.006	25	0.8	0.13	6.2	12.5	5.4
7	12.5	0.25	0.004	>50	1.6	0.2	3.1	25	1.3
8	3.1	0.06	0.003	1.6	0.2	0.06	25	3.1	1.7
9	12.5	0.2	0.002	12.5	0.8	0.2	50	6.2	2.2
10	12.5	0.3	0.01	25	0.8	0.31	25	50	10
11	>1	0.5	0.013	25	1.6	0.25	25	25	9.2
12	0.8	0.5	0.016	50	1.6	0.25	25	25	5
13	3.1	0.13	0.001	12.5	0.8	0.06	6.2	12.5	2.5
14	25	0.5	0.013	50	1.6	0.25	12.5	50	6.2
15	3.1	0.13	0.002	6.2	0.8	0.62	6.2	3.1	3.0
16	6.2	0.4	0.006	6.2	0.8	0.08	12.5	25	14
17	3.1	0.13	0.006	25	0.8	0.12	12.5	12.5	11
18	3.1	0.4	0.016	12.5	1.6	0.4	12.5		9.0
19	1.6	0.16	0.016	6.2	0.8	0.16	12.5	3.1	1.5
20	3.1	0.03	0.003	6.2	0.5	0.03	6.2	6.2	3.2
21	1.6	0.03	0.002	12.5	0.2	0.02	1.6	1.6	3.0
22	6.2	0.13	0.006	6.2	0.2	0.06	3.1	6.2	1.8
23	12.5	1.6	0.25	12.5	3.1	>100	100	>100	22
24	25	0.13	0.10	>50	3.1	1.0	>100	>100	45
25	100	>1.6	>0.1	>50	>100	>1	>100	>100	>100
26	50	0.08	0.25	>50	25	3.1	>100	>100	15
27	3.1	0.2	0.002	25	0.4	6.2	25	100	12
28	3.1	≦0.2	0.002	>50	0.4	≦0.2	12.5	50	9.0
29	25	1.6	0.25	>50	50	6.2	100		38
Novobiocin	3.1	0.8	0.062	6.2	25	0.8	25	>100	10
Coumermycin	0.31	0.08	0.0008	1.6	6.2	0.8	3.1	25	12

Values for oral CD_{50}'s in mice infected with *S. aureus* (SMITH) are not precise, but parallel the *in vitro* data obtained in the presence of serum. In some cases increased fat solubility increases both *in vitro* activity and irreversible serum binding.

Experimental*

Methyl 2-acetoxy-3-O-(5-methyl-2-pyrrolylcarbonyl)-4-O-methyl-5,5-dimethyl-L-lyxoside (IIIa, Fig. 3).

3-O-(5-Methyl-2-pyrrolylcarbonyl)-4-O-methyl-5,5-dimethyl-L-lyxoside was prepared according to KAWAGUCHI *et al.*[9]. The acetate was prepared from 624 mg of this compound by treatment with acetic anhydride (2 ml) and pyridine (0.2 ml) at room temperature for 12 hours and recrystallization from ether-Skellysolve B (yield, 500 mg); mp 94.5°C; $[\alpha]_D^{25}$ +13.5° (c=1, methanol).

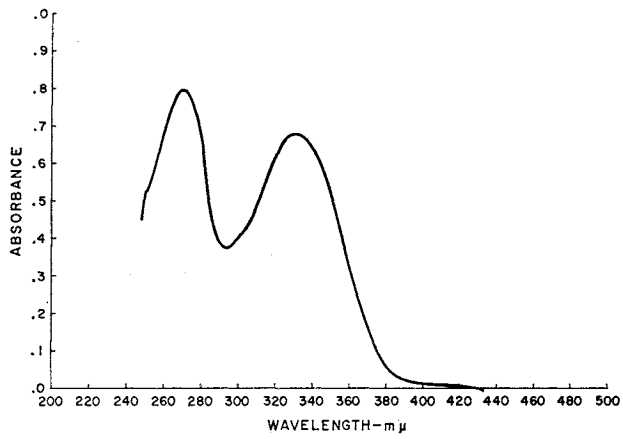
Analysis. Calculated for $C_{17}H_{25}O_7N$: C 57.45, H 7.09, N 3.94.
Found: C 57.13, H 7.22, N 4.06.

Deacetylation occurred by dissolution in liquid ammonia; on evaporation, the starting glycoside was obtained unchanged.

3-[3-(3-Methylbutyl)-4-hydroxybenzamido]-4-hydroxy-8-methyl-7-[3-O-(5-methyl-2-pyrrolylcarbonyl)noviosyloxy]coumarin (Compound 20).

The lyxoside (2.7 g) above was converted to the chloride (IIIb, Fig. 3) according to VATERLAUS and SPIEGELBERG[16] and reacted immediately with 3-[4-acetoxy-3-(3-methylbutyl) benzamido]-4-benzyloxy-7-hydroxy-8-methylcoumarin (IIa, Fig. 2 (3.17 g), obtained in the manner described by VATERLAUS *et al.*[15]) in quinoline (65 ml) containing calcium sulfate (6 g) and silver oxide (3 g). The reaction mixture was diluted with ethyl acetate (150 ml). The mixture was filtered, the solution was washed successively with dilute phosphoric acid (25 ml), hydrochloric acid (25 ml), and water, and the organic phase was evaporated to dryness. The residue was dissolved in ethanol (50 ml), and the 4-benzyl group was removed by hydrogenolysis over Pd/C (300 mg) at 25°C and 50 psi of hydrogen. After removal of the catalyst the solution was evaporated to dryness and the residue was dissolved in liquid ammonia (75 ml) to solvolyze the acetyl groups. After evaporation of the ammonia, counter-current distribution of the residue in 0.25 M aqueous triethanolamine-methyl ethyl ketone (pH 7.8) afforded a peak fraction which proved to be identical with the compound obtained by direct "transacylation" of coumermycin A_1 ditetrahydropyranyl ether, as shown by comparison of chromatograms and of physical data. The uv, ir and nmr spectra are shown in Figs. 4, 5 and 6, respectively.

Fig. 4. Ultraviolet spectrum of 3-[3-(3-methylbutyl)-4-hydroxybenzamido]-4-hydroxy-8-methyl-7-[3-O-(5-methyl-2-pyrrolylcarbonyl)noviosyloxy]coumarin



Typical procedures for the preparation of the precursor acids:

Method A

4-Acetoxy-3-hexylbenzoic acid.

Ethyl *p*-hydroxybenzoate (0.10 mole) and *n*-valeroyl chloride (0.10 mole) in tetrachloroethane (150 ml) were treated with aluminum chlo-

* All melting points are uncorrected.

Fig. 5. Infrared spectrum of 3-[3-(3-methylbutyl)-4-hydroxybenzamido]-4-hydroxy-8-methyl-7-[3-O-(5-methyl-2-pyrrolylcarbonyl)noviosyloxy]coumarin

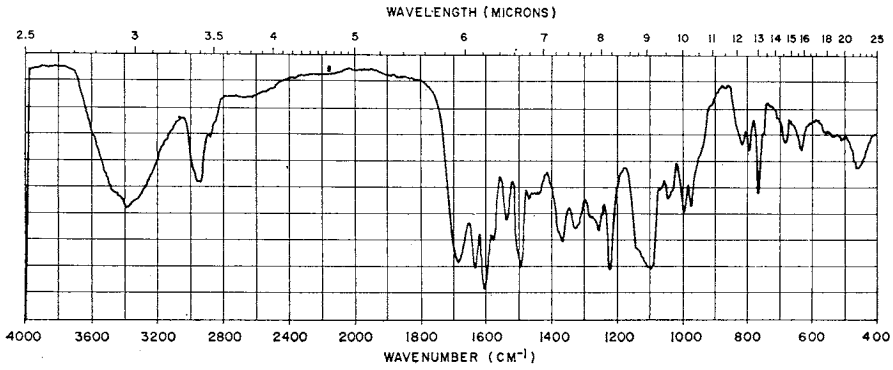
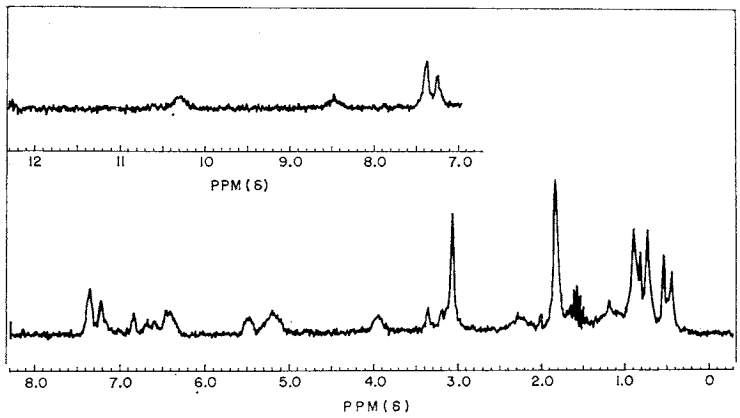


Fig. 6. Nuclear magnetic resonance spectrum of 3-[3-(3-methylbutyl)-4-hydroxybenzamido]-4-hydroxy-8-methyl-7-[3-O-(5-methyl-2-pyrrolylcarbonyl)-noviosyloxy]coumarin



ride (28 g) according to FADIA *et al.*[6] 4-Hydroxy-3-valeroylbenzoic acid (60 % yield, recrystallized from aqueous ethanol), melted at 190~191°C.

Analysis. Calculated for $C_{13}H_{16}O_4$: C 66.08, H 6.83.
Found: C 65.91, H 6.87.

The keto acid was reduced with zinc amalgam[5] and hydrochloric acid, and yielded 4-hydroxy-3-hexylbenzoic acid, mp 97~98°C.

Analysis. Calculated for $C_{13}H_{18}O_3$: C 70.24, H 8.16.
Found: C 70.29, H 8.16.

Acetylation with pyridine and acetic anhydride afforded the acetoxy acid (Table 1) which was converted to the acid chloride by refluxing with an excess of thionyl chloride for 1.5 hours. The excess reagent was removed by repeated distillation with dry benzene. The infrared spectrum in chloroform solution showed complete conversion to the acid chloride.

Method B

4-Acetoxy -3-α-phenylallylbenzoic acid.

The procedure of LAUER and SANDERS[12] was adapted to this preparation. Ethyl *p*-hydroxybenzoate (36.5 g) was dissolved in ethanol (50 ml) and stirred with a solution of sodium ethoxide (7 g) in ethanol (175 ml). To this was added cinnamyl bromide (47.3 g) prepared from cinnamyl alcohol and fuming HBr[3], and the mixture was stirred for 41

hours at 23°C. The alcohol was distilled, water added, and the organic layer diluted with ether. The ether solution was washed with 10 % aqueous sodium hydroxide and water to remove unreacted phenol. On evaporation of the ether a light tan oil remained which crystallized on standing at 6°C. Ethyl 4-α-phenylallylbenzoate was recrystallized from Skellysolve B (750 ml) and formed 37.6 g of colorless crystals, mp 66~68°C.

Analysis. Calculated for $C_{18}H_{18}O_3$: C 76.57, H 6.43.
Found: C 76.46, H 6.44.

The ether-ester (30 g) was heated at 40 mm pressure until the reflux temperature held at 243°C. The rearrangement product was heated with 3 % sodium hydroxide to effect hydrolysis of the remaining ester. The aqueous solution was washed with ether and acidified with 6 N hydrochloric acid. The crude 4-hydroxy-3-α-phenylallylbenzoic acid which precipitated was filtered and dried. It was dissolved in pyridine and treated with an excess of acetic anhydride to yield 17.8 g of the acetoxy acid (Table 1).

Method C

4-Acetoxy-3-cyclohexylbenzoic acid.

o-Cyclohexylphenol (17.2 g) was acetylated in pyridine-acetic anhydride (yield 18 g, mp below room temperature). It was reacted with aluminum chloride (13 g) in nitrobenzene (80 ml). After 24 hours the mixture was poured onto an ice-concentrated hydrochloric acid mixture, extracted with ether, and finally extracted into dilute sodium hydroxide solution. 3-Cyclohexyl-4-hydroxyacetophenone (75 % yield) was recrystallized from pentane-hexane, mp 152~153°C.

Analysis. Calculated for $C_{14}H_{18}O_2$: C 77.03, H 8.31.
Found: C 77.08, H 8.44.

The acetophenone (6.6 g) was oxidized with iodine (7.62 g) in pyridine (20 ml) according to KING[11] to yield 3-cyclohexyl-4-hydroxybenzoic acid containing some ring-substituted iodo compound. Repeated crystallizations from cyclohexane and benzene gave the acid, mp 129~130°C.

Analysis. Calculated for $C_{13}H_{16}O_3$: C 70.88, H 7.32.
Found: C 70.38, H 7.34.

Alternatively *o*-cyclohexylphenol was treated with benzoyl chloride and aluminum chloride to yield 3-cyclohexyl-4-hydroxybenzophenone in a modification of the FRIES rearrangement due to CLOSE *et al.*[4], mp 210°C.

Analysis. Calculated for $C_{19}H_{20}O_2$: C 81.39, H 7.19.
Found: C 81.27, H 7.37.

Alkali fusion[1] gave the acid, which was acetylated as above (Table 1).

Method D

4-Hydroxy-3-(3-methyl-2-butenyl)benzoic acid, 4-hydroxy-3-(3-methylbutyl)benzoic acid, and 2,2-dimethyl-6-carboxychromane were obtained from novobiocin by published procedures[7].

The acyl exchange at the 3-amido function of the coumarin portion was carried out as described by KEIL *et al.*[10] by short boiling of coumermycin, protected at the 3-hydroxyls of the noviose moieties by tetrahydropyranyl ether formation, with the requisite acid chloride in pyridine. The ether linkage was cleaved by mild acid hydrolysis, and the acetyl group removed by dissolution in liquid ammonia. Unsaturated side chains of the benzamido portion were hydrogenated over platinum oxide in ethanol solution. Final purification of the semisynthetic antibiotics was achieved by fractional precipitation from solution in ethyl acetate with Skellysolve B. In some cases gel filtration on Sephadex LH20 with methanol-acetone (1 : 1) as solvent was used. TLC's on silica gel (solvent: *i*-propanol, methyl acetate ammonia (105 : 45 : 40) or on cellulose (solvent: 0.25 M triethanolamine, pH 7.0/acetone 3 : 1)) were visualized by spraying with ninhydrin reagent or by bioautography *via* overlay with suspensions of *B. subtilis*.

Acknowledgments

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