Tetrahedron. Vol. 32, pp 2057 to 2065. Pergamon Press 1976. Printed in Great Britain

STABILITY DETERMINING FACTORS IN ANOMERIC COUMEROSIDES

A. E. WICK,† J. F. BLOUNT and W. LEIMGRUBER*
Chemical Research Department, Hoffmann-La Roche Inc., Nutley, NJ 07110, U.S.A.

(*Received in the USA* 14 *November* 1975; *Received in the UK for publication* 11 *March* 1976)

Abstract—The thermodynamic equilibrium between the anomeric coumerosides **3** and **4** differs drastically from that which exists between their C(2)-epimers **7** and **8**. Stability determining factors which govern the position of these equilibria include in addition to steric interactions the Δ2 effect and the anomeric effect. The latter is discussed in terms of orbital overlap between nonbonding electrons on oxygen and *anti*-bonding σ orbitals. The α-configuration of the glycoside linkages of coumermycin A_1 was secured by X-ray analysis of compound **12**.

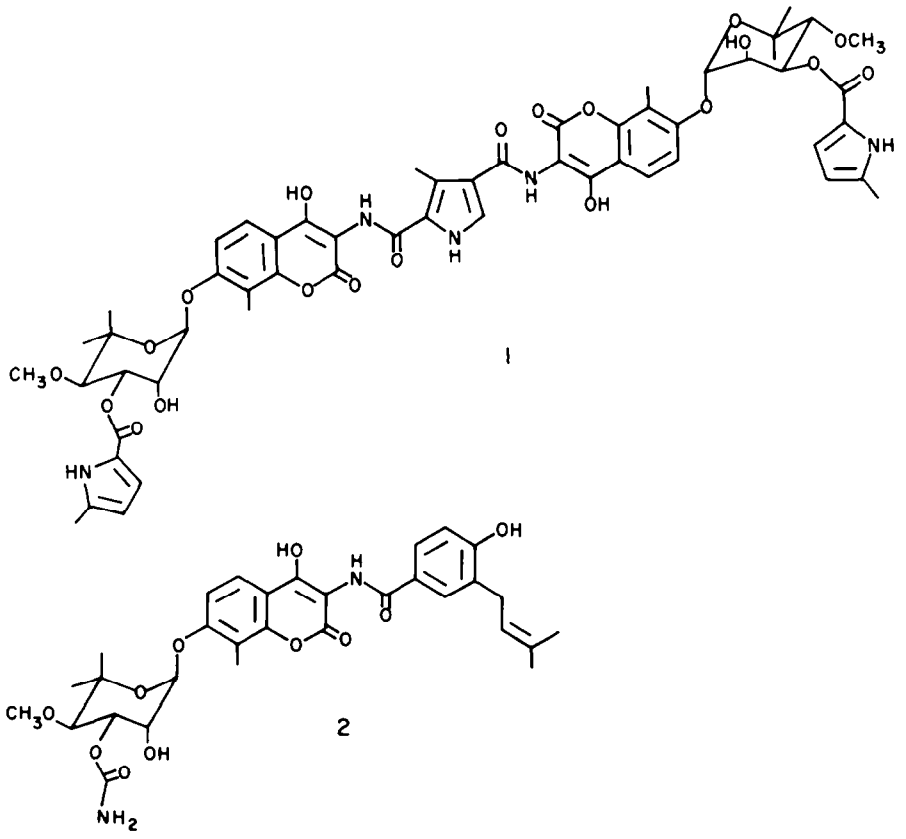
The structure of the antibiotic coumermycin A_1 (**1**) is firmly established[1] except for the configuration of the glycoside linkages. The configurational assignment for the anomeric centers of the coumerose moieties in structure **1** is based in principle on the structural relationship between this antibiotic and novobiocin (**2**) which has been recognized as an α-glycoside.[2] Since the total syntheses of both coumermycin A_1[3] and novobiocin (**2**)[4] utilize a common glycosidic intermediate, the α-configuration of coumermycin A_1 can be considered as established. However, this assignment relies in essence only on the predictions of the Hudson Rules because the configuration of novobiocin had been derived on this basis.

In the course of structural work concerning fermentation products closely related to coumermycin A_1, the opportunity arose to examine the configuration of its anomeric centers. We now wish to record the results of this investigation.

When coumermycin A_1 (**1**) was subjected to acid catalyzed methanolysis, a 55% yield of the α-coumeroside **3** ($[\alpha]_D + 17.0°$)‡ and a 22% yield of the corresponding β-anomer **4** ($[\alpha]_D + 120.2°$) were obtained. The configurations of these methyl glycosides are presented in Scheme 1 in conformity with those of the corresponding α- and β- methyl noviosides.[2] Direct evidence for the correctness of the assigned configurations

†Present address: Chemische Forschungsabteilung, F. Hoffmann-La Roche & Co. AG., Basel.

‡The properties of this compound are in agreement with those reported[1] for a methyl coumeroside that had been obtained in similar fashion.



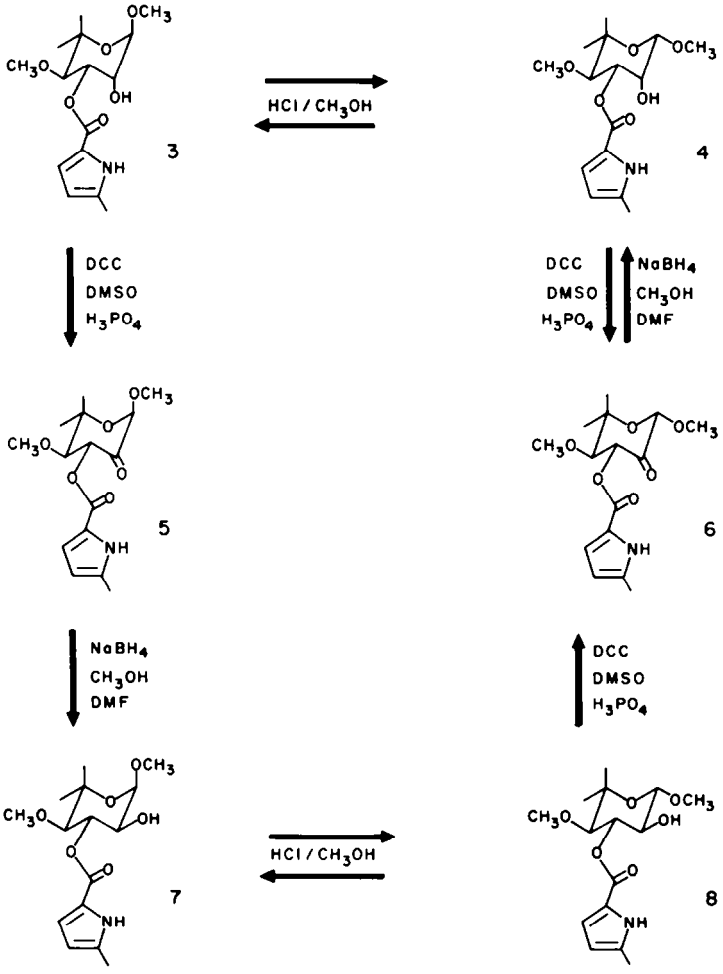
could not be obtained by NMR spectroscopy because the coupling constants J_{12} of both anomers are small and of similar magnitude, thus reflecting the common 60° dihedral angle between H_1 and H_2. However, the observed large coupling between H_3 and H_4 clearly reveals that both anomers possess the 1C (normal) conformation which has also been established for a series of α- and β-noviosides.[5]

In order to corroborate the structures **3** and **4** we envisaged the inversion of the stereochemistry at C(2); of the anticipated epimers **7** and **8**, the latter is expected to exhibit only large coupling constants because of an all-axial arrangement of its ring protons. This objective was realized by the reaction sequences outlined in Scheme 1.

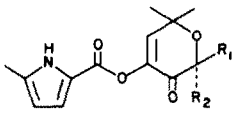
Oxidation of the anomer **3** according to Pfitzner and Moffatt[6] gave the crystalline ketone **5** in 75% yield. A minor by-product of this reaction was recognized as the α,β-unsaturated ketone **9**, which could also be obtained by pyrolysis of **5**. Sodium borohydride reduction of ketone **5** in methanol–DMF produced a high yield of the desired alcohol **7** without formation of detectable amounts of the initial alcohol **3**. This highly stereospecific reduction is remarkable since the examination of the Dreiding model of **5** does not even predict its preferential course. The NMR spectrum of **7** shows only one small coupling constant (J_{12}), and a triplet for H_3 due to the approximately equal coupling constants J_{23} and J_{34}. Pfitzner–Moffatt oxidation of the anomer **4** afforded the desired ketone **6** as a liquid. Upon distillation, **6** was converted to a mixture of two inseparable products, the NMR spectrum of which indicated the presence of the α,β-unsaturated ketone **10** (the enantiomer of **9**). Sodium borohydride reduction of the ketone **6** gave none of the anticipated alcohol **8**; only the starting alcohol **4**, accompanied by some of its 2-acyl isomer **11**, was formed. However, the desired alcohol **8** was accessible by anomerization of **7**, which was effected with methanolic hydrogen chloride. From the resulting mixture of anomers, compound **8** could be isolated in crystalline form. Its NMR spectrum shows a doublet with $J_{12} = 8.5$ Hz for H_1, as expected from its diaxial relationship with H_2. The fact that the alcohol **8** could be oxidized to the ketone **6** established that no unexpected configurational changes had occurred in either of the oxidation or reduction steps.

The chemical transformations outlined above in conjunction with the detailed NMR analysis of the products secure the assigned configurations of the anomeric coumerosides **3** and **4**. The relevant NMR data are summarized in Table 1. It may be noted that the observed δ and J values of the ring protons conform with the following empirical rules:[7,8] (1) In a similar environment, axial protons appear at higher field than equatorial protons.† (2) Protons which are in a 1,3-diaxial arrangement with either a methoxyl or hydroxyl function experience a significant

†Except for ketones **5** and **6**.

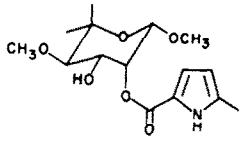


Scheme 1.



9 $R_1 = OCH_3$ $R_2 = H$

10 $R_1 = H$ $R_2 = OCH_3$



11

by subjecting the individual anomers to treatment with hot methanol in the presence of a trace of concentrated hydrochloric acid. The resulting equilibrium mixtures were subsequently analyzed for their content of α- and β-anomers by NMR and VPC. The accuracy of both techniques was checked by simultaneous analysis of anomeric mixtures of known composition; the method of choice was clearly VPC, the accuracy of which was determined as $\pm 1\%$.

The fact that the β-anomer **8** is favored in the

Table 1. Proton signals of compounds **3–8**

Protons		3	4	5	6	7	8
H_1	δ	4.66	4.55	4.70	4.89	4.73	4.44
	J_{12}	2.5	1.5	----	----	4.5	8.5
H_2	δ	4.09	4.11	----	----	3.66	3.51
	J_{23}	3.0	3.0	----	----	10.5	9.0
H_3	δ	5.47	5.16	5.89	5.93	5.48	5.26
	J_{34}	9.5	10.0	10.0	10.0	10.5	9.0
H_4	δ	3.52	3.51	3.41	3.50	3.07	3.10
OH	δ	2.79	2.67	----	----	2.46	3.00
	J_{2OH}	3.5	?	----	----	11.0	?
CH_3	ax.δ	1.33	1.20	1.37	1.40	1.29	1.26
	eq.δ	1.33	1.35	1.52	1.42	1.34	1.36
OCH_3	δ	3.38/ 3.47	3.43/ 3.44	3.44/ 3.54	3.50/ 3.50	3.42/ 3.45	3.46/ 3.50

The corresponding 100 MHz spectra were recorded in $CDCl_3$ solution and the chemical shifts are reported in ppm (δ) downfield from an internal tetramethylsilane reference. The coupling constants are given in Hz-units.

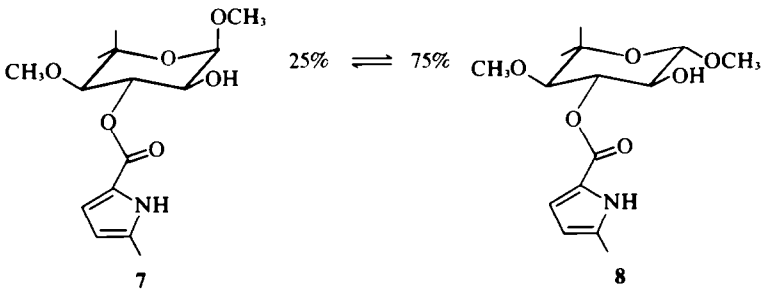
deshielding effect. (3) Large coupling constants vary between 8.5 and 10.5 Hz, while small ones are in the range of 1.5–4.5 Hz.

An attempt was made to correlate the NMR data of either the α-coumeroside **3** or the β-coumeroside **4** with those of courmermycin A_1(**1**) in order to establish the configuration of its glycoside linkages. It was not possible, however, to make such a correlation because the pertinent ring protons of **1**, in particular those at the anomeric centers, experience long range shielding effects due to the coumarin moieties, a fact which makes their chemical shifts unreliable. As will be shown later, the configuration of the glycoside linkages could eventually be secured by X-ray crystallography.

At this point of our investigation, we redirected our attention to the result of the acid catalyzed methanolysis of coumermycin A_1 (**1**) which suggests that the α-anomer **3**, despite its sterically unfavorable 1,3-diaxial OMe/Me group interaction, is thermodynamically more stable than the β-anomer **4**. That this is factual was shown by the determination of the equilibrium **3**$\rightleftharpoons$**4** in which the α-anomer **3** is favored over the β-anomer **4** in a ratio of 79:21 (Fig. 1). In contrast, the similarly determined equilibrium **7**$\rightleftharpoons$**8** revealed that the β-anomer **8** is favored over the α-anomer **7** in a ratio of 75:25. Both of these equilibria were established under standardized conditions equilibrium **7**$\rightleftharpoons$**8** can be rationalized by the consideration of steric interactions as outlined in Fig. 1. However, the free energy calculated for these interactions (2.15 kcal/mole) differs significantly from that which has been found experimentally (0.75 kcal/mole). The difference of 1.40 kcal/mole† must be ascribed to the well-known "anomeric effect". The destabilization of equatorial glycosides has been explained in terms of unfavorable interactions between parallel oriented lonepair orbitals of the O atoms.[10] Such interactions do occur in all of the three staggered conformations of equatorial anomers (such as **8**) but are absent in one of the staggered conformers of axial anomers (such as **7**).[12] On this basis, the preferred conformer of axial anomers has been predicted to possess the geometry depicted in Fig. 2; X-ray studies of various glycosides have confirmed this prediction.[13]

A theoretically attractive interpretation of the anomeric effect which was first suggested by Altona considers stabilization by orbital overlap[14–18] rather than repulsion by nonbonding orbitals. Thus, orbital overlap can be anticipated between the anti-bonding orbitals of the C–O bonds and suitably oriented nonbonding sp^3 orbitals of the O atoms. In the case of the axial anomers, two possibilities exist for electron delocalization, whereas only one is available for equatorial anomers (Fig. 3). This rationalization of the anomeric effect can explain why, in a variety of α- and β-glycosides, certain C–O bonds are shortened relative to other C–O single-bond lengths,

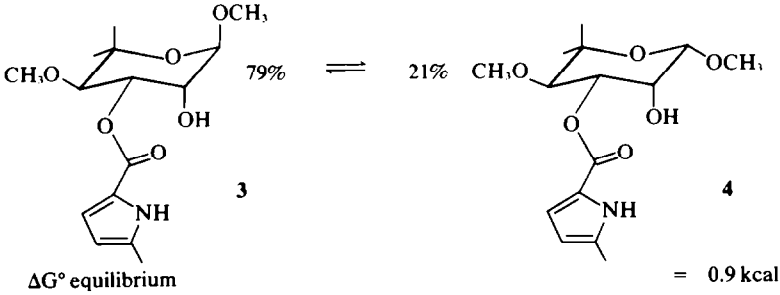
†For the anomeric effect of methyl glycosides in methanol, a value of 1.4 kcal/mole has been determined.[9]



$\Delta G°$ equilibrium = −0.75 kcal/mole

$\Delta G°$ interactions† = $CH_3/\!/H$–$CH_3/\!/OCH_3$–$H/\!/OCH_3$ = 0.9 − 2.6‡ − 0.45 = −2.15 kcal/mole

anomeric effect = 1.40 kcal/mole



$\Delta G°$ equilibrium = 0.9 kcal/mole

$\Delta G°$ interactions† = $CH_3/\!/H + OCH_3/OH - CH_3/\!/OCH_3 - H/\!/OCH_3$

0.9 + 0.35 − 2.6‡ − 0.45 = −1.80 kcal/mole

Δ2 effect + anomeric effect = 2.70 kcal/mole

†Unless indicated otherwise, energies of interactions between substituents in cyclitols [Ref. 9, p. 356] were used; for an explanation of symbols, see Ref. 10, p. 737.

‡For the energy of 1,3-diaxial methyl/hydroxyl interactions in cyclohexanes, values ranging from 1.9–2.4 kcal/mole have been cited [Ref. 9, p. 52]; the energy of such interactions in pyranoses has been estimated to range between 2.5 and 2.6 kcal/mole.[11]

Fig. 1. Calculation of the anomeric and Δ2 effect from the equilibria 3⇌4 and 7⇌8.

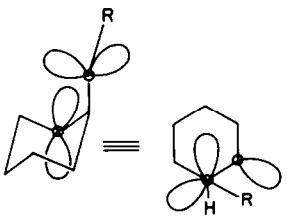


Fig. 2. Preferred conformation of axial anomers. R signifies the aglycon moiety.

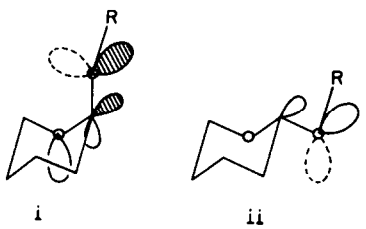
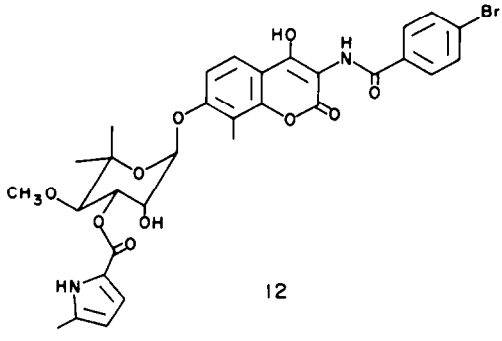


Fig. 3. Conformations of axial (i) and equatorial (ii) anomers which allow electron delocalization. R signifies the aglycone moiety.

notably the C(1)–O(1) bond of equatorial anomers and the C(1)–O(5) bond of their axial counterparts.[19] In conjunction with the consideration of steric factors, it also predicts the preferred conformation of axial anomers.[13]

The position of the equilibrium 3⇌4 is more difficult to explain due to the axially positioned 2-hydroxyl group which is known to cause destabilization of equatorial anomers. This phenomenon, which has never been rationalized satisfactorily, is referred to in the literature as Reeves' "Δ2 effect".† Since the calculation of steric interactions shows that 2.7 kcal/mole must be attributed to the sum of the anomeric and the Δ2 effect (Fig. 1), it is evident that the latter accounts for 1.3 kcal/mole.‡

In summary, the positions of the equilibria 7⇌8 and 3⇌4 demonstrate that the Δ2 and the anomeric effect are of similar magnitude§ and that the free energy of a



†This effect represents the interaction of an axial OH group at C(2) with the ring oxygen and with an equatorial oxygen function at C(1).[20]

‡It should be noted that this value is actually independent of the anomeric effect and most of the steric interactions since one can derive from both equilibria the following equation: Δ2 effect = $\Delta\Delta G° - OCH_3/OH$ = 1.65 − 0.35 = 1.3 kcal/mole. Although Reeves may have overrated the importance of the Δ2 effect, it would appear that its magnitude has been underestimated in the recent literature (cf. ref. 9, p. 377).

§In view of this fact it is not justified to regard the Δ2 effect as an integral part of the anomeric effect.[21]

1,3-diaxial OMe/Me interaction is about equal to the sum of both effects.

Direct proof for the α-configuration of coumermycin A_1 (**1**) was obtained from the X-ray crystallographic data of the bromo derivative **12** which was prepared from the antibiotic by a known reaction sequence.[22]

Pertinent results of the crystallographic study are shown in Figs. 4–6. The stereodrawing in Fig. 4 clearly reveals the axial arrangement of the glycoside linkage and the anticipated conformation of the aglycone moiety (cf. Fig. 2). The stereochemical features of the coumerose moiety can best be visualized in Fig. 5 which shows in particular the distortional effects caused by the non-bonded interaction between O(1) and C(7).† Several of the bond lengths and angles which are recorded in Fig. 6 are of special interest in connection with earlier advanced considerations. Thus, it is evident that the C(1)–O(1) bond (1.41 Å) is shortened relative to other C–O single bonds, notably the C(5)–O(5) bond (1.45 Å). This result is in contrast with the previously mentioned finding that the C(1)–O(5) bond of axial anomers is usually shortened.[19] It is, however, in conformity with the concept of bond stabilization by orbital overlap which, in the case of axial anomers, provides two alternatives for electron delocalization, namely the C(1)–O(5) or the C(1)–O(1) bond (cf. Fig. 3). The observed choice of the latter is probably a consequence of the severe non-bonded interaction between O(1) and C(7) which would be unduly enhanced by the shortening of the alternative C(1)–O(5) bond. Finally, it should be noted that the angles C(5)–O(5)–C(1) and C(1)–O(1)–C(21) are virtually 120° thus indicating sp^2 hybridization at these O atoms.

Whether or not the concept of bond stabilization by orbital overlap will lend itself to rationalize the shortening of specific C–O bonds in other glycosides remains to be seen.

†The calculated distance between these atoms is 3.10 Å.

EXPERIMENTAL

Physical data were obtained as follows: m.p. (uncorrected), Reichert hot stage; $[\alpha]_D$, Perkin–Elmer 141 polarimeter; IR, Beckman IR-9 or Perkin–Elmer 621; UV, Cary 14 or 15; MS, CEC-110 or Jeolco-01SG at 70 eV; NMR, Varian HA-100 using TMS as internal standard. Abbreviations: b, broad; w, weak; m, medium; sh, shoulder for IR; inf, inflection for UV; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet for NMR.

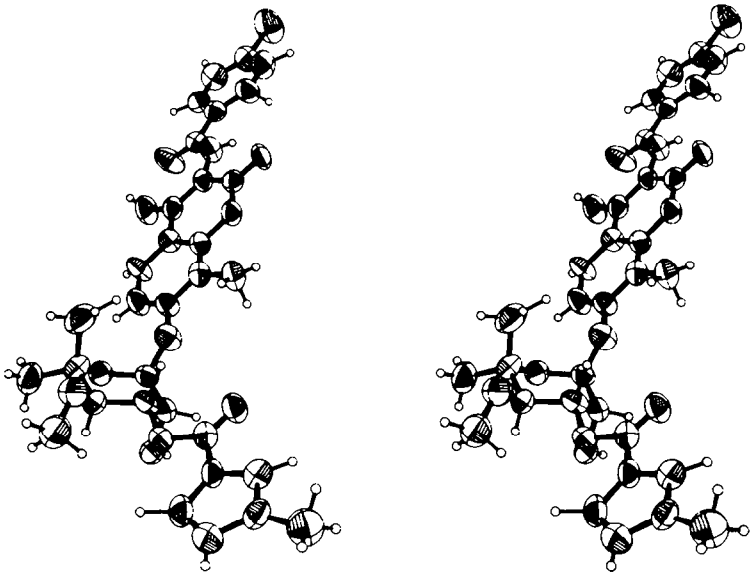


Fig. 4. A stereodrawing of **12** showing its structure and conformation in the crystalline state. The thermal ellipsoids are scaled to the 50% probability level.

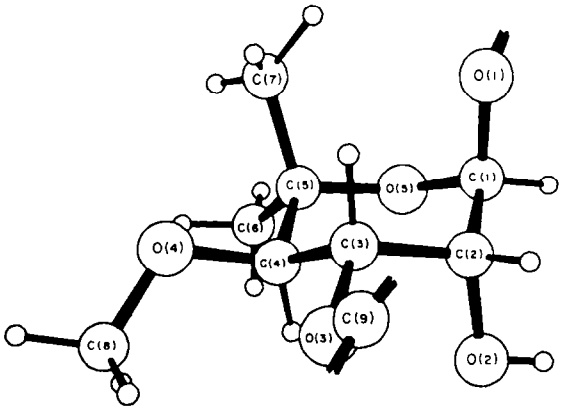


Fig. 5. Three-dimensional projection of the coumerose moiety of **12**.

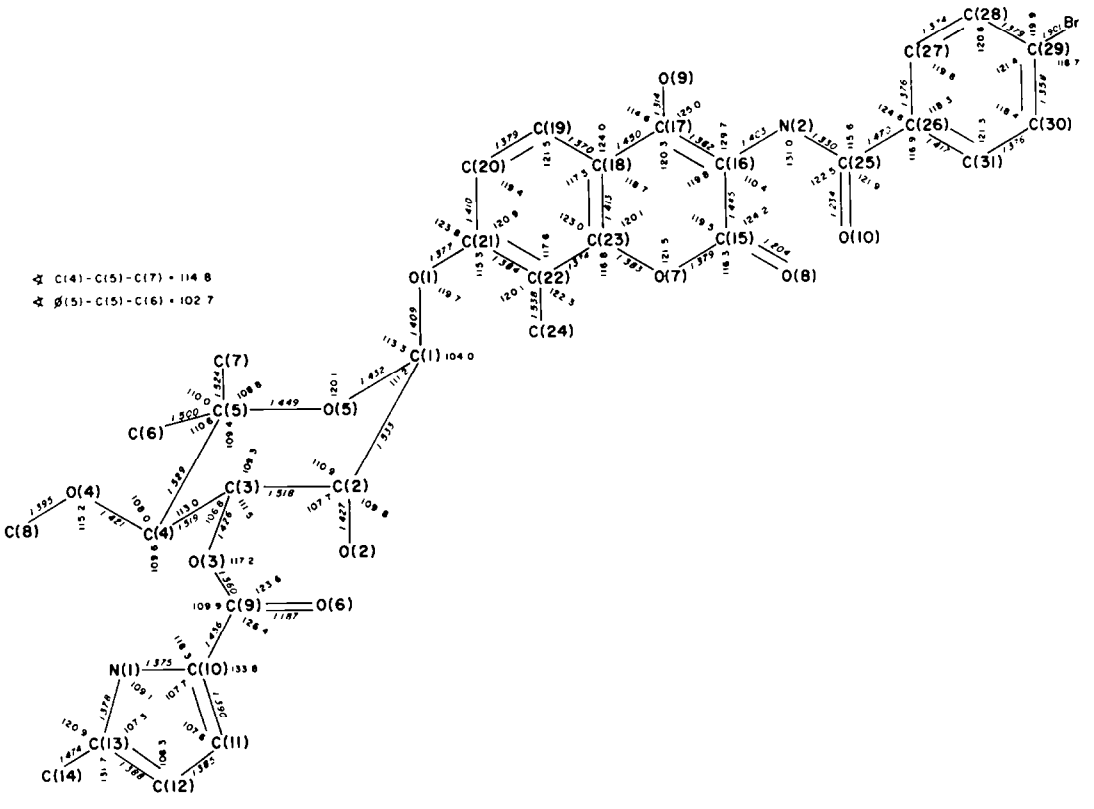


Fig. 6. The bond lengths and bond angles in **12**. The estimated standard deviations of C–O and C–C bonds are 0.010 and 0.014 Å, respectively.

Methanolysis of coumermycin A_1 to **3** *and* **4**

A mixture of **1** (2.0 g; 1.8 mmol) MeOH (330 ml) THF (10 ml) and conc. HCl (28 ml) was heated at reflux for 1 hr. The mixture was cooled, the grey ppt (912 mg) filtered off, and the filtrate concentrated to 50 ml. The pH of the filtrate was adjusted to 8 by addition of Na_2CO_3 in the presence of ice and extraction of the resulting slurry with EtOAc gave, after drying and removal of the solvent, 1.23 g of a brownish oil. This oil was applied to three silica gel thick layer plates (20 × 20 × 0.2 cm) which were developed with CH_2Cl_2–MeOH (95:5). Extraction of the main band gave 1.038 g (92%) of a mixture of the anomeric coumerosides **3** and **4** which was rechromatographed on thick layer plates with benzene–EtOAc (1:1). Crystallization, from an ether–petroleum ether mixture, of the material extracted from the top band (R_f 0.33) gave 620 mg (55%) of pure α-methyl coumeroside, α-methyl 3 - 0 - (5 - methyl - 2 - pyrrolylcarbonyl) - 4 - 0 - methyl - 5,5 - dimethyl - L - lyxoside (**3**): m.p. 196–197°; $[\alpha]_D^{25}$ + 17.0° (1, $CHCl_3$); IR ($CHCl_3$): 3620w, 3465m, 3350m, 1700, 1585w, 1500, 1340, 1235b, 1130b, 1075, 1050, 865w cm^{-1}; UV (EtOH): 230 nm (3760), 279 nm (21600); NMR ($CDCl_3$): δ 1.33 (s, 6H), 2.30 (s, 3H), 2.79 (d, J = 3.5, 1H), 3.38 (s, 3H), 3.47 (s, 3H), 3.52 (d, J_{34} = 9.5, 1H), 4.09 (m, J_{12} = 2.5, J_{23} = 3.0, J_{2OH} = 3.5, 1H), 4.66 (d, J_{12} = 2.5, 1H), 5.47 (dd, J_{23} = 3.0, J_{34} = 9.5, 1H), 5.93 (dd, J = 4, J = 3, 1H), 6.84 (dd, J = 4, J = 3, 1H), 10.16 (broad, 1H); MS (*m/e*): 313 (2), 182 (6), 165 (3), 138 (5), 136 (2), 135 (20), 109 (12), 108 (100), 107 (12), 86 (25). (Found: C, 57.46; H, 7.64; N, 4.34. Calc. for $C_{15}H_{23}NO_6$ (313.36): C, 57.50; H, 7.40; N, 4.47%).

Crystallization, from an ether–petroleum ether mixture, of the material extracted from the lower band (R_f 0.24) gave 250 mg (22%) of pure β-methyl coumeroside, β-methyl 3 - 0 - (5 - methyl - 2 - pyrrolylcarbonyl) - 4 - 0 - methyl - 5,5 - dimethyl - L - lyxoside (**4**): m.p. 141–143°; $[\alpha]_D^{25}$ + 120.2° (1, $CHCl_3$); IR ($CHCl_3$): 3570w, 3450m, 3310bw, 1690, 1575w, 1490, 1320, 1225b, 1165, 1115, 1070, 1040, 1023, 875w cm^{-1}; UV (EtOH): 230 nm (3500), 279 nm (20900); NMR ($CDCl_3$): δ 1.20 (s, 3H), 1.35 (s, 3H), 2.25 (s, 3H), 2.67 (broad, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 3.51 (d, J_{34} = 10.0, 1H), 4.11 (m, 1H), 4.55 (d, J_{12} = 1.5, 1H), 5.16 (dd, J_{23} = 3.0, J_{34} = 10.0, 1H), 5.92 (dd, J = 4, J = 3, 1H), 6.88 (dd, J = 4, J = 3, 1H), 9.50 (broad, 1H); MS (*m/e*): 314 (16), 313 (100), 281 (15), 255 (11), 236 (13), 192 (11), 182 (23), 181 (16), 167 (18), 157 (13), 138 (36), 135 (55), 109 (25), 108 (93), 107 (19), 86 (30). (Found: C, 57.39; H, 7.31; N, 4.32. Calc. for $C_{15}H_{23}NO_6$ (313.36): C, 57.50; H, 7.40; N, 4.47%).

The grey ppt mentioned above, dissolved in 60 ml DMF, was heated in the presence of charcoal and filtered through a bed of Celite. Upon addition of 100 ml of EtOH and cooling to room temp. fine needles of the aglycon, coumermic acid, crystallized: m.p. > 350°; IR(KBr): 3370bm, 1635, 1590b, 1550sh, 1530sh, 1450b, 1400b, 1320, 1260m, 1123m, 1090m, 882w, 823w, 800w, 762w, 742w cm^{-1}; UV (EtOH + 4% MCS): 243 nm (36800 infl.), 305 nm (30150 infl.), 343 nm (51500); NMR (NaOD): δ 2.5 (s, 6H), 2.60 (s, 3H), 4.80 (s, HDO), 6.60 (AB, J = 8, 2H), 7.55 (AB, J = 8, 2H), 7.61 (s, 1H). (Found: C, 59.02; H, 3.99; N, 7.42. Calc. for $C_{27}H_{21}N_3O_{10}$ (547.48): C, 59.23; H, 3.87; N, 7.68%).

Oxidation of **3** *to* **5** *and* **9**

To a soln of **3** (1.25 g; 4 mmol) and N,N'-dicyclohexylcarbodiimide (3.17 g; 15.3 mmol) in DMSO (30 ml) 99.6% phosphoric acid (1.4 g) was added dropwise by means of a syringe. The resulting mixture was stirred for 2.5 hr, the crystalline ppt was filtered off, washed with DMSO–acetone and the filtrate was concentrated under vacuum at 30°. The residual oil was dissolved in chloroform, water was added and the pH of the aqueous phase was adjusted to 8 by addition of $KHCO_3$. The chloroform extracts were washed with brine, dried, the solvent was removed, and the residue was applied to twelve silica gel thick layer plates (20 × 20 × 0.2 cm) which were developed with a mixture of benzene and EtOAc (1:1). Crystallization, from an ether–petroleum ether mixture, of the extract of the major upper band gave 585 mg of pure ketone **5**: m.p. 130–132°; $[\alpha]_D^{25}$ + 0.4° (1, $CHCl_3$). Re-chromatography of the mother liquors in the same fashion gave an additional 546 mg for a total of 931 mg (75%) of 5,6 - dihydro - 2,5 α - dimethoxy - 6,6 - dimethyl - 4(5 - methyl - 2 - pyrrolylcarbonyloxy) - 2H - pyran -

3(4H) - one (**5**): IR ($CHCl_3$): 3450m, 3320bw, 1753m, 1700, 1490, 1330 m, 1222, 1147, 1100, 1060, 1040 cm^{-1}; UV (EtOH): 230 nm (3540), 278 nm (20820); NMR ($CDCl_3$): δ 1.37 (s, 3H), 1.52 (s, 3H), 2.26 (s, 3H), 3.41 (d, J_{34} = 10, 1H), 3.44 (s, 3H), 3.54 (s, 3H), 4.70 (s, 1H), 5.89 (d, J_{34} = 10, 1H), 5.93 (dd, J = 4, J = 3, 1H), 6.88 (dd, J = 4, J = 3, 1H), 9.90 (broad, 1H); MS (*m/e*): 311 (7), 283 (3), 219 (2), 191 (2), 171 (2). 165 (4), 125 (4), 109 (8), 108 (100), 101 (4), 99 (26), 80 (5). (Found: C, 57.78; H, 6.78; N, 4.60. Calc. for $C_{15}H_{21}NO_6$ (311.34): C, 57.86; H, 6.80; N, 4.50%).

Kugelrohr distillation of **5** at 140° gave a colorless oil which, upon crystallization from an ether–petroleum ether mixture, afforded 2(*R*) - methoxy - 6,6 - dimethyl - 4 - (5 - methyl) - 1H - 2 - pyrrolylcarbonyloxy) - 2H - pyran - 3(6H) - one (**9**): m.p. 159–160°; $[\alpha]_D^{25}$ – 83° (0.2, $CHCl_3$); IR(CH_2Cl_2): 3430m, 3290w, 1720sh, 1710, 1660w, 1573w, 1490, 1365m, 1312m, 1210, 1187, 1164m, 1130, 1097, 1060, 1040, 968m, 957m cm^{-1}; UV(EtOH): 237 nm (11620) 283 nm (21100); NMR($CDCl_3$): δ 1.49 (s, 3H), 1.61 (s, 3H), 2.28 (s, 3H), 3.53 (s, 3H), 4.95 (s, 1H), 6.01 (dd, J = 4, J = 3, 1H), 6.71 (s, 1H), 7.00 (dd, J = 4, J = 3, 1H), 9.6 (broad, 1H). MS (*m/e*): 279 (2), 219 (7), 176 (3), 109 (10), 108 (100), 83 (19), 80 (12). (Found: C, 60.01; H, 6.06; N, 4.88. Calc. for $C_{14}H_{17}NO_5$ (279.31): C, 60.21; H, 6.14; N, 5.02%).

Reduction of **5** *to* **7**

A soln of **5** (455 mg; 1.46 mmol) and $NaBH_4$ (450 mg; 12 mmol) in MeOH (37 ml) and DMF (1.2 ml) was stirred at room temp. for 1.5 hr. The mixture was taken up in EtOAc and the soln was washed 3 times with brine, dried over Na_2SO_4 and evaporated. Thick layer chromatography of the residue gave 336 mg (90%) of an oil which was pure according to TLC and which could be crystallized from an ether–petroleum ether mixture to afford α-methyl 3 - 0 - (5 - methyl - 2 - pyrrolylcarbonyl) - 4 - 0 - methyl - 5,5 - dimethyl - L - xyloside (**7**): m.p. 164–166°; $[\alpha]_D^{25}$ – 64.5° (1, $CHCl_3$); IR ($CHCl_3$): 3555w, 3445m, 3300bw, 1690, 1485, 1322m, 1230m, 1150, 1065b, 905w cm^{-1}; UV (EtOH): 232 nm (3200), 278 nm (18850); NMR ($CDCl_3$): δ 1.29 (s, 3H), 1.34 (s, 3H), 2.29 (s, 3H), 2.46 (d, J_{20H} = 11, 1H), 3.07 (d, J_{34} = 10.5, 1H), 3.42 (s, 3H), 3.45 (s, 3H), 3.66 (dd, J_{12} = 4.5, J_{23} = 10.5, J_{20H} = 11, 1H), 4.73 (d, J_{12} = 4.5, 1H), 5.48 (dd, J_{23} = J_{34} = 10.5, 1H), 5.93 (dd, J = 4, J = 3, 1H), 6.85 (dd, J = 4, J = 3, 1H), 9.85 (broad, 1H); MS (*m/e*): 313 (13), 192 (4), 182 (9), 181 (5), 157 (5), 118 (10), 116 (8), 115 (40), 109 (26), 108 (200), 107 (15), 99 (12), 97 (8), 87 (12), 86 (71), 80 (10). (Found: C, 57.30; H, 7.56; N, 4.32. Calc. for $C_{15}H_{23}NO_6$ (313.36); C, 57.50; H, 7.40; N, 4.47%).

Anomerization of **7** *to* **8**

A soln of **7** (63 mg; 0.2 mmol) in MeOH (10 ml) to which 2 drops of conc HCl had been added was heated at reflux for 45 min. The soln was taken to dryness on a rotary evaporator, the residue was dissolved in CH_2Cl_2 and the resulting soln was dried over Na_2SO_4 and evaporated. The residue was applied to a silica gel thick layer plate which was developed with a benzene–EtOAc mixture (1 : 1). The two resulting bands were eluted (upper band 33 mg, lower band 27 mg) and crystallized separately from an ether–petroleum ether mixture to give 18 mg of starting material **7** and 21 mg of its β-anomer, β-methyl 3 - 0 - (5 - methyl - 2 - pyrrolylcarbonyl) - 4 - 0 - methyl - 5,5 - dimethyl - L - xyloside (**8**): m.p. 164°; $[\alpha]_D^{25}$ + 106.2° (1.4, $CHCl_3$); IR($CHCl_3$): 3610w, 3460m, 3320bw, 1700, 1495, 1328m, 1210b, 1139, 1075, 1050, 1022m, 800bw cm^{-1}; UV (EtOH): 231 nm (3600), 278 nm (21400); NMR($CDCl_3$): δ 1.26 (s, 3H), 1.36 (s, 3H), 2.30 (s, 3H), 3.00 (broad, 1H), 3.10 (d, J_{34} = 9.0, 1H), 3.46 (s, 3H), 3.50 (s, 3H), 3.51 (dd, J_{12} = 8.5, J_{23} = 9.0, 1H), 4.44 (d, J_{12} = 8.5, 1H), 5.26 (dd, J_{23} = J_{34} = 9.0, 1H), 5.97 (dd, J = 4, J = 3, 1H), 6.87 (dd, J = 4, J = 3, 1H), 9.42 (broad, 1H); MS(*m/e*): 313 (25), 281 (1), 255 (4), 192 (8), 182 (17), 181 (10), 167 (19), 138 (24), 137 (10), 136 (10), 135 (65), 109 (28), 108 (200), 107 (22), 101 (7), 99 (17), 97 (11), 87 (10), 86 (100), 80 (15). (Found: C, 57.81; H, 7.72; N, 4.61. Calc. for $C_{15}H_{23}NO_6$ (313.36): C, 57.50; H, 7.40; N, 4.47%).

Oxidation of **4** *to* **6**

Applying the procedure already described for the conversion of **3** to **5** to the oxidation of **4** (170 mg; 0.54 mmol) gave, after 2-fold thick layer chromatography, 132 mg (78%) of 5,6-dihydro-2,5 β - dimethoxy - 6,6 - dimethyl - 4 - (5 - methyl - 2 - pyrrolylcarbonyloxy) - 2H - pyran - 3(4H) - one (**6**) as a colorless liquid: $[\alpha]_D^{25}$ + 46° (1, $CHCl_3$); IR ($CHCl_3$): 3450m, 3325bw, 1765m, 1710, 1495, 1325m, 1240m, 1145, 1105, 1040, 800bw cm^{-1}; UV (EtOH): 229 nm (3740), 279 nm (16,110); NMR ($CDCl_3$); δ 1.40 (s, 3H), 1.42 (s, 3H), 2.22 (s, 3H), 3.50 (d, J_{34} = 10.0, 1H), 3.50 (s, 6H), 4.89 (s, 1H), 5.62 (d, J_{34} = 10, 1H), 5.93 (dd, J = 4, J = 3, 1H), 6.89 (dd, J = 4, J = 3, 1H), 9.54 (broad, 1H); MS (*m/e*): 311 (2), 283 (5), 224 (3), 219 (2), 191 (3), 165 (2), 143 (2), 139 (2), 127 (4), 125 (8), 109 (16), 108 (200), 107 (7), 105 (7), 101 (8), 100 (4), 99 (42), 98 (6), 86 (10), 80 (13).

Reduction of **6** *to* **4** *and* **11**

A soln of **6** (127 mg; 0.41 mmol) and $NaBH_4$ (175 mg; 4.6 mmol) in MeOH (6 ml) and DMF (1 ml) was stirred at room temp. for 1.25 hr. The mixture was taken up in EtOAc, and the soln was washed 4 times with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Thick layer chromatography of the residue on silica gel, developed with benzene and EtOAc (1 : 1), gave two bands which were eluted with EtOAc–MeOH (9 : 1). The eluate of the upper band (82 mg, 64%) was crystallized from an ether–heptane mixture to give **4**: m.p. 146–147°; mixture m.p. with authentic **4** 144–146°.

The eluate of the lower band gave 27 mg (21%) of β-methyl 2 - 0 - (5 - methyl - 2 - pyrrolylcarbonyl) - 4 - 0 - methyl - 5,5 - dimethyl - L - lyxoside (**11**) as a colorless liquid: NMR ($CDCl_3$): 1.22 (s, 3H), 1.43 (s, 3H), 2.27 (s, 3H), 2.96 (broad, 1H), 3.21 (d, J_{34} = 8.5, 1H), 3.42 (s, 3H), 3.54 (s, 3H), 3.95 (m, J_{34} = 8.5, 1H), 4.64 (d, J_{12} = 1.5, 1H), 5.44 (dd, J_{12} = 1.5, J_{23} = 4, 1H), 5.96 (dd, J = 4, J = 3, 1H), 6.95 (dd, J = 4, J = 3, 1H), 9.38 (broad, 1H).

Oxidation of **8** *to* **6**

Using the procedure already described for the conversion of **3** to **5** for the oxidation of **8** (195 mg; 0.62 mmol) gave **6** (120 mg; 62%) as a colorless liquid exhibiting spectral data identical with those reported for authentic **6**.

Equilibrations **3**⇄**4** *and* **7**⇄**8**

The positions of the anomeric equilibria **3**⇄**4** and **7**⇄**8** were determined as follows: Between 30 and 50 mg of each of the four anomers was heated at reflux for 1 hr (**3**⇄**5**) or 4 hr (**7**⇄**8**) in 10 ml of dry MeOH to which 2 drops of conc. HCl had been added. The mixture was then taken to dryness, dissolved in CH_2Cl_2 and the soln was dried over Na_2SO_4. The recovery of material after removal of the solvent was always quantitative. The mixture, dissolved in CH_2Cl_2, was applied to a silica gel thick layer plate which was developed with benzene–EtOAc (1 : 1). The mixture of anomers which appeared as two very close bands with R_f 0.3 was isolated in each instance in greater than 90% yield and its composition was determined quantitatively by NMR (60 Mc, in pyridine d-5) and GLC (glass column 180 × 0.2 cm; 10% OV-225 as liq. phase at 230°; 27 ml N_2/min; retention times: **3**, 22.0 min; **4**, 18.0 min; **7**, 20.5 min; **8**, 24.7 min. The resulting equilibrium compositions are recorded in Fig. 1.

Preparation of **12**

A soln of 2', 2'-0,0-ditetrahydropyranyl coumermycin A_1[22] (12.78 g; 10 mmol), water (360 mg; 20 mmol) and *p*-bromobenzoyl chloride (8.77 g; 40 mmol) in dry pyridine (160 ml) was stirred under N_2 at 55° for 22 hr. The mixture was concentrated on a rotary evaporator to one-third of the original volume and the pH adjusted to 2 by the addition of ice cold 6N HCl. The resulting ppt was collected, washed with water, taken up in CH_2Cl_2 and the soln was washed with brine and dried over Na_2SO_4. To the residual oil (15 g) obtained upon evaporation of the solvent was added a soln of 3.8 g (20 mmol) of *p*-toluenesulfonic acid monohydrate in 160 ml of MeOH and the resulting suspension was stirred for 5 hr at room temp. The mixture was poured onto 800 ml of ice water, extracted with EtOAc and the organic phase was washed with Na_2CO_3aq and finally with brine. Removal of the solvent left 3.74 g (55.8%) of crystalline material which was crystallized twice from a THF–cyclohexane mixture, then once from a THF–ether mixture and finally twice from a THF-acetonitrile mixture to give 3 - (4 - bromobenzamido) - 4 - hydroxy - 8 - methyl - 7 - [3 - 0 - (5 - methyl - 2 - pyrrolylcarbonyl)noviosyloxy] - coumarin (**12**) as pale yellow needles: m.p. 274–276° dec (lit.[22] 165° dec); $[\alpha]_D^{25}$ – 84.2° (1, THF); IR (KBr): strong bands at 1705, 1690sh, 1635, 1605, 1485, 1215, 1138, 1112, 1095, 762, 737 cm^{-1}; NMR (DMSO-d_6): δ 1.10 (s, 3H), 1.30 (s,

3H), 2.21 (s, 3H), 2.25 (s, 3H), 3.45 (s, 3H), 3.64 (d, J_{34} = 10, 1H), 4.16 (m, 1H), 5.50 (dd, J_{23} = 3, J_{34} = 10, 1H), 5.59 (d, J_{12} = 2, 1H), 5.89 (dd, J = 4, J = 3, 1H), 6.74 (dd, J = 4, J = 3, 1H), 7.17 (AB, J = 8, 1H), 7.65 (*AA'*BB', J = 9, 2H), 7.72 (AB, J = 8, 1H), 7.94 (AA'*BB'*, J = 9, 2H), 9.53 (s, 1H), 12.0 (s, 1H). (Found: C, 55.43; H, 4.86; Br, 12.07; N, 4.04. Calc. for $C_{31}H_{31}BrN_2O_{10}$ (671.51): C, 55.45; H, 4.65; Br, 11.90; N, 4.17%).

Crystallography

Crystals of **12** are orthorhombic, space group $P2_12_12_1$, with 4 molecules in a unit cell of dimensions a = 7.676(3), b = 13.422(8) and c = 29.523(12) Å. Intensity data were collected from two crystals (0.25 × 0.30 × 0.12 mm and 0.25 × 0.40 × 0.14 mm) on a Hilger–Watts model Y290 four circle diffractometer by a moving crystal-moving detector method. Nickel filtered CuK_α radiation and pulse height discrimination were used. The two data sets were corrected for absorption and then placed on a single scale. Of the 2379 independent reflections (after scaling) in the octant out to θ = 57°, 1568 had intensities significantly greater than background and these data were used in the structure analysis.

The structure of **12** was solved by the heavy atom method and was refined by block-diagonal least squares (BDLS). A difference map calculated at the conclusion of anisotropic refinement of the non-H atoms revealed 28 of the 31 H atoms. The three missing atoms were included at their calculated positions. The refinement converged after five additional cycles of BDLS in which the H atoms had individual isotropic temp. factors. The final unweighted and weighted discrepancy indices are R = 0.047 and wR = 0.062 for the 1528 observed reflections.

The final atomic parameters and their estimated standard deviations are listed in Tables 2 and 3. The bond lengths and angles involving the non-hydrogen atoms are presented in Fig. 6. A table of the observed and calculated structure factors is not included, but is available on request from us.

Table 2. Final atomic parameters for **12** with standard deviations in parentheses

Atom	x	y	z	B
Br	0.5817(3)	-0.60216(12)	-0.19002(7)	*
O(1)	0.8371(10)	-0.2269(6)	0.0508(3)	*
O(2)	0.8290(9)	-0.0794(6)	-0.0008(3)	*
O(3)	0.3163(8)	0.0087(4)	0.0022(2)	*
O(4)	0.2354(9)	-0.1261(5)	0.0343(2)	*
O(5)	0.4524(8)	0.2948(5)	0.0856(2)	*
O(6)	0.6818(8)	0.3559(4)	0.1318(2)	*
O(7)	0.4054(10)	0.4182(5)	0.2285(2)	*
O(8)	0.2563(8)	0.5359(4)	0.1612(2)	*
O(9)	0.5453(8)	0.5526(4)	0.1063(2)	*
O(10)	0.0385(8)	0.4913(5)	0.1146(2)	*
N(1)	0.5481(11)	-0.2032(6)	-0.0445(3)	*
N(2)	-0.1733(10)	0.6384(6)	0.1554(2)	*
C(1)	0.6091(18)	-0.4985(9)	-0.1467(4)	*
C(2)	0.4658(15)	-0.4454(9)	-0.1322(4)	*
C(3)	0.4850(15)	-0.3665(8)	0.1029(4)	*
C(4)	0.6488(13)	-0.3384(7)	-0.0890(3)	*
C(5)	0.7926(14)	-0.3972(8)	-0.1027(3)	*
C(6)	0.7718(18)	-0.4769(9)	-0.1315(4)	*
C(7)	0.6866(14)	-0.2523(7)	-0.0598(3)	*
C(8)	0.5350(12)	-0.1136(7)	-0.0202(3)	*
C(9)	0.6620(12)	-0.0582(7)	-0.0001(3)	*
C(10)	0.6185(12)	0.0342(7)	0.0226(3)	*
C(11)	0.4434(12)	0 0664(7)	0.0225(3)	*
C(12)	0.3559(13)	-0.0808(8)	-0.0183(3)	*
C(13)	0.7370(12)	0.0924(7)	0.0450(3)	*
C(14)	0.6898(13)	0.1818(8)	0.0645(4)	*
C(15)	0.5139(12)	0.2099(7)	0.0649(3)	*
C(16)	0.3885(12)	0.1513(7)	0.0443(3)	*
C(17)	0.5673(12)	0.3744(6)	0.0945(3)	*
C(18)	0.6126(13)	0.3479(7)	0.1774(3)	*
C(19)	0.4902(12)	0.4356(7)	0.1864(3)	*
C(20)	0.3549(12)	0.4497(6)	0.1494(3)	*
C(21)	0.4463(12)	0.4627(6)	0.1042(3)	*
C(22)	0.0920(11)	0.5427(7)	0.1442(3)	*
C(23)	-0.0005(11)	0.6244(7)	0.1659(3)	*
C(24)	-0.2391(14)	0.7142(7)	0.1818(3)	*
C(25)	-0.1038(15)	0.7487(8)	0.2088(3)	*
C(26)	0.0428(14)	0.6918(8)	0.1998(3)	*
C(27)	0.1953(13)	0.1811(8)	0.0469(3)	*
C(28)	0.7730(16)	0.3557(8)	0.2061(3)	*
C(29)	0.5300(16)	0.2454(9)	0.1831(4)	*
C(30)	0.3989(18)	0.4999(9)	0.2576(3)	*
C(31)	-0.4210(15)	0.7477(9)	0.1767(4)	*
HO(2)	0.857(12)	-0.113(7)	0.016(3)	7.1(22)
HO(9)	0.569(9)	0.562(5)	0.080(2)	3.2(16)
HN(1)	0.457(9)	-0.207(5)	-0.056(2)	3.3(16)
HN(2)	-0.241(11)	0.621(6)	0.128(2)	5.2(19)
H(2)	0.337(14)	-0.454(7)	-0.143(3)	9.0(28)
H(3)	0.376(11)	-0.314(6)	-0.104(2)	5 1(19)
H(5)	0.896(11)	-0.384(6)	-0.084(2)	5.0(19)
H(6)	0.844(16)	-0.534(9)	-0.139(4)	12.5(35)
H(13)	0.848(10)	0.090(5)	0.039(2)	4.4(18)
H(14)	0.768(11)	0.212(6)	0.080(2)	4.7(19)
H(17)	0.674(9)	0.376(5)	0.064(2)	3.4(16)
H(19)	0.563(9)	0.496(5)	0.186(2)	2.7(14)
H(20)	0.274(9)	0.378(5)	0.145(2)	2.9(15)
H(21)	0.376(9)	0.486(5)	0.080(2)	3.6(16)
H(25)	-0.135(9)	0.797(5)	0.224(2)	2.4(15)
H(26)	0.153(14)	0.683(7)	0.223(3)	9.7(28)
H(27)A	0.149(10)	0.165(6)	0.025(2)	4.0(18)
H(27)B	0.199(12)	0.244(7)	0.031(3)	6.5(22)
H(27)C	0.156(11)	0.207(6)	0 077(3)	5.2(20)
H(28)A	0.739(10)	0.347(5)	0.238(2)	3.5(16)
H(28)B	0.834(11)	0.311(6)	0.203(3)	5.6(20)
H(28)C	0.805(12)	0.418(7)	0.211(3)	6.2(21)
H(29)A	0.430(11)	0.214(6)	0.156(3)	4.7(20)
H(29)B	0.438(12)	0.241(7)	0.183(3)	5.2(21)
H(29)C	0.588(14)	0.233(7)	0.208(3)	8.4(26)
H(30)A	0.383(11)	0.479(6)	0.292(3)	5.6(21)
H(30)B	0.528(11)	0.523(6)	0.260(3)	4.7(20)
H(30)C	0.324(11)	0.553(6)	0.245(3)	4.9(20)
H(31)A	-0.434(11)	0.759(6)	0.142(3)	5.7(20)
H(31)B	0.473(11)	0.780(6)	0.200(3)	5.4(19)
H(31)C	-0.495(13)	0.680(7)	0.180(3)	8.5(24)

* Anisotropic thermal parameters are given in Table 3.

Table 3. Final anisotropic thermal parameters for 12 with standard deviations in parentheses

Atom	B11x10^4	B22x10^5	B33x10^5	B12x10^4	B13x10^5	B23x10^5
Br	456(5)	1156(12)	387(3)	40(2)	-332(11)	-354(6)
O(1)	194(17)	1016(62)	289(15)	-22(8)	152(40)	-181(25)
O(2)	170(16)	1085(63)	220(12)	11(8)	-125(33)	-70(22)
O(3)	162(12)	642(41)	156(9)	23(6)	-125(28)	-52(16)
O(4)	188(14)	770(45)	169(10)	-5(7)	-233(30)	-71(18)
O(5)	161(12)	805(45)	200(10)	5(7)	2(30)	-70(18)
O(6)	154(11)	666(40)	157(9)	0(6)	-27(28)	23(16)
O(7)	319(17)	785(48)	127(8)	-8(8)	85(33)	-4(17)
O(8)	196(13)	578(37)	135(8)	-3(7)	-93(27)	-41(14)
O(9)	235(13)	643(37)	108(7)	-15(7)	-7(27)	58(14)
O(10)	173(13)	815(45)	164(9)	10(7)	-100(30)	-78(18)
N(1)	196(17)	820(56)	153(11)	3(9)	-55(38)	-75(22)
N(2)	202(17)	700(53)	115(9)	17(8)	49(35)	13(19)
C(1)	330(30)	894(84)	197(18)	-7(15)	-162(66)	-44(32)
C(2)	213(24)	913(87)	257(20)	42(13)	112(60)	-53(37)
C(3)	275(27)	742(74)	216(17)	4(13)	-128(57)	-104(31)
C(4)	232(21)	642(58)	108(11)	-14(10)	48(41)	20(22)
C(5)	246(23)	771(71)	151(14)	13(12)	-13(48)	53(29)
C(6)	332(33)	955(96)	176(17)	18(16)	67(64)	-74(35)
C(7)	206(21)	614(62)	149(14)	3(11)	-57(48)	-1(25)
C(8)	190(21)	739(65)	87(10)	-6(10)	-33(38)	4(22)
C(9)	148(21)	747(66)	132(13)	0(10)	-31(40)	47(25)
C(10)	153(17)	638(59)	134(12)	12(10)	43(39)	-36(22)
C(11)	156(18)	619(61)	142(13)	0(9)	-45(40)	4(24)
C(12)	167(21)	720(73)	147(15)	-5(11)	-49(44)	69(27)
C(13)	146(17)	723(69)	204(15)	-12(11)	-14(47)	-161(29)
C(14)	156(20)	844(77)	196(16)	0(10)	-145(46)	-81(31)
C(15)	171(19)	593(59)	133(12)	4(10)	17(41)	-67(23)
C(16)	152(16)	782(67)	104(11)	-5(10)	30(38)	34(24)
C(17)	192(19)	522(54)	144(12)	2(9)	-51(43)	-46(21)
C(18)	211(20)	616(58)	138(13)	14(10)	17(44)	71(23)
C(19)	239(20)	579(54)	101(11)	-10(10)	-39(41)	54(21)
C(20)	183(19)	553(57)	156(14)	-13(9)	-14(43)	-67(23)
C(21)	193(18)	625(58)	103(10)	-3(10)	-53(38)	-13(21)
C(22)	144(19)	741(65)	102(11)	-4(10)	23(39)	21(23)
C(23)	140(18)	698(64)	130(12)	19(9)	-133(36)	-20(24)
C(24)	233(21)	665(62)	121(13)	22(11)	-69(47)	64(25)
C(25)	264(25)	712(68)	156(15)	6(13)	-84(54)	-57(26)
C(26)	270(25)	860(75)	108(12)	21(12)	-179(48)	-10(25)
C(27)	205(21)	965(79)	156(13)	3(11)	-131(46)	-46(28)
C(28)	322(28)	933(82)	178(15)	67(14)	-202(58)	-19(30)
C(29)	351(28)	903(78)	215(18)	-9(14)	-7(63)	182(31)
C(30)	431(35)	922(80)	151(15)	58(16)	-61(64)	-51(30)
C(31)	266(28)	1034(87)	204(18)	35(15)	18(59)	-86(33)

The anisotropic temperature factor has the form

$$\exp(-(\underline{h}^2 B11 + \underline{k}^2 B22 + \underline{\ell}^2 B33 + 2\underline{hk}B12 + 2\underline{h\ell}B13 + 2\underline{k\ell}B23)).$$

Acknowledgements—The authors wish to thank Mr. R. Girven and Mr. J. Tortora for their experimental assistance in certain phases of this work.

REFERENCES

[1]H. Kawaguchi, T. Naito and H. Tsukiura, *J. Antibiotics Japan* Ser. A **18**, 11 (1965).

[2]E. Walton, J. O. Rodin, F. W. Holly, J. W. Richter, C. H. Shunk and K. Folkers, *J. Am. Chem. Soc.* **82**, 1489 (1960).

[3]J. Berger, A. J. Schocher, A. D. Batcho, B. Pecherer, O. Keller, J. Maricq, A. E. Karr, B. Vaterlaus, A. Furlenmeier and H. Spiegelberg, *Antimicrobial Agents and Chemotherapy* 778 (1965).

[4]B. P. Vaterlaus, K. Doebel, J. Kiss, A. I. Rachlin and H. Spiegelberg, *Helv. Chim. Acta* **47**, 390 (1964).

[5]B. T. Golding and R. W. Rickards, *Chem. & Ind.* 1081 (1963).

[6]K. E. Pfitzner and J. G. Moffat, *J. Am. Chem. Soc.* **87**, 5661 (1965).

[7]E. L. Eliel, M. H. Gianni and T. H. Williams, *Tetrahedron Letters* 741 (1962).

[8]A. C. Huitric, J. B. Carr, W. F. Trager and B. J. Nist, *Tetrahedron* **19**, 2145 (1963).

[9]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, in *Conformational Analysis*, p. 412. Wiley, New York (1965).

[10]R. V. Lemieux in *Molecular Rearrangements* (Edited by P. deMayo), Vol. 2, p. 739. Wiley, New York (1964).

[11]S. J. Angyal, V. A. Pickles and R. Ahluwahlia, *Carbohydrate Res.* **1**, 365 (1966).

[12]A. J. DeHoog, H. R. Buys, C. Altona and E. Havinga, *Tetrahedron* **25**, 3365 (1969).

[13]E. L. Eliel and C. A. Giza, *J. Org. Chem.* **33**, 3754 (1968).

[14]C. Altona, Ph.D. Thesis, University of Leiden (1964); p. 117; C. Romers, C. Altona, H. R. Buys and E. Havinga, In *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger) Vol. 4, p. 76. Interscience, New York (1969).

[15]G. A. Jeffrey, J. A. Pople and L. Radom, *Carbohydrate Res.* **25**, 117 (1972).

[16]S. David, O. Eisenstein, W. J. Hehre, L. Salem and R. Hoffmann, *J. Am. Chem. Soc.* **95**, 3806 (1973).

[17]G. Baddeley, *Tetrahedron Letters* 1645 (1973).

[18]W. F. Bailey and E. L. Eliel, *J. Am. Chem. Soc.* **96**, 1798 (1974).

[19]H. M. Berman, S. S. C. Chu and G. A. Jeffrey, *Science* **157**, 1576 (1967).

[20]R. E. Reeves, *J. Am. Chem. Soc.* **71**, 215 (1949); *Adv. Carbohydrate Chem.* **6**, 107 (1951).

[21]S. J. Angyal, *Austral. J. Chem.* **21**, 2737 (1968). *Angew. Chem. Int. Ed.* **8**, 157 (1969).

[22]J. G. Keil, I. R. Hooper, M. J. Cron, O. B. Fardig, D. E. Nettleton, F. A. O'Herron, E. A. Ragan, M. A. Rousche, H. Schmitz, R. H. Schreiber and J. C. Godfrey, *J. Antibiotics (Japan) Ser. A* **21**, 551 (1968).