special destabilization of 7-norbornyl cations is much clearer in these data than it ever could be by considering solvolysis results, in which the effect of flattening at carbon is superimposed on the orbital symmetry effect.[7,9]

Registry No. 1, 51689-29-3; $1^{+\cdot}$, 95484-94-9; 2, 88656-03-5; $2^{+\cdot}$, 95484-95-0; 3, 95484-96-1; 8-(bicyclo[3.2.1]octan-8-ylidene)bicyclo[3.2.1]octane, 95484-97-2; 9-(bicyclo[3.3.1]nonan-9-ylidene)-bicyclo[3.3.1]nonane, 55993-21-0; 2-(2-adamantanylidene)-adamantane, 30541-56-1; tetracyclo[6.2.1.1^{3,6}.0^{2,7}]tetradec-2,7-ene, 73321-28-5; 1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-1,5:3,7:8,12:10,14-tetramethanononalene, 30614-34-7.

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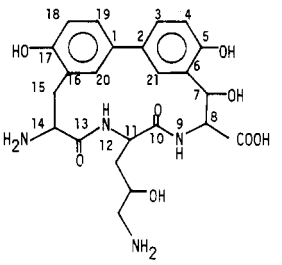

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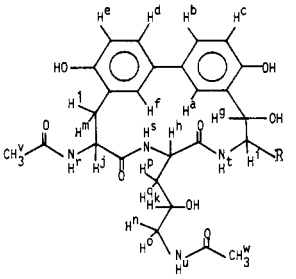
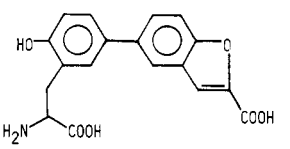


2 R = $COOCH_3$

5 R = CH_2OH



3

Structure of WS-43708A, a Novel Cyclic Peptide Antibiotic

Summary: On the basis of chemical and spectroscopic evidence, the antibiotic WS-43708A ($C_{23}H_{28}N_4O_8$) has been shown to be a cyclic peptide (1) containing a biphenyl moiety included in a 15-membered ring.

Sir: WS-43708A (1), recently isolated from *Streptomyces griseorubiginosus* No. 43078, is a novel cyclic peptide with potent antibacterial acctivity.[1] Herein, we report the structure eludication of this antibiotic on the basis of chemical and spectroscopic evidence.

WS-43708A was isolated as colorless needles from dilute HCl (pH 4): $C_{23}H_{28}N_4O_8 \cdot 2HCl$ (FABMS and elemental analysis);[2] mp 205–209 °C dec; $[\alpha]^{20}_D$ −22.5° (*c* 0.1, 1 N HCl); IR (KBr) 3200, 3000–2300, 1690, 1640 cm^{-1}; UV (H_2O) 264 (ε 18 600), 287 nm (sh); UV (0.1 N NaOH) 288 (ε 24 000), 303 nm (sh); positive ninhydrin test. Acetylation of 1 with Ac_2O in MeOH (0 °C), followed by methylation with CH_2N_2 in MeOH (0 °C), gave the diacetyl monomethyl ester 2 (FABMS, *m/z* 587 ($M^+ + 1$)). Hence, one carboxyl and two amino groups are present in 1. The ^{13}C NMR spectrum (D_2O–DCl) of 1 showed in the sp^3-carbon region eight signals including five methine signals attributable to two secondary alcohol carbons (64.4 (d) and 65.2 (d) ppm) and three α-amino acid carbons (50.9 (d), 55.0 (d), and 57.4 (d) ppm), the remainder being three methylene signals (30.4 (t), 37.9 (t), and 44.9 (t) ppm). In the sp^2-carbon region 15 signals were assignable to three carbonyl groups (168.6 (s), 173.2 (s), and 174.0 (s) ppm) and two phenyl rings substituted totally with six substituents (116.4 (d), 116.9 (d), 120.3 (s), 126.2 (d), 127.2 (d), 127.6 (d), 127.9 (s), 130.6 (d), 132.9 (s), 133.0 (s), 152.8 (s), and 154.2 (s) ppm). Extensive spin decoupling (Table I) of the 400-MHz ^1H NMR spectra of 1 and 2 revealed ^1H–^1H relationships as shown in Figure 1, leading to partial structures A, B, and C, which are quite consistent with the ^{13}C NMR data described above.

The partial unit A was confirmed by the fact that hydrolysis of 1 with 6 N HCl (110 °C, 24 h) gave, after chromatography on Toyopearl HW40S, *erythro*-γ-hydroxy-L-ornithine (HCl salt; mp 176–178 °C dec; $[\alpha]^{23}_D$ +10.9° (*c* 1.0, H_2O)) which was identified by comparison with an authentic sample.[3] The partial units B and C can be combined and extended to partial structure B + C (Figure 2) based on the following grounds. The acid hydrolysis described above also gave compound 3 (FDMS, *m/z* 341 (M^+)),[4] which was converted, by acetylation with Ac_2O in MeOH followed by treatment with CH_2N_2 in MeOH, to the monoacetyl trimethyl derivative 4 (high-resolution EIMS, *m/z* 425.1457, calcd for $C_{23}H_{23}NO_7$ 425.1472). The ^1H NMR analysis of 4 with the aid of decoupling (Table I) and NOE experiments (Figure 2) revealed the structure of 3. The genesis of 3 is rationalized by the following, plausible reaction mechanism from the partial units B and C: (1) dehydration of the β-hydroxy amino acid residue in C to the dehydro amino acid; (2) hydrolysis to the keto acid;[5] (3) dehydrative condensation

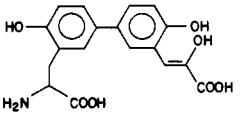
(1) Umehara, K.; Ezaki, M.; Iwami, M.; Yamashita, M.; Hashimoto, S.; Komora, T.; Uchida, I.; Hashimoto, M.; Mine, Y.; Kohsaka, M.; Aoki, H.; Imanaka, H. "Abstracts of Papers", 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 1984, Abstr. No. 1141.

(2) FABMS, *m/z* 489 ($M^+ + 1$) (free base); elemental analysis. Anal. Calcd for $C_{23}H_{28}N_4O_8 \cdot 2HCl \cdot H_2O$: C, 47.65; H, 5.62; N, 9.67; Cl, 12.23. Found: C, 47.80; H, 5.85; N, 9.75; Cl, 12.11.

(3) (a) Mizusaki, K.; Yamamoto, H.; Makizumi, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2605. (b) Mizusaki, K.; Makizumi, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 470.

(4) ^1H NMR (CD_3OD–D_2O) δ 3.19 (dd, *J* = 7.5, 14 Hz, 1 H), 3.47 (dd, *J* = 5, 14 Hz, 1 H), 4.29 (dd, *J* = 5, 7.5 Hz, 1 H), 7.01 (d, *J* = 8.7 Hz, 1H), 7.49 (m, 2 H), 7.64 (s, 1 H), 7.66 (d, *J* = 8.7 Hz, 1 H), 7.70 (dd, *J* = 2, 8.7 Hz, 1 H), 7.90 (d, *J* = 2 Hz, 1 H).

(5) A subsequent inspection of the acid hydrolysate revealed the presence of keto acid i as a minor product, firmly supporting the mechanism leading to 3: ^1H NMR (CD_3OD–D_2O) δ 3.07 (dd, *J* = 8.8, 14 Hz, 1 H), 3.44 (dd, *J* = 4, 14 Hz, 1 H), 6.93 (d, *J* = 8.7 Hz, 1 H), 7.12 (s, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.42 (dd, *J* = 2.5, 8.7 Hz, 1 H), 7.49 (d, *J* = 2.5 Hz, 1 H), 7.59 (dd, *J* = 2.5, 8.7 Hz, 1 H), 7.67 (d, *J* = 2.5 Hz, 1 H).



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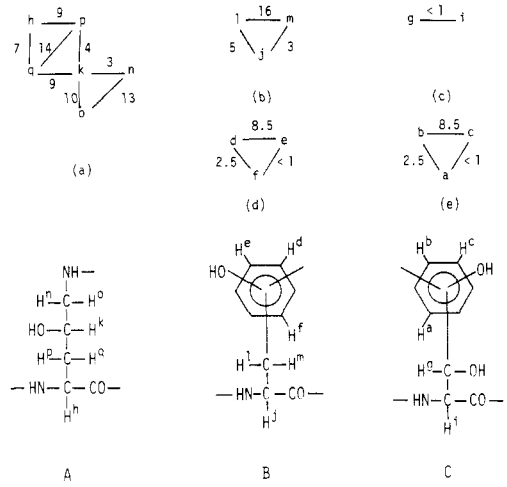

Figure 1. Partial structures A–C and the ^1H–^1H relationships a–e. The ^1H–^1H relationships a, b, and c were obtained by decoupling experiments on 1, while d and e were derived by those on 2. The very small vicinal coupling constant of the H^g–H^i is presumably due to a dihedral angle close to 90° caused by a restricted conformation of WS-43708A.

Table I. ^1H NMR (400 MHz) Chemical Shifts, Multiplicities, and Coupling Constants (J, Hz) for WS-43708A (1), 2, and 4

	1[a]	2[b]	4[c]
H^a	7.40, m (3 H)	7.39, d (2.5)	7.78, br d (2)
H^b	and	7.17, dd (2.5, 8.5)	7.61, dd (2, 8.5)
H^c	6.93, m (2 H)	6.83, d (8.5)	7.62, br d (8.5)
H^d		7.11, dd (2.5, 8.5)	7.48, dd (2.5, 8.5)
H^e		6.78, d (8.5)	6.96, d (8.5)
H^f	6.87, br s	6.88, d (2.5)	7.33, d (2.5)
H^g	5.84, br s	5.70, br s	7.57, s
H^h	5.02, dd (7, 9)	5.09, dt (8.8, 7.5)	
H^i	4.91, br s	4.63, br d (9.5)	
H^j	4.47, dd (3, 5)	4.56, dt (7.5, 3.3)	4.80, dt (7.5, 7.5)
H^k	4.09, dddd (3, 4, 9, 10)	3.64, m	
H^l	3.55, dd (5, 16)	3.16[d]	3.22, d (7.5)
H^m	3.03, dd (3, 16)	2.77, dd (3.3, 15)	
H^n	3.17, dd (3, 13)	3.16[d]	
H^o	2.97, dd (10, 13)	3.07, m	
H^p	2.11, ddd (4, 9, 14)	1.79, m	
H^q	1.95, ddd (7, 9, 17)	1.50, m	
H^r		7.62, d (7.5)	6.23, d (7.5)
H^s		8.50, d (8.8)	
H^t		8.53, d (9.5)	
H^u		7.88, t (5.5)	
H^v		1.84, s (6 H)	1.95, s (3 H)
H^w			
H^x		3.71, s (3 H)	4.10, s (3 H)
H^y			3.73, s (3 H)
H^z			3.91, s (3 H)

[a] D_2O–DCl. [b] Me_2SO-d_6. [c] $CDCl_3$. [d] Overlapping signals of H^l and H^n prevented the examination of their multiplicities.

with the phenolic hydroxy group to the benzofuran structure 3. These chemical evidence thus leads to the partial structure B + C.

The problem remaining is to link A and B + C for the full structure of WS-43708A. Since a molecular model study indicated that an intramolecular cyclization of B + C itself is practically impossible, insertion of fragment A was proposed. This was corroborated by the ^1H NMR spectrum of 1 in D_2O–NaOD, in which, in contrast to upfield shifts of 0.36 and 0.67 ppm, respectively, for H^i and H^j (δ 4.90 and 4.47 in D_2O–DCl), no shift was observed on

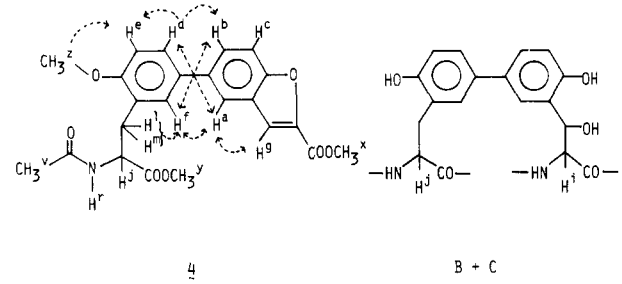

Figure 2. Structure of 4 and the partial structure B + C. The observed NOEs in 4 are shown by dotted line arrows.

H^h (δ 5.02 in both D_2O–DCl and D_2O–NaOD), indicating that the α-amino acid group of A is incorporated in a cyclic peptide structure.[6,7] Reduction of 2 with $NaBH_4$ in MeOH gave alcohol 5 (FABMS, m/z 559 (M^+ + 1)), in the ^1H NMR spectrum (CD_3OD) of which a singlet-like signal (δ 4.89, CD_3OD) corresponding to H^i in 2 was changed to a triplet (δ 4.20, J = 7.5 Hz) coupled to the newly formed methylene group (δ 3.65 (dd, J = 7.5, 11 Hz) and 3.78 (dd, J = 7.5, 11 Hz)). This indicates that the carboxylic acid function in 1 is bonded to C-8 bearing H^i. Consequently, peptide bonds between N-9/C-10 and N-12/C-13 are postulated to give the full structure of 1, without stereochemistry, for WS-43708A.[8]

The biphenyl group incorporated in the 15-membered cyclic peptide portion of WS-43708A is unique and such compounds are rarely found in nature.[9] The exceptional activity of WS-43708A against gram-positive bacteria will be reported separately.

Registry No. 1, 95485-50-0; 2, 95485-51-1; 3, 95485-52-2; 4, 95485-53-3; 5, 95485-54-4; *erythro*-γ-hydroxy-L-ornithine hydrochloride, 95485-55-5.

(6) For the pH-dependent chemical shifts of the α-methine protons of peptides, see: Sheinblatt, M. *J. Am. Chem. Soc.* **1966**, *88*, 2845.
(7) The ^1H NMR spectrum (Me_2SO-d_6) of 2 showed a triplet (J = 5.5 Hz) corresponding to the amido H originated from the δ-amino group of A at δ 7.88 coupled to H^n and H^o (δ 3.07 (m) and 3.16 (m)), thus supporting that the δ-amino group of A in 1 is unsubstituted.
(8) Stereochemical deductions aside from that of the ornithine portion are the subject of future publications.
(9) As far as we are aware, the only antibiotics that contain a biphenyl group as part of a cyclic peptide system are those that belong to the vancomycin group of antibiotics, see: Barna, J. C. J.; Williams, D. H. *Annu. Rev. Microbiol.* **1984**, *38*, 339.

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Total Synthesis of (–)-Gilmicolin

Summary: The total synthesis of (–)-gilmicolin is disclosed; assignment of absolute stereochemistry is thereby secured.

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