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A REARRANGEMENT IN THE BICYCLOMYCIN SERIES

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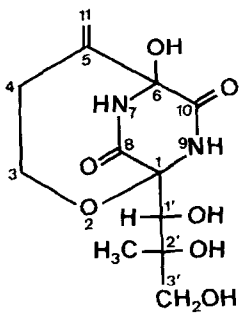
Summary: A rearrangement of 7-N-methyl-3'-O-benzoyl-(3) and 7,9-N,N-dimethyl-bicyclomycin (5) is described, which proceeds by opening of the aminal diketopiperazine ring and subsequent recyclization.

Several synthetic approaches to the bicyclomycin ring system have been attempted [1], but no total synthesis of 1 has yet been achieved.

Judging from the hitherto published reports [1] the major problems in synthesizing bicyclomycin 1 arise through the difficulty of introducing the C-6 hydroxyl group, since the thermodynamically more stable bis-spiro derivative 2 [1(a)] is easily formed in acid-catalyzed reactions, and through the lack of suitable N-protecting groups which would allow efficient cleavage



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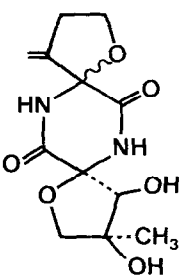
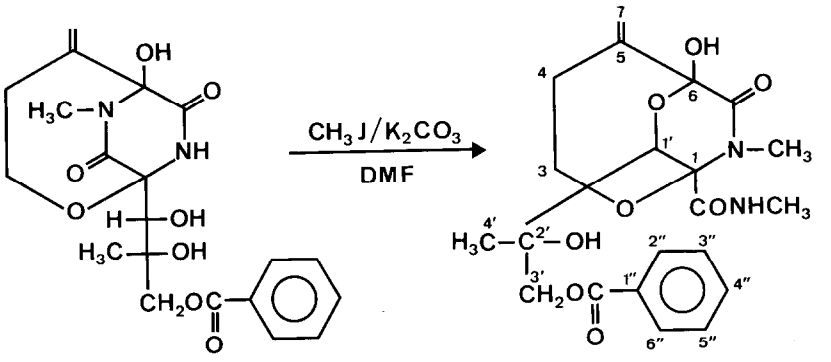


2

advantageously under non-acidic conditions.

The above-mentioned synthetic studies now prompt us to report a rearrangement in the bicyclomycin series which we found during our work on semisynthetic derivatives[2]. In our opinion knowledge of this rearrangement might contribute towards the solution of the problems associated in the synthesis of 1.



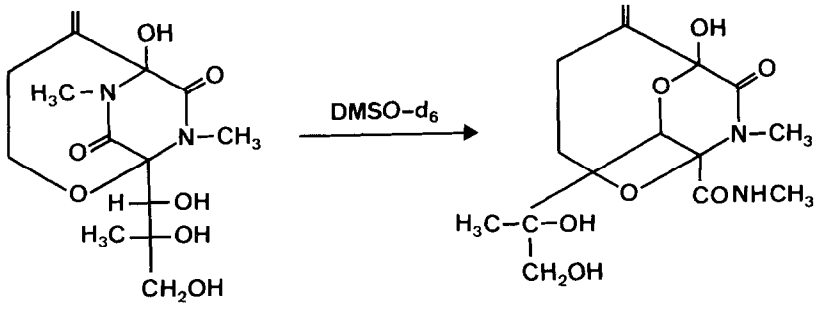
3 4

Methylation of 3 [3] with CH_3J (1.7 eq.) in the presence of anhydrous K_2CO_3 in DMF (30 hrs., 40°C) produced a mixture, which TLC (silica gel Merck 60 F_{254}, $CHCl_3$/MeOH 9:1) showed to consist of a small amount of unreacted 3, 4 as the major component, and three faster-running minor products which have not been characterized. 4 has been isolated from the mixture by column chromatography (silica gel Merck, 0.063-0.200 mm; $CHCl_3$/MeOH 9:1) and subsequently recrystallized twice from ethyl acetate/pentane 1:5 [22%, hygroskopic, colourless crystals, melting at 102-113°C (dec.)].

The structure of 4 was confirmed by ^{1}H-NMR and ^{13}C-NMR [4]. ^{1}H-NMR shows a broad quartet at δ (ppm) 8.15 for -NH-CH_3 and a doublet at δ(ppm) 2.65 for -NH-CH_3. No coupling of H-C-1' with -OH [δ(ppm) 4.33/s/H-C-O] is observed. ^{13}C-NMR is also consistent with the structure. The signal of C-6 appears at δ(ppm) 96.4 (s) compared with 84.1 (s) for 3, while the signals of C-1 and C-1' shifted from δ (ppm) 87.6(s) for 3 to 90.6(s) and 69.7(d) to 76.1(d), respectively.

The rearrangement seems likely to proceed by opening of the aminal diketopiperazine ring and recyclization by attack of C-1'-O[6].

This is supported by the observation that methylation with CH_3J under the above-mentioned conditions produced no rearranged compound of type 4 either with 1',3'-O,O-dibenzoylbicyclomycin [5] or with 2,'3'-O,O-isopropylidene-bicyclomycin [6], in the latter case probably because of steric hindrance of the acetonide group.



5 6

The rearrangement could also be achieved under even milder conditions. ^{1}H-NMR and ^{13}C-NMR studies showed that when 5 [2] was stored in DMSO-d_6 at 25°C for 24 hrs. the major part underwent rearrangement to 6. After 96 hrs. the reaction was almost complete. DMSO is obviously a suitable solvent for the rearrangement. Attempts to convert 5 to 6 in $CDCl_3$ at 25°C failed. Furthermore, the participation of the bridge-head (C-6) hydroxy group has been indicated by the impossibility of rearranging 6,7,9-O,N-N-trimethyl-bicyclomycin [2] in DMSO-d_6 at 25°C.

In contrast to 5, 7-N-monomethyl-bicyclomycin [2] could not be converted to the corresponding rearrangement product, even in DMSO-d_6 at 25°C. It seems to us that in the case of 5 this remarkably smooth rearrangement is probably made easy because 5 does not possess the stabilizing intramolecular hydrogen bond N(9)....HO(C-2'). [7]

Knowledge of this rearrangement might be helpful in the selection of suitable N-protecting groups and cleavage conditions for use in the synthesis of 1.

Acknowledgment: We are indebted to Dr. T. Winkler, CIBA-GEIGY Ltd., for the interpretation of the NMR spectra. We also wish to thank Dr. R. Scartazzini, CIBA-GEIGY Ltd., for stimulating discussions.

Note: After completion of the present paper the authors learned that J. Yoshimura, M. Yamaura, T. Suzuki, and H. Hashimoto (Chemistry Letters 1983, 1001) have reported on the oxidative removal of the N-(p-methoxybenzyl) group from the diketopiperazine skeleton with ceric ammonium nitrate. In a foot-note (10) these authors also mention that at the 47th National Meeting of the Chemical Society of Japan, Kyoto, April 1983 (Abstr. No. 3H-14), S. Nakatsuka, K. Yamada, O. Asano, K. Yoshida, and T. Goto reported on their use of the benzyl group for protection in the synthesis of bicyclomycin. This work has not yet been published elsewhere.

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2. B.W. Müller, O. Zak. W. Kump, W. Tosch, and O. Wacker, J.Antibiotics 32, 689 (1979).

3. T. Kamiya, S. Maeno, Y. Kitaura (Fujisawa), Brit.Patent 1 568961.

4. Data for 4: $[\alpha]_D^{20}$: -74.0 ± 1.0° (c=0.932, dioxane); R_f: 0.54 ($CHCl_3$/MeOH 9:1); UV (EtOH): $\lambda_{max.}$ = 227.5 mμ (ε=12'600); IR (nujol): 3400, 2900, 2880 (shoulder), 1730 (shoulder), 1700, 1530, 1470, 1380 cm^{-1}; ^{1}H-NMR (DMSO-d_6): 1.31 (s/CH_3), ~2.12-2.41 (m/CH_2-CH_2-O), 2.65 (d/NH-CH_3), 2.67 (s/N-CH_3), ~2.81-3.46 (m/1H/OCH_2CH_2/HDO), 4.17 (sb/2H/CH_2-OCO/1H/OCH_2CH_2), 4.33 (s/H-C-O), 4.60(s/OH), 5.02 and 5.33 (2 x m/CH_2=C), 7.06 (s/OH), ~7.40-7.73 (m/3H/C_6H_5-C=O), ~8.0-8.12(m/2H, C_6H_5-C=O), 8.15 (qb/NH-CH_3); ^{13}C-NMR (DMSO-d_6): 168.8, 166.1, 165.7 3 x C=O, 148.2 C-5, 133.1 C-4", 130.0 C-1", 129.3 C-2" and C-6", 128.5 C-3" and C-5", 115.7 C-7, 96.4 C-6, 90.6 C-1, 76.7 C-1', 71.9 C-2', 70.1 C-3', 64.6 C-3, 36.5 C-4, 30.9 N-CH_3, 25.8 N-CH_3, 19.8 C-4'; X-Ray: Could not be obtained because of decomposition during the exposure; MS: 434 (>>1, M^+, $C_{21}H_{26}N_2O_8$), 348(1), 299(4), 255(5), 239(13), 226(15), 208(6), 183(7), 168(47), 167(18), 140(22), 105(100), 99(18), 77(28), 58(16); Anal. $C_{21}H_{26}N_2O_8 \cdot 0.268\ H_2O$ (439.28): C, H, N, O, H_2O.

5. T. Kamiya, S. Maeno, M. Hashimoto, and Y. Mine, J.Antibiotics 25, 576 (1972).

6. T. Kamiya, S. Maeno, and Y. Kitaura (Fujisawa), Belgian Patent 847,475.

7. For X-Ray diffraction analysis see Y. Tokuma, Sh. Koda, T. Miyoshi, and Y. Morimoto, Bull.Chem.Soc. (Japan), 47, 18 (1974).

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