SYNTHESIS OF THE CARBOCYCLIC ANALOGUE OF OXETANOCIN A[1)]

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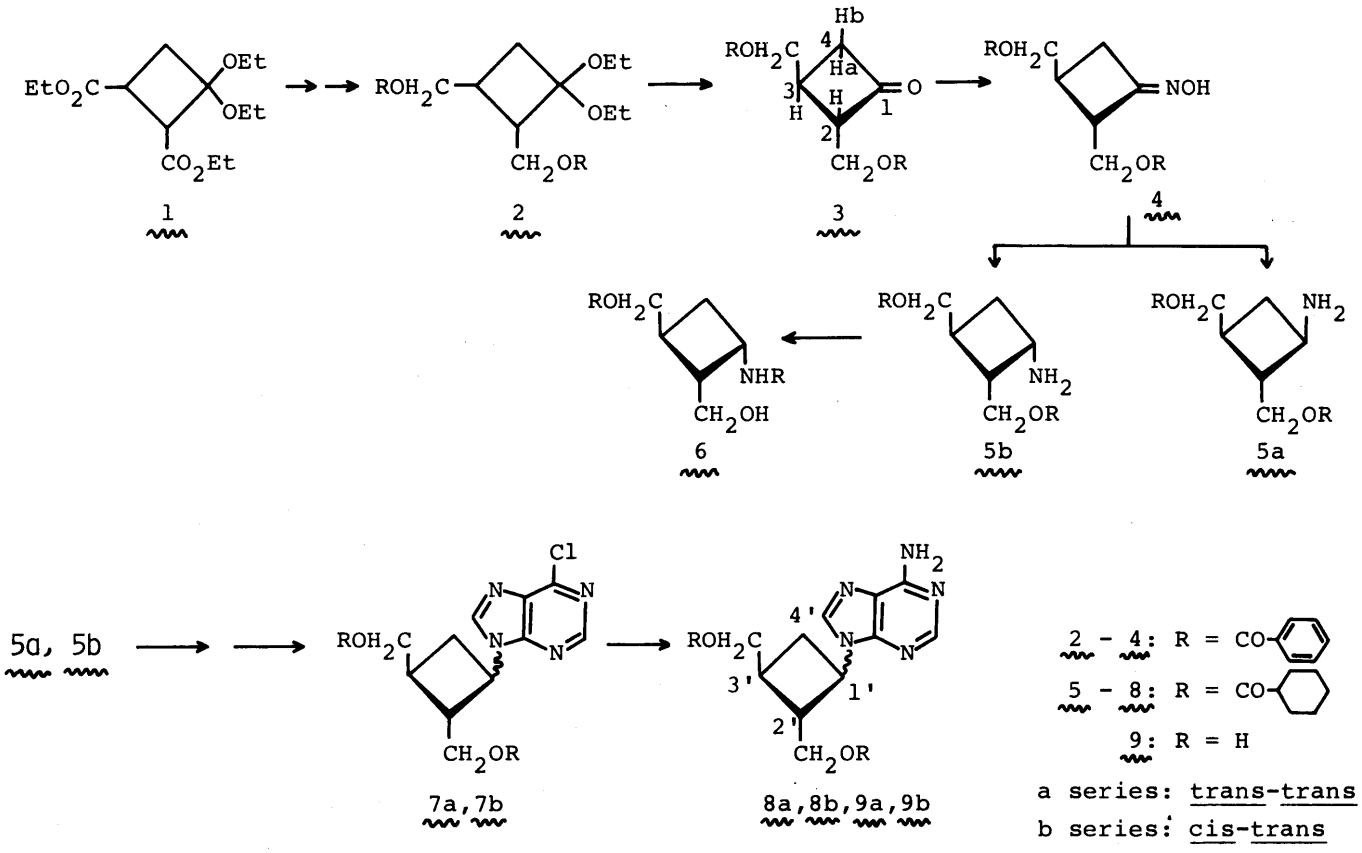
2,3-Bis(benzoyloxymethyl)cyclobutanone (3) was prepared in three steps from diethyl 3,3-diethoxy-1,2-cyclobutanedicarboxylate (1). Hydrogenation of the oxime (4) of 3 provided the two amino compounds (5a and 5b), from which 9-[2,3-bis(hydroxymethyl)cyclobutyl]adenines (9a and 9b) were synthesized in four steps. The steric configurations of 3, 5a, 5b, 9a and 9b were established by ^{1}H-NMR spectroscopies including the NOE difference experiments.

KEYWORDS oxetanocin; carbocyclic nucleoside; 9-[2,3-bis(hydroxymethyl)-cyclobutyl]adenine; bis(hydroxymethyl)cyclobutane; adenine; diastereomer; NOE

Since the isolation of aristeromycin[2)] and neplanocins (A[3)], B and C[4)]), which are the naturally occurring carbocyclic analogues of adenosine, much attention has been focussed on the synthesis of carbocyclic analogues of purine and pyrimidine nucleosides.[5)] Recently, there has been reported the isolation, biological evaluation[6)] and synthesis[7)] of oxetanocin A, which contains adenine and an oxetane ring, and has antiviral, antitumor and antibacterial activities. This paper deals with the synthesis of potential antiviral or antitumor carboxetanocin A.

Reduction of diethyl 3,3-diethoxy-1,2-cyclobutanedicarboxylate (1)[8)] with lithium aluminum hydride in a mixture of THF and ether, followed by treatment with benzoyl chloride in pyridine afforded a dibenzoate (2) as white needles (mp 71.0-71.5°C)[9)] in 60% overall yield from 1. Cleavage of the ketal of 2 with p-toluenesulfonic acid in acetone gave quantitatively a ketone (3) as white needles (mp 77.5-78.0°C). The structure of 3 was established by MS, ^{1}H-NMR spectrum ($CDCl_3$) and elemental analysis.[10)] The trans configuration of 2- and 3-benzoyloxymethyl groups of 3 was supported by the NOE difference experiment: irradiation of the multiplet centered at 2.96 ppm, corresponding to H-3 resulted in the expected NOE (ca. 7%) to H-4a at 3.25 ppm, but not to H-2 at 3.66 ppm. Treatment of 3 with hydroxylamine gave an oxime (4) as white needles (mp 114-115°C)[11)] in 93% yield. Compound 4 was subjected to hydrogenation in the presence of platinum oxide to yield 5a [white needles, (mp 100-103°C)] and 5b (a caramel) in 20% and 28% yields respectively, after purification by a silica gel column chromatography. The two compounds exhibited positive ninhydrin tests and were assigned the 1-amino-2,3-bis(cyclohexylcarbonyloxymethyl)cyclobutane structures by their MS, ^{1}H-NMR spectra and elemental analyses.[12)] The ^{1}H-NMR spectrum of 5a showed the presence of multiplet peaks at 4.08-4.15 ppm attributable to the methylene protons attached to C-2. The spectrum of 5b revealed each double doublet peaks at 4.14 and 4.36 ppm, both of which can be analyzed as an ABX spin system and are attributable to the corresponding C-2 methylene protons. This shows that 5a has the free rotation of the C-2 methylene group (1-2 trans), while 5b has the restricted rotation of the C-2 methylene group, because of steric hindrance due to the C-1 amino group



(1-2 cis). When 5b was allowed to stand at room temperature over a month, it was converted to white crystalline mass (mp 112-113°C). The structure of the product was identified as 1-(cyclohexylcarbonyl)amino-3-(cyclohexylcarbonyloxy)methyl-2-cyclobutanemethanol (6) by MS, ^{1}H-NMR spectrum and elemental analysis,[13] as well as a negative ninhydrin test. This intramolecular O→N acyl migration of 5b to 6 supports the correctness of the 1-2 cis configuration of 5b.

Reaction of 5a with 5-amino-4,6-dichloropyrimidine, followed by treatment with triethyl orthoformate afforded the 6-chloropurine derivative (7a) as a caramel. The structure was ascertained by MS, UV absorption and ^{1}H-NMR spectra.[14] Amination of 7a with liquid ammonia at 40°C overnight gave the adenine derivative (8a) as a caramel.[15] Hydrolysis of 8a with sodium hydroxide afforded racemic carboxetanocin A (9a) as white crystalline mass (mp 190.5-192°C), whose structure was established by MS, UV absorption and ^{1}H-NMR (DMSO-d_6) spectra as well as elemental analysis.[16]

A series of analogous reactions of 5b gave the corresponding diastereomer, 7b,[17] 8b[18] and 9b[19]. The 1'-2' trans configuration of 9a and the 1'-2' cis configuration of 9b were further established by the NOE difference experiments, respectively: in the case of 9b, irradiation of the multiplet centered at 2.60 ppm corresponding to H-2' gave the NOE to H-1' at 5.13 ppm, while in the case of 9a, irradiation of the multiplet centered at 2.79 ppm corresponding to H-2' did not give the NOE to H-1' at 4.63 ppm. The 2'-3' trans configurations of both 9a and 9b were also evidenced by the NOE difference experiments. Thus, the steric configurations of 9a and 9b are trans-trans and cis-trans, respectively.

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9) Anal. Calcd for $C_{24}H_{28}O_6$: C,69.88; H,6.84. Found: C,70.05; H,6.91. MS(m/z):291 ($M^+-C_6H_5CO_2$).
10) Anal. Calcd for $C_{20}H_{18}O_5$: C,70.99; H,5.36. Found: C,71.03; H,5.44. MS(m/z):310 (M^+-CO). δ:7.4-8.05 (10H, m, COC_6H_5), 4.5-4.65 (4H, m, $-CH_2O-$), 3.66 (1H, m, H2), 3.25 (1H, ddd, H4a), 3.07 (1H, ddd, H4b), 2.96 (1H, m, H3).
11) Anal. Calcd for $C_{20}H_{19}NO_5$: C,67.98; H,5.42; N,3.96. Found: C,68.06; H,5.49; N,3.93. MS(m/z):353(M^+), 336(M^+-OH). δ:8.29-8.49 (1H,br s, =N-OH), 7.2-8.1 (10H, m, COC_6H_5), 4.4-4.7 (4H, m, $-CH_2O-$), 2.6-3.3 (4H, m, H2, H3, H4).
12) 5a— Anal. Calcd for $C_{20}H_{33}NO_4 \cdot 1/5\ H_2O$: C,67.65; H,9.48; N,3.94. Found: C,67.47; H,9.54; N,3.49. MS(m/z):352 (M+1). δ:4.08-4.15 (2H, m, 2-CH_2O-), 4.00-4.10 (2H, m, 3-CH_2O-), 3.13 (1H, ddd, H1), 2.24-2.37 (4H, m, H4, $-OCOC\underline{H}(-)(CH_2)_5-$), 1.98-2.05 (2H, m, H2, H3), 1.18-1.97 (m, $-OCOCH(-)(C\underline{H}_2)_5-$).
5b— MS(m/z):352 (M+1). δ:4.36,4.14 (2H, each dd, 2-CH_2O-), 4.08 (2H, d, 3-CH_2O-), 3.69 (1H, ddd, H1), 2.0-2.5 (4H, m, H2, H3, H4), 1.2-2.0 (m, $-OCOC\underline{H}(-)(C\underline{H}_2)_5-$).
13) Anal. Calcd for $C_{20}H_{33}NO_4$: C,68.34; H,9.46; N,3.98. Found: C,68.42; H,9.66; N,3.88. MS(m/z):352(M+1). δ:6.1 (1H, d, N-H), 4.35 (1H, m, H1), 4.10,4.04 (2H, each dd, 3-CH_2O-), 3.56(2H, d, $-C\underline{H}_2OH$), 3.06 (1H, br s, $-CH_2O\underline{H}$), 2.55 (1H, m, H2), 2.39 (1H, ddd, H3), 2.3 (2H, m, H4), 1.2-2.2 (m, $-OCOC\underline{H}(-)(C\underline{H}_2)_5-$, $-NHCOC\underline{H}(-)(C\underline{H}_2)_5-$).
14) λ_{max}^{MeOH} nm: 266, λ_{max}^{pH1} nm:266, λ_{max}^{pH11}nm:265, MS(m/z):488,490(M^+). δ: 8.75 (1H, s, H8), 8.18 (1H, s, H2), 4.6-4.95 (1H, m, H1'), 4.2-4.3 (4H, m, $-CH_2O-$).
15) λ_{max}^{MeOH} nm: 262, λ_{max}^{pH1} nm:261, λ_{max}^{pH11}nm:262, MS(m/z):469(M^+).
16) Anal. Calcd for $C_{11}H_{15}N_5O_2 \cdot 1/10H_2O$: C,52.62; H,6.10; N,27.89. Found: C,52.33; H,5.97; N,28.34. UV $\lambda_{max}^{H_2O}$nm (ε):261(14600), λ_{max}^{pH1}nm (ε):259.5(14400), λ_{max}^{pH11}nm (ε):261(14700). MS(m/z):249(M^+). δ:8.24 (1H, s, H8), 8.13 (1H, s, H2), 7.20 (2H, s, NH_2), 4.65, 4.79 (each 1H, br s, $-CH_2O\underline{H}$), 4.63 (1H, ddd, H1'), 3.52 (4H, s-like, $-C\underline{H}_2OH$), 2.78 (1H, m, H2'), 2.43 (1H, ddd, H4'a), 2.24 (1H, ddd, H4'b), 2.10 (1H, m, H3').
17) λ_{max}^{MeOH}nm: 265, λ_{max}^{pH1}nm: 264, λ_{max}^{pH11}nm: 264, MS(m/z):488,490(M^+).
18) λ_{max}^{MeOH}nm: 261, λ_{max}^{pH1}nm: 260, λ_{max}^{pH11}nm: 261, MS(m/z):469(M^+).
19) mp 220-221°C. Anal. Calcd for $C_{11}H_{15}N_5O_2 \cdot 4/5H_2O$: C,50.11; H,6.35; N,26.56. Found: C,49.84; H,6.40; N,26.86. UV $\lambda_{max}^{H_2O}$nm (ε):261(14700), λ_{max}^{pH1}nm (ε):260(14500), λ_{max}^{pH11}nm (ε): 261(14600). MS(m/z):249(M^+). δ:8.30 (1H, s, H8), 8.11 (1H, s, H2), 7.15 (2H, s, NH_2), 5.13 (1H, ddd, H1'), 4.73 (1H, dd, 3'-$CH_2O\underline{H}$), 4.3 (1H, dd, 2'-$CH_2O\underline{H}$), 3.55 (2H, dd, 3'-$C\underline{H}_2OH$), 3.2-3.3 (2H, m, 2'-$C\underline{H}_2OH$), 2.93 (1H, ddd, H4'a), 2.60 (1H, m, H2'), 2.28-2.40 (2H, m, H3', H4'b).

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