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SYNTHESIS OF CLEONINE, AMINO(1-HYDROXYCYCLOPROPYL)ACETIC ACID, A NOVEL AMINO ACID CONTAINED IN CLEOMYCIN

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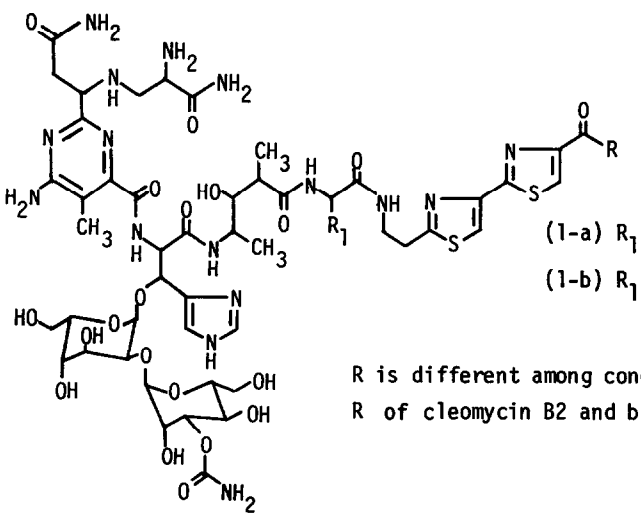
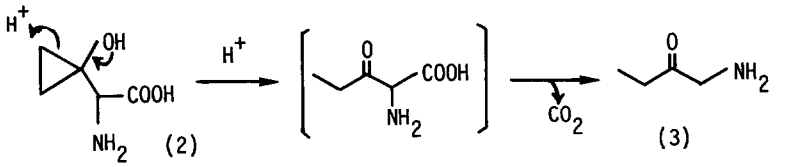
Summary: The synthesis of cleonine, amino(1-hydroxycyclopropyl)acetic acid, a novel amino acid contained in cleomycin, a new bleomycin-phleomycin group antibiotic, is described.

Cleomycin (1-a) is a new family of bleomycin-phleomycin group antibiotics and is different from bleomycin (1-b) only in its threonine moiety.[1] A novel amino acid designated cleonine, amino(1-hydroxycyclopropyl)acetic acid (2), is located in the place of the threonine of bleomycin. Acid hydrolysis of cleomycin did not give cleonine, but gave 1-amino-2-butanone (3). The stereochemistry of the cleonine appears to be S from biosynthetic viewpoint.[1] We report here a facile synthesis of DL-cleonine.

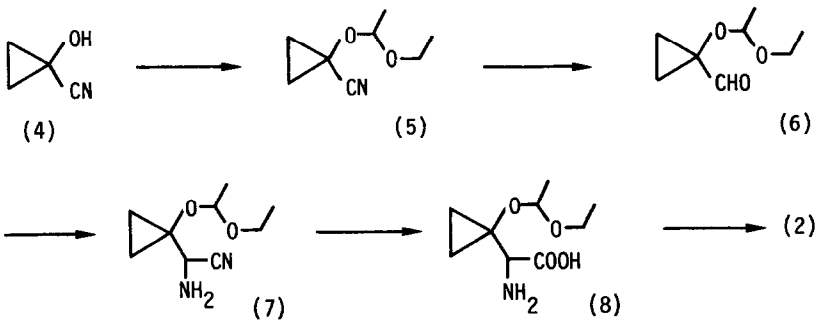


(1-a) R_1 = 1-hydroxycyclopropyl
(1-b) R_1 = 1-hydroxyethyl

R is different among congeners. For an example, R of cleomycin B2 and bleomycin B2 is agmatine.



Readily available cyclopropanone cyanohydrin (4)[2] was treated with excess ethyl vinyl ether at room temperature overnight to give the acetal (5) quantitatively, which was formerly obtained from acrolein by Stork et al.[3] Reduction of (5) with sodium dihydro-bis(2-methoxyethoxy)aluminate[4] (70% in toluene) at 0° followed by neutralization with 0.5N sulfuric acid yielded the aldehyde (6)[5] [65% yield; bp 50-51°(1 mm); ir: ν(film) 3060 and 1710 cm^{-1}; nmr: δ($CDCl_3$) 9.63 (1H singlet: aldehyde) and 1.31 (4H multiplet: ethylene in cyclopropane ring)]. It was converted to the aminonitrile (7)[5] [92% yield as a diastereo mixture; ir: ν(film) 3350, 3060 and 2205 cm^{-1}] followed by hydrolysis with saturated barium hydroxide at reflux for 3 hr. to afford the protected amino acid (8)[5] [62% yield as a diastereo mixture; m.p. 176-178°(dec.)]. Deprotection of (8) was accomplished by stirring with 0.2N sulfuric acid at room temperature for 5 min. to yield DL-cleonine (2)[5] [82% yield; m.p. 223-225°(dec.); ir: ν(nujol) 3400, 3075, 2725, 2620 and 1600 cm^{-1}; nmr: δ[D_2O, internal reference: sodium 3-(trimethylsilyl)propane sulfonate] 3.43 (1H singlet: α-methine) and 0.97 (4H multiplet: ethylene in cyclopropane ring)]. Treatment of the synthetic cleonine (2) with 6N HCl at reflux gave 1-amino-2-butanone (3). Thus, this synthetic study is a confirmative evidence for the structure of cleomycin.



References and note

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2. W. J. M. Van Tilborg, S. E. Schaafsma, H. Steinberg and Th. De Boer, Rec. Trav. Chim. Pays-Bas, 86, 419 (1967)
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4. M. Schlosser and Z. Brich, Helv. Chim. Acta, 61, 1903 (1978)
5. Compound which gave satisfactory result for elemental analyses

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