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Synthesis of α-Amino-cycloheptatriene-1-acetic Acids and Their 7-Acylaminocephalosporin Derivatives

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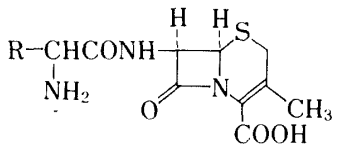
tert-Butyl α-amino-2,4,6-cycloheptatriene-1-acetate (**6**) was prepared by treatment of *tert*-butyl *N*-benzylideneglycinate (**5**) with *n*-butyllithium followed by reaction with tropylium tetrafluoroborate. Heating **6** in xylene resulted in isomerization to *tert*-butyl α-amino-1,3,6-cycloheptatriene-1-acetate (**7**). Both the glycine derivatives were utilized for the acylation of a 7-amino-3-deacetoxycephalosporanic acid (7-ADCA) derivative (**10**) to obtain the orally active acyl derivative (**14**).

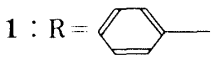
Keywords——tropylium salt; cycloheptatriene; glycine derivative; 7-ADCA derivative; β-lactam; thermal isomerization; orally active cephalosporin.

Although a wide variety of parenterally administrable cephalosporins has been developed in the past decade, surprisingly few cephalosporin compounds have been reported as orally useful. The 7-acyl moieties of orally active cephalosporins are limited to phenylglycyl or related groups, and the compounds are characterized by similarity in antibacterial spectrum as well as chemical structure. The purpose of the present work was to synthesize 7-(α-amino-cycloheptatriene-1-acetamido)cephalosporin derivatives whose acyl moiety is similar to those of orally absorbed cephalexin and cephradine (**1** and **2**). This paper reports the synthesis of two α-amino-cycloheptatriene-1-acetic acids (**3**[1] and **4**) and their cephalosporin derivatives for testing to determine their antibacterial activities and bioavailabilities.

Previous papers[2] described the usefulness of *tert*-butyl *N*-benzylideneglycinate (**5**) for the preparation of amino acid derivatives for cephalosporin synthesis. This synthetic method was successfully applied in the present work for the synthesis of the α-amino-cycloheptatriene-1-acetic acid derivatives. The glycinate **5** was, after being treated with *n*-butyllithium in tetrahydrofuran (THF), allowed to react with tropylium tetrafluoroborate[3] followed by treatment with Girard reagent T to yield *tert*-butyl α-amino-2,4,6-cycloheptatriene-1-acetate (**6**). The structure of **6** was confirmed by the nuclear magnetic resonance (NMR) spectrum which indicated the presence of six olefinic protons and two methine protons, as well as amino and *tert*-butyl groups. The 2,4,6-cycloheptatriene-1-acetate derivative **6** was heated under reflux in xylene for 26 h, resulting in isomerization to the α-amino-1,3,6-cycloheptatriene-1-acetic acid derivative (**7**).[4] Treatment of **7** with trifluoroacetic acid at room temperature afforded the amino acid (**4**) as the trifluoroacetic acid salt. Prior to the use of this product as an acylating agent, the amino group of **4** was protected by blocking with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile(boc-on) to give **8**. The initially formed cycloheptatriene-1-acetic acid derivative **6** was also treated with trifluoroacetic acid followed by protection of the



1 : R =



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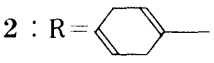

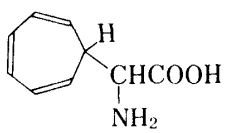

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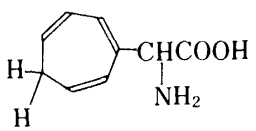

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Chart 1

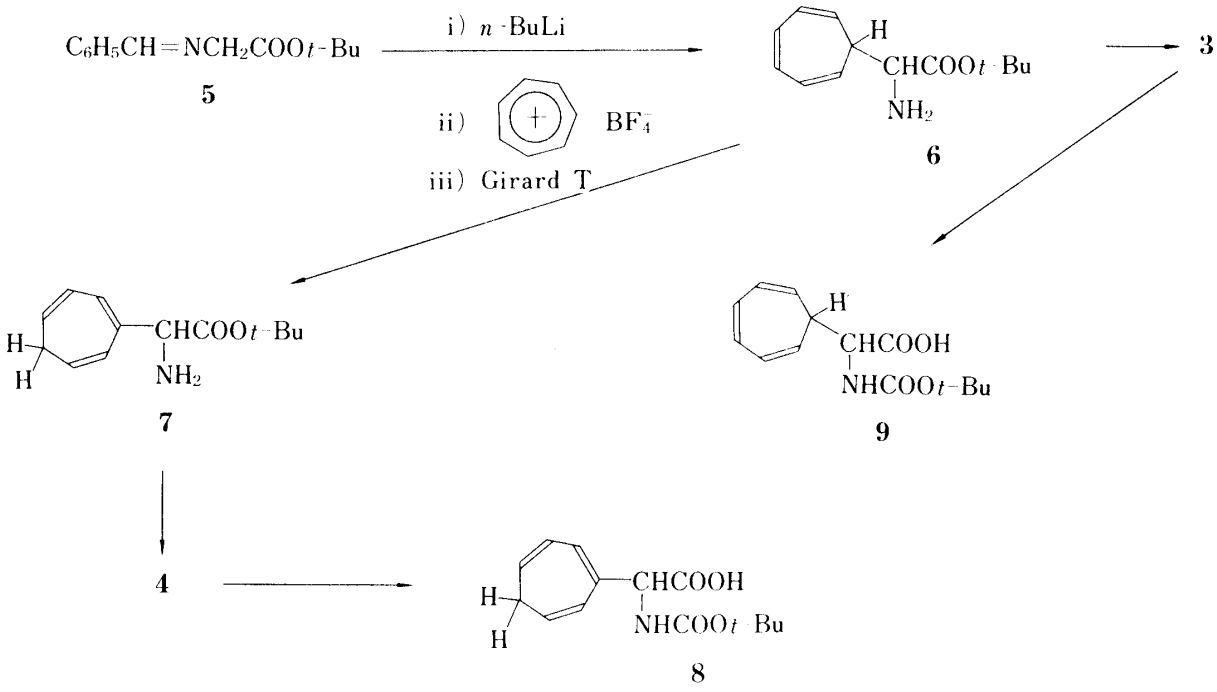
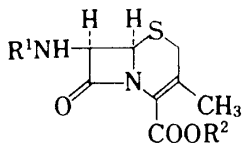
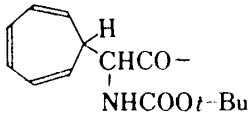


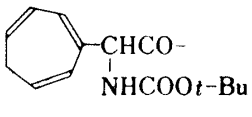
Chart 2



10 : R^1=H, R^2=*t*-Bu

11 : R^1=  R^2=*t*-Bu

12 : R^1=  R^2=H

13 : R^1=  R^2=*t*-Bu

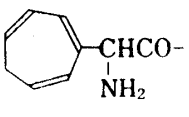
14 : R^1=  R^2=H

Chart 3

amino group to yield **9**. The two *α-tert*-butoxycarbonylaminocycloheptatriene-1-acetic acid derivatives thus formed were utilized for the acylation of a 7-aminocephalosporin derivative (**10**). The acylation of **10** was carried out after the two acids (**3** and **4**) had been converted to mixed anhydrides by treatment with isobutyl chloroformate and triethylamine. The resultant glycine products (**11** and **13**) consisting of two isomers with respect to the 2-position of the acyl moiety were treated with trifluoroacetic acid to yield the 4-carboxylic acids **12** and **14**, respectively.

For comparison with cephalexin, **14** was orally administered to mice (50 mg/kg) to examine the urinary and fecal recoveries of **14**. The 1,3,6-cycloheptatriene-1-acetamido derivative was largely recovered from the urine in an amount (79%) comparable to that of cephalexin (68%), although it is only approximately half as active against gram-negative bacteria as the latter. The 2,4,6-cycloheptatriene-1-acetamidocephalosporin compound **12** displayed almost no antibacterial activity against gram-negative bacteria; this result suggests the importance of the position of the double bond.

Experimental

Solutions were concentrated below 30°C in rotary evaporators under reduced pressure. The silica gel plates used for preparative thick layer chromatography were obtained from E. Merck, Darmstadt, West Germany. NMR spectra were recorded on a Varian A-60, a Hitachi R-24 or a Varian HA-100 spectrometer and signals are given in δ units downfield from tetramethylsilane as an internal standard. Infrared (IR) spectra were measured on a Nihon-Bunko Jasco IR-A machine. A Nihon-Denshi JMS-01-SG spectrometer was used to obtain mass spectra.

***tert*-Butyl α-Amino-2,4,6-cycloheptatriene-1-acetate (6)**——A solution of *n*-butyllithium in *n*-hexane (19.0 ml, 1.63 mmol/ml) was added to a stirred solution of *tert*-butyl *N*-benzylideneglycinate (**5**, 6.60 g) in THF (100 ml) with cooling at −78°C under nitrogen. The mixture was stirred for 30 min, then tropylium tetrafluoroborate (5.35 g) was added to the above solution and the whole was stirred for 30 min and gradually warmed to room temperature. After removal of the solvent, the residue was dissolved in MeOH (150 ml) containing Girard reagent T (6.0 g) and the mixture was stirred for 2 h at room temperature. The solvent was removed, the residue was shaken with AcOEt and H_2O, and the insoluble material was removed by filtration. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated to give a residue. The crude poduct was chromatographed on a column of silica gel, eluting with benzene–AcOEt (10: 1) to give **6** (5.0 g) as an oil. NMR ($CDCl_3$) δ: 1.44 (9H, s, *t*-Bu), 1.65 (2H, s, NH_2), 1.94 (1H, td, J=6.0, 7.0 Hz, 1-H), 3.63 (1H, d, J=7.0 Hz, CHCOO), 5.39 (2H, dd, J=10.0, 6.0 Hz, 2-H, 7-H), 6.45—6.10 (2H, m, 3-H, 6-H), 6.68 (2H, t, J=3.0 Hz, 4-H, 5-H).

***tert*-Butyl α-Amino-1,3,6-cycloheptatriene-1-acetate (7)**——A solution of the 2,4,6-cycloheptatriene isomer (**6**, 1.1 g) in xylene (70 ml) was refluxed for 26 h under nitrogen. The solvent was evaporated off and the residue was purified by preparative thin-layer chromatography (TLC) (benzene–AcOEt=2: 1) to give **7** (376 mg) as an oil. NMR ($CDCl_3$) δ: 1.42 (9H, s, *t*-Bu), 2.16 (1H, ddd, J=13.0, 6.5, 6.5 Hz, 5-H), 2.35 (1H, ddd, J=13.0, 7.0, 7.0 Hz, 5-H), 3.91 (2H, s, NH_2), 4.12 (1H, s, CHCOO), 5.40 (1H, ddd, J=9.5, 7.0, 6.5 Hz, 4-H or 6-H), 5.46 (1H, ddd, J=9.5, 7.0, 6.5 Hz, 6-H or 4-H), 6.15 (1H, dd, J=9.5, 5.5 Hz, 3-H), 6.16 (1H, dd, J=9.5, 1.0 Hz, 7-H), 6.61 (1H, dd, J=5.5, 1.0 Hz, 2-H).

α-*tert*-Butoxycarbonylamino-1,3,6-cycloheptatriene-1-acetic Acid (8)——A solution of the *tert*-butyl ester (**7**, 376 mg) in CF_3COOH (5 ml) was stirred for 2.5 h at room temperature. After removal of the CF_3-COOH, the resultant crude amino acid (**4**) was dissolved in dioxane (6 ml)–H_2O (6 ml), then triethylamine (630 μl) and boc-on (462 mg) were added. The mixture was stirred for 4 h at room temperature, diluted with AcOEt and extracted with aq. $NaHCO_3$. After being washed with AcOEt, the aq. layer was acidified with 5% aq. citric acid and extracted with AcOEt. The extracts were combined, washed with H_2O, dried over $MgSO_4$ and concentrated to give a residue. The crude product was purified by preparative TLC (AcOEt–MeOH=4: 1) to give **8** (336 mg) as a powder. NMR ($CDCl_3$) δ: 1.35 (9H, s, *t*-Bu), 2.20 (2H, m, 2×5-H), 4.80 (1H, br, CHCOO), 5.40 (2H, m, 4-H, 6-H), 6.16 (1H, dd, J=9.0, 5.0 Hz, 3-H), 6.20 (1H, d, J=9.0 Hz, 7-H), 6.68 (1H, d, J=5.0 Hz, 2-H), 10.78 (1H, s, COOH).

α-*tert*-Butoxycarbonylamino-2,4,6-cycloheptatriene-1-acetic Acid (9)——A solution of the *tert*-butyl ester (**6**, 464 mg) in CF_3COOH (3 ml) was stirred for 2 h at room temperature. The CF_3COOH was evaporated off and the resulting amino acid (**3**) was treated with boc-on (620 mg) and triethylamine (740 μl) as described for the preparation of **8**. The reaction mixture was worked up as usual to give **9** (394 mg) as crystals. NMR ($CDCl_3$) δ: 1.44 (9H, s, *t*-Bu), 2.10 (1H, bq, J=7.0 Hz, 1-H), 4.67 (1H, br, CHCOO), 5.37 (2H, m, 2-H, 7-H), 6.05—6.43 (2H, m, 3-H, 6-H), 6.07 (2H, bt, J=3.0 Hz, 4-H, 5-H), 10.68 (1H, s, COOH).

***tert*-Butyl 7β-(*RS*-α-*tert*-Butoxycarbonylamino-1,3,6-cycloheptatriene-1-acetamido)-3-methyl-3-cephem-4-carboxylate (13)**——Triethylamine (48 μl), *N*,*N*-diethylaniline (3 drops) and isobutyl chloroformate (45 μl) were added to a stirred solution of the acetic acid derivative (**8**, 86 mg) in THF (5 ml) with cooling at −8—−10°C. The mixture was stirred for 3 h, then a solution of *tert*-butyl 7β-amino-3-methyl-3-cephem-4-carboxylate (**10**, 92 mg) in THF (1 ml) was added and the whole was stirred for 4 h. After standing overnight at −20°C, the reaction mixture was diluted with AcOEt, washed successively with H_2O, 5% HCl, 5% aq. $NaHCO_3$ and H_2O, and dried over $MgSO_4$. The solvent was evaporated off and the residue was purified by preparative TLC (benzene–AcOEt=4: 1) to give **13** (91 mg). NMR ($CDCl_3$) δ: 1.37 (9H, s, *t*-Bu), 1.46 (1H, s, *t*-Bu), 2.03 (3H, s, Me), 2.20 (2H, m, 2×5-H), 3.05, 3.48 (2H, AB-q, J=19 Hz, 2×2-H), 4.92 (1H, d, J=5.0 Hz, 6-H), 5.6 (1H, dd, J=5.0, 9.0 Hz, 7-H), 4.92 (1H, d, J=8—9 Hz, CHCONH), 5.2—5.8 (2H, m, olefinic 4-H and 6-H), 6.0—6.4 (2H, m, olefinic 3-H and 7-H), 6.78 (1H, d, J=5.0 Hz, olefinic 2-H), 7.18 1H, d, J=9.0 Hz, CONHCH).

7β-(*RS*-α-Amino-1,3,6-cycloheptatriene-1-acetamido)-3-methyl-3-cephem-4-carboxylic Acid CF_3COOH (14)——A solution of the *tert*-butyl ester (**13**, 91 mg) in CF_3COOH (2 ml) was stirred for 2 h at room temperature. After removal of the CF_3COOH, the residue was dissolved in a small amount of AcOEt, and ether was added to give **14** (35 mg) as a powder. NMR (CD_3OD) δ: 2.09 (1H, br s, Me), 2.33 (2H, m, 2×5-H), 3.16, 3.56 (2H, AB-q, J=18.0 Hz, 2×2-H), 4.80 (1H, br s, CHNH$_2$), 5.28—5.83 (4H, m, 6-H, 7-H, olefinic 4-H and 6-H), 6.03—6.48 (2H, m, olefinic 3-H and 7-H), 7.00 (1H, br d, J=5.0 Hz, olefinic 2 H). IR ν_{max}^{KBr} cm^{-1}: 1765 (β-lactam).

References and Notes

1) The Squibb group has claimed that the glycine derivative can be obtained in three steps from tropylium tetrafluoroborate and dimethyl formamidomalonate: J. Bernstein, P.A. Diassi, and F.L. Weisenborn, Japanese patent 47-175, Jan. 7, 1972.
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