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Studies on Lactams. V.*,[1] Nucleophilic Reaction of Benzylpenicillin with Lithiated Compounds

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Nucleophilic reaction of penicillin lactam with various lithiated compounds was discussed. Phenacyl benzylpenicillanate was reacted with phenylethynyllithium in tetrahydrofuran at −75° to yield a phenylethynyl derivative (**2**). When methyllithium or phenyllithium was used as the reagent in ether at −75°, only a ring-opened compound (**4**) was obtained. On the other hand, use of butyllithium or phenyllithium in tetrahydrofuran at −75° afforded an unexpected butoxycarbonyl derivative (**5**). The butoxyl group was derived from tetrahydrofuran, and which was confirmed by the formation of butanol from the reaction of tetrahydrofuran and phenyllithium at −75°.

We have previously reported on the lithiation of ethynyl compounds[3] and direct lithiation of ethynyl compounds,[4] and their nucleophilic reaction with lactones and sugar lactones.[5,6] These results suggest a nucleophilic reaction of lactams with various lithiated compounds. There is only one report by Pohland, *et al.*[7] on the reaction of a lactam and lithiated compounds. They obtained dehydrated compound from the reaction of γ-lactam with ethyllithium by refluxing in ether.

In connection with our synthetic work on C-nucleosides a reaction of penicillin with lithiated compounds was developed to obtain 7-substituted penicillin derivatives. A nucleophilic attack of the lithiated compounds probably occurs at three carbonyls of benzylpenicillin, and this has been suggested from the net atomic charge measurement by the extended Hückel MO calculation of 6-aminopenam-3-carboxylic acid by Boyd.[8]

Treatment of benzylpenicillin phenacyl ester (**1**) at −75° with lithiated phenylacetylene, which was prepared directly from phenylacetylene and lithium,[4] followed by treatment with ammonia or ammonium chloride afforded 2-hydroxy-2,4-diphenyl-3-butynyl 5,5-dimethyl-2-(1-phenylacetamino)acetamidothiazolidine-4-carboxylate (**2**) in a fair yield. This reaction progressed stereoselectively and isomeric compound was not detected by liquid chromato-

* Dedicated to the memory of Prof. Eiji Ochiai.

1) This constitutes Part II of "Direct Lithiation."

2) Location: *Shirokane, Minato-ku, Tokyo, 108, Japan.*

3) H. Ogura, H. Takahashi, and T. Itoh, *J. Org. Chem.*, 37, 72 (1972).

4) H. Ogura and H. Takahashi, *Synthetic Commun.*, 3, 135 (1973).

5) H. Ogura and H. Takahashi, 1st Symposium of the Chemistry of Nucleic Acids, Abstr. Papers, 1973, p. 65.

6) H. Ogura and H. Takahashi, *J. Org. Chem.*, 39, 1374 (1974).

7) A. Pohland, H.E. Boaz, and H.R. Sullivan, *J. Med. Chem.*, 14, 194 (1971).

8) D.B. Boyd, *J. Am. Chem. Soc.*, 94, 6513 (1972).

graphy. Previously, we reported the similar asymmetric synthesis of C-nucleoside analogs with lithiated compounds.[3-6]

The NMR spectrum of **2** suggested the presence of an amide group at 7.06, 6.17 ppm (NHa, NHb, J=89 Hz). Similarly, phenacyl 5,5-dimethyl-2-(1-phenylacetamino)acetamidothiazolidine-4-carboxylate (**7**) prepared from 1 with ammonia, showed the 1′-amide group in NMR spectrum at 6.84, 5.90 ppm (NHa, NHb, J=56 Hz). These values for amide group in NMR spectra are similar to those of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carboxamide [6.50 and 5.30 ppm (J=70 Hz)].[9]

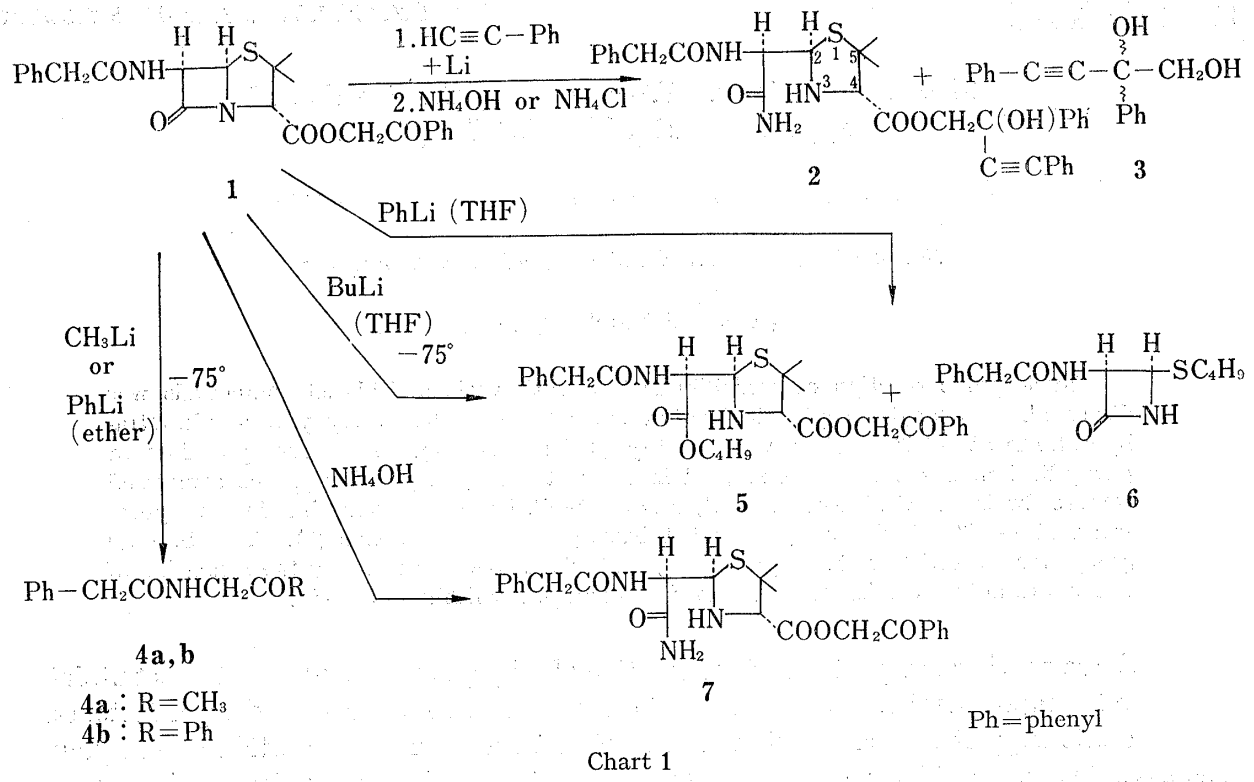

Chart 1

Chromatography of mother liquor of **2** over silica gel gave 3,4-dihydroxy-1,3-diphenyl-1-butyne (**3**) in 5% yield, which probably originated from the phenacyl group in **1**. When the reaction mixture was treated with buffer solution (pH 6.86) or ethanol instead of ammonium chloride, decomposed compound (**3**) was obtained quantitatively.

Eggers, *et al.*[10] already reported that the nucleophilic reaction of 7-phenylacetamidocephalosporanic acid (**8**) with two equivalents of sodium benzyloxide gave a lactam-ring opened compound (**9**). Similar reaction might have occurred under a condition of an excess lithiated phenylacetylene with **1** to form intermediates (A, B), followed by amination with ammonia to yield the ring-opening compound (**2**).

Treatment of **1** with methyllithium or phenyllithium, prepared from methyl iodide or phenyl bromide and lithium in ether, gave an unexpected ring-opened compound (**4a** or **4b**). When **1** was treated with butyl bromide and lithium in tetrahydrofuran, phenacyl 5,5-dimethyl-2-(1-butoxycarbonyl-1-phenylacetamido)methylthiazolidine-4-carboxylate (**5**) was obtained unexpectedly in 75% yield, and an azetidinone derivative (**6**) was obtained as a by-product. Similar reaction occurred with **1** and lithiated 1-benzylbenzimidazole with butyllithium in tetrahydrofuran, **5** was a sole product and expected 5-substituted compound could not be obtained. NMR spectrum of **5** suggested the presence of 3-amino group at 3.26 ppm, which disappeared in addition of deuterium oxide.

9) R.H. Bible, Jr., "Guide to the NMR Empirical Method," Plenum Press, New York, 1967.
10) S.H. Eggers, V.V. Kane, and G. Lowe, *J. Chem. Soc.*, **1965**, 1262.

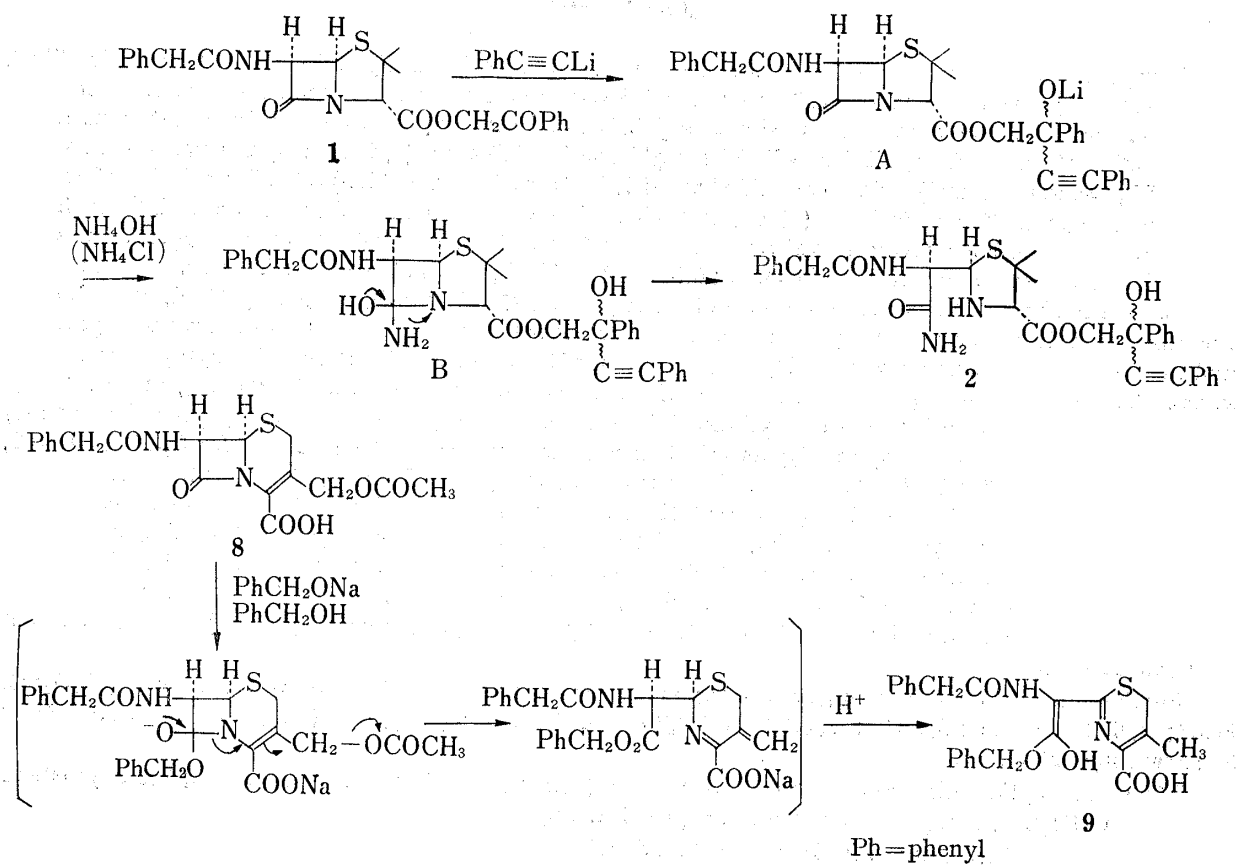

Chart 2

Mechanism of this reaction is difficult to explain, but the butoxyl group probably originates from tetrahydrofuran. Decomposition of tetrahydrofuran with alkyllithium yielding ethylene and an enolate ion of acetaldehyde was examined by Tomboulian, *et al.*[11] Tetrahydrofuran ring opening to lithium butoxide has not been reported previously. On the other hand Maercker and Demuth[12] reported a mechanism of decomposition of diethyl ether with alkyllithium to yield ethylene and lithium ethoxide.[13] This reaction was further supported by the experiment in which **5** was obtained when phenyllithium was used instead of butyllithium in this reaction. When this reaction was carried out without penicillin derivative, butanol was obtained as a phenylurethan.

Azetidinone derivative (**6**) may have been formed from a nucleophilic attack of butyllithium on the 1-position of **1**. Similar decomposed derivatives were obtained by Barton, *et al.*[14] from the reaction of penicillin sulfoxides with vinyl ethers, and by Stoodley, *et al.*[15] from penicillin derivatives with mercuric acetate. Stereochemistry of **6** was confirmed by the lactam rule[16,17] as 3*R*,4*R*-configuration from the negative Cotton effect of circular dicroism (CD) curves ($[\theta]^{23}_{225}$ −22300 (methanol) and $[\theta]^{23}_{229}$ −31630 (dioxane)) due to n-π^* transition of the lactam chromophore.

11) P. Tomboulian, D. Amick, S. Beare, K. Dumke, D. Hart, R. Hites, A. Metzger, and R. Nowak, *J. Org. Chem.*, **38**, 322 (1973).
12) A. Maercker and W. Demuth, *Angew. Chem. Int.*, **12**, 75 (1973).
13) R.G. Jones and H. Gilman, "Organic Reactions," Vol. VI, John Wiley & Sons, Inc., New York, 1969, p. 339.
14) I. Ager, D.H.R. Barton, G. Lucente, and P.G. Sammes, *Chem. Commun.*, **1972**, 601.
15) R.J. Stoodley and N.R. Whitehouse, *J. Chem. Soc.*, (*I*), **1973**, 32.
16) H. Ogura, H. Takayanagi, and K. Furuhata, *Chemistry Letters* (Tokyo), **1973**, 387.
17) H. Ogura, H. Takayanagi, K. Kubo, and K. Furuhata, *J. Am. Chem. Soc.*, **95**, 8056 (1973).

Experimental

Temperatures are uncorrected. NMR spectra were measured in $CDCl_3$ at 60 MHz with a Varian T-60, and at 100 MHz with a Varian HA-100 and a JMS-PS 100 spectrometers, and Me_4Si was used as an internal reference. Mass spectra were determined with a JEOL-OlS spectrometer by a direct inlet system at 75 eV.

Reaction of Phenylethynyllithium with Phenacyl Benzylpenicillanate (1) in Tetrahydrofuran——To a mixture of Li (0.35 g; 0.005 mol) in freshly distilled and dried tetrahydrofuran (THF) (50 ml), a solution of phenylacetylene (5.1 g; 0.005 mol) in THF (10 ml) was added dropwise during 30 min at 0° under introducing of nitrogen. The reaction mixture was stirred for 5 hr at 0° and then overnight at room temperature, which was added dropwise into a solution of **1** (4.5 g; 0.01 mol) in THF (50 ml) at −75° during 1 hr. After stirring the reaction mixture at the same temperature for 3 hr, NH_4Cl (13 g) or 28% NH_4OH (100 ml) was added to the mixture to decompose the reagent and then the organic solvent was removed under a reduced pressure, and the residue was extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ extract left a syrup or crystalline syrup. This was chromatographed on silica gel with CCl_4–$CHCl_3$–MeOH to elute 1.0 g (19%) or 1.8 g (28%; decomposed with 28% NH_4OH) of 2-hydroxy-2,4-diphenyl-3-butynyl 5,5-dimethyl-2-(1-phenylacetamino) acetamidothiazolidine-4-carboxylate (**2**) as colorless needles, mp 165°. *Anal.* Calcd. for $C_{32}H_{33}O_5N_3S$: C, 67.23; H, 5.82; N, 7.35; O, 14.44; S, 5.61. Found: C, 67.24; H, 5.76; N, 7.32; O, 14.32; S, 5.73. IR ν_{max}^{KBr} cm^{-1}: 2210 (C≡C), 1740 (ester), 1725 (CO), 1665 (CONH), 1598 (phenyl), $\nu_{max}^{CCl_4}$ 3603 (OH), 3491, 3453 (NH_2), 3340 (NH). NMR δ (ppm): 1.15 (3H, singlet, 5α-CH_3), 1.49 (3H, singlet, 5β-CH_3), 3.51 (2H, singlet, PhC$\underline{H}_2$), 3.59 (1H, singlet, 4-H), 4.15—4.65 (1H, broad, 2-OH), 4.25, 4.47 (2H, double doublet, 4-COOC$\underline{H}_2$), 4.42—4.70 (1H, broad double doublet, 1′-H), 5.12 (1H, doublet, J=4.0 Hz, 2-H), 6.17, 7.06 (2H, doublet, J=89 Hz, 7-NHb, 7-Ha), 6.88 (1H, doublet, J=8.0 Hz, 1′-NH), 7.43 (5H, multiplet, aromatic protons). Mass Spectrum *m/e*: 553 (M^+–H_2O).

Further elution of the column gave **3** (5%) as colorless needles, mp 106°. *Anal.* Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.75; H, 5.92. IR ν_{max}^{KBr} cm^{-1}: 3200, 3175 (OH), 2200 (C≡C), 1595 (phenyl). Mass Spectrum *m/e*: 238 (M^+).

When the reaction mixture was treated with EtOH (100 ml) or buffer solution (pH 6.86; 100 ml) instead of NH_4Cl or NH_4OH, **3**, mp 106° was obtained quantitatively.

Reaction of Methyllithium with Phenacyl Benzylpenicillanate (1) in Ether——To a suspension of Li (1.5 g; 0.2 mol) in dry $(C_2H_5)_2O$ (50 ml), MeI (14.2 g; 0.1 mol) was added dropwise during 20 min at room temperature. A solution of **1** (4.5 g; 0.01 mol) in THF (50 ml) was added to the reaction mixture at −75° during 3 hr, and the mixture was decomposed with saturated NH_4Cl. Evaporation of the dried $(C_2H_5)_2O$ solution gave a syrup, which was chromatographed on silica gel to elute 10% of N-acetonylphenylacetamide (**4a**) as colorless leaflets, mp 129°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.74; H, 6.86; N, 7.25. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1725 (CO), 1640 (CONH), 1600 (phenyl). NMR δ (ppm): 2.12 (3H, singlet, CH_3), 3.59 (2H, singlet, PhC$\underline{H}_2$), 4.08 (2H, doublet, NC$\underline{H}_2$), 6.20 (1H, broad, NH), 7.34 (5H, singlet, aromatic protons). Mass Spectrum *m/e*: 191 (M^+).

Reaction of Phenyllithium with Phenacyl Benzylpenicillanate (1) in Ether——In a similar reaction as above 4.71 g (0.03 mol) of bromobenzene was used in place of MeI. N-Phenacylphenylacetamide (**4b**) was obtained in 12% yield as colorless fine needles, mp 98°. *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.61; H, 6.06; N, 5.53. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1730 (CO), 1660 (CONH), 1580 (phenyl). NMR δ (ppm): 3.67 (2H, singlet, PhC$\underline{H}_2$), 4.71 (2H, doublet, NC$\underline{H}_2$), 6.60 (1H, broad, NH), 7.33 (5H, singlet, aromatic protons). Mass Spectrum *m/e*: 253 (M^+).

Phenacyl 5,5-Dimethyl-2-(1-butoxycarbonyl-1-phenylacetamido)methylthiazolidine-4-carboxylate (5)——(a) With Butyllithium: To a suspension of Li (0.35 g; 0.005 mol) in dry $(C_2H_5)_2O$ (30 ml), $(C_2H_5)_2O$ (5 ml) solution of BuBr (3.0 g; 0.021 mol) was added dropwise during 30 min at −10°. After stirring at 0—2° for 1.5 hr a solution of **1** (4.5 g; 0.01 mol) in THF (50 ml) was added dropwise to the above during 1 hr at −75°. After stirring at the same temperature for 3 hr, the reaction mixture was treated with saturated NH_4Cl, and extracted with $(C_2H_5)_2O$ at pH 7.5. Evaporation of the dried $(C_2H_5)_2O$ solution left a syrup, which was chromatographed on silica gel with $(C_2H_5)_2O$–$CHCl_3$–MeOH to yield 3.9 g (75%) of **5**, mp 102—103°. Recrystallization from petr. ether–$(C_2H_5)_2O$ raised mp to 122—124°. *Anal.* Calcd. for $C_{28}H_{34}O_6N_2S$: C, 63.85; H, 6.50; N, 5.31; O, 18.26; S, 6.29. Found: C, 64.03; H, 6.80; N, 5.27; O, 18.60; S, 6.01. IR ν_{max}^{KBr} cm^{-1}: 3450 (NH), 3350 (NH), 1739 (COO), 1710 (CO), 1665 (CONH), 1598 (phenyl). NMR δ (ppm): 0.85 (3H, triplet, COO$(CH_2)_2$C$\underline{H}_3$), 1.36 (3H, singlet, 5α-CH_3), 1.60 (3H, singlet, 5β-CH_3), 3.26 (1H, broad singlet, 3-NH), 3.53 (1H, singlet, 4-H), 3.67 (2H, singlet, PhC$\underline{H}_2$), 4.13 (2H, triplet, 1′-COOC$\underline{H}_2$), 4.65 (1H, double doublet, J=16.0 Hz, 1′-H), 5.11 (1H, doublet, J=4.5 Hz, 2-H), 5.41 (2H, quartet, J=16.0 Hz, 4-COOC$\underline{H}_2$), 6.28 (1H, doublet, J=9.0 Hz, 1′-NH), 7.50 (5H, multiplet, aromatic protons). Mass Spectrum *m/e*: 526 (M^+).

From further elution of the column, 4.2% of 3-benzylcarboxamido-4-butylthioazetidinone (**6**) was obtained as colorless needles, mp 137°. *Anal.* Calcd. for $C_{15}H_{20}O_2N_2S$: C, 61.60; H, 6.89; N, 9.58. Found: C, 61.58; H, 6.89; N, 9.48. IR ν_{max}^{KBr} cm^{-1}: 3400, 3200 (NH), 1780 (lactam CO), 1725, 1660 (amide CO), 1600 (phenyl). NMR δ (ppm): 0.9 (3H, broad multiplet, CH_3), 1.4 (4H, broad multiplet, $(CH_2)_2$), 2.3 (2H, broad multiplet, S–CH_2), 3.60 (2H, singlet, PhC$\underline{H}_2$), 4.80 (1H, doublet, 4-H), 5.50 (1H, double doublet, 3-H), 6.82

(1H, doublet, 3-NH), 7.02 (1H, singlet, 1-NH), 7.30 (5H, singlet, aromatic protons). Mass Spectrum *m/e*: 292 (M^+).

(b) With N-Benzylbenzimidazole: To a solution of BuLi prepared as described in (a), N-benzylbenzimidazole (2.0 g) in THF (10 ml) was added at −75° under stirring for 1.5 hr. A solution of **1** (4.5 g) in THF (120 ml) was added dropwise to the above mixture during 0.5 hr. After stirring for 3 hr at −70°, the reaction mixture was treated similarly as in (a) and 3.4 g (65%) of **5**, mp 122—124° (mixed mp) was obtained.

(c) With Phenyllithium: To a solution of C_6H_5Li prepared from C_6H_5Br (3.2 g; 0.02 mol) and Li (0.4 g; 0.006 mol), **1** (4.5 g; 0.01 mol) in THF (100 ml) was added dropwise during 1 hr at −75° under stirring. After 2.5 hr at −70°, the reaction mixture was decomposed with NH_4Cl and extracted from $(C_2H_5)_2O$. Dried $(C_2H_5)_2O$ solution was evaporated to a syrup (3.7 g), which was chromatographed on silica gel with hexane–CCl_4–$CHCl_3$ to yield 0.8 g (15%) of **5** as colorless needles, mp 122—124° (mixed mp).

Butanol from Tetrahydrofuran with Phenyllithium——A solution of C_6H_5Li in THF (100 ml) was prepared from C_6H_5Br (4.71 g) and Li (0.42 g). After decomposition with H_2O, organic layer was evaporated to dryness. Phenylurethan crystallized from the remaining liquid melted at 55—56°. Mixed mp with the authentic phenylurethan of BuOH showed no depression.

Phenacyl 5,5-Dimethyl-2-(1-phenylacetamino)acetamidothiazolidine-4-carboxylate (7)——To a stirred solution of **1** (4.52 g; 0.01 mol) in THF (100 ml), 28% NH_4OH (50 ml) was added dropwise at 0°. After 1 hr, the solution was evaporated under a reduced pressure and the remained residue crystallized from MeOH. **7** was obtained quantitatively as white needles, mp 171°. *Anal.* Calcd. for $C_{24}H_{27}O_5N_3S$: C, 61.39; H, 5.79; N, 8.94. Found: C, 61.28; H, 5.79; N, 9.05. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH_2), 1740 (ester), 1650 ($CONH_2$), 1600 (phenyl). NMR δ (ppm): 3.17 (1H, singlet, 3-NH), 4.57 (1H, double doublet, 1′-H), 5.20 (1H, doublet, 2-H), 5.90, 6.84 (2H, doublet, J=56 Hz, 1′-NHb, 1′-NHa), 6.78 (1H, doublet, 1′-NH). Mass Spectrum *m/e*: 469 (M^+).