original ethereal layer and two 100-ml ethereal extracts of the aqueous layer. The total crude product was recrystallized from absolute ethanol to afford 3.55 g of **3a**: pmr (DMSO-d_6) δ 10.68 (s, 1, NH), 7.56 (m, 12, NH_2 and Ph), 4.28 (m, 1, CHCO), and 3.28 ppm (m, 2, CH_2Ph); ir (KBr) 2.93 (NH_2), 3.07 (NH), 5.95 (imide C=O), and 6.31 μ (amide C=O).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.79; H, 6.10; N, 10.27.

Alkylations of **1a** with benzyl chloride in the presence of 4.5 equiv of sodium amide or lithium amide were carried out in a similar manner.

Alkylation of tripotassio salt **2a** with sodium chloroacetate to afford 3-carboxy-2-phenylpropionylurea (**3e**) was conducted as described above except that the reaction time was extended to 2 hr and the product was isolated by acidification of the basic aqueous phase.

Attempted alkylation of 2,3-diphenylpropionylurea (**3a**) with ethyl bromide in the presence of excess potassium amide as described above afforded a mixture of products. Analysis of this mixture by tlc (THF–heptane) revealed the presence of unreacted **3a** along with traces of 2,3-diphenylpropionamide.

Although the observed melting points of alkyl derivatives **3c** and **3d** were somewhat higher than previously reported values (Table I), both of these compounds had analytical and spectral properties consistent with the assigned structures.

Formation and Attempted Benzylation of Dianion 4.—To a stirred suspension of 0.02 mol of potassium amide in 150 ml of liquid ammonia was added 1.78 g (0.01 mol) of **1a**. The resulting mixture was allowed to stir for 1 hr, and 1.26 g (0.01 mol) of benzyl chloride in 20 ml of ether was added; there was no evidence of stilbene formation. After 1 hr the ammonia was replaced by 200 ml of anhydrous ether and the resulting suspension treated with 10 ml of deuterium oxide. Filtration of the ethereal suspension and recrystallization of the residue from acetone–heptane afforded 1.36 g (76%) of recovered **1a**, the pmr (DMSO-d_6) spectrum of which had no absorption for imide or amide protons, but still retained a singlet (2 H) at 3.68 ppm for benzylic hydrogens. Analysis of the ethereal layer by tlc (ether–heptane) revealed traces of **1a** but no stilbene. Concentration of the ethereal layer afforded a nearly quantitative recovery of benzyl chloride.

Attempted Formation and Benzylation of Trialkali Salts 2a–c with 3 Equiv of Potassium Amide.—Each of the ureides **1a–c** (0.01 mol) was treated with 0.03 mol of potassium amide in liquid ammonia for 1 hr. Benzyl chloride (0.011 mol) was added, stirring was continued for 1 hr, and the reaction mixture was neutralized with ammonium chloride and processed in the usual fashion. In all cases addition of the halide resulted in appearance of the purple color accompanying stilbene formation. Each of the crude product mixtures was analyzed by tlc (THF–heptane), which revealed the presence of unreacted starting material, the appropriate *C*-benzyl derivative, and stilbene.

Formation and Alkylation of 1b (M = Li) Using LDA.—To a solution of 12.14 g (0.12 mol) of diisopropylamine in 200 ml of THF, maintained at 0° under a nitrogen atmosphere, was added 0.12 mol of *n*-butyllithium in hexane. The reaction mixture was allowed to stir for 15 min to form LDA and 7.62 g (0.03 mol) of solid **1b** was added. The resulting yellow solution was allowed to stir for 20 min, and 6.87 g (0.063 mol) of ethyl bromide in 50 ml of THF was added. The reaction mixture was stirred for 1 hr at 25° and then poured into a slurry of 200 g of ice and 15 ml of 12 *N* HCl. The THF layer was separated and combined with three 100-ml ethereal extracts of the aqueous solution. The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting solid was recrystallized to give 4.8 g of **3h** (Table I).

In a similar experiment **1a** (0.015 mol) was treated with 0.07 mol of lithium diisopropylamide and 0.03 mol of ethyl bromide to afford a mixture (tlc) of ethyl derivative **3c** and unreacted **1a**.

Attempted Ethylation of 3a by Means of LDA.—To a solution of 0.07 mol of LDA in 160 ml of THF–hexane, maintained at 0° under nitrogen, was added 4.02 g (0.015 mol) of **3a**. After 20 min, 3.43 g (0.03 mol) of ethyl bromide was added, the reaction mixture was allowed to warm to 25°, and stirring was continued for 1 hr. The reaction was processed as described above and the solid residue remaining after concentration of the organic extracts was analyzed by tlc (benzene–acetone) to reveal the presence of traces of **3a** and one other product. The crude product mixture was chromatographed on silica gel (benzene–acetone) to afford, after one recrystallization from aqueous ethanol, 2.3 g (66%) of 2,3-diphenylpropionamide, mp 131–132° (lit.[18] mp 133–134°). The ir spectrum of this material was identical with that of an authentic sample of 2,3-diphenylpropionamide. The aqueous layer was freeze-dried. The ir spectrum of the resulting solid has an intense band at 4.48 μ attributable to cyanate.[14]

Registry No.—**2a** (K), 37991-57-4; **2a** (Na), 37991-58-5; **2a** (Li), 37991-59-6; **2b** (K), 37991-75-6; **2b** (Li), 37991-76-7; **2c** (K), 37991-77-8; **3a**, 37991-66-5; **3b**, 37991-67-6; **3c**, 90-49-3; **3d**, 37991-69-8; **3e**, 37991-70-1; **3f**, 37991-71-2; **3g**, 37991-72-3; **3h**, 4287-43-8; **3i**, 37991-74-5.

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Studies on Lactams. XXII.[1] An Unusual Reaction of Some 6-Azidopenams

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As a continuation of our work on the synthesis of penicillin analogs *via* α-azido-β-lactams,[2] we prepared the 6-azidopenams **3** and **4** by the reaction of azidoacetyl chloride and triethylamine on the appropriate thiazolines (**1** and **2**). Catalytic reduction of **3** led to the disappearance of the ir band characteristic of the azido group and gave a material which was used without further purification for reaction with phenoxyacetyl chloride and triethylamine. We had expected to obtain the penicillin V analog **5**, but, to our surprise, the crystalline product formed in high yield was found to be **6**, a penam that is readily synthesized from the thiazoline **1**, phenoxyacetyl chloride, and triethylamine. Similarly, **4** was transformed into **7** in about 80% yield by catalytic reduction followed by treatment with phenoxyacetyl chloride and triethylamine.

In a recent communication Bell and coworkers[3] have described the degradation of penicillin G methyl ester (**8**) and penillonic acid methyl ester (**11**) in refluxing trifluoroacetic acid to the thiazoline D-5,5-dimethyl-2-thiazoline-4-carboxylic acid methyl ester (**12**). This cleavage of the β-lactam in **8** is reminiscent of the fragmentation of 6-aminopenicillanic acid (**9**) under photolytic conditions. Gotfredsen and coworkers[4] observed that photolysis of an aqueous solution of the potassium salt of **9** resulted in a new penicillin, **10**. They proposed that the β-lactam ring was cleaved with the generation of the thiazoline **13** and amino ketene or its equivalent which reacted with 6-APA (**9**) to give **10**.

Our own observations on the formation of **6** and **7** from **3** and **4** can be easily accounted for if by analogy with 6-aminopenicillanic acid fragmentation we assume

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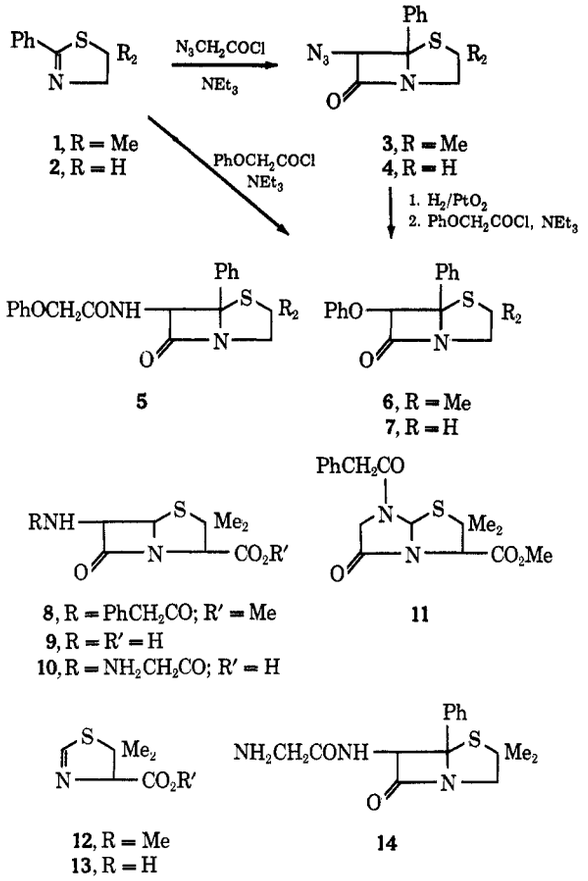

that the amino compounds formed by the reduction of **3** and **4** undergo β-lactam ring scission to the thiazolines **1** and **2**, respectively. To test this possibility, **1** in ethyl acetate solution was shaken with hydrogen for about 70 hr at room temperature in presence of Adams catalyst. From this reaction mixture a small amount of a solid and a yellow liquid were isolated. The solid, which was insoluble in common organic solvents, showed the highest peak in its mass spectrum at *m/e* 305 and a strong peak at *m/e* 191. We believe this product to be **14** (mol wt 305) by analogy with **10**. The main constituent of the liquid was deduced to be the thiazoline **1** on the basis of the mass spectrum (M^+, *m/e* 191), nmr peaks, and tlc comparison with authentic **1**. Further studies on this unusual β-lactam cleavage are necessary for establishing the exact pathway from the α-azido-β-lactams to the thiazolines under our reaction conditions.

Experimental Section

The melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer, the nmr spectra were taken on a Varian A-60A instrument, and the mass spectra were obtained on a Hitachi Perkin-Elmer RMU-7 mass spectrometer. The microanalysis were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.

6-Azido-7-oxo-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptane (4).—A solution of triethylamine (7.2 g) in 250 ml of CH_2Cl_2 was added dropwise with constant stirring and under anhydrous conditions to a refluxing solution containing 12.65 g of 2-phenyl-2-thiazoline in 800 ml of CH_2Cl_2 and 9.2 g of azidoacetyl chloride in 750 ml of CH_2Cl_2. The addition of triethylamine was completed in 1 hr and the reaction mixture was stirred for an additional period of 17 hr. The solvent was then evaporated and the residue was extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to a viscous residue. Chromatography of this residue over a Florisil column using benzene as the eluent afforded 12.73 g (70%) of the pure title compound: mp 65–67°; ir (Nujol) 4.75 (azide), 5.64 μ (β-lactam carbonyl); nmr ($CDCl_3$) τ 2.55 (s, 5), 5.07 (s, 1), 5.67 (m, 1), 6.75 (m, 3 H); mass spectrum M^+ at *m/e* 246.

Anal. Calcd for $C_{11}H_{10}N_4OS$: C, 53.66; H, 4.09; N, 22.76; S, 13.39. Found: C, 53.72; H, 4.06; N, 22.83; S, 13.13.

6-Azido-3,3-dimethyl-7-oxo-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptane (3).—This penam was prepared in 87% yield from 5,5-dimethyl-2-phenyl-2-thiazoline and azidoacetyl chloride using the procedure outlined above: mp 102–104°; ir (Nujol) 4.7 (azide), 5–6 μ (β-lactam carbonyl); nmr (CDCl) τ 2.58 (s, 5), 4.98 (s, 1), 5.92 (d, 1, *J* = 12.5 Hz), 7.05 (d, 1, *J* = 12.5 Hz), 8.43 (s, 3), 8.56 (s, 3); mass spectrum M^+ at *m/e* 274.

Anal. Calcd for $C_{13}H_{14}N_4OS$: C, 56.97; H, 5.14; N, 20.43; S, 11.63. Found: C, 56.97; H, 5.27; N, 20.47; S, 11.67.

Reduction of 3 and Its Reaction with Phenoxyacetyl Chloride.—6-Azido-3,3-dimethyl-7-oxo-5-phenyl-4-thia-1-azabicyclo-[3.2.0]heptane (3.5 g) was dissolved in 50 ml of ethyl acetate and 2.1 g of Adams catalyst was added to it. The mixture was stirred in an atmosphere of hydrogen (41 psi pressure) for 54 hr. Solvent and the catalyst were removed and the product was used for the next operation without further purification.

The reduced material was dissolved in 200 ml of CH_2Cl_2, and 2 g of triethylamine was added to it. Phenoxyacetyl chloride (2.15 g) in 50 ml of CH_2Cl_2 was then added dropwise over a period of 0.5 hr. The reaction mixture was stirred overnight, then washed with water and dried ($MgSO_4$). Removal of solvent and chromatography over Florisil using methylene chloride–hexane (2:1) provided 3 g (70%) of 3,3-dimethyl-7-oxo-5-phenyl-6-phenoxy-4-thia-1-azabicyclo[3.2.0]heptane (6): mp 93–95°; ir (Nujol) 5.6 μ (β-lactam carbonyl); nmr ($CDCl_3$) τ 2.92 (broad, 10), 4.38 (s, 1), 5.9 (d, 1, *J* = 12 Hz), 7.08 (d, 1, *J* = 12 Hz), 8.4 (s, 3), 8.52 (s, 3); mass spectrum M^+ at *m/e* 325.

Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 68.68; H, 5.09; N, 4.71; S, 10.76. Found: C, 68.70; H, 5.12; N, 4.60; S, 10.80.

Reduction of **4** using Adams catalyst followed by treatment with phenoxyacetyl chloride under conditions outlined above afforded **7**, mp 132–134°, in 80% yield: ir (Nujol) 5.65 μ; nmr ($CDCl_3$) τ 2.9 (broad, 10), 4.5 (s, 1), 5.65 (m, 1), 6.7 (m, 3); mass spectrum M^+ at *m/e* 297.

Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 70.14; H, 5.89; N, 4.31; S, 9.83. Found: C, 70.31; H, 5.86; N, 4.24; S, 9.74.

Registry No.—**1**, 37950-61-1; **2**, 2722-34-1; **3**, 37950-63-3; **4**, 37950-64-4; **6**, 37950-65-5; **7**, 37950-66-6; azidoacetyl chloride, 30426-58-5; phenoxyacetyl chlorides, 701-99-5.

Synthesis and Some Properties of *O*-Acyl- and *O*-Nitrophenylhydroxylamines

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O-Acyl- and *O*-nitrophenylhydroxylamines, useful aminating agents,[1,2] have usually been prepared by the following two methods:[3] (i) Carpino's method[2]

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