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Synthesis and Reactions of 7-Hydrazonocephalosporanates

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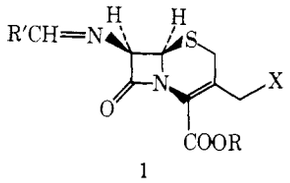
p-Nitrobenzyl 7-hydrazonocephalosporanates **3** (R_1 = *p*-NO_2PhCH_2; R_2 = H) were synthesized and identified as isomers. Thienylacetylation and reduction gave the hydrazino compound **5**. Compounds **3** react with NBS in aqueous acetone to give ketones **6**. Reduction of **6** gives alcohol **7** (R_1 = CH_2Ph; R_3 = H) which was acylated and deblocked to give a series of cephalosporin oxygen analogues.

Many chemical modifications at C_7 of cephalosporins have been achieved through activation of the C_7 position in such structures as **1**. Another method of entry into this posi-

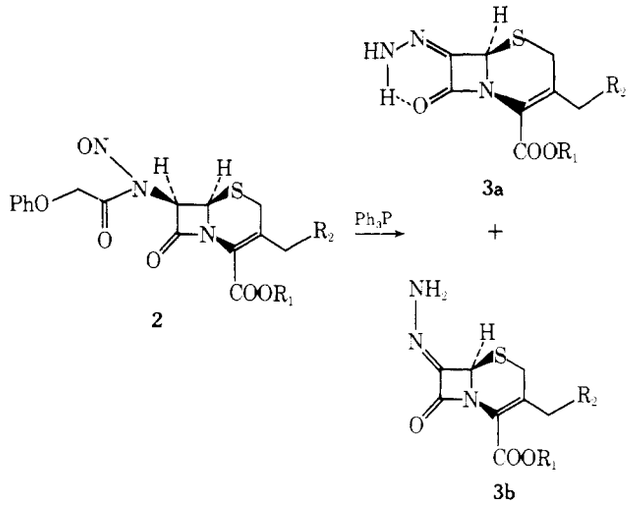


1

tion involves oxidation of C_7 to form the diazo compound followed by further reactions characteristic of this group.[1]

7-Diazocephalosporanates have been synthesized via diazotization of the amine,[2,3] and rearrangement of 6β-*N*-nitrosophenoxyacetamidocephalosporanates in the presence of base.[4] The latter reaction gives a poor yield since the *N*-nitroso amide is surprisingly resistant to rearrangement. Several new methods have been applied to this system and will be reported here.

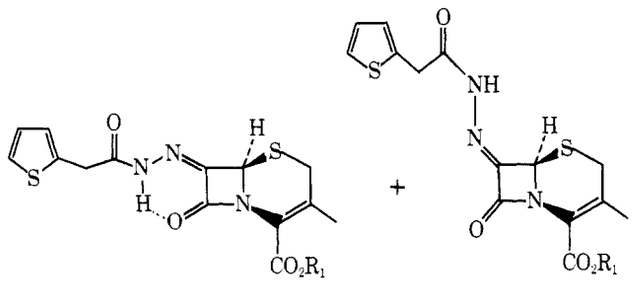
The nitroso compound, *p*-nitrobenzyl 7β-*N*-nitrosophenoxyacetamidodeacetoxycephalosporanate **2** (R_1 = *p*-NO_2PhCH_2; R_2 = H), reacts with triphenylphosphine to give a mixture of *p*-nitrobenzyl 7-hydrazonocephalosporanates **3** (R_1 = *p*-NO_2PhCH_2; R_2 = H). It is postulated that the triphenylphosphine forces the *N*-nitroso–diazo rearrangement, giving the diazo derivative, which forms an adduct generating **3** on hydrolysis. Phenoxyacetic acid was isolated as a byproduct. The trichloroethyl ester of **3** (R_1 = CCl_3CH_2; R_2 = H) has been reported derived from the diazotization of 7-aminocephalosporanate with isoamyl nitrite in formic acid.[5] The analogous hydrazono compounds have also been synthesized in the penicillin series.[6] However, the existence of two isomers has not been reported in either series. The isomers are separable by chromatography and can be distinguished by



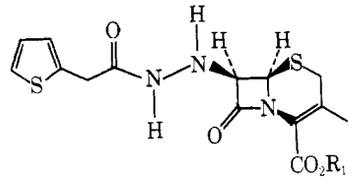
2 **3a** **3b**

their physical properties. The intramolecular hydrogen bonding of structure **3a** is expected to produce a less polar and lower melting compound. In addition the infrared absorption of the β-lactam carbonyl should be lowered by this bonding effect by about 20 cm^{-1}.[7] These effects are observed and the structure assignments made accordingly. The isomers are interconvertible in the presence of base. Starting with either isomer, a mixture of both is obtained in the presence of pyridine.

Thienylacetylation of **3a** or **3b** (R_1 = *p*-NO_2PhCH_2; R_2 = H) gave a pair of isomers **4** (R_1 = *p*-NO_2PhCH_2). Stereospecific reduction of the hydrazones with potassium borohydride and removal of the blocking group gave one product from both isomers, the hydrazino analogue of deacetoxycephalothin **5** (R_1 = H). The phenoxyacetyl, acetyl, and free hydrazino an-



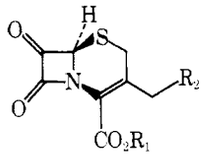
4a 4b



5

alogues have been reported[5] but without experimental details.

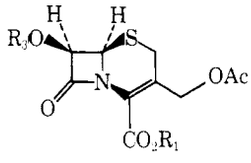
The hydrazono compound **3** (R_1 = p-NO_2PhCH_2 or Ph_2CH; R_2 = H or OAc) reacts with N-bromosuccinimide in aqueous acetone to give the ketone **6**. The same compound can be synthesized from 7-diazocephalosporanates[2] by treatment with N-bromosuccinimide or N-bromoacetamide in aqueous acetone. This method is applicable to cephalosporin C to produce esters of **6**. N,N-Phthaloylcephalosporin C di-



6

benzhydryl ester was treated with dinitrogen tetroxide and triphenylphosphine to give **3a** and **3b** (R_1 = Ph_2CH; R_2 = OAc), which react further with N-bromosuccinimide to give **6** (R_1 = Ph_2CH; R_2 = OAc).

Ketone **6** (R_1 = Ph_2CH; R_2 = OAc) was reduced with potassium borohydride to give the alcohol **7** (R_1 = Ph_2CH; R_3



7

= H). Spectral data indicate that only the cis isomer is formed. Removal of the protecting group gave the oxygen analogue of 7-ACA, **7** (R_1 = R_3 = H). Acylation prior to deblocking gave the oxygen analogues of cephalosporin **7** [R_1 = H; R_3 = $PhCH(NH_2)CO$, $PhCH_2SO_2$, $PhOCH_2CO$, $C_4H_3SCH_2CO$].

Compounds **7** (R_1 = H) were tested for bioactivity with the following (minimum inhibitory concentration, μg/ml against *Staph. aureus* A100): R_3 = $PhCH_2SO_2$, 12.5; $PhOCH_2CO$, 12.5; $C_4H_3SCH_2CO$, 12.5.

Experimental Section

General. Melting points were determined on a Fisher-Johns melting point apparatus. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. IR spectra were recorded on a Perkin-Elmer 237 spectrophotometer. NMR spectra were taken on a Varian T-60 spectrometer and are reported in parts per million downfield from Me_4Si. Baker-flex silica gel 1B-F was used for thin layer chromatography.

***p*-Nitrobenzyl 7β-*N*-Nitrosophenoxyacetamidodeacetoxycephalosporanate 2 (R_1 = p-NO_2PhCH_2; R_2 = H).** Dinitrogen tetroxide (7 g) was dissolved in 100 ml of methylene chloride. A solution of p-nitrobenzyl 7β-phenoxyacetamidodeacetoxycephalosporinate in methylene chloride (30 ml) was added in 20 min with stirring at 0 °C to a mixture of anhydrous sodium acetate (7 g), dinitrogen tetroxide (50 ml of above solution), and methylene chloride (50 ml). The mixture was stirred at 0 °C for 1 h. Additional portions of dinitrogen tetroxide (30 ml, 20 ml) were added immediately after and 30 min after addition of the cephalosporin derivative. Excess dinitrogen tetroxide was consumed by adding saturated sodium bicarbonate. The aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to a yellow oil. Crystallization from acetone–petroleum ether gave 3.0 g of yellow solid, 81%: mp 120–121 °C dec; $[\alpha]^{25}D$ −25.2° (c 0.76, $CHCl_3$); IR (CH_2Cl_2) 1790, 1745, 1725, 1535, 1350, 1225 cm^{-1}; NMR ($CDCl_3$) δ 8.28–7.50 (q, 4 H), 7.35–6.83 (m, 5 H), 5.87 (d, J = 4.5 Hz, 1 H), 5.57 (s, 2 H), 5.33 (d, J = 4 Hz, 2 H), 5.00 (d, J = 4.5 Hz, 1 H), 3.62–2.75 (q, J = 16 Hz, 2 H), 2.36 (s, 3 H).

Anal. Calcd for $C_{23}H_{20}N_4SO_8$ (512.49): C, 53.90; H, 3.93; N, 10.93; S, 6.26. Found: C, 53.82; H, 3.86; N, 10.76; S, 6.40.

Benzhydryl 7β-(Benzhydryl-5-*N,N*-phthaloyl-5-aminoadipamido)cephalosporanate. N,N-Phthaloylcephalosporin C dibenzhydryl ester was prepared according to published procedures:[6] mp 165–167 °C (lit. 161–163 °C); IR ($CDCl_3$) 3410, 3330, 1780, 1740, 1730, 1685, 1510, 1385, 1230 cm^{-1}; NMR ($CDCl_3$) δ 7.80 (m, 4 H), 7.30 (m, 20 H), 6.95 (s, 1 H), 6.90 (s, 1 H), 6.45 and 6.30 (2 s, 1 H), 5.82 (q, 1 H), 5.20–4.62 (m, 4 H), 3.70–3.02 (q, J = 19 Hz, 2 H), 2.43–2.22 (m, 4 H), 2.05 (s, 3 H), 1.90–1.60 (m, 2 H).

Benzhydryl 7β-*N*-Nitrosobenzhydryl-5-*N,N*-phthaloyl-5-aminoadipamidocephalosporanate. The above compound (0.5 g) was treated with dinitrogen tetroxide in the same manner as **2**. A yellow oil was obtained: IR (film) 1780, 1730, 1720, 1525, 1385, 1240 cm^{-1}; NMR ($CDCl_3$) δ 7.80 (m, 4 H), 7.30 (m, 20 H), 6.95 (s, 1 H), 6.90 (s, 1 H), 5.79 (d, J = 4.5 Hz, 1 H), 5.30–4.70 (m, 4 H), 3.30 (s, br, 4 H), 2.40 (br, 2 H), 1.95 (s, 3 H), 1.90 (br, 2 H).

***N*-Nitrosoamide–Hydrazone Transformations.** N-Nitrosoamide **2** was refluxed with 1 equiv of triphenylphosphine in benzene for 45 min. The reaction mixture was cooled to room temperature and was stirred vigorously with excess water for 2 h. Methylene chloride was added and the organic layer was washed with 5% sodium bicarbonate solution and water, dried (Na_2SO_4), and evaporated to a brown oil. Separation of products (**3**) was effected by chromatography on silicic acid eluted by a mixture of methylene chloride and ethyl ether.

***p*-Nitrobenzyl 7-Hydrazonodeacetoxycephalosporanate 3a (R_1 = p-NO_2PhCH_2; R_2 = H).** R_f 0.45 (1:10 Et_2O–CH_2Cl_2). The product was crystallized from chloroform–petroleum ether, 28%: mp 115–116 °C; IR (CH_2Cl_2) 3435, 3300, 1760, 1730, 1610, 1525, 1350 cm^{-1}; NMR ($CDCl_3$) δ 8.25–7.50 (q, 4 H), 6.80 (s, 2 H), 5.38 (s, 2 H), 5.17 (s, 1 H), 3.73–3.00 (q, J = 19 Hz, 2 H), 2.19 (s, 3 H); MS M^+ m/e 362; high-resolution mass spectrum gave molecular formula $C_{15}H_{14}N_4SO_5$.

***p*-Nitrobenzyl 7-Hydrazonodeacetoxycephalosporanate 3b (R_1 = p-NO_2PhCH_2; R_2 = H).** R_f 0.20 (1:10 Et_2O–CH_2Cl_2). The product was crystallized from chloroform, 58%: mp 165–166 °C; IR (CH_2Cl_2) 3430, 3290, 1780, 1730, 1615, 1525, 1350 cm^{-1}; NMR ($CDCl_3$) δ 8.25–7.50 (q, 4 H), 6.10 (s, 2 H), 5.35 (s, 2 H), 5.30 (s, 1 H), 3.65–3.00 (q, J = 18 Hz, 2 H), 2.20 (s, 3 H); MS M^+ m/e 362; high-resolution mass spectrum gave molecular formula $C_{15}H_{14}N_4SO_5$.

Anal. Calcd for $C_{15}H_{14}N_4SO_5$ (362.36): C, 49.72; H, 3.89; N, 15.46; S, 8.85. Found: C, 49.54; H, 3.90; N, 15.32; S, 8.93.

Benzhydryl 7-Hydrazonocephalosporanate 3a (R_1 = Ph_2CH; R_2 = OAc). R_f 0.44 (1:10 Et_2O–CH_2Cl_2); oily product, yield 20%; IR ($CHCl_3$) 3455, 3320, 1760, 1730, 1620, 1375, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.38 (s, 10 H), 7.00 (s, 1 H), 6.85 (s, 2 H), 5.25 (s, 1 H), 5.23–4.55 (q, J = 14 Hz, 2 H), 3.75–3.10 (q, J = 19 Hz, 2 H), 2.02 (s, 3 H).

Benzhydryl 7-Hydrazonocephalosporanate 3b (R_1 = Ph_2CH; R_2 = OAc). R_f 0.24 (1:10 Et_2O–CH_2Cl_2). The product was crystallized from benzene: yield 45%; mp 152–154 °C; IR ($CDCl_3$) 3430, 3310, 1780, 1730, 1230 cm^{-1}; NMR ($CDCl_3$) δ 7.40 (s, 10 H), 6.98 (s, 1 H), 6.25 (s, 2 H), 5.28 (s, 1 H), 5.08–4.55 (q, J = 14 Hz, 2 H), 3.72–3.05 (q, J = 18 Hz, 2 H), 2.02 (s, 3 H).

Isomerizations of the Geometrical Isomers 3a and 3b. Starting with a pure isomer (either **3a** or **3b**, R_1 = p-NO_2PhCH_2; R_2 = H) in methylene chloride in the presence of 1.5 equiv of pyridine, after a month at room temperature, a mixture of both isomers (**3a** and **3b**) results. The isomers were separated by chromatography and their amounts were determined. Thus from 1 g of **3b**, 0.45 g of **3a** and 0.45 g of **3b** were isolated; from 76 mg of **3a**, 40 mg of **3a** and 25 mg of **3b** were isolated.

2-Thienylacetylation of 3b. p-Nitrobenzyl 7-hydrazonodeacetoxycephalosporanate **3b** (R_1 = p-NO_2PhCH_2; R_2 = H; 1 g, 2.76

mmol), pyridine (0.33 ml, 1.5 equiv), and 2-thienylacetyl chloride (0.72 g, 1.5 equiv) were dissolved in methylene chloride (60 ml) at 0 °C. The solution was stirred at room temperature for 18 h and then diluted with methylene chloride (100 ml). The organic phase was successively washed by cold, dilute (0.1 N) hydrochloric acid, cold 5% sodium bicarbonate solution, and ice water, dried (Na_2SO_4), and evaporated to a brown oil. Products **4a** (0.7 g, 52%) and **4b** (R_1 = p-NO_2PhCH_2; R_2 = H; 0.5 g, 37%) were isolated by column chromatography on silicic acid eluted with 1:10 Et_2O–CH_2Cl_2.

2-Thienylacetylation of 3a. p-Nitrobenzyl 7-hydrazonodeacetoxycephalosporanate **3a** (R_1 = p-NO_2PhCH_2; R_2 = H; 0.2 g) was treated with pyridine and 2-thienylacetyl chloride as in the case of **3b.** After column chromatography, the two products isolated were identical with those isolated in 2-thienylacetylation of **3b** based on IR, NMR, and TLC data. Yields of products isolated were **4a** (0.11 g, 41%); **4b** (0.07 g, 23%).

***p*-Nitrobenzyl 7-(2-Thienylacetyl)hydrazonodeacetoxycephalosporanate 4a.** R_f 0.45 (1:10 Et_2O–CH_2Cl_2); IR (CH_2Cl_2) 3290, 1770, 1720, 1680, 1520 cm^{-1}; NMR (acetone-d_6) δ 8.35–7.70 (q, 4 H), 7.35 (m, 1 H), 7.00 (m, 2 H), 5.58 (s, 1 H), 5.50 (s, 2 H), 4.20 (s, br, 2 H), 4.02–3.28 (q, J = 19 Hz, 2 H), 2.97 (s, br, 1 H), 2.24 (s, 3 H).

Anal. Calcd for $C_{21}H_{18}N_4S_2O_6$ (486.53): C, 51.84; H, 3.73; N, 11.52; S, 13.18. Found: C, 51.81; H, 3.70; N, 11.50; S, 13.17.

***p*-Nitrobenzyl 7-(2-Thienylacetyl)hydrazonodeacetoxycephalosporanate 4b.** R_f 0.19 (1:10 Et_2O–CH_2Cl_2); mp 178– 179 °C; IR (CH_2Cl_2) 3300, 1785, 1725, 1670, 1525 cm^{-1}; NMR (acetone-d_6) δ 8.38–7.72 (q, 4 H), 7.37 (m, 1 H), 7.00 (m, 2 H), 5.72 (s, 1 H), 5.50 (s, 2 H), 4.28 (s, br, 2 H), 3.84–3.21 (q, J = 18 Hz, 2 H), 2.90 (br, 1 H), 2.28 (s, 3 H).

Anal. Calcd for $C_{21}H_{18}N_4S_2O_6$ (486.53): C, 51.84; H, 3.73; N, 11.52; S, 13.18. Found: C, 51.56; H, 3.69; N, 11.26; S, 12.93.

Borohydride Reduction of 4a. To a cooled, stirred solution of p-nitrobenzyl 7-(2-thienylacetyl)hydrazonodeacetoxycephalosporanate (**4a,** R_1 = p-NO_2PhCH_2; R_2 = H; 0.65 g, 1.34 mmol) in tetrahydrofuran (20 ml) was added a cold solution of potassium borohydride (0.16 g, 2.2 molar equiv) in 50% aqueous THF (30 ml). After 3 min, 1 N hydrochloric acid was added to bring the pH of the solution to 2. The solution was diluted with water and extracted twice with methylene chloride. The combined extracts was washed once with 5% sodium bicarbonate solution and once with water, dried (Na_2SO_4), and evaporated to a yellow solid. Crystallization from chloroform gave white crystalline p-nitrobenzyl 7β-(2-thienylacetyl)hydrazinodeacetoxycephalosporanate **5** (R_1 = p-NO_2PhCH_2), 0.50 g, 72%: mp 183–184 °C dec; IR (CH_2Cl_2) 3390, 3280, 1775, 1725, 1680, 1520 cm^{-1}; NMR ($CDCl_3$) δ 8.20 (d, 2 H), 7.58 (d over br s, 3 H), 7.20 (m, 1 H), 6.95 (m, 2 H), 5.32 (s, 2 H), 5.27 (br, 1 H), 4.98 (d, J = 4.2 Hz, 1 H), 4.75 (m, 1 H), 3.78 (s, 2 H), 3.60–2.98 (q, J = 18 Hz, 2 H), 2.20 (s, 3 H).

Anal. Calcd for $C_{21}H_{20}N_4S_2O_6$ (488.54): C, 51.63; H, 4.13; N, 11.47; S, 13.13. Found: C, 51.44; H, 4.17; N, 11.25; S, 12.97.

Borohydride Reduction of 4b. p-Nitrobenzyl 7-(2-thienylacetyl)hydrazonodeacetoxycephalosporanate (**4b,** R_1 = p-NO_2PhCH_2; R_2 = H; 0.61 g) was treated with potassium borohydride in the same manner as in the reduction of **4a.** TLC (silica gel, 1:4 Et_2O–CH_2Cl_2) of the workup showed starting material (**4b,** R_f 0.50) and a product (R_f 0.17). Column chromatography gave 0.35 g of unreacted **4b** (58% recovery) and a white crystalline solid (0.12 g, 20%) which is identical with **5** (R_1 = p-NO_2PhCH_2) based on melting point, IR, NMR, and TLC data.

7β-(2-Thienylacetyl)hydrazinodeacetoxycephalosporanic Acid 5 (R_1 = H). p-Nitrobenzyl 7β-(2-thienylacetyl)hydrazinodeacetoxycephalosporanate (**5,** R_1 = p-NO_2PhCH_2, 0.10 g) was dissolved in glacial acetic acid (20 ml) and hydrogenated (1 atm) at room temperature for 2 h in the presence of 10% Pd/C (0.4 g). The catalyst was removed by filtration and washed with glacial acetic acid. The solvent was partially removed at reduced pressure and then freeze-dried together with an excess of benzene, leaving a pale yellow solid, 60 mg: IR (KBr) 3500–2700, 1770, 1730–1650 cm^{-1}; NMR (Me_2SO-d_6) δ 9.83 (br, 1 H), 7.45 (m, 1 H), 7.05 (m, 2 H), 6.65 (br, 1 H), 5.10–4.80 (m, 2 H), 3.75–3.15 (m, 2 H), 2.10 (br s, 3 H).

***p*-Nitrobenzyl 7-Oxodeacetoxycephalosporanate 6 (R_1 = p-NO_2PhCH_2; R_2 = H).** p-Nitrobenzyl 7-hydrazonodeacetoxycephalosporanate (**3b,** 0.9 g, 2.49 mmol) was dissolved in 10% aqueous acetone (200 ml), and the solution was cooled in an ice bath. Pyridine (3.65 ml, 0.04 mol) and N-bromosuccinimide (0.97 g, 2.2 equiv) were added to the stirred solution. After 45 min the reaction mixture was diluted with methylene chloride and cold water. Extraction with cold methylene chloride was repeated three times. The organic layer was washed successively with cold hydrochloric acid (0.1 N), cold 5% sodium bicarbonate solution, and ice water, dried (Na_2SO_4), and evaporated to a yellow oil, 0.94 g. Chromatography on silicic acid eluted with 1:10 Et_2O–CH_2Cl_2 gave one major fraction, R_f 0.36 (1:10 Et_2O–CH_2Cl_2); 0.65 g (75%); IR (film) 1825, 1780, 1725, 1515 cm^{-1}; NMR of the product **6** (R_1 = p-NO_2PhCH_2; R_2 = H) after chromatography gave complicated signals suspected to be the result of a mixture of the ketone and the hydrate of the ketone. The same sample was refluxed in benzene under a Dean-Stark trap for 16 h and the following NMR was obtained after removal of solvent at reduced pressure: NMR ($CDCl_3$) δ 8.25–7.50 (q, 4 H), 5.40 (s, 2 H), 5.30 (s, 1 H), 3.78–3.10 (q, J = 19 Hz, 2 H), 2.25 (s, 3 H).

Benzhydryl 7-Oxocephalosporanate 6 (R_1 = Ph_2CH; R_2 = OAc). Compound **3b** (R_1 = Ph_2CH; R_2 = OAc) (0.5 g, 1.11 mmol) was treated with N-bromosuccinimide in the same way as **3b** (R_1 = p-NO_2PhCH_2; R_2 = H). A yellow oil was obtained after chromatography: 0.24 g, 49%; R_f 0.40 (1:9 Et_2O–CH_2Cl_2); IR (film) 1825, 1785, 1735, 1385, 1240 cm^{-1}; NMR of the product after chromatography indicated partial hydration. The sample after refluxing in benzene gave the following spectrum: NMR ($CDCl_3$) δ 7.39 (s, 10 H), 7.00 (s, 1 H), 5.21 (s, 1 H), 5.10–4.65 (q, J = 13 Hz, 2 H), 3.80–3.15 (q, J = 18 Hz, 2 H), 2.01 (s, 3 H).

Benzhydryl 7β-Hydroxycephalosporanate 7 (R_1 = Ph_2CH; R_3 = H). Crude **6** (R_1 = Ph_2H; R_2 = OAc) (2.95 g) was dissolved in THF (150 ml) and cooled to 0 °C. Potassium borohydride (0.74 g, 13.7 mmol) in 1:1 THF–H_2O (150 ml) was added quickly. The reaction was quenched after 2 min by addition of 1 N HCl to pH 2. The solution was diluted with water and extracted with methylene chloride, and the organic layer was washed with bicarbonate solution and salt solution. Drying and evaporation gave a yellow oil which was chromatographed to give 1.2 g of solid. Recrystallization from benzene gave mp 122–123 °C; IR (CH_2Cl_2) 3540, 1785, 1735, 1225 cm^{-1}; NMR ($CDCl_3$) δ 2.04 (s, 3 H), 3.45 (d, 2 H), 3.90 (s, 1 H), 4.62–5.20 (m, J_1 = 4.5, J_2 = 13 Hz, 3 H), 5.29 (d, J = 4.5 Hz, 1 H), 7.00 (s, 1 H), 7.39 (s, 10 H).

7β-Hydroxycephalosporanic Acid 7 (R_1 = R_3 = H). Compound **7** (R_1 = Ph_2H; R_3 = H) (0.3 g, 0.68 mmol) was dissolved in trifluoroacetic acid (7 ml) and anisole (1 ml) at 0 °C. After 1 h the solvents were evaporated and the residual oil washed with petroleum ether. The oil was dissolved in ethyl acetate and decolorized with charcoal. Crystallization from ethyl acetate gave 0.17 g (99%): mp 132 °C dec; IR (KBr) 3430, 3100, 1780–1700, 1625, 1380, 1220 cm^{-1}; NMR (acetone-d_6) δ 2.04 (s, 3 H), 3.55 (d, 2 H), 4.80–5.15 (m, J = 4.8, 13 Hz, 3 H), 5.40 (d, J = 4.8 Hz, 1 H).

Benzhydryl 7β-Phenoxyacetoxycephalosporanate 7 (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$). Compound **7** (R_1 = $CHPh_2$; R_3 = H) (0.8 g, 1.8 mmol) and phenoxyacetyl chloride (0.42 g, 1.5 equiv) were dissolved in CH_2Cl_2 (50 ml). Pyridine (0.15 ml, 1.5 equiv) was added to the cooled, stirred solution. After 3 h stirring at room temperature, the solution was washed with water, bicarbonate, and salt solution. The solution was dried and evaporated and the residue was chromatographed on silicic acid with Et_2O–CH_2Cl_2 (1:20) to give 0.85 g (88%) of an oil: IR (film) 1785, 1730, 1600, 1495, 1380, 1225 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (s, 3 H), 3.38 (s, 2 H), 4.75 (s, 2 H), 4.65–5.20 (q, J = 4.8, 14 Hz, 3 H), 6.10 (d, J = 4.8 Hz, 1 H), 6.80–7.54 (m, 16 H).

7β-Phenoxacetoxycephalosporanic Acid 7 (R_1 = H; R_3 = $PhOCH_2CO$). Compound **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$) was deblocked in the same way as **7** (R_1 = $CHPh_2$; R_3 = H) to give a 93% yield: IR (film) 3580, 3520–2500, 1785–1690, 1635, 1600, 1495, 1380, 1230 cm^{-1}; NMR (acetone-d_6) δ 2.02 (s, 3 H), 3.60 (d, 2 H), 4.92 (s, 2 H), 4.70–5.28 (q, J = 14 Hz, 2 H), 5.25 (d, J = 4.8 Hz, 1 H), 6.32 (d, J = 4.8 Hz, 1 H), 6.87–7.42 (m, 5 H), 8.10 (s, 1 H).

Benzhydryl 7β-(2-Thienyl)acetoxycephalosporanate 7 (R_1 = $CHPh_2$; R_3 = $C_4H_3SCH_2CO$). Compound **7** (R_1 = $CHPh_2$; R_3 = H) (0.45 g, 1.0 mmol), 2-thienylacetic acid (0.21 g, 1.5 equiv), and pyridine (0.1 ml, 1.2 equiv) were dissolved in CH_2Cl_2 (50 ml) at 0 °C. Diisopropylcarbodiimide (0.13 g, 1 equiv) was added and the solution stirred at 0 °C for 1 h and stored at 5 °C for 17 h. The solution was filtered, diluted with CH_2Cl_2, and washed with cold dilute HCl, bicarbonate, and salt solution. Drying and evaporation gave a yellow oil which was chromatographed on silicic acid with Et_2O–CH_2Cl_2 (1:20) to give 0.6 g (95%): IR (film) 1785, 1730, 1360, 1235 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (s, 3 H), 3.36 (s, 2 H), 3.91 (s, 2 H), 4.60–5.20 (d on q, J = 4.8, 14 Hz, 3 H), 6.05 (d, J = 4.8 Hz, 1 H), 6.90–7.54 (m, 14 H).

7β-(2-Thienyl)acetoxycephalosporanic Acid 7 (R_1 = H; R_3 = $C_4H_3SCH_2CO$). Compound **7** (R_1 = $CHPh_2$; R_3 = $C_4H_3SCH_2CO$) was deblocked as described for **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$). Freeze-drying from benzene gave 98%: IR (film) 3560–2540, 1780, 1725, 1380, 1225 cm^{-1}; NMR ($CDCl_3$) δ 2.13 (s, 3 H), 3.47 (s, 2 H), 4.00 (s, 2 H), 4.82–5.38 (d on q, J = 4.8, 15 Hz, 3 H), 6.19 (d, J = 4.8 Hz, 1 H), 7.00 (d, 1 H), 7.20–7.40 (m, 2 H), 7.73 (s, 1 H).

Benzhydryl 7β-Benzylsulfonylcephalosporanate 7 (R_1 = $CHPh_2$; R_3 = $PhCH_2SO_2$). Compound **7** (R_1 = $CHPh_2$; R_3 = H) was

benzylsulfonated with benzylsulfonyl chloride and pyridine as described for 7 (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$). The product was chromatographed on silica gel with Et_2O–CH_2Cl_2 (1:20) to give 74% of an oil: IR (film) 1780, 1725, 1625, 1495, 1450, 1370, 1220 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, 3 H), 3.45 (s, 2 H), 4.58 (s, 2 H), 4.55–5.20 (d on q, J = 13, 21 Hz, 3 H), 5.70 (d, J = 4.5 Hz, 1 H), 6.95 (s, 1 H), 7.45 (m, 15 H).

7β-Benzylsulfonylcephalosporanic Acid 7 (R_1 = H; R_3 = $PhCH_2SO_2$). Compound 7 (R_1 = $CHPh_2$; R_3 = $PhCH_2SO_2$) was deblocked as described for 7 (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$) to give a yellow oil. Treatment with potassium 2-ethyl hexanoate gave 60 mg of the potassium salt: IR (KBr) 2910, 1755, 1725, 1600, 1360, 1225 cm^{-1}.

Benzhydryl 7β-(2-*tert*-Butoxycarbonylamino-D-phenylacetoxy)cephalosporanate 7 [R_1 = $CHPh_2$; R_3 = $PhCH(NHCO_2$-*t*-Bu)CO]. Compound 7 (R_1 = $CHPh_2$; R_3 = H) (2.8 g, 6.4 mmol) was esterified with 2-*tert*-butoxycarbonylamino-D-phenylacetic acid as described for 7 (R_1 = $CHPh_2$; R_3 = $C_4H_3SCH_2CO$). Chromatography on silicic acid with Et_2O–CH_2Cl_2 (1:20) gave 0.5 g (11%) of oil: IR (film) 3300, 2960, 1790, 1720, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (s, 3 H), 4.06 (q, J_{gem} = 15 Hz, 2 H), 4.82 (d, J = 4 Hz, 2 H), 5.35 (d, J = 13 Hz, 1 H), 5.60 (m, 2 H), 6.03 (d, J = 4.8 Hz, 1 H), 6.86 (s, 1 H), 7.24 (m, 15 H).

7β-(2-Amino-D-phenylacetoxy)cephalosporanic Acid 7 [R_1 = H; R_3 = $PhCH(NH_2)CO$]. Compound 7 [R_1 = $CHPh_2$; R_3 = $PhCH(NHCO_2$-*t*-Bu)CO] (0.13 g, 0.149 mmole) was deblocked as described for 7 (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$). After evaporation of the solvents the residue was dissolved in 10 ml of cold dioxane and 20 ml of cold methylene chloride. Toluenesulfonic acid (29 mg) was added and the solution freeze-dried. The residue was crystallized from dioxane–ether to give a white solid 7 [R_1 = H; R_3 = D-$PhCH(NH_3^+CH_3PhSO_3^-)CO$]: mp 138–140 °C; IR (KBr) 3400, 2900, 1760, 1730, 1610, 1500, 1375 cm^{-1}; NMR (acetone-d_6) δ 1.80 (s), 2.13 (s, 3 H), 3.12 (m, 2 H), 4.70 (d, J = 4 Hz, 2 H), 4.90 (d, J = 5 Hz, 1 H), 5.33 (s, 1 H), 6.15 (d, J = 4 Hz, 1 H), 6.90–7.50 (m, 9 H).

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Registry No.—**2** (R_1 = p-NO_2PhCH_2; R_2 = H), 51056-21-4; **3** (R_1 = p-NO_2PhCH_2; R_2 = H), 61394-33-0; **3** (R_1 = Ph_2CH; R_2 = OAc), 61394-34-1; **4** (R_1 = p-NO_2PhCH_2; R_2 = H), 61394-35-2; **5** (R_1 = p-NO_2PhCH_2), 61394-36-3; **5** (R_1 = H), 61394-37-4; **6** (R_1 = p-NO_2PhCH_2; R_2 = H), 61394-38-5; **6** (R_1 = Ph_2CH; R_2 = OAc), 59128-53-9; **7** (R_1 = Ph_2CH; R_3 = H), 59128-54-0; **7** (R_1 = R_3 = H), 59128-55-1; **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$), 59128-56-2; **7** (R_1 = H; R_3 = $PhOCH_2CO$), 57792-80-0; **7** (R_1 = $CHPh_2$; R_3 = $C_4H_3SCH_2CO$), 59128-57-3; **7** (R_1 = H; R_3 = $C_4H_3SCH_2CO$), 59128-58-4; **7** (R_1 = $CHPh_2$; R_3 = $PhCH_2SO_2$), 61394-39-6; **7** (R_1 = H; R_3 = $PhCH_2SO_2$), 61394-40-9; **7** (R_1 = $CHPh_2$; R_3 = $PhCHNHCO_2$-*t*-Bu)CO, 61436-64-4; **7** (R_1 = H; R_3 = $PhCHNH_2COMeC_6H_4SO_3H$), 61394-42-1; dinitrogen tetroxide, 10544-72-6; p-nitrobenzyl 7β-phenoxyacetamidodeacetoxycephalosporanate, 28974-31-4; benzhydryl 7β-(benzhydryl-5-*N*,*N*-phthaloyl-5-aminoadipamido)cephalosporanate, 16361-81-2; benzhydryl 7β-*N*-nitrosobenzhydryl-5-*N*,*N*-phthaloyl-5-aminoadipamidocephalosporanate, 61394-43-2; 2-thienylacetyl chloride, 50529-60-7; phenoxyacetyl chloride, 701-99-5; 2-thienylacetic acid, 1918-77-0; benzylsulfonyl chloride, 1939-99-7; 2-*tert*-butoxycarbonylamino-D-phenylacetic acid, 33125-05-2.

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1-Oxo-1,2,5-thiadiazolidin-3-ones. A Structural Reassignment

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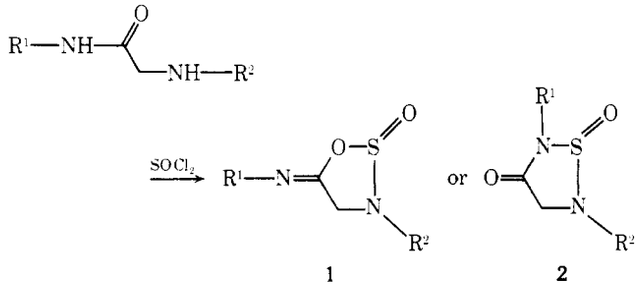
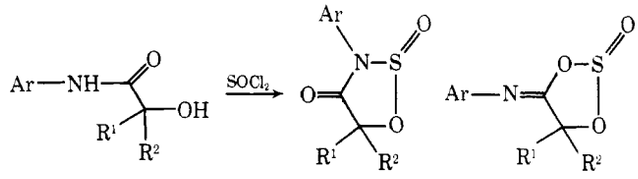
The structure of the products obtained from the reactions of 2-aminoamides with thionyl chloride has been reinvestigated by means of ^{13}C NMR spectroscopy. As a result of these investigations and comparisons with appropriate model compounds, the revised 1-oxo-1,2,5-thiadiazolidin-3-one structure has been assigned.

We reported previously the reaction of 2-aminoamides with thionyl chloride to produce 2-oxo-5-imino-1,2,3-oxathiazolidines (**1**).[1] This structure was based on IR and NMR spectral data as well as the mild acid hydrolysis of **1a** to its precursor 2-aminoamide. Subsequently, Chupp reported on a similar reaction between 2-hydroxyarylamides and thionyl chloride.[2] Consideration of the IR and NMR spectral data led this author to prefer the 2-oxo-1,2,3-oxathiazolidin-4-one structure (**3**) over the isomeric 2-oxo-4-imino-1,3,2-dioxathiolane structure (**4**). Chupp and Dahm later employed ^{18}O labeling and x-ray crystallography to confirm structure **3a** (Ar = 3,4-$Cl_2C_6H_3$; R^1 = CH_3; R^2 = H; 5-methyl group trans to the sulfinyl oxygen).[3] At the same time Chupp



1 **2**

a, R^1 = *o*-$C_6H_4CH_3$; R^2 = *t*-Bu
b, R^1 = *o*-$C_6H_4CH_3$; R^2 = C_6H_5
c, R^1 = *t*-Bu; R^2 = C_6H_5
d, R^1 = $CH_2C_6H_5$; R^2 = *t*-Bu



3 **4**