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Synthesis of Substituted β-Lactams by Addition of Nitromethane to 6-Oxopenicillanates and 7-Oxocephalosporanates[1]

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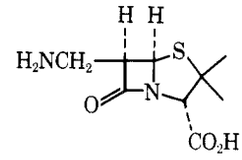
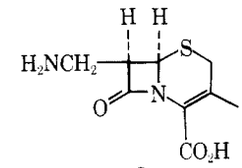
As part of our program of investigation of modified β-lactams we decided to explore the synthesis of 6-aminomethylpenicillin (**1**) and 7-aminomethyldeacetoxycephalosporin (**2**). These compounds represent an interesting hypothetical basis for the preparation of a family of homologous penicillins and cephalosporins.

Our synthetic plan was conditioned by the requirement that we needed to have starting materials which could be prepared in gram quantities and in relatively few steps. In a manner consistent with these objectives, we chose a scheme which utilized 6-oxopenicillanate **3** since it was known to undergo ready reaction with nucleophiles[3-6] and it was conveniently available from 6-hydroxypenicillanate **4**.[7]

The preparation of 6-oxopenicillanate **3** was not as straightforward as one was led to believe from literature reports. Sheehan's original report of the synthesis of **3** by the Pfitzner–Moffatt oxidation of **4** did not include a mention of the yield.[3] Vanderhaeghe[8] has published experimental details of a comparison of oxidative methods which have been applied to the synthesis of **3**. He found that oxidation with Me_2SO–acetic anhydride gave **3** in 92% yield, whereas the Pfitzner–Moffatt oxidation using as catalyst either orthophosphoric acid or pyridinium trifluoroacetate afforded **3** in only 50% yield. Our initial attempts at reproducing the Me_2SO–acetic anhydride oxidation of **4** were rewarded with the preparation of the trivial benzyl 6α-acetoxypenicillanate. We did manage to reproduce the literature report[8] by using acetic anhydride which had been purified by distillation from either aluminum chloride or calcium carbide.[9] We also found that the Pfitzner–Moffatt oxidation of **4** using dichloroacetic acid[10] gave **3** in 78–83% yield. Our attempts at converting **4** to **3** using *N*-chlorosuccinimide–dimethyl sulfide,[11] Jones reagent,[12] or silver carbonate on Celite[13] all met with failure.



1



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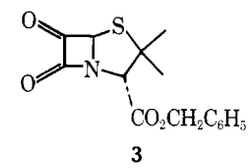

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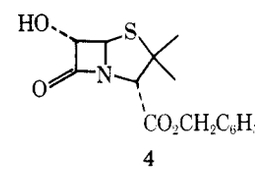

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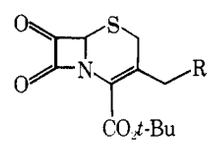
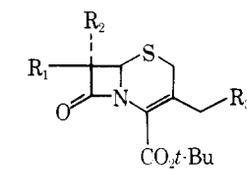
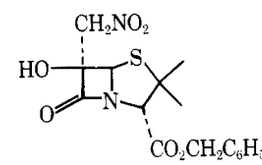


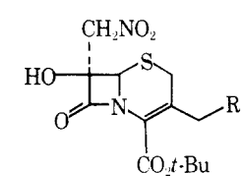
5, R = H
9, R = OAc



6, $R_1 = R_3 = H$, $R_2 = OH$
7, $R_1 = OH$, $R_2 = R_3 = H$
8, $R_1 = NH_2$, $R_2 = R_3 = H$
10, $R_1 = H$, $R_2 = OH$, $R_3 = OAc$
11, $R_1 = OH$, $R_2 = H$, $R_3 = OAc$



12

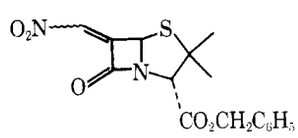


13, R = H
14, R = OAc

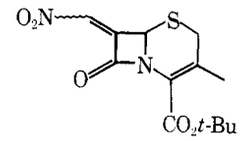
The route to the deacetoxycephalosporin **2** utilized the 7-oxo-3-deacetoxycephalosporanate **5**, which was prepared by the oxidation of the epimer mixture **6**:**7**. The alcohols **6**:**7** (3:1) were prepared in 37% yield by treatment of amine **8**[14] with nitrous acid. We were unable to find satisfactory conditions for the oxidation of **6**:**7** using either Me_2SO–acetic anhydride[8] or Me_2SO–trifluoroacetic anhydride.[15] Oxidation of **6**:**7** with Me_2SO–dicyclohexylcarbodiimide–dichloroacetic acid proceeded smoothly to give **5** in 70% yield.

The 7-oxocephalosporanate **9** was prepared by Me_2SO–dicyclohexylcarbodiimide oxidation of the epimer mixture **10**:**11**. In this instance the Pfitzner–Moffatt oxidation was not as clean as with **6**:**7**.

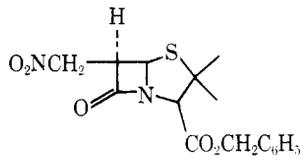
The scheme chosen for the conversion of the keto compounds into the aminomethyl compounds involved the addition of nitromethane, followed by elimination of water and reduction. Reaction of the keto compounds **3**, **5**, and **9** with nitromethane and potassium *tert*-butoxide in THF at 0 °C gave the α-nitromethyl compounds **12** (51%), **13** (39%), and **14** (21%).[16] The assignment of stereochemistry in **12**–**14** is based on the known course of nucleophilic addition in this series.[3-6] Compounds **12** and **13** were converted into nitroolefins **15** (47%) and **16** (55%) by reaction with mesyl chloride–triethylamine in CH_2Cl_2 at −40 °C. Catalytic hydrogenation using tris(triphenylphosphine)rhodium chloride[17] afforded the reduced compounds **17** (64%), **18** (11%), and **19** (46%). Compounds **18** and **19** were also obtained by $NaBH_4$



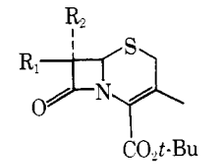
15



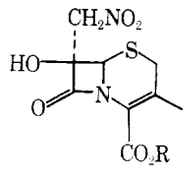
16



17



18, R_1 = H, R_2 = CH_2NO_2
19, R_1 = CH_2NO_2, R_2 = H



20, R = H
21, R = Na

reduction of **16**. The production of a mixture of α and β isomers in the hydrogenation of **16** is similar to a case reported by Sheehan[5] where he obtained a β to α ratio of ~4:1. The assignment of β stereochemistry to the nitromethyl in **17** is consistent with the preferred delivery of hydrogen on the less-hindered α face of the olefin. No detectable quantity of an α isomer was found in the reaction mixture.

All attempts at catalytic reduction of nitro compounds **17** and **19** to form the desired aminomethyl compounds were unfruitful. Our best result was obtained with the reduction of **19** with PtO_2 in ethanol where we obtained in about 60% purity an amine along with five lesser components. All attempts at chromatographic purification or at forming a derivative resulted in extensive decomposition. Attempted reduction of **17** with Raney Ni failed to yield a characterizable product. The difficulty of reducing aliphatic nitro compounds has been discussed by Freifelder.[18]

Compound **13** was deblocked to give acid **20**, which was in turn converted to sodium salt **21**. Compound **21** was inactive at levels below 200 μg/mL against a number of gram-positive and gram-negative bacteria.

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Spectra were obtained with a Varian HA 100 using, except where noted, ca. 5% wt/v solutions in $CDCl_3$ with tetramethylsilane as an internal standard. Combustion analyses were performed by the Syntex Analytical Staff and by A. Berhardt, Muhleim-Ruhr. IR spectra were recorded on a Perkin-Elmer 237.

***tert*-Butyl 7α-Hydroxy- and 7β-Hydroxydeacetoxycephalosporanate (6 and 7).** To a mechanically stirred solution of amine **8** (10.8 g, 40 mmol) in THF (140 mL) and H_2O (30 mL) cooled to 0 °C was added an ice-cold solution of 1 N $HClO_4$ (140 mL). A solution of $NaNO_2$ (6.21 g, 90 mmol) in 40 mL of H_2O was added over 20 min, and the resulting mixture was stirred for an additional hour at 0 °C. The reaction mixture was diluted with 250 mL of CH_2Cl_2 and the organic layer was separated. The aqueous layer was extracted with two 150-mL portions of CH_2Cl_2. The combined organic extract was washed with 100 mL of ice–water, 100 mL of 6% $NaHCO_3$ solution, and 100 mL of saturated NaCl solution. After drying over Na_2SO_4, the organic solution was concentrated to a brown oil (8.4 g) which was chromatographed on 220 g of SiO_2 with 45% Et_2O–hexane to give a mixture of α and β epimers **6** and **7** (ca. 3:1), 4.01 g (37%). A portion of this mixture was further separated by preparative TLC with 45% Et_2O–hexane to give: **6**, mp 60–61 °C (Et_2O–hexane); IR (KBr) 3350, 1772, 1725 cm^{-1}; NMR δ 1.55 (s, 9 H, $(CH_3)_3C$), 2.0 (s, 3 H, CH_3C=), 3.04 (d, 1 H, J = 18 Hz, SCH_AH_B), 3.47 (d, 1 H, J = 18 Hz, SCH_AH_B), 4.65 (d, 1 H, J = 1.5 Hz, C-6 H), 4.75 (d, 1 H, J = 1.5 Hz, C-7 H). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16. Found: C, 53.16; H, 6.26; N, 4.86. **7**, mp 149–150 °C (Et_2O–hexane); IR (KBr) 3400, 1775, 1725 cm^{-1}; NMR δ 1.5 (s, 9 H, $(CH_3)_3C$), 2.1 (s, 3 H, CH_3C=), 3.14 (d, 1 H, J = 18 Hz, SCH_AH_B), 3.46 (d, 1 H, J = 18 Hz, SCH_AH_B), 4.1 (s, 1 H, OH), 4.9 (d, 1 H, J = 4 Hz, C-6 H), 5.25 (d, 1 H, J = 4 Hz, C-7 H). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16. Found: C, 53.29; H, 6.22; N, 4.79.

***tert*-Butyl 7α-Hydroxy- and 7β-Hydroxycephalosporanate (10 and 11).** To a mechanically stirred mixture of 656 mg (2 mmol) of *tert*-butyl 7β-aminocephalosporanate[14] in 10 mL of THF plus 5 mL of water at 0 °C was added 10 mL of 1 N $HClO_4$, followed by addition over 10 min of a solution of 345 mg of $NaNO_2$ in 3 mL of water. The mixture was stirred for 90 min at 0 °C and was throughly extracted with CH_2Cl_2. The combined organic extract after washing with water and saturated NaCl solution was dried over Na_2SO_4. Removal of solvent left a brown oil (579 mg) which was chromatographed on 20 g of SiO_2 with 30% Et_2O–hexane. Three fractions were obtained: Fraction I, 73 mg of *tert*-butyl 7α-hydroxycephalosporanate (**10**), mp 137–138 °C (Et_2O–hexane); IR (KBr) 3400, 1755, 1720 cm^{-1}; NMR δ 1.54 (s, 9 H, $(CH_3)_3C$), 2.05 (s, 3 H, CH_3CO), 3.24 (d, 1 H, J = 18 Hz, SCH_AH_B), 3.58 (d, 1 H, J = 18 Hz, SCH_AH_B), 4.45 (b, 1 H, OH), 4.6–5.0 (m, 4 H, CH_2OAc, C-6 H, C-7H). Anal. Calcd for $C_{14}H_{19}NO_6S$: C, 51.05; H, 5.81; N, 4.25. Found: C, 51.17; H, 5.8; N, 4.29. Fraction II, 37 mg, mixture of **10** and **11**. Fraction III, 36 mg of *tert*-butyl 7β-hydroxycephalosporanate (**11**), mp 148–152 °C (Et_2O–hexane); IR (KBr) 3380, 1750, 1720 cm^{-1}; NMR δ 1.53 (s, 9 H, $(CH_3)_3C$), 2.08 (s, 3 H, CH_3CO), 3.32 (d, 1 H, J = 18 Hz, SCH_AH_B), 3.57 (d, 1 H, J = 18 Hz, SCH_AH_B), 4.8 (d, 1 H, J = 12.5 Hz, CH_AH_BOAc), 4.95 (d, 1 H, J = 4.4 Hz, C-6 H), 5.09 (d, 1 H, J = 12.5 Hz, CH_AH_BOAc), 5.33 (br d, 1 H, J = 4.4 Hz, C-7 H). Anal. Calcd for $C_{14}H_{19}NO_6S$: C, 51.05; H, 5.81; N, 4.25. Found: C, 50.9; H, 6.12; N, 4.23.

General Procedure for Me_2SO–DCC Oxidation. To a solution of 10 mmol of alcohol in 40 mL of Me_2SO–benzene (1:1) was added 30 mmol of dicyclohexylcarbodiimide, and the mixture was stirred for 5 min. Dichloroacetic acid (5 mmol) was added and the mixture was stirred for ca. 10 min. The mixture was diluted with 150 mL of Et_2O and a solution of 25 mmol of oxalic acid in ca. 10 mL of CH_3OH was added with stirring. After the cessation of gas evolution, the solution was filtered from the precipitated dicyclohexylurea. The filtrate was washed with two 30-mL portions of water, 30 mL of 6% $NaHCO_3$, and 30 mL of saturated NaCl solution. The organic phase was dried ($MgSO_4$), filtered, and evaporated to give the ketones as oils.

***tert*-Butyl 7β-Hydroxy-7α-nitromethyldeacetoxycephalosporanate (13).** To a mixture of nitromethane (2.135 g, 35 mmol) and potassium *tert*-butoxide (0.896 g, 8 mmol) in 50 mL of THF at 0 °C under argon was added a solution of ketone **5** (4.58 g, 17 mmol) in 50 mL of THF. The reaction mixture was stirred at 0 °C for 45 min and was diluted with 250 mL of CH_2Cl_2. The mixture was washed with two 50-mL portions of saturated NaCl solution and was dried over $MgSO_4$. Removal of solvent gave a brown oil which was chromatographed on 160 g of SiO_2 with 30% Et_2O–hexane to give **13** as a pale-yellow solid, mp 158–160 °C (CH_2Cl_2–hexane), 2.197 g (39%), IR (CH_2Cl_2) 3660, 3520, 1780, 1720, 1562, 1370 cm^{-1}; NMR δ 1.5 (s, 9 H, $(CH_3)_3C$), 1.6 (s, 1 H, OH), 2.15 (s, 3 H, CH_3C=), 3.16 (d, 1 H, J = 16.5 Hz, SCH_AH_B), 3.38 (d, 1 H, J = 16.5 Hz, SCH_AH_B), 4.72 (d, 1 H, J = 13 Hz, $O_2NCH_AH_B$), 4.9 (d, 1 H, J = 13 Hz, $O_2NCH_AH_B$), 5.1 (s, 1 H, C-6 H). Anal. Calcd for $C_{13}H_{18}N_2O_6S$: C, 47.27; H, 5.45; N, 8.48. Found: C, 47.43; H, 5.64; N, 8.31.

***tert*-Butyl 7β-Hydroxy-7α-nitromethylcephalosporante (14).** A magnetically stirred solution of nitromethane (61 mg, 1 mmol) in 6 mL of THF was cooled to 0 °C under argon. Potassium *tert*-butoxide (14 mg, 0.125 mmol) was added. After 10 min a solution of 116 mg of crude **9** (from Me_2SO–DCC oxidation of 0.3 mmol of **10**:11) in 3 mL of THF was added, and the mixture was stirred at 0 °C for 90 min. The mixture was diluted with 40 mL of CH_2Cl_2 and was washed with 10 mL of water and 10 mL of saturated NaCl solution. After drying over $MgSO_4$, the solution was evaporated to give 79 mg of a brown oil. Purification by preparative TLC (80% Et_2O–hexane) gave **14** as white crystals, mp 190–191 °C dec (CH_2Cl_2), 25 mg (21% based on **10**:11); IR (CH_2Cl_2) 3500, 1780, 1735, 1725, 1565, 1365 cm^{-1}; NMR (CD_3COCD_3) δ 1.49 (s, 9 H, $(CH_3)_3C$), 3.43 (d, 1 H, J = 18.5 Hz, SCH_AH_B), 3.72 (d, 1 H, J = 18.5 Hz, SCH_AH_B), 4.68 (d, 1 H, J = 12.5 Hz, CH_AH_BOAc), 4.93 (d, 1 H, J = 13.5 Hz, $O_2NCH_AH_B$), 5.03 (d, 1 H, J = 12.5 Hz, CH_AH_BOAc), 5.21 (d, 1 H, J = 13.5 Hz, $O_2NCH_AH_B$), 5.27 (s, 1 H, C-6 H). Anal. Calcd for $C_{15}H_{20}N_2O_8S$: C, 46.38; H, 5.19; N, 7.22. Found: C, 46.24; H, 5.06; N, 6.97.

Benzyl 6β-Hydroxy-6α-nitromethylpenicillanate (12). Using the same procedure as was used for the preparation of **13**, 20 mmol of nitromethane, 3 mmol of potassium *tert*-butoxide, and 8.5 mmol of **3** gave 3.25 g of an oily crude product. This material was crystallized

from Et_2O–hexane to give 0.737 g of **12**, mp 134–136 °C dec. Chromatography of the mother liquor on 30 g of SiO_2 with 30% Et_2O–hexane gave an additional 0.843 g of crystalline **12** (total = 1.58 g, 51%). An analytical sample crystallized from Et_2O–hexane had mp 137–138 °C: $[\alpha]_D$ $CHCl_3$ +45.7°; IR (CH_2Cl_2) 3650, 1785, 1745, 1562, 1375 cm^{-1}; NMR δ 1.45 and 1.6 (two s, 6 H, $(CH_3)_2C$), 3.5 (br s, 1 H, OH), 4.55 (s, 1 H, $CHCO_2$), 4.74 (d, 1 H, J = 13 Hz, $O_2NCH_AH_B$), 4.96 (d, 1 H, J = 13 Hz, $O_2NCH_AH_B$), 5.2 (s, 2 H, CO_2CH_2), 5.85 (s, 1 H, C-5 H), 7.4 (s, 5 H, C_6H_5). Anal. Calcd for $C_{16}H_{18}N_2O_6S$: C, 52.45; H, 4.95; N, 7.65. Found: C, 52.45; H, 5.14; N, 7.62.

Benzyl 6-Nitromethylenepenicillanate (15) and *tert*-Butyl 7-Nitromethylenedeacetoxycephalosporanate (16). To a solution of 2 mmol of nitromethylcarbinol (**12** or **13**) in 40 mL of CH_2Cl_2 at −40 °C (argon) was added triethylamine (690 μL, 5 mmol), followed by dropwise addition of mesyl chloride (230 μL, 3 mmol) over 3 min. This mixture was stirred at −40 °C for 20 min. The mixture was diluted with 100 mL of CH_2Cl_2 and was washed with 40 mL of ice-cold 10% HCl solution, 40 mL of water, and 40 mL of saturated NaCl solution. After drying ($MgSO_4$), the solution was evaporated to give an oily crude product.

Compound **15** was purified by chromatography on 20 g of SiO_2 with 30% Et_2O–hexane and was obtained as a yellow oil (0.327 g, 47%): IR (CH_2Cl_2) 1776, 1745, 1530, 1375, 1350 cm^{-1}; NMR δ 1.4 and 1.55 (two s, 6 H, $(CH_3)_2C$), 4.65 (s, 1 H, $CHCO_2$), 5.2 (s, 2 H, CO_2CH_2), 6.15 (s, 1 H, C-5 H), 7.25 (s, 1 H, $=CHNO_2$), 7.35 (s, 5 H, C_6H_5). Anal. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.64; N, 8.04. Found: C, 55.43; H, 4.97; N, 7.67.

Compound **16** was purified by preparative TLC (80% Et_2O–hexane) and it was obtained as a light-yellow solid, mp 152–154 °C dec (Et_2O–hexane), 0.335 g (55%): IR(CH_2Cl_2) 1776, 1720, 1535, 1370, 1345 cm^{-1}; NMR δ 1.5 (s, 9 H, $(CH_3)_3C$), 2.15 (s, 3 H, $CH_3C=$), 3.21 (d, 1 H, J = 18 Hz, SCH_AH_B), 3.56 (d, 1 H, J = 18 Hz, SCH_AH_B), 5.58 (br s, 1 H, C-7 H), 7.32 and 7.34 (two s, 1 H, $=CHNO_2$). Anal. Calcd for $C_{13}H_{16}N_2O_5S$: C, 49.99; H, 5.16; N, 8.97. Found: C, 49.93; H, 5.04; N, 8.96.

Benzyl 6β-Nitromethylpenicillanate (17). Wilkinson's catalyst (0.116 g) was prereduced with H_2 at 45 psi in 20 mL of EtOH–benzene (1:1, degassed with argon prior to loading the catalyst). The nitroolefin **15** (0.116 g, 0.33 mmol) in 20 mL of degassed EtOH–benzene (1:1) was added, and the mixture was shaken with H_2 at 55 psi for 16 h. The mixture was concentrated to give a reddish-brown oil which was purified by preparative TLC to give 74 mg (64%) of **17** as an oil: IR (CH_2Cl_2) 1776, 1745, 1535, 1375 cm^{-1}; NMR δ 1.4 and 1.56 (two s, 6 H, $(CH_3)_2C$), 4.22 (m, 1 H, $J_{5,6}$ = 4 Hz, $J_{A,6}$ = 4.5 Hz, $J_{B,6}$ = 11 Hz, C-6 H), 4.42 (s, 1 H, $CHCO_2$), 4.63 (d of d, 1 H, $J_{6,A}$ = 4.5 Hz, $J_{A,B}$ = 15 Hz, $O_2NCH_AH_B$), 4.95 (d of d, 1 H, $J_{6,B}$ = 11 Hz, $J_{A,B}$ = 15 Hz, $O_2NCH_AH_B$), 5.15 (s, 2 H, CH_2O), 5.6 (d, 1 H, $J_{6,5}$ = 4 Hz, C-5 H), 7.35 (s, 5 H, C_6H_5); m/e 350 (M^+). Anal. Calcd for $C_{16}H_{18}N_2O_5S$: C, 54.84; H, 5.18; N, 8.0. Found: C, 55.17; H, 4.98; N, 7.69.

***tert*-Butyl 7β-Nitromethyldeacetoxycephalosporanate (19) and *tert*-Butyl 7α-Nitromethyldeacetoxycephalosporanate (18).** Hydrogenation of **16** (0.24 g, 0.77 mmol) under the same conditions used to prepare **17** afforded 0.111 g of **19** (46%) as an oil after preparative TLC (80% Et_2O–hexane): IR (CH_2Cl_2) 1776, 1720, 1560, 1360 cm^{-1}; NMR δ 1.5 (s, 9 H, $(CH_3)_3C$), 2.1 (s, 3 H, $CH_3C=$), 3.14 (d, 1 H, J = 18 Hz, SCH_AH_B), 3.47 (d, 1 H, J = 18 Hz, SCH_AH_B), 4.2–4.47 (m, 1 H, C-7 H), 4.65 (d of d, 1 H, $J_{7,A}$ = 4.5 Hz, $J_{A,B}$ = 15.5 Hz, $O_2NCH_AH_B$), 4.92 (d of d, 1 H, $J_{7,B}$ = 11 Hz, $J_{A,B}$ = 15.5 Hz, $O_2NCH_AH_B$), 4.99 (d, 1 H, $J_{7,6}$ = 4.5 Hz, C-6 H); m/e 314 (M^+). Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91. Found: C, 50.02; H, 6.09; N, 8.58. Compound **19** was also obtained in 31% yield through $NaBH_4$ reduction of **16** in EtOH.

The α-nitromethyl compound **18** was obtained in impure form as an oil in 11% yield by the hydrogenation of **16** and in ca. 14% yield through the $NaBH_4$ reduction of **16**: IR (CH_2Cl_2) 1775, 1715, 1560, 1360 cm^{-1}; m/e 314 (M^-).

7β-Hydroxy-7α-nitromethyldeacetoxycephalosporanic Acid (20). Alcohol **13** was dissolved in 5 mL of 100% formic acid and the solution was left at room temperature for 3 h. The solution was concentrated in vacuo to give a film. The residue was mixed with 10 mL of ice-cold 6% $NaHCO_3$ and the resulting mixture was throughly extracted with EtOAc. The aqueous phase at 0 °C was acidified with HCl and was extracted with EtOAc. The EtOAc extract was dried (Na_2SO_4) and concentrated to a film. Recrystallization from Et_2O–hexane afforded 11 mg of **20** as a tan powder which decomposed at ca. 160 °C: IR (CH_2Cl_2) 3500, 1780, 1725, 1555, 1360 cm^{-1}; NMR (Me_2SO-d_6) δ 1.98 (s, 3 H, $CH_3C=$), 3.27 (d, 1 H, J = 17 Hz, SCH_AH_B), 3.56 (d, 1 H, J = 17 Hz, SCH_AH_B), 4.82 (d, 1 H, J = 13.5 Hz, $O_2NCH_AH_B$), 5.12 (s, 1 H, C-6 H), 5.19 (d, 1 H, J = 13.5 Hz, $O_2NCH_AH_B$), 7.5 (s, 1 H, OH). Anal. Calcd for $C_9H_{10}N_2O_6S$: C, 39.41; H, 3.68; N, 10.22. Found: C, 39.24; H, 3.87; N, 10.19.

The sodium salt **21** was prepared in 91% yield by mixing **20** in EtOAc with 1.2 equiv of sodium 2-ethylhexanoate in EtOAc, followed by addition of Et_2O: IR (KBr) 1760 (br) cm^{-1}.

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Reference and Notes

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Synthesis of Quinolizinones by the Condensation of Ylidenemalonodinitriles with Quinoline 1-Oxide

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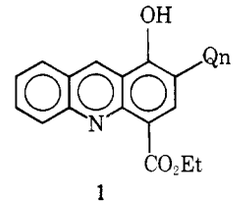
Several years ago we reported that quinoline 1-oxide reacts with diethyl glutaconate in the presence of acetic anhydride to yield the substituted acridine **1**, the product of a 2,3-annelation on the quinoline nucleus.[1] The inherently more likely



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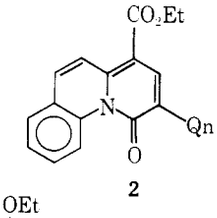

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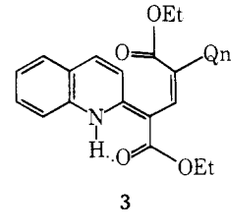

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