The Synthesis of Oxygen Analogs of Cepham. A New Bicyclic System.

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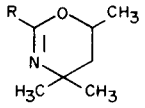
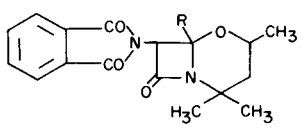
The synthesis of a new bicyclic system has been reported. Three substituted 5,6-dihydro-1,3-oxazines have been condensed to a fused β-lactam ring system by use of phthaloylglycyl chloride. The resulting phthalimido compounds were dephthaloylated to the corresponding oxygen analogs of cepham (2).

A series of oxygen analogs of the cepham ring system have been prepared by condensation of 2-aryl-5,6-dihydro-1,3-oxazines and phthaloylglycyl chloride in the presence of triethylamine according to the general procedure developed earlier in this laboratory for the penicillin series (3). The oxazines (I-III) were prepared following essentially the procedure described by E. J. Tillmanns and J. J. Ritter (4).



I II III
R= phenyl benzyl *m*-nitrophenyl

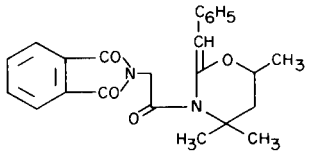
The 4,4,6-trimethyl-2-aryl-5,6-dihydro-1,3-α-phthalimido-2-oxazineacetic acid β-lactams (IV-VI) were obtained in the best yields (approximately 60%) by carrying out the reactions with equimolar amounts of the oxazine and phthaloylglycyl chloride (5) in refluxing benzene while triethylamine was added dropwise through a high dilution cycle (3,6) over a period of 3-5 hours.



IV V VI
R= phenyl benzyl *m*-nitrophenyl

Compounds IV-VI were identified by infrared and nmr spectra as well as by elemental analyses. The infrared spectra in methylene chloride exhibited a strong β-lactam carbonyl band at 1760 cm^{-1}. The nmr spectra in deuteriochloroform showed a sharp one proton singlet at τ 4.80 which was assigned to the β-lactam ring proton.

It is noteworthy that in the reaction of II with phthaloylglycyl chloride two different products were isolated: the phthalimido-β-lactam V along with the product VII. Both the infrared and nmr spectra of VII showed clearly the absence of the fused β-lactam ring.

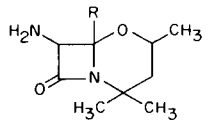


VII

In all condensation experiments leading to compounds IV-VII some phthalimidoacetic anhydride was isolated presumably due to traces of moisture.

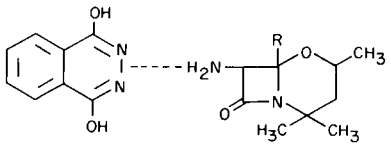
Dephthaloylation of the compounds IV-VI was studied in different reaction media under various conditions and using a variety of agents, namely 95% hydrazine, hydrazine hydrate, hydrazine acetate and phenylhydrazine. The best results were obtained by use of 95% hydrazine in methylene chloride with stirring for 24 hours at room temperature. It should be pointed out that the attempted dephthaloylation in refluxing absolute ethanol led invariably to the cleavage of the β-lactam system.

However, in addition to the desired amino β-lactams (VIII-X) which were obtained in an average yield of 40-45%, the complex salts (XI-XIII) were isolated in about the same yield and identified by analytical and spectral data. The attempts to convert these compounds into the



VIII IX X
R= phenyl benzyl *m*-nitrophenyl

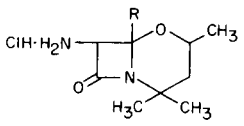
corresponding free amines (VIII-X) involved the treatment with a diluted aqueous sodium bicarbonate solution as well as dilute hydrochloric and acetic acids, but resulted in the substantial cleavage of the fused β-lactam structure.



XI XII XIII
R= phenyl benzyl *m*-nitrophenyl

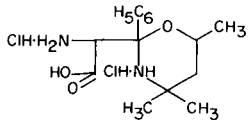
The infrared spectra of the free amino β-lactams in methylene chloride exhibited very strong β-lactam type carbonyl maxima unchanged at 1760 cm^{-1}. The nmr spectra in deuteriochloroform showed a sharp one proton singlet around τ 5.80 which was assigned to the β-lactam ring proton. The deshielding of the nmr maxima in the corresponding phthalimido derivatives IV-VI is attributed to the presence of the electron-withdrawing phthaloyl group.

The free amino β-lactams VIII-X were converted to the corresponding hydrochlorides by introducing dry hydrogen chloride into their ethereal solutions. The hydrochlorides XV and XVI crystallized as monohydrates.



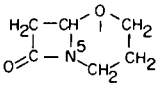
XIV XV XVI
R= phenyl benzyl *m*-nitrophenyl

An attempt to purify the crude XIV from ethanol resulted in cleavage of the β-lactam ring, whereupon the dihydrochloride XVII was identified.



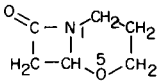
XVII

It is suggested that the compounds containing the bicyclic system XVIII be named in accord to their relationship to cephams *i.e.* as substituted *O*-cephams.



XVIII

The *O*-cepham system can be also named 8-oxo-5-oxa-1-azabicyclo[4.2.0]octane (XIX).



XIX

These substituted *O*-cephams contain a fused 1,3-oxazine ring system. Certain compounds having a 1,3-oxazine ring fused to aromatic or heterocyclic nuclei have been reported (7,8,9) to possess considerable antibacterial, antifungal or cancerostatic activity.

EXPERIMENTAL

All melting points were taken on a Kofler hot stage microscope. Infrared spectra were recorded with a Perkin Elmer 237 recording spectrophotometer. The absorptions are given in frequency units and assignments are made. Nmr spectra were run on a Varian Associates A-60 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Purity of the compounds was also verified by t.l.c.; plates were coated with silica gel G according to Stahl and developed in different solvent systems. Microanalyses were performed by Dr. S. M. Nagy and his associate.

4,4,6-Trimethyl-2-phenyl-5,6-dihydro-1,3-oxazine (I).

This compound was prepared in a 48% yield as previously described (4) by the reaction of 2-methyl-2,4-pentanediol with benzonitrile in the presence of 92% sulfuric acid, m.p. 32.5-33° (reported (4) m.p. 34-35°); infrared spectrum (methylene chloride), 1100, 1150 (N-C-O,C-O-C), 1375, 1390 (*gem*-dimethyls), and 1650 (C=N) cm^{-1}.

The picrate of I was prepared by stirring an ethereal solution of the oxazine I and picric acid (in equimolar amounts) for 2 hours at room temperature; the yellow needles were recrystallized from ethanol, m.p. 170-171°.

Anal. Calcd. for $C_{19}H_{20}N_4O_8$: C, 52.78; H, 4.66; N, 12.96. Found: C, 52.85; H, 4.91; N, 12.95.

4,4,6-Trimethyl-2-phenyl-5,6-dihydro-1,3-α-phthalimido-2-oxazineacetic Acid β-Lactam (IV).

(Suggested name: 2,4,4-Trimethyl-6-phenyl-7-phthalimido-*O*-cepham.)

To a solution of oxazine I (4.7 g., 23 mmoles) and phthaloylglycyl chloride (5.15 g., 23 mmoles) in 200 ml. of dry benzene there was added dropwise through a high dilution cycle (3,6) triethylamine (3.18 ml., 23 mmoles, freshly distilled over potassium hydroxide). The addition of triethylamine was carried out with stirring and under reflux over a period of 4 hours. The precipitate was collected and washed with 50 ml. of benzene. The benzene mother liquor and washings were evaporated under reduced pressure to yield a crystalline residue (8.3 g.) which was recrystallized from benzene-petroleum ether (b.p. 50-55°); needles (5.0 g., 57%), m.p. 220-225°; infrared spectrum (methylene chloride), 1075, 1150, (C-O-C,N-C-O), 1375, 1390 (*gem* dimethyls), 1725, 1790 (C=O, phthaloyl), and 1765 (C=O, β-lactam) cm^{-1}; NMR, τ 8.70 (m, 3H), 8.50 (m,2H), 8.45 (s, 3H), 8.25 (s, 3H), 5.60 (m, 1H), 4.80 (s, 1H), 2.70 (m, 5H), and 2.35 (s, 4H).

Anal. Calcd. for $C_{23}H_{22}N_2O_4$: C, 70.74; H, 5.69; N, 7.17. Found: C, 70.37; N, 5.69; N, 7.14.

The crystalline precipitate (phthalimidoacetic anhydride) after washing with 50 ml. of benzene (4.1 g.) was extracted with 100 ml. of water, the residue dried at 80° (0.9 g., 19%) and recrystallized from nitrobenzene-ethanol, m.p. 241-242° (reported (10) m.p. 242°); infrared spectrum (potassium bromide), 1125, 1200, 1400, 1425, 1650, 1775 and 1835 cm^{-1}.

Anal. Calcd. for $C_{20}H_{12}N_2O_7$: C, 61.22; H, 3.08; N, 7.14. Found: C, 61.14; H, 3.08; N, 7.31.

The water extract after separation of phthalimidoacetic anhydride was evaporated under reduced pressure to give a theoretical yield of triethylamine hydrochloride (3.2 g.), m.p. 245-250° (with sublimation). Mixed melting point with an authentic sample was undepressed.

4,4,6-Trimethyl-2-phenyl-5,6-dihydro-1,3-α-amino-2-oxazineacetic Acid β-Lactam (VIII).

(Suggested name: 2,4,4-Trimethyl-6-phenyl-7-amino-*O*-cepham.)

Phthalimido-β-lactam IV (2.5 g., 6.3 mmoles) was stirred with 95% hydrazine (0.43 g., 12.6 mmoles) in 150 ml. of methylene chloride for 24 hours at room temperature. The precipitated phthalylhydrazide was collected (1.2 g., 49%), m.p. 300-350°. dec. The methylene chloride mother liquor was evaporated under reduced pressure and the residue (1.7 g.) was extracted with 150 ml. of dry ether. Ether was removed under reduced pressure to give an oily residue (0.67 g., 41%) which was recrystallized from benzene, m.p. 94°; infrared spectrum (methylene chloride), 1075, 1100 (N-C-O,C-O-C), 1375, 1390 (*gem* dimethyls), 1630 (free amino), 1760 (C=O, β-lactam), 3300 and 3400 (free amino) cm^{-1}; NMR, τ 8.80-8.25 (complex, 8H), 8.55 (s, 3H), 8.35(s, 3H), 5.85 (s, 1H), and 2.70 (m, 5H).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: N, 10.76. Found: N, 10.81.

The crystalline residue after extraction of VIII with ether (1.1 g., 40%) was identified as the complex salt XI, m.p. 275-280° dec.; infrared spectrum (potassium bromide), 1050, 1150 (N-C-O, C-O-C), 1375, 1390 (*gem* dimethyls), 1650 (C=N), 1760 (C=O, β-lactam), and 3100-3300 cm^{-1}.

Anal. Calcd. for $C_{23}H_{26}N_4O_4$: N, 13.26. Found: N, 13.52.

4,4,6-Trimethyl-2-phenyl-5,6-dihydro-1,3-α-amino-2-oxazineacetic Acid β-Lactam Hydrochloride (XIV).

(Suggested name: 2,4,4-Trimethyl-6-phenyl-7-amino-*O*-cepham Hydrochloride.)

The free amino β-lactam VIII (0.5 g., 2 mmoles) was dissolved in 50 ml. of dry ether and dry hydrogen chloride was introduced for 5 minutes. The sticky precipitate was thoroughly washed with dry ether to yield hygroscopic crystals (0.41 g., 72%); after drying over phosphorus pentoxide *in vacuo* the m.p. was 159-160° dec. The compound is very soluble in water and gives a positive chloride-ion reaction with silver nitrate; infrared spectrum (potassium bromide), 820 (NH_3^+ rocking v.), 1050, 1120, (N-C-O, C-O-C), 1310 (NH_3^+ symmetric mode), 1370, 1390 (*gem* dimethyls), 1625 (NH_3^+ asymmetric deformation), 1760 (C=O, β-lactam) and 3250, 3350 (NH_3^+ stretching v.) cm^{-1}.

An attempt to recrystallize the crude hydrochloride XIV from absolute ethanol resulted in substantial cleavage of the β-lactam ring to yield XVII, m.p. 140-142° dec.; infrared spectrum (potassium bromide), 1150 (N-C-O,C-O-C), 1370, 1395 (*gem*-dimethyls), 1630 (NH_3^+), 1740 (C=O), and 2700-3200 cm^{-1}.

Anal. Calcd. for $C_{15}H_{24}Cl_2N_2O_3$: N, 7.97; Cl, 20.18. Found: N, 7.90; Cl, 20.13.

4,4,6-Trimethyl-2-benzyl-5,6-dihydro-1,3-oxazine (II).

This compound was prepared in a 30% yield as previously described (4) by the reaction of 2-methyl-2,4-pentanediol with phenylacetonitrile in the presence of 92% sulfuric acid, b.p. 95-100° at 3 mm (reported (4) b.p. 116-119° at 5 mm); infrared spectrum (methylene choride), 1100, 1150 (N-C-O,C-O-C), 1375, 1390 (*gem*-dimethyls) and 1650 (C=N).

The picrate of II was prepared by stirring an ethereal solution of the oxazine II and picric acid (in equimolar amounts) for 2 hours at room temperature. The yellow needles were recrystallized from absolute ethanol, m.p. 169°.

Anal. Calcd. for $C_{20}H_{22}N_4O_8$: N, 12.55. Found: N, 12.16.

4,4,6-Trimethyl-2-benzyl-5,6-dihydro-1,3-α-phthalimido-2-oxazineacetic Acid β-Lactam (V).

(Suggested name: 2,2,4-Trimethyl-6-benzyl-7-phthalimido-*O*-cepham.)

To a solution of oxazine II (7.0 g., 32 mmoles) and phthaloylglycylchloride (7.2 g., 32 mmoles) in 320 ml. of dry benzene there was added dropwise through a high dilution cycle (3,6) triethylamine (4.42 ml., 32 mmoles, freshly distilled over potassium hydroxide). The addition of triethylamine was carried out with stirring and under reflux over a period of 4 hours. The precipitate was collected and washed with 50 ml. of benzene (5.4 g.) wherefrom triethylamine hydrochloride (4.4 g., 100%) and phthalimidoacetic anhydride (1.0 g., 15%) were isolated as described for IV and identified by m.p. and mixed m.p. with authentic specimens.

The benzene mother liquor and washings were evaporated under reduced pressure to give a yellow oil (12.0 g.) which was triturated with 70 ml. of dry ether and stored in a refrigerator. The crystalline product was collected 3.2 g., 25%) and recrystallized from 20 ml. of benzene (activated charcoal); after drying over phosphorus pentoxide *in vacuo* the m.p. was 147-148°; infrared spectrum (methylene chloride), 1075, 1150 (N-C-O,C-O-C), 1375, 1390 (*gem*-dimethyls), 1725, 1785 (C=O, phthaloyl) and 1765 (C=O, β-lactam) cm^{-1}; NMR, τ 8.95-8.45 (complex, 6H), 8.55 (s, 3H), 8.32(s, 3H), 6.65(m, 2H), 4.80(s, 1H), 2.90(m, 5H), and 2.35 (s, 4H).

Anal. Calcd. for $C_{24}H_{24}N_2O_4$: C, 71.26; H, 5.99; N, 6.93. Found: C, 70.91; H, 5.91; N, 6.84.

N-Phthalimidoacetyl-2-benzal-4,4,6-trimethyl-tetrahydro-1,3-oxazine (VII).

The ethereal mother liquor, after separating the compound V in the previous experiment, was evaporated under reduced pressure and the oily residue (8.8 g.) triturated with absolute ethanol; after a short period at 0-5° the product was collected (13.2 g., 25%) and recrystallized from 90 ml. of methanol (activated charcoal), m.p. 248-249°; infrared spectrum (methylene chloride), 1075, 1120 (N-C-O,C-O-C), 1375, 1390 (*gem*-dimethyls), 1610 (C=C), and 1725, 1785 (C=O, phthaloyl) cm^{-1}; NMR, τ 8.95-8.65 (complex, 10H), 8.30(m, 2H), 5.85(s, 3H), 2.85(s, 5H), and 2.55(m, 4H).

Anal. Calcd. for $C_{24}H_{24}N_2O_4$: C, 71.26; H, 5.99; N, 6.93. Found: C, 71.45; H, 5.78; N, 7.03.

4,4,6-Trimethyl-2-benzyl-5,6-dihydro-1,3-α-amino-2-oxazineacetic Acid β-Lactam (IX).

(Suggested name: 2,4,4-Trimethyl-6-benzyl-7-amino-*O*-cepham.).

Phthalimido-β-lactam V (1.62 g., 4 mmoles) was stirred with 95% hydrazine (0.27 g., 8 mmoles) in 200 ml. of methylene chloride for 24 hours at room temperature. The precipitated phthalylhydrazide was collected (0.4 g., 60%), m.p. 300-350° dec. The methylene chloride mother liquor was evaporated under reduced pressure and the residue (1.4 g.) extracted with 200 ml. of dry ether. Removal of ether under reduced pressure gave a clear oil (0.46 g., 42%) which did not crystallize on standing in a refrigerator; infrared spectrum (methylene chloride), 1075, 1100 (N-C-O,C-O-C), 1375, 1390 (*gem*-dimethyls), 1630 (free amino), 1760 (C=O, β-lactam), and 3300, 3370 (amino) cm^{-1}; NMR τ 8.90-8.60 (complex, 11H), 8.45(m, 3H), 6.70(m, 2H), 5.90(s, 1H), and 2.70(m, 5H).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$: N, 10.21. Found: N, 9.98.

The crystalline residue remaining after extraction of IX with ether (0.9 g., 51%) was identified as the complex salt XII, m.p. 280-285° dec.; infrared spectrum (potassium bromide), 1080, 1230 (N-C-O,C-O-C), 1375, 1390 (*gem*-dimethyls), 1650 (C=N). 1760 (C=O, β-lactam), and 3100-3300 cm^{-1}.

Anal. Calcd. for $C_{24}H_{28}N_4O_4$: N, 12.84. Found: N, 13.12.

4,4,6-Trimethyl-2-benzyl-5,6-dihydro-1,3-α-amino-2-oxazineacetic Acid β-Lactam Hydrochloride (XV).

Suggested name: 2,4,4-Trimethyl-6-benzyl-7-amino-*O*-cepham Hydrochloride.)

The free amino-β-lactam IX (0.8 g., 3 mmoles) was dissolved in 100 ml. of dry ether and dry hydrogen chloride was introduced for 5 minutes. The sticky precipitate was thoroughly washed with dry ether to yield hygroscopic crystals (0.3 g., 35%); after drying over phosphorus pentoxide *in vacuo* the m.p. was 125° dec. Compound XV is very soluble in water and gives a positive chloride-ion reaction with silver nitrate; infrared spectrum (potassium bromide), 820 (NH_3^+), 1100 (N-C-O,C-O-C), 1310 (NH_3^+), 1370, 1390 (*gem*-dimethyls), 1635 (NH_3^+), 1760 (C=O, β-lactam), 3250, 3370 (NH_3^+), and 3500 (hydroxyl) cm^{-1}.

Anal. Calcd. for $C_{16}H_{23}ClN_2O_2 \cdot H_2O$: C, 58.42; H, 7.67; N, 8.53. Found: C, 58.19; H, 7.54; N, 9.02.

4,4,6-Trimethyl-2-(*m*-nitrophenyl-5,6-dihydro-1,3-Oxazine (III).

m-Nitrobenzonitrile (44.4 g., 0.3 mole) was added portion wise over 30 minutes to 150 g. of 92% sulfuric acid with stirring at 0°. To the grey solution was added dropwise over 1 hour 2-methyl-2,4-pentanediol (35.4 g., 0.3 mole) with stirring at 0-5°. The red-brown solution was stirred for an additional 30 minutes at 0-5° and poured onto 0.5 kg. of cracked ice. The yellow hydrolyzate was half neutralized with 100 ml. of 40% aqueous sodium hydroxide, cooled to room temperature and extracted with five 100-ml. portions of chloroform (chloroform extracts deep red colored). The upper acidic layer was then made alkaline with an additional 100 ml. of 40% aqueous hydroxide, the yellow solution cooled to room temperature and extracted with three 200-ml. portions of ether. The ethereal extracts were dried over potassium carbonate and evaporated to give yellowish crystals (27.0 g., 37%). The crude oxazine was recrystallized from benzene-petroleum ether (20.5 g., 28%), m.p. 85°. Infrared spectrum (methylene chloride), 1075, 1125 (N-C-O,C-O-C), 1360 (nitro, symm. v.), 1375, 1390 (*gem*-dimethyls), 1530 (nitro, antisymm. v.), and 1650 (C=N) cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.51; N, 11.28. Found: C, 63.10; H, 6.54; N, 11.52.

The picrate of III was prepared by stirring an ethereal solution of the oxazine III and picric acid (in equimolar amounts) for 2 hours at room temperature. The yellow needles were recrystallized from methanol, m.p. 210°.

Anal. Calcd. for $C_{19}H_{19}N_5O_{10}$: N, 14.67. Found: N, 14.71.

4,4,6-Trimethyl-2-(*m*-nitrophenyl)-5,6-dihydro-1,3-α-phthalimido-2-oxazineacetic Acid β-Lactam (VI).

(Suggested name: 2,4,4-Trimethyl-6-(*m*-nitrophenyl)-7-phthalimido-*O*-cepham.)

To a solution of oxazine III (6.0 g., 24 mmoles) and phthaloylglycyl chloride (5.4 g., 24 mmoles) in 150 ml. of dry benzene there was added dropwise through a high dilution cycle (3,6) triethylamine (3.4 ml., 24 mmoles, freshly distilled from potassium hydroxide). The addition of triethylamine was carried out with stirring and under reflux over a period of 3 hours. Stirring was continued overnight at room temperature. The crystalline precipitate (3.9 g.) was worked up as described for IV to give a theoretical yield of triethylamine hydrochloride (3.3 g.) as well as some phthalimidoacetic anhydride (0.6 g., 7%).

The benzene mother liquor after separation of triethylamine hydrochloride and phthalimidoacetic anhydride was evaporated under reduced pressure to give yellowish crystals (9.8 g.), m.p. 180-182°; after recrystallization from ethyl acetate crystals (6.8 g., 65%) melted at 185°. Infrared spectrum (methylene chloride), 1075, 1150 (N-C-O,C-O-C), 1360, 1530 (nitro), 1375, 1385 (*gem*-dimethyls), 1725, 1790 (C=O, phthaloyl), and 1760 (C=O, β-lactam) cm^{-1}.

Anal. Calcd. for $C_{23}H_{21}N_3O_6$: C, 63.43; H, 4.87; N, 9.65. Found: C, 63.33; H, 4.83; N, 9.51.

4,4,6-Trimethyl-2-(*m*-nitrophenyl)-5,6-dihydro-1,3-α-amino-2-oxazineacetic Acid β-Lactam (X).

(Suggested name: 2,4,4-Trimethyl-6-(*m*-nitrophenyl)-7-amino-*O*-cepham.)

To a solution of phthalimido-β-lactam VI (4.0 g., 9.3 mmoles) in 150 ml. of methylene chloride was added 95% hydrazine (0.62 g., 18.6 mmoles). The reaction mixture was stirred for 24 hours at room temperature. Phthalylhydrazide (0.9 g., 56%) was collected, m.p. 300-350° dec. The methylene chloride mother liquor was evaporated under reduced pressure and the residue (3.7 g.) extracted with 100 ml. of dry ether. Ether was removed under pressure to give crystals (1.35 g., 44%); after recrystallization from benzene-petroleum ether (b.p. 40-55°) the m.p. was 133-134°; infrared spectrum (methyl chloride), 1075, 1125 (N-C-O, C-O-C), 1360, 1530 (nitro), 1375, 1385 (*gem*-dimethyls), 1625 (amino), 1760 (C=O, β-lactam), and 3300, 3400 (amino) cm^{-1}; NMR, τ 8.75-8.45 (complex, 8H), 8.55 (s, 3H), 8.35 (s, 3H), 5.75 (s, 1H), and 2.75-1.85 (complex, 4H).

Anal. Calcd. for $C_{15}H_{19}N_3O_4$: C, 59.00; H, 6.28; N, 13.76. Found: C, 59.28; H, 6.33; N, 13.66.

The crystalline residue after extraction of X with ether (2.1 g., 45%) was identified as complex salt XIII, m.p. 260° dec.; infrared spectrum (potassium bromide), 1100 (N-C-O,C-O-C), 1360, 1530 (nitro), 1375, 1385 (*gem*-dimethyls), 1650 (C=N), 1760 (C=O, β-lactam), and 3100-3300 cm^{-1}.

Anal. Calcd. for $C_{23}H_{25}N_5O_6$: N, 14.98. Found: N, 15.24.

4,4,6-Trimethyl-2-(*m*-nitrophenyl)-5,6-dihydro-1,3-α-amino-2-oxazinecacetic Acid β-Lactam Hydrochloride (XVI).

(Suggested name: 2,4,4-Trimethyl-6-(*m*-nitrophenyl)-7-amino-*O*-cepham Hydrochloride.)

The free amino β-lactam X (0.5 g., 1.6 mmoles) was dissolved in 70 ml. of dry ether and dry hydrogen chloride was introduced for 5 minutes. The sticky precipitate was washed thoroughly with dry ether to yield hygroscopic crystals (0.5 g., 83%); after drying over phosphorus pentoxide *in vacuo* the m.p. was 115-117° dec. The product is very soluble in water and gives a positive chloride-ion test with silver nitrate. Infrared spectrum (potassium bromide), 820 (NH_3^+), 1050, (N-C-O,C-O-C), 1360, 1530 (nitro), 1375, 1385 (*gem*-dimethyls), 1625 (NH_3^+), 1760 (C=O, β-lactam), 3250, 3350 (NH_3^+), and 3500 (hydroxyl) cm^{-1}.

Anal. Calcd. for $C_{15}H_{20}ClN_3O_4 \cdot H_2O$: C, 50.06; H, 6.17; N, 11.68. Found: C, 50.08; H, 5.98; N, 11.32.

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