Notes

Novel Cephalosporins. Modification of the C-4 Carboxyl Group

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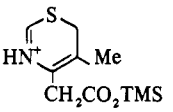
In spite of the massive effort devoted to modifying cephalosporins in a manner similar to that employed in penicillin chemistry,[1] modification of the C-4 carboxyl group has remained largely unexplored. This was perhaps influenced by the discouraging results of carboxyl group modification in penicillin chemistry[2] and also by the disappointing antibiotic activity of an early series of cephalosporin amides and esters.[3] A free carboxyl group appears to be required for activity in the β-lactam antibiotics. However, lactones of desacetyl cephalosporins had activity *vs.* a strain of *Staphylococcus aureus* equal to that of the parent cephalosporins from which the lactones were derived.[4] Since these lactones proved resistant to chemical hydrolysis,[5] it is unlikely that they are converted to the free acid prior to reaching the active site of the bacterial enzyme system. This unusual activity of the cephalosporin lactones prompted us to investigate structural requirements at the C-4 position of cephalosporins by making further modifications.

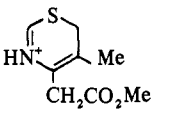
It seemed desirable to replace the carboxyl group with other polar moieties. The crystalline acid chlorides **1** and **2**[6] prepared from the corresponding acids and oxalyl chloride using DMF as a catalyst were converted to the versatile intermediate diazo ketones **3** and **4** by treatment with ethereal diazomethane. The methyl ketone **5** was prepared from **4** by reduction with concentrated HI.[7] Treatment of **4** with ethereal HCl furnished the chloromethyl ketone **6**. The acetoxymethyl ketone **7** was obtained by warming **4** with AcOH. Methanolysis of **4** to **8** was catalyzed by BF_3 etherate.

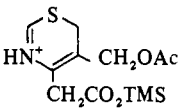
The acetic acid derivatives **9-12** were prepared by photolysis[8] of diazo ketones **3** and **4** in appropriate solvents; chemical methods (for attempted procedures see ref 9) for this rearrangement were unsuccessful. Similar photolytic rearrangement in the penicillin series was reported to give "homopenicillins."[10] Except for **10** which was obtained in crystalline form, we encountered difficulty in purifying these amorphous materials; their postulated structures were confirmed by spectral analysis.

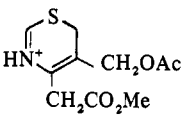
The mass spectra of methyl esters **10** and **12** and the trimethylsilyl (TMS) derivatives of acids **9** and **11** showed the expected molecular ion peaks. Moreover, the observed fragments† a-d further support our structural assignments of **9-12**.

Acid chloride **2** was efficiently reduced to alcohol **13** by LiAl(*tert*-BuO)$_3$H without affecting the β-lactam ring. $NaBH_4$ gave a mixture of products. The analogous penicillanyl alcohols have been prepared by a less direct route *via* reduction of the acyl azides with $NaBH_4$.[12]

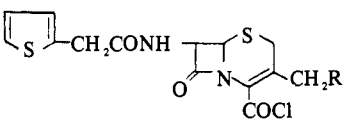

a, *m/e* 244

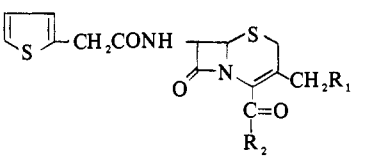

b, *m/e* 186

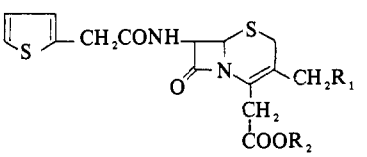

c, *m/e* 302

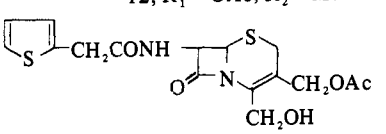

d, *m/e* 244

These new cephalosporin derivatives **4-13** were tested *in vitro* against several strains of Gram-positive and Gram-negative bacteria.‡ The reference antibiotic cephalothin showed minimum inhibitory concentrations (MIC's) of 0.5 μg/ml against *S. aureus*, 0.1 μg/ml against *Streptococcus pyogenes*, 24 μg/ml against *Strep. faecalis*, 12.5 μg/ml against *Escherichia coli*, and 3.1 μg/ml against *Klebsiella pneumoniae*. Compounds **4**, **5**, **10**, and **12** exhibited MIC's of >200 μg/ml against most bacteria tested. Compounds **6-9**, **11**, and **13** had MIC's of 25-100 μg/ml against *S. aureus* and *Strep. pyogenes*, but against *Strep. faecalis* and Gram-negative bacteria, these compounds had MIC's of >200 μg/ml.


1, R = H
2, R = OAc


3, R_1 = H; R_2 = CHN_2
4, R_1 = OAc; R_2 = CHN_2
5, R_1 = OAc; R_2 = Me
6, R_1 = OAc; R_2 = CH_2Cl
7, R_1 = OAc; R_2 = CH_2OAc
8, R_1 = OAc; R_2 = CH_2OMe


9, R_1 = H; R_2 = H
10, R_1 = H; R_2 = Me
11, R_1 = OAc; R_2 = H
12, R_1 = OAc; R_2 = Me


13

†For postulated pathways to similar fragments see ref 11.

‡Test against *S. aureus* HH 127, *S. aureus* SK&F 23390, *Streptococcus pyogenes* C203, *Strep. faecalis* HH 34358, *Escherichia coli* SK&F 12140, and *Klebsiella pneumoniae* SK&F 4200. An agar-inclusion technique was employed: the compound was incorporated in melted agar at halved concentrations from 200 μg/ml downward; after hardening, the agar surface was inoculated with suspensions of the bacterial strains. Following overnight incubation at 37°, plates were examined and the minimum concentration of the compound inhibiting bacterial growth (MIC) was determined.

Our present findings indicate that all of the new structural modifications of the C-4 carboxyl group gave much less active cephalosporins.

Experimental Section §

7β-(2-Thienylacetamido)desacetoxycephalosporanoyl Chloride (1). A soln of 13.0 g (0.0384 mole) of 7β-(2-thienylacetamido)-desacetoxycephalosporanic acid[13] in 200 ml of CH_2Cl_2 was treated with 10.6 g (0.0836 mole) of oxalyl chloride as described in the prepn of **2** to give 13.0 g (recrystd from CH_2Cl_2–hexane) of **1**: mp 179° dec; ir λ_{max} 5.63, 5.71, 6.04 μ.

7β-(2-Thienylacetamido)cephalosporanoyl Chloride (2).# To a stirred suspension of 29.5 g (0.07 mole) of the sodium salt of 7β-(2-thienylacetamido)cephalosporanic acid (Keflin) in a mixt of 400 ml of anhyd CH_2Cl_2 and 1 ml of DMF at 0° was slowly added a soln of 23.2 g (0.18 mole) of oxalyl chloride in 35 ml of anhyd CH_2Cl_2. As the reaction proceeded, the insol starting material gradually went into soln. After 1 hr, the solvent was evapd at a temp below 15°. The oily residue solidified on trituration with Et_2O. Recrystn from CH_2Cl_2–hexane gave 26.5 g (87%) of **2**: mp 117–118° dec; ir λ_{max} 5.63, 5.70, 6.09 μ.

4-Diazoacetyl-3-methyl-7β-(2-thienylacetamido)-3-cephem (3). A suspension of 11.0 g (0.0308 mole) of **1** was treated with an ethereal soln of CH_2N_2 as described for the prepn of **4** to give 9.2 g (83%) of **3**: mp 183–185° (recrystd from Me_2CO–hexane); ir λ_{max} 4.80 μ; nmr (DMSO-*d*) δ 6.35 (s, 1 H, CHN_2).

3-Acetoxymethyl-4-diazoacetyl-7β-(2-thienylacetamido)-3-cephem (4). To a stirred soln of 7.3 g (17.6 mmoles) of **2** in 100 ml of CH_2Cl_2 at −20° was slowly added an ethereal soln of CH_2N_2 prepd from 10.0 g of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.[14] After stirring for 1 hr at −20°, the solvent was removed and the residue taken up in a minimum of Me_2CO. Addn of hexane and cooling caused crystn of 3.57 g (48%) of **4**. Analytical sample (Me_2CO–hexane) had mp 169–174°; ir λ_{max} 4.74 μ; nmr (DMSO-*d*) δ 6.45 (s, 1 H, CHN_2). *Anal.* ($C_{17}H_{16}N_4O_5S_2$) C, H, N.

3-Acetoxymethyl-4-acetyl-7β-(2-thienylacetamido)-3-cephem (5). A soln of 1.0 g (2.38 mmoles) of **4** in 120 ml of $CHCl_3$ was shaken with 4 ml of 47% HI for a few min and was washed with a soln of $Na_2S_2O_3$. Following the usual work-up, the solid residue was recrystd from Me_2CO–hexane (some insol material was removed by filtration) to give 0.68 g of **5**: mp 200–202°; ir λ_{max} 5.60, 5.75, 5.90, 6.00 μ; nmr ($CDCl_3$) δ 2.41 (s, 3 H, Me ketone). *Anal.* ($C_{17}H_{18}N_2O_5S_2$) C, H, N.

3-Acetoxymethyl-4-chloroacetyl-7β-(2-thienylacetamido)-3-cephem (6). To a stirred soln of 1.0 g (2.38 mmoles) of **4** in 35 ml of THF was added 3 ml of ethereal HCl. After 30 min at 25°, the solvent was evapd and the residue recrystd from Me_2CO–hexane to give 0.50 g (49%) of **6**: mp 194–197°; ir λ_{max} 5.62, 5.73, 5.88, 6.00 μ; nmr (DMSO-*d*) δ 4.76 (s, 2 H, CH_2Cl); mass spectrum *m/e* 428 (M^+). *Anal.* ($C_{17}H_{17}ClN_2O_5S_2$) C, H, N.

4-Acetoxyacetyl-3-acetoxymethyl-7β-(2-thienylacetamido)-3-cephem (7). A soln of 2.0 g (4.75 mmoles) of **4** in 50 ml of AcOH was heated to 80°. After 90 min, the cooled soln was dild with 200 ml of H_2O and extd with CH_2Cl_2. The CH_2Cl_2 ext was washed with a 5% $NaHCO_3$ soln and H_2O, dried ($MgSO_4$), and evapd to dryness. The residue was recrystd from Me_2CO–hexane to give 1.05 g (49%) of **7**: mp 164–166°; ir λ_{max} 5.60, 5.73, 5.88, 6.00 μ; nmr ($CDCl_3$) δ 2.14 (s, 3 H), 4.97 (s, 2 H); mass spectrum *m/e* 452 (M^+). *Anal.* ($C_{19}H_{20}N_2O_7S_2$) H, N; C: calcd, 50.43; found, 49.97.

3-Acetoxymethyl-4-methoxyacetyl-7β-(2-thienylacetamido)-3-cephem (8). To a stirred suspension of 2.16 g (5.15 mmoles) of **4** in 100 ml of anhyd MeOH was added 0.2 ml of $BF_3 \cdot Et_2O$, and the mixt was kept at 55° for 30 min. After evapg the solvent, the residue was taken up in 100 ml of EtOAc. The EtOAc soln was washed with H_2O, dried ($MgSO_4$), and evapd to dryness. The residue was recrystd from Me_2CO–hexane to give 0.95 g (44%) of **8**: mp 189–190°; nmr ($CDCl_3$) δ 3.46 (s, 5 H, C-2 CH_2 and OMe), 4.41 (s, 2 H, $COCH_2O$); mass spectrum *m/e* 424 (M^+). *Anal.* ($C_{18}H_{20}N_2O_6S_2$) C, H, N.

2-[3-Methyl-7β-(2-thienylacetamido)-3-cephem-4-yl]acetic Acid (9). A soln of 3.0 g (8.28 mmoles) of **3** in 500 ml of 15% aqueous dioxane at 0° under N_2 was irradiated with uv light.** The progress of the reaction was monitored by tlc on silica plate (9:1, Et_2O–EtOAc). Following the disappearance of **3** (*ca.* 18 hr), the solvent was evapd *in vacuo*. The residue was dissolved in $CHCl_3$ and adsorbed on a column of Florisil. The major fraction was eluted with MeOH to give 0.87 g (32%) of **9**: mp 230–232°; ir λ_{max} 5.73, 6.04 μ; mass spectrum (as TMS derivative)†† *m/e* 496 (M^+ for di-TMS), 481, 255, 244, 97.

Methyl 2-[3-Methyl-7β-(2-thienylacetamido)-3-cephem-4-yl]-acetate (10). A stirred suspension of 0.5 g (1.38 mmoles) of **3** in 100 ml of anhyd MeOH was irradiated with uv light as described in the prepn of **9**. The resulting clear soln was evapd to dryness. The residue was chromatogd on a Florisil column. The major fraction was eluted with EtOAc to give 0.125 g (25%) of **10** (recrystd from Me_2CO–hexane): mp 180–182°; ir λ_{max} 5.66, 5.80, 5.90, 6.00 μ; mass spectrum *m/e* 366 (M^+), 335, 196, 186, 172, 154, 129, 97. *Anal.* ($C_{16}H_{18}N_2O_4S_2 \cdot 0.5H_2O$) C, H, N.

2-[3-Acetoxymethyl-7β-(2-thienylacetamido)-3-cephem-4-yl]-acetic Acid (11). A soln of 2.0 g (4.76 mmoles) of **4** in 500 ml of 25% aqueous dioxane was irradiated with uv light as described for the prepn of **9**. After evapn of the solvent, the residue was taken up in EtOAc and filtered. The filtrate was treated with dicyclohexylamine to give 0.8 g of the salt. Further purification was carried out by chromatography of the salt on a Florisil column. Initial elution with EtOAc removed the less polar impurities. Successive elution with 1:2 MeOH–EtOAc and 1:1 MeOH–EtOAc gave the product. An aqueous solution of the salt (350 mg) was acidified with dilute HCl to pH 2 and extracted with EtOAc. After washing with H_2O and drying ($MgSO_4$), the solvent was evaporated to give the free acid (110 mg) as an amorphous solid which was indicated by tlc analysis (silica plate, 1:2 MeOH–EtOAc) to be homogeneous: mp 70–72°; ir λ_{max} 5.70, 5.80, 6.06 μ; mass spectrum (as TMS derivative)†† *m/e* 482 (M^+ for mono-TMS derivative), 467, 422, 313, 302, 242, 194, 97.

Methyl 2-[3-Acetoxymethyl-7β-(2-thienylacetamido)-3-cephem-4-yl]acetate (12). A soln of 2.0 g (4.76 mmoles) of **4** in 35 ml of a mixt of MeOH–dioxane (3:7) was irradiated with uv light as described in the prepn of **9**. Following the work-up described for the prepn of **10**, **12** was obtained as a glass (0.47 g): ir λ_{max}^{film} 5.73, 6.00 μ; mass spectrum *m/e* 424 (M^+), 364, 244, 184, 97.

3-Acetoxymethyl-4-hydroxymethyl-7β-(2-thienylacetamido)-3-cephem (13). To a soln of 15.0 g (0.0392 mole) of **2** in 250 ml of anhyd THF at 0° was added a soln of 22 g (0.082 mole) of $LiAl(tert\text{-}BuO)_3H$ in 150 ml of anhyd THF during 20 min. After further stirring for 30 min, the mixt was poured into a chilled soln of dil HCl (pH 1) and the soln was adjusted to pH 2. It was extd with EtOAc, and the ext was washed with a 5% $NaHCO_3$ soln and brine. Evapn of the solvent gave 9.2 g of crude **13** (s) with only a trace of impurities as shown by tlc analysis (silica plate, 7:3 EtOAc–Et_2O). Further purification by passing through a column of Florisil in EtOAc, evapn of the solvent, and recrystn (Me_2CO–hexane) gave pure **13**: mp 172–173°; ir λ_{max} 3.00, 5.59, 5.70, 6.00 μ; nmr ($CDCl_3$–DMSO-*d*–D_2O) δ 4.73 (s, 2 H, CH_2OH). *Anal.* ($C_{16}H_{18}N_2O_5S_2$) C, H, N.

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§ Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline and French Laboratories. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMN-6E Spectrometer. Nmr spectra were obtained on a Varian T-60 instrument (Me_4Si). Ir spectra were obtained with samples in Nujol on a Perkin-Elmer Infracord instrument. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

#Modification of the procedure given in ref 6; replacing C_6H_6 with CH_2Cl_2 as the solvent gave a cleaner product.

**A Hanovia high-pressure mercury lamp in an immersion well equipped with a Pyrex glass filter was used. For other smaller scale (<1 g) reactions carried out in a Pyrex flask, a Hanovia uv quartz lamp (140 W) was used.

††The TMS derivatives (mono- and di-TMS) were obtained by treatment of the compounds with *N,O*-bis(trimethylsilyl)trifluoroacetamide.

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Iodophenyl Derivatives of α-Methylalanine and Isovaline as Potential Oral Cholecystographic Agents

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Gastrointestinal absorption as well as gall bladder accumulation are prime factors in determining the efficacy of oral cholecystographic agents. In this connection, the biological properties of α-aminoisobutyric acid (AIB; 2-methylalanine), are of particular interest. AIB is a nonmetabolizable amino acid,[1] which undergoes active intestinal transport against a concentration gradient[2] and accumulates in the liver.[3] Since the presence of iodine atoms in organic compounds markedly enhances their biliary excretion,[4] it was hoped that combination of iodinated aromatic nucleus with AIB and its homolog, isovaline, would result in new efficient oral cholecystographic agents.

Chemistry. The new iodophenyl derivatives of AIB (**22**) and of isovaline (**23-26**) were prepared as outlined in Scheme I. The requisite benzyl and phenethyl methyl ketones (**3, 5, 9, 10**) were prepared in good yields using known procedures. Thus, 3-nitrophenylacetone (**3**) was prepared by acetylation of 3-nitrophenylacetic acid (**1**), according to Smith's method,[5] *via* the enol acetate (**2a, 2b**). Nmr analysis of the enol acetate, which was isolated as a crystalline, analytically pure material, revealed the existence of two isomeric products. The major one (**2a**, 75%), 1-(3′-nitrophenyl)-2-acetoxyprop-1-ene, exhibited resonances centered at 2.14 (s, CCH_3) and 2.25 ppm (s, $COCH_3$), and the minor one (**2b**, 25%), 2-acetoxy-3-(3′-nitrophenyl)prop-1-ene, exhibited resonances centered at 2.25 (s, $COCH_3$), 3.85 (s, benzylic CH_2), and 6.00 ppm (br s, vinylic protons $=CH_2$). Acid hydrolysis of the enol acetates yielded the desired benzyl methyl ketone (**3**). 3-Methoxyphenylacetone (**5**)—a known compound[6]—was prepared in a better yield and more conveniently, by condensing 3-methoxybenzaldehyde (**4**) with nitroethane, in the presence of piperidine as a catalyst, followed by Fe-HCl reduction of the resulting 1-(3′-methoxyphenyl)-2-nitroprop-1-ene, in a procedure analogous to that described recently.[7] Aldol condensation of either 3-methoxybenzaldehyde (**4**) or 3-nitrobenzaldehyde with acetone, followed by catalytic reduction of the resulting benzalacetones (**7, 8**), afforded the phenethyl methyl ketones (**9, 10**), of which the 3-amino derivative (**9**) is a new compound. The hydantoins (**11-15**), prepared in high yields by the reaction of the corresponding ketones with sodium cyanide and ammonium carbonate, according to the Bucherer-Bergs method,[8] were hydrolyzed to give the DL-ω-phenyl-α-methyl-α-amino acids (**16-21**). Aromatic iodination of the amino acids, employing either iodine monochloride (in the case of **23**) or iodine-potassium iodide (in the case of **22, 25**) as iodinating agents, afforded the final products (**22, 23, 25**). Whereas 4-(3′-aminophenyl)isovaline (**19**) and 4-(3′-hydroxyphenyl)isovaline (**21**) reacted smoothly with the iodinating agents to yield the 2,4,6-triiodophenyl derivatives (**23, 25**), *N*-acetyl-2-methyl-3-(3′-hydroxyphenyl)alanine (**18**) yielded only the 2,4-diiodophenyl derivative (**22**), and 2-methyl-3-(3′-aminophenyl)alanine (**16**) was completely resistant to iodination under normal iodinating conditions, due to steric hindrance exerted by the 2-methylalanine side chain. Positions of the two iodine atoms in DL-2-methyl-3-(2′,4′-diiodo-5′-hydroxyphenyl)alanine (**22**) were unequivocally established by means of nmr spectra, exhibiting two distinct singlets for two separated aromatic protons at 7.02 ppm—aromatic hydrogen at position 6′—and at 8.76 ppm—aromatic hydrogen at position 3′. Acetylation of **23** with 1 equiv of Ac_2O yielded the aromatic acetamido derivative (**24**), as proved by oxidative degradation of **24** to the known 2,4,6-triiodo-3-acetamidobenzoic acid.[9] Physical constants and analytical values for the newly synthesized ketones, hydantoins, and amino acids are tabulated in Tables I-IV.

Biological Testing. Compounds **22, 23, 24**, and **25** were each tested orally in dogs and cats at 100 mg of I/kg body wt. No gall bladder visualization up to 18 hr postdose was observed. The insoluble nature of the compounds (as sodium salts), precluded any iv radiographic or toxicity studies.

Table I. Benzyl and Phenethyl Methyl Ketones

No.	Ketones	Mp (crystn solvent) or bp (mm), °C	Formula	Analyses
3	3-Nitrobenzyl methyl ketone	62 (MeOH)	$C_9H_9NO_3$	C, H, N
5	3-Methoxybenzyl methyl ketone	113-115 (1.5)[a]	$C_{10}H_{12}O_2$	C, H
9	4-(3′-Aminophenyl)-butan-2-one	58 (hexane)	$C_{10}H_{13}NO$	C, H, N
10	4-(3′-Methoxyphenyl)-butan-2-one	121-123 (1.2)[b]	$C_{11}H_{14}O_2$	C, H,

[a] Lit.[6] bp 95-97° (0.7 mm). [b] Lit.[13] bp 151-152° (10 mm).

Experimental Section†

3-Nitrobenzyl Methyl Ketone (3-Nitrophenylacetone) (3). 3-Nitrophenylacetic acid[10] (80 g, 0.44 mole) was refluxed for 4 hr under N_2 in a mixture of pyridine (180 ml) and Ac_2O (440 ml).

†All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Ir spectra were detd either neat or in KBr disks (Perkin-Elmer 337). Nmr spectra were obtd with a Varian A-60 spectrometer (TMS). Nmr and ir spectra of new compounds were compatible with related structures and are on file with the authors. Tlc's were performed on silica gel G plates, spots detected by exposure to I_2 vapor. Paper chromatography (of the amino acids) was carried out on Whatman No. 1 paper, using *n*-BuOH–AcOH–H_2O (60:20:20) as the solvent system. Chromatograms were developed for *ca.* 22 hr at room temp, and the amino acids were detected by ninhydrin or Bromocresol Green indicator. Titrimetric analyses and molecular weights detn of the amino acids were done either in water, using NaOH and Methyl-Red as an indicator, or in glacial AcOH, using $HClO_4$ and Methyl-Violet as the indicator.