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Total Synthesis of β-Lactam Antibiotics. VI. 3-Arylcephalosporins[1]

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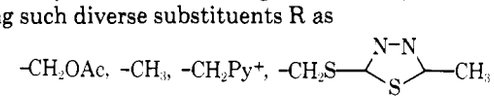
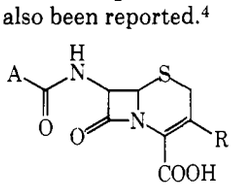
The total synthesis of *dl*-3-phenyl-, 3-*p*-carbomethoxyphenyl-, and 3-(4-thiazolyl)-7β-(2-thienyl)acetamidodecephalosporanic acids **12a–c** is described.

Cephalosporins **1** are a class of semisynthetic antibiotics that are being increasingly used because of their breadth of spectrum, potency, acid stability, and high degree of tolerance by man. In recent years an intensive worldwide effort has been made to obtain modified cephalosporins with improved properties.[2] Variations at the 3 position have been particularly fruitful, resulting in clinically useful drugs having such diverse substituents R as



Many other modifications have also been reported, the vast majority of which have $-CH_2X$ as the 3 substituent,[2,3] although R = H has also been reported.[4]



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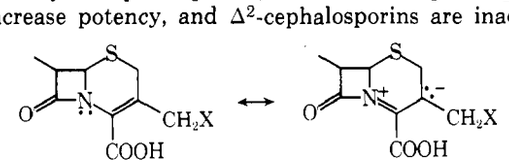
It is believed that resonance of type **2** plays a role in the bioactivity of cephalosporins, since electronegative groups X increase potency, and Δ^2-cephalosporins are inactive.[2]



2

However, the activity of 3-methylcephems such as cephalexin (X = H) shows that X^- does not have to depart during the bioactive event. Furthermore, a theoretical study also concluded that during thiolation of cephalosporins at the β-lactam carbonyl, negative charge tends to accumulate at C-3 but that the CH_2–X bond does not break.[5]

For these reasons it seemed worthwhile to prepare cephems bearing aromatic rings directly attached to C-3. At the inception of this project, there was no known way to do this by partial synthesis.[6] However, the total synthesis recently developed in these laboratories[7] has the capability of great variation in the 3 substituent, and this route (Scheme I) was therefore chosen for the preparation of 3-aryl cephems.

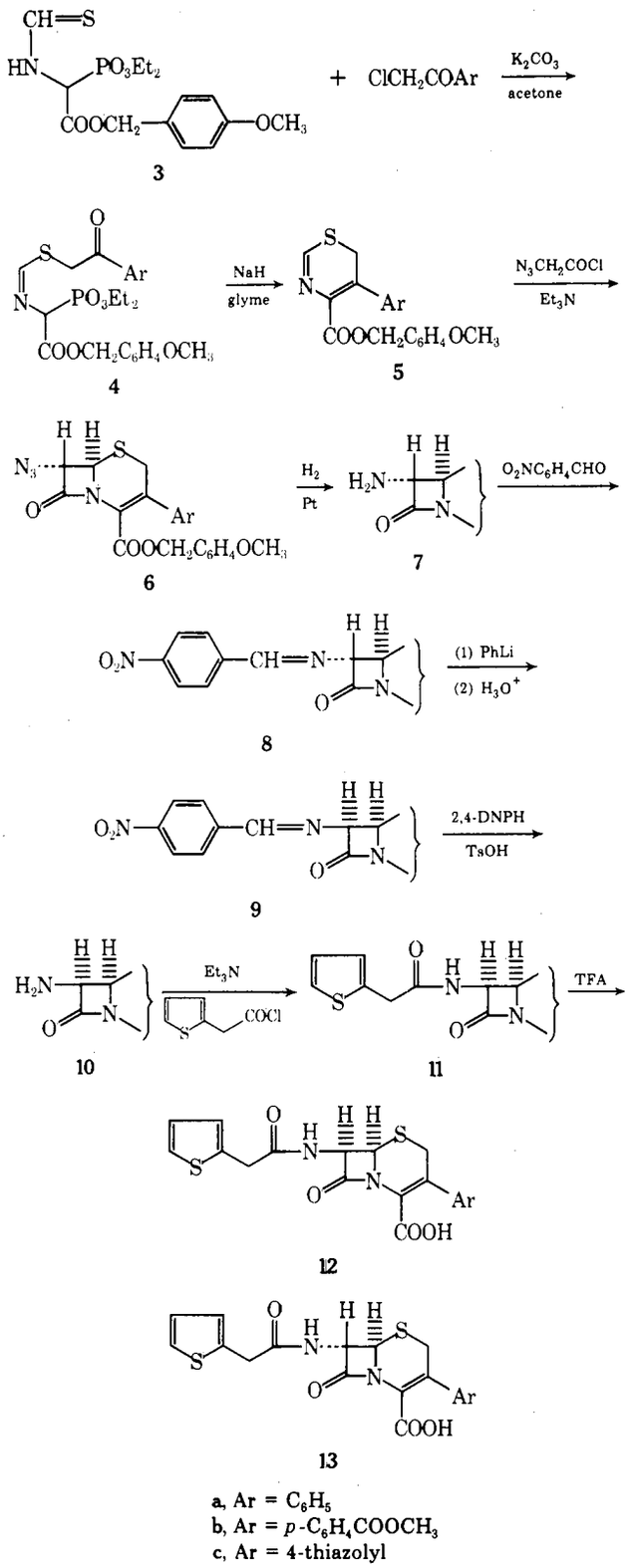
The alkylation of thioamide **3**[7] with phenacyl chloride and cyclization of **4a** to the thiazine **5a** were best done sequentially, with isolation of **4a.** When more than 1 equiv of K_2CO_3 was used with phenacyl chloride as had previously been done with 1-chloro-3-acetoxy-2-propanone,[7] extensive decomposition occurred. Phenacyl bromide could be used in place of the chloride, but in addition to **4a** it gave an isomer, presumably trans. Both isomers were stable to interconversion in refluxing $CDCl_3$.

Many conditions were tried for the cyclization of **4a** to **5a,** including K_2CO_3–acetone,[7] $KHCO_3$–acetone, Et_3N–$CHCl_3$, PhLi–THF, NaH–THF, LDA–THF, and NaH–glyme. Of these, the latter gave the cleanest product and was used in all subsequent work.

Cycloaddition of azidoacetyl chloride to **5a** gave cephem **6a,** sometimes containing the Δ^2 isomer, which was formed from **6a** with catalysis by triethylamine. The isomers were separable by chromatography, but with care the problem was avoidable altogether.

The stereochemistry of **6a** was established as trans by the coupling constant of 1.5 Hz for H-6 and H-7, in accord with previous observations[7] as well as our own subsequent examples. Since all naturally occurring cephalosporins and penicillins have cis stereochemistry, and trans compounds are inactive, it was necessary to epimerize the 7 substituent. This could not be done by simple equilibration because the trans isomers are generally the more stable ones, and so our procedure based upon steric approach control was used.[8] Azidocephem **6a** was reduced to amine **7a,** which was converted to its Schiff base **8a** with *p*-nitrobenzaldehyde. Formation of the 7 anion with phenyllithium, activation with DMF, and then acidification under kinetically controlled conditions, which occurs preferentially from the less hindered side, provided the cis Schiff base **9a** with the natural configuration at C-7, along with recovered **8a,** in a 2:1 ratio.

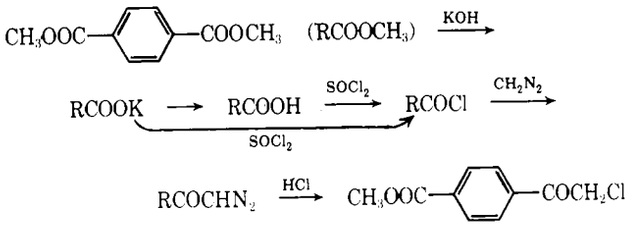
Scheme I



a, Ar = C_6H_5
b, Ar = p-$C_6H_4COOCH_3$
c, Ar = 4-thiazolyl

The steps **9a** → **12a** were done in the usual manner,[7,8] providing totally synthetic *dl*-3-phenyl cephem **12a.** It contained some 7-epi isomer **13a** carried through from the epimerization and some Δ^2 formed during thienylacetylation, but these, being inactive, did not interfere with the bioassay.[9]

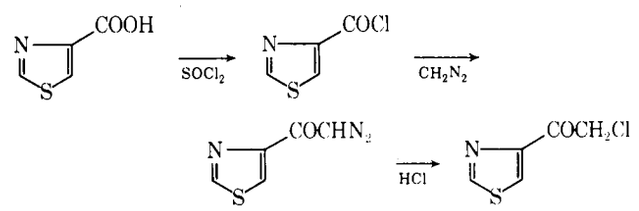
With the expectation that an additional electron-withdrawing group would increase bioactivity, the p-carbomethoxyphenyl cephem **12b** was also synthesized. The required p-carbomethoxyphenacyl chloride was prepared by the sequence below.



Our mp for the acid chloride, 50–55°, was different from that reported,[10] 130°; so we prepared it by an alternate route to be secure.

The sequence of Scheme I was repeated, starting with **3** and p-carbomethoxyphenacyl chloride. The reactivity of the latter was much greater than that of phenacyl chloride, forming **4b** in minutes instead of hours. The epimerization of **8b** gave a normal:epi ratio (**9b:8b**) of only about 1:1, not separable at the **11b** stage, so that the final product *dl*-**12b** contained also **13b** in about a 1:1 ratio.[9] Isomerization to Δ^2 was less than in the phenyl series, and in other respects the sequence was done in the same way as before.

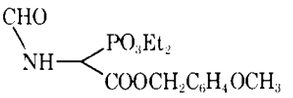
To provide an example of a 3-heteroaryl cephem, the 4-thiazolyl analog **12c** was made by the same route. The required chloromethyl 4-thiazolyl ketone was prepared from the acid as before.



The pathway of Scheme I was again followed, furnishing *dl*-**12c**[9] which was free of both Δ^2 isomer and **13c.**

In all three syntheses, the yields of thiazines **5a–c** were critically dependent on the purity of **3,** which must be carefully chromatographed even though this does not change the ir or nmr spectra. We believe that crude **3,** which is made from the amino compound by thioformylation in liquid H_2S, contains some form of active sulfur because sulfides of the type $(ArCOCH_2)_2S$ (**14**) have been obtained from poor preparations of **5.**

An unexpected transformation occurred on compounds **4a** and **4c.** On several days' standing, they were transformed into the formamide **15.** We do not know the path-



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way of this reaction, or the fate of the other fragment of the molecule.

A final point of interest concerns the conformation of the 3-aryl substituents. The phenyl and p-carbomethoxyphenyl groups have hydrogen atoms on both carbons adjacent to the point of attachment, which project in the plane of the ring and prevent it from becoming planar with the thiazine ring, in all compounds from **5a,b** to **12a,b.** On the other hand, the thiazole ring has only one such hydrogen, which is apparently not sufficient to prevent it from enjoying planarity, and thus conjugation, with the thiazine ring in **5c–12c.** We infer this from the nmr spectra on these grounds. In the **a** and **b** series relative to the **c** series, SCH_2, OCH_2Ar, and the two hydrogens in $CH_2C_6H_4OCH_3$ ortho

to CH_2 appear *ca.* 0.2 ppm upfield. In the thiazolyl series, the latter two chemical shifts are about the same as those of the corresponding 3-alkyl compounds, showing that the protons in question are in the shielding cone of the phenyl rings in the **a** and **b** series.

The preparation of other totally synthetic β-lactam antibiotics will be reported in due course.

Experimental Section

Nmr spectra were taken on a Varian T-60; ir spectra were taken on a Perkin-Elmer Infracord.

Preparation of 4a–c. A mixture of 77 mg (0.2 mmol) of **3,** 32 mg of phenacyl chloride (0.2 mmol), 29 mg of ground K_2CO_3, and 2 ml of acetone was stirred 18 hr at 25° under N_2, filtered, and evaporated, affording 111 mg of crude **4a,** suitable for further reactions: 112% wt yield; ir (film) 5.72 (ester), 5.93 (COPh), 6.20, 6.28 μ (Ar, C=N); nmr ($CDCl_3$) δ 1.20 (t, J = 7 Hz, CH_2CH_3), 3.79 (s, OCH_3), 4.08 (d of q, J_{HP} = 8 Hz and J = 7 Hz, CH_2CH_3), 4.56 (s, SCH_2), 4.69 (d, J_{HP} = 21 Hz, CHP), 5.16 (s, OCH_2Ar), 6.9 (d, J = 9 Hz), 7.3 (d, J = 9 Hz, C_6H_4), 7.5, 8.0 (m, C_6H_5), 8.49 (d, J_{HP} = 4 Hz, CH=N). When this reaction was done using 53 mg of phenacyl bromide, 37 mg of K_2CO_3, 100 mg of **3,** and 2 ml of acetone (0.267 mmol scale), nmr showed two products. From plc on silica gel with 4:1 $CHCl_3$–EtOAc was obtained 35 mg of **4a** and 34 mg of an isomer, ir similar to **4a,** nmr similar except for CH=N at δ 9.06 (d, J_{HP} = 4 Hz), mass spectrum 493. The nmr spectra of **4a** and its isomer did not change after brief boiling in $CDCl_3$.

Compound **4b** was prepared by the same procedure but with only 25 min reaction time. The ir was similar to that of **4a** with an added $COOCH_3$ at 5.78 μ, and the nmr was also similar, with an added $COOCH_3$ at δ 3.98.

Compound **4c** was best prepared by a slightly modified procedure, using a threefold excess of K_2CO_3 and stirring 1 hr. After filtering, evaporating, and flushing with benzene, the crude **4c** was ready for the next step. The ir and nmr spectra resembled those of **4a,** lacking the C_6H_5 bands and with additional ones at δ 8.31 and 8.85 (m, thiazolyl).

Cyclization of 4a–c to 5a–c. Crude **4a,** prepared as above from 77 mg of **3,** was dissolved three times in glyme and evaporated and then treated 5 min in 1 ml of glyme with 1 equiv of NaH (10 mg of 50% NaH in oil, washed twice with hexane to remove oil) suspended in 1 ml of glyme. The reaction mixture was diluted with 10 ml of benzene, washed with water, dried with $MgSO_4$, filtered, and evaporated. Weight yields of crude **5a** generally ran >100%. Purification by chromatography was not successful, but crude **5a** was suitable for cycloaddition. The ir showed only ester carbonyl at 5.78 μ: nmr ($CDCl_3$) δ 3.58 (s, SCH_2), 3.76 (s, OCH_3), 4.93 (s, OCH_2), 6.71 (d, J = 9 Hz), 6.80 (d, J = 9 Hz, C_6H_4), 7.25 (s, C_6H_5), 8.30 (s, CH=N); mass spectrum 339.

Compound **5b** was made as above: ir 5.80 μ; nmr ($CDCl_3$) δ 3.60 (s, SCH_2), 3.81 (s, OCH_3), 3.97 (s, $COOCH_3$), 4.98 (s, OCH_2), 6.78 (d, J = 9 Hz), 6.96 (d, J = 9 Hz, $C_6H_4OCH_3$), 7.27 (d, J = 8 Hz, $C_6H_4COOCH_3$), 8.40 (s, CH=N); mass spectrum 397. Crude yield >100%, 30% of crystalline **5b,** mp 144–6° from 1:1 benzene–cyclohexane.

Compound **5c** was prepared similarly, ~100% crude yield, 39% crystalline, mp 134° from benzene–cyclohexane: ir 5.79 μ; nmr ($CDCl_3$) δ 3.84 (s, OCH_3), 5.22 (s, OCH_2), 6.91 (d, J = 9 Hz), 7.27 (d, J = 9 Hz, C_6H_4), 8.43 (s, CH=N), 7.3 (d, J = 2 Hz), 8.75 (d, J = 2 Hz, thiazolyl); mass spectrum 346.

Cycloaddition of Azidoacetyl Chloride[12] to 5a–c Forming 6a–c. Crude **5a** prepared from 0.25 mmol of **3,** in 2 ml of CH_2Cl_2, was treated with 0.139 ml (1 mmol) of Et_3N. Then, under N_2, 0.033 ml of azidoacetyl chloride (0.37 mmol) in 2 ml of CH_2Cl_2 was added at 0° over 30 min. The mixture was allowed to warm to 25°, diluted with 30 ml of benzene, washed successively with pH 3 aqueous phosphate, water, and aqueous K_2HPO_3, dried with $MgSO_4$, filtered, and evaporated, leaving 106 mg of crude cephem **6a.** This was chromatographed on 5 g of silica gel (E. Merck's) with 10:1 $CHCl_3$–EtOAc, providing 28.5 mg (27%) of pure **6a:** ir (film) 4.73 (azide), 5.61 (β-lactam), 5.79 μ (ester); nmr ($CDCl_3$) δ 3.66 (s, SCH_2), 4.59, 4.70 (d's, J = 1.5 Hz, H-6 and -7), other peaks correct; mass spectrum 422, 394.

Crystalline **5b** was similarly treated with 4 equiv of Et_3N and 2 equiv of azidoacetyl chloride, affording 130 mg of crude (83%) and 29 mg of crystalline cephem **6b.** Chromatography of the crude gave 33 mg more **6b,** 40% total: ir like **6a;** mass spectra 480, 452; nmr ($CDCl_3$) δ 3.63 (s, SCH_2), 4.62, 4.70 (d's, J = 1.5 Hz, H-6 and -7), other peaks correct.

Crystalline **5c** similarly gave, after chromatography, 28% of **6c:** ir like **6a,b;** mass spectrum 429, 401; nmr ($CDCl_3$) δ 3.81 (s, SCH_2 and OCH_3), 4.67, 4.73 (d's, J = 1.5 Hz, H-6 and -7), other peaks correct.

Caution! Vigorous explosions have been reported[13] during the preparation of azidoacetyl chloride. Using a modified procedure[14] we have had no trouble, but we urge the greatest caution in making and handling this compound.

Hydrogenation of 6a–c to 7a–c. Azidocephem **6a,** 170 mg, was hydrogenated in 25 ml of benzene with 170 mg of PtO_2 for 45 min at 40 psi, filtered through a bed of Supercel and evaporated, affording 101 mg of **7a,** 63%: ir (film) 5.66, 5.78 μ; nmr ($CDCl_3$) δ 2.0 (m, NH_2), 3.59 (s, SCH_2), 4.16, 4.52 (d's, J = 1.5 Hz, H-6 and -7), other peaks correct. Also present was the Δ^2 isomer, nmr ($CDCl_3$) δ 4.26 (d, J = 1 Hz, H-7), 5.51 (m, H-6), 6.45 (d, J = 1.5 Hz, SCH=).

Likewise **6b** was reduced to **7b,** 67%: ir (film) 2.9, 5.63, 5.78 μ; mass spectrum 454; nmr ($CDCl_3$) δ 2.3 (m, NH_2), 3.60 (s, SCH_2). 4.24, 4.58 (d's, J = 2 Hz, H-6 and -7), other peaks correct.

Similarly **6c** gave 56% **7c:** ir (film) 2.9, 5.64, 5.77 μ; mass spectrum 403; nmr ($CDCl_3$) δ 2.25 (m, NH_2), 3.80 (s, SCH_2), 4.30, 4.60 (d's, J = 2 Hz, H-6 and -7), other peaks correct.

Preparation and Epimerization of Schiff Bases 8a–c to 9a–c. Compounds **7a–c,** *ca.* 2.5% in CH_2Cl_2, were treated 2 hr with 1 equiv of *p*-nitrobenzaldehyde in the presence of $MgSO_4$, filtered, and evaporated, providing 7α-Schiff bases **8a–c.** Excess of $MgSO_4$ should be avoided. Epimerization was done by the published procedure,[8] giving mixtures of **8a–c** and the 7β-Schiff bases **9a–c** in these ratios: **9a:8a,** 2:1; **9b:8b,** 1:1; **9c:8c,** 1:1. Epimerization was gauged by comparing in the nmr the CH=N peaks, δ 8.55 for 7α and δ 8.75 for 7β.

9a–c → 10a–c → 11a–c. Deblocking of epimerized Schiff bases **9a–c** and thienylacetylation of amines **10a–c** were done as before.[8] The crude amines were checked by ir only (similar to **7a–c**) and carried forward without purification. Esters **11a–c** were isolated by chromatography on silica gel (E. Merck, 70–230 mesh) in weight ratios of about 30:1, 40:1, and 50:1 respectively, eluting with 10:1 chloroform–ethyl acetate, and the single-spot products had R_f's of about 0.3, 0.2, and 0.3, respectively, on tlc in the same system. Compound **11a** had ir (film) 3.06 (NH), 5.62 (β-lactam), 5.77 (ester), 5.97 μ (amide); nmr ($CDCl_3$) δ 3.59 (s, SCH_2), 3.79 (s, OCH_3), 3.82 (s, CH_2C=O), 4.90 (s, OCH_2), 4.97 (d, J = 4 Hz, H-6), 5.87 (d of d, J = 4, 8 Hz, H-7), other peaks correct; mass spectrum 520, 340. Compound **11b** had ir (film) 3.0, 5.61, 5.79, 5.95 μ; nmr ($CDCl_3$) δ 3.58 (s), 3.78 (s), 3.84 (s), 3.93 (s, $COOCH_3$), 4.92 (s), 4.99 (d, J = 4 Hz), 5.86 (d of d, J = 4, 8 Hz), *et al.;* mass spectrum 578, 397. Compound **11c** had ir (film) 3.04, 5.62, 5.80, 5.98 μ; nmr ($CDCl_3$) δ 3.72 (s, SCH_2), 3.81 (s, OCH_3), 3.88 (s, CH_2C=O), 5.07 (d, J = 4 Hz, H-6), 5.14 (s, OCH_2), 5.89 (d of d, J = 4, 8 Hz, H-7), *et al.;* mass spectrum 527, 347.

De-esterification of 11a–c to 12a–c. Samples of 20–25 mg of **11a–c** were taken up in 0.5 ml of anisole, cooled to 0°, and treated with 2.5 ml of trifluoroacetic acid for 4–5 min. Vacuum of <1 Torr was then applied while the sample warmed gradually to 30°; this removes first TFA, then anisole. Another 2.5 ml of anisole was added and pumped off to assure quantitative removal of TFA. The residue was taken up in a few ml of water containing excess $NaHCO_3$, washed 3 times with CH_2Cl_2, acidified with pH 2 phosphate, and extracted 3 times with AcOH-free EtOAc. The EtOAc was sometimes dried with $MgSO_4$, filtered, and evaporated to obtain the free acids **12,** or else re-extracted directly with water containing the calculated amount of $NaHCO_3$ and lyophilized to obtain **12a–c** as sodium salts. Samples of **12a–c** were treated with CH_2N_2 and sent for mass spectrum without purification.

Our general de-esterification procedure more recently is to treat one part ester with 2 parts anisole and 10 parts TFA for 2.0 min at 0° and work up as above. Sometimes good sodium salts are obtained simply by treating the residue with water containing the calculated amount of $NaHCO_3$, washing with CH_2Cl_2, and lyophilizing. Yields vary from 60 to 95%.

Compound **12a** had ir (film) 2.9–3.7, 5.60, 5.8, 6.0 μ; nmr (Na salt, D_2O) δ 3.70, (s, SCH_2), 3.92 (s, CH_2C=O), 4.63 (HDO), 5.15 (d, J = 4 Hz, H-6), 5.67 (d, J = 4 Hz, H-7), *et al.;* also δ 6.50 (broad s, SCH= of Δ^2 isomer). High resolution mass spectrum of Me ester, 414.0713; calcd for $C_{20}H_{18}N_2O_4S_2$, 414.0707. Compound **12b** had nmr (Na salt, D_2O) δ 3.68 (s), 3.88 (s, $COOCH_3$ and CH_2C=O), 4.68 (HDO), 5.16 and 5.67 (d's, J = 5 Hz), *et al.;* also δ 6.65 (m, SCH= of Δ^2 isomer). High resolution mass spectrum of Me ester, 472.0714; calcd for $C_{22}H_{20}N_2O_6S_2$ 472.076. Compound **12c**'s Me ester had mass spectrum 421, 241, 208, 181.

***p*-Carbomethoxybenzoyl Chloride.** Following the published

procedure,[10] dimethyl terephthalate was saponified to the monopotassium salt monoester and converted to the monoacid chloride monoester with $SOCl_2$. The crystalline product had good ir and nmr spectra, but melted at *ca.* 50° instead of the reported 130°. Therefore another method was also used. To a solution of 21.4 g (0.11 mol) of dimethyl terephthalate in 100 ml of MeOH and 100 ml of ether was slowly added a solution of 5.6 g (0.1 mol) of KOH in 100 ml of MeOH and 5 ml of H_2O. After being stirred for 18 hr the mixture had pH 7 and a white precipitate which was filtered, dissolved in H_2O, filtered to clarify, and acidified to pH 2 with HCl. A white precipitate of monomethyl terephthalate appeared which was filtered, washed, and dried, 11.4 g, mp 218–220° (reported[15] 230°). One gram was refluxed 2 hr with 1.5 ml of $SOCl_2$ and evaporated, leaving a white powder, mp 50–55°, identical with the sample made by the first method: ir (Nujol) 5.63, 5.76 μ; nmr ($CDCl_3$) δ 3.98 (s, OCH_3), 8.15 (s, C_6H_4).

***p*-Carbomethoxydiazoacetophenone.** Diazomethane was made by adding 27.2 g of Diazald in 165 ml of ether to 6.34 g of KOH in 10 ml of H_2O and 31.5 ml of EtOH. Over 1 hr, the CH_2N_2 solution was added to 6 g of *p*-carbomethoxybenzoyl chloride in 200 ml of ether at 0°. The volume was reduced to *ca.* 150 ml and the crystalline product was filtered and dried, 4.3 g, mp 98–101°: ir ($CDCl_3$) 4.74, 5.79, 6.16 μ; nmr ($CDCl_3$) δ 3.95 (s, $COOCH_3$), 5.93 (s, CHN_2), 7.81, 8.09 (d's, J = 8 Hz, C_6H_4).

***p*-Carbomethoxyphenacyl Chloride.** The diazo compound, 4 g, was dissolved in 40 ml of AcOH and 4 ml of concentrated HCl. When effervescence ceased, 200 ml of H_2O was added, precipitating the product which was filtered, washed with water, and dried, 3.8 g, mp 144–7°: ir ($CDCl_3$) 5.79, 5.9 μ (sh); nmr ($CDCl_3$) δ 3.95 (s, $COOCH_3$), 4.70 (s, $COCH_2Cl$), 8.02, 8.07 (d's, J = 8 Hz, C_6H_4).

Thiazole-4-carbonyl Chloride. Thiazole-4-carboxylic acid, 0.97 g (0.01 mol), was refluxed with 10 ml of $SOCl_2$ for 90 min. The solution was evaporated and the residue flushed with benzene and recrystallized from 50 ml of hexane: mp 85–86.5°; ir ($CDCl_3$) 5.64 μ; nmr ($CDCl_3$) δ 8.59, 9.01 (d's, J = 2 Hz).

4-Diazoacetylthiazole. The acid chloride, 4.01 g (0.027 mol), was added to 680 ml of 0.1 *N* CH_2N_2 in ether (0.068 mol) at 0°. The reaction took *ca.* 5 min and was stirred 30 min at 0° and 30 min at 25°. The solution was partly concentrated, filtered to clarify, and evaporated to dryness, leaving 4.4 g of yellow solid which was washed with petroleum ether; mp 80–82°. It was recrystallized from ether–petroleum ether and then from ether, giving 1.8 g of pure product: ir ($CDCl_3$) 4.72, 6.17 μ; nmr ($CDCl_3$) δ 6.48 (s, $COCHN_2$), 8.27, 8.84 (d's, J = 2 Hz, thiazolyl).

4-Chloroacetylthiazole. The diazo compound, 3 g, was added at 0° to 50 ml of EtOH saturated with HCl. The mixture was stirred 5 min and evaporated to dryness. The solid was washed with a little ether, then stirred with pH 8 aqueous phosphate, and extracted 4 times with ether. The ether solution was dried with $MgSO_4$, filtered and evaporated, leaving 2.62 g of yellow solid, 83%; ir ($CDCl_3$) 5.85 μ; nmr ($CDCl_3$) δ 4.95 (s, $COCH_2Cl$), 8.40, 8.94 (m's, thiazolyl).

Sulfides 14a–c. From chromatography of cephems **6a–c** and crystallization of thiazines **5b,c** were obtained variable yields of **14a–c**, depending on the quality of **3**. Compound **14a** had ir (film) 5.92 (sh), 5.97 μ; mass spectrum 302 [$(C_6H_5COCH_2)_2S_2$], 270, 237, 165, 152, 119, 105, 77. Compound **14b** had ir ($CHCl_3$) 5.80, 5.92, 5.97 μ; nmr ($CDCl_3$) δ 3.94 (s, $COOCH_3$), 3.97 (s, SCH_2), 7.98, 8.10 (d's, J = 8 Hz, C_6H_4); mass spectrum 386, 355, 353, 223, 178, 163, 135. Compound **14c**, in mixtures with cephem **6c**, had ir 5.93, 5.98 μ and a sample purified by tlc had mass spectrum 284, 158, 126, 112, 84.

Formamide 15. On standing for several days, **4a** and (more rapidly) **4c** were transformed into **15**: ir (film) 3.1–3.2, 5.74, 5.96 μ; nmr ($CDCl_3$) δ 5.30 (d of d, J_{HP} = 22 Hz and J = 8 Hz, CHP), 8.20 (s, CH=O), *et al.*; mass spectrum 359, 331, 210, 195, 166, 138, 121.

Registry No.—**3**, 50917-87-8; **4a**, 52539-73-8; **4b**, 52539-74-9; **4c**, 52539-75-0; **5a**, 52539-76-1; **5b**, 52539-77-2; **5c**, 52539-78-3; **6a**, 52539-82-9; **6b**, 52539-83-0; **6c**, 52539-84-1; **7a**, 52539-85-2; **7a** Δ^2 isomer, 52539-79-4; **7b**, 52539-86-3; **7c**, 52539-87-4; **8a**, 52539-88-5; **8b**, 52539-89-6; **8c**, 52539-90-9; **9a**, 52539-91-0; **9b**, 52539-92-1; **9c**, 52539-93-2; **10a**, 52539-94-3; **10b**, 52539-95-4; **10c**, 52585-05-4; **11a**, 52539-96-5; **11b**, 52539-97-6; **11c**, 52539-98-7; **12a**, 52539-99-8; **12a** Na salt, 52540-00-8; **12a** Δ^2 isomer Na salt, 52539-80-7; **12a** Me ester, 52540-01-9; **12b**, 52540-02-0; **12b** Na salt, 52540-03-1; **12b** Δ^2 isomer Na salt, 52539-81-8; **12b** Me ester, 52540-04-2; **12c**, 52540-05-3; **12c** Na salt, 52540-06-4; **12c** Me ester, 52540-07-5; **14a**, 2461-80-5; **14b**, 52540-19-9; **14c**, 52540-20-2; **15**, 52540-21-3; phenacyl chloride, 532-27-4; *p*-carbomethoxyphenacyl chloride, 52540-22-4; thiazole-4-carbonyl chloride, 52540-23-5; azedoacetyl chloride, 30426-58-5; *p*-carbomethoxybenzayl chloride, 7377-26-6; *p*-carbomethoxydiazoacetophenone, 22744-13-4; thiazole-4-carboxylic acid, 3973-08-8; 4-diazoacetylthiaziole, 52540-24-6; 4-chloroacetylthiazole, 52540-23-5.

References and Notes

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