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REDUCTION OF CEPHALOSPORANIC ACIDS WITH CHROMIUM(II) SALTS

SYNTHESIS OF 3-METHYLENECEPHAM DERIVATIVES[1]

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Abstract—7-Acylaminocephalosporanic acid derivatives (**1**) were converted into 7-acylamino-3-methylenecepham-4-carboxylic acids (**2**) by treatment with chromium(II) salts in aqueous media. The esters (**4a** or **4b**) of 7-acylamino-3-methylenecepham compounds were readily isomerized to the 3-methyl-3-cephem compounds (**5a** or **5b**) under basic conditions. The reaction mechanism is discussed.

Cephalosporins have several points where modification of substituents might produce improved biological activity. Among these the 3-position with chemical reactivity inherent to the 3-cephem structure has presented a major challenge. Chromium(II) salts can be used for reduction of various compounds, for example, alkyl halides are reduced to alkanes[2] and allyl halides to terminal olefins[3] under mild conditions. Since the 3-acetoxymethyl group of cephalosporanic acids in aqueous media shows a behaviour similar to alkyl halide in nucleophilic displacement reactions,[4] it was anticipated that the reaction of cephalosporanic acids with chromium(II) salts may give 3-desacetoxycephalospornic acids or 3-methylenecepham compounds.

RESULTS AND DISCUSSION

Determination of the products. Treatment of sodium 7-(2-thienylacetamido)cephalosporanate (**1a**) with chromium(II) acetate[5] in aqueous acetone under an atmosphere of N_2 followed by chromatographic purification on Amberlite XAD-2 afforded two components. The minor component was sodium 7 - (2 - thienylacetamido) - 3 - methyl - 3 - cephem - 4 - carboxylate (**3a**) which was identified with an authentic sample[6] by comparison of NMR and IR spectra. The major component did not show the UV absorption at 260 nm associated with the 3-cephem chromophore in cephalosporanic acid. The NMR spectrum of the major component in D_2O showed a broad doublet at 5·42 ppm for the vinyl protons and a singlet at 5·16 ppm for one proton, and no absorption due to the $-CH_2OAc$ group. Its IR spectrum showed the absorptions of β-lactam at 1761 cm^{-1} and terminal olefin at 910 cm^{-1}. In view of these results, sodium 7 - (2 - thienylacetamido) - 3 - methylenecepham - 4 - carboxylate (**2a**)†‡ was assigned to the major component. The 3-methylenecepham compound, a new class of cephalosporins, has thus been first isolated, although it had been proposed as a possible product in the discussion of the mechanism of the conversion of penicillin sulphoxides to desacetoxycephalosporins.[12]

Treatment of **2a** with diazomethane gave the methyl ester (**4a**). Figure 1 shows the mass spectrum of **4a**. The elemental composition of the principal peaks was obtained from the high resolution mass spectrum (Table 4) and a possible fragmentation pathway of **4a** is depicted (Scheme 1). The fragmentation pathway of **4a** shows the typical fragmentations observed with other cephalosporins.[13] The molecular formula, $C_{15}H_{16}N_2O_4S_2$, was confirmed by the parent peak at *m/e* 352·0534 and the typical β-lactam type fragmentation at *m/e* 172 was observed as the base peak. The fragment at *m/e* 293 arises from a loss of $COOCH_3$ and then expels carbon monoxide to form the fragment at *m/e* 265. These fragmentation patterns support the assigned structure of **4a**.

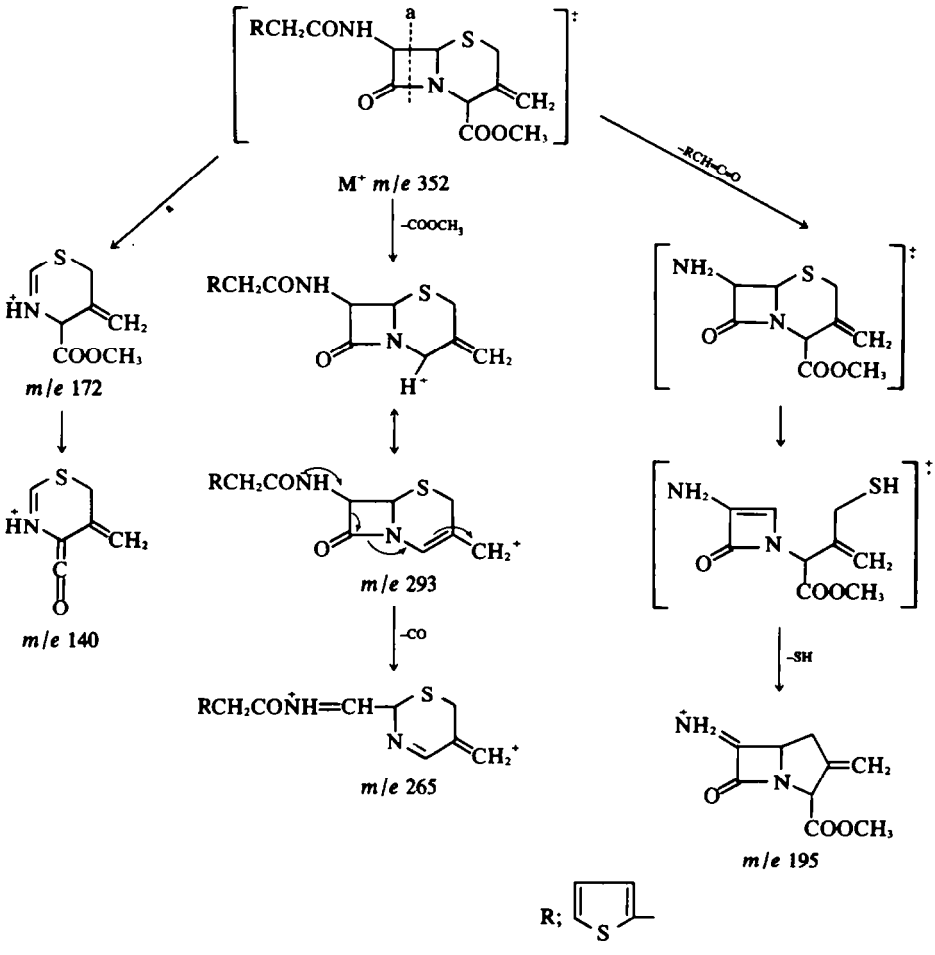
Scope and limitation. In an attempt to optimize the yield of **2a**, the reductions were carried out under various conditions as recorded in Table 5.

Chromium(II) chloride[14] and sulphate[15] appear to be less suitable reagents for the present reduction. The reduction did not occur in non-aqueous media, and in all cases two molar equivalents of chromium(II) salt appear to be necessary for giving **2a** in reasonable yields. Homogeneous reduction using aqueous-DMF or -DMSO as solvent gave better yields than that obtained in aqueous acetone. From these results the Method B is pertinent to the present reduction.

A variety of cephalosporanic acid derivatives, **1b**, **1c**, **1d**[16] and **1e**, which have various substituted Me groups at the 3-position with the same 7-acylamino group, were also reduced to **2a** by the Method B in yields of 20·1, 27·0, 40·1 and 10·5%, respectively. The treatment of the methyl

†3-Methylenecepham derivatives were also obtained by the electrochemical reduction.[7] After our preliminary communication[1], R. R. Chauvette *et al.*[8] reported the preparation of 3-methylenecepham derivatives by the Raney nickel or zinc-formic acid reduction of cephalosporanic acids in which the acetoxy group is displaced by sulphur nucleophile.

‡The stereochemistry of 4-carboxy group was determined to be α-configuration.[9,10] The same stereochemistry was later reported.[11]



SCHEME 1.

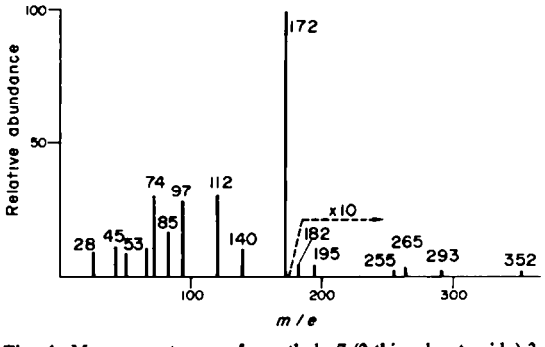


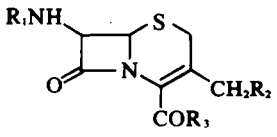
Fig 1. Mass spectrum of methyl 7-(2-thienylacetamido)-3-methylenecepham-4-carboxylate (4a)

ester (1f) by the Method B, however, resulted in the recovery of the starting material.

To investigate the influence of 7-acyl side chains upon the chromium(II) reduction, compounds 1g–1l were treated by the Method B. 1g, 1h, 1j and 1l were reduced to the corresponding 3-methylenecepham derivatives, 2g (23·1%), 2h (44·1%), 2j (35·3%) and 2l (40·8%), respectively. However, 1i and 1k containing free amino group failed to give the corresponding 3-methylenecepham compounds due perhaps to preferential complexation[17] of the amino group with chromium(II) ion. The corresponding 3-methylenecepham derivatives, 2i and 2k, were obtained by removal of methylsulphonylethoxycarbonyl group[18] of 2j and 2l with sodium hydroxide.

Consideration on the reaction mechanism. The reduction of cephalosporanic acid with chromium(II) salt was observed only in aqueous media, while the methyl ester (1f) was indifferent to the reduction. These results led to a suggestion that the initial step is the formation of allyl cation (6) which is entirely analogous to the process elaborately described by Cocker *et al.*[4] for the displacement of 3-acetoxy group by nucleophiles. By analogy to the mechanism proposed[3] for the reduction of allyl halide to olefin, a possible mechanistic interpretation of the present reaction is given (Scheme 2): The allyl cation (6) is then reduced by chromium(II) ion to form a radical species (7) followed by the formation of a complex (8) with another chromium(II) ion. The subsequent pro-

Table 1. Cephalosporanic acid derivatives (1)



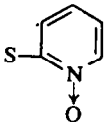
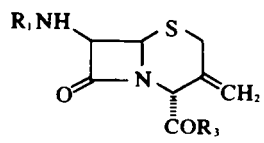
	R_1	R_2	R_3
1a		$OCOCH_3$	ONa
1b		$SCOCH_3$	ONa
1c		$SCOC_6H_5$	ONa
1d			ONa
1e			O^-
1f		$OCOCH_3$	OCH_3
1g	$C_6H_5CH_2CO$	$OCOCH_3$	ONa
1h	$C_6H_5OCH_2CO$	$OCOCH_3$	ONa
1i	H	$OCOCH_3$	ONa
1j	$CH_3SO_2CH_2CH_2OCO$	$OCOCH_3$	ONa
1k	C_6H_5CHCO | NH_2	$OCOCH_3$	ONa
1l	C_6H_5CHCO | $NHCOOCH_2CH_2SO_2CH_3$	$OCOCH_3$	ONa

Table 2. 3-Methylenecepham derivatives (2 and 4)



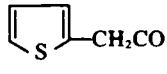
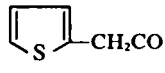
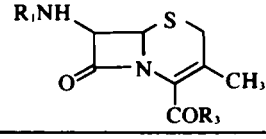
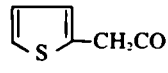
	R_1	R_3
2a		ONa
2g	$C_6H_5CH_2CO$	ONa
2h	$C_6H_5OCH_2CO$	ONa
2i	H	OH
2j	$CH_3SO_2CH_2CH_2OCO$	ONa
2k	C_6H_5CHCO | NH_2	ONa
2l	C_6H_5CHCO | $NHCOOCH_2CH_2SO_2CH_3$	ONa
4a		OCH_3
4b		$OSi(CH_3)_3$
4c		OH

Table 3. 3-Methyl-3-cephem derivatives (3 and 5)



	R_1	R_3
3a		ONa
5a		OCH_3
5b		$OSi(CH_3)_3$
5c		OH

tonolysis of this intermediate affords, *via* **9** or **11**, the 3 - methylenecepham (**10**) or 3 - methyl - 3 - cephem (**12**) derivatives. The predominant formation of 3-methylenecepham derivatives may be reasonably explained as follows: Castro *et al.*[3] reported that the nature of the olefinic product obtained in the reduction of allyl halide by chromium(II) ion is controlled by the stability of an intermediate olefin-chromium complex. Taking into consideration that the stability of the relevant transition metal-olefin complexes is in the order of terminal olefin ≫ *cis* olefin > *trans* olefin,[19] the complex (**9**) may be more stable than **11**.

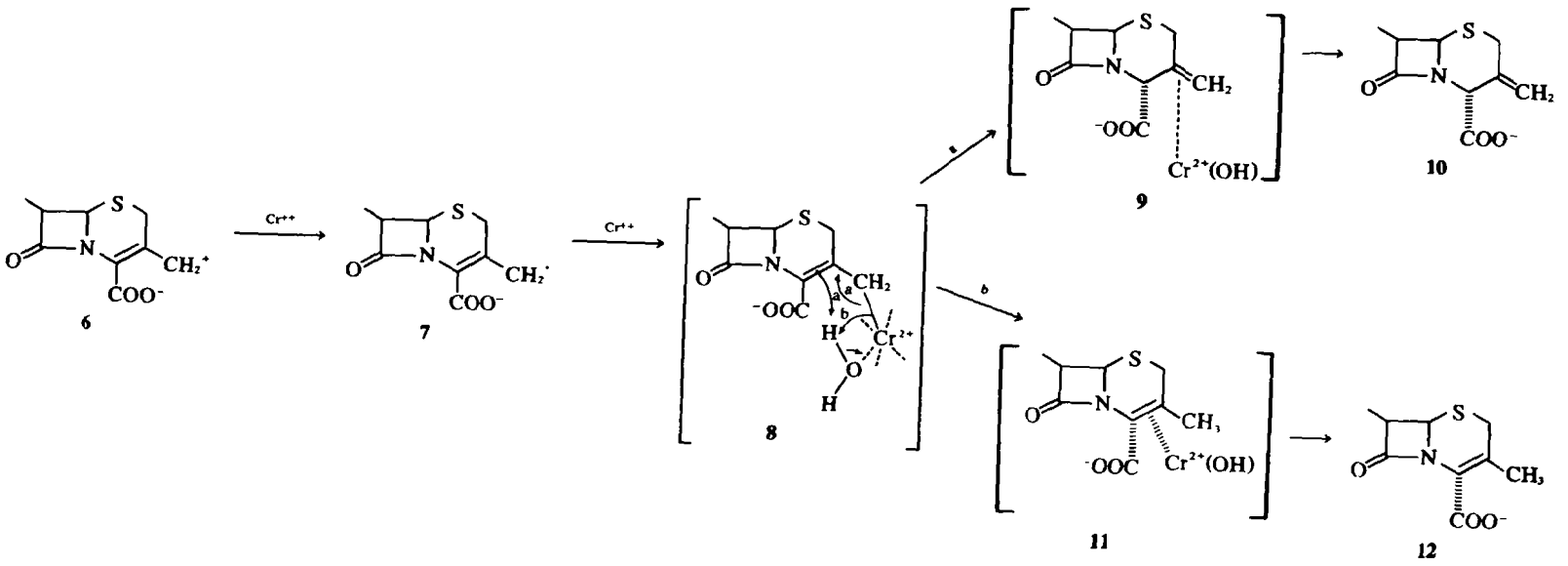
The stereochemistry at the 4-position (α-COOH) of the 3-methylenecepham derivatives may be caused by the steric factors of the whole molecule.

Isomerization of 3-methylenecepham derivatives to 3-methyl-3-cephem derivatives. Isomerization of 7 - (2 - thienylacetamido) - 3 - methylenecepham derivatives (**4**) was carried out under various conditions as shown in Table 6. Isomerization of the esters (**4a** and **4b**) to **5a** and **5b**, respectively, occurred readily in the presence of base such as pyridine and triethylamine, or silica gel (Merck, 0·08 mm) but did not occur in the presence of N,N-dimethylaniline. An attempt to isomerize 7 - (2 - thienylacetamido) - 3 - methylenecepham - 4 - carboxylic acid (**4c**) to **5c** was unsuccessful.

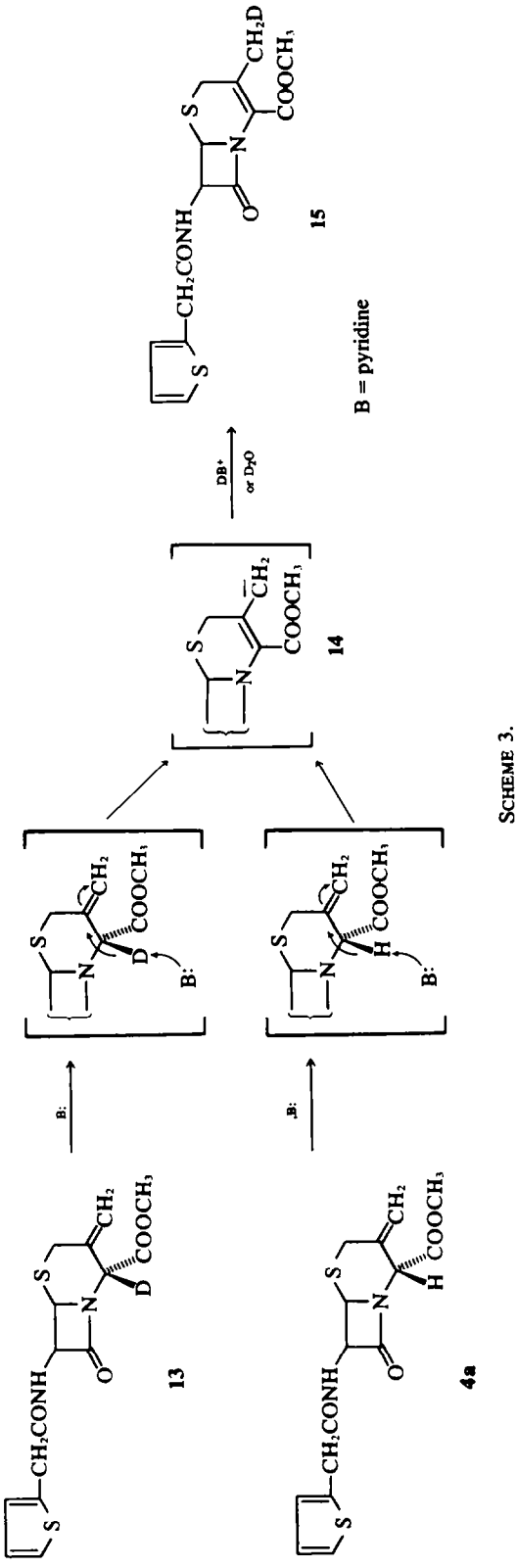
Table 4. High resolution mass spectrum of **4a**

m/e (Obsd.)	Analysis	error[a]
352·0534	$C_{15}H_{16}N_2O_4S_2$	−1·7
293·0447	$C_{13}H_{13}N_2O_2S_2$	−1·1
265·0456	$C_{12}H_{13}N_2OS_2$	−1·2
195·0816	$C_9H_{11}N_2O_3$	+4·7
172·0455	$C_7H_{10}NO_2S$	+2·2
140·0199	C_6H_6NOS	+2·9

[a](obsd. *m/e*−calcd. *m/e*) × 10^3.



SCHEME 2.



SCHEME 3.

Table 5. Reduction of **1a** with chromium(II) salts

Method	Chromium(II) salt	Mol. ratio[a]	Solvent	Time (hr)	Temp	Product (%)
A	$Cr(OAc)_2$	2·5	H_2O-acetone	24	50–60°	**2a** (9), **3a** (1)
B	$Cr(OAc)_2$	2·5	H_2O-DMSO or H_2O-DMF	24	r.t.	**2a** (45), **3a**(2-3)
C	$Cr(OAc)_2$	1	H_2O-DMSO	24	r.t.	**1a** (40)[b], **2a** (7)
D	$CrCl_2$ or $CrSO_4$	large excess	H_2O-DMSO	24	r.t.	**2a** (7-10), **3a** (2-3)
E	$Cr(OAc)_2$	2·5	DMSO	24	r.t.	**1a** (62)[b]

[a] Molar ratio of chromium(II) salt to **1a**.
[b] Starting material recovered unchanged.

Table 6. Isomerization of **4** to **5**

Compound	Method	Solvent and Catalyst	Time (hr)	Product (%)
4a	A	C_5H_5N	24	**5a** (100), ——
4a	B	C_5H_5N:$CDCl_3$ (1:1)	24	**5a** (40), **4a** (60)
4a	C	$CHCl_3$-silica gel	48	**5a** (42), **4a** (58)
4a	D	Et_3N:$CDCl_3$ (1:1)	24	**5a** (100),——
4a	E	Me_2NPh	24	——, **4a** (100)
4b	F	C_5D_5N	24	**5b** (100), ——
4c	G	C_5H_5N	24	——, **4c** (100)

The deuteriated 3-methylenecepham derivative (**13**) was obtained by the treatment of **1a** with chromium(II) acetate in D_2O, followed by treatment with diazomethane. NMR spectrum of **13** revealed that the deuterium was incorporated at 4β-position, since the singlet of **4a** at 5·01 ppm had disappeared. High resolution mass spectrum showed a molecular ion at *m/e* 353·0636 corresponding to formula $C_{15}H_{15}DN_2O_4S_2$ (Calcd. M^+ *m/e* 353·0629). Compound **13** was isomerized in pyridine to the deuteriated 3 - methyl - 3 - cephem compound (**15**). The isomerization possibly proceeds through an intermediate formation of **14**. Compound **15** was also obtained when **4a** was treated with pyridine containing a small amount of D_2O. The isomerization in this case may also proceed through the intermediate (**14**) as depicted in Scheme 3. The structure of **15** in which the deuterium is incorporated at 3-methyl group was verified by the spectroscopy. The mass spectrum confirmed the molecular formula, $C_{15}H_{15}DN_2O_4S_2$. The NMR spectrum showed that the integration of the singlet for 3-methyl group of **15** had diminished to 2/3 compared with that of **5a**.

3-Methylenecepham compounds (**2**) have no significant antibacterial activity. However, the chromium(II) reduction of cephalosporanic acids followed by the isomerization of **2** to 3 - methyl - 3 - cephem compounds (**3**) adds a new route to 3 - methyl - 3 - cephem compounds from cephalosporanic acids.

EXPERIMENTAL

M. ps are uncorrected. NMR spectra were recorded on a Varian HA-100 spectrometer. The chemical shifts are reported in ppm from TMS as an internal standard in $CDCl_3$ soln, or an external standard in D_2O. IR spectra were recorded on a Hitachi Type 215 spectrophotometer; mass spectra on a Hitachi RMU-6D spectrometer.

Reduction of cephalosporanic acids with chromium(II) salts

Method A. To a soln of **1a** (1·254 g) in 50% aqueous acetone (20 ml) was added chromium(II) acetate (1·359 g) and the mixture was stirred at 50–60° for 24 hr under N_2. After evaporation of acetone under reduced pressure, the soln was neutralized with $NaHCO_3$. Purification by column chromatography on Amberlite XAD-2 eluted with water gave 3-*methylenecepham compound* (**2a**, 99 mg) and 3 - methyl - 3 - cephem compound (**3a**, 10 mg).

Method B. To a soln of **1a** (1·254 g) in 50% aqueous DMF (20 ml) was added chromium(II) acetate (1·359 g) and the mixture was stirred at room temp for 24 hr under N_2. The mixture was poured into ice-water and brought to pH 2·0 with 1N HCl and extracted with EtOAc. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo*. The ratio of **2a** and **3a** was calculated on the basis of NMR spectrum of the residue (Table 5). For further purification, the residue was dissolved in a mixture of 5 ml of THF and 1·5 ml of 2N sodium 2-ethylhexanoate in isopropanol. The addition of 100 ml of ether caused precipitation of 480 mg of 3-*methylenecepham compound* (**2a**).

Methods C–E were carried out by a similar procedure. Analysis and physical data of 3-*methylenecepham derivatives* (**2a**, **2g**, **2h**, **2j**, and **21**) are summarized in Table 7.

Table 7. Analysis and physical data of 3-methylenecepham derivatives (2)

Compound	m.p. (°C)	ν_{max}(KBr) cm^{-1}	NMR(ppm, 100 MHz, D_2O)	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	175–177*	1761, 910	3·66(2H, q, 2-CH_2), 4·10(2H, s, CH_2CO), 5·16 (1H, s, 4-CH), 5·42(2H, d, C=CH_2), 5·59(2H, q, 6-CH and 7-CH), 7·17–7·60(3H, m, thiophene).	$C_{14}H_{13}N_2O_4S_2Na\cdot\frac{1}{2}H_2O$	45·52 (45·36	4·36 4·04	7·58 7·41)
2g	220–222	1740, 910	3·50(2H, q, 2-CH_2), 3·86(2H, s, CH_2CO), 5·14 (1H, s, 4-CH), 5·41(2H, d, C=CH_2), 5·55(2H, q, 6-CH and 7-CH), 7·54(5H, s, C_6H_5).	$C_{16}H_{15}N_2O_4SNa\cdot\frac{3}{2}H_2O$	48·12 (48·10	5·05 4·54	7·01 6·53)
2h	208–212	1745, 910	3·62(2H, q, 2-CH_2), 5·23(1H, s, 4-CH), 5·60(2H, q, 6-CH and 7-CH), 5·81(2H, d, C=CH_2), 7·08–7·64(5H, m, C_6H_5).	$C_{16}H_{15}N_2O_5SNa\cdot2H_2O$	47·29 (47·56	4·71 4·10	6·89 6·69)
2j	165–167	1750, 910	3·36(3H, s, CH_3), 3·68(2H, q, 2-CH_2), 3·82 and 4·76(4H, two ts, $SO_2CH_2CH_2O$), 5·14(1H, s, 4-CH), 5·43(2H, d, C=CH_2), 5·54(2H, q, 6-CH and 7-CH).	$C_{12}H_{15}N_2O_7S_2Na\cdot H_2O$	35·64 (35·62	4·23 4·35	6·92 6·94)
2l	179–181	1740, 910	3·32(3H, s, CH_3), 3·56(2H, q, 2-CH_2), 3·77 and 4·72(4H, two ts, $SO_2CH_2CH_2O$), 5·11(1H, s, 4-CH), 5·38(2H, s, C=CH_2), 5·47(1H, s, CHCO), 5·59(2H, q, 6-CH and 7-CH), 7·61(5H, s, C_6H_5).	$C_{20}H_{22}N_3O_8S_2Na\cdot H_2O$	44·68 (44·41	4·50 4·03	7·81 7·65)

*The melting point recorded in the communication[1] should be revised.

Methyl 7-(2-thienylacetamido)-3-methylenecepham-4-carboxylate (**4a**)

A soln of **2a** (1·00 g) in water (20 ml) was brought to pH 2·0 with 5% HCl and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). To the extract was added a soln of diazomethane in ether and left standing at room temp for 15 min. The solvent was removed and the residue was recrystallized from ether to give 940 mg (92%) of the *methyl ester* (**4a**), m.p. 77–78° (Found: C, 51·38; H, 4·34; N, 7·92. $C_{14}H_{14}N_2O_4S_2$ requires: C, 51·12; H, 4·57; N, 7·94%), ν_{max} (KBr): 1765 (β-lactam) and 910 cm^{-1} (C=CH_2), NMR($CDCl_3$): 3·49 (2H, q, 2-CH_2), 3·72 (3H, s, $COOCH_3$), 3·78 (2H, s, CH_2CO), 5·01 (1H, s, 4-CH), 5·17 (2H, s, C=CH_2), 5·32 (1H, d, 6-CH), 5·60 (1H, d of d, 7-CH), 6·45 (1H, d, NH) and 6·80–7·20 (3H, m, thiophene).

7-Amino-3-methylenecepham-5-carboxylic acid (**2i**)

To a soln of **2j** (200 mg) was added a soln of NaOH (23 mg) in water (0·5 ml). After stirring for 20 min, the soln was acidified to pH 1·5 with 5% HCl and then neutralized with $NaHCO_3$ and lyophilized. The residue was dissolved in water (1 ml) and the soln was brought to pH 3·5 with 5% HCl and left overnight at 5°. The resulting ppt was collected and dried to give 11 mg (9·9%) of **2i** which was identified with an authentic sample[7] by comparison of IR and NMR spectra

Sodium 7-(D-2-amino-2-phenylacetamide)-3-methylenecepham-4-carboxylate (**2k**)

To a soln of **2l** (519 mg) in water (10 ml) was added 1·1 ml of INNaOH and the mixture was stirred for 10 min. The soln was brought to pH 1·5 and neutralized with 5% NaOH. The resulting neutral soln was purified by column chromatography on Amberlite XAD-2 eluted with water to give 130 mg (35·2%) of **2k**. The latter (**2k**) was identified with an authentic sample[7] by comparison of IR and NMR spectra.

Isomerization of **4** *to* **5**

Method A. **4a** (30 mg) was dissolved in pyridine (0·4 ml) and the mixture was left standing at room temp for 24 hr. The mixture was poured into water and extracted with chloroform. The organic layer was washed with 5% HCl and dried ($MgSO_4$). Evaporation of the solvent gave **5a** (30 mg).

Methods B, D, E and G were carried out by a similar procedure.

Method C. A soln of **4a** (50 mg) in chloroform (2 ml) was absorbed on silica gel (5 g, Merck, 0·08 mm) and left standing for 2 days. Elution with chloroform gave an oily substance (50 mg). NMR spectrum of the oil showed that it is a mixture of **5a** and **4a** (42:58).

Method F. To a soln of **4c** (30 mg) in d_5-pyridine (0·4 ml) was added trimethylsilyl chloride (14 mg) and the mixture was left standing at room temp for 24 hr. Comparison of the NMR spectrum of the mixture with that of a mixture of **5c** (30 mg), trimethylsilyl chloride (14 mg) and d_5-pyridine (0·4 ml) indicated quantitative isomerization of **4c** to **5c**.

Methyl 7-(2-thienylacetamido)-3-methylenecepham-4β-deuterio-4α-carboxylate (**13**)

To a soln of **1a** (418 mg) in a mixture of D_2O (5 ml) and DMSO (5 ml) was added chromium(II) acetate (450 mg) under N_2 at room temp and the mixture was stirred for 24 hr. The mixture was poured into ice-water and brought to pH 2·0 with 1N HCl and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$), and evaporated. The residual oil was esterified with diazomethane in ether followed by chromatographic purification on silica gel to give **13** (85 mg, 24%), which contained more than 0·90 g atom deuterium per mole (NMR spectroscopy).

Methyl 7-(2-thienylacetamido)-3-monodeuteriomethyl-3-cephem-4-carboxylate (**15**)

(a) *From methyl 7-(2-thienylacetamido)-3-methylenecepham-4β-deuterio-4α-carboxylate* (**13**). **13** (30 mg) was dissolved in pyridine (0·4 ml) and the mixture was left standing at room temp for 24 hr. The mixture was poured into water and extracted with chloroform. The extract was washed with 5% HCl and dried ($MgSO_4$). Evaporation of the solvent gave **15** (30 mg), m. p. 193–197° [Found: M^+, 353·0619 (mass spectrum). $C_{15}H_{15}DN_2O_4S_2$ requires: M^+, 353·0629]. NMR ($CDCl_3$): 2·10 (2H,

s, CH_2D), 3·28 (2H, q, 2-CH_2), 3·69 (3H, s, $COOCH_3$), 4·01 (2H, s, CH_2CO), 5·10(1H, d, 6-CH), 5·70 (1H, d of d, 7-CH), 6·52 (1H, d, NH), and 6·9–7·3 (3H, m, thiophene).

(b) *From methyl* 7 - (2 - *thienylacetamido*) - 3 - *methylenecepham* - 4 - *carboxylate* (**4a**). **4a** (30 mg) was dissolved in pyridine (0·4 ml) containing D_2O (50 mg). After 24 h, the mixture was poured into water, extracted with chloroform and washed with 5% HCl and water, and dried ($MgSO_4$). Evaporation of the solvent afforded **15** (25 mg, 83%) which contained more than 0·74 g atom deuterium per mole (NMR spectroscopy).

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