COMMUNICATIONS

- New or improved synthetic methods
- Key intermediates
- with full experimental and analytical data

A New Approach to the "Cephem" System; Synthesis of 3-Acetyl-7,7-dimethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-2-octene

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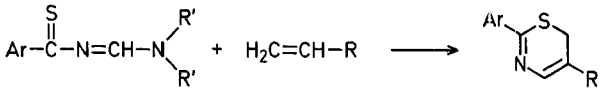
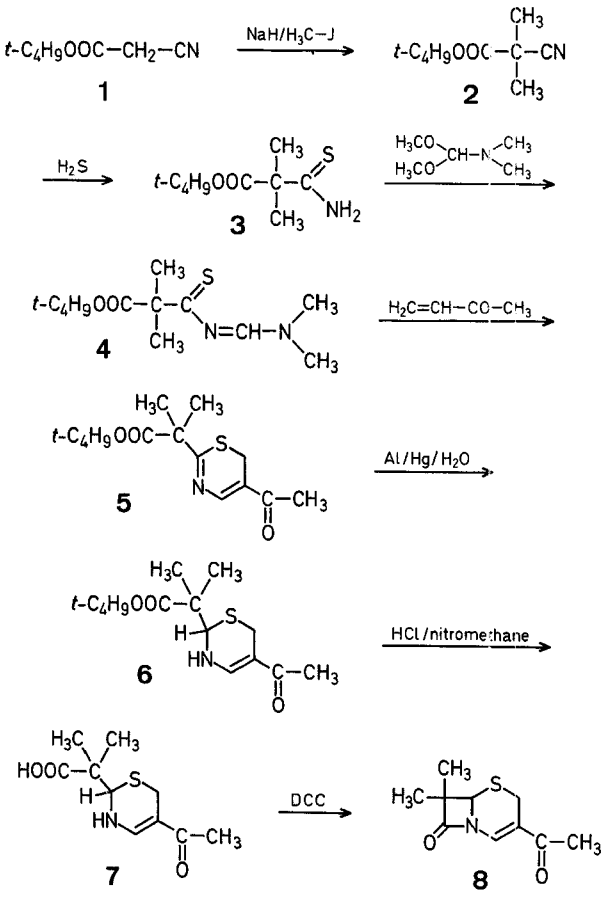
Several publications[1,2,3] have dealt with the synthesis of cephalosporins lactonized or lactamized in the 3,4 positions from 3,6-dihydro-2*H*-1,3-thiazines suitably substituted in position 2.

Recent work carried out in the laboratory[4] has shown that *N'*-thioaroylformamidines react with various dienophiles to give 6*H*-1,3-thiazines.



Following the studies reported in Ref.[5,6], we showed[7] that the C=N double bond of acetyl-1,3-thiazines may be selectively reduced using aluminum amalgam; the two other reducible centers in the system C=S C=N C=C C(CH$_3$)=O remain unaffected. We report here that a suitably substituted 5-acetyl-3,6-dihydro-2*H*-1,3-thiazine obtained in this manner can be cyclized to give 3-acetyl-7,7-dimethylcephem (**8**).



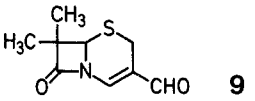
In the reaction sequence **1**→**8**, the carboxy group required for cyclization to lactam **8** is introduced in the form of its *t*-butyl ester which can be easily cleaved.

The two methyl groups in position α with respect to the thiocarbonyl group in **3** prevent another possible condensation reaction at C-α in the reaction of **3** with dimethylformamide dimethylacetal to give the formamidine derivative **4**. Further, the absence of reactive hydrogen at C-α precludes the formation of a 3,6-dihydro-2*H*-1,3-thiazine in place of the desired 6*H*-1,3-thiazine **5** in the reaction of **4** with butenone.

The selective reduction of the exocyclic double bond in 2-alkylidene-3,6-dihydro-2*H*-1,3-thiazines is, in fact, still an unsolved problem.

The last two steps of the sequence (**6**→**7**→**8**) were performed following the method of Ref.[1,2,3] which is based on Ref.[10]: cleavage of the *t*-butyl ester group of **6** with dry hydrogen chloride followed by cyclization of the β-amino acid **7** using dicyclohexylcarbodiimide.

The analogous preparation of the formyl derivative **9**



is still faced with the difficulty of selectively reducing the C=N double bond in the formyl derivative corresponding to **5**.

It should be mentioned that unsubstituted and monosubstituted cephems have earlier been obtained by a different route[8]: dehydration of 4-hydroxycephems which are, in turn, prepared from 2-oxoazetidines and 3-mercaptopropanals or 3-mercaptopropanones.

t-Butyl 2-Cyano-2-methylpropanoate (2):
Prepared following a similar method to that described in Ref.[9] by twofold methylation of *t*-butyl cyanoacetate; yield: 60%; b.p. 82 °C/20 torr.

t-Butyl 3-Amino-2,2-dimethyl-3-thioxopropanoate (3):
Hydrogen sulfide is bubbled through a solution of *t*-butyl 2-cyano-2-methylpropanoate (**2**; 12.50 g, 74 mmol) in triethylamine/pyridine (1/1; 160 ml). After 70 h, the solvents are evaporated. The residue is dissolved in benzene and chromatographed on a column of neutral alumina using ether as eluent; quantitative yield; m.p. 119 °C (from ethyl acetate/ligroin).

$C_9H_{17}NO_2S$	calc.	C 53.17	H 8.43	S 15.77
(203.3)	found	52.97	8.35	15.88

M.S.: $m/e = 203$ (M^+).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.48$ (s, 9H); 1.50 (s, 3H); 1.56 (s, 3H); 8.20 ppm (s, 2H).

t-Butyl 2,2-Dimethyl-3-(dimethylaminomethylene)-3-thioxopropanoate (4):
A mixture of compound **3** (4.07 g, 20 mmol) and dimethylformamide dimethyl acetal (2.38 g, 20 mmol) is stirred for 2 h at room tem-

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perature. The methanol which forms is evaporated and the residue dissolved in benzene. This solution is column-chromatographed on silica gel using ether as eluent to give **4** as a yellow oil; quantitative yield.

$C_{12}H_{22}N_2O_2S$	calc.	C 55.78	H 8.58	S 12.41
(258.4)	found	55.58	8.49	12.46

M.S.: *m/e* (relative intensity) = 258 (M^+, 4), 115 (100).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.40$ (s, 3H); 1.42 (s, 9H); 1.45 (s, 3H); 3.10 (s, 3H); 3.20 (s, 3H); 8.43 ppm (s, 1H).

t-Butyl 2-(5-Acetyl-6*H*-1,3-thiazin-2-yl)-2-methylpropanoate (5):
Butenone (0.435 g, 62 mmol) is added to a solution of compound **4** (1.60 g, 6.2 mmol) in benzene (15 ml) containing a trace of hydroquinone, the mixture is heated to reflux for 12 h, and then evaporated to dryness. The residue is dissolved in benzene (10 ml) and column-chromatographed on neutral alumina using benzene/ether (95/5) as eluent to give **5** as yellow oil; yield: 1.4 g (80%).

$C_{14}H_{21}NO_3S$	calc.	C 59.33	H 7.47
(283.4)	found	59.56	7.70

M.S.: *m/e* = 283 (M^+).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.47$ (s, 15H); 2.37 (s, 3H); 3.50 (s, 2H); 7.75 ppm (s, 1H).

t-Butyl 2-(5-Acetyl-3,6-dihydro-2*H*-1,3-thiazin-2-yl)-2-methylpropanoate (6):
Strips of aluminum (351 mg, 13 mmol) are covered with a 5% aqueous solution of mercury(II) chloride. After a few minutes, the supernatant liquid is discarded and the amalgam washed twice with water. A solution of compound **5** (920 mg, ~3.25 mmol) in ethanol (20 ml) is added to the amalgam and the mixture is stirred for 12 h at room temperature. The aluminum hydroxide formed is filtered off. The filtrate is evaporated, the residue dissolved in ether, and column-chromatographed on silica gel using ether as eluent to give **6** as a colorless oil; yield: 611 mg (66%).

Microanalysis is not reliable in this case since compound **6** completely decomposes within one week at room temperature. However, T.L.C. on silica gel plates (eluent: ether) shows only one spot (iodine vapors).

$C_{14}H_{23}NO_3S$ (285.3)

M.S.: *m/e* (relative intensity) = 285 (M^+, 6), 142 (100).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.30$ (s, 3H); 1.38 (s, 3H); 1.48 (s, 9H); 2.20 (s, 3H); 3.40, 3.66 (2d, 2H, S—CH_2, $J = 18$ Hz); 4.45 (d, 1H, S—CH—N; $J = 3$ Hz); 5.88 (2d, 1H, N—H, $J = 3$ Hz, 6.5 Hz); 7.55 ppm (d, 1H, $J = 6.5$ Hz).

2-(5-Acetyl-3,6-dihydro-2*H*-1,3-thiazin-2-yl)-2-methylpropanoic Acid (7):
Dry hydrogen chloride is bubbled through a solution of compound **6** (941 mg, 3.3 mmol) in dry nitromethane (30 ml) at 0 °C. After 30 min, the solvent is evaporated at 40 °C to give **7** as an unstable colorless oil; yield: 680 mg (90%).

[Due to the insolubility and instability of compound **7** we were not able to obtain microanalytical data or an N.M.R. spectrum].

$C_{10}H_{15}NO_3S$ (229.2)

M.S.: *m/e* (relative intensity) = 229 (M^+, 10), 142 (100).

3-Acetyl-7,7-dimethylcephem (3-Acetyl-7,7-dimethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-2-octene) (8):
Dicyclohexylcarbodiimide (728 mg, 3.3 mmol) is added to a suspension of compound **7** (756 mg, 3.3 mmol) in nitromethane/dichloromethane (1/1; 110 ml) under nitrogen and the mixture is stirred for 3 days at room temperature. The dicyclohexylurea is then filtered off, the filtrate is evaporated and the residue taken up twice in boiling benzene. The solution is column-chromatographed on silica gel using benzene/ether (95/5) as eluent to give **8** as a pale-yellow oil; yield: 397 mg (57%).

$C_{10}H_{13}NO_2S$	calc.	C 56.84	H 6.20
(211.3)	found	57.02	6.47

M.S.: *m/e* (relative intensity) = 211 (M^+, 35), 183 (8), 168 (12), 142 (39), 70 (100).

I.R.: $\nu = 1780$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.36$ (s, 3H); 1.51 (s, 3H); 2.29 (s, 3H); 3.23 (2d, 1H, $J = 17$ Hz, 2 Hz); 3.97 (d, 1H, $J = 17$ Hz); 4.67 (s, 1H, S—CH—N); 7.70 ppm (d, 1H, $J = 2$ Hz, N—CH=).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 16.3$ (7-CH_3, $J_{^{13}C\ H} = 129.0$ Hz); 22.1 (7-CH_3, $J_{^{13}C\ H} = 128.0$ Hz); 23.5 (C-4, $J_{^{13}C\ H} = 143.0$ Hz); 24.5 (CO—CH_3, $J_{^{13}C\ H} = 128.0$ Hz); 56.9 (C-7); 63.9 (C-6, $J_{^{13}C\ H} = 169.0$ Hz); 119.0 (C-3); 130.8 (C-2, $J_{^{13}C\ H} = 179.0$ Hz); 170.3 (C-8); 194.6 ppm (CO—CH_3).

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[1] R. Heymès, G. Amiard, G. Nominé, *C. R. Acad. Sci.* **263**, 170 (1966).
[2] R. Heymès, G. Amiard, G. Nominé, *Bull. Soc. Chim. Fr.* **1974**, 563.
[3] R. Heymès, J. Martel, G. Nominé, *Bull. Soc. Chim. Fr.* **1977**, 906.
[4] J. C. Meslin, H. Quiniou, *Bull. Soc. Chim. Fr.* **1979**, 347.
[5] G. C. Barrett, S. H. Eggers, T. R. Emerson, G. Lowe, *J. Chem. Soc.* **1964**, 788.
[6] D. M. Green, A. G. Long, P. J. May, A. F. Turner, *J. Chem. Soc.* **1964**, 766.
[7] G. Duguay et al., *J. Heterocycl. Chem.*, in press and unpublished results.
[8] H. W. Schnabel, D. Grimm, H. Jensen, *Justus Liebigs Ann. Chem.* **1973**, 477.
H. W. Schnabel, H. Jensen, *German Patent (DOS)* 2337447 (1975), Farbwerke Hoechst AG; *C. A.* **82**, 171006 (1975).
[9] S. O. Lawesson, E. H. Larsen, H. J. Jakobsen, *Arkiv Kemi* **23**, 453 (1965).
[10] J. C. Sheehan, K. R. Henery-Logan, *J. Am. Chem. Soc.* **84**, 2983 (1962).

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