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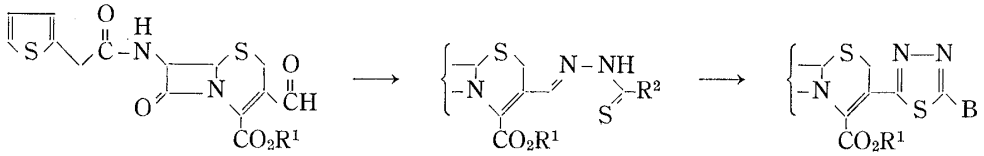
Synthesis of Cephalosporins with Substituted Thiadiazoles directly attached to the C_3-Position

Synthesis of cephalosporins with substituted thiadiazoles directly attached to the C_3-position starting from 3-formylceph-3-em derivative (**1**) is described. Thiocarbonylhydrazones of **1** were readily cyclized to the corresponding thiadiazole derivatives (**3**) by treating with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Keywords——1,3,4-thiadiazoles; oxidative ring closure; thiocarbonylhydrazines; thiocarbonylhydrazones; benzhydryl 7-thienylacetamido-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylates

In order to obtain modified cephalosporins with improved properties, many modifications at the C_3-position have been reported, and majority of them have a substituent linked to the C_3-position through a methylene group. Recently, new potent cephalosporins with a substituent such as methoxyl or halogeno group at the C_3-position have been reported.[1] Interesting properties of these compounds prompted us to synthesize cephalosporins bearing a heterocyclic ring directly attached to the C_3-position.[2] This paper deals with a new and efficient synthesis of ceph-3-ems (**3**) bearing a thiadiazole ring at the C_3-position by application of the oxidative ring closure reaction of thiocarbonylhydrazones (**2**) which were obtained from 3-formylceph-3-em derivative (**1**).

Treatment of 3-formylceph-3-em compound (**1**) with thiocarbonylhydrazines (1.2 mol equivalents) in dimethyl sulfoxide at room temperature gave the correspoding thiocarbonylhydrazones (**2**) in quantitative yields.



1

R^1 : $-CHPh_2$

2a : $R^2 = -NMe_2$
2b : $R^2 =$
2c : $R^2 = -Me$
2d : $R^2 = -Ph$
2e : $R^2 = -NH_2$
2f : $R^2 = -NHMe$

3a : $B = -NMe_2$
3b : $B =$ 
3c : $B = -Me$
3d : $B = -Ph$
3e : $B = -NHAc$
3f : $B =$ 
3g : $B = -NHMe$

Chart 1

Oxidative ring closure of **2** by the use of conventional reagents including $FeCl_3$ or peroxides[3] often led to side reactions. However, it has been found that thiocarbonylhydrazones (**2a**—**d**) were readily cyclized to the corresponding thiadiazole derivatives (**3a**—**d**) by treating with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane in high yields (Table

1) J. Elks (ed.), "Recent Advances in the Chemistry of β-lactam Antibiotics," The Chemical Society, London, Chapter 19, 1977.
2) *a*) R.A. Firestone, N.S. Maciejewicz, and B.G. Christensen, *J. Org. Chem.*, **39**, 3384 (1974); *b*) D.O. Spry, *ibid.*, **40**, 2411 (1975); *c*) J.L. Fahey, R.A. Firestone, and B.G. Christensen, *J. Med. Chem.*, **19**, 562 (1976).
3) S.C. De and S.K. Roy-chondhury, *J. Indian Chem. Soc.*, **5**, 269 (1928); P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **41**, 2058 (1958).

I). In the case of **2e** and **2f**, however, the thiadiazole derivatives were obtained in low yields by the direct treatment with DDQ. Therefore, they were led to the corresponding thiadiazole derivatives after acetylation. Compound **2e** was heated in Ac_2O–AcOH to yield two diacetates which were separated by silica gel chromatography and assigned the structures **4a** (45%), mp 211—214° and **4b** (51%), mp 173—176°, respectively.[4] Compound **4a**: NMR ($CDCl_3$ containing 5% DMSO-d_6) δ: 2.10 (3H, s), 2.20 (3H, s), 3.35 (2H, s, C_2–H), 4.95 (1H, d, J=5 Hz, C_6–H), 5.79 (1H, q, J=5 Hz and 8 Hz, C_7–H), 6.74 (1H, s, C_3–C<u>H</u>–S–). Compound **4b**: NMR ($CDCl_3$) δ: 2.11 (3H, s), 2.22 (3H, s), 3.24 and 3.47 (2H, ABq, J=18 Hz, C_2–H), 4.97 (1H, d, J=5 Hz, C_6–H), 5.70 (1H, q, J=5 Hz and 8 Hz, C_7–H). By treatment of **2f** in the same manner, the diacetate **5a** (37%) and monoacetate **5b** (51%) were isolated.[4] Compound **5a**: NMR ($CDCl_3$) δ: 2.24 (3H, s), 2.26 (3H, s), 3.36 (5H, s, C_2–H and –NHC<u>H</u>$_3$), 4.92 (1H, d, J=5 Hz, C_6–H), 5.83 (1H, q, J=5 Hz and 9 Hz, C_7–H), 6.98 (1H, s, C_3–C<u>H</u>–S–). Compound **5b**: NMR ($CDCl_3$) δ: 2.19 (3H, s), 2.84 (3H, d, J=5 Hz, –NHC<u>H</u>$_3$), 3.39 (2H, s, s, C_2–H), 4.48 (1H, q, J=5 Hz, –N<u>H</u>CH$_3$), 4.90 (1H, d, J=5 Hz, C_6–H), 5.79 (1H, q, J=5 Hz and 9 Hz, C_7–H), 7.03 (1H, s, C_3–C<u>H</u>–S–). The diacetates (**4a** and **4b**), upon treatment with DDQ in dioxane, gave the thiadiazole derivative **3e** (71—78%), and the diacetate (**5a**) gave **3f** (86%) by a similar reaction. On the other hand, the monoacetyl derivative (**5b**) gave **3f** (16%) and **3g** (52%), which were separated by chromatography. To explain the above results, the mechanism can be proposed as follows; the reaction of the diacetates (**4a** and **5a**) with DDQ would give the intermediates (**A**), which presumably undergo intramolecular acyl migration to form the products (**3e** and **3f**). L'abbé has reported the similar intramolecular tosyl migration of 2-benzylamino- and 2-anilino-5-phenyl-1,3,4-thiadiazoles.[5] On the other hand, the formation of **3f** from **5b** would result from the formation of **3g** and subsequent intermolecular migration of acetyl group from 2,3-dichloro-5,6-dicyanobenzoquinone diacetate. The reaction of **3g** with the hydroquinone acetate proceeded more slowly than that of **5a** with DDQ. Consequently, it is considered that in the reaction of **4a** or **5a** with DDQ intramolecular acyl migration takes place predominantly.

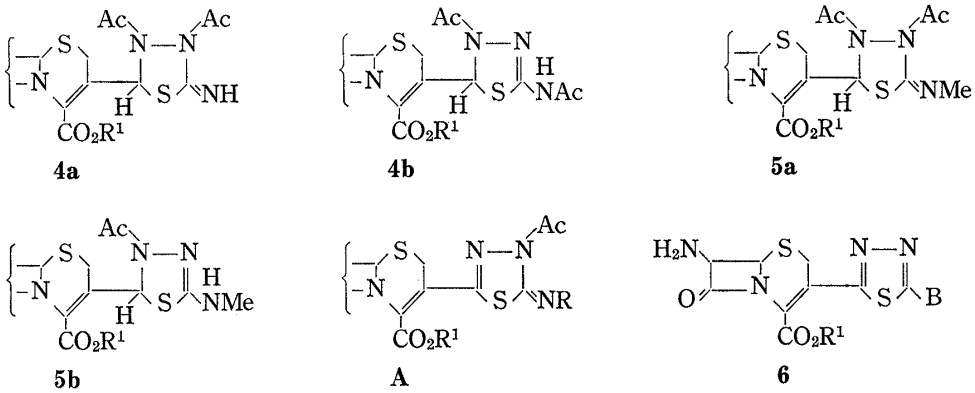


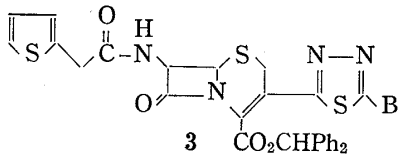
Chart **2**

Removal of the benzhydryl protecting group from **3** gave the corresponding free acids. The antibacterial activities of these compounds against gram-positive organisms were similar to that of cephalothin, but the activities against gram-negative organisms were superior to that of cephalothin.

4) Further details about the structure of acetates will be mentioned in a subsequent paper: Recently, Kubota *et al.* reported that the compounds obtained by the reaction of thiosemicarbazones with Ac_2O are 2-acetamido-4-acetyl-1,3,4-thiadiazolines and not N^4,S-diacetyl-thiosemicarbazones as thought previously. *cf*) S. Kubota, K. Fujikane, M. Uda, and T. Yoshioka, *Heterocycles*, **4**, 1907 (1976).

5) G. L'abbé, G. Verhelst, L. Huybrechts, and S. Toppet, *J. Heterocyclic Chem.*, **14**, 515 (1977).

TABLE I. Yields and Physical Constants of Benzhydryl 7-Thienylacetamido-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylates (3)



3 CO_2CHPh_2

Product (3) B	Yield (%)	mp (°C)	IR ν_{max}^{KBr} cm^{-1} β-lactam	NMR (DMSO-d_6, ppm) C_2–H[a]	C_6–H[b]	C_7–H[c]
$-NMe_2$	90	190—191	1785	3.78, 4.05	5.23	5.81
	91	209—211	1778	3.79, 4.03	5.23	5.83
–Me	93	192—194	1785	3.80, 4.04	5.26	5.84
–Ph	90	226—228	1790	3.97, 4.20	5.35	5.92
$-N\langle^{H}_{Ac}$	71—78	213—215	1790	3.82, 4.06	5.25	5.71
$-N\langle^{Me}_{Ac}$	81[d] 72	205—208	1782	3.86, 4.08	5.28	5.88
$-N\langle^{H}_{Me}$	9	130—133	1783	3.83, 4.03	5.26	5.84

a) ABq, J=18 Hz.
b) d, J=5 Hz.
c) q, J=5 Hz and 9 Hz.
d) Total yield without isolation of acetates (**5a** and **5b**).

The 7-thienylacetyl side chain of **3** was removed by the usual manner[6] to give the corresponding 7-amino derivatives (**6**), which were subsequently derived to various 7-acylated cephalosporins.

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6) E.H. Flynn (ed.), "Cephalosporins and Penicillins," Academic Press, New York and London, Chapter 2, 1972.