SYNTHESIS OF 7α-SUBSTITUTED CEPHALOSPORINS. V[4] NOVEL OXIDATION PROCEDURE FOR SYNTHESES OF 7α-METHOXYCEPHALOSPORINS AND 6α-METHOXYPENICILLINS

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Previously we presented novel syntheses of 7α-substituted cephalosporins which involved the oxidation of the SCHIFF base **I** with lead dioxide followed by treatment with various nucleophiles.[1~4] We have been investigating reagents other than lead dioxide for the oxidation of **I** and now wish to report a novel oxidation method which gives directly the 7α-methoxy SCHIFF bases **II** or **VI**, the important intermediates for the synthesis of potent 7α-methoxycephalosporins.[1,5]

Treatment of **I** with lithium methoxide (LiOMe) in THF-methanol at −78°C followed by addition of *tert*-butyl hypochlorite (*t*-BuOCl) afforded the 7α-methoxy SCHIFF base **II** in 61% yield. Halogenating reagents other than *t*-BuOCl were also successfully employed as reagents for the oxidation (Table 1).

Moderate yields were obtained with N-bromosuccimide (NBS), N-bromoacetamide (NBA) and N-chlorosuccimide (NCS), but only a 4% yield was obtained with bromine (Br_2). Higher reaction temperatures with *t*-BuOCl or NBA resulted in lower yields.

When **I** was treated initially with *t*-BuOCl and then with LiOMe, in a reverse addition sequence, only the 2-methoxy SCHIFF base **III*** was obtained in 48% yield.

Table 1. Yields of the 7α-methoxy SCHIFF base (**II**)

Halogenating reagent	Reaction temp. (°C)	Yield (%)
t-BuOCl	−78	61
t-BuOCl	3	43
NBS	−78	58
NBA	−78	58
NBA	−5	34
NCS	−78	34
Br_2	−78	4

The former procedure was applied successfully to the methoxylation of the SCHIFF base having an unprotected carboxyl group at the C–4 position. Thus the benzyltrimethylammonium salt of SCHIFF base **V**, which was prepared from 7β-amino-3-[[(1-methyl-1H-tetrazol-5-yl) thio]methyl]-3-cephem-4-carboxylic acid (**IV**) and 3, 5-di-*tert*-butyl-4-hydroxybenzaldehyde in the presence of benzyltrimethylammonium hydroxide in methanol, was converted to the corresponding 7α-methoxy derivative **VI**. Treatment of **VI** with phenylhydrazine gave the salt of 7β-amino-7α-methoxy compound **VII** which was acylated with cyanomethylthioacetyl chloride to afford the 7α-methoxycephalosporin **VIII**, CS–1170,[5] which has strong activity against Gram-positive and Gram-negative bacteria.

This simple method was also used for the synthesis of the 6α-methoxypenicillin derivative **XI**. The SCHIFF base **IX** was treated with LiOMe and then *t*-BuOCl to give the 6α-methoxy SCHIFF base **X** in 51% yield. Treatment of **X** with GIRARD T reagent in methanol followed by acylation with phenylacetyl chloride gave pivaloyloxymethyl 6α-methoxy-6β-phenylacetamidopenicillanate (**XI**) in 57% yield. After incubation with rabbit serum[8] this compound (**XI**) inhibited the growth of *Staphylococcus aureus* FDA 209P at 100 mcg/ml, but did not inhibit the growth of Gram-negative bacteria.[7]

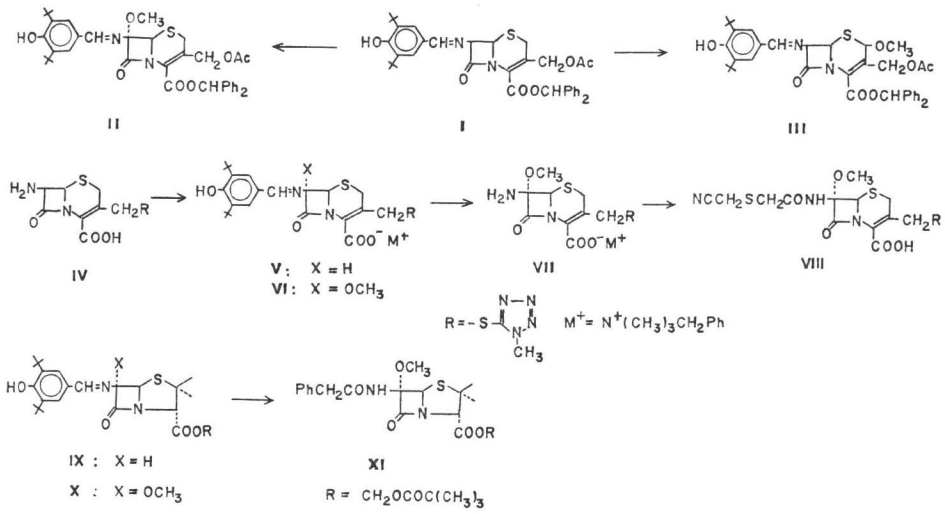
Experimental

Diphenylmethyl 3-Acetoxymethyl-7β-(3, 5-di-*tert*-butyl-4-hydroxybenzylideneamino)-7α-methoxy-3-cephem-4-carboxylate (II)

To a solution of 330 mg (0.5 mmol) of SCHIFF base **I**[1] in 9 ml of THF and 1 ml of methanol was added 1 ml of 0.55 N LiOMe in methanol followed by a solution of 65 mg (0.6 mmol) of *t*-BuOCl in 1 ml of THF at −78°C. The mixture was stirred for 40 minutes at −78°C and then concentrated *in vacuo*. The residue was chromatographed over 10 g of dried silica gel. Elution with cyclohexane - ethyl acetate (5: 1)

* The results[6] of an analogous reaction suggest that the stereochemistry of the 2-methoxy group is α-configuration.

Chart 1



produced 210 mg (61%) of **II** as amorphous powder of which IR and NMR spectra were identical to those of an authentic sample.[1]

Diphenylmethyl 3-Acetoxymethyl-7β-(3, 5-di-*tert*-butyl-4-hydroxybenzylideneamino)-2-methoxy-3-cephem-4-carboxylate (**III**)

To a solution of 330 mg (0.5 mmol) of the SCHIFF base **I**[1] in 7 ml of THF and 3 ml of methanol was added a solution of 65 mg (0.6 mmol) of *t*-BuOCl in 1 ml of THF at $-78°C$. After the mixture was stirred for 30 minutes at $-78°C$, 1 ml of 0.5 N LiOMe in methanol was added and the stirring was continued for 10 minutes at $-78°C$. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed over 10 g of silica gel. Elution with cyclohexane-ethyl acetate (5: 1) produced 166 mg (48%) of **III** as amorphous powder. IR (Nujol): 3620, 1785, 1735 cm^{-1}. NMR ($CDCl_3$): δ 1.47 (18H, s, *tert*-butyl), 1.98 (3H, s, $OCOCH_3$), 3.47 (3H, s, C–2 OCH_3), 4.72 and 5.03 (2H, ABq, J=13Hz, C–3 CH_2O), 5.03 (1H, s, C–2 H), 5.26 (1H, d, J=5Hz, C–6 H), 5.53 (1H, d–d, J=2 and 5Hz, C–7 H), 5.59 (1H, s, OH), 7.05 (1H, s, CH in ester group), 7.38 (10H, s, phenyl protons in ester group), 7.67 (2H, s, phenyl protons in benzylidene group), 8.55 (1H, d, J=2Hz, CH=N).

Anal. Calcd. for $C_{39}H_{44}N_2O_7S$:
C, 68.40; H, 6.48; N, 4.09; S, 4.68.
Found: C, 68.81; H, 6.62; N, 3.84; S, 4.60.

Benzyltrimethylammonium Salt of 7β-(3, 5-Di-*tert*-butyl-4-hydroxybenzylideneamino)-3-[[(1-methyl-1H-tetrazol-5-yl) thio]methyl]-7α-methoxy-3-cephem-4-carboxylic Acid (**VI**)

To a suspension of 984 mg (3 mmol) of 7β-amino-3-[[(1-methyl-1H-tetrazol-5-yl) thio] methyl]-3-cephem-4-carboxylic acid (**IV**) in 8 ml of methanol and 13 ml of THF was added 1.36 ml (3 mmol) of 40% benzyltrimethylammonium hydroxide in methanol at 0°C and then the mixture was stirred at room temperature. After **IV** dissolved, 712 mg (3.04 mmol) of 3, 5-di-*tert*-butyl-4-hydroxybenzaldehyde and 2 g of dried Drierite were added and the mixture was stirred overnight at room temperature. The precipitates were removed by filtration and washed with a small amount of methanol - THF (1: 1). The filtrate containing **V** was used without purification in the next reaction.

To the above filtrate was added a solution of 42 mg (6 mmol) of lithium in 4 ml of methanol followed by a solution of 780 mg (7.2 mmol) of *t*-BuOCl in 2 ml of dichloroethane at $-78°C$. After stirring for 35 minutes in an ethanol - dry ice bath, the reaction mixture was concentrated to about 5 ml under 35°C *in vacuo*. The concentrate was dissolved in 50 ml of chloroform and the solution was washed with water four times, dried over $MgSO_4$ and concentrated to about 5 ml *in vacuo*. To the concentrate was added cyclohexane and the precipitates of **VI** were collected: pale brown powder; yield 1.50 g (66.3%). This crude **VI** was used without purification in the next reaction. NMR (DMSO–d_6): δ 1.35

(18H, s, *tert*-butyl), 3.40 (3H, s, C–7 OCH_3), about 3.6 (2H, C–2 H), 3.85 (3H, s, N–CH_3), 4.30 (2H, br s, C–3 CH_2), 5.13 (1H, s, C–6 H), 7.57 (2H, s, phenyl protons), 8.36 (1H, s, CH=N).

Benzyltrimethylammonium Salt of 7β-Amino-7α-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic Acid (VII)

To a solution of 1.50 g of **VI** in 5 ml of dichloroethane was added a solution of 0.8 g of phenylhydrazine in 1 ml of dichloroethane under ice-cooling. After the mixture was stirred for 30 minutes, 40 ml of cyclohexane was added. The precipitates of **VII** were collected and washed with cyclohexane - diethyl ether (1: 1) to yield 1.03 g (100%) of pale brown powder. This crude **VII** was acylated without purification. NMR (DMSO–d_6): δ 3.22 (3H, s, C–7 OCH_3), about 3.4 (2H, C–2 H), 3.80 (3H, s, N–CH_3), 4.15 (2H, br s, C–3 CH_2), 4.64 (1H, s, C–6 H).

7β-[[(Cyanomethyl)thio]acetamido]-7α-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic Acid (CS-1170) (VIII)

To a solution of 1.03 g of **VII** in 14 ml of dichloroethane was added a solution of 0.90 g of N, N-diethylaniline in 1 ml of dichloroethane and then a solution of 0.90 g of cyanomethylthioacetyl chloride in 1 ml of dichloroethane in an ice-salt bath. After the mixture was stirred for 40 minutes in an ice-salt bath, 20 ml of methanol was added and the stirring was continued for 1 hour in an ice-salt bath. The solution was concentrated *in vacuo* and the residue was dissolved in 10 ml of chloroform and 30 ml of 10% aqueous K_2HPO_4. The aqueous layer was separated and the organic layer was extracted with 10 ml × 2 of 10% aqueous K_2HPO_4. The aqueous layer and extracts were combined, washed with ethyl acetate, covered with 50 ml of ethyl acetate and then adjusted to pH 2.0 with 3 N HCl with stirring. After separation of the organic layer, the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to give 0.71 g of crude **VIII**. This acid was dissolved in 4 ml of ethyl acetate, 0.45 ml of dicyclohexylamine was added under ice-cooling and the precipitated salt of **VIII** was triturated with diethyl ether: yield 1.0 g. Recrystallization from ethanol gave the pure dicyclohexylamine salt of **VIII**: yield 473 mg (36.3%); mp 158°C. This compound was confirmed to be identical with an authentic sample of **VIII**[5] by the comparison of the IR and NMR spectra.

Pivaloyloxymethyl 6β-(3,5-di-*tert*-butyl-4-hydroxybenzylideneamino)-6α-methoxypenicillanate (X)

The SCHIFF base **IX** was prepared from pivaloyloxymethyl 6β-aminopenicillanate and 3, 5-di-*tert*-butyl-4-hydroxybenzaldehyde in refluxing benzene and used without purification in the next reaction. A solution of 274 mg (0.5 mmol) of **IX** in 9 ml of THF and 1 ml of methanol was treated by the same procedure as described for the preparation of **II**. The reaction product was purified on a column of 10 g of dried silica gel. Elution with cyclohexane - ethyl acetate (10: 1) afforded 147 mg (51%) of **X** as amorphous powder. IR ($CHCl_3$): 3630, 1760 cm^{-1}. NMR ($CDCl_3$): δ 1.22 (9H, s, *tert*-butyl in pivaloyl group), 1.45 (21H, s, C–2 CH_3 and *tert*-butyl in benzylidene group), 1.60 (3H, s, C–2 CH_3), 3.55 (3H, s, C–6 OCH_3), 4.45 (1H, s, C–3 H), 5.53 (1H, s, C–5 H), 5.58 (1H, s, OH), 5.84 (2H, s, CH_2 in ester group), 7.64 (2H, s, phenyl protons), 8.45 (1H, s, CH=N).

Anal. Calcd. for $C_{30}H_{44}N_2O_7S$:
C, 62.47; H, 7.69; N, 4.86; S, 5.56.
Found: C, 62.31; H, 7.79; N, 4.50; S, 5.45.

Pivaloyloxymethyl 6α-Methoxy-6β-phenylacetamidopenicillanate (XI)

To a solution of 350 mg (0.6 mmol) of **X** in 3.5 ml of methanol was added 350 mg of GIRARD T reagent and the mixture was stirred for 25 minutes in an ice-salt bath. The reaction mixture was diluted with 20 ml of dichloromethane and washed with water. After drying over $MgSO_4$, the solution was concentrated *in vacuo* to give crude pivaloyloxymethyl 6β-amino-6α-methoxypenicillanate as syrup which was immediately acylated as follows. To a solution of the 6β-amino-6α-methoxy compound in 2 ml of dichloroethane was added a solution of 95 mg (0.64 mmol) of N, N-diethylaniline in 0.3 ml of dichloroethane followed by a solution of 100 mg (0.64 mmol) of phenylacetyl chloride in 0.3 ml of dichloroethane and the mixture was stirred for 50 minutes in an ice-salt bath. The reaction mixture was diluted with ethyl acetate and washed successively with 10% aqueous $KHSO_4$, 5% aqueous $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$, concentrated *in*

vacuo, and the residue was chromatographed over 10 g of silica gel. Elution with cyclohexane-ethyl acetate (2: 1) afforded 165 mg (57%) of XI as syrup. IR (film): 3280, 1780, 1755, 1670 cm^{-1} NMR ($CDCl_3$): δ 1.19 (9H, s, *tert*-butyl), 1.35 (3H, s, C–2 CH_3), 1.41 (3H, s, C–2 CH_3), 3.38 (3H, s, C–6 OCH_3), 3.64 (2H, s, CH_2 in benzyl group), 4.38 (1H, s, C–3 H), 5.57 (1H, s, C–5 H), 5.81 (2H, s, CH_2 in ester group), 7.30 (5H, s, phenyl). Mass: *m/e* 478 (M^+), 273.

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