SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 7β-[2-(2-AMINOTHIAZOL-4-YL)ACETAMIDO]CEPHALOSPORIN DERIVATIVES

VI. ALTERNATIVE SYNTHESES OF 7β-[2-(2-AMINOTHIAZOL-4-YL)-(*Z*)-2-METHOXYIMINO-ACETAMIDO]CEPHALOSPORIN DERIVATIVES

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Alternative syntheses of 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-cephalosporins (**1**) were investigated. Of these, a sequence of reactions starting from **6a** *via* **8a**, **9a**, **13a** and **13b** afforded a convenient route to **1a** which is especially useful for the preparation of labeled cefmenoxime. Structures of nitrone compounds which were formed as by-products are discussed.

An extensive study[1] of structure-activity relationships of 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporins (**1**) and related compounds led to the selection of 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid (**1a**), cefmenoxime, for further biological evaluations. These compounds (**1**) were prepared basically by acylating 7-aminocephalosporins with 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid followed by removal of the protecting group.

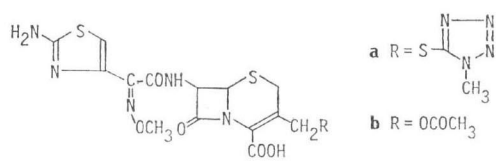
In this paper will be described* alternative synthetic routes to these compounds (**1**), one of which has good applicability for the preparation of labeled cefmenoxime (**1a**).

1. Alternative Synthesis of 7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]cephalosporanic Acid (1b)

Conventional methylation of 7β-(4-chloro-2-hydroxyimino-3-oxobutyrylamino)cephalosporanic acid (**2**)[2] with dimethyl sulfate gave a methoxyimino compound (**3**). Because of its low stability, **3** was reacted with thiourea in DMA, without purification, to afford the anticipated compound (**1b**) as its sodium salt.

7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-hydroxyiminoacetamido]cephalosporanic acid (**4**)[2] obtainable from **2** was then treated with dimethyl sulfate. In this reaction, the main product was the (*Z*)-nitrone compound (**5**) accompanied by the anticipated compound (**1b**).

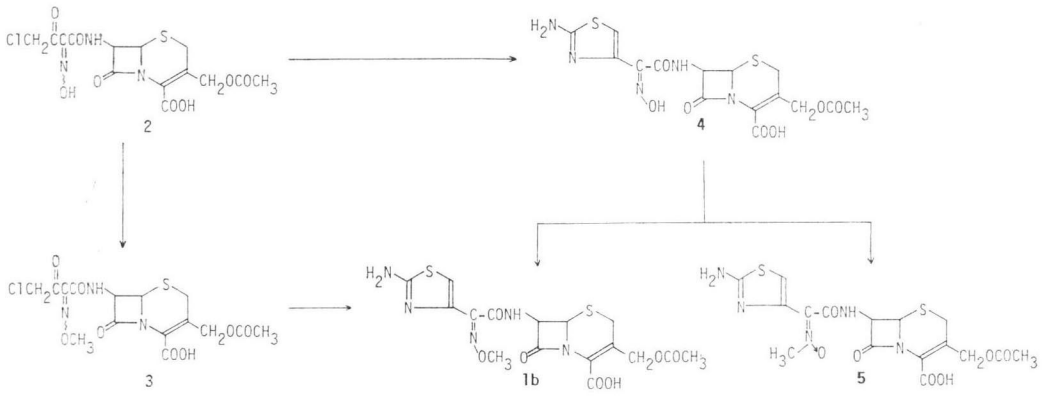
Chart 1.



1

* Part of this paper was presented at the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy.[3]

Chart 2.



2. Alternative Synthesis of Cefmenoxime (1a)

Alternative synthetic routes to **1a** were investigated including those which might be applicable to the preparation of the labeled compound.

Diphenylmethyl 7β-(4-chloro-3-oxobutyrylamino)-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylate (**8b**) was prepared either by acylating 7-amino-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid (7-ACT, **6a**) with 4-chloro-3-oxobutyryl chloride[2] followed by esterification or by esterifying 7-ACT followed by acylation with 4-chloro-3-oxobutyryl chloride. Oxyimination of **8b** with sodium nitrite readily gave a hydroxyimino compound (**9b**) together with a compound to which the structure **10b** was assigned on the basis of analytical and spectral data. Compound **10b** was presumably formed from **9b** *via* **11b**.

Conventional methylation of **9b** with dimethyl sulfate in the presence of potassium carbonate caused isomerization of Δ^3-double bond to give diphenylmethyl 7β-(4-chloro-3-methoxyimino-3-oxobutyrylamino)-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]ceph-2-em-4-carboxylate (**12b**). In order to avoid isomerization, methylation of **9b** with diazomethane was examined. A mixture (*ca.* 1 : 1) of a methoxyimino compound (**13b**) and an (*E*)-nitrone compound (**14b**) was obtained. Since isolation of each pure compound by chromatography on silica gel without substantial loss was difficult, this mixture was reacted with thiourea followed by deesterification to give **1a** and a nitrone compound (**15a**) as their sodium salts after repeated chromatography on Amberlite XAD-2 and Sephadex LH-20.

The compound **1a** thus obtained was not, however, completely free from the (*E*)-nitrone compound (**15a**). Therefore, another route to obtain **1a** of high purity was investigated.

Considering that methylation of **2** with dimethyl sulfate did not give a nitrone compound, 7β-(4-chloro-3-hydroxyimino-3-oxobutyrylamino)cephalosporin derivative (**9a**)[2] was treated under similar conditions to give **13a**. The reaction products were, without purification, esterified with diphenyldiazomethane. Chromatography on silica gel readily afforded **13b** of high purity.

Reaction of **13b** with thiourea followed by deesterification afforded highly pure **1a*** (isolated as its sodium salt).

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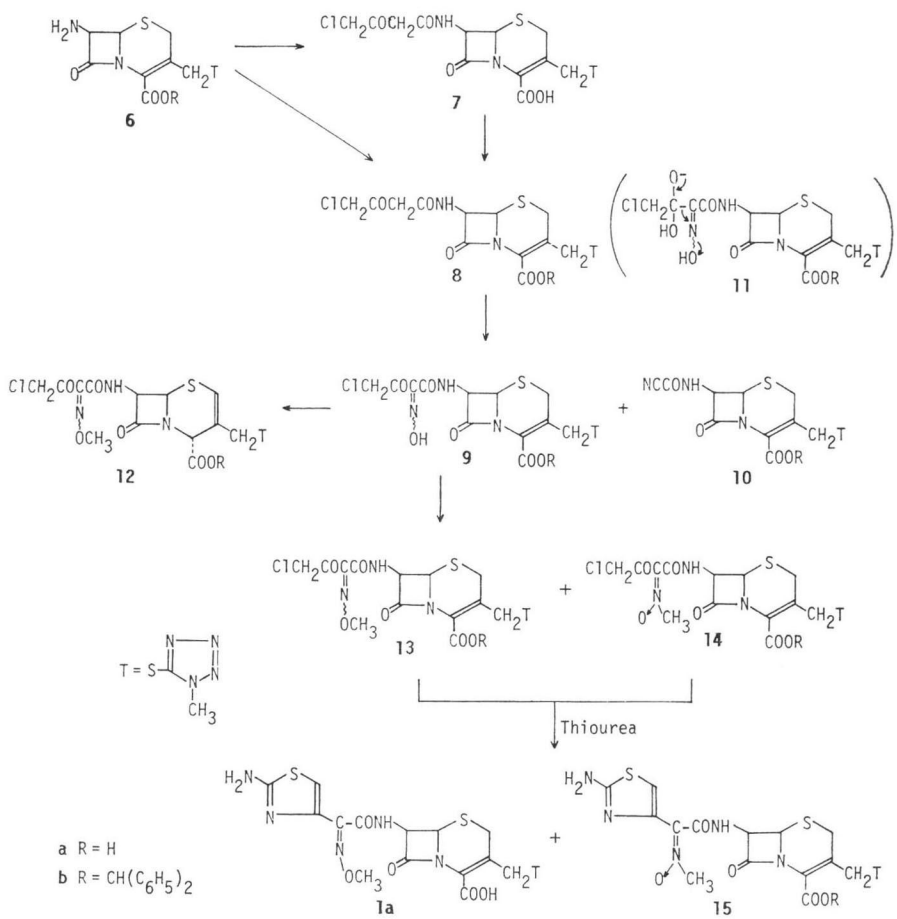
* 7β-[2-(2-^{14}C)-2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid was prepared in the Radio Isotope Department of this Division by reacting the ester (**13b**), obtained from **9a** *via* **13a**, with ^{14}C-thiourea.

Chart 3.



3. Structure of Nitrone Compounds

It is known[4] that alkylation of a hydroxyimino compound affords an O-alkylated compound and/or a nitrone compound, but the factors governing the site of alkylation are not well established.

In a previous paper[1a] we reported the formation and chemical behaviour of the nitrones (**18**, **19**). As is described in this paper methylation of **4** with dimethyl sulfate, and **9b** with diazomethane gave nitrone compounds **5** and **14b**, respectively. **14b** was converted into a 2-aminothiazole derivative (**15a**).

In order to assign structures to these compounds (**5**, **14b**, **15a**), ^{1}H- and ^{13}C NMR spectra were studied. The principal chemical shifts of these compounds and the related compounds compatible with structure elucidation are given in Chart 4.

It is evident that signals for the methyl carbon atom of the nitrones (**18**, **19**) appear at apparently higher field (*ca.* 10 ppm) than those of the methoxyimino compounds (**16**, **17**, **20**, **21**). From these results, the signal at 51.4 ppm of **15a** (sodium salt) can reasonably be assigned to a methyl carbon atom of a nitrone moiety. Furthermore, configuration of the nitrone moiety in **15a** (sodium salt) was assigned by ^{1}H NMR. The thiazole 5-H of the (*E*)-isomer (**18**) appears at a clearly lower field (8.56 ppm) than that of the (*Z*)-isomer (**19**) (6.62 ppm). The signal of thiazole 5-H of **15a** (sodium salt) is

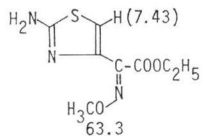
Chart 4. Chemical shift in ^{1}H- and ^{13}C NMR spectra (ppm).

Shift in ^{1}H NMR is given in parentheses.

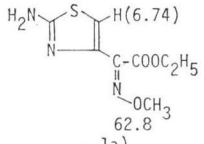
Solvent: $CDCl_3$ for **16, 17, 18, 19.**

D_2O for **20, 21,** 15(Na), **5**(K).

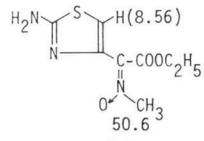
* Not measured.



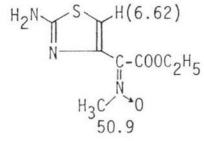
16[1a]



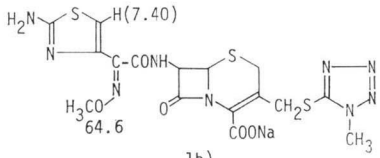
17[1a]



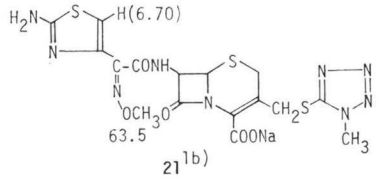
18[1a]



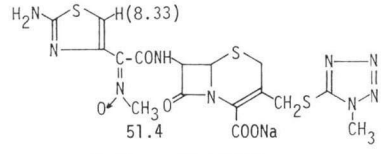
19[1a]



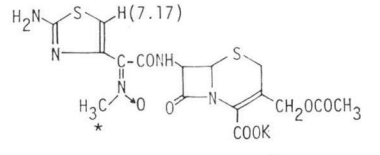
20[1b]



21[1b]



Sodium salt of **15a**



Potassium salt of **5**

observed at 8.33 ppm which is apparently ascribable to (*E*)-configuration.

From both of these observations, the structure **15a** was reasonably assigned to an (*E*)-nitrone compound. That isomerization of a nitrone compound has not been observed[4] might well be an indication that **14b** is of the (*E*)-nitrone configuration.

The potassium salt of **5** was assigned to a (*Z*)-nitrone structure on the basis that the thiazole 5-H appears at remarkably higher field (7.17 ppm) than that of **15a** salt (8.33 ppm) and the starting material (**4**) with (*Z*)-configuration was methylated under conditions devoid of geometrical isomerization.[4]

Experimental

Infrared spectra were measured in KBr disk on a Hitachi Type 215 spectrometer. ^{1}H NMR spectra were run on a Varian T-60 (60 MHz) or EM-390 (90 MHz) spectrometer using tetramethylsilane as a standard. ^{13}C NMR spectra were done on a Varian XL-100-12 spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane. Melting points are uncorrected.

Conversion of 7β-(4-chloro-2-hydroxyimino-3-oxobutyrylamino)cephalosporanic acid (**2**) into **1b**

To an ice-cooled solution of **2**[2] (410 mg) in a mixture of water (10 ml) and acetone (10 ml) were added $NaHCO_3$ (300 mg) and dimethyl sulfate (1.5 g) dropwise with stirring. After stirring for 1 hour under ice-cooling, the mixture was adjusted to pH 2.0 with 1 N HCl and extracted with AcOEt. The

extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a crude 7β-(4-chloro-2-methoxyimino-3-oxobutyrylamino)cephalosporanic acid (**3**), as a powder, 250 mg. The crude acid (**3**) (210 mg) was dissolved in DMA (4 ml) and after addition of thiourea (100 mg) the mixture was stirred for 4 hours at room temperature. Et_2O (30 ml) was added to the reaction mixture which caused precipitation of an oil. The supernatant was removed by decantation and the residual oil was dried under reduced pressure. The oil was dissolved in a small amount of 5% aqueous $NaHCO_3$ and chromatographed on an Amberlite XAD-2 column. Elution with water followed by lyophilization afforded **1b** as its sodium salt, 31 mg.

The identity was established by comparison of NMR spectrum with the sample prepared previously.[1]

Methylation of 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-hydroxyiminoacetamido]cephalosporanic acid (**4**)

To an ice-cooled solution of **4**[2] (477 mg) in a mixture of water (20 ml) and acetone (10 ml) were added K_2CO_3 (280 mg) and dimethyl sulfate (300 mg) dropwise with stirring. After stirring for 1 hour under ice-cooling, the mixture was concentrated under reduced pressure to remove acetone. The residue which contained the (*Z*)-nitrone compound (**5**) and a small amount of **1b** was chromatographed on an Amberlite XAD-2 column. Elution with water followed by lyophilization gave the (*Z*)-nitrone compound (**5**) as its potassium salt, 87 mg. NMR (60 MHz, D_2O) δ: 2.13 (3H, s, $OCOCH_3$), 3.61 (2H, q, 2-CH_2), 4.02 (3H, s, CH_3), 4.90 (2H, q, 3-CH_2), 5.15 (1H, d, 6-H), 5.90 (1H, d, 7-H), 7.17 (1H, s, thiazole 5-H).

TLC (Merck TLC plate, silica gel $60F_{254}$: AcOH - H_2O - AcOEt = 1: 1: 4) indicated that this product contained a small amount of **1b** (*ca.* 10%, measured on a Shimadzu Dual Wavelength TLC Scanner CS-910). Separation of **1b** from the product without substantial loss of **5** by repeated chromatography was unsuccessful.

Diphenylmethyl 7β-(4-chloro-3-oxobutyrylamino)-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylate (**8b**)

(a) To a solution of **7**[2] (5.0 g) in THF (30 ml) was added a THF solution (20 ml) of diphenyldiazomethane (0.02 mol.). After stirring for 1 hour at room temperature, Et_2O was added to the mixture to precipitate an oil. The supernatant was removed by decantation and the residual oil was chromatographed on a silica gel column. Elution with AcOEt - $CHCl_3$ (2: 3) gave crude **8b**, as a powder, 2.2 g. NMR (60 MHz, $CDCl_3$), δ: 3.66 (2H, q, 2-CH_2), 3.74 (2H, s, $COCH_2CO$), 3.79 (3H, s, N-CH_3), 4.21 (2H, s, $ClCH_2$), 4.30 (2H, q, 3-CH_2), 5.00 (1H, d, 6-H), 5.85 (1H, dd, 7-H), 6.94 (1H, s, CH), 7.34 (10H, m, $C_6H_5\times2$).

(b) To a suspension of 7-ACT (**6a**) (32.8 g) in DMSO (500 ml) was added a THF solution (150 ml) of diphenyldiazomethane (0.2 mol.). After stirring for 15 hours at room temperature the mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of $CHCl_3$ under reduced pressure gave an oil which upon treatment with a small amount of AcOEt crystallized to give **6b**, 25.7 g. NMR (60 MHz, d_6-DMSO) δ: 3.65 (2H, bs, 2-CH_2), 3.80 (3H, s, N-CH_3), 4.16 (2H, q, 3-CH_2), 4.80 (1H, d, 6-H), 4.96 (1H, d, 7-H), 6.84 (1H, s, CH), 7.30 (10H, m, $C_6H_5\times2$).

6b (19.8 g) was dissolved in CH_2Cl_2 (200 ml) and pyridine (40 ml) was added. To the stirred solution was added a CH_2Cl_2 solution (34 g) of 4-chloro-3-oxobutyryl chloride[2] (0.048 mol.) dropwise under cooling (−40°C). After stirring for 30 minutes at −30°C, the mixture was poured into water and the organic layer was separated after shaking. Conventional work-up of the organic layer afforded **8b**, as a powder, 26.0 g.

Diphenylmethyl 7β-(4-chloro-2-hydroxyimino-3-oxobutyrylamino)-3-[(1-methyl-1*H*-tetrazol-5-yl)-thiomethyl]ceph-3-em-4-carboxylate (**9b**)

To an ice-cooled solution of **8b** (22.3 g) in a mixture of THF (100 ml) and AcOH (50 ml) was added a solution of $NaNO_2$ (3.8 g) in water (50 ml) dropwise with stirring over a period of 30 minutes. After stirring for 30 minutes at room temperature, the mixture was poured into water and extracted with AcOEt. The reaction product, obtained by conventional work-up of the extract, was chromatographed on a silica gel column. Elution with AcOEt - *n*-hexane (4: 1) afforded **9b**, as a powder,

14.0 g. NMR (90 MHz, $CDCl_3$) δ: 3.73 (2H, bs, 2-CH_2), 3.78 (3H, s, N-CH_3), 4.32 (2H, q, 3-CH_2), 4.69 (2H, s, $ClCH_2$), 5.00 (1H, d, 6-H), 5.81 (1H, dd, 7-H), 6.82 (1H, s, CH), 7.33 (10H, m, $C_6H_5\times2$), 9.29 (1H, d, NH).

Further elution with AcOEt - *n*-hexane (1: 1) gave diphenylmethyl 7β-cyanocarbonylamino-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylate (**10b**) as colorless crystals, 0.98 g. Mp 173~174°C. *Anal.* Calcd. for $C_{25}H_{21}N_7O_4S_2$: C, 54.83; H, 3.87; N, 17.90. Found: C, 54.83; H, 3.74; N, 17.68. IR (KBr): 2230 cm^{-1}, 1790 cm^{-1}. NMR (90 MHz, d_6-DMSO) δ: 3.76 (2H, q, 2-CH_2), 3.86 (3H, s, N-CH_3), 4.29 (2H, q, 3-CH_2), 5.20 (1H, d, 6-H), 5.88 (1H, dd, 7-H), 6.88 (1H, s, CH), 7.33 (10H, m, $C_6H_5\times2$), 11.02 (1H, d, NH).

Diphenylmethyl 7β-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-[(1-methyl-1*H*-tetrazol-5-yl)-thiomethyl]ceph-2-em-4-carboxylate (**12b**)

To an ice-cooled solution of **9b** (1.29 g) in acetone (50 ml) were added K_2CO_3 (0.26 g) and dimethyl sulfate (0.38 ml) with stirring. After stirring for 1.5 hours under ice-cooling and then for 3.5 hours at room temperature, the mixture was filtered to remove a small amount of insoluble material and the filtrate was poured into water followed by extraction with AcOEt. The product, obtained by conventional work-up of the extract, was chromatographed on a silica gel column. Elution with AcOEt - *n*-hexane (4: 1) afforded **12b** as a powder, 0.63 g. NMR (60 MHz, $CDCl_3$) δ: 3.78 (3H, s, N-CH_3), 4.09 (3H, s, N-OCH_3), 4.24 (2H, q, 3-CH_2), 4.56 (2H, s, $ClCH_2$), 5.02 (1H, d, 6-H), 5.28 (2H, m, 7-H and 4-H), 6.54 (1H, bs, 2-H), 6.90 (1H, s, CH), 7.30 (10H, m, $C_6H_5\times2$), 8.16 (1H, d, NH).

Diphenylmethyl 7β-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-[(1-methyl-1*H*-tetrazol-5-yl)-thiomethyl]ceph-3-em-4-carboxylate (**13b**)

(a) To a solution of **9b** (14.0 g) in a mixture of THF (20 ml) and AcOEt (10 ml) was added an Et_2O solution of diazomethane until **9b** disappeared on TLC monitoring. After excess diazomethane was quenched with AcOH, the reaction mixture was washed with water, 5% aqueous $NaHCO_3$, and then again with water and dried over Na_2SO_4. The reaction product obtained by evaporation of the solvent was chromatographed on a silica gel column. Elution with AcOEt - *n*-hexane (1: 1) afforded a mixture (*ca.* 1: 1) of **13b** and (*E*)-nitrone compound (**14b**) as a powder, 8.7 g.

13b NMR (90 MHz, $CDCl_3$) δ: 3.66 (2H, bs, 2-CH_2), 3.73 (3H, s, N-CH_3), 4.07 (3H, s, N-OCH_3), 4.26 (2H, q, 3-CH_2), 4.54 (2H, s, $ClCH_2$), 4.98 (1H, d, 6-H), 5.87 (1H, dd, 7-H), 6.86 (1H, s, CH), 7.30 (10H, m, $C_6H_5\times2$).

14b NMR (90 MHz, $CDCl_3$) δ: 3.66 (2H, bs, 2-CH_2), 3.75 (3H, s, N-CH_3), 3.85 (3H, s, CH_3-$\overset{\uparrow}{N}$-O), 4.26 (2H, q, 3-CH_2), 4.50 (2H, s, $ClCH_2$), 4.98 (1H, d, 6-H), 5.87 (1H, dd, 7-H), 6.90 (1H, s, CH), 7.30 (10H, m, $C_6H_5\times2$).

(b) To an ice-cooled solution of **9a**[2] (35 g) in a mixture of water (180 ml) and acetone (180 ml) were added K_2CO_3 (13.6 g) and dimethyl sulfate (20 ml) with stirring. After stirring for 3.5 hours under ice-cooling, the mixture was neutralized with H_3PO_4 and extracted with AcOEt. Conventional work-up of the extract gave crude **13a** as a powder. This was dissolved in THF (100 ml) and to the solution was added a CH_2Cl_2 solution (110 ml) of diphenyldiazomethane (55 mmol). After stirring for 1 hour, the mixture was concentrated under reduced pressure and the residue was poured into water. This was extracted with AcOEt and the product obtained by conventional work-up of the extract was chromatographed on a silica gel column. Elution with AcOEt - *n*-hexane (1: 1) afforded pure **13b**, as a powder, 15.0 g.

Conversion of **13b** into **1a**

(a) To a solution of a mixture (*ca.* 1: 1) (787 mg) of **13b** and **14b** from above in DMA (8 ml) was added thiourea (76 mg). After stirring for 2.5 hours at room temperature, the mixture was poured into Et_2O (100 ml). The precipitated solids were collected by suction and added to a mixture of AcOEt (100 ml), water (10 ml) and 5% aqueous $NaHCO_3$ (5 ml). After shaking vigorously, the organic layer was separated. Conventional work-up of the organic layer afforded a mixture of diphenylmethyl ester of **1a** and an (*E*)-nitrone compound (**15b**) as a powder, 530 mg.

The mixture was dissolved in a mixture of CF_3COOH (6 ml) and anisole (0.6 ml). After stirring

for 1 hour at room temperature, the mixture was concentrated under reduced pressure. Et_2O (50 ml) was added to the residue and the mixture was stirred for 15 minutes under ice-cooling. The separated solids were collected by suction and dissolved in water (4 ml) with addition of $NaHCO_3$. The solution thus obtained was chromatographed on an Amberlite XAD-2 column. Elution with 2% aqueous EtOH afforded a mixture of **1a** and **15a** as their sodium salts, 290 mg.

The salts were dissolved in a small amount of water and chromatographed on Sephadex LH-20 column. Elution with water followed by lyophilization gave rise to sodium salt of **15a** as a powder, 168 mg. *Anal.* Calcd. for $C_{16}H_{16}N_9O_5S_3Na \cdot 2.5H_2O$: C, 33.21; H, 3.66; N, 21.79; S, 16.63. Found: C, 33.46; H, 3.44; N, 21.70; S, 16.17. NMR (60 MHz, D_2O) δ: 3.67 (2H, q, 2-CH_2), 3.89 (3H, s, –N-CH_3), 4.00 (3H, s, N-CH_3), 4.20 (2H, q, 3-CH_2), 5.22 (1H, d, 6-H), 5.87 (1H, d, 7-H), 8.33 (1H, s, thiazole 5-H).

Further elution followed by lyophilization afforded the sodium salt of **1a**, as a powder, 145 mg. *Anal.* Calcd. for $C_{16}H_{16}N_9O_5S_3Na \cdot 2H_2O$: C, 33.74; H, 3.54; N, 22.13. Found: C, 33.98; H, 3.67; N, 21.96. NMR spectrum established the identity of this material with the sample prepared previously.[1]

(b) To a solution of **13b** (787 mg) in DMA (8 ml) was added thiourea (76 mg). After stirring for 2.5 hours at room temperature, the mixture was poured into Et_2O (100 ml) and the separated solids were collected by suction. The solids were added to a mixture of AcOEt (100 ml), water (10 ml) and 5% aqueous $NaHCO_3$ (5 ml). After shaking vigorously, the organic layer was separated. Conventional work-up of the organic layer gave crude diphenylmethyl ester of **1a** as a powder, 520 mg. NMR (60 MHz, $CDCl_3$) δ: 3.59 (5H, bs, 2-CH_2 and N-CH_3), 3.91 (3H, s, OCH_3), 4.25 (2H, q, 3-CH_2), 5.02 (1H, d, 6-H), 5.95 (3H, bs, NH_2 and 7-H), 6.62 (1H, s, thiazole 5-H), 6.86 (1H, s, CH), 7.26 (10H, m, $C_6H_5 \times 2$).

The above was dissolved in a mixture of CF_3COOH (6 ml) and anisole (0.6 ml) under ice-cooling. After stirring for 1 hour, the mixture was concentrated under reduced pressure. Et_2O (50 ml) was added to the residue and the mixture was stirred for 15 minutes under ice-cooling. The separated solids were collected by suction and dissolved in water (4 ml) with addition of $NaHCO_3$. The aqueous solution thus obtained was chromatographed on an Amberlite XAD-2 column. Elution with 2% aqueous EtOH followed by lyophilization gave the sodium salt of **1a** as a powder, 291 mg.

The sodium salt of **1a** was further purified by chromatography on a Sephadex LH-20 column using water as eluant to afford sodium salt of **1a** as a colorless powder, 257 mg.

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