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EFFICIENT PROCEDURE FOR C'-3 SUBSTITUTION AND C-7 N-ACYLATION OF 7-AMINOCEPHALOSPORANIC ACID (7-ACA): SYNTHESIS OF CEFAZOLIN ANTIBIOTIC AND RELATED COMPOUNDS[1].

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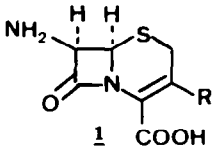
Summary: A new preparative method for the C'-3 substitution of 7-aminocephalosporanic acid (7-ACA), is described. The key feature of our method is based on the protection of the amino group as a Schiff base instead of the usual procedure based on the acylation of the amino group. The relative incapacity of 7-ACA derivatives to produce organic solutions with usual tertiary bases is easily overcome with bicyclic amidines. Catalytic amounts of these bases and N-trimethylsilyl-2-oxazolidinone are used to obtain the silylated products. Activation of sensitive tetrazolylacetic acid by means of N,N-dimethylchlorosulfitemethaniminium chloride ($SOCl_2$-DMF) and preparation of cefazolin antibiotic under anhydrous conditions is also described.

The beta-lactam antibiotics are the most widely used antimicrobial agents. However, the bacterial development of beta-lactamase enzymes[2], which render some of the antibiotics ineffective, has prompted a persistent search for modified antibiotic forms. The chemical behaviour of 7-aminocephalosporanic acid (7-ACA) **1b**, Figure I, constitutes the key feature of all strategies leading to the preparation of various cephalosporin antibiotics **2**. These strategies involve substitution at C'-3 and N-acylation at C-7 position of the mentioned acid.

R		Compound
CH_3		a
CH_2OCOCH_3		b
CH_2S–(N,X)	X = S,N,C	c
CH_2S–(N–N, S) –CH_3		d



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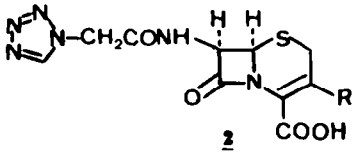

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Figure 1

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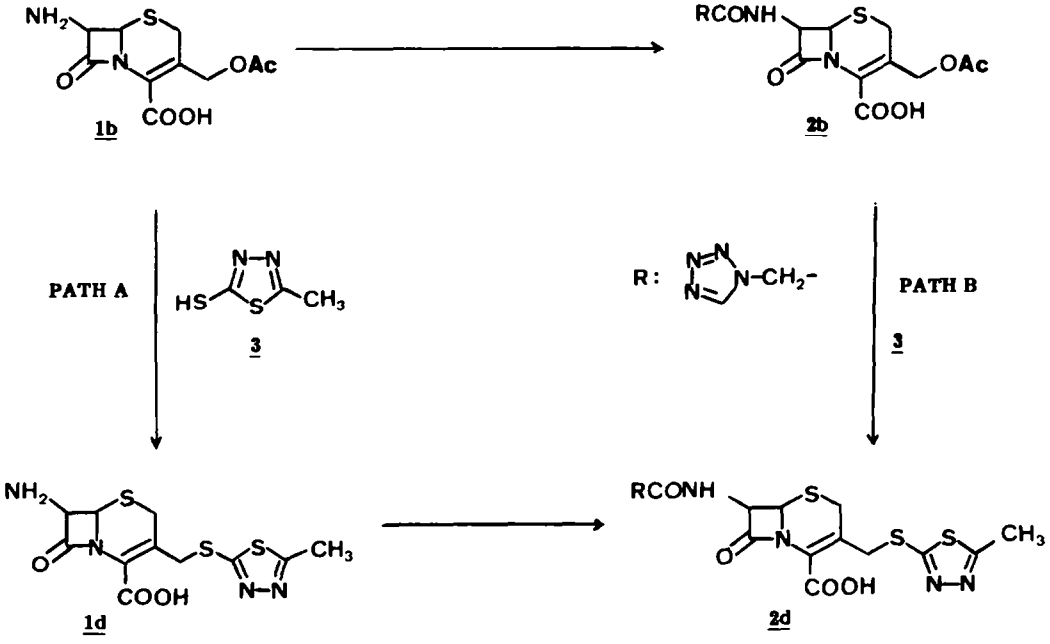
In this paper we report a quite fruitful investigation on a practical method involving C'-3 substitution of 7-ACA **1b** as well as C-7 N-acylation of the resulting cephalosporin **1c** and/or **1d** which would be appear a synthetically useful method for the semi-synthesis of a wide range of cephalosporin antibiotics of therapeutic interest.

Nucleophilic Substitution at C'-3

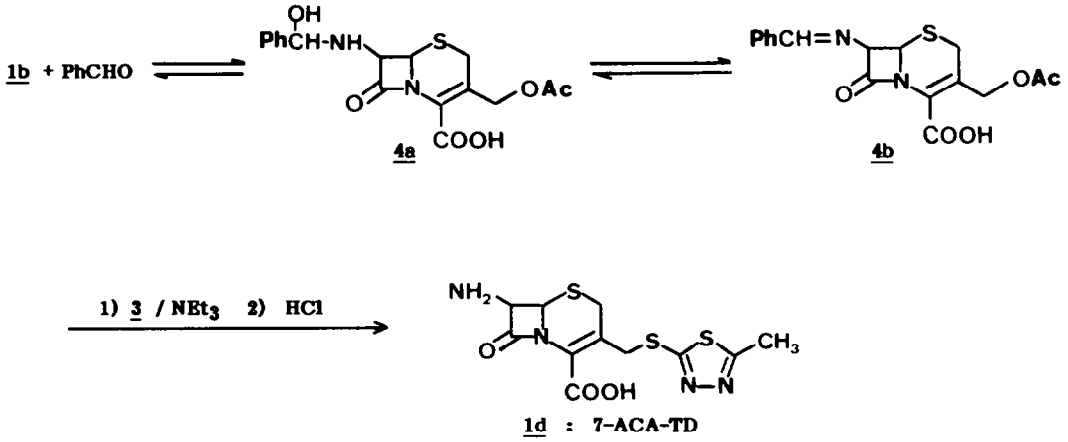
Concerning C'-3 substitution of 7-ACA **1b**, (Scheme 1, path A), De Marinis and coworkers[3a] prepared 7-amino-3-heterocyclic thiomethyl-3-cephem-4-carboxylic acids **1c-d** by treatment of 7-ACA **1b** with the appropriate thiol in aqueous acetone under reflux conditions. This method also was followed by Nannini and coworkers[3b] for the synthesis of some 7-substituted alkyltio-acylaminocephalosporins possesing antibacterical activity. Also, Gericke and Rogalski[3c] treated-7-amino-3-cephem-4--carboxylic acids **1c-d** with acyl chlorides in the synthesis of 4-pyridonylacetamidocephalosporins. However, the reported procedures suffer from several disadvantanges. For example, a careful control of the pH of the reaction medium was needed during the C'-3 substitution process[3a]. In addition, no yields were given and there was a systematic lack of information concerning both physical and chemical characteristics of pure compounds of type **1c**. Saikowa et al[4] have revealed that from these procedures the product obtained is extremely impure and the yields are in the range 30 to 50% at most. Moreover the resulting product is admixed with the starting 7-ACA **1b**. To overcome these drawbacks several papers[5] have shown the convenience of protecting the amino group of 7-ACA **1b** (Scheme 1, path B) and then carrying out the C'-3 substitution in an organic or aqueous-organic solvent at pH∿7. In this way, some heterocyclic mercapto-compounds have been introduced at the C'-3 position to give cephalosporins **2c-d** of therapeutic interest[6]. Kariyone and coworkers[7] have reported that reaction of 7-1-(1H)tetrazolylacetamidocephalosporanic acid **2d** with 2-mercapto-5-methy-1,3,4--thiadiazole **3** led to the widely used parenteral cephalosporin **2d**, cefazolin.



- Scheme 1 -

In view of the interest in cephalosporins, we have been interested in developing other methods for C'-3 substitution of the readily available 7-ACA **1b** for simplified and general use.

This led us to explore the surprisingly simple and inexpensive alternative of Schiff bases derived from aldehydes and 7-ACA **1b** to protect the amino function. Our finding is that when the substitution reaction is carried out in water in the presence of an aldehyde a satisfactory result is obtained. Thus, treatment of 7-ACA **1b** with heterocyclic thiols and triethylamine in the presence of aromatic aldehydes in equimolar amounts gives the expected cephalosporins **1c-d** in excellent yields[8]. Under these conditions, cephalosporin **1d** was obtained in high yield and in fairly pure form after purification of its hydrochloride salt. Thus, when equimolar amounts of 7-ACA **1b**, benzaldehyde and triethylamine were mixed in water at pH 6.48 a clear solution was obtained which was treated with a 3-fold excess of 5-methyl-2-mercapto-1,3,4-thiadiazole and triethylamine at 60-62ºC for 2 h. Under these conditions, the pH of the reaction medium was autocontrolled at 7.3-7.4 and, after the work-up, 7-ACA-TD **1d** was obtained in 80% yield. The purification process was achieved by mixing the product 7-ACA-TD with hydrochloric acid and treating the resulting hydrochloride salt with concentrated ammonia solution to give pure 7-ACA-TD. Without protection of the amino group as Schiff base, a tarry product was obtained, tedious purification was needed and the yield decreased dramatically.



1d : 7-ACA-TD

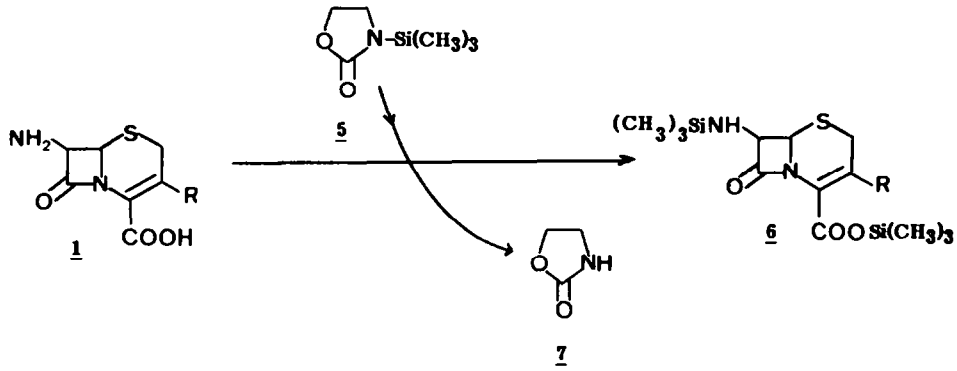
- Scheme 2 -

Acylation reaction of C-7 amino group.

Although the last step in the preparation of a semi-synthetic cephalosporin may appear to be a straightforward acylation of a 7-ACA derivative, the wealth of functionality and reactivity of the beta-lactam requires highly specialized conditions for achieving this transformation. Acylation of cephalosporins in aqueous alkaline solution often gives N-acylaminocephalosporins in low yields due to partial hydrolysis of the acylating agent. Moreover, under the basic conditions used, epimerization[9,11a] at C-7, $\Delta^3 \rightarrow \Delta^2$ isomerization[10,11b] and opening of the β-lactam ring[11] are also to be expected. Better results can be obtained by using cephalosporin triethylammonium salts in aprotic solvents such as N,N-dimethylformamide (DMF)[7c] or dichloromethane[7a]. Nevertheless, in contrast to these previous reports, pure compounds **1c**, especially **1d**, are difficult to dissolve in dichloromethane when triethylamine as well as 4-N,N-dimethylaminopyridine are used to form the corresponding ammonium salts. Under these heterogeneus conditions, we found that N-acylation of cephalosporins **1c-d** give either poor yields or undesired products.

Recently a method[12] has been reported for the acylation of 7-ACA benzhydryl ester under anhydrous and mild reaction conditions by the use of 2-chloro-1-methylpyridinium halides as activating reagents of a carboxyl group. However, from this procedure, a further step would be necessa-

ry for deblocking the benzyhydryl ester group. In order to overcome the above difficulties, the silyl esters, known to be hydrolyzed under extremely mild conditions, were employed instead[13a]. Recently we have described[13b] a mild procedure for silylation of 6-aminopenicillanic acid, as well as other substrates by means of N-trimethylsilyl-2-oxazolidinone 5 (TMSO) which has many advantages over the known reagents. We now have found that 7-aminocephalosporanic acids 1a-d can be easily silylated with this reagent 5 using either 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) as catalysts. Thus, different suspensions of 7-ADCA 1a, 7-ACA 1b and 7-ACA-TD 1d in dichloromethane were treated under reflux conditions with TMSO 5 and DBU or DBN in a molar ratio 1/2.5/0.1, respectively, until a clear solution was formed (5-15 min.). In contrast, triethylamine and 4-N,N-dimethylaminopyridine were found ineffective for such transformation. The starting material was recovered, in each case, by precipitation with water or methanol and was identified by comparison with standard samples; no $\Delta^3 \rightarrow \Delta^2$ isomerization or C-7 epimerization was detected.

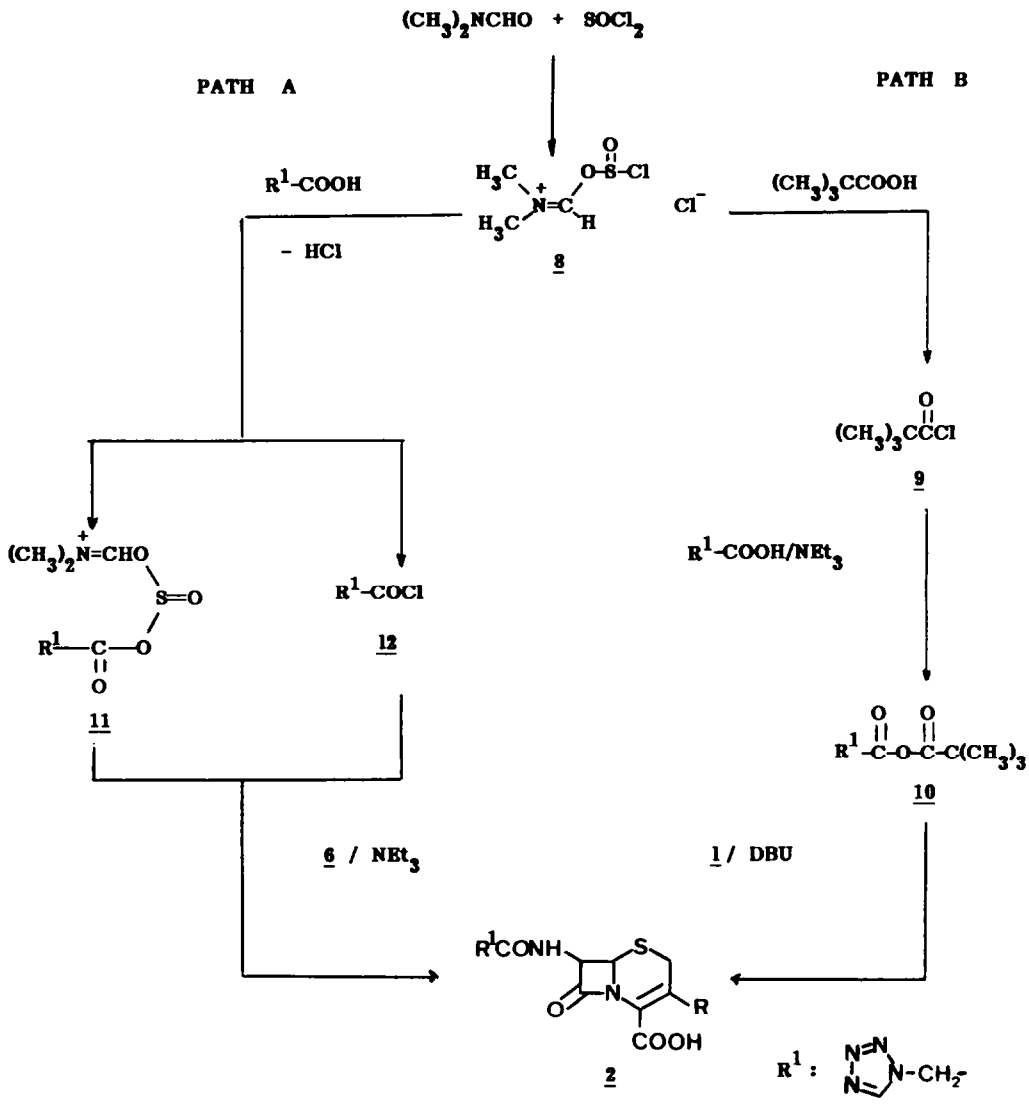


- Scheme 3 -

It is worth mentioning that the inert nature[14] of the side product 7 makes possible the further conversion of 6 into the corresponding acylated derivatives 2 in the reaction mixture without its previous isolation.

Concerning acylating agents, preparation of compounds 2b and 2d are described using tetrazolylacetylchloride and mixed anhydrides in aqueous-acetone medium[6]; however the yields obtained are low due to partial hydrolysis of these acylating reagents. Recently, thionyl chloride-DMF complex 8 has been preliminarily reported[15] to be quite suitable for activating carboxylic acids under anhydrous and mild reaction conditions for some synthetically useful transformations. This led to explore the potential use of this reagent for activating tetrazolylacetic acid. Thus, treatment of tetrazolylacetic acid in dichloromethane as solvent with the reagent 8, prepared by addition of thionyl chloride to DMF in benzene, gave tetrazolylacetylchloride 12 or an active tetrazolylacetic acid species 11 which efficiently acylated compounds 6a-d under anhydrous and neutral conditions.

An alternative pathway was also developed under anhydrous conditions from the mixed anhydride 10 derived from tetrazolylacetic acid and 2,2-dimethylpropanoyl chloride (pivaloyl chloride) 9. The key to this approach was the use DBU and DBN salts of acids of type; other bases such as triethylamine, 4-dimethylaminopyridine, N-ethylpiperidine and N-ethylmorpholine were ineffective in forming the corresponding cephalosporanic acid salts in apolar solvents. The low boiling point of dichloromethane proved to be advantageous during isolation and later purification steps because of the unstable nature of compounds of type 1.



- Scheme 4 -

Conclusions

A surprisingly simple procedure has been developed for a practical C'-3 substitution of 7-ACA 1b as well as a method for the acylation of the amino group of cephalosporanic acids under anhydrous conditions. The feature of our procedure is the use of TMSO 5 and amidine bases (DBU, DBN) as catalysts for forming the corresponding silylated compounds as well as the use of thionyl chloride-DMF complex for activation of sensitive tetrazolylacetic acid. The method would be appear an excellent general procedure for a semi-synthetic preparation of cephalosporin antibiotics as reported here by the rather limited number of examples, and may by readily extended to further applications in beta-lactam chemistry.

EXPERIMENTAL

Melting points were determined with a Thermovar Reicher Kofler-type apparatus and are un-

corrected; crystalline particles were examined with a Kyowa-SDZ-PL stereoscopic zoom microscope. Optical activities were measured at ± 0.5º precision with a Carl Zeiss polarimeter. IR spectra were registered in a Beckman Acculab-4 apparatus and frequencies given in cm^{-1}; ^{1}H-NMR spectra were measured on a Hitachi Perkin-Elmer spectrometer (60 MHz) and chemical shifts are given in δ units.

7-Amino-3-[(5-methyl-1,3,4-thiadiazol-2-yl) thiomethyl]-Δ^3-cephem-4-carboxylic acid (7-ACA-TD) 1d

A solution of 7-ACA **1b** (12.0 g, 44.1 mmol), water (600 ml), benzaldehyde (44.1 ml, 44.1 mmol) and triethylamine (6 ml, 42.0 mmol) at pH 6.48 and 26ºC was added to a solution of 5-methyl-2-mercapto-1,3,4-thiadiazole (15.0 g, 114 mmol), water (1200 ml) and triethylamine (5.75 ml, 114 mmol) at pH 7.3 and 70ºC. The mixture was maintained at 60-62ºC with constant stirring for a period of 120 min. The solution was cooled down to 20ºC and adjusted to pH 1.85 with concentrated hydrochloric acid. The solid product was filtered off and washed with acetone and dried at 40ºC to yield 12.3 g (80%) of 7-ACA-TD **1d** which was purified as follows: crude **1d** (10.33 g, 30 mmol) was added stepwise at 20ºC and with constant stirring to a mixture of hydrochloric acid (60 ml, 36-37%) and water (15 ml). The resulting solution was stirred for 10 min and cooled down to 0-2ºC. After one hour standing at this temperature, 11.2 g (80%) of 7-ACA-TD-HCl were recovered. The same procedure was repeated to yield 92% of the white hydrochloride with m.p 157-160ºC (d), $C_{11}H_{12}N_4O_3S_3.2HCl.H_2O$ % Cl 16.3, found 16.8, $[\alpha]_D^{20}$ = +28.5º (c=2%, conc.HCl/H_2O, 50% v/v), -107.3º (c=1%, DMSO), -125.6º (c=1%, DMF), I.R (KBr) 3328 (NH_3), 1756 (C=O, β-lactam), 1716 (C=O, COOH), ^{1}H-NMR (d-TFA): 4.97 (2H,s,C-6,C-7), 4.30 (2H,q,S-CH_2-, Jab=13Hz), 3.48 (2H,s,C-2), 2.67(3H,s, CH_3), ^{1}H-NMR(d-DMSO): 5.24 (2H,s,C-6,C-7), 4.48 (2H,q,S-CH_2, Jab = 13Hz), 2.72 (2H,s,C-2), 2.65 (3H,s,CH_3). The 7-ACA-TD.HCl (6.0 g, 14.0 mmol) thus formed was added at 20ºC to a mixture of water (30 ml) and concentrated hydrochloric acid (70 ml). The resulting solution was diluted with water (30 ml) and treated with three 0.5 g portions of activated charcoal. After this, concentrated ammonia solution was added dropwise, until pH 1.90-1.95 was reached. The solid product was filtered off and washed with acetone to yield 4.13 g (85%) of 7-ACA-TD **1d** as white plates with m.p. 222-225ºC, $C_{11}H_{12}N_4O_3S_3$ % C 38.4, 3.5H, 16.3N, 27.9S, found 38.2, 3.4, 16.2, 27.6; $[\alpha]_D^{20}$=-70º (c=1%, H_2O/Et$_3$N), -180º (c=0.5%, DBU/1% DMF (p/v), I.R(KBr) 1802 (C=O, β-lactam), 1618 (C=N, C=C), 1534(C=O,COO^-).

DBN and DBU salts of 7-ADCA 1a, 7-ACA 1b and 7-ACA-TD 1d

DBN (1.2 ml, 10 mmol) or DBU (1.5 ml, 10 mmol) was added, at room temperature and with constant stirring to different suspensions of 7-ACA, 7-ADCA and 7-ACA-TD (10 mmol) in dichloromethane (60 ml). The resulting solutions thus prepared were used such as for the next step.

N,O-Bis-trimethylsilyl derivatives of 7-ADCA 1a, 7-ACA 1b and 7-ACA-TD 1d

Different suspensions of 7-ADCA, 7-ACA and 7-ACA-TD (10 mmol) in dichloromethane (40 ml) were refluxed with DBN (0.12 ml, 1 mmol) or DBU (0.15 ml, 1 mmol) and TMSO **5** (4.0 ml, 25 mmol) until a clear solution was formed, which was used such as for the next step.

7-[1-(1H)-tetrazolylacetamido]-3-methyl-Δ^3-cephem-4-carboxylic acid 2a

A solution of pivaloyl chloride (1.45 ml, 12 mmol) in dichloromethane (5 ml) was added to a cold solution (-5ºC) of 1-(1H)-tetrazolylacetic acid (1.54 g, 12 mmol) and triethylamine (1.7 ml, 12 mmol) in dichloromethane (15 ml); the mixture was stirred for 30 min., maintaining the temperature between -5ºC and 0ºC, and was immediately used. Dichloromethane solution of 7-ADCA-DBN salt (10 mmol) was added dropwise together with triethylamine (1.4 ml, 10 mmol) to a cold (-10ºC to -5ºC) dichloromethane solution of the mixed anhydride prepared as above. The temperature was maintained at -5ºC for 60 min. and then the mixture was extracted with water. The aqueous layer was acidified to pH 1.9 with hydrochloric acid to yield a solid which was treated with ethyl acetate (50 ml) under reflux for 15 min, cephalosporin **2a** (3.0 g, 92%) was recovered from the hot ethyl acetate suspension, m.p. 217-8ºC(d), $C_{11}H_{12}N_6O_4S$ % C 40.7, H 3.7, N 25.9, S 9.9 found 40.3, 3.7, 26.0, 9.7, $[\alpha]_D^{20}$ = +182.2 (c=1%,DMSO); I.R(KBr) 3298, (NH), 1780 (C=O, β-lactam), 1715 (C=O,COOH), 1668, 1558 (C=O, CONH), ^{1}H-N.M.R.(d-TFA), 9.15 (1H,s,-CH-tetrazol), 5.35 (1H,d,C-7, J=4.5Hz), 5.23 (2H,s,-N-CH_2-CO-), 4.75 (1H,d,C-6, J=4.5Hz) 3.06 (2H,s,C-2), 1.90 (3H,s,CH_3).

7-[1-(1H)-tetrazolylacetamido]-3-[2-(5-methyl-1,3,4-thiadiazoly)-thiomethyl]-Δ^3-cephem-4-carboxylic acid 2d: cefazolin.

Triethylamine (1.4 ml, 10 mmol) was added to a solution of 7-ACA-TD.HCl (4.35 g, 10 mmol) and DBU (4.65 ml, 30 mmol) in dichloromethane (60 ml). The resulting mixture was poured over a cold solution (-10 to -5ºC) of the mixed anhydride (tetrazolylacetic acid-pivaloyl chloride) prepared as above and maintained at this temperature for 60 min with constant stirring. Then, it was extracted with water and the aqueous layer was chilled, adjusted to pH 1.5 and stirred with 40 ml of hexane. The recovered was dried and refluxed for 30 min in ethyl acetate to yield cefazolin **2d** (4.05 g, 90%) which was recrystallized from acetone-water, m.p. 197-199ºC(d) (lit. 198-200ºC (d)); $[\alpha]_D^{20}$ = -50ºC (c=1%, DMSO), I.R(KBr)ν cm^{-1}: 3295 (NH), 1785 (C=O, β-lactam), 1725 (C=O,COOH), 1682, 1586 (C=O, CONH-).

Cefazolin 2d sodium salt

Cephalosporin **2d** (4.54 g, 10 mmol) was added dropwise and with vigorous stirring to a warm solution (40ºC) of sodium ethyl acetoacetate (2.0 g) in methanol (20 ml). The mixture was kept at the same temperature for 60 min, then diluted with 200 ml of ethyl acetate and cooled to 20ºC, yielding cefazolin **2d** sodium salt (4.61 g, 6% H_2O, 90%) m.p 188-190ºC, $[\alpha]_D^{20}$ = -66.9º (c=1%, DMF),

I.R(KBr)ν cm^{-1}: 3285 (NH), 1760 (C=O, β-lactam), 1685, 1550 (C=O, CONH), 1600 (COO^-) ^{1}H-NMR (D_2O) δ ppm: 9.25(1H,s,CH-tetrazol), 5.70(1H,d,C-7, J:4.5Hz) 5.12(1H,d,C-6, J:4.5Hz), 4.25(2H,q,-S-CH_2, J_{AB}: 17.7Hz), 3.60(2H,q,C-2, J_{AB}:17.7Hz), 2.75(3H,s,CH_3).

3-[(Acetoxy)methyl]-7-[1-(1H)-tetrazolylacetamido]-Δ^3-cephem-4-carboxylic acid 2b sodium salt.

In a 25 ml dropping funnel, benzene (5 ml), DMF (1 ml, 10.2 mmol) and thionyl chloride (0.8 ml, 11 mmol) were consecutively added; after 3-5 min two phases were separated and the reagent 8 (lower layer) was added at 0-5ºC and in short time to a well-stirred suspension of 1-(1H)-tetrazolylacetic acid (1.54 g, 12 mmol) in dichloromethane (8 ml). After 1 h at room temperature, the solution was refluxed during 30 min. The resulting activated tetrazolylacetic acid was added at -5ºC to a solution of 7-ACA-N,O-bis-trimethylsilyl derivative 6b (2.82 g, 10 mmol) and triethylamine (2.8 ml, 20 mmol) in dichloromethane (20 ml). The mixture was maintained at pH 4.5 for 60 min and then diluted with isopropanol (40 ml) and water (20 ml). The organic layer was mixed with a solution of sodium ethyl acetoacetate (12 mmol) in isopropanol (10 ml) and adjusted to pH 6.8 yielding cephalosporin 2b sodium salt (3.80 g, 93%); the crude product was then suspenden in methanol/isopropanol (20/30) and stirred for 15 min.[20] to give the monohydrate salt in 92% yield m.p 173-178ºC(d) (lit 176-179ºC, hemihydrate)[5], $[\alpha]_D^{20}$: +13.2º (c=1%, H_2O), I.R(KBr)ν cm^{-1}: 3450 (OH,H_2O), 3290 (NH), 1765 (C=O, β-lactam), 1740 (C=O,COO^-), 1682 (C=O,CONH), NMR (D_2O)δ ppm: 9.38 (1H,s,CH-tetrazol), 5.77(1H,d,C-7,J:4.5Hz), 5.60(2H,s,NCH_2CO), 5.22(1H,d,C-6,J=4.5Hz), 4.90(2H,d, CH_2OCO-), 3.52(2H,d,-S-CH_2), 2.12(3H,s,CH_3).

Cephalosporin 2d sodium salt.

From 7-ACA-TD-N,O-bis-trimethylsilyl derivative 6d (10 mmol) and activated tetrazolylacetic acid (10 mmol); yield 85%.

Cephalosporin 2a sodium salt.

From 7-ADCA-N,O-bis-trimethylsilyl derivative 6a (10 mmol) and activated tetrazolylacetic acid (10 mmol); yield 91%.

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