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SYNTHESIS OF β-LACTAMS FROM ACETIC ACIDS AND IMINES INDUCED BY PHENYL DICHLOROPHOSPHATE REAGENT [1]

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Abstract - The development of a practical method for the preparation of vinylamino-β-lactams from Dane salts and Schiff bases is described. Among the reagents known to produce β-lactams from imines and acetic acids, only phenyl dichlorophosphate and 1-methyl-2-chloropyridinium iodide are suitable for the synthesis of vinylamino-β-lactams. Reaction of acetic acids with ethanolimine derivatives promoted by phenyl dichlorophosphate affords oxazolidines instead β-lactams. Protection of the hydroxyl group as the trimethylsilyl ether in the starting Schiff bases provides a convenient route to the corresponding β-lactams instead oxazolidines. Some observations on the scope of the method are made.

In recent years there has been renewed interest in the development of efficient methods for the production of cis-3-amino-β-lactams because of the importance of these systems in penicillins, in cephalosporins and in related antibiotics.[2] Several methods are available for the synthesis of β-lactams.[3] Among some conceptual approaches to accomplish highly stereospecific azetidinone formation, the annelation of imino compounds with an activated Dane salt of aminoacetic acid has received much attention in recent years.[4] The key to this approach is the use of an efficient activating agent for the Dane salt. In the continous search for suitable reagents for actiavting the carboxyl group under mild conditions, Liu et al.[5] have reported that phenyl dichlorophosphate is a superior phosphorylating agent to diphenyl chlorophosphate. The latter, along with the closely related compounds diphenylphosphoryl azide and diethyl cyanophosphate, have successfully been used as activating reagents for the carboxyl function.[6] In this paper we describe the synthetic utility of this readily available reagent for the synthesis of β-lactams and oxazolidines.

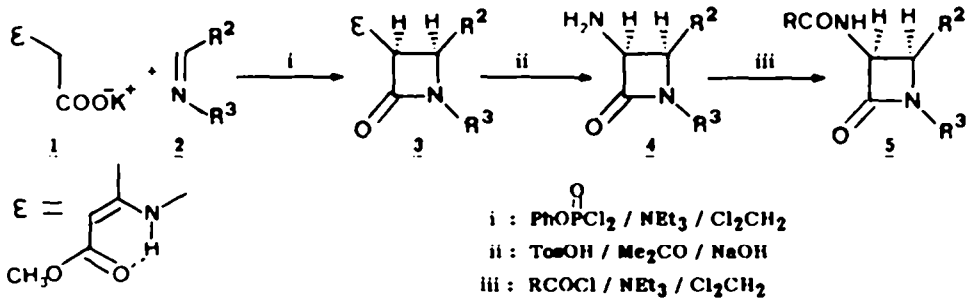
Phenyl dichlorophosphate reagent has been reported[7] to be quite suitable for the efficient synthesis of some α-amino-β-lactams from Dane salts and imino compounds. Thus, treatment of a Dane salt of aminoacetic acid and an appropriate imine in equimolar amounts with phenyl dichlorophosphate in the presence of triethylamine gave the corresponding vinylamino-β-lactam in excellent yield. Hydrolysis of the side chain with p-toluenesulfonic acid monohydrate in acetone-water followed by acylation with an acyl chloride provided the amido-β-lactams 5. (Scheme I)

The results are compiled in Table I. The structure of these β-lactams were confirmed by their I.R. and ^{1}H-N.M.R. spectra. Thus, the configuration of the C-3 and C-4 protons in all of these monocyclic β-lactams was observed to be cis ($J \simeq 5$ Hz). These results assume added significance in view of the fact that the β-lactam protons in active penicillins, cephalosporins, and other β-lactam antibiotics for clinical use are in a cis relationship. The utility of this method can be exemplified by the synthesis of cis-1-(3,4-dimethoxybenzyl)-3-(α-methyl-β-methoxycarbonylvinylamino)-4-phenyl-2-azetidinone 3a and cis-1-(2,4-dimethoxybenzyl)-3-(α-methyl-β-methoxycarbonylvinylamino)-4-phenyl-2-azetidinone 3b as precursors of cis-3-phenoxyacetamido-4-phenyl-2-azetidinone 5i, a compound reported to show anti-β-lactamase activity.[8] For example, reaction of the potassium salt of (α-methyl-β-methoxycarbonyl)vinylaminoacetic acid with phenyl dichlorophosphate reagent and the imine formed from benzaldehyde and 3,4-dimethoxybenzylamine in the presence of triethylamine led

Table I. Preparation of β-lactams 3 - 5

Compound	Yield [a] (%)	M.p. (°C)	Found (Required) C	H	N	Spectral Data [g]
3a	70	156-157 [f]	—	—	—	IR : 1780,1655 (C=O) ; ^{1}H-NMR : 8.5(1H,d,NH), 7.4-6.7(8H,m,arom.),5.2-4.6(4H,m,CH_2,CH,CH), 4.25(1H,s,CH=), 3.8(3H,s,OCH_3), 3.7(3H,s,OCH_3), 3.4(3H,s,OCH_3), 1.7(3H,s,CH_3)
3b	50	118-119	66.9 (67.3	6.1 6.4	6.7 6.8)	IR : 1790,1650 (C=O); ^{1}H-NMR : 8.3(1H,d,NH), 7.3-6.1(8H,m,arom.), 5.1-4.3(4H,m,CH_2,CH,CH), 4.2(1H,s,CH=), 3.7(3H,s,OCH_3), 3.3(3H,s,OCH_3), 3.1(3H,s,OCH_3), 1.6(3H,s,CH_3)
3c	65	177-178	—	—	—	IR : 1790,1650 (C=O); ^{1}H-NMR : 8.5-8.1(1H,s_b, NH), 7.3-6.6(8H,m,arom.), 5.1(1H,d,J= 5 Hz,CH), 4.8(1H,d,J= 5 Hz,CH), 4.3(1H,s,CH=), 3.7(3H,s, OCH_3), 3.4(3H,s,OCH_3), 2.2(3H,s,CH_3),1.8(3H,s, CH_3)
3d	55	182-183	68.2 (68.8	5.9 6.0	7.8 7.6)	IR : 1790,1650(C=O); ^{1}H-NMR : 8.4(1H,d,NH), 7.3-6.6(9H,m,arom.), 5.1(1H,d,J= 5 Hz,CH), 4.9 (1H,d,J= 5 Hz,CH), 4.3(1H,s,CH=), 3.6(3H,s,OCH_3) 3.3(3H,s,OCH_3), 1.8(3H,s,CH_3)
3e	50	161-162	71.2 (71.4	5.7 6.0	8.3 8.3)	IR : 1790,1650(C=O); ^{1}H-NMR : 8.3(1H,d,NH), 7.15(10H,s_b,arom.), 5.1(1H,d,J= 5 Hz,CH),4.9(1H, d,J= 5 Hz,CH), 4.3(1H,s,CH=), 3.3(3H,s,OCH_3), 1.8(3H,s,CH_3)
3f	55	139-142	—	—	—	IR : 1790,1650 (C=O); ^{1}H-NMR : 8.9(1H,d,NH), 7.4-6.7(10H,m,arom.),6.7(1H,d,J= 16 Hz,CH=),6.0 (1H,dd,J= 9 Hz, J'= 16 Hz,CH=),4.9(1H,dd,J= 4.5 Hz,J'= 9 Hz,CH), 4.7(1H,dd,J= 4.5 Hz,J'= 9 Hz,CH), 4.5(1H,s,CH=),3.4(3H,s,OCH_3), 1.8(3H,s,CH_3)
4c	43(78) [h]	125	72.7 (72.3	6.4 6.4	10.0 9.9)	IR : 1780 (C=O); ^{1}H-NMR : 7.4-6.2(8H,m,arom.), 5.0(1H,d,J= 5 Hz,CH), 4.3(1H,d,J= 5 Hz,CH), 3.7 (3H,s,OCH_3), 2.2(3H,s,CH_3),1.3(2H,s_b,NH_2)
4f	57	143-144	76.7 (77.2	5.9 6.1	10.6 10.6)	IR : 1780(C=O); ^{1}H-NMR : 7.4-6.7(10H,m,arom.), 6.5(1H,dd,J= 9 Hz,J'= 16 Hz,CH=), 6.2(1H,dd,J= 9 Hz,J'= 16 Hz,CH=), 4.7(1H,t,CH),4.3(1H,d,J= 5 Hz, CH), 1.7(2H,s_b,NH_2)
5a	57 [b]	129-131 [f]	—	—	—	IR : 1770,1690(C=O); ^{1}H-NMR : 7.6-6.7(14H,m, arom.),5.7(1H,q,CH), 5.2(1H,d,J= 5 Hz,CH), 4.9 (2H,s,CH_2), 4.3(2H,q,CH_2), 3.9(3H,s,OCH_3), 3.8 (3H,s,OCH_3)
5b	61	150-151				see experimental
5g	63 [c,e]	141-143	66.9 (66.6	5.9 5.6	8.5 8.2)	IR : 1780,1700 (C=O); ^{1}H-NMR : 7.1(10H,m,arom.) 5.3(1H,dd,J= 5 Hz,J'= 16 Hz,CH), 4.9(1H,d,J= 5 Hz, CH), 3.5(4H,m,CH_2), 3.1(2H,s,CH_2)
5h	61 [d,e]	208-210	65.3 (65.7	5.6 5.2	8.3 8.5)	IR : 1800,1700(C=O); ^{1}H-NMR : 7.2(10H,m,arom.) 5.5(1H,t,CH), 5.1(1H,d,J= 5 Hz,CH),3.3(4H,m,CH_2)
5i	30 [b]	135-137 [f]	—	—	—	IR : 1765,1680(C=O); ^{1}H-NMR : 7.4-6.5(12H,m, arom.,NH,NH), 5.6(1H,q,CH), 5.0(1H,d,J= 4 Hz,CH), 4.2(2H,dd,J= 15 Hz,CH_2),

a) Yield of isolated pure product by crystallization from EtOH. A single spot was detected by TLC analysis. b) R= $C_6H_5OCH_2$. c) R= $C_6H_5CH_2$. d) R= C_6H_5 . e) overall yield . f) lit. data ref. 19b (compound, m.p.°C) : (3a, 155-156°C) (5a,130°C) (5i, 134-136°C) . g) The I.R. and ^{1}H-N.M.R. spectra were measured in $CHCl_3$ and $CDCl_3$ respectively. h) Reaction conditions : 3c (5 mmol), HCl conc. (10 ml), H_2O (10 ml), CH_2Cl_2(20 ml), room temp. overnight.



a	R^2 = Ph	R^3 = 3,4$(CH_3O)_2C_6H_3CH_2$	
b	R^2 = Ph	R^3 = 2,4$(CH_3O)_2C_6H_3CH_2$	
c	R^2 = 4-$CH_3OC_6H_4$	R^3 = 4-$CH_3C_6H_4$	
d	R^2 = 4-$CH_3OC_6H_4$	R^3 = Ph	
e	R^2 = Ph	R^3 = Ph	
f	R^2 = C_6H_5CH=CH	R^3 = Ph	
g	R^2 = Ph	R^3 = $(CH_2)_2Cl$	R = $C_6H_5CH_2$
h	R^2 = Ph	R^3 = $(CH_2)_2Cl$	R = Ph
i	R^2 = Ph	R^3 = H	R = $C_6H_5OCH_2$

- Scheme I -

to the formation of a single stereoisomer of the α-vinylamino-β-lactam 3a. The vinylamino group of 3a was cleaved under mild conditions to produce the free amino compound 4a which was acylated "in situ" to 5a. The N-benzyl group in 5a was removed by persulfate oxidation following the method of Huffmann and coworkers[9] to give the β-lactam 5i. In a similar manner the imine formed from benzaldehyde and 2,4-dimethoxybenzylamine yielded the β-lactam 5b. In general, the vinylamino cleavage was achieved by the method of Bose and coworkers[4a] by using p-toluenesulfonic acid in acetone-water. However, for insoluble β-lactams, such as 3c it was found more convenient to carry out the cleavage in dichloromethane-water. In this way the 43% yield of 4c obtained by the former method increased to 78% by the latter one.

The phenyl dichlorophosphate method has special importance because only three activating agents of the carboxyl group, haloformate esters[4a], cyanuric chloride[4b] and phosphorus oxychloride[4c], have been reported to be suitable for the synthesis of α-vinylamino-β-lactams. Bose and coworkers[4a] have shown that trifluoroacetic acid anhydride and chloroacetonitrile are ineffective for this conversion. Similarly diethyl chlorophosphate and diphenyl chlorophosphate give very low yields of the expected β-lactams, and diphenylphosphoryl azide, diethyl cyanophosphate and diphenyl phosphite pyridine do not lead to the formation of β-lactams.[10] On the other hand, we have investigated the behaviour of other known carboxyl group activating agents. Examination of Table II reveals that only 1-methyl-2-chloropyridinium iodide[11] seems to be moderately efficient for this approach, giving α-vinylamino-β-lactams in 30-50% isolated yields. Diethyl bromophosphate, which is an effective coupling agent for peptide bond formation[12a] and N,N-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (BOPDC) recently used in β-lactam synthesis[12b] showed low efficiency for Dane salt activation. Phosphorus trichloride, a reagent also used in peptide synthesis[12c], tosyl chloride[12d], saccharyl chloride[12e], and phenyl N-phenylphosphoramidochloridate[12f,3h] did not lead to the formation of α-vinylamino-β-lactams from the Dane salt and imino compounds. Recently we have described[12g] the use of the thionyl chloride--dimethylformamide complex for the synthesis of β-lactams. We have found however that this reagent is not efficient for activating Dane salts. In the case of phosphorus trichloride, which has not previously been applied to β-lactam synthesis, we have found that reaction between imines and substituted acetic acids other than the Dane salt, gave the corresponding β-lactams, although in poor yields. For example, treatment of phthalimidoacetic acid and 4-methoxybenzalaniline with phosphorus trichloride in the presence of triethylamine gave the corresponding β-lactams in 35% and 11% yield respectively.

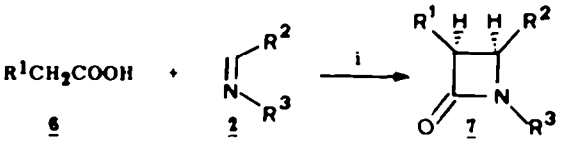
To explore the general applicability of phenyl dichlorophosphate reagent, several α-substituted acetic acids, phthalimidoacetic acid, methoxyacetic acid, benzyloxyacetic acid and acetoxyacetic acid were successfully

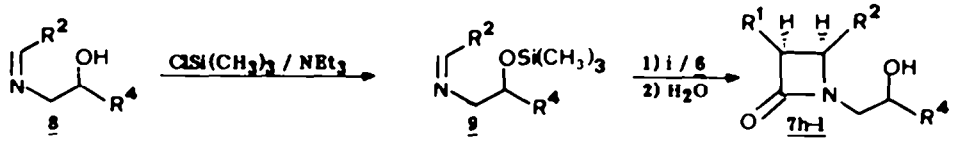
used to give the corresponding α-substituted-β-lactams. (Scheme II)

The yields of β-lactam products 7 from phenyl dichlorophosphate annelation of the corresponding acetic acids 6 and imines 2 are given in Table III. The stereochemistry of these monocyclic β-lactams shown in Table III was also derived from their ^{1}H-N.M.R. spectra. The coupling constant of 2 Hz was considered to indicate trans disposition of the C-3 and C-4 protons.

β-lactams 7a-g

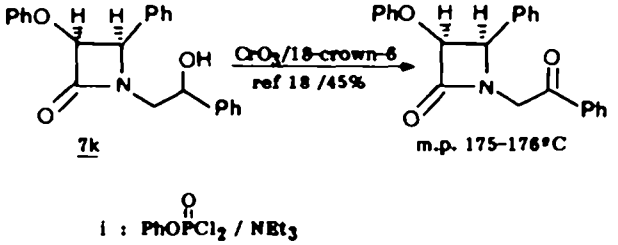
7	R^1	R^2	R^3
a	PhO	Ph	Ph
b	PhO	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$
c	Phth	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$
d	PhO	4-$CH_3OC_6H_4$	$PhCH_2$
e	CH_3O	Ph	Ph
f	$PhCH_2O$	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$
g	CH_3COO	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$





β-lactams 7h-l

7	R^1	R^2	R^4
h	PhO	4-$CH_3OC_6H_4$	Ph
i	Phth	4-$CH_3OC_6H_4$	Ph
j	PhO	4-$CH_3OC_6H_4$	H
k	PhO	Ph	Ph
l	PhO	4-$NO_2C_6H_4$	Ph

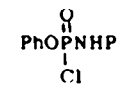
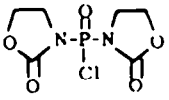
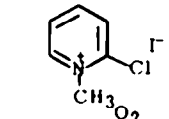
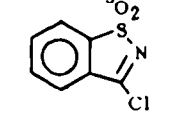
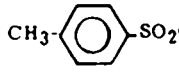
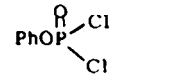


- Scheme II -

As shown in Scheme II when the method was applied to imines derived from aldehydes and ethanolamine derivatives prior protection of the hydroxyl group as the trimethylsilyl ether was required. A solution of triethylamine and the imine derived from an aldehyde and 2-amino-1-phenyl-ethanol was treated with trimethylchlorosilane in dichloromethane as solvent until the complete formation of the intermediate trimethylsilyl ether 9 as monitored by tlc analysis (silica gel plates, eluent AcOEt /hexane 1/1). Formation of the corresponding β-lactams 7h-m was carried out by consecutively adding at 0°C the acetic acid, triethylamine and the reagent. The resulting mixture was subsequently allowed to react at room temperature for 24 h. After work-up the unsilylated β-lactams 7h-m were obtained in high yield. It is interesting to note that β-lactams derived from phthalimidoacetic acid and ethanolimine derivatives have cis-stereochemistry whereas β-lactams having the phthalimido group often have trans-stereochemistry. On the basis of available data, the steric course of annelation using the phenyl dichlorophosphate reagent does not appear to be predictable. In all the reactions, however, only a single isomer was obtained. In the case of 7k because of its insolubility in common deuterated solvents, its configuration at C-3 and C-4 was determined from the ^{1}H-N.M.R. spectra of the oxidized product (Scheme II). A further observation is that these new β-lactams 7h-m appear to be interesting compounds for synthesis of N-unsubstituted β-lactams.[13]

When the reaction was carried out without previous protection of hydroxyl group in the starting ethanol-

Table II. Summary of reagents tested for the synthesis of α-vinylamino-β-lactams 3

Reagent [a]	3c	3d	3e
Cl_3P	0	0	—
Cl_3PO	45	22	16
	0	0	—
	30	30	—
$(EtO)_2PBr$	25	—	—
	50	35	30
	0	0	—
	0	0	—
$SOCl_2$-DMF	0	0	—
	65	55	50

a) Reaction Conditions : Reagent (10 mmol), imine (10 mmol), triethylamine (25 mmol), at room temperature for 20-24 h.

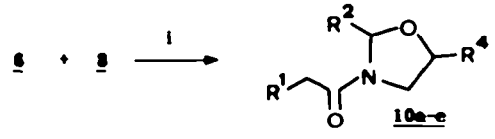
imines, formation of the azetidinone ring did not take place and the product was an oxazolidine 10. Thus the reaction between acetic acids and ethanolimines can be directed to the formation of oxazolidines and/or β-lactams according to the desired synthetic purposes.

In 1981 Badr et al. [14] have described that fusion of aromatic aldehydes with α-aminoacid ethyl esters containing a hydroxyl group in the β-position afforded N-unsubstituted oxazolidines, which can be acylated by means of the corresponding acyl halide. Our procedure gives the N-acyloxazolidines directly under mild conditions. Thus, treatment of a Schiff base formed from an aromatic aldehyde and 2-amino-1-phenylethanol, with phenoxyacetic acid or phthalimidoacetic acid by means of phenyl dichlorophosphate reagent in the presence of base, gave the corresponding N-acyloxazolidine in excellent yield. The structure of these oxazolidines were also confirmed by I.R., ^{1}H-N.M.R. spectroscopy and microanalysis. The I.R. spectra of these compounds showed an absorption band at 1660-1700 cm^{-1} due to the amide group but no NH-stretching vibration band and no β-lactam carbonyl absorption.

In an attempt to introduce the amido chain directly into the β-lactam product using N-acylamino acids as the starting acetic acids, we have found that the scope of the method is limited by reaction of these compounds to produce oxazolones. For example, under the conditions used in the synthesis of β-lactams, hippuric acid 11 failed to provide a substituted β-lactam when treated with Schiff bases. Mukerjee et al. [15] have reported a similar result when 5-oxazolones were treated with imines in the presence of base, although in some cases low yields have been obtained in the expected products. Manhas et al. [11] have reported that under similar conditions, reactions of hippuric acid with imines promoted by 2-chloro-1-methylpyridinium iodide afforded 5-oxazolones and not the corresponding 4-alkylideneoxazolones. We have found that under the conditions employed for the synthesis of β-lactams the reaction between imines and hippuric acid induced by phenyl dichlorophosphate afforded the corresponding 4-alkylidene-2-phenyl-5-(4H)-oxazolones 13 , in some cases in higher yield than those reported by earlier workers. (Scheme IV)

We next examined the use of N-aryldithiocarbonimidates 14 as the starting imines, for synthesis of 4-unsubstituted β-lactams 15 . We found that acylamino dithiocarbamic esters 16 were formed instead of the expected

	R^1	R^2	R^4
a	PhO	4-$CH_3OC_6H_4$	Ph
b	Phth	4-$CH_3OC_6H_4$	Ph
c	PhO	Ph	Ph
d	PhO	4-$NO_2C_6H_4$	Ph



i : $PhOP(O)Cl_2$ / NEt_3 / CH_2Cl_2 / 24 h / r.t.

- Scheme III -

Table III. β-lactams 7

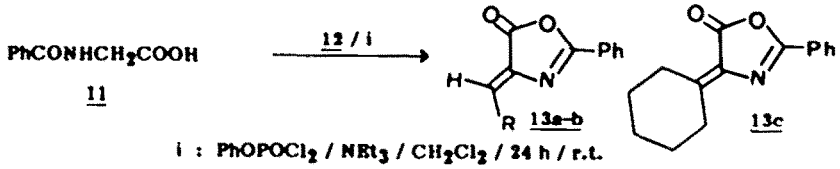
Compound [a]	Formula	Yield (%)	M.p.(°C)	lit M.p.(°C)
a	———	75	192-193	191-193 [12e]
b	———	65	182-183	182-183 [19]
c	———	70	189-190	174-175 [12e]
d	$C_{21}H_{21}NO_3$	84	125-126	——
e	———	30	139-140	141-142 [12e]
f	———	70	159-160	158-159 [12e]
g	———	50	128-131	128-130 [12e]
h	$C_{24}H_{23}NO_4$	91	175-177	——
i	$C_{26}H_{22}N_2O_5$	60	230-236	——
j	$C_{18}H_{19}NO_4$	70	146-148	——
k	$C_{23}H_{21}NO_3$	86	185-190	——
l	$C_{23}H_{20}N_2O_5$	80	175-178	——

a) All Products have cis-stereochemistry (J ≃ 5 Hz) except for the entry c which has trans-stereochemistry (J ≃ 2 Hz).

β-lactams. The same result was obtained when phenoxyacetic acid was treated with N-aryldithiocarbamates 17 in the presence of phenyl dichlorophosphate. (Scheme V)

Conclusions

Dane salts of aminoacetic acid can be activated under mild conditions by means of the readily available and economical reagent phenyl dichlorophosphate. Other known activating agents failed to provide such activation. Reaction of activated Dane salts with imines gave after hydrolysis of the side chain, α-amino- β-lactams in good to excellent yields. From acetic acids and ethanolimines the nature of the product is highly dependent on the reaction conditions used for the cycloaddition. Thus, when the hydroxyl group of the starting imines was protected as trimethylsilyl ether, the product obtained was the corresponding β-lactam. In the presence of a



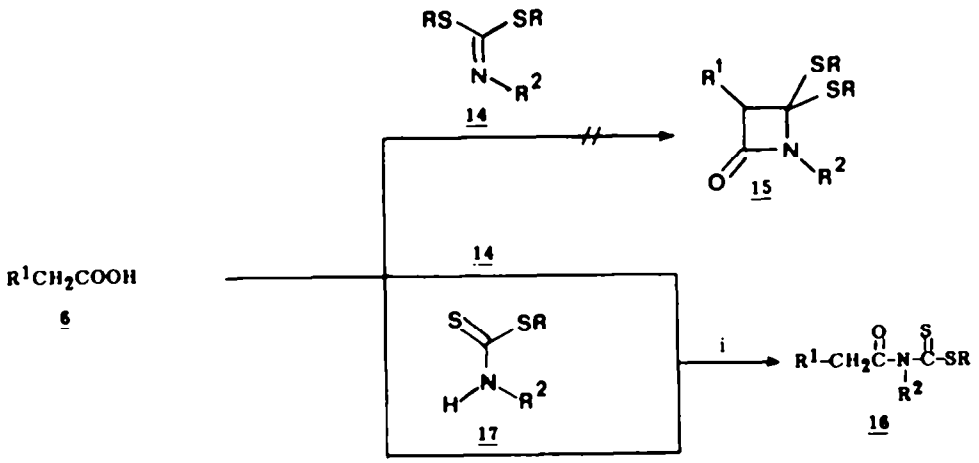
i : $PhOPOCl_2$ / NEt_3 / CH_2Cl_2 / 24 h / r.t.

12a : 4-$CH_3OC_6H_4CH$=N-Ph — 13a R : 4-$CH_3OC_6H_4$ — 85% — m.p. 155-157°C (lit. 156°C) [20]

12b : PhCH=N-Ph — 13b R : Ph — 80% — m.p. 165-166°C (lit. 167°C) [20]

12c :  =N-Ph — 13c — 70% — m.p. 138-140°C (lit. 136°C) [21]

– Scheme IV –



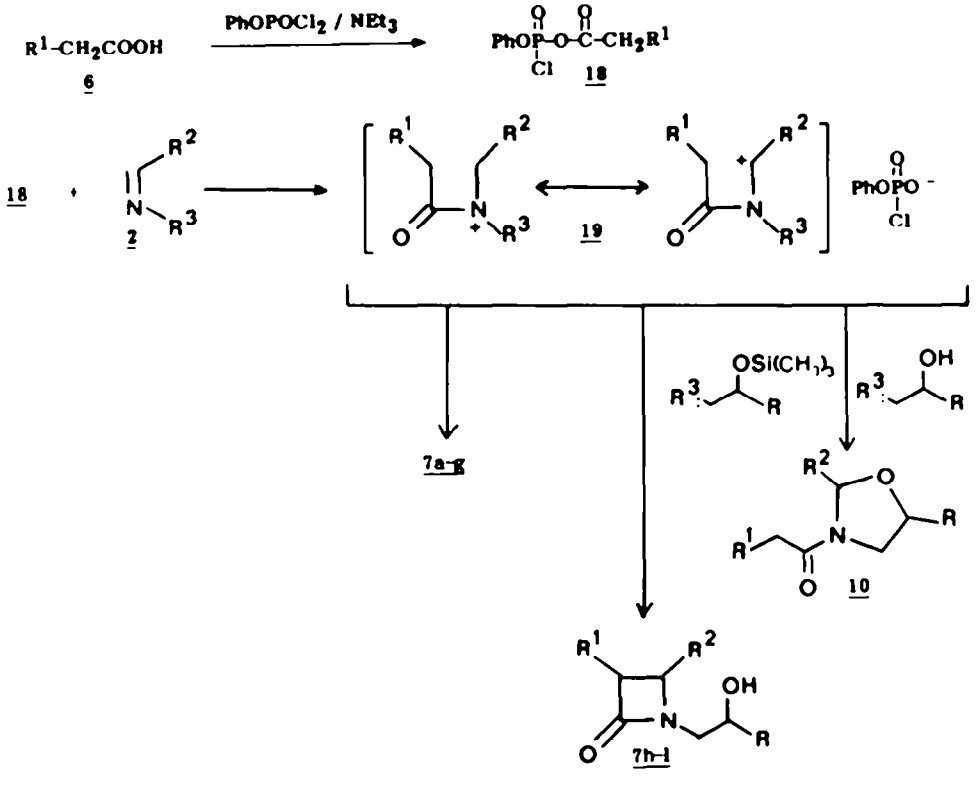
i : $PhOPOCl_2$ / NEt_3 / CH_2Cl_2 / 20-24 h / r.t.

R^1 = PhO

16a R = CH_3 R^2 = Ph

16b R = C_2H_5 R^2 = 4-CH_3Ph

- Scheme V -



- Scheme VI -

free hydroxyl group the reaction product was an oxazolidine. Reaction and cyclizations promoted by phenyl dichlorophosphate take place under mild conditions in good to excellent yields.

These results may have significance in view of a mechanism for the formation of β-lactams proposed by Manhas et al. [10,11]. They suggest the involvement of the active mixed carboxylic-phosphoric acid anhydride 18 as an intermediate which then reacts with an imino compound and triethylamine to produce the four membered heterocycle 7 (Scheme VI). In the case of oxazolidine 10 formation, the reaction may take place through prior acylation of the imine nitrogen on the Schiff base followed by attack of the hydroxyl group on the intermediate carbonium ion 19. When the hydroxyl group is protected as the trimethylsilyl ether, the reaction proceeds to formation of the expected β-lactams 7h-l.

EXPERIMENTAL

Melting points were taken on a Buchi SMP-20 melting point apparatus and are uncorrected. Proton N.M.R. spectra were measured on a Varian EM-360 A spectrometer, are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained using a Hewlett-Packard 5930 A mass spectrometer operated at 70 eV. All the starting materials used in this work were either commercially available in generally 98% or higher purity and used without further purification or prepared by standard literature procedures. Dichloromethane was purufied by the usual methods and stored over molecular sieves. The potassium salt of (α-methyl- β-methoxycarbonylvinyl)aminoacetic acid (Dane salt) was prepared according to the method described by Bose et al. [4a] Phenyl dichlorophosphate can be conveniently prepared by the method of Baer.[17] Trimethylchlorosilane was obtained from Wacker-Chemie GMBH (Munchen, Germany), and methyl acetoacetate was obtained from Lonza A.G. (Switzerland).

General procedure for the preparation of Schiff bases (8)

All the Schiff bases were prepared in a similar manner and used without purification. The following are representative of general procedures.

Method A. The liquid aldehyde (10 mmol) was added to the finely powdered 2-amino-1-phenylethanolamine (1.4 g, 10 mmol) and the mixture was heated until total solution was obtained and then was allowed to stand at room temperature. The precipitate product was disolved in dichloromethane and dried with magnesium sulfate. Filtration and evaporation of the solvent gave the imine in sufficient purity for use in the next step.

Method B. A mixture of the aldehyde (10 mmol), 2-amino-1-phenylethanolamine (10 mmol) and magnesium sulfate in dichloromethane (30 ml) was stirred at room temperature for 2 h. The work-up as described in method A gave the corresponding Schiff base.

2-Phenyl-N-(4'-methoxybenzylidene)ethanolamine (8 $R^2 = 4\text{-}CH_3OC_6H_4$, $R^4 = Ph$)

by method A : From anisaldehyde (1.25 ml, 10 mmol) ; yield 97% , m.p. 114-116°C ; N.M.R. ($CDCl_3$) : 8.00(1H,s, CH=), 7.50(2H,d, J= 8 Hz, arom.), 7.20 (5H,s_b,arom.), 6.70(2H,d,J= 8 Hz, arom.), 4.80(1H,dd, J= 8 Hz, J'= 4 Hz, CH), 3.9-3.5(2H,m,CH_2), 3.7(3H,s,OCH_3), 3.30(1H,s,OH); I.R.($CHCl_3$) : 3570 cm^{-1} (OH), 1640 cm^{-1} (C=N); ($C_{16}H_{17}NO_2$ Requires C, 75.3 ; H, 6.7 ; N, 5.5 . Found C,75.0 ; H, 6.5 ; N, 5.7 %)

2-Phenyl-N-benzylidenethanolamine (8 $R^2 = R^4 = Ph$)

by method A : From benzaldehyde (1.1 ml, 10 mmol) ; yield 86% m.p. 112-114°C ; N.M.R. ($CDCl_3$) : 8.10(1H,s, CH=), 7.7-7.0(10H,m,arom.), 4.8(1H,dd, J= 8 Hz, J'= 4 Hz, CH), 3.8-3.5 (2H,m,CH_2), 3.10 (1H,s,OH); I.R.($CHCl_3$): 3580 cm^{-1} (OH), 1640 cm^{-1} (C=N); ($C_{15}H_{15}NO$ Requires C,80.0 ; H, 6.7 ; N, 6.2 . Found C, 79.9 ; H, 6.7 ; N, 6.4 %)

2-Phenyl-N-(4'-nitrobezylidene)ethanolamine (8 $R^2 = 4\text{-}NO_2$, $R^4 = Ph$)

by method B : From 4-nitrobenzaldehyde (1.51 g, 10 mmol) ; yield 92% m.p. 141-142°C ; N.M.R. ($CDCl_3$) : 8.20 (2H,d, J = 4 Hz, arom.), 8.0 (1H,s,CH=), 7.70 (2H,d, J= 4 Hz, arom.), 7.20 (5H,s_b,arom.), 4.90(1H,dd, J = 8 Hz, J' = 4 Hz, CH), 3.9-3.4 (2H,m,CH_2) and 2.8 (1H,s,OH); I.R. ($CHCl_3$) : 3580 cm^{-1}(OH) and 1640 cm^{-1}(C=N) ($C_{15}H_{14}N_2O_3$ Requires C, 66.6 ; H, 5.2 ; N, 10.4 . Found C, 66.4 ; H, 5.1; N, 10.7 %)

General method for the synthesis of β-lactams (3a-f)

Potassium N-(α-methyl- β-methoxycarbonylvinyl)aminoacetate (2.12 g, 10 mmol) was suspended in anhydrous CH_2Cl_2 (25 ml) to which was added Et_3N (4.2 ml, 30 mmol) and the imine (10 mmol). The reaction mixture was cooled at 0°C and phenyl dichlorophosphate (1.5 ml, 10 mmol) was added. The mixture was stirred overnight at room temp., washed with water (2 x 20 ml) , 5% $NaHCO_3$-aq (20 ml) and dried (Na_2SO_4). Evaporation of the solvent gave the crude β-lactam (3) which was crystallized from EtOH.

cis-1-(2,4-Dimethoxybenzyl)-3-(α-methyl- β-methoxycarbonylvinylamino)-4-phenyl-2-azetidinone (3b)

A mixture of benzaldehyde (1.06 ml, 10 mmol), 2,4-dimethoxybenzylamine hydrochloride (2.03 g, 10 mmol), triethylamine (1.4 ml, 10 mmol) and $MgSO_4$ in CH_2Cl_2 (20 ml) was heated to reflux for 1.5 h. The mixture was filtered and potassium N-(α-methy- β-methoxycarbonylvinyl)aminoacetate (2.12 g, 10 mmol),Et_3N (4.2 ml, 30 mmol) and phenyl dichlorophosphate (1.5 ml, 10 mmol) were succesively added. Following the general procedure, the β-lactam (3b) was obtained in 50% yield (Table I).

cis-1-(2,4-Dimethoxybenzyl)-3-phenylacetamido-4-phenyl-2-azetidinone (5b)

A solution of vinylamino- β-lactam (3b) (2 g, 5 mmol) in EtOH (10 ml) and 2N HCl (10 ml) was stirred for 15 min. at room temp. The solution was diluted with water and extracted with CH_2Cl_2 (20 ml). The remaining aqueous solution was made alkaline with 40% NaOH-aq (3 ml) and extracted with CH_2Cl_2 (2 x 20 ml). The organic layer was separated and dried (Na_2SO_4). Removal of the solvent provided β-lactam (4b) as an oil (0.63 g, 40%) which

was used for the next step without further purification.
A solution of phenylacetyl chloride (0.29 ml, 2.2 mmol) in CH_2Cl_2 (2 ml) was added dropwise to a solution of the β-lactam (4b) (0.63 g, 2 mmol) and Et_3N (0.51 ml, 3.6 mmol) in the same solvent (5 ml). The reaction mixture was stirred at room temp. for 3 h and then washed with water (10 ml) and 1N HCl (10 ml), followed by saturated $NaHCO_3$-aq (10 ml). The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent gave a waxy residue which was triturated with EtOH-H_2O. The solid product was filtered off to yield 0.55 g (61%) of the β-lactam (5b) ; IR ($CHCl_3$) : 1780,1700 (C=O); NMR ($CDCl_3$) : 7.2-6.2 (14H,m,arom.), 5.7(1H,m,CH), 5.2 (1H,d,J= 4.8 Hz,CH), 4.5(2H,dd,J= 9 Hz, J'= 4 Hz,CH_2), 3.7(3H,s,OCH_3), 3.4(3H,s,OCH_3) and 3.1(2H,s,CH_2).

General Method for the synthesis of β-lactams (7a-g)

A mixture of an imine (10 mmol), a substituted acetic acid (10 mmol) and Et_3N (4.2 ml, 30 mmol) in CH_2Cl_2 (25 ml) was stirred at room temp. and phenyl dichlorophosphate (1.5 ml, 10 mmol) was added dropwise. The resulting mixture was stirred at room temp. for 24 h ; washed with H_2O (25 ml) and dried (Na_2SO_4). Removal of the solvent followed by recrystallization from EtOH-H_2O gives the pure β-lactam (7a-g).

General method for the synthesis of β-lactams (7h-l)

To a solution of an imine (2) (10 mmol) and Et_3N (1.4 ml, 10 mmol) in dry CH_2Cl_2 (25 ml) cooled at 0°C was added trimethylchlorosilane (1.2 ml, 10 mmol). The resulting mixture was stirred at room temp. for 60 min. A substituted acetic acid (10 mmol), Et_3N (4.2 ml, 30 mmol) and phenyl dichlorophosphate (1.5 ml, 10 mmol) were consecutively added at 0°C. The resulting mixture was stirred for 24 h at room temp. H_2O (20 ml) was added and stirring was continued for a further 15 min. This washing was repeated and finally the organic layer was separated and dried ($NaSO_4$). Evaporation of the solvent gave a waxy residue which was treated with EtOH-H_2O to give the β-lactam (7h-l).

cis-4-(4'-Methoxyphenyl)-3-phenoxy-1-(2'-phenyl-2'-hydroxyethyl)azetidin-2-one (7h)

From phenoxyacetic acid (1.52 g, 10 mmol) and 2-phenyl-N-(4'-methoxybenzilidene)ethanolamine (2.55 g, 10 mmol); yield 91% m.p. 175-177°C ; IR ($CHCl_3$) : 1760 (C=O) ; NMR ($CDCl_3$) :7.2-6.5(14H,m,arom.), 5.1 (1H,d,J= 5 Hz,CH), 4.9-4.6(1H,m,CH), 4.3(1H,d,J= 5 Hz,CH) and 3.7 (6H,s_b,OCH_3,CH_2,OH) ($C_{24}H_{23}NO_4$ Requires C, 74.0 ; H 6.0 ; N, 3.6 . Found C,74.4 ; H, 6.2 ; N, 3.4 %) .

cis-4-(4'-Methoxyphenyl)-1-(2'-phenyl-2'-hydroxyethyl)-3-phthalimidoilazetidin-2-one (7i)

From phthalimidoacetic acid (2.05 g, 10 mmol) and 2-phenyl-N-(4'-methoxybenzylidene)ethanolamine (2.55 g, 10 mmol) ; yield 60% m.p. 230-236°C ; IR(KBr) : 1780,1765 and 1730 (C=O) ; NMR (DMSO-d_6) : 7.7(4H,s, arom.), 7.3(5H,s,arom.), 7.1-6.5(4H,m,arom.), 5.6(1H,d,J= 5 Hz,CH), 5.3(1H,m,CH), 4.8(3H,m,CH,CH_2), 3.55 (1H,s,OH) and 3.3(3H,s,OCH_3) ($C_{26}H_{22}N_2O_5$ Requires C, 70.6 ; H, 5.0 ; N, 6.3 . Found C, 70.1 ; H, 5.4 ; N, 6.0 %)

cis-1-(2'-Hydroxyethyl)-4-(4'-methoxyphenyl)-3-phenoxyazetidin-2-one (7j)

Anisaldehyde (1.2 ml, 10 mmol) was added to ethanolamine (0.6 ml, 10 mmol) at room temp. and the mixture was mechanically stirred until a viscous oil was formed. CH_2Cl_2 (25 ml) was added and the solution was dried ($MgSO_4$) for 20-30 min.
Following the general procedure described above, the title compound was obtained in 70% yield m.p.146-148°C ; IR (KBr) : 1750 (C=O) ; NMR ($CDCl_3$) : 7.2-6.5(9H,m,arom.), 5.3(1H,d,J= 5 Hz,CH), 4.8(1H,d,J= 5 Hz,CH), 3.6(3H,s,OCH_3), 3.8-3.5(2H,m,CH_2) and 3.3-2.9(3H,m,CH_2,OH) ($C_{18}H_{19}NO_4$ Requires C,64.0 H, 6.1 ; N, 4.5 . Found C, 63.2 ; H, 6.0 ; N, 4.4 %).

cis-3-Phenoxy-4-phenyl-1-(2'-phenyl-2'-hydroxyethyl)azetidin-2-one (7k)

From phenoxyacetic acid (1.52 g, 10 mmol) and 2-phenyl-N-benzylidenethanolamine (2.25 g, 10 mmol) ; yield 86% m.p. 185-190°C ; IR ($CHCl_3$) : 1750 (C=O) ; NMR ($CDCl_3$) (oxidized product) : 7.7-6.4 (15H,m,arom.), 5.5(1H,d,J= 5 Hz,CH), 5.2(1H,d,J= 5 Hz,CH), 5.0(1H,d,J= ~18 Hz,CH) and 4.0(1H,d,J= ~18 Hz,CH) ($C_{23}H_{21}NO_3$ Requires C,76.9 ; H, 5.9 ; N, 3.9 . Found C, 76.6 ; H, 6.2 ; N, 4.0 %).

cis-4-(4'-Nitrophenyl)-3-phenoxy-1-(2'-phenyl-2'-hydroxyethyl)azetidin-2-one (7l)

From phenoxyacetic acid (1.52 g, 10 mmol) and 2-phenyl-N-(4'-nitrobenzylidene)ethanolamine (2.70 g, 10 mmol); yield 80% m.p. 175-178°C ; IR ($CHCl_3$) : 1780 (C=O) ; NMR ($CDCl_3$/ DMSO-d_6) : 8.1-6.3 (14H,m,arom.), 5.3 (1H,d,J= 5 Hz,CH), 5.1-4.5(3H,m,CH,CH_2) and 3.4 (2H,m,CH,OH) ($C_{23}H_{20}N_2O_5$ Requires C, 68.3 ; H, 5.0 N, 6.9 . Found C, 68.7 ; H, 4.7 ; N, 5.9 %) .

General method for the synthesis of oxazolidines (10)

To a solution of a carboxylic acid (10 mmol) and Et_3N (4.2 ml, 30 mmol) in dry CH_2Cl_2 (30 ml) cooled at 0-5°C was added the imine (10 mmol) and phenyl dichlorophosphate (1.5 ml, 10 mmol). The resulting mixture was stirred at room temp. for 20-24 h and washed with H_2O (2 x 20 ml). The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent gives a waxy residue which was treated with EtOH-H_2O to give the oxazolidine (10).

2-(4'-Methoxyphenyl)-3-phenoxy-5-phenyloxazolidine (10a)

From phenoxyacetic acid (1.52 g, 10 mmol) and N-(4'-methoxybenzylidene)-2-phenylethanolamine (2.55 g,10 mmol); yield 90% m.p. 99-100°C ; IR ($CHCl_3$) : 1660 (C=O); NMR ($CDCl_3$) : 7.5-6.5(14H,m,arom.), 5.1 (1H,t,J= 6 Hz,CH), 4.5(2H,s,CH_2), 4.3(1H,s,CH), 4.0(2H,d,J= 6 Hz,CH_2) and 3.7(3H,s,OCH_3) ; M^+ : 389 ($C_{24}H_{23}NO_4$ Requires C,74.0 ; H, 6.0 ; N, 3.6 . Found C, 73.7 ; H, 6.0 ; N, 3.6 %).

2-(4'-Methoxyphenyl)-3-phthalimidoacetyl-5-phenyloxazolidine (10b)

From phthalimidoacetic acid (2.05 g, 10 mmol) and N-(4'-methoxybenzylidene)-2-phenylethanolamine (2.55 g, 10 mmol) ; yield 70% m.p. 179-180°C ; IR ($CHCl_3$) : 1700 (C=O) ; NMR ($CDCl_3$) : 8.7-6.6(13H,m,arom.), 5.0(1H,m,CH), 4.3(2H,s,CH_2), 4.1(1H,s,CH), 4.0(2H,d,J= 6 Hz,CH_2) and 3.7 (3H,s,OCH_3) ($C_{26}H_{22}N_2O_5$ Requires C, 70.6 ; H, 5.0 ; N, 6.3 . Found C, 70.2 ; H, 5.0 ; N, 6.4 %).

3-Phenoxyacetyl-2,5-diphenyloxazolidine (10c)

From phenoxyacetic acid (1.52 g, 10 mmol) and N-benzylidene-2-phenylethanolamine (2.25 g, 10 mmol) ; yield

55% m.p. 106-107°C ; IR ($CHCl_3$) : 1660 (C=O) ; NMR : 7.3-6.4(15H,m,arom.), 5.0(1H,t,J= 6 Hz,CH), 4.4 (2H,s,CH_2) and 3.9 (2H,d,J= 6 Hz,CH_2) ($C_{23}H_{21}NO_3$ Requires C,76.8 ; H, 5.9 ; N, 3.9 . Found C,76.8 H,6.0 ; N, 3.9 %).

2-(4'-Nitrophenyl)-3-phenoxy-5-phenyloxazolidine (10d)

From phenoxyacetic acid (1.52 g, 10 mmol) and N-(4'-nitrobenzylidene)-2-phenylethanolamine (2.70 g, 10 mmol); yield 40% m.p. 129-134°C ; IR ($CHCl_3$) : 1680 (C=O) ; NMR ($CDCl_3$) : 7.9(2H,d,J= 8 Hz, arom.), 7.5-6.5(12H, m,arom.), 5.1(1H,s,CH), 5.0(1H,m,CH), 4.5(2H,s,CH_2) and 4.0 (2H,d,J= 6 Hz,CH_2) ($C_{23}H_{20}N_2O_5$ Requires C, 68.3 ; H, 5.0 ; N, 7.0 . Found C, 68.4; H, 5.1 ; N, 6.8 %).

General method for the synthesis of 4-alkylidene-2-phenyl-5(4H)-oxazolones (13)

To a solution of hippuric acid (11) (1.79 g, 10 mmol) and the Schiff base (12) (10 mmol) in CH_2Cl_2 (25 ml) containing Et_3N (4.2 ml, 30 mmol) was added phenyl dichlorophosphate (1.5 ml, 10 mmol) at 0°C. The mixture was stirred overnight at room temp., washed with H_2O (2 x 20 ml), 5% $NaHCO_3$-aq (20 ml) and dried(Na_2SO_4). Evaporation of the solvent gave the crude compound (13) which was crystallized from EtOH.

Reaction of N-aryldithiocarbonimidates (14) with activated phenoxyacetic acid

The same procedure as for the synthesis of β-lactams was followed.

N-Phenyl-N-phenoxyacetyldithiocarbamic methyl ester (16a)

From phenoxyacetic acid (1.33 g, 8.75 mmol) and dimethyl N-phenyldithiocarbonimidate (1.02 g, 6.75 mmol); yield 84% m.p. 125-126°C ; NMR ($CDCl_3$) : 7.2(10H,m,arom.), 4.46(2H,s,CH_2) and 2.4(3H,s,CH_3); M^+: 317.

N-(4-Methylphenyl)-N-phenoxyacetyldithiocarbamic ethyl ester (16b)

From phenoxyacetic acid (0.97 g, 6.4 mmol) and diethyl N-(4-methylphenyl)dithiocarbonimidate (1.46 g, 6.4 mmol) ; yield 60% ; m.p. 119-121°C ; NMR ($CDCl_3$) : 7.0(9H,m,arom.), 4.6(2H,s,CH_2), 3.1(2H,q,CH_2), 2.4 (3H,s,CH_3) and 1.3 (3H,t,CH_3) ; M^+ : 345 .

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