SYNTHESIS OF 2-(PHENYLTHIOMETHYLENE)OXAPENAM DERIVATIVES

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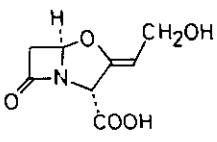
Abstract - Copper-catalysed decomposition of azetidinone diazoketones 3a and 3c, resulted in the formation of 2-(phenylthiomethylene)oxapenams, 7a and 11, respectively. Similarly, decomposition of diazoketone 21b gave a mixture of 19 and 22 whose carboxylation afforded an oxapenam-3-carboxylic acid 23a, a novel clavulanic acid analog.

The recent finding of clavulanic acid[1] (1) and thienamycin[2] (2) produced by various species of Streptomyces has aroused considerable attention among medicinal chemists because of their potent β-lactamase inhibitory or marked wide-spectrum antibacterial activity and their novel structural features. In the course of synthetic research directed toward new fused β-lactams, we became interested in reactions of acylcarbenes liberated from azetidinone diazoketones represented as 3a-c. This was because we expected an insertion reaction of the acylcarbene into the S-C bond on the β-lactam ring via Stevens rearrangement of an S-ylid intermediate which might form a 1-carbapenem 4 related to thienamycin (2). In fact, Ernest[3] recently reported that copper-catalysed decomposition of penicillin-derived diazoketones 5 provided tricyclic ketones 6, supporting our plan. However, the results of recent studies carried out at these laboratories fell short of our expectation. It was observed that copper-catalysed decomposition of the azetidinone diazoketones 3a-c did not give 1-carbapenams 4, but oxapenams such as 7a and 11, which form the topic of this paper. Further, we wish to report that similar decomposition of diazoketone 21b gave oxapenams 19 and 22 whose carboxylation afforded an oxapenam carboxylic acid 23a, a novel clavulanic acid analog.

Treatment of 4-phenylthio-2-azetidinone[4] (8) with sodium hydride and successively with methyl bromoacetate in a mixture of N,N-dimethylformamide (DMF) and tetrahydrofuran (THF) gave an azetidinone acetate 9a whose conversion into the



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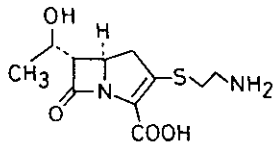

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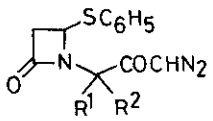
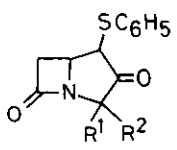


3a: $R^1=R^2=H$
3b: $R^1=R^2=CH_3$
3c: $R^1=CH_3$, $R^2=COOCH_3$



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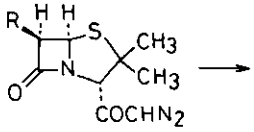

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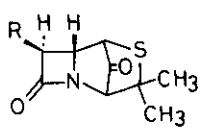

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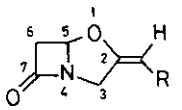
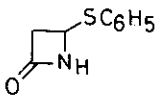
R=acylamino or phthaloylimino



7a: $R=SC_6H_5$
7b: $R=COOCH_3$



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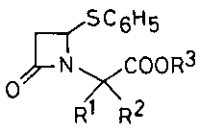
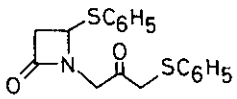


9a: $R^1=R^2=H$, $R^3=CH_3$
9b: $R^1=R^2=R^3=H$
9c: $R^1=R^2=R^3=CH_3$
9d: $R^1=R^2=CH_3$, $R^3=H$
9e: $R^1=R^3=CH_3$, $R^2=H$
9f: $R^1=R^3=CH_3$, $R^2=COOH$



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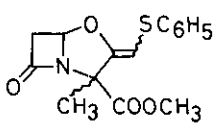

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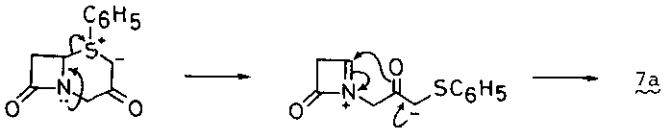
Chart 1

corresponding acid 9b was successfully carried out by treatment with lithium iodide in pyridine. A mixed anhydride prepared from the acid 9b in the usual manner was treated with diazomethane to give a diazoketone 3a. Decomposition of 3a was carried out by reflux in benzene in the presence of copper powder,[5] affording a 27% yield of the oxapenam 7a along with a small amount of an α-phenylthioketone 10.

The mass spectrum of 7a exhibited a molecular ion peak (m/e 233) fitting a molecule derived from the starting diazoketone 3a by loss of nitrogen. The infrared spectrum revealed the presence of the fused β-lactam group (1796 cm^{-1}) but showed no absorption due to the ketone function. On the other hand, a marked absorption at 1652 cm^{-1} was observed and suggested the presence of an enol ether group. Further, in the nuclear magnetic resonance (NMR) spectrum of 7a, six non-

aromatic protons were analysed as due to two series of the ABX absorption system. One of the series, centering at 3.12 (d, J=16.5 Hz), 3.52 (dd, J=16.5, 2.5 Hz) and 5.65 ppm (d, J=2.5 Hz), was ascribed to the protons on the β-lactam ring. The other, at 3.76 (dd, J=16, 2 Hz), 4.76 (dd, J=16, 2 Hz) and 5.71 ppm (t, J=2 Hz), indicated the presence of methylene protons coupled with an allylic olefinic proton. The above spectral data supported the proposed structure for 7a. The double bond geometry for the side chain of 7a was assigned as E, since the observed shift of the vinyl proton (5.71 ppm) in the NMR spectrum agreed well with the value (5.8 ppm) predicted for the E-form.[6] The possible isomeric counterpart of 7a was not detected in the decomposition mixture of the diazoketone 3a.

Formation of the oxapenam 7a can be explained as depicted in Chart 2. Initial formation of the S-ylid 12 by intramolecular addition of the acylcarbene to the sulfur atom and successive cleavage of the C-S bond of 12 into the intermediate 13 whose ring closure with the ketone oxygen gives the oxapenam 7a.



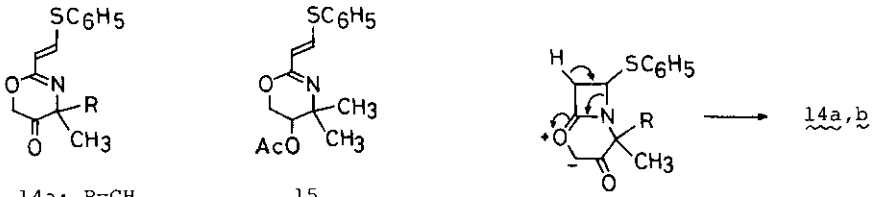
12 13

Chart 2

The structure of the minor product 10 was determined on the basis of the spectral data as shown in the experimental section. Compound 10 may arise from attack of liberated thiophenol on the acylcarbene or the intermediate 12 or 13.

This cyclization reaction was extended to analogs of the diazoketone.[8] Lithiation of the azetidinone acetate 9a with lithium bis(trimethylsilyl)amide followed by treatment with methyl iodide in THF gave a dimethylated product 9c (13 % yield) and a diastereomeric mixture of monomethylated products 9e (73% yield). The dimethyl compound 9c was converted into the acid 9d and then into the diazoketone 3b, whose decomposition in the presence of copper powder gave no oxapenam but a 48% yield of the dihydro-1,3-oxazine derivative 14a. A molecular ion peak (m/e 305) shown in the mass spectrum of 14a indicated a loss of nitrogen from the starting diazoketone 3b. The infrared spectrum of 14a did not exhibit absorption due to the β-lactam, but showed the presence of the ketone group (1729 cm^{-1}) and

an imino group (1637 cm^{-1}). The NMR spectrum revealed the presence of isolated methylene protons (4.48 ppm, s) and two protons on the trans-double bond (3.83 and 7.52 ppm, d, J=15 Hz) in addition to the gem-dimethyl and phenyl protons. Sodium borohydride reduction of 14a gave an alcohol whose acetylation formed an acetate 15. NMR analysis of 15 also revealed an ABX coupling system due to O-CH_2-CH(OAc)- with absorptions at 4.15, 4.30 and 4.92 ppm. All of these data supported the proposed structure for the dihydro-1,3-oxazine 14a. Formation of 14a from the diazoketone 3b can be explained as an attack of the liberated acylcarbene at the oxygen of the β-lactam accompanied by cleavage of the N-C bond as shown in Chart 3.



14a: R=CH_3
14b: R=$COOCH_3$

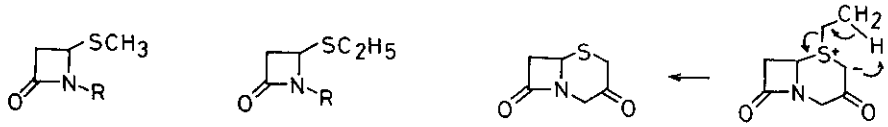
15

Chart 3

Lithiation of the monomethyl compound 9e followed by treatment with carbon dioxide gave the carboxylic acid 9f in quantitative yield which was transformed to a diastereomeric mixture (3:4) of the diazoketones 3c (59% yield) by the same procedure described for the conversion of 9b to 3a. Both isomers were separated by chromatography and each isomer was decomposed in the presence of copper powder, giving mainly a dihydro-1,3-oxazine 14b along with a small amount of an inseparable isomeric mixture of three oxapenams 11 (60:25:15 on the basis of 100 MHz NMR analysis).

Further, we would like to add the results obtained for S-alkyl analog of diazoketones. 4-Methylthio- (16a) and 4-ethylthio-2-azetidinone (17a) were prepared[4] and similarly converted into the corresponding diazoketones, 16d and 17d, respectively via the reaction sequence 16a → 16b → 16c → 16d and 17a → 17b → 17c → 17d. Copper-catalysed decomposition of the methylthio derivative 16d gave no identifiable products. In the case of the ethylthio derivative 17d, a 3-oxocepham (18) was obtained in 38% yield. The mass spectrum of 18 indicated a molecular ion peak (m/e 157), suggesting a molecule formed by loss of nitrogen and ethylene. The infrared spectrum exhibited the presence of the ketone group (1735

cm^{-1}), while the NMR spectrum showed a disappearance of the S-ethyl group and also the existence of a newly formed S-CH_2-CO group with an AB quartet at 3.02 and 3.60 ppm (J=15 Hz). These facts provided evidence for the structure 18. Formation of 18 can be explained in terms of S-ylid formation and successive elimination of the ethylene molecule via a sigmatropic [2.3] shift as shown below. Furthermore, it might be worth noting that such decomposition of the diazoketone 17d provides a novel method for synthesis of the 3-oxocepham skeleton.



16a: R=H
16b: R=CH_2COOCH_3
16c: R=CH_2COOH
16d: R=CH_2COCHN_2

17a: R=H
17b: R=CH_2COOCH_3
17c: R=CH_2COOH
17d: R=CH_2COCHN_2

18

Chart 4

Next, we investigated the introduction of the carboxyl group at the 3-position of the oxapenam nucleus thus obtained, which forms analogs of clavulanic acid amenable to biological tests. As described above, transformations of diazoketones, having substituents at the methylene carbon between the lactam nitrogen and the diazoketone group, into oxapenams were limited. In addition, anion formation at the 3-position of these oxapenams and successive introduction of the carboxyl group appeared to be exceedingly difficult because of low acidity of the proton of the 3-position. Thus, we attempted synthesis of an oxapenam 19 having an additional ester function at the exocyclic double bond which might confer an elevated acidity of the C-3 proton favoring anion formation.

N-Lithiation of the azetidinone 8 followed by treatment with ethyl γ-bromo-β-methoxycrotonate[9] gave azetidinonylcrotonate 20 whose acid hydrolysis gave a β-ketoester 21a. Diazo transfer reaction[10] to 21a with tosyl azide and triethylamine afforded the diazoketoester 21b. Decomposition of 21b was carried out in the presence of copper(II) acetylacetonate,[11] giving an isomeric mixture of oxapenams, 19 and 22, which were separated by silica gel chromatography. The assignment of double bond geometry to these oxapenams was suggested by their NMR analysis. The C-3 protons of the minor Z-isomer 22 absorb at a lower field (4.11 and 5.19 ppm)

than those of the major E-isomer 19 (3.91 and 4.93 ppm) because of a greater deshielding effect of the ester group compared with the phenylthio group.[12]

Both oxapenams, 19 and 22, were treated with lithium bis(trimethylsilyl)amide at -110° and then with carbon dioxide, giving a single oxapenam carboxylic acid 23a in 9.9% yield which formed the methyl ester 23b on treatment with diazomethane. The oxapenam carboxylate 23b thus obtained has the same ultraviolet absorption maximum at 246 nm as the starting oxapenams. An ABX absorption pattern due to the β-lactam ring protons was also present in the NMR spectrum. In addition, a singlet at 5.8 ppm in place of the AB quartet due to the C-3 protons of the starting oxapenams newly appeared, suggesting the existence of an ester group at the 3-position.

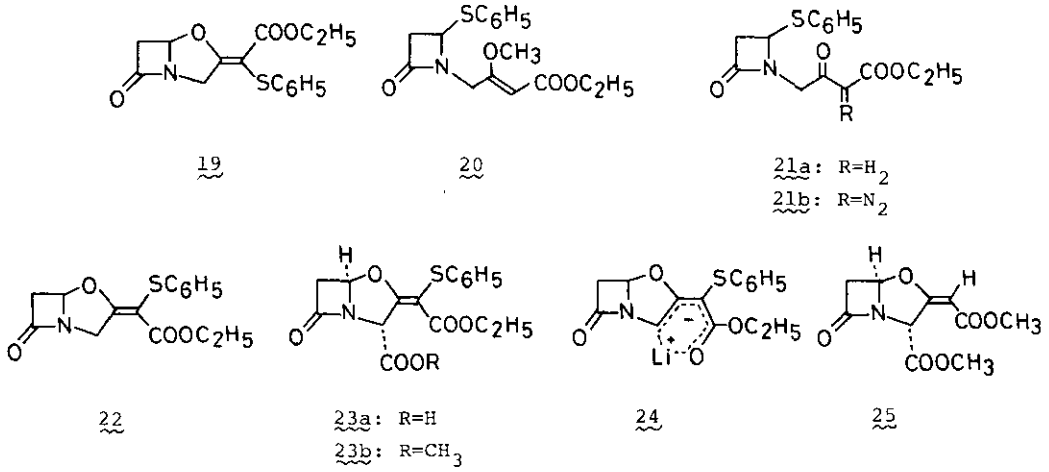


Chart 5

Oxapenam carboxylate 23b thus obtained was subjected to epimerization and exchange studies, which Brown et al. have applied to benzyl ester of clavulanic acid,[13] to determine the relative stereochemistry at C-3 and C-5. Treatment of 23b with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in chloroform did not result in C-3 epimerization: in the presence of deuterium oxide only exchange of the C-3 proton was observed. This fact suggested that the relative configuration at C-3 and C-5 in 23b is the thermodynamically more stable one, being the same as that of the clavulanic acid ester.

Formation of the single product 23a from each isomer of oxapenams 19 and 22 indicates that the reaction proceeded via the same intermediate anion stabilized

by chelation as shown in 24,[14] further suggesting that the double bond geometry of 23a thus formed implies a Z-form on the basis of electrophilic attack on the intermediate 24. Further, the Z-configuration in 23b could be assigned from the NMR absorption (5.82 ppm) due to the C-3β proton which agrees with the value (5.9 ppm) for the Z-form predicted according to the following discussion: Comparison of the absorption peaks due to the 3β protons of oxapenam dicarboxylates (5.71 ppm for the E-isomer 25; 5.20 ppm for the Z-isomer)[15] with those of the aforementioned monocarboxylate (5.02 ppm for the E-form 7b; 4.51 ppm for the Z-isomer)[7] shows a downfield shift of about 0.7 ppm. Application of this value to the chemical shifts observed for the starting oxapenams (5.19 ppm for 19; 4.93 ppm for 22) gives a predicted value of 5.9 ppm for the Z-form and 5.6 ppm for the E-form for the corresponding 3β protons of 23b.

In bioassay, these oxapenams did not show any antibacterial activity or β-lactamase inhibitory activity.

Experimental

Melting points are not corrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer, ultraviolet spectra (UV) on a Cary 14 (Serial No. 1258) spectrometer, NMR spectra on a Hitachi Perkin-Elmer R-24 spectrometer, 60 MHz, unless otherwise specified, or on a Varian HA-100 spectrometer, 100 MHz, and mass spectra (MS) on a JEOL-01SG mass spectrometer. Thin layer chromatography (TLC) was performed on precoated TLC-plates, Silica gel F_{254}, layer thickness 0.25 mm (E. Merck). Columns for ordinary chromatography were prepared with Wakogel C-200 (Wako Pure Chemical Industries, Ltd.) and plates for preparative TLC were provided with Silica gel $60F_{254}$ (E. Merck). The amount of silica gel and the developing solvents are shown in parenthesis. Solvents were removed by a rotary flash evaporator at diminished pressure and usually at 15-35°. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad.

Methyl 2-Oxo-4-phenylthio-1-azetidinylacetate (9a) ----- To a stirred mixture of NaH (0.69 g, 14.4 mmol, 50% mineral oil dispersion, washed with hexane), DMF (25 ml) and THF (25 ml) was added 4-phenylthio-2-azetidinone[4] (8) (2.58 g, 14.4 mmol) at -50°. The temperature was kept at -30° and stirring was continued for 30 min. After the mixture was cooled again at -50°, methyl bromoacetate (3.0 g, 19.6 mmol) was added and the temperature was raised to 0° over a 1 hr period. The mixture was then partitioned between AcOEt and water, and filtered. The organic layer was collected, dried and evaporated. Chromatography of the residue (40 g, benzene : AcOEt=3 : 1, v/v) gave 2.48 g (69%) of 9a.

The conversion of 4-methylthio- (16a) and 4-ethylthio-2-azetidinone[4] (17a)

into the corresponding 4-(alkylthio)azetidinylacetate, 16b and 17b, was analogously carried out. Spectral data are shown in Tables I and II.

Preparation of Diazoketones ----- The conversion of 9a into the corresponding diazoketone 3a was carried out as below. Other substituted diazoketones were synthesized in similar fashion and spectral and analytical data are shown in Tables I and II.

i) 2-Oxo-4-phenylthio-1-azetidinylacetic acid (9b) ----- A mixture of 9a (1.03 g, 4.10 mmol), pyridine (10 ml), and LiI (1.5 g, 11 mmol) was heated at 110° (bath temp.) for 3 hr with stirring. The mixture was cooled, diluted with AcOEt and was poured into water. The aqueous layer was collected, acidified with dil. HCl, then extracted with AcOEt twice. The combined extracts were washed with brine, dried, and evaporated, giving crude 9b (0.87 g, 89%) as a crystalline mass.

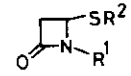
ii) 1-(3-Diazo-2-oxopropyl)-4-phenylthio-2-azetidinone (3a) ----- To a solution of crude 9b (700 mg, 2.95 mmol) and Et_3N (298 mg, 2.95 mmol) in THF (15 ml) was added dropwise at -20° a solution of isobutyl chloroformate (403 mg, 2.95 mmol) in THF (2 ml). After 20 min stirring, a diazomethane ethereal solution (12.5 ml, 20 mg CH_2N_2/ml, 5.90 mmol) was added at the same temperature. Stirring was continued for 1.5 hr, whereupon the temperature was slowly raised to 0°. After excess of diazomethane was decomposed by addition of AcOH, the mixture was diluted with AcOEt (20 ml), washed with dil. $NaHCO_3$ and then with water, dried and evaporated. The product was purified by silica gel chromatography (20 g, benzene: AcOEt=10 : 1, v/v) to give 520 mg (67%) of 3a.

3-Phenylthiomethylene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane (7a) ----- A mixture of 3a (204 mg), copper powder (10 mg) and benzene (25 ml) was refluxed for 4.5 hr with stirring. After cooling, the solvent was evaporated and preparative TLC of the residue (benzene:AcOEt = 3 : 1, v/v) gave 69 mg (34%) of the starting material 3a, 33 mg (27% based on 66% conversion) of 7a and 5 mg (2%) of 1-(3-phenylthio-2-oxopropyl)-4-phenylthio-2-azetidinone (10). IR $\nu_{max}^{liq.}$ cm^{-1}: 1796 (β-lactam), 1652. NMR ($CDCl_3$) δ: 3.12 (1H, d, J=16.5 Hz), 3.52 (1H, dd, J=16.5, 2.5 Hz), 3.76 (1H, dd, J=16, 2 Hz), 4.76 (1H, dd, J=16, 2 Hz), 5.65 (1H, d, J=2.5 Hz), 5.71 (1H, t, J=2 Hz), 7.28 (5H, s). MS m/e: 233 (M^+, $C_{12}H_{11}O_2NS$), 191 (M^+-CH_2CO), 149, 96 (base peak, $M^+-CO-C_6H_5S$).

Spectral data of the minor product 10 are shown in Tables I and II.

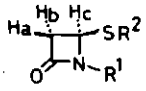
Methyl 2-(2-Oxo-4-phenylthio-1-azetidinyl)propionate (9e) and Its 2-Methyl Homolog 9c ----- A 15% n-butyllithium hexane solution (3.4 ml) was added dropwise to a solution of hexamethyldisilazane (1.09 g) in THF (23 ml) at -20° with stirring. After 10 min stirring at 0°, the mixture was cooled at -78° and a solution of 9a (1.14 g) in THF (11 ml) and then HMPA (3 ml) were added dropwise. After stirring for 30 min at the same temperature, CH_3I (1.16 g) was added with stirring. Stirring was continued, whereupon the temperature was allowed to raise to -20° over a 1 hr period. The mixture was cooled again to -78°, then quenched with AcOH (0.5

Table I. Spectral and Analytical Data of 1,4-Disubstituted 2-Azetidinones



Compd.	R^1	R^2	Appearance mp	IR ν_{max} cm^{-1} β-lactam	IR ν_{max} cm^{-1} others	State	Formula	Analysis % or MS Found (Calcd.) C	H	N	S
3a	CH_2COCHN_2	C_6H_5	yellow oil	1760	2100(diazo) 1640(ketone)	liq.	$C_{12}H_{11}O_2N_3S$	55.11 (55.15	4.56 4.24	15.89 16.08	12.00 12.27)
3b	$C(CH_3)_2COCHN_2$	C_6H_5	yellow foams	1755	2110(diazo) 1635(ketone)	Nujol	$C_{14}H_{15}O_2N_3S$	m/e: 261(M^+-N_2), 220, 180, 110, 109, 84			
3c	$C(CH_3)(COOCH_3)COCHN_2$	C_6H_5	(isomer A) yellow needles mp 114-115°	1780	2140(diazo) 1740(ester) 1627(ketone)	Nujol	$C_{15}H_{15}O_4N_3S$	54.03 (54.04	4.46 4.54	12.44 12.61	9.83 9.62)
			(isomer B) yellow oil	1767	2130(diazo) 1750(ester) 1650(ketone)	$CHCl_3$	$C_{15}H_{15}O_4N_3S$	m/e: 333(M^+), 305(M^+-N_2), 265, 224, 196, 168, 156			
9a	CH_2COOCH_3	C_6H_5	oil	1772	1748(ester)	liq.	$C_{12}H_{13}O_3NS$	57.51 (57.35	5.42 5.21	5.49 5.57	12.77 12.76)
9b	CH_2COOH	C_6H_5	prisms mp 143-144°	1740	~2600 1700(carboxy)	Nujol	$C_{11}H_{11}O_3NS$	55.56 (55.68	4.54 4.67	6.07 5.90	13.42 13.51)
9c	$C(CH_3)_2COOCH_3$	C_6H_5	oil	1765	1735(ester)	liq.	$C_{14}H_{17}O_3NS$	m/e: 279(M^+), 220, 170, 142, 128, 101, 84			
9d	$C(CH_3)_2COOH$	C_6H_5	viscous oil	1760 (br.)	~2600(carboxy)	liq.	$C_{13}H_{15}O_3NS$	m/e: 265(M^+), 218, 186, 154, 109			
9e	$CH(CH_3)COOCH_3$	C_6H_5	oil	1770	1745(ester)	liq.	$C_{13}H_{15}O_3NS$	m/e: 265(M^+), 206, 156, 128, 114 , 86			
10	$CH_2COCH_2SC_6H_5$	C_6H_5	viscous oil	1763	1725(ketone)	liq.	$C_{18}H_{17}O_2NS_2$	m/e: 343(M^+), 234, 165, 123			
16b	CH_2COOCH_3	CH_3	viscous oil	1770	1742(ester)	liq.	$C_7H_{11}O_3NS$	m/e: 189(M^+)			
16d	CH_2COCHN_2	CH_3	viscous oil	1752	2110(diazo) 1645(ketone)	$CHCl_3$	$C_7H_9O_2N_3S$	m/e: 156($M^+-N_2-CH_3$)			
17b	CH_2COOCH_3	C_2H_5	viscous oil	1772	1655(ester)	$CHCl_3$	$C_8H_{13}O_3NS$	m/e: 203(M^+), 142			
17c	CH_2COOH	C_2H_5	oil	1760	~2600(carboxy)	$CHCl_3$	$C_7H_{11}O_3NS$	m/e: 189(M^+), 128			
17d	CH_2COCHN_2	C_2H_5	viscous oil	1758	2120(diazo) 1648(ketone)	$CHCl_3$	$C_8H_{11}O_2N_3S$	m/e: 156($M^+-N_2-C_2H_5$), 152			
20	$CH_2C(OCH_3)=CHCOOC_2H_5$	C_6H_5	viscous oil	1758	1709(ester)	$CHCl_3$	$C_{16}H_{19}O_4NS$	m/e: 321(M^+), 212, 185, 136			
21b	$CH_2COC(N_2)COOC_2H_5$	C_6H_5	viscous oil	1763	2160(diazo) 1717(ester) 1663(ketone)	$CHCl_3$	$C_{15}H_{15}O_4N_3S$	m/e: 333(M^+), 224, 197			

Table II. NMR Data of 1,4-Disubstituted 2-Azetidinones
60 MHz, $CDCl_3$, δ ppm (coupling constants, Hz)



Compd.	R^1	R^2	Ha	Hb	Hc	Others
3a	CH_2COCHN_2	C_6H_5	2.88dd (15.5, 2.5)	3.48dd (15.5, 5)	5.23dd (5, 2.5)	3.73d(18, 1H), 4.20d(18, 1H), 7.43s(5H)
3b	$C(CH_3)_2COCHN_2$	C_6H_5	2.81dd (15, 2.5)	3.35dd (15, 5)	5.10dd (5, 2.5)	1.46s(3H), 1.51s(3H), 5.75s(1H), 7.39s(5H)
3c (isomer A)	$C(CH_3)(COCHN_2)(COOCH_3)$	C_6H_5	2.87dd (15.5, 2.5)	3.45dd (15.5, 5)	5.25dd (5, 2.5)	1.81s(3H), 3.80s(3H), 5.77s(1H), 7.45br.s(5H)
3c (isomer B)	$C(CH_3)(COCHN_2)(COOCH_3)$	C_6H_5	2.87dd (15.5, 2.5)	3.45dd (15.5, 5)	5.22dd (5, 2.5)	1.79s(3H), 3.78s(3H), 5.83s(1H), 7.45br.s(5H)
9a	CH_2COOCH_3	C_6H_5	2.86dd (15, 2.5)	3.45dd (15, 5)	5.25dd (5, 2.5)	3.69s(3H), 3.73 & 4.34 ABq (18, 1H each), 7.43s(5H)
9b	CH_2COOH	C_6H_5	2.85dd (15.5, 2.5)	3.44dd (15.5, 5)	5.23dd (5, 2.5)	3.76 & 4.36 ABq(18, 1H each), 7.41s(5H)
9c	$C(CH_3)_2COOCH_3$	C_6H_5	2.83dd (15.5, 2.5)	3.35dd (15.5, 5)	5.10dd (5, 2.5)	1.63s(3H), 1.67s(3H), 3.73s(3H), 7.45br.s(5H)
9d	$C(CH_3)_2COOH$	C_6H_5	2.82dd (15.5, 2.5)	3.35dd (15.5, 5)	5.14dd (5, 2.5)	1.62s(3H), 1.70s(3H), 7.40s(5H)
9e (major isomer)	$CH(CH_3)COOCH_3$	C_6H_5	2.82dd (15, 2.5)	3.31dd (15, 5)	4.99dd (5, 2.5)	1.64d(7.5, 3H), 3.69s(3H), 4.13q(7.5, 1H), 7.45m(5H)
9e (minor isomer)	$CH(CH_3)COOCH_3$	C_6H_5	2.84dd (15, 2.5)	3.38dd (15, 5)	5.30dd (5, 2.5)	1.56d(7.5, 3H), 3.69s(3H), 4.50q(7.7, 1H), 7.45m(5H)
9f	$C(CH_3)(COOH)(COOCH_3)$	C_6H_5	2.78dd (15.5, 2.5)	3.37dd (15.5, 5)	5.22dd (5, 2.5)	1.94s(3H), 3.74s(3H), 7.45m(5H)
10	$CH_2COCH_2SC_6H_5$	C_6H_5	2.88dd (15, 2.5)	3.46dd (15, 5)	5.19dd (5, 2.5)	3.58s(2H), 3.99 & 4.57 ABq (19, 1H each), 7.40s(10H)
16b	CH_2COOCH_3	CH_3	2.94dd (15, 3)	3.36dd (15, 5)	4.87dd (5, 3)	1.97s(3H), 3.63 & 4.22 ABq (18, 1H each), 3.69s(3H)
16c	CH_2COOH	CH_3	3.02dd (16, 2.5)	3.47dd (16, 5)	4.98dd (5, 2.5)	2.07s(3H), 3.66 & 4.34 ABq (17, 1H each)
16d	CH_2COCHN_2	CH_3	2.97dd (15.5, 3)	3.46dd (15.5, 5)	4.90dd (5, 3)	2.04s(3H), 3.69 & 4.24 ABq (18, 1H each), 5.54s(1H)
17b	CH_2COOCH_3	C_2H_5	2.97dd (15.5, 3)	3.41dd (15.5, 5)	4.93dd (5, 3)	1.12t(7, 3H), 2.54q(7, 2H), 3.72s(3H), 3.70 & 4.24 ABq (18.5, 1H each)
17c	CH_2COOH	C_2H_5	3.05dd (15, 5)	3.47dd (15, 5)	4.99dd (5, 2.5)	1.29t(7, 3H), 2.61q(7, 2H), 3.77 & 4.32 ABq(19, 1H each)
17d	CH_2COCHN_2	C_2H_5	2.98dd (15, 2)	3.48dd (15, 5)	5.01dd (5, 2)	1.27t(7, 3H), 2.61q(7, 2H), 3.72 & 4.18 ABq(18, 1H each), 5.67s(1H)
20	$CH_2C(=CHCOOC_2H_5)-OCH_3$	C_6H_5	2.84dd (15, 2.5)	3.36dd (15, 5)	5.03dd (5, 2.5)	1.22t(7, 3H), 3.61 & 4.23 ABq (16, 1H each), 3.83s(3H), 4.11 q(7, 2H), 4.91s(1H), 7.41m(5H)
21b	$CH_2COCCOOC_2H_5$ ($=N_2$)	C_6H_5	2.89dd (15, 2.5)	3.40dd (15, 5)	5.23dd (5, 2.5)	1.35t(7, 3H), 4.13 & 4.72 ABq (19, 1H each), 4.32q(7, 2H), 7.40br.s(5H)

ml), diluted with AcOEt, washed with water and dried. Evaporation of the solvent left 1.23 g of an oil which was chromatographed (30 g, benzene : AcOEt = 10 : 1, v/v), giving 160 mg (13%) of 9c and 880 mg (73%) of 9e (3 : 1 diastereomeric mixture on the basis of NMR analysis).

4,4-Dimethyl-5-oxo-2-(2-phenylthioethylene)-5,6-dihydro-1,3-oxazine (14a) and Its Conversion to 5-Acetoxy Derivative 15 ----- A mixture of 1-(3-diazo-1,1-dimethyl-2-oxopropyl)-4-phenylthio-2-azetidinone (3b, 55 mg), derived from 9c via carboxylic acid 9d, copper powder (5 mg) and benzene (3.5 ml) was refluxed for 3 hr and then, after filtration, evaporated to dryness. Preparative TLC of the residue (benzene : AcOEt = 3 : 1, v/v) gave 24 mg (48%) of 14a along with 6 mg of the starting material 3b. IR $\nu_{max}^{liq.}$ cm^{-1}: 1729 (C=O), 1637 (C=N). NMR ($CDCl_3$) δ: 1.31 (6H, s), 4.88 (2H, s), 5.82 (1H, d, J=15 Hz), 7.44 (1H, d, J=15 Hz), 7.46 (5H, br. s). MS m/e: 261 (M^+, $C_{14}H_{15}O_2NS$), 163 (base peak, C_6H_5S-CH=CH-C≡N^+).

To a solution of 14a (23 mg) in a mixture of THF-methanol (1 : 1, v/v) (0.6 ml) was added $NaBH_4$ (2 mg) at 0°. After stirring for 10 min, the mixture was diluted with AcOEt, washed with brine, dried and evaporated. Preparative TLC of the residue (benzene : AcOEt = 2 : 1, v/v) gave 15 mg (65%) of the hydroxy compound. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400 (br.), 1630.

Treatment of the hydroxy compound thus obtained with acetic anhydride and Et_3N in CH_2Cl_2 in the usual manner and preparative TLC of the product gave 14 mg (80%) of 15. IR $\nu_{max}^{liq.}$ cm^{-1}: 1745 (ester), 1640 (C=N). NMR ($CDCl_3$) δ: 1.19 (3H, s), 1.25 (3H, s), 2.09 (3H, s), 4.15 (1H, dd, J=12, 3.5 Hz), 4.30 (1H, dd, J=12, 2.5 Hz), 4.92 (1H, dd, J=3.5, 2.5 Hz), 5.72 (1H, d, J=15 Hz), 7.30 (1H, d, J=15 Hz), 7.45 (5H, m). MS m/e: 305 (M^+, $C_{16}H_{19}O_3NS$), 163 (base peak, C_6H_5SCH=CH-C≡N^+).

2-Methoxycarbonyl-2-(2-oxo-4-phenylthio-1-azetidinyl)propionic Acid (9f) ----- To a solution of hexamethyldisilazane (360 mg) in THF (10 ml) was added a 15% n-butyllithium hexane solution (1.12 ml) at -20° and the mixture was stirred for 10 min at 0°. The mixture was then cooled at -78° and a solution of 9e (396 mg) in THF (4 ml) was added. After addition of HMPA (1 ml), the solution was stirred for 20 min and an excess of CO_2 gas was bubbled at -78° with stirring. The mixture was further stirred for 40 min with cooling and then partitioned between AcOEt and water. The aqueous layer was collected, acidified with dil. HCl, and extracted with AcOEt. The extract was dried, and evaporated, leaving 463 mg of a diastereomeric mixture of acids 9 which was pure enough for the next conversion reaction into the corresponding diazoketone 3c without further purification.

Methyl 4-Diazo-2-methyl-3-oxo-2-(2-oxo-4-phenylthio-1-azetidinyl)butanoate (3c) ----- To a solution of 9f (1.27 g, 4.17 mmol) and Et_3N (0.51 g, 5.0 mmol) in THF (25 ml) was added isobutyl chloroformate (0.68 g, 5.0 mmol) at -15°. After 35 min stirring at the same temperature, a diazomethane ethereal solution (12 ml, 20 mg CH_2N_2/ml, 5.7 mmol) was added and the mixture was kept at 0° for 1 hr. After excess of diazomethane was decomposed by addition of AcOH, the mixture was diluted with AcOEt, washed with dil. $NaHCO_3$ and then with water, dried and

evaporated. The partly crystallized residue was recrystallized from benzene-hexane to give 234 mg of a diastereomer 3c (isomer A, mp 114 - 115°). The mother liquor was evaporated and chromatography of the residue on silica gel (25 g, benzene : AcOEt = 10 : 1, v/v) gave 457 mg (33%) of another diastereomer 3c (isomer B, oil) and then 115 mg of additional crystalline isomer A (total 349 mg, 25%). Spectral data for these diastereomeric diazoketones 3c are shown in Tables I and II.

Decomposition of 1-(3-Diazo-1-methoxycarbonyl-1-methyl-2-oxopropyl)-4-phenylthio-2-azetidinone (3c) ----- A mixture of 3c (190 mg, crystalline isomer A), copper powder (15 mg) and benzene (20 ml) was refluxed for 2 hr and then, after addition of copper powder (10 mg), refluxing was continued for 3.5 hr. The mixture was cooled, filtered and evaporated to dryness. Preparative TLC of the residue (benzene : AcOEt = 4 : 1, v/v) gave the dihydro-1,3-oxazine 14b (103 mg) and the oxapenam 11 (16 mg) along with the starting material 3c (31 mg). Spectral data for 14b is shown below. IR $\nu_{max}^{liq.}$ cm^{-1}: 1755 (ester), 1735 (C=O), 1635 (C=N). NMR ($CDCl_3$) δ: 1.54 (3H, s), 3.73 (3H, s), 4.54 (2H, d-like), 5.83 (1H, d, J=15 Hz), 7.52 (1H, d, J=15 Hz), 7.47 (5H, br. s). MS m/e: 305 (M^+, $C_{15}H_{15}O_4NS$), 163 (base peak, $C_6H_5SCH{=}CH{-}C{\equiv}N^+$).

The oxapenam 11 thus obtained was a mixture of three isomers, A, B and C, whose relative ratio are shown as 60:25:15 by NMR analysis. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1795 (β-lactam), 1750 (ester), 1640 (C=C). NMR (100 MHz, $CDCl_3$) δ for A: 2.11 (3H, s), 3.11 (1H, dd, J=16.5, 1 Hz), 3.37 (1H, dd, J=16.5, 2.5 Hz), 3.65 (3H, s), 5.77 (1H, s), 5.61 (1H, dd, J=2.5, 1 Hz); for B: 1.95 (3H, s), 3.13 (1H, dd, J=16.5, 1 Hz), 3.42 (1H, dd, J=16.5, 2.5 Hz), 3.78 (3H, s), 5.32 (1H, s), 5.72 (1H, dd, J=2.5, 1 Hz); for C: 1.67 (3H, s), 3.16 (1H, dd, J=16.5, 1 Hz), 3.37 (1H, dd, J=16.5, 2.5 Hz), 3.59 (3H, s), 5.66 (1H, s), 5.61 (1H, dd, J=2.5, 1 Hz). MS m/e: 305 (M^+, $C_{15}H_{15}O_4NS$), 204 (M^+-CH_2CO-CO_2CH_3), 149 (base peak).
Decomposition of the diastereomer 3c (oily isomer B) also gave the same results.

3,8-Dioxo-5-thia-1-azabicyclo[4.2.0]octane (18) ----- A mixture of 1-(3-diazo-2-oxopropyl)-4-ethylthio-2-azetidinone (17d) (110 mg), copper powder (10 mg) and toluene (13 ml) was refluxed for 1 hr. Removal of the solvent and preparative TLC of the product (benzene : AcOEt = 2 : 3, v/v) gave 18 (31 mg, 38%) as a syrup. IR $\nu_{max}^{liq.}$ cm^{-1}: 1766, 1735. NMR ($CDCl_3$) δ: 3.02 and 3.60 (1H, each, ABq, J=15 Hz), 3.25 (1H, dd, J=16, 2 Hz), 3.63 (1H, dd, J=16, 4.5 Hz), 3.81 and 4.43 (1H, each, ABq, J=19 Hz), 4.88 (1H, dd, J=4.5, 2 Hz). MS m/e: 157 (M^+, $C_6H_7NO_2S$), 129 (M^+-CO), 115 (M^+-CH_2CO).

Ethyl 3-Methoxy-4-(2-oxo-4-phenylthio-1-azetidinyl)-2-butenoate (20) ----- A 15% n-butyllithium hexane solution (0.45 ml) was added to a solution of hexamethyldisilazane (118 mg) in THF (3 ml) at 0°, then stirring was continued for 5 min. After cooling, a solution of 8 (120 mg) in THF (0.5 ml) was added dropwise at -78° with stirring. After further stirring for 15 min at -78°, HMPA (1 ml) and then ethyl γ-bromo-β-methoxycrotonate[9] (164 mg) were added portionwise at -78°. The temperature was raised to -20° over a 1 hr period. The mixture was worked up

as described for the preparation of 9a from 8, and preparative TLC of the product (benzene : AcOEt = 4 : 1, v/v) afforded 20 (142 mg, 66%) as a syrup. See Table I.

Ethyl 3-Oxo-4-[2-oxo-4-phenylthio-1-azetidinyl]butanoate (21a) ----- A mixture of 20 (448 mg), acetone (21 ml) and conc. HCl (0.6 ml) was allowed to stand at room temperature for 2.5 hr. The mixture was extracted with AcOEt, washed with brine and then with dil. $NaHCO_3$, dried and evaporated, leaving 21a (384 mg, 90%) which was used for the next reaction without further purification.

Ethyl 2-Diazo-3-oxo-4-(2-oxo-4-phenylthio-1-azetidinyl)butanoate (21b) ----- A solution of 21a (384 mg) obtained as above, tosyl azide (380 mg), and Et_3N (140 mg) in CH_3CN (5 ml) was allowed to stand overnight. The solvent was evaporated and the residue was extracted with benzene-hexane (1 : 1, v/v). The extract was evaporated and the residue was chromatographed (15 g, benzene : AcOEt = 6 : 1, v/v) to give 21b (380 mg, 91%) as a syrup. See Tables I and II.

3-(1-Ethoxycarbonyl-1-phenylthio)methylene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane (19 and 22) ----- A stirred mixture of 21b (110 mg), $Cu(acac)_2$ (30 mg), and toluene (10 ml) was refluxed for $1\frac{1}{3}$ hr. The mixture was cooled, filtered and evaporated and the residue was chromatographed by preparative TLC (benzene : AcOEt = 5 : 1, v/v) to give 22 (8 mg) as a fast-running isomer and 19 (33 mg) as a slow-running isomer. IR $\nu_{max}^{CHCl_3}$ cm^{-1} for 19: 1800 (β-lactam), 1697 (ester), 1608; for 22: 1802 (β-lactam), 1690 (ester), 1604. UV λ_{max}^{EtOH} nm (ε) for 19: 245 (16,400), 300 (sh.); for 22: 244 (16,600), 300 (sh.) NMR (100 MHz, $CDCl_3$) δ for 19: 1.16 (3H, t, J=7 Hz), 3.30 (1H, d, J=17 Hz), 3.57 (1H, dd, J=17, 3 Hz), 3.91 and 4.93 (1H each, ABq, J=17 Hz), 4.16 (2H, q, J=7 Hz), 5.91 (1H, d, J=3 Hz); for 22: 1.15 (3H, J=7 Hz), 3.10 (1H, d, J=17 Hz), 3.51 (1H, dd, J=17, 3 Hz), 4.11 and 5.19 (1H each, ABq, J=18 Hz), 4.13 (2H, q, J=7 Hz), 5.71 (1H, d, J=3 Hz). MS m/e for 19 and 22: 305 (M^+, $C_{15}H_{15}NO_4S$), 277 (M^+-CO), 222 (O=C=C(SC_6H_5)$COOC_2H_5$), 168 (base peak, M^+-CO-SC_6H_5).

3-(1-Ethoxycarbonyl-1-phenylthio)methylene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid (23a) and Its Methyl Ester (23b) ----- A lithium amide solution prepared from hexamethyldisilazane (121 mg) and 15% n-butyllithium hexane solution (0.46 ml) in THF (3 ml) was cooled at -110° with a CS_2-liq.N_2 bath and a solution of 19 (230 mg) in THF (0.5 ml) was added dropwise. After a DMF-THF (1 : 1, v/v) mixture (1 ml) was added, the mixture was stirred for 10 min at the same temperature, then an excess of CO_2 gas was carefully bubbled for 10 min. After an exchange of the bath with a dry ice-acetone bath, the mixture was allowed to stand for 10 min at -78°, and then partitioned between AcOEt and water. The aqueous layer was collected, acidified with 2N HCl, and extracted several times with AcOEt. The combined extracts were washed with brine, dried and evaporated, giving 26 mg (9.9%) of 23a. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1815 (β-lactam), 1740 (COOH), 1697 (ester), 1617. NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7 Hz), 3.01 (1H, d, J=18 Hz), 3.46 (1H, dd, J=18, 3 Hz), 4.12 (2H, q, J= 7 Hz), 5.85 (1H, s), 5.86 (1H, d, J=3 Hz).

Treatment of an ethereal solution of 23a (26 mg) with diazomethane in the

usual manner followed by work-up as usual and chromatography of the product on silica gel (2 g, benzene : AcOEt = 14 : 1, v/v) gave 23b (25 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1810 (β-lactam), 1743 (ester), 1685 (αβ-unsaturated ester), 1609. UV λ_{max}^{EtOH} nm (ε): 246 (16,400), 302 (3,100). NMR (100 MHz, $CDCl_3$) δ: 1.12 (3H, t, J=7 Hz), 3.13 (1H, d, J=17 Hz), 3.54 (1H, dd, J=17, 3 Hz), 3.81 (3H, s), 4.12 (2H, q, J=7 Hz), 5.81 (1H, d, J=3 Hz), 5.82 (1H, s). MS m/e: 363 (M^+, $C_{17}H_{17}NO_6S$), 335 (M^+-CO), 226 (M^+-CO-SC_6H_5), 222 (O=C=C(SC_6H_5)$COOC_2H_5$), 109 (base peak, $C_6H_5S^+$).

References and Notes

1. T.T. Howarth, A.G. Brown, and T.J. King, J. Chem. Soc., Chem. Commun., 1976, 266; A.G. Brown, D. Butterworth, M. Cole, G. Hanscomb, J.D. Hood, C. Reading, and G.N. Rolinson, J. Antibiotics, 29, 668 (1976).
2. G. Albers-Schönberg, B.H. Arison, O.D. Hensens, J. Hirshfield, K. Hoogsteen, E.A. Kaczka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratcliffe, E. Walton, L.J. Ruswinkel, R.B. Morin, and B.G. Christensen, J. Am. Chem. Soc., 100, 6491 (1978).
3. I. Ernest, Tetrahedron, 33, 547 (1977).
4. K. Clauss, D. Grimm, and G. Prossel, Ann. Chem., 1974, 539.
5. Uses of copper (II) acetate, copper (II) acetylacetonate, and rhodium (II) acetate as catalysts were attempted but without success, giving resinous products.
6. The coefficients of Matter et al [U.E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, Tetrahedron, 25, 691 (1969)] were applied to the corresponding methoxycarbonyl derivative 7b of established geometry[7] as follows. Addition of [Z_{gem}(SR)-Z_{gem}($COOCH_3$)] to the observed chemical shift for the vinyl proton of 7b (5.45) gives 5.76. On the same basis, the predicted value for the Z-isomer of 7a is 5.24. See reference 7.
7. E. Hunt, P.H. Bentley, G. Brooks, and M.L. Gilpin, J. Chem. Soc., Chem. Commun., 1977, 906.
8. Diazoketones having the p-chloro- or p-methyl-phenylthio group or phenylseleno group in place of the phenylthio group in 3a were synthesized, and subjected to decomposition to give the corresponding oxapenams, indicating that such manipulations did not affect this reaction.
9. C. Piantadosi and V.G. Skulason, J. Pharm. Sci., 53, 902 (1964).
10. M. Regitz, Synthesis, 1972, 351.
11. Use of copper powder in this case showed the reaction giving no oxapenam products.
12. The C-3 protons of the aforementioned oxapenam carboxylate derivative 7b having an E-configuration appear at 3.88 and 5.02 ppm,[7] while the corresponding protons in the oxapenam 7a appear at 3.76 and 4.76 ppm, indicating a marked difference in the deshielding effect of the two functions.
13. A.G. Brown, D.F. Corbett and T.T. Howarth, J. Chem. Soc., Chem. Commun., 1977, 359.
14. It was observed that treatment of the major isomer 19 of these oxapenams with lithium bis(trimethylsilyl)amide followed by quenching with acetic acid

afforded a low yield of compounds 19 and 22 in a ratio of 1 : 2.

15. P.H. Bentley, P.D. Berry, G. Brooks, M.L. Gilpin, E. Hunt, and I.I. Zomaya, J. Chem. Soc., Chem. Commun., 1977, 748.

Note added in proof:

Very recently, Ponsford reported that reinvestigation of copper-catalysed decomposition of 5 revealed the formation of a small amount of the tricyclic oxapenam derivative related to 7a in addition to the tricyclic ketone 6 : R.J. Ponsford, Tetrahedron Letters, 21, 2451 (1980).

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