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[2+2] CYCLOADDITION REACTIONS OF ISOTHIAZOLES INTRAMOLECULAR NUCLEOPHILIC ATTACK ON ISOTHIAZOLIUM SALTS PREPARATION OF NEW β-LACTAM SYSTEMS BASED ON ISOTHIAZOLE NUCLEUS

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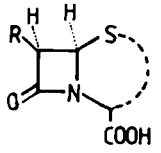
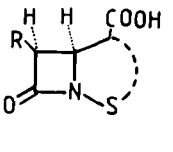
ABSTRACT

[2+2] cycloaddition reactions of isothiazoles with diphenyl ketene afford new fused β-lactam systems. The intramolecular nucleophilic attack of carbanions on isothiazolium salts is found to take place on the ring sulphur atom. 2-H-2-benzoyl-1,3-thiazines were prepared and allowed to react with diphenyl ketene, or with acid chloride in the presence of a tertiary amine, to afford the corresponding β-lactams.

Numerous β-lactam antibiotics have been prepared in recent years, and new synthetic approaches to these compounds have continued to appear in the literature. It is remarkable however, that most of the known β-lactam antibiotics are bicyclic and contain the partial structure I, where the two heteroatoms (S,N) are part of either a heterocyclic nucleus (thiazolidine or thiazine ring), or an acyclic system. It would be of interest to prepare the isomeric system II, where the β-lactam ring is constructed on an isothiazolidine nucleus in order to study its potential antibiotic activity in comparison with system I.

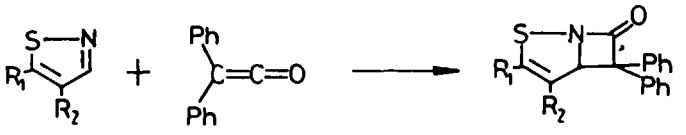


I



II

With this in mind we have investigated the applicability of Standinger's[1] method for the preparation of β-lactams from ketenes and imines. It has already been shown that several bicyclic β-lactams have been prepared from the reaction of diphenylketene with Δ^2-thiazolines[2-5]. Treatment of isothiazoles III with diphenyl ketene in T.H.F. under nitrogen and subsequent chromatographic separation afforded the expected bicyclic systems IV (Scheme 1).



III

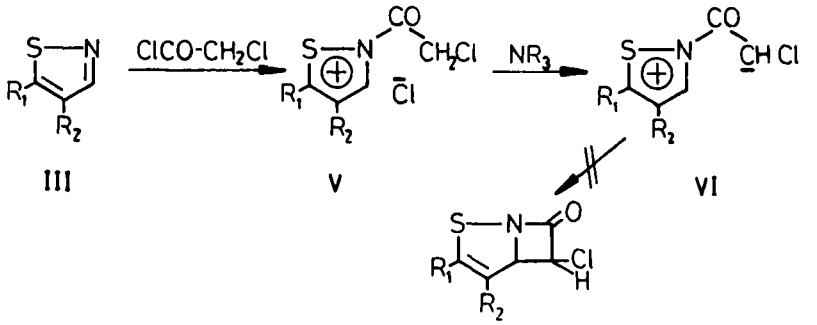
SCHEME 1

IV

An alternative route to the β-lactam ring is the reaction of an acid chloride with the heterocycle in the presence of tertiary amine[6]. Sheenan and Rayan already suggested that this reaction does not proceed via a ketene intermediate, but probably involves the addition of the acid chloride to the imine and subsequent cyclization under the influence of the tertiary amine[7].

However, when the isothiazoles III were allowed to react under these conditions, either decomposition products were obtained or starting isothiazoles were recovered with no trace of β-lactam. Monitoring the reaction by IR did not show any evidence of β-lactam formation during the course of reaction, indicating that the β-lactam is not a precursor of the decomposition products.

When the reaction was carried out in the absence of tertiary amine, alkylation of the isothiazole took place and the isothiazolium salt V was precipitated by the addition of ether. Subsequent treatment of this salt with triethylamine at room temperature gave back the starting isothiazole, via a simple dealkylation process. Heating the reaction mixture on a water-bath for 30 minutes gave similar decomposition products. This suggests that the site of intramolecular attack of the carbanion of VI does not take place on carbon 3 of the isothiazolium nucleus.

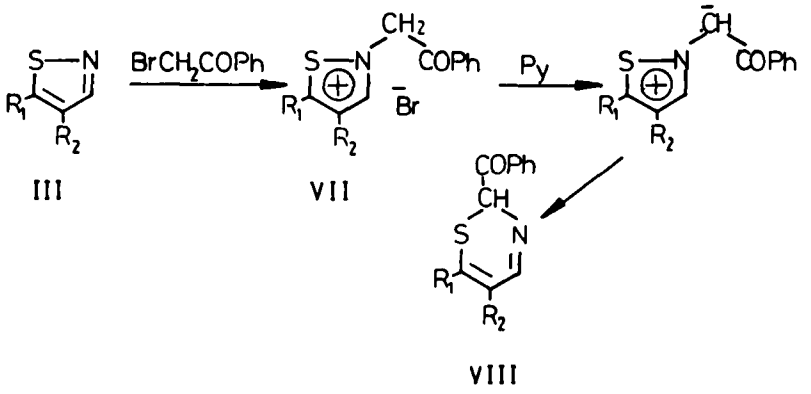


SCHEME 2

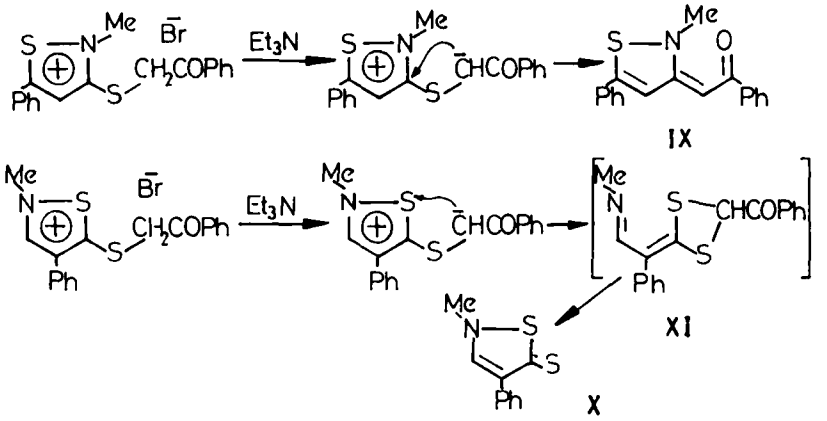
This led us to study the chemistry of intramolecular reactions of carbon nucleophiles with isothiazolium salts in some details.

2-Phenacylisothiazolium salts VII were prepared by the fusion of isothiazoles III with phenacyl bromide. Treatment of VII with tertiary amines afforded the 2-N-2-benzoyl-1,3-thiazines VIII, via intramolecular nucleophilic attack on the sulphur atom (Scheme 3).

Treatment of 3-phenacylthio and 5-phenacylthioisothiazolium salts with tertiary amines afforded 3-phenacylideneisothiazoline IX, and isothiazoline-5-thione X, respectively (Scheme 4). In the first case, nucleophilic attack on the ring sulphur is sterically impossible, and reaction occurs at the carbon-3 atom. In the second case, however, nucleophilic attack takes place at the ring sulphur atom leading to the formation of a dealkylated product most probably via an unstable intermediate of the type XI.



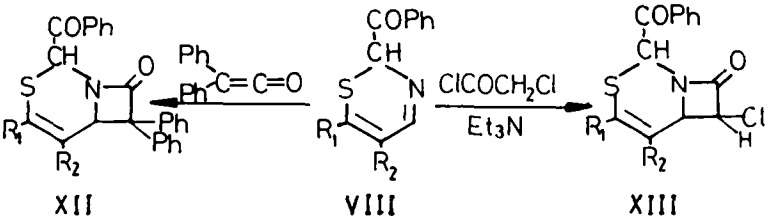
SCHEME 3



SCHEME 4

From these results we postulate that the intramolecular nucleophilic attack of the carbanion in intermediate VI takes place on the ring sulphur atom (rather than on carbon 3), leading to the observed decomposition products.

The new β-lactam systems XII and XIII, were obtained when the 1,3-thiazine derivatives VIII were allowed to react with diphenyl ketene or with chloroacetyl chloride and tertiary amine respectively (Scheme 5).



SCHEME 5

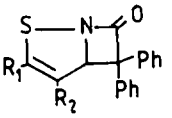
EXPERIMENTAL

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a Varian 56/60 A, and Mass Spectra on a Varian CH5 mass spectrometer. IR spectra were measured on a Unicam S.P 2006. Unless indicated C,H,N analysis were ± 0.4 % of the calculated values, and were performed by Cairo University Micro-analytical Center.

Reaction of isothiazoles III with diphenyl ketene :

Isothiazole III_a (500mg, 3.1 mmol) and diphenyl ketene (660mg, 3.4 mmol) in tetrahydrofuran (100ml), were stirred at room temperature for two days, then refluxed on a waterbath for 6 hrs., and left to stand for 12 hrs. The solvent then was removed under vacuum and the residue was chromatographed on silica gel with benzene-pet. ether (50%). The product was recrystallised from pet. ether (693mg, 63 % yield) m.p. 165°C; mass spectrum : m/e 355; calculated for $C_{23}H_{17}NOS$, 355; IR spectrum : (Nujol) 1760 cm^{-1} (β-lactam C=O); NMR spectrum : τ ($CDCl_3$) 5.03 (1H singlet, C-5 proton "the fused carbon proton"), 3.20 (1H singlet, the isothiazoline ring proton), 2.5-2.9 (15H bands, the aromatic protons). The analytical results of compounds IV_a-IV_c are listed in Table 1.

TABLE 1



Comp.	R_1	R_2	Yield %	M.P °C	Formula	Calcd. %				Found %			
						C	H	N	S	C	H	N	S
IV_a	H	ph	63	165	$C_{23}H_{17}NOS$	77.75	4.79	3.94	9.01	77.41	5.16	3.73	9.38
b	H	4-tolyl	59	164	$C_{24}H_{19}NOS$	78.05	5.15	3.79	8.67	77.65	5.32	3.21	8.40
c	ph	H	65	161	$C_{23}H_{17}NOS$	77.75	4.79	3.94	9.01	77.59	5.09	3.64	8.74

Reaction of isothiazoles III with chloroacetyl chloride and triethylamine :

To a stirred solution of isothiazole III (500mg, 3.1 mmol) and triethylamine (313mg, 3.1 mmol) in dry tetrahydrofuran (100ml) was added dropwise chloroacetyl chloride (350mg, 3.1 mmol) at room temperature. A white precipitate was formed, the mixture became red and a rise in temperature was noted. Monitoring the reaction iwth I.R. did not show any evidence for β-lactam formation (no abs. in the region of 1780-1740 cm^{-1}). After stirring for 3 days the solid (triethyl ammonium hydrochloride) was filtered off and washed with T.H.F. The combined T.H.F. filtrates and washings were evaporated under reduced pressure and the residue was chromatographed (silica; benzene, pet. ether 50%) to afford starting isothiazole and decomposition products.

2-(Chloroacetyl) isothiazolium chloride V

Chloroacetyl chloride (350mg, 3.1 mmol) and isothiazole III_a (500mg, 3.1 mmol) were heated gently together at 80° for 30 minutes. Cooling and dilution with ether afforded V as a white crystaline material. The product was recrystallized from benzene (620mg, 73% yield) m.p. 181°C.

Analysis for $C_{11}H_9$ N OS Cl; calcd. % : C,55.35; H,3.78; N, 5.87; S, 13,42. Found : C, 55.18; H, 3.92; N, 5.64; S,13.31.

Reaction of 2-(chloroacetyl) isothiazolium chloride V with triethylamine :

Triethylamine (200mg, 2 mmol) was added dropwise to a stirred solution of isothiazolium chloride V (550mg, 2 mmol) in tetrahydrofuran (100ml) at room temperature.

The reaction was monitored by IR to detect any evidence for β-lactam formation. After 3 days, the solvent was removed and the residue was chromatographed (silica; benzene-pet. ether 50%) to afford isothiazole III as well as decomposition products.

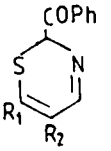
2H-2-Benzoyl-1,3-thiazines VIII :

(A) Phenacyl bromide (1.99g, 0.01 mol) and isothiazole III (1.61g, 0.01 mol) were fused together gently on a steam-bath for 10 minutes. The cooled product was extracted with ether, then the residue was crystallised from ethanol to give the 2-phenacylisothiazolium bromides VII_a-VII_c.

(B) Isothiazolium bromide VII_a (1000mg, 2.28 mmol) was treated with approximately a five-fold excess of dry pyridine, and refluxed until homogeneous. The mixture was diluted with water and extracted with benzene. The benzene extracts were washed with dil. HCl, water and dried. Evaporation, and chromatography (silica; benzene-pet. ether 70%) afforded $VIII_a$; the I.R. spectrum showed three characteristic bands at 1570, 1610, and 1695, which were attributed to *C=N, C=C,* and *C=O* stretching vibrations respectively; mass spectrum m/e 279, calculated for $C_{17}H_{13}NOS$, 279; NMR spectrum : τ ($CDCl_3$) 6.48 (1H singlet, C-2 proton), 3.14 (1H singlet, C-6 proton), 2.72-2.50 (10H bands, the aromatic protons), 1.76 (1H singlet, the C-4 proton).

The analytical results for compounds $VIII_a$-$VIII_c$ are listed in Table II.

TABLE 2



Comp.	R_1	R_2	Yield %	M.P °C	Formula	Calcd. %				Found %			
						C	H	N	S	C	H	N	S
$VIII_a$	H	ph	74	142	$C_{17}H_{13}NOS$	73.12	4.66	5.02	11.47	73.46	4.81	5.34	11.80
b	H	4-tolyl	72	147	$C_{18}H_{15}NOS$	73.72	5.12	4.78	10.92	73.23	5.54	4.49	10.67
c	ph	H	65	139	$C_{17}H_{13}NOS$	73.12	4.66	5.02	11.47	73.50	4.95	4.78	11.02

2-Methyl-3-phenacylidine-5-phenylisothiazoline IX :

2-Methyl-3-phenacylthio-5-phenylisothiazolium bromide[8] (0.01 mol) was treated with approximately a five-fold excess of dry pyridine and refluxed until homogeneous. The mixture was diluted with water and extracted with benzene. The benzene extracts were washed with dil. HCl, water and dried. Evaporation, and chromatography afforded IX m.p. 163° (39% yield); mass spectrum : m/e 293, calculated for $C_{18}H_{15}NOS$ 293; NMR spectrum : τ ($CDCl_3$) 3.5 (1H singlet, the isothiazoline hydrogen), 2.1-2.95 (5H bands, the aromatic protons of the side-chain phenyl), 2.6 (5H singlet, the aromatic protons of the isothiazoline phenyl).

2-Methyl-4-phenyl-isothiazoline-5-thione X :

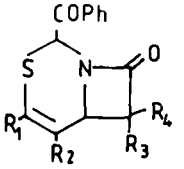
2-Methyl-4-phenyl-5-phenacylthioisothiazolium bromide[8] (0.01 mole) was treated with dry pyridine as described above, and afforded X m.p. 150°C[9] (50% yield).

Reaction of 2H-2-Benzoyl-1,3-thiazine VIII with diphenyl ketene :

This reaction was carried out as described above for the reaction of isothiazole with diphenyl ketene to afford the β-lactams XII. Compound XII_a was obtained in 32% yield, m.p. 206°C; mass spectrum : m/e 473; calculated for $C_{31}H_{23}NO_2S$ 473; IR spectrum : (Nujol) 1755 cm^{-1} (β-lactam C=O). The NMR spectrum : τ ($CDCl_3$) 6.82 (1H singlet, C-2 proton), 5.48 (1H singlet, the fused carbon proton), 4.1 (1H singlet, thiazine ring proton), 2.94-2.56 (20H m., the aromatic protons).

The analytical results for compounds XII_a-XII_c are listed in Table III.

TABLE 3



Comp.	R_1	R_2	R_3	R_4	Yield %	M.P °C	Formula	Calcd. %				Found %			
								C	H	N	S	C	H	N	S
XII_a	H	ph	ph	ph	32	206	$C_{31}H_{23}NO_2S$	78.65	4.86	2.96	6.76	78.83	4.98	2.60	6.45
b	H	4-tolyl	ph	ph	28	209	$C_{32}H_{25}NO_2S$	78.85	5.13	2.87	6.57	78.46	5.41	2.53	6.88
c	ph	H	ph	ph	37	214	$C_{31}H_{23}NO_2S$	78.65	4.86	2.96	6.76	78.51	5.12	2.71	6.53
$XIII_a$	H	ph	H	Cl	26	225	$C_{19}H_{14}NO_2SCl$	64.14	3.94	3.94	9.00	63.79	3.61	3.68	8.68
b	H	4-tolyl	H	Cl	30	217	$C_{20}H_{16}NO_2SCl$	64.95	4.33	3.79	8.66	64.67	4.74	3.91	8.32
c	ph	H	H	Cl	22	229	$C_{19}H_{14}NO_2SCl$	64.14	3.94	3.94	9.00	63.85	3.80	3.43	8.76

Reaction of 2-H-2-Benzoyl-1,3-thiazine VIII with chloroacetyl chloride and triethylamine :

The reaction was carried out according to the procedure described for the reaction of isothiazoles with chloroacetyl chloride and triethylamine. However the β-lactams XIII were obtained in this case. Compound $XIII_a$ was obtained in 26% yield, m.p. 225°C; mass spectrum : m/e 355; calculated for $C_{19}H_{14}N\ O_2S\ Cl$, 355; IR spectrum : (Nujol) 1772 cm^{-1} (β-lactam C=O).
The analytical results for compounds $XIII_a$-$XIII_c$ are listed in Table III.

REFERENCES

1. H. Staudinger, H.W. Klever, and P. Kober, Annalen, 374, 1, (1910).
2. H.T. Clarke, J.R. Johnson, and R. Robinson, eds.; The Chemistry of Penicillin, P. 973, Princeton Univ. Press, Princeton, (1949).
3. R. Pfleger and A. Jaeger, Chem. Ber. 90, 2460, (1957).
4. R.D.G. Cooper, MTP International Review of Science, Organic Chemistry, Series I, Vol. 6, 247, D.H. Hey and D.I. John, eds., Publisher Butterworth, London.
5. A.K. Mukerjee, and R.C. Srivastava, Synthesis 327 (1973).
6. J.C. Sheehan and E.J. Coery, Org. Reactions, 9, 388, (1957).
7. J.C. Sheehan and J.J. Ryan, J. Am. Chem. Soc., 73, 1204, (1951).
8. M.E. Hassan, and Ali K. Khalafalla, to be published.
9. M.S. Chauhan, M.E. Hassan, and D.M. Mckinnon, Canadian J. Chem. 52, 1738, (1974).