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BICYCLIC 1,2-OXAZINE N-OXIDES. DIFFERENT BEHAVIOUR IN RING FISSION BETWEEN SYSTEMS DERIVED FROM 5- AND 6-MEMBERED RING CYCLIC ENAMINES

S. DANEO†, G. PITACCO, A. RISALITI, and E. VALENTIN*
Istituto di Chimica, Università, 34127 Trieste, Italy

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Abstract—1,2-Oxazine N-oxides derived from aminocyclohexenes open into the corresponding nitroalkylated trisubstituted enamines, whereas those derived from aminocyclopentenes give stable tetrasubstituted enamines. Both open-chain systems are easily hydrolyzed to the corresponding γ-nitrocycloalkanones.

Aliphatic nitrocompounds are important intermediates in organic synthesis.[1] Among them γ-nitroketones of the type **5** (Scheme 1) are receiving particular attention since they can be converted into the corresponding 1,4-dicarbonyl compounds **6**, which are precursors of a series of other compounds.[2]

Synthesis of several γ-nitroketones can be accomplished through reaction of enamines **1** with nitro-olefins **2**.[3]

In general the first step involves a [4+2]‡ cycloaddition reaction[6-8] with formation of 1,2-oxazine N-oxides **3**, which can be isolated in some cases, their stability being dependent on the parent enamine, the type of substituents in the nitroolefin and the conditions used.

Direct hydrolysis of **3** is unsatisfactory, as the desired ketones **5** are generally accompanied by tars. On the other hand, opening of **3** into the corresponding nitroalkylated enamines **4** and subsequent hydrolysis gives no problems, provided the pH is maintained between 5–6.

In the reactions of (E) - 1 - phenyl - 2 - nitro - propene with enamines derived from cyclohexanone, such as **7a** and **b** (Scheme 2), and from cyclopentanone, such as **7c**, the corresponding 1,2-oxazine N-oxides **8** are stable and can be stored unaltered at −15°C for several days. At room temperature and in solution of suitable solvents, they open to give the corresponding nitroalkylated enamines **9**, which can undergo hydrolyses to the corresponding γ-nitroketones **10** (Scheme 2). In the case of **7a** (B = morpholine, piperidine) an equilibrium between the two forms has been observed.[9]

Several problems arise regarding (a) the type of ring fusion in **8**; (b) the configurations around the chiral centres both in the enamines **9** and in the ketones **10**; and (c) the double bond position in the enamines **9**.

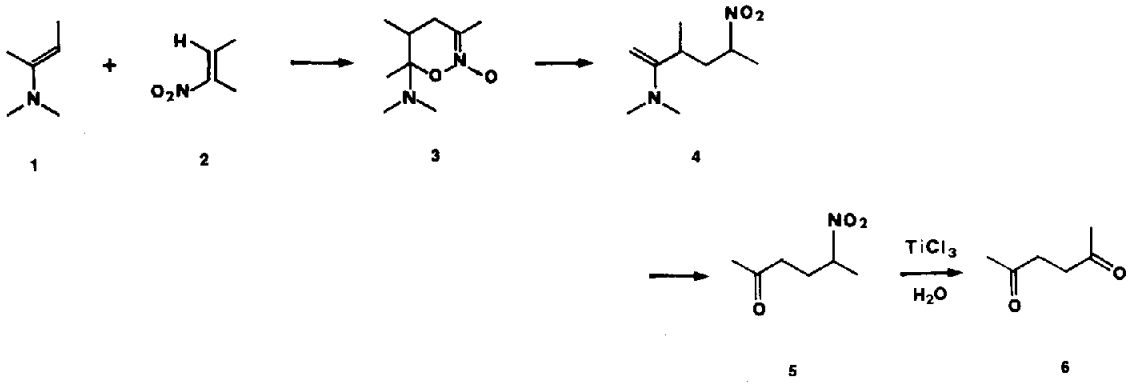
As for the ring fusion in the 1,2-oxazine N-oxides **8**, it has been determined to be *cis*. In fact when the anancomeric morpholino system **8a** opens into **9a** and is hydrolysed to the ketone **10a** under non-epimerizing conditions, this latter compound undergoes equilibration into its diastereoisomer **11a** (Scheme 3).

From the thermal instability of **10a** it follows that the nitroalkyl group –CH(Ph)CH(Me)NO_2 is axial and hence the fusion between the rings in **8a** is *cis*.

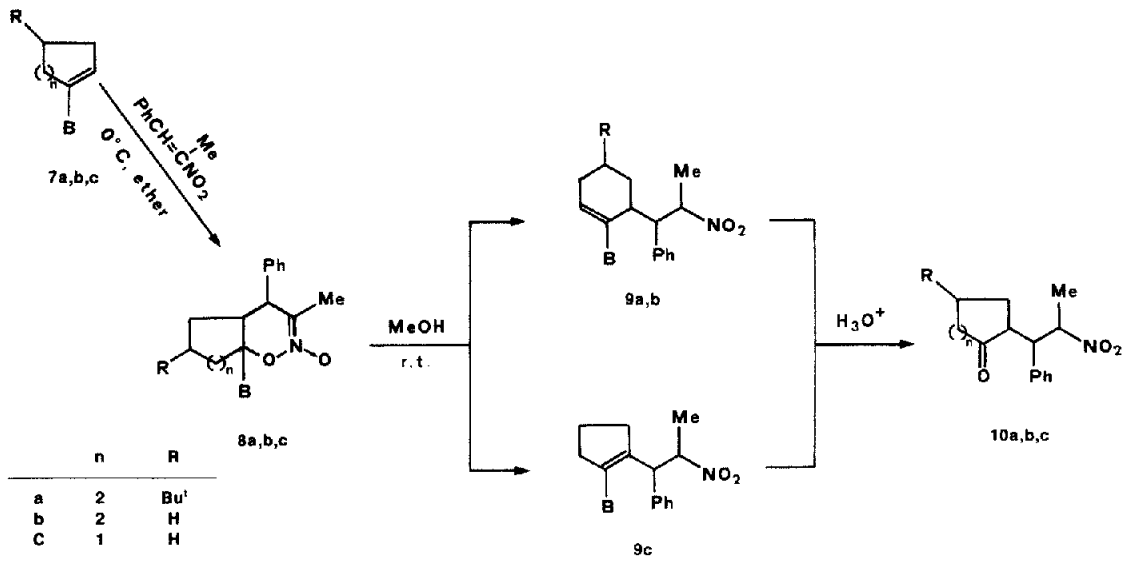
It should be noted that both **10a** and **11a** are diastereoisomeric pairs, inasmuch as the configuration around the respective nitromethinic β-carbons is easily inverted under the conditions used both in the hydrolysis and in the equilibration reactions.

†Contribution limited to the six-membered ring systems.

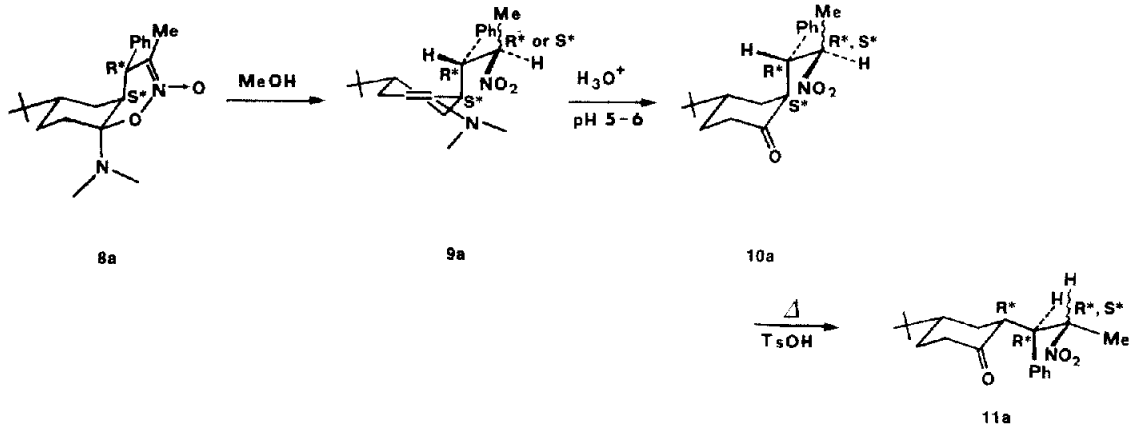
‡Some examples of [2+2] cycloaddition reactions are also reported.[4,5]



Scheme 1.



Scheme 2.



Scheme 3.

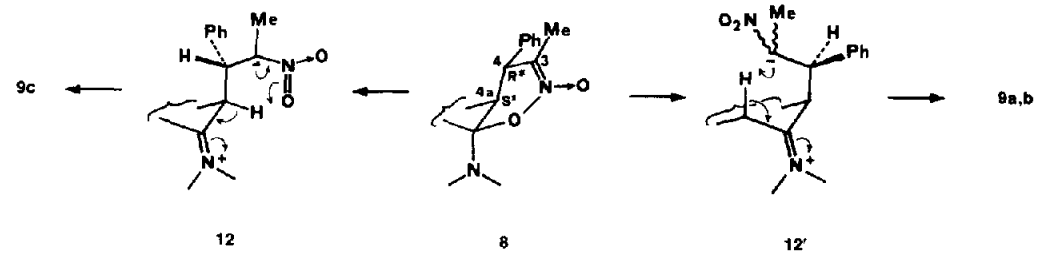
It seems reasonable to assume that also in the analogous non-biased systems **8b** the fusion between the rings is *cis*, as already found in other bicyclic systems derived from enamines.[10] This assumption is surely more valid for the 5-membered ring systems **8c**, in which strong interanuclar strains make the *trans* fusion even more unlikely.

The configurations around the chiral centres in **8** are determined both by the type of approach of the electrophile onto the parent enamine systems and by the type of fusion. Since in the approach of the nitro-olefin, the phenyl group is directed away from the cycloalkene ring,[3] C–4 and C–4a must have unlike chiralities (say R* and S* respectively as in Fig. 1.; we are dealing with racemic systems).

During the opening of **8** both these configurations are retained in the dipolar intermediate **12**⇄**12'**. Although a new chiral centre is created, as a consequence of the protonation of the prochiral carbon anion both in **12** and in **12'**, interestingly the resulting enamines **9** are always single products.

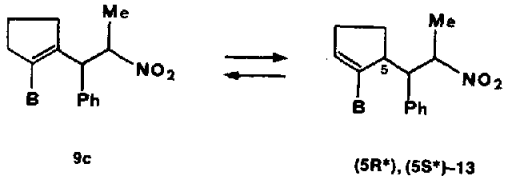
In this regard, the most striking result is the isolation of stable tetrasubstituted enamines, i.e. **9c**, from a cyclopentanone system, which had not been separated so far. In solution however, enamines **9c** are in equilibrium with their trisubstituted isomers **13**, as already postulated by Mazarguil and Lattes for the simpler 2-methylcyclopentanone systems.[11] The ratio **9c**/**13** is **3**/**7** (Scheme 4).

Formation of two diastereoisomers (5R*)- and (5S*)-**13** is related to the non stereospecific attack of the proton onto C-2 in **9c**. Further epimerization at the nitromethinic carbon atom in **9c** and **13** occurs but an analysis is difficult owing to the concomitant partial hydrolysis of the trisubstituted forms. In fact only the diastereoisomer of **9c** is detected in the NMR spectrum after standing in $CDCl_3$ for few days.



This type of equilibrium has been also observed in other nitroalkylated cyclopentanone systems, derived from **7c** (B = morpholino and piperidino) and β-nitrostyrene (Scheme 5).
(The more significant data relative to the cyclic compounds 8 and their corresponding open chain enamines **9** are summarized in Table 1).

Finally, something must be said about the acid catalyzed hydrolyses of the nitroalkylated enamines. Protonation of the trisubstitued enamines **9a** and **b** presents no special problems from the stereochemical point of view, as no new chiral centre is created. Therefore ketones **10a** and **b** obtained from **9a,b** under non epimerizing conditions (pH 5-6) can be assigned the same configuration around C-2 as in both the respective parent enamines and the heterocycles (S* in Fig. 1) (C-β are

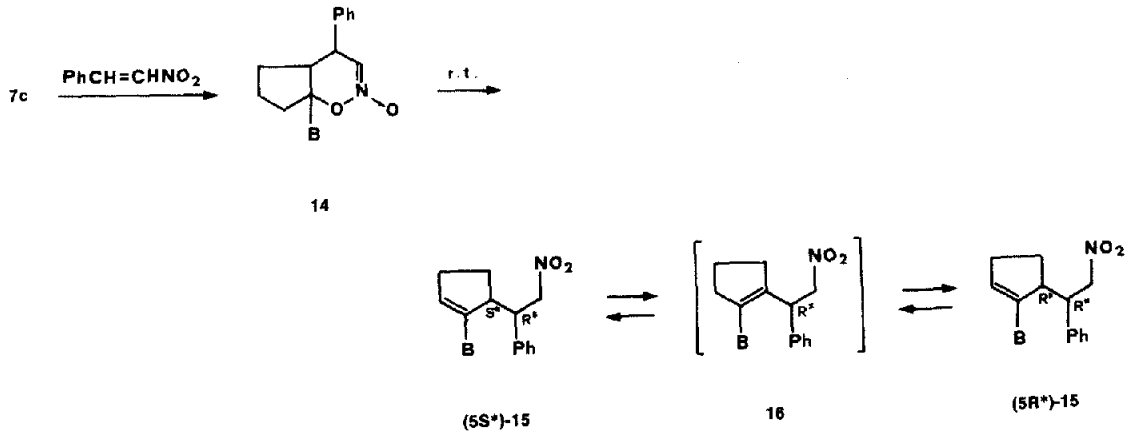


Scheme 4.

Table 1. The more significant analytical and spectroscopic data for the 1,2-oxazine N-oxides and the enamines

			IR(nujol), cm^{-1}			^{1}H-NMR, δ from TMS				% calc.			% found		
Entry	B	m.p.°C	C=N	N-C=C	NO_2	CH_3(d) (J,Hz)	CHPh(m)	$CHNO_2$	C=CH	C	H	N	C	H	N
8a	M	112-3	1616			1.68(1.5)[d]	3.5[g]			71.47	8.87	7.25	71.15	8.55	7.13
	PP	101-2	1610			1.70(1.5)[d]	3.6			74.96	9.44	7.28	74.68	9.57	7.64
	P	92-3	1618			1.80(1.5)[d]	3.5			74.56	9.25	7.56	73.87	8.61	7.28
8b	M	96-8	1615			1.95(1.5)[d]	3.6[g]			69.06	7.93	8.48	70.23	8.18	8.72
	PP	75-7	1612			1.75(1.5)[d]	3.5			73.14	8.59	8.53	73.60	8.32	8.76
	P	100-3	1608			1.70(1.5)[d]	3.6			72.58	8.33	8.91	71.98	7.97	8.29
8c	M	93-4	1612			1.80(1.5)[d]	3.6[g]			68.33	7.65	8.85	68.70	7.68	8.54
	PP	84-6	1600			1.80(1.5)[d]	3.5			72.58	8.33	8.91	72.90	8.34	8.80
	P[b]		1600			1.65(1.5)[d]	3.5								
9a	M	126-8		1648	1542	1.43(6.75)[e]	3.7[g]	5.6	4.8	71.47	8.87	7.25	71.71	9.23	7.30
	PP	108-10		1646	1530	1.47(6.75)[e]	3.5	5.7	4.9	74.96	9.44	7.28	72.72	9.48	7.45
	P[b]														
9b	M	85-6		1640	1542	1.40(6.75)[e]	3.8[g]	5.3	4.9	69.06	7.93	8.48	70.15	7.75	8.72
	PP	72-4		1638	1540	1.40(6.75)[e]	3.6	5.3	4.9	73.14	8.59	8.53	72.85	8.38	8.64
	P					1.15(6.75)[f]	3.9	5.3	4.6						
9c	M	125-6		1660	1555	1.35(6.75)[e]	4.5	5.1		68.33	7.65	8.85	68.15	7.54	8.68
	PP	90-2		1660	1550	1.30(6.75)[e]	4.4	5.1		72.58	8.33	8.91	73.10	8.41	8.35
	P[c]					1.30(6.75)[e]	4.4	5.1							
(5S*)-13[a]	M	110		1632	1542	1.20(6.75)[e]	3.40[g]	5.2	4.50	68.33	7.65	8.85	67.88	7.15	8.87
	PP			1630	1545	1.15(6.75)[e]	3.25	5.0	4.35	72.58	8.33	8.91	72.71	8.52	8.70
	P			1630	1550										
(5R*)-13[a]	M	106-7		1640	1545	1.40(6.75)[e]	3.45[g]	5.1	4.20	68.33	7.65	8.85	68.90	7.80	9.01
	PP			1640	1550	1.38(6.75)[e]	3.30	5.0	4.10	72.58	8.33	8.91	72.90	8.52	8.63
	P			1640	1540										
14	M			1605					6.40[d]						
(5S*)-15	M			1625	1550		3.6[g]	4.80	4.45						
	PP			1625	1550		3.6[e]	4.65	4.35						
(5R*)-15	M			1615	1540		3.6[g]	4.80	4.60						
	PP			1615	1545		3.7[e]	4.75	4.45						

a: only the morpholino derivative isolated; b: very unstable; c: it rapidly isomerizes; d: for CCl_4 soln; e: for $CDCl_3$ soln; f: for C_6D_6 soln; g: concealed beneath other signals.



Scheme 5.

Table 2. The more significant analytical and spectroscopic data for the ketones

Entry	Relative configuration C-2 , C-α , C-β	Decreasing order of R_f^a	m.p. C	IR(nujol) cm^{-1} C=O	IR(nujol) cm^{-1} NO_2	^{1}H-NMR, δ from TMS CH_3(d)	^{1}H-NMR, δ from TMS CHPh(dd)	^{1}H-NMR, δ from TMS $CHNO_2$(m)
10a	R* R* R* or S*	.70		1702	1540	1.28	3.2	5.8
		.60	97-8	1700	1535	1.54	3.3	5.7
	S* R* R* or S*	.50	149-51	1698	1535	1.38	4.0	4.6
		.50		1692	1545	1.48	3.4	5.0
10b	R* R* R* or S*	.65		1700	1540	1.28,1.50	3.2	5.2,5.7
	S* R* R* or S*	.60	62-3	1705	1550	1.34	3.3	5.4
		.50		1700	1545	1.36	4.0	5.0
10c	S* R* R* or S*	.60	70-2	1730[b]	1545	1.25	3.30	5.7
	R* R* R* or S*	.55		1735	1550	1.35	3.70	5.2
	R* or S* R* R* or S*	.45		1735	1545	1.36	3.35	5.7
	R* or S* R* R* or S*	.40		1730	1550	1.55	3.55	5.7

a: eluent: acetone: benzene 1:9; b: for $CHCl_3$ soln.

already epimerized). Equilibration of **10a** and **10b** carried out in refluxing benzene with added TsOH, changes the arrangement of C-2. As a consequence, four pairs of diastereoisomers are obtained in each case. Most of them can be separated and analyzed (Table 2), although the configuration of C-β remains unassigned.

As in the isomerization, protonation of **9c** is non-stereospecific, yielding **10c** as two pairs of diastereoisomers, differing in the arrangement of C-2. Their equilibration furnishes two new pairs of diastereoisomers, owing to the epimerization of C-β (Table 2).

Surprisingly, it has been observed that when enamine **9c** (B = morpholine) is left in the air for some time, only one ketone, namely the R*R*R* or S* (Table 2) is formed. Evidently, under these particular conditions, the hydrolysis reaction is under stereospecific control. However, no mechanism is suggested.

EXPERIMENTAL

M.ps were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer and NMR spectra on a JNM-60-HL Jeol spectrometer.

General Procedure for the reaction of enamine **7** *(B = morpholine, piperidine, pyrrolidine) with the nitroolefin*

1 - Phenyl - 1 - nitropropene was added dropwise to a soln of **7** in dry ether at 5° (−15° when the nitroolefin is β-nitrostyrene). After standing at 5° for 72 h, the ppt **8** was filtered off. By dissolution of **8** in cold methanol, followed by rapid precipitation by water, enamines **9** were separated.

Hydrolysis. Hydrolyses of **9** were carried out in a mixture of ethanol and water, with acetic acid in equimolar amount, in ice bath. After a few hours, the corresponding ketone precipitated.

Equilibration. The ketones were refluxed in benzene in the presence of TsOH for 6 h.

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