210. Cycloaddition of 2*H*-Pyran-2-thiones with Nitroso Derivatives. An Unexpected Cycloaddition-Rearrangement Reaction

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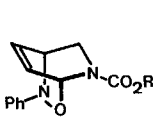
(15.VII.85)

Reaction of pyran-2-thiones **4** with nitroso derivatives led surprisingly to type-**8** (**19**) adducts which proved to be isomeric with the initially expected primary *Diels-Alder* cycloadducts **5**. Methyl 2-thioxo-2*H*-pyran-5-carboxylate (**4f**), when reacted with nitrosobenzene at −10°, led quantitatively to the thieto-oxazine intermediate **13**, which turned out to be the cornerstone of the complex cycloaddition-rearrangement **5**→**8** reaction pathway *(Scheme 3)*. Differential scanning calorimetry, as performed for the **18a**→**19a** conversion, permitted to demonstrate that this multistep rearrangement is overall a highly exothermal process, the final product **19** representing an energy-sink along this reaction pathway.

Introduction. – In [1], we have described a simple three-step synthesis of some racemic diamino-sugars **3**, starting from 1,2-dihydropyridines and from nitrosobenzene. During the first reaction step, *Diels-Alder* cycloaddition led regiospecifically to the bicyclic products **1** which were oxidized to the glycols **2** and then hydrogenolyzed to the expected racemic diamino-sugars **3**.



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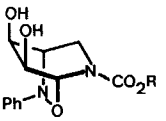

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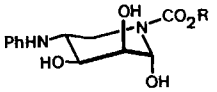

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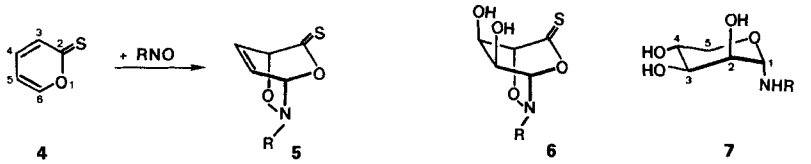
These syntheses permitted as a rule to obtain one racemic stereoisomer (**3**) out of the four possible ones. They seem to be of interest since a few naturally occurring piperidine amino-sugars have been isolated [2–4].

It was, therefore, of some interest to explore the feasibility of a similar reaction sequence starting from 2*H*-pyran derivatives of some sort. The unsubstituted 2*H*-pyran has never been prepared and should be an unstable species [5]. Only highly substituted 2*H*-pyran derivatives have been synthesized [5]; they do not seem to be of any use for the synthesis of amino-sugars. On the other hand, coumalin (2*H*-pyran-2-one) and its derivatives yielded the expected *Diels-Alder* adducts, for example when activated thermally in the presence of maleic anhydride [6][7]. These adducts are known to lose CO_2 when heated at higher temperatures. Coumalin has also been shown to react with nitrosobenzene; unfortunately the expected 1:1 adduct could not be obtained, since the only isolated product stems *in toto* from a double addition of nitrosobenzene, a loss of CO_2 and a rearrange-

ment to a five-membered ring system [8], which cannot be used for the synthesis of amino-sugar derivatives.

Thiocoumalins (2*H*-pyran-2-thiones) like **4a** were rarely used in *Diels-Alder* reactions; nevertheless cycloaddition does occur with dienophiles and is usually followed by loss of COS [9]. To our knowledge, nitroso derivatives had not yet been reacted with thiocoumalins. We surmised that nitroso compounds would undergo a regiospecific cycloaddition with thiocoumalins **4** leading thereby to the adducts **5** (or to their regioisomers). It was hoped that these compounds **5** would be stable enough to be oxidized to the corresponding glycols **6**. Catalytic hydrogenolysis of the N–O and of the C=S bonds of **6** was expected to lead, *e.g.* to the racemic glycosylamine derivatives **7** *(Scheme 1)*.

Scheme 1



As will be seen in the next section, the very first reaction which we have postulated above, *i.e.* cycloaddition of thiocoumalin **4a** with nitrosobenzene, gave the expected adduct if only as an intermediate **5a**. The final compound turned out to be **8a**, which was a puzzling one indeed[1]).

Addition Reactions of 2*H*-Pyran-2-thiones with Nitrosobenzene. – The 2*H*-pyran-2-thiones **4a–g** were prepared by reacting the corresponding 2*H*-pyran-2-ones (coumalin derivatives) in boiling benzene or toluene with *Lawesson*'s reagent [11] *(Table 1)*. They were all obtained as yellow-to-orange crystalline compounds and were sometimes accompanied by their dithio derivatives **10**. All 2*H*-pyran-2-thiones have been characterized by their ^{1}H-NMR spectra *(Table 2)* and ^{13}C-NMR spectra *(Table 3)*. When left to react with nitrosobenzene they led to 1:1 adducts **8** which are colourless crystalline substances *(Table 4)*. We notice, however, that 4,6-dimethyl-2*H*-pyran-2-thione (**4d**) does not react at all. Furthermore, two particular cases have been encountered: whereas it takes usually

Table 1. *2H-Pyran-2-thiones* **4a–g** *and 2H-Thiopyran-2-thiones* **10a** *and* **10f** *as Prepared from the Corresponding 2H-Pyran-2-ones*

Yield [%]	V	W	Y	Z	**4**	**10**
a	H	H	H	H	55	11
b	H	H	H	D	[a])	–
c	Me	H	H	Me	85	–
d	H	Me	H	Me	70	–
e	H	H	CF_3	H	83	–
f	H	H	CO_2Me	H	56	15
g	H	CO_2Me	H	CF_3	58	–

[a]) The exact amount of the deuterated compound **4b** has not been determined.

[1]) For a preliminary report see [10].

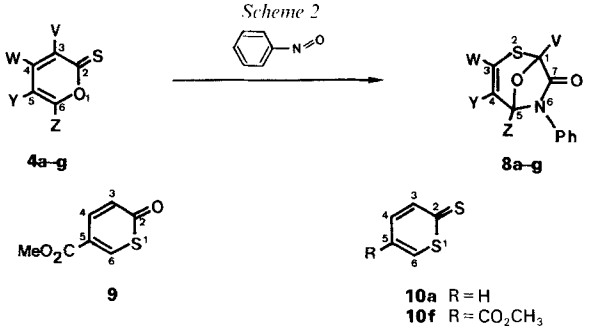
Table 2. *^{1}H-NMR Data* (in $CDCl_3$, at 80 MHz) *of* **4a–g**, *of Methyl 2-Ox*

	H–C(3)	H–C(4)	H–C(5)	H–C(6)	*J*(3,4)	*J*(3,5)	*J*(3,6)	*J*(4,
4a[a][b])	7.25	7.10	6.51	7.80	9.2	1.3	1.3	6.6
4b	7.26	7.16	6.56	–	9.2	1.3	–	6.7
4c	–	7.10	6.26	–	–	–	–	6.9
4d[b])	6.99	–	6.17	–	–	1.6	–	–
4e	7.20	7.10	–	8.06	10.0	–	1.1	–
4f	7.20	7.48	–	8.43	9.6	–	1.2	–
4g	7.71	–	7.15	–	–	–	–	–
Methyl 2-oxo-2*H*-pyran-5-carboxylate [13]	6.31	7.77	–	8.28	9.8	–	1.2	–
9	6.53	7.97	–	8.61	10.8	–	0.9	–
10f	7.43	7.58	–	8.48	10.4	–	1.2	–

[a]) Measured at 360 MHz.
[b]) *Cf.* [12].

several days to bring the addition reaction to completion, methyl 2-thioxo-2*H*-pyran-2-carboxylate (**4f**) led in less than 1 h at room temperature to adduct **8f** and to methyl 2-oxo-2*H*-thiopyran-2-carboxylate (**9**). To the contrary, 2*H*-pyran-2-thione **4g** reacted sluggishly (5 d) with nitrosobenzene and gave adduct **8g** in moderate yield only *(Scheme 2)*.

Scheme 2



Mechanism of the Cycloaddition-Rearrangement Reaction. – The reaction of **4f** with nitrosobenzene turned out to be the most interesting one, and led to the elucidation of the complex reaction mechanism of the above cited cycloaddition-rearrangements. At room temperature, **4f** reacted quickly with nitrosobenzene leading to the expected adduct **8f** (69%) and to **9** (20%), this latter compound being an isomer of **4f**. At about −10°, the reaction of equimolar amounts of **4f** and of nitrosobenzene led quantitatively to an intermediate product, whose structure could be ascertained as **13** by ^{1}H- and by ^{13}C-NMR (*Tables 5* and *6*). When heated to room temperature, **13** disappeared in favour of adduct **8f**, and of equal amounts of **9** and nitrosobenzene.

2H-pyran-5-carboxylate, of its Monothio Derivative **9**, *and of its Dithio Derivative* **10f**

J(4,6)	J(5,6)	Additional data pertaining to substituents					
1.8	5.1						
–	–						
–	–	CH_3–C(3)	CH_3–C(6)	J(4,CH_3–C(3))	J(4,CH_3–C(6))	J(5,CH_3–C(3))	J(5,CH_3–C(6))
		2.27	2.37	1.0	0.8	0.6	0.8
–	–	CH_3–C(4)	CH_3–C(6)	J(3,CH_3–C(4))	J(5,CH_3–C(6))	J(3,CH_3–C(6))	
		2.09	2.35	1.0	*ca.* 0.5	*ca.* 0.5	
2.3	–	J(3,CF_3)	J(6,CF_3)				
		0.7	1.7				
2.0	–	CO_2Me					
		3.90					
–	–	CO_2Me					
		3.96					
2.6	–	CO_2Me					
		3.88					
2.6	–	CO_2Me					
		3.90					
1.8	–	CO_2Me					
		3.91					

Scheme 3

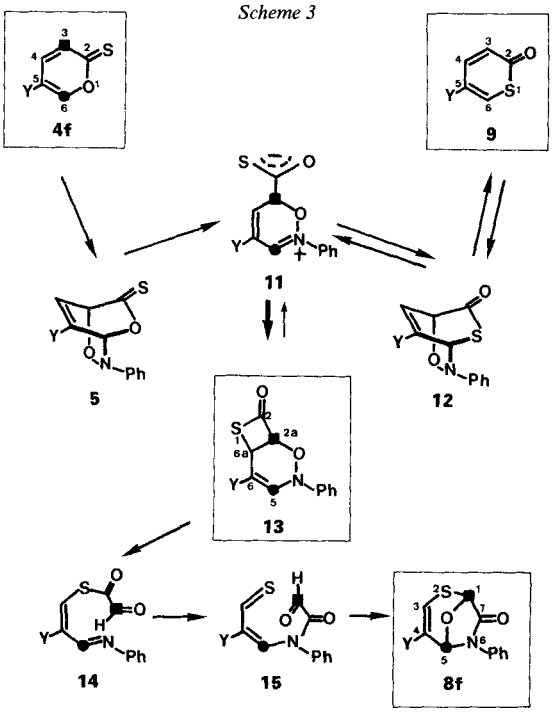


Table 3. *^{13}C-NMR Data* (in $CDCl_3$, at 20.1 MHz) *of* **4a–g**, *of Methyl 2-Oxo-2*H*-pyran-5-carboxylate and of its Monothio Derivative* **9**, *and of its Dithio Derivative* **10f** (^1J(C,H) values in parentheses)

	C(2)	C(3)	C(4)	C(5)	C(6)	Additional data pertaining to substituents	
4a[a])	197.8	132.2	134.9	109.9	155.9		
4c	198.9	135.3	134.8 (165)	107.8 (171)	165.9	CH_3–C(3) 21.0 (130)	CH_3–C(6) 19.8 (130)
4d	197.3	126.8 (174)	150.2	110.6 (170)	166.2	CH_3–C(4) 20.4 (130)	CH_3–C(6) 19.6 (131)
4e	195.6	132.2 (179)	128.5 (172)	114.9 (36)[b])	154.5 (206)	CF_3 122.2 (272)[c])	
4f	196.0	130.7 (178)	132.3 (173)	114.8	160.2 (206)	CO_2Me 162.7, 52.3 (149)	
4g	193.7	135.3 (181)	131.6	106.0 (180)	151.8 (40)[b])	CO_2Me 162.9, 53.2 (150)	CF_3 117.5 (273)[c])
Methyl 2-oxo-2*H*-pyran-5-carboxylate [13]	159.4	114.9 (175)	141.3 (170)	111.6	157.9 (205)	CO_2Me 163.1, 52.0 (150)	
9	182.4	124.4 (169)	140.2 (165)	121.4	146.1 (182)	CO_2Me 163.2, 52.6 (149)	
10f	204.9	139.1 (174)	130.7 (168)	125.0	148.0 (183)	CO_2Me 162.7, 52.6 (150)	

[a]) Measured at 90.52 MHz with TMS as internal reference, *cf.* [14]. [b]) ^2J(C,F). [c]) ^1J(C,F).

Table 4. *Yields of the Addition Products* **8** *and* **9** *during the Reaction of Nitrosobenzene with Thiones* **4**

	V	W	Y	Z	Duration and temp. of the reaction	Yield [%]	
						8	**9**
a (b)	H	H	H	H (D)	3 d; 20°	92	–
c	Me	H	H	Me	10 d; 20°	61	–
d	H	Me	H	Me	14 d; 20°	No reaction	
e	H	H	CF_3	H	1.5 d; 40°	93	–
f	H	H	CO_2Me	H	< 1 h; 20°	69	20
g	H	CO_2Me	H	CF_3	5 d; 40°	34	–

Compound **13** appears to be the cornerstone of a complex reaction mechanism whose multiple steps are represented in *Scheme 3*[2]). According to this mechanistic manifold, a regiospecific *Diels-Alder* cycloaddition occurs indeed in the first reaction step, which should be the rate-determining step, leading to the postulated adduct **5**, which opens up to the zwitterion **11**. This latter one being an inner iminium salt undergoes reversible ring closure to the bridged bicyclic isomer **12**, which, by way of a reversible *retro-Diels-Alder* reaction, leads to **9** and to nitrosobenzene. That these two reactions are reversible could easily be demonstrated: reaction of equimolar amounts of **9** and of nitrosobenzene gave – albeit with a very small reaction rate – the expected adduct **8f** quantitatively. As the thiocarboxylate anion of **11** is obviously more nucleophilic at S- than at O-atom, it is unlikely that **11** undergoes ring closure back to **5**.

The zwitterion **11** may also undergo ring closure reversibly to **13**, which, by way of an irreversible *retro-Diels-Alder* reaction, gives the acyclic intermediate **14**. Next, a 1,5-sigmatropic shift leads to the more stable isomer **15** [15]. Intramolecular *Diels-Alder* reaction of **15** gives the final product **8**.

The *retro-Diels-Alder* reaction of **13** to the acyclic intermediate **14** finds its driving force in the easy fragmentation of the 1,2-oxazine low-energy N–O bond[3]). Therefore, this reaction step can only be an irreversible one. The final intramolecular hetero-*Diels-Alder* reaction follows from the electronic polarisations of the interacting moieties [17].

The proposed mechanism must fit the substitution patterns, both of **4** and **8**. For example, deuterium, which is connected to C(6) of **4b**, should show up at C(5) of **8b**; the C(5)-methoxycarbonyl substituent of **4f** should appear at C(4) of **8f**[4]) (see below for the observed results).

Addition Reactions of 2*H*-Pyran-2-thiones with Acylnitroso Derivatives. – The 2*H*-pyran-2-thiones **4a–g** have also been reacted with the acylnitroso derivatives **16** and **17**, which were prepared *in situ* by oxidation of the corresponding hydroxamic acids with tetrapropylammonium periodate [18]. The reaction of **16** with equimolar amounts of 2*H*-pyran-2-thiones **4a–c** led in moderate yields to the corresponding thieto-oxazines **18a–c** *(Scheme 4)*, which proved to be stable entities at room temperature. When heated

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[2]) For the sake of clarity, substituents have been left out. The round and square-shaped dots represent labelling of corresponding C-atoms in **4** and **8**.

[3]) *retro-Diels-Alder* reactions of Δ^3-oxazines are known to occur readily even below 0° [16].

[4]) The C(3), C(4), C(5) and C(6) substituents of **4**, correspond to the C(1), C(3), C(4) and C(5) substituents of **8**, respectively.

Table 5. *^{1}H-NMR Data of the Thieto-oxazine Derivatives* **13f**, **18a–c** (in $CDCl_3$ at 80 MHz), *and of the Thietanones* **25** *and* **26** (in CCl_4 at 60 MHz)

	H–C(2a)	H–C(5)	H–C(6)	H–C(6a)	*J*(2a,5)	*J*(2a,6)	*J*(2a,6a)	*J*(5,6)	*J*(6,6a)	Additional data pertaining to substituents				
13f	5.92	8.16	–	4.81	[a])	–	7.4	–	–	CO_2Me 3.83	C_6H_5 *ca.* 7.3			
18a	5.83	7.22	5.62	4.41	0.6	0.8	7.1	8.3	4.2	CH_2–C_6H_5 5.28, 7.38				
18b	5.83	–	5.62	4.41	–	0.7	7.2	–	4.2	$CH_2C_6H_5$ 5.27, 7.34				
18c	–	–	5.57	4.11	–	–	–	–	5.8	CH_3–C(2a) 1.67	CH_3–C(5) 2.19	$CH_2C_6H_5$ 5.22, 7.38	*J*(6,CH_3–C(5)) 1.3	*J*(6a,CH_3–C(5)) 0.5

	H–C(3)	H–C(4)	*J*(3,4)		
25	6.49	5.05	6.9	AcO 1.70	C_6H_5 *ca.* 7.4
26	6.01	4.85	4.8	AcO 2.12	C_6H_5 *ca.* 7.4

[a]) Not observed.

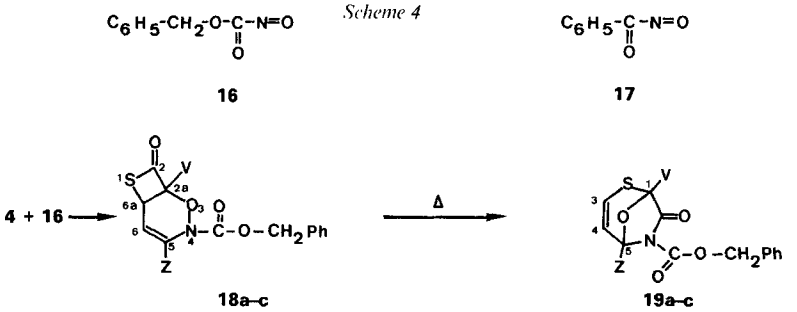
Table 6. *^{13}C-NMR Data* ($CDCl_3$ at 20.1 MHz) *of the Thieto-oxazine Derivatives* **13f** *and* **18a** *and of the Thietanones* **25** *and* **26** (^1J (C,H) values in parentheses)

	C(2)	C(2a)	C(5)	C(6)	C(6a)	C(1′)	C(2′,6′)	C(3′,5′)	C(4′)	Additional data pertaining to substituents
13f	193.6	90.0 (156)	136.2 (181)	100.8	35.8 (164)	140.4	115.2 (165)	129.2 (164)	124.8 (164)	CO_2Me 166.1, 51.7 (149)
18a	191.0	93.6 (158)	127.7[a])	107.5 (176)	34.4 (163)	135.0	128.1 (164)	128.5 (164)	128.4 (164)	CO_2CH_2 150.9, 68.6 (152)

	C(2)	C(3)	C(4)	C(1′)	C(2′,6′)	C(3′,5′)	C(4′)		
25	189.4	86.3 (157)	45.5 (154)	134.2	129.3 (160)	128.3 (163)	128.6 (161)	AcO 167.9, 19.5 (131)	
26	188.2	89.8 (156)	46.9 (154)	136.6	127.5 (160)	129.1 (162)	128.9 (164)	AcO 168.5, 20.1 (132)	^2J(C(3),H–C(4)) 6

[a]) ^1J could not be determined.

Scheme 4



	V	Z
a	H	H
b	H	D
c	Me	Me

above 40–50° in $CHCl_3$ or in benzene, these oxazines isomerized quantitatively to the expected bicyclic compounds **19a–c** *(Scheme 4)*[5][6].

The fact that **18a–c** were obtained only in moderate yields when reacted with equimolar amounts of **16**, led us to increase the relative amount of this latter reagent. This was to no avail: although **4a–g** disappeared during the reaction – with the exception of **4d** which did not react at all – no definite compounds could be isolated. Similarly, **4a–c** and **4e–g** did undergo reaction with the nitroso derivative **17**, but no definite compounds could be isolated. It is believed that the acylnitroso derivatives **16** and **17** react with the olefinic double bond of the oxazines **18**, thereby leading to complex reaction mixtures. Furthermore, it was shown that pyranthiones **4** do not react either with the two hydroxamic acids (from which **16** and **17** are obtained *in situ*) or with tetrapropylammonium periodate alone.

Synthesis of the Thietan-2-one Model Substances 25 and 26. – Since only but a few thietanones have been described so far [19] [20], we decided to synthesize specifically thietanones **25** *(cis)* and **26** *(trans)*, in order to correlate their IR and NMR data (see below) with those of the thietanone moieties of compounds **13** and **18**, whose formation has been described above.

The *trans*-sodium 2-phenyloxiranecarboxylate (**20**) [21] was reacted with aqueous HBr in Et_2O, whereby the expected *erythro*-bromohydrine **21** was obtained as a crystalline compound in 67% yield. Surprisingly, the *threo*-stereoisomer **22** formed also (presumably *via* a carbonium-ion mechanism) in 10% yield and was purified by crystallisation. Treatment of **21** with AcCl and then with H_2O led to **23**; its acid chloride **24** gave the *cis*-thietan-2-one **25** when reacted with H_2S and then with Et_3N *(Scheme 5)*. Starting from the *threo*-isomer **22**, a similar reaction sequence led to the *trans*-thietan-2-one **26**.

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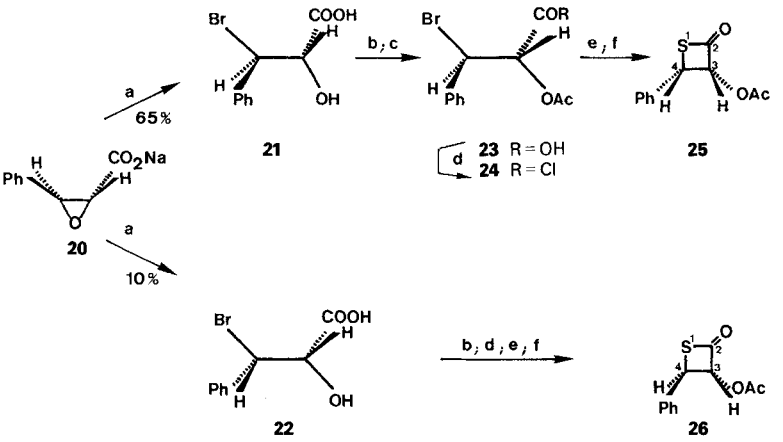
[5] The C(2a), C(5), C(6), and C(6a) substituents of compounds **18**, correspond to the C(1), C(5), C(4), and C(3) substituents of adducts **19**, respectively.

[6] DSC measurements, as determined in 1,2-dichlorobenzene, led to the following two thermodynamic parameters for the **18a**→**19a** rearrangement: $\Delta H = -45 \pm 2$ kcal/mol; $\Delta H^* = 24 \pm 1$ kcal/mol.

Scheme 5



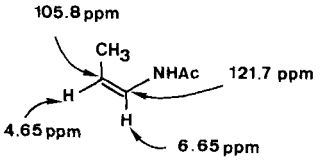
a) aq. HBr, Et_2O; b) AcCl; c) H_2O; d) $(COCl)_2$, CCl_4; e) H_2S, CCl_4; f) Et_3N, CCl_4

Structure Determinations. – ^{1}H- and ^{13}C-NMR spectral analyses permitted to determine the structure of the newly described compounds unambiguously. Some of the 2*H*-pyran-2-thiones **4a–g** are known compounds; the structures of the remaining ones could be established without any difficulty (*Tables 2* and *3*).

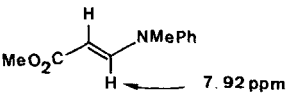
*Methyl 2-Oxo-2*H*-thiopyran-5-carboxylate* (**9**). That **9** is an isomer of **4f** could be determined easily by its elemental analysis. In addition the C(5)-methoxycarbonyl substituent had similar effects – upon ^{1}H- and ^{13}C-NMR chemical shifts with respect to the unsubstituted and known parent compound [12] [14] – when compared to those observed in the 2*H*-pyran-2-thione series (*Tables 2* and *3*). Furthermore, 2*H*-thiopyran-2-thione **10f**, when treated either with HONO [22] or with nitrosamines [23], led specifically to the replacement of the exocyclic S-atom by an O-atom, leading thereby to **9**. The IR spectrum of **9** exhibits a characteristic thiolactone carbonyl band at 1665 cm^{-1}.

Thieto-oxazines **13**, **18a–c**, *and Thietanones* **25** *and* **26**. Some NMR data of **13**, **18a**, **18b**, and **18c** are given in *Tables 5* and *6*. The thieto-oxazine **18a** is only a moderately stable compound, but nevertheless it could be characterized by its physical properties. Besides the benzyloxycarbonyl moiety ($\tilde{\nu}$(C=O) *ca.* 1720 cm^{-1}), which was easily identified, the thietanone carbonyl appears at 1765 cm^{-1}, and it follows from the ^{1}H- and from the ^{13}C-NMR spectra of **18a** that the non-aromatic C-atoms are connected in a linear fashion, *i.e.* C(2)–C(2a)–C(6a)–C(6)–C(5). The four remaining non-aromatic C-atoms bear one H-atom each, and these four H-atoms lead to sequential couplings. The thieto-oxazine **13**, which could not be isolated since it proved stable only at −10° in the NMR probe, shows very similar NMR patterns when compared with those of **18a** (*Tables 5* and *6*). The two remaining thieto-oxazines **18b** and **18c** show IR and NMR spectra similar to those of **18a.**

We notice in particular in the ^{1}H- and ^{13}C-NMR spectra of **18a** the two olefinic protons and C-atoms of an enamide function whose chemical shifts are to be compared with those of the known enamide **27** ((*Z*)-product) [24]. The presence of a CO_2Me substituent at C(6) of **13** leads to a strong deshielding effect upon H–C(5) – which is to be



27



28

compared with the corresponding chemical shift of compound **28** ((*E*)-product) [25] – and also to a strong deshielding effect upon C(5). The magnitude of the $J(5,6)$ coupling constant (J = 8.3 Hz) clearly indicates that the corresponding double bond is part of a six-membered ring. We notice furthermore the presence of two tertiary C-atoms C(2a) and C(6a). The coupling constant (J = 7 Hz) between the corresponding H–C(2a) and H–C(6a) is in good agreement with their bridgehead-position in a small sized ring, which can only be a four-membered ring.

That the four-membered ring of **18a** is a thietan-2-one follows from IR and NMR spectral comparisons with the thietanones **25** and **26** (*Tables 5* and *6*). Spectral data of **25** and of **26** are in good agreement with those of the few thietanones which have been reported in [19] [20]. The ^{13}C-NMR chemical shift of the carbonyl portion of **25** (δ = 189.4 ppm) is to be compared with the one of tetraphenylthietanone (δ = 194 ppm) [19]. Likewise, the IR carbonyl ($\tilde{\nu}$(C=O)) bands appear at similar wavelengths: *ca.* 1760–1785 cm^{-1} for **25** and **26** (the acetate carbonyl absorbs in the same spectral region), and *ca.* 1770 cm^{-1} for some known thietanones [20]. The *cis*-configuration of **25** is clearly demonstrated by the vicinal $J(3,4)$coupling constant ($J(3,4)$ = 6.9 Hz) and by the shielding effect (δ = 1.70 ppm) exerted by the Ph moiety upon the Me group of the AcO substituent (*Table 5*).

Comparison of NMR spectra of **18a** with those of the reference compound **25** shows that there is a fairly good agreement. However, care must be taken when comparing corresponding C-atoms (C(6a) of **18a** and C(4) of **25**) and corresponding H-atoms (H–C(6a) of **18a** and H–C(4) of **25**): replacement of a double bond (as in **18a**) by a Ph moiety (as in **25**) leads to a down-field shift of *ca.* 8 ppm [26] in ^{13}C-NMR, and to a down-field shift of *ca.* 0.5 ppm [27] in the ^{1}H-NMR (*Tables 5* and *6*).

Bicyclic Adducts **8a–g** *and* **19a–c**. Products **8a–g** and **19a–c** formally result from addition reactions of 2*H*-pyran-2-thiones **4a–g** with nitroso derivatives. Their ^{13}C-NMR spectra show the presence of a carbonyl group ($\delta \approx$ 165–168 ppm) which absorbs in IR at *ca.* 1720 cm^{-1} for the *N*-phenyl adducts **8a–g**. These values are typical for γ-lactones. The adducts **19a–c** which are doubly acylated at the N-atom exhibit more complex carbonyl bands as expected ($\tilde{\nu}$(C=O) $\approx$ 1710–1790 cm^{-1}) [28].

The unsubstituted adduct **8a** was taken as a model for some extensive ^{1}H- and ^{13}C-NMR measurements, its structure having been proven in the meantime by an X-ray analysis [10]. The ^{1}H-NMR spectrum (*Table 7*), and in particular the $^1J(^{13}C, ^{13}C)$ values permit to demonstrate that two well-separated C moieties are present in **8a** [10]: *i*) a C_2 moiety which comprises the carbonyl group and a C-atom which bears the most shielded H-atom; *ii*) a C_3 moiety, each C-atom of which bearing one H-atom. That H–C(1) is spatially removed from the other protons was also shown by a ^{1}H-NMR inversion-recovery experiment: the spin-lattice relaxation time is about 40 s for H–C(1) and only 9 s for H–C(3), 4 s for H–C(4) and H–C(5). Furthermore, irradiation of the aromatic *ortho*-

Table 7. *^{1}H-NMR Data* (in $CDCl_3$ at 80.1 MHz) *of* **8a–g**, *and* **19a–c**

	H–C(1)	H–C(3)	H–C(4)	H–C(5)	^4J(1,3)	^3J(3,4)	^4J(3,5)	^3J(4,5)	^5J(1,4)	Additional data pertaining to substituents
8a	5.62	6.42	6.26	5.79	2.2	10.0	1.0	4.2	0.4	H–C(2′,6′) H–C(3′,5′) H–C(4′) 7.50 7.41 7.22
8b	5.62	6.40	6.27	–	2.0	10.1	–	–	0.5	
8c	–	6.53	6.03	–	–	9.7	–	–	–	Me–C(1) Me–C(5) J(3,CH_3–C(1)) 1.95 1.61 0.4
8e	5.70	7.15	–	6.06	2.0	–	1.6	–	–	^4J(3,CF_3) ^4J(5,CF_3) 1.8 0.5
8f	5.65	7.78	–	6.52	2.0	–	1.4	–	–	CO_2Me C_6H_5 3.72 *ca.* 7.4
8g	5.91	–	7.3	–	–	–	–	–	–	CO_2Me 3.90
19a	5.48	6.27	6.16	5.74	1.8	10.0	1.3	4.0	0.5	$CH_2C_6H_5$ 5.27, 7.37
19b[a])	5.53	6.34	6.21	–	1.8	9.9	–	–	0.4	$CH_2C_6H_5$ 5.31, 7.39
19c	–	6.37	6.15	–	–	9.9	–	–	–	Me Me $CH_2C_6H_5$ 1.81 1.84 5.31, 7.36

[a]) Highly dilute solution.

Table 8. *^{13}C-NMR Data* (in $CDCl_3$ at 20.1 MHz) *of* **8a**, **8c**, **8e–g**, *and* **19a** (^1J(C,H) values in parentheses)

	C(1)	C(3)	C(4)	C(5)	C(7)	C(2′,6′)	C(3′,5′)	C(4′)	C(1′)	Additional data pertaining to substituents
8a[a])	77.5	124.3	118.0	84.9	165.9	119.5	129.3	125.6	134.8	
	(177.6)	(180.6)	(171.7)	(170.1)	–	(162)	(162)	(163)	–	
8c	84.0	125.2	121.2	91.0	168.2	126.3	129.1	127.6	134.2	Me Me
	–	(180)	(169)	–	–	(162)	(163)	(163)	–	22.9 (129) 21.1 (130)
8e	76.4	129.9	119.8	84.0	165.3	123.0	129.4	127.3	132.8	CF_3
	(181)	(180)	(33.5)[c])	(172)	–	(163)	(162)	(163)	–	121.6 (271)[b])
8f	76.8	138.8	120.8	84.6	165.4	120.3	129.1	125.9	134.4	CO_2Me
	(182)	(183)	–	(175)	–	(164)	(163)	(163)	–	162.6, 51.9 (149)
8g	75.8	132.0[d])	122.6	89.4	166.3	127.9	129.6	129.5	133.1[d])	CO_2Me CF_3
	(183)		(179)	(35)[c])	–	(164)	(165)	(160)	–	162.3, 53.2 (150) 120.7 (283)[b])
19a	76.3	123.3	118.0	82.6	164.7	128.0	128.5	128.5	134.5	CO_2CH_2
	(180)	(182)	(177)	(178)	–	(162)	(164)	(164)	–	148.3, 68.5 (151)

[a]) Measured at 90.52 MHz. [b]) ^1J(C,F). [c]) ^2J(C,F). [d]) Or *vice versa*.

protons led to a substantial nuclear *Overhauser* enhancement for H–C(5) (20%), proving that this proton is spatially close to the *N*-phenyl group. Last but not least, when the peak frequencies of the partially decoupled ^{13}C-NMR spectra of **8a** are plotted against the proton-irradiating frequencies, according to *Feeney*'s graphical method [29], one can readily identify the connected proton and C nuclei (*Tables 7* and *8*).

NMR-spectral data clearly show that all the other adducts **8b–g** and **19a–c** (*Tables 7* and *8*) have the same bicyclic skeleton as the one found for **8a**. Substituent effects upon chemical shifts show up as would have been expected. For example the CF_3 and CO_2Me groups, which are connected to the sp^2 C-atom C(4) of **8e** and **8f**, lead to a strong deshielding effect upon H–C(3) and C(3) (*Tables 7* and *8*). In adducts **8c** and **8g**, the Ph moiety is much less conjugated with the lactam function, which is due to a steric interaction with the C(5) substituents (*Table 8*).

It was of the utmost importance to correlate precisely the substitution patterns of the educts **4b–g** with those of the corresponding adducts **8b–g**, and **19b**, **19c**. These correlations clearly follow from the NMR-data which are presented in *Tables 7* and *8*. For example, the D-atom at C(6) in **4b** appears at C(5) in **8b** and **19b**, as would have been expected according to the mechanism described in *Scheme 4*. Likewise, the Me groups at C(3) and C(6) in **4c** appear at C(1) and C(5), respectively, of the corresponding adducts **8c** and **19c**. The C(5) substituents of **4e** (CF_3) and of **4f** (CO_2Me) appear at C(4) of the corresponding adducts **8e** and **8f**.

Clearly, in all these addition-rearrangement reactions, the S-atom was introduced between C(3) and C(4) of the 2*H*-pyran-2-thiones.

We wish to thank the *Centre National de la Recherche Scientifique* for its financial support and in particular for a *BDI* grant to one of us (*G.A.*). We address our sincere thanks to Dr. *H. Strub* for the measurement and the interpretation of ^{13}C-NMR spectra, to Prof. *C. W. Rees*, Imperial College, London, and to Prof. *R. A. Abramovitch*, Clemson University, USA, for their conceptual contribution to the elucidation of the reaction mechanism which is represented in *Scheme 3*. Last but not least, we greatly appreciated the cooperation of *D. Gicquel* and *L. Villien*, from the Laboratoire de la Sécurité de la Réaction Chimique, for the DSC measurements of the **18a**→**19a** conversion.

Experimental Part

General. Flash chromatographies (FC) [30] were carried out with silica gel (*Merck 60;* 230–400 mesh) and TLC on alumina roll (*Merck 60 F_{254}*). M.p. were taken on a *Kofler* hot bench or on a *Büchi SMP 20* apparatus and are corrected. IR spectra (cm^{-1}) were determined on a *Perkin-Elmer-157-G* spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained with *Varian-T-60* (^{1}H-NMR only), *Bruker-WP-80-DS*, and *Bruker-WH-360* instruments using double-irradiation techniques, with TMS (for ^{1}H-NMR spectra), and with $CDCl_3$ (δ $CDCl_3$ = 77.00 ppm with respect to TMS for ^{13}C-NMR spectra) as internal references (δ[ppm], *J*(Hz]). High-resolution MS were measured on a *MAT-311* spectrometer. Microanalyses were carried out by the Service Central de Microanalyses of the C.N.R.S.

2*H*-Pyran-2-thiones 4a–g. All pyran-2-thiones were prepared by reacting the corresponding 2*H*-pyran-2-ones with *Lawesson*'s reagent [11].

2H-Pyran-2-thione (**4a**). A stirred soln. of 2*H*-pyran-2-one [31] (10 g; 0.1 mol) and *Lawesson*'s reagent (21.5 g; 53 mmol) in anh. benzene (80 ml) was heated at reflux under Ar for 40 h. The mixture turned gradually from yellow to orange and to red. The soln. was evaporated to dryness *i.v.* and the resulting red oil separated by FC (toluene), whereby 2H-*thiopyran-2-thione* (**10a**; 1.79 g; 11%), m.p. 63–64° (i-PrOH) ([32a]: 64°) and **4a** (5.8 g; 41%), m.p. 50.5–51° (benzene/cyclohexane 1:2) ([32b]: 49–50°) were obtained. An additional amount of **4a** (2.0 g; 14%) was isolated by chromatography of the mother liquors and of the mixed fractions of the preceding chromatography. Total amount of **4a**: 7.8 g (55%).

4a: IR (CCl_4): 1628, 1528, 1442, 1385, 1240, 1210, 1112, 918. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR: see *Table 3.*

10a: IR (CCl_4): 1597, 1502, 1413, 1155, 1052.

*[6-$^2H_1$]-2*H*-Pyran-2-thione* (**4b**). Same reaction conditions as above starting from [6-$^2H_1$]-2*H*-pyran-2-one [33]. IR (CCl_4): 1612, 1523, 1516, 1435, 1422, 1332, 1212, 1114, 931. ^{1}H-NMR: see *Table 2.*

*3,6-Dimethyl-2*H*-pyran-2-thione* (**4c**). Reaction conditions similar to the ones described for the preparation of **4a**. Starting from 3,6-dimethyl-2*H*-pyran-2-one [34] (1.9 g; 15.3 mmol) and *Lawesson*'s reagent (3.2 g; 7.9 mmol) in anh. toluene (20 ml) at reflux for 4 h, **4c** was isolated *via* FC (AcOEt/cyclohexane 4:6) as orange crystals (1.79 g; 85%) m.p. 29.5° (sublimation). IR (CCl_4): 1642, 1560, 1370, 1212, 1111. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR: see *Table 3.* Exact mass calc. for C_7H_8OS (MS): 140.02958, found: 140.0298. Anal. calc. for C_7H_8OS (140.20): C 59.97, H 5.75, S 22.87; found: C 60.3, H 5.7, S 22.4.

*4,6-Dimethyl-2*H*-pyran-2-thione* (**4d**). Same reaction conditions as above starting form 4,6-dimethyl-2*H*-pyran-2-one[7]) (1.9 g; 15.3 mmol). FC (AcOEt/cyclohexane 3:7) of the crude mixture led to **4d** (1.51 g; 70%), as a crystalline yellow compound, m.p. 70.5° (sublimation). IR (CCl_4): 1650, 1536, 1345, 1205, 1083. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR: see *Table 3.* Anal. calc. for C_7H_8OS (140.20): C 59.97, H 5.75, S 22.87; found: C 60.3, H 5.7, S 22.9.

*5-(Trifluoromethyl)-2*H*-pyran-2-thione* (**4e**). Preparation similar to the one described for **4a**. 5-(Trifluoromethyl)-2*H*-pyran-2-one[8]) (7.6 g; 46.2 mmol) and *Lawesson*'s reagent (9.6 g; 23.8 mmol) at reflux for 28 h in anh. toluene (76 ml) led, after FC of the crude mixture (cyclohexane/toluene 77:23) to **4e** (6.9 g; 83%) as orange needles, m.p., 40.5–41.5° (hexane). IR (CCl_4): 1645, 1540, 1330, 1232, 1202, 1189, 1156, 1142, 1085, 1043. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR: see *Table 3.* Exact mass calc. for $C_6H_3F_3OS$ (MS): 179.985667; found: 179.9858.

*Methyl 2-Thioxo-2*H*-pyran-5-carboxylate* (**4f**) *and Methyl 2-Thioxo-2*H*-thiopyran-5-carboxylate* (**10f**). Preparation similar to the one described for **4a**. Methyl 2-oxo-2*H*-pyran-5-carboxylate (7.0 g; 45.5 mmol) and *Lawesson*'s reagent (14.7 g; 36 mmol) at reflux for 7 d in anh. benzene (100 ml) led, after FC (toluene) of the crude mixture, to **10f** and **4f**. Additional amounts of these two compounds were obtained after chromatography of the mixed fractions of the preceding chromatography. Total amount of **4f**: 4.28 g (56%); of **10f**: 1.24 g (15%).

4f: orange crystals (benzene/cyclohexane 1:4), m.p. 98–99° ([36]: 94–95°). IR (CCl_4): 1735, 1627, 1532, 1339, 1300, 1226, 1098, 1082. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR: see *Table 3.* Anal. calc. for $C_7H_6O_3S$ (170.18): C 49.40, H 3.55, S 18.84; found: C 49.5, H 3.3, S 18.7.

10f: red needles (EtOH), m.p. 99.5–100.5°. IR (CCl_4): 1729, 1590, 1403, 1309, 1254, 1210, 1160, 1039. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR: see *Table 3.* Anal. calc. for $C_7H_6O_2S_2$ (186.18): C 45.14, H 3.25, S 34.43; found: C 44.8, H 2.9, S 34.0.

*Methyl 2-Thioxo-6-(trifluoromethyl)-2*H*-pyran-4-carboxylate* (**4g**). Preparation similar to the one described for **4a**. Methyl 2-oxo-6-(trifluoromethyl)-2*H*-pyran-4-carboxylate [35] (10 g; 45 mmol) and *Lawesson*'s reagent (14.6 g; 36 mmol) at reflux for 4 d in anh. toluene (200 ml) led, after separation of the crude reaction by means of two consecutive FC (cyclohexane/AcOEt 9:1), to **4g** (6.2 g; 58%) as red crystals (sublimation) m.p. 33–34°. IR (KBr): 1770, 1550, 1445, 1345, 1315, 1268, 1203, 1150, 1088. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR: see *Table 3.* Exact mass calc. for $C_8H_5F_3O_3S$ (MS): 237.991145; found: 237.9914.

6-Phenyl-8-oxa-2-thia-6-azabicyclo[3.2.1]oct-3-en-7one (8a). – A soln. of **4a** (4.4 g; 39.3 mmol) and nitrosobenzene (4.75 g; 44.3 mmol) in CH_2Cl_2 (100 ml) which had been kept over Na_2CO_3 was stirred at r.t. under Ar during 3 d until complete disappearance of **4a**. The solvent was evaporated *i.v.* to dryness and the residue crystallized (EtOH), the collected crystals being washed three times with small amounts of EtOH to give a beige compound (7.95 g; 92.5%). These crystals were purified by FC (AcOEt/cyclohexane 2:8) and recrystallized (EtOH) to yield the colourless compound **8a**, m.p. 115.5–116.5°. IR (KBr): 3060, 1710, 1590, 1500, 1385. IR (CH_2Cl_2): 1723, 1598, 1588, 1495, 1381, 1112, 870. ^{1}H-NMR: see *Table 7.* ^{13}C-NMR: see *Table 8.* MS: 219 (100, M^+), 190 (75), 162 (70), 104 (25), 100 (82). Anal. calc. for $C_{11}H_9NO_2S$ (219.26): C 60.26, H 4.14, N 6.39, S 14.62; found: C 60.4, H 3.9, N 6.3, S 14.6.

6-Phenyl-8-oxa-2-thia-6-aza[5-$^2H_1$]bicyclo[3.2.1]oct-3-en-7-one (8b). – Same procedure as above starting from **4b**. Compound **8b** was obtained as colourless crystals, m.p. 115.5–116.5°. IR (KBr): 3062, 1715, 1600, 1498, 1372, 750. ^{1}H-NMR: see *Table 7.*

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[7]) We thank Prof. *J. Dreux,* University of Lyon, for the gift of a substantial amount of 4,6-dimethyl-2*H*-pyran-2-one.

[8]) We thank Dr. *P. Martin, Ciba-Geigy,* Basel, for the gift of substantial amounts of methyl 2-oxo-2*H*-pyran-5-carboxylate, 5-(trifluoromethyl)-2*H*-pyran-2-one, and methyl 2-oxo-2*H*-pyran-4-carboxylate [35].

1,5-Dimethyl-6-phenyl-8-oxa-2-thia-6-azabicyclo[3.2.1]oct-3-en-7-one (8c). – To a stirred soln. of **4c** (0.70 g; 5 mmol) in $CHCl_3$ (20 ml) was added under Ar a soln. of nitrosobenzene (0.59 g; 5.5 mmol) in $CHCl_3$ (20 ml). The resulting homogeneous soln. was stirred at r.t. during 10 d until complete disappearance of **4c**. The solvent was evaporated *i.v.* to dryness and the residue purified by FC (AcOEt/cyclohexane 2:8) to give **8c** as a colourless oil which crystallized on standing at r.t. (0.75 g; 61%), m.p. 40–41.5°. IR (CH_2Cl_2): 3040, 2990, 1715, 1595, 1585, 1495, 1390, 1375, 1370. ^{1}H-NMR: see *Table 7*. ^{13}C-NMR: see *Table 8*. MS: 247 (13, M^+), 204 (100), 176 (42), 128 (7), 118 (10). Exact mass calc. for $C_{13}H_{13}NO_2S$ (MS): 247.06669; found: 247.0665.

6-Phenyl-4-trifluoromethyl-8-oxa-2-thia-6-azabicyclo[3.2.1]oct-3-en-7-one (8e). – A soln. of **4e** (5.0 g; 28 mmol) and nitrosobenzene (3.1 g; 29 mmol) in CH_2Cl_2 (50 ml) was stirred under Ar at 40° during 36 h until complete disappearance of **4e**. The solvent was evaporated to dryness *i.v.* and the resulting solid washed with i-PrOH to give **8e** as colourless crystals (8.4 g; 93%), m.p. 128.5–129° (i-PrOH). IR (KBr): 3030, 1710, 1612, 1593, 1500, 1394, 1372, 1287, 1268, 1160, 1115, 1028, 909. ^{1}H-NMR: see *Table 7*. ^{13}C-NMR: see *Table 8*. Anal. calc. for $C_{12}H_8F_3NO_2S$ (287.26): C 50.17, H 2.81, N 4.88, F 19.84, S 11.16; found: C 50.2, H 2.7, N 5.0, F 20.0, S 11.2.

Methyl 7-Oxo-6-phenyl-8-oxa-2-thia-6-azabicyclo[3.2.1]oct-3-ene-4-carboxylate (8f). – *a) Starting from* **4f**. To a stirred soln. of **4f** (1 g; 5.9 mmol) in dry benzene (20 ml) was added nitrosobenzene (0.63 g; 5.9 mmol) at r.t. After 1 h, the soln. was cooled to 0°, whereby some crystals precipitated which were filtered off and washed with small amounts of EtOH to yield **8f** (0.8 g; 49%). The mother liquor was evaporated to dryness *i.v.* and recrystallized from EtOH to yield an additional crop of **8f** (0.32 g; 20%). The resulting mother liquor was evaporated to dryness and submitted to sublimation (80°/1 Torr) leading thereby to orange crystals of **9** (0.198 g; 20%) which was characterized by its IR and NMR spectra and identified with an authentic sample (see below).

*b) Starting from Methyl 2-Oxo-2*H*-thiopyran-5-carboxylate* (**9**). A soln. of **9** (17 mg; 0.1 mmol) and nitrosobenzene (10.7 mg; 0.1 mmol) in deuterated benzene (0.7 ml) was checked several times by ^{1}H-NMR: after 24 d the starting materials had completely disappeared in favour of **8f**. The solvent was evaporated *i.v.* to dryness and the resulting compound **8f** (25.5 mg; 92%) characterized by its IR and ^{1}H-NMR-spectra.

8f: colourless crystals (EtOH), m.p. 154–155°. IR (KBr): 1708, 1692, 1595, 1570, 1502, 1385, 1262, 1163, 1144, 802, 755. ^{1}H-NMR: see *Table 7*. ^{13}C-NMR: see *Table 8*. Anal. calc. for $C_{13}H_{11}NO_4S$ (277.29): C 56.31, H 4.00, N 5.05, S 11.56; found: C 56.3, H 3.9, N 5.2, S 11.4.

Methyl 7-Oxo-6-phenyl-5-(trifluoromethyl)-8-oxa-2-thia-6-azabicyclo[3.2.1]oct-3-en-7-one (8g). – A stirred soln. of **4g** (2.0 g; 8.4 mmol) and nitrosobenzene (2.7 g; 25.2 mmol) in dry benzene (20 ml) was heated at 40° under Ar during 5 d until complete disappearance of **4g**. The solvent was evaporated to dryness *i.v.* and the resulting black residue purified by FC (toluene/Et_2O 95:5) to give **8g** as a crude compound (1.0 g; 34%) which gave colourless crystals when recrystallized from cyclohexane/i-PrOH 4:1, m.p. 106–107°. IR (KBr): 1750, 1732, 1605, 1592, 1500, 1335, 1278, 1262, 1205, 1185. ^{1}H-NMR: see *Table 7*. ^{13}C-NMR: see *Table 8*. Anal. calc. for $C_{14}H_{10}F_3NO_4S$ (345.29): C 48.69, H 2.92, N 4.06, F 16.51, S 9.29; found: C 48.8, H 3.1, N 4.1, F 16.5, S 9.3.

Methyl 2-Oxo-2*H*-thiopyran-5-carboxylate (9). – *a) From Methyl 2-Thioxo-2*H*-thiopyran-5-carboxylate* (**10f**) *with a Nitrosoamine* [23]. To a stirred soln. of *N*-nitrosopiperidine (75 mg; 0.66 mmol) and **10f** (93 mg; 0.5 mmol) in 4N HCl (1 ml) and CH_2Cl_2 (0.5 ml), solid KI (83 mg; 0.5 mmol) was added at r.t. After 29 h, 1N KOH (4 ml) was added under continuous stirring, and the soln. was extracted twice with CH_2Cl_2 (6 ml). The resulting org. soln. was washed with H_2O, dried ($MgSO_4$) and evaporated to dryness *i.v.* Separation of the crude residue by prep. TLC (CH_2Cl_2) led to **10f** (7 mg; 8%; R_f 0.7) and to **9** (47 mg; 56%; R_f 0.5).

b) From **10f** *with Nitrous Acid* [22]. To a stirred soln. of **10f** (98 mg; 0.53 mmol) in 4N HCl (2 ml) and CH_2Cl_2 (2 ml) was added solid $NaNO_2$ (52 mg; 0.76 mmol) at r.t. After 1.5 h, the soln. turned from red to brown, with simultaneous formation of a yellow sulphur emulsion, and was diluted with H_2O (10 ml), extracted twice with CH_2Cl_2 (20 ml). The resulting org. soln. was washed with water, dried ($MgSO_4$), and evaporated to dryness *i.v.* The resulting brown resinuous residue was extracted twice with boiling cyclohexane. The resulting org. soln. was evaporated to dryness *i.v.*, and the residue sublimed (80°/1 Torr) to yield yellow crystals of **9** (57 mg; 64%), m.p. 103–104° (after recrystallisation from cyclohexane). IR (CCl_4): 1728, 1665, 1600, 1518, 1438, 1313, 1252. ^{1}H-NMR: see *Table 2*. ^{13}C-NMR: see *Table 3*. Anal. calc. for $C_7H_6O_3S$ (170.18): C 49.40, H 3.55, S 18.84; found: C 49.6, H 3.2, S 18.4.

Benzyl 2-Oxo-2a, 6a-dihydrothieto[2,3-*e*][1,2]-oxazine-4-carboxylate (18a). – To a stirred soln. of **4a** (0.1 g; 0.89 mmol) and tetrapropylammonium periodate (0.112 g; 0.3 mmol) in $CHCl_3$ (1 ml) at 0° under Ar were added a few grains of 4-Å molecular sieves and then portionwise benzyloxycarbohydroxamic acid (0.149 g; 0.89 mmol) [37]. After 30 min, the mixture was separated by column chromatography (AcOEt/cyclohexane 3:7) and led to the

isolation *i.a.* of **18a** (20 mg; 8%) and to some unreacted **4a** (40–50%). Compound **18a** appeared as colourless crystals, m.p. 85° (Et_2O). IR ($CHCl_3$): 2950, 1765, 1725, 1640, 1405, 1345, 1312, 1110, 855. ^{1}H-NMR: see *Table 5*. ^{13}C-NMR: see *Table 6*. Anal. calc. for $C_{13}H_{11}NO_4S$ (277.27): C 56.31, H 3.99, N 5.05, S 11.56; found: C 56.3, H 3.9, N 5.0, S 11.7.

Benzyl 2-Oxo-2a,6a-dihydro[5-$^2H_1$]thieto[2,3-*e*][1,2]oxazine-4-carboxylate (18b). – Same preparation as for **18a** starting from **4b**. IR ($CHCl_3$): 1765, 1730, 1620, 1310, 1122. ^{1}H-NMR: see *Table 5*.

Benzyl 2a,5-Dimethyl-2-oxo-2a,6a-dihydrothieto[2,3-e][1,2]oxazine-4-carboxylate (18c). – Similar preparation as for **18a** starting from **4c** (0.1 g; 0.71 mmol), tetrapropylammonium periodat (0.09 g; 0.25 mmol), and benzyloxycarbohydroxamic acid (0.119 g; 0.71 mmol). FC (AcOEt/cyclohexane 3:7) of the crude mixture permitted to isolate, *i.a.* some unreacted **4c** (40–50%) and **18c** (126 mg; 58%), the latter being further purified by a second column chromatography to yield a colourless oil. IR ($CHCl_3$): 3030, 1765, 1720, 1655, 1400, 1355, 1315, 1117, 910. ^{1}H-NMR: see *Table 5*. Elemental analyses were not performed.

Benzyl 7-Oxo-8-oxa-2-thia-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (19a). – Compound **18a** (100 mg; 0.36 mmol) was heated in benzene (2 ml) for 15 min at 80°. The resulting soln. was evaporated to dryness *i.v.*, and the crystalline residue washed with cyclohexane containing a few drops of AcOEt to yield **19a** as colourless crystals (91 mg; 91%), m.p. 97–98° (AcOEt/cyclohexane 1:3). IR (KBr): 3050, 3000, 2970, 1785, 1712, 1365, 1350, 1282, 1242. ^{1}H-NMR: see *Table 7*. ^{13}C-NMR: see *Table 8*. Anal. calc. for $C_{13}H_{11}NO_4S$ (277.27): C 56.31, H 3.99, N 5.05, S 11.56; found: C 56.3, H 3.9, N 4.9, S 11.4.

Benzyl 7-Oxo-8-oxa-2-thia-6-aza[5-$^2H_1$]bicyclo[3.2.1] oct-3-ene-6-carboxylate (19b). – Same procedure as for the preparation of **19a**, starting from **18b**. Compound **19b** was obtained in small amounts as an oil. ^{1}H-NMR: see *Table 7*.

Benzyl 1,5-Dimethyl-7-oxo-8-oxa-2-thia-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (19c). – Compound **18c** (100 mg; 0.33 mmol) was heated in $CDCl_3$ (1 ml) at 55° for 2 h (or, alternatively, in benzene (1 ml) at 80° for 30 min). The resulting soln. was evaporated to dryness *i.v.*, and the viscuous residue purified by FC (AcOEt/cyclohexane 3:7) to give **19c** (70 mg; 70%) as colourless crystals, m.p. 74–74.5° (cyclohexane). IR ($CHCl_3$): 3020, 1795, 1763, 1727, 1626, 1590, 1378, 1312, 1282, 906. ^{1}H-NMR: see *Table 7*. Anal. calc. for $C_{15}H_{15}NO_4S$ (305.35): C 59.00, H 4.95, N 4.59, S 10.50; found: C 59.0, H 4.7, N 4.5, S 10.4.

***erythro*- and *threo*-3-Bromo-2-hydroxy-3-phenylpropionic Acids (21 and 22, resp.).** – To a stirred soln. of sodium 2-phenyloxirane carboxylate [21] (5.0 g; 27 mmol) in Et_2O (50 ml) at 0° was added dropwise 48% aq. HBr (20 ml) during 15 min[9]). After 1 h, the resulting yellow soln. was diluted with H_2O (50 ml) and extracted several times with Et_2O. The combined org. solns. were washed twice with H_2O, dried ($MgSO_4$), and evaporated to dryness *i.v.* The oily crystals were washed with a small amount of toluene and led to a mixture (4.9 g; 75%) **21**/**22** (10%). This crystalline mixture was then washed several times with toluene and CH_2Cl_2 leading thereby to the pure *erythro*-isomer **21** (4.37 g; 67%) as colourless crystals, $m.p._{inst.}$: 149–150° (dec.; $CHCl_3$/AcOEt 9:1) ([38]: m.p. 143°). IR (KBr): 3445, 2980, 1730, 1104. ^{1}H-NMR ($CDCl_3$, 10% CD_3OD) 4.65 (*d*, *J*(2,3) = 4.6, H–C(2)); 5.30 (*d*, H–C(3)); 4.07 (*s*, OH and CO_2H); *ca.* 7.4 (*m*, arom. H).

Evaporation of the mother liquors (obtained above by washing the crystals of **21**) and recrystallisation of the residue led to the *threo*-isomer **22**, $m.p._{inst.}$ 162–165° (dec.; [38]: m.p. 155°). IR (KBr): 3500, 2850, 3030, 1708, 1455, 1118, 694. ^{1}H-NMR ($CDCl_3$, 10% CD_3OD): 4.43 (*d*, *J*(2,3) = 2.7, H–C(2)); 5.65 (*d*, H–C(3)); 4.76 (*s*, OH and CO_2H), *ca.* 7.5 (m, arom. H).

***erythro*-2-Acetoxy-3-bromo-3-phenylpropionic Acid (23).** – Similar preparation as for 2-acetoxy-3-phenylpropionic acid [39]. To **21** (0.543 g; 2.22 mmol) was added AcCl (*ca.* 2 ml). The inhomogeneous mixture was stirred at 25–30° for 2 h, heat being thereby evolved. Eventually the mixture became a homogeneous soln. which was evaporated *i.v.* to dryness at 30° after adding twice some dry CCl_4. The residue appeared as a faint yellow oil which was used as such for the preparation of **24** (see below). This oil was dissolved in Et_2O (10 ml) and the resulting soln. was stirred and hydrolysed with H_2O (0.5 ml) over a 2 h period. The org. soln. was dried ($MgSO_4$) and evaporated to dryness *i.v.* The viscuous residue was dried *i.v.* over P_2O_5 and led thereby to a crystalline material which was washed with a small amount of benzene/cyclohexane 1:1. Compound **23** (0.522 g; 82%) was obtained as colourless crystals, $m.p._{inst.}$ 89–90° (dec.; benzene). IR (CCl_4): 1765, 1737, 1223, 694. IR (KBr): 3290, 1775, 1720,

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[9]) The preparation of **21** and **22** in Et_2O using dry HBr [38] gave a mixture which contained 30% of the *threo*-isomer **22**.

1245, 1180, 1095, 697. ^{1}H-NMR (CCl_4): 5.66 (*d*, *J*(2,3) = 5.7, H–C(2)); 5.35 (*d*, H–C(3)); 2.09 (*s*, AcO); 8.87 (*s*, CO_2H); *ca.* 7.4 (*m*, arom. H). Anal. calc. for $C_{11}H_{11}BrO_4$ (287.11): C 46.02, H 3.86, Br 27.83; found: C 46.2, H 3.6, Br. 27.9.

***erythro*-[2-Bromo-1-(chloroformyl)-2-phenyl]ethyl Acetate (24).** – Preparation according to [40] in CCl_4. A stirred soln. of crude acetyl derivative (prepared from **21** (0.50 g, 2.05 mmol)) and oxalyl chloride (2.6 g; 20.5 mmol) in dry CCl_4 (10 ml) was heated to 50° for 3 h under anh. conditions ($CaCl_2$ protection). The resulting soln. was evaporated to dryness at 30° *i.v.* after addition of CCl_4. This operation was repeated twice leading thereby to the crude **24** which was not purified further. IR (CCl_4): 1808, 1767, 1218, 1200, 695. ^{1}H-NMR (CCl_4): 5.70 (*d*, *J*(2,3) = 6.0, H–C(2)); 5.40 (*d*, H–C(3)); 2.13 (*s*, AcO), *ca.* 7.4 (*m*, arom. H).

***cis*-2-Oxo-4-phenylthietan-3-yl Acetate (25).** – Preparation according to [41]. A soln. of CCl_4 (10 ml) sat. with H_2S cooled to –20° was added to **24** (see above), and kept at –20° during 1 h while continuously sat. with H_2S. Et_3N (0.57 ml, *i.e.* 0.41 g; 4.1 mmol) was added dropwise and the mixture was kept at –20° for 1 h, and then left to warm up to r.t. Ammonium salts (562 mg) which precipitated were filtered off, washed twice with dry Et_2O (5 ml), and the combined org. solns. were evaporated to dryness. The resulting residue was purified by chromatography (CH_2Cl_2) which led to **25** (368 mg; 82%) as a colourless oil which crystallized at low temp. only, m.p. 11–12°. IR (CCl_4): 1785, 1772, 1756, 1218. ^{1}H-NMR: see *Table 5*. ^{13}C-NMR: see *Table 6*. Exact mass calc. for $C_{11}H_{10}O_3S$ (MS): 222.03506; found: 222.0350. Anal. calc. for $C_{11}H_{10}O_3S$ (222.26): C 59.44, H 4.52, S 14.42; found: C 59.3, H 4.5, S 14.9.

***trans*-2-Oxo-4-phenylthietan-3-yl Acetate (26).** – Preparation similar to the one of **25**, starting from **22** (106 mg; 0.43 mmol). The final crude mixture was purified by chromatography (CH_2Cl_2) and led to **26** (69 mg; 72%) as colourless needles, m.p. 54–57° (after sublimation at 80° under 1 Torr). IR (CCl_4): 1783, 1770, 1210. ^{1}H-NMR: see *Table 5*. ^{13}C-NMR: see *Table 6*. Anal. calc. for $C_{11}H_{10}O_3S$ (222.26): C 59.44, H 4.52, S 14.42; found: C 59.3, H 4.5, S 14.7.

Some Thermodynamic Parameters of the Thermal 18a→19a Conversion as Determined by Differential Scanning Calorimetry (DSC). – DSC measurements have been determined with a *SETARAM DSC 111* apparatus, using a soln. of **18a** (4.32 mg) in 1,2-dichlorobenzene (30.21 mg) which was heated up at a rate of 4°/min. An exothermic peak appeared between 28.7° and 115.3°. The heating process was interrupted at 130° and after cooling to r.t., the sample was shown by TLC and by ^{1}H-NMR to be composed of at least 93% of **19a**. The reaction enthalpy was determined by integration:

$$\Delta H = -45 \pm 2 \text{ kcal/mol.}$$

Line-shape analysis [42] led to the activation energy:

$$\Delta H^* = 24 \pm 1 \text{ kcal/mol.}$$

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