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CYCLOADDITION REACTIONS OF 1,3-BENZOTHIAZINES—I. REACTIONS OF 2-PHENYL-4-H AND 4-PHENYL-2H-1,3-BENZOTHIAZINE DERIVATIVES WITH SUBSTITUTED ACETYL CHLORIDES[1]

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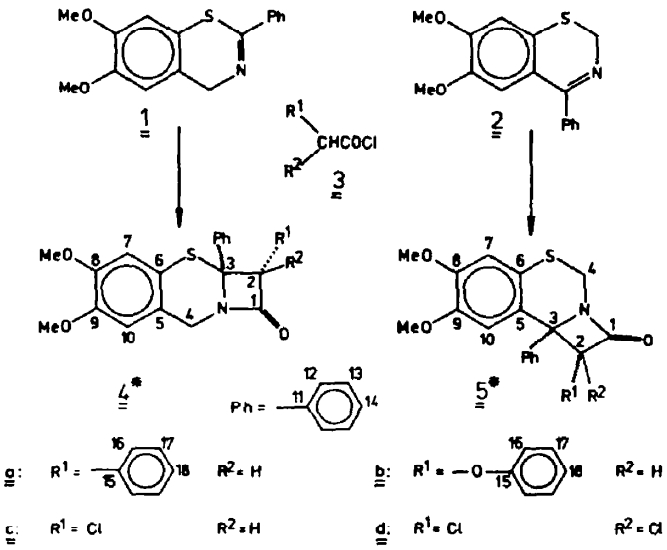
Abstract—6,7-Dimethoxy-2-phenyl-4H-1,3-benzothiazine (**1**) and 6,7-dimethoxy-4-phenyl-2H-1,3-benzothiazine (**2**) react with substituted acetyl chlorides to give linearly, and new angularly condensed β-lactam derivatives (**4, 5**). Heating of the latter compounds with hydrogen chloride in anhydrous ethanol leads to the formation of the corresponding 4H- and 2H-1,3-benzothiazinium chloride, respectively. The configurations of these compounds (the mutual positions of the substituents relative to the β-lactam ring) were determined by ^1H and ^{13}C studies, also making use of the aromatic solvent-induced shifts.

Cycloaddition reactions of 4H- and 2H-1,3,-benzothiazine derivatives, prepared by us earlier,[2,3] permit the construction of new cyclic systems.

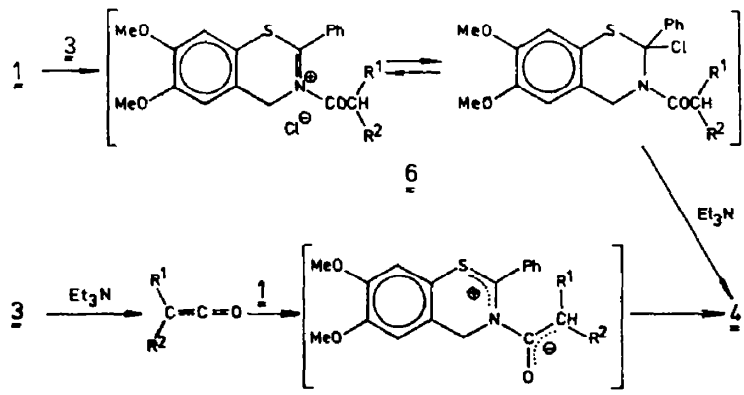
In this paper we report on the cycloaddition reactions of 6,7-dimethoxy-2-phenyl-4H- and 6,7-dimethoxy-4-phenyl-2H-1,3-benzothiazines (**1, 2**) with acetyl chlorides (**3**), taking place in the presence of triethylamine. According to a known method,[4] linearly and angularly condensed β-lactam derivatives (**4a–d, 5a–c**) have been prepared.

As shown by investigations of the mechanism,[5–7] this reaction may take place through the intermediate **6** or **7**, depending on whether triethylamine or the substituted acetyl chloride is added first to the solution of the 1,3-benzothiazine derivative **1**. A similar mechanism may also be assumed in the β-lactam-forming reaction of the 2H-1,3-benzothiazine derivative **2**.

However, when the reaction was effected in ethereal solution at −80° with an axcess of the acetyl chloride



* The numbering of the hydrogen and carbon atoms (see Formulae, text and Tables) is not identical with that of the compounds numbered according to the IUPAC nomenclature. This was necessary for ease of comparison of spectroscopically analogous atoms in **4** and **5**, respectively



derivative and in the absence of triethylamine, instead of adduct **6** we observed, in each case, the formation of the hydrochlorides[8,9] of the starting benzothiazine derivatives (**1**, **2**) and that of the corresponding β-lactams (**4**, **5**) in about 55% yields.

As the benzothiazine bases may equally function in this reaction as proton-acceptor or generating ketene, the formation of the β-lactams may follow either reaction pathway.

A study was made of the splitting of the β-lactams (**4**, **5**) with hydrogen chloride in anhydrous ethanol. In every case the product was, in nearly quantitative yield, the hydrochloride[8,9] of the starting benzothiazine derivative (**1**, **2**). We suggest that the splitting by hydrogen chloride of the β-lactams (**4**, **5**) occurs *via* adducts of type **6**.

All the β-lactam derivatives prepared in this work (**4a–d**, **5a–c**) were found stereohomogeneous according to spectroscopic evidence. Hence the cyclizations to β-lactam are, in these cases, regio- and stereospecific reactions.

The configurations of the compounds (the steric positions of the substituents R relative to the four-membered ring) have been established by spectroscopic methods. The spectral data (Tables 1–3) unambiguously support the structures proposed.

In $CDCl_3$ solution the ^1H NMR spectra show an *AB* multiplet for the methylene protons, whose δA and δB chemical shifts are hardly different in the compounds investigated: the $\Delta\delta A$ and $\Delta\delta B$ intervals are of the magnitude 0.36 and 0.30 ppm, respectively (Table 1).

On the other hand, the J_{AB} (geminal) coupling constants in compounds **4** and **5** differ characteristically: for compounds **4** it is 16–18 Hz, whereas in the analogous derivatives **5** this value is, as a result of the *–I*-effect of the neighbouring sulphur atom,[10a] significantly lower, 11–12 Hz.

Determination of the configurations of compounds

Table 1. The carbonyl IR-band and ^1H NMR data of compounds **4a–d**, **5a**, **c**, **d**

Compound	IR-data in KBr νC=O /cm^{-1}/	Solvent	^1H NMR data in $CDCl_3$ (a) and C_6D_6 (b) /δ_{TMS} = 0 ppm/								
			δH-4			δH-8, 9 (OMe)		δH-2	δH-7	δH-10	δH-11–14+ δH-15–18
			A* (1H)	B* (1H)	J$^x_{AB}$	2 x s (2 x 3H)		s (1H)	s (1H)	s (1H)	(10H$^+$ or 5H$^•$)
4a	1745	a	4.36	5.01	16	3.80	3.85	4.85	6.65	6.70	~7.0 ~s
		b	4.05	4.95		3.15	3.30	4.90	6.30	6.60	~6.90 ~s ~7.15 ~s
4b	1775	a	4.20	4.90	17	4.05		5.45	6.60	6.70	390 – 460 m§
4c	1790	a	4.48	5.15	18	3.90	3.95	5.40	6.98		~7.7 m
		b	3.72	4.55		3.05	3.15	4.85	6.10	6.35	~7.0 m
4d	1775	a	4.16	4.84	16	3.75	3.80	–	6.70		~7.35 ~s
		b	3.68	4.52		3.15	3.25		6.30	6.60	~7.20 ~s
5a	1740	a	4.40	5.00	11	3.85	4.00	4.95	6.80	7.25	~7.1 ~s
		b	4.00	4.85		3.25	3.50	4.90	6.60	7.10	~7.15 ~s ~6.9 ~s
5c	1775°	a	4.52	5.08	11	4.00	4.10	5.45	7.07	7.33	~7.65 ~s
	1760°	b	3.77	4.55		3.20	3.25	5.00	6.50	6.70	~7.15 ~s
5d	1775	a	4.45	4.98	12	3.85	3.95	–	6.65	7.20	~7.4 m
		b	3.90	3.53		3.25	3.35		6.45	7.10	~7.15 ~s ~7.4 m

* Calculated from the AB spectrum of the methylene hydrogens

° Splitted bands,
s: singulet,
~s: singulet-like signal
m: multiplet

x Coupling constant in Hz

+ In case of compounds 4a, b and 5a

• In case of compounds 4c, d and 5c, d

§ Multiplet in Hz (at 60 MHz)

Table 2. Chemical shift differences (aromatic solvent induced shifts, ASIS) for protons of compounds **4a**, c, d, **5a**, c, d ($\Delta\delta = \delta_{CDCl_3} - \delta_{C_6D_6}$ ppm)

Compound	H-4 (A)	H-4 (B)	H-8, 9 (OMe)		H-2	H-7	H-10	H-11–18	
4a	0.31	0.06	0.65	0.55	−0.05	0.10	0.35	−0.15	0.10
4c	0.76	0.60	0.85	0.80	0.55	0.63	0.88	0.7	
4d	0.48	0.32	0.60	0.55	−	0.10	0.40	0.15	
5a	0.40	0.15	0.60	0.50	0.05	0.15	0.20	−0.05	0.20
5c	0.75	0.53	0.85	0.80	0.45	0.63	0.57	0.5	
5d	0.55	0.45	0.60	0.60	−	0.10	0.20	0.25	0.0

4a and **5a** is possible by considering the mutual anisotropic effect of the two vicinal phenyl groups attached to the 4-membered ring. If their configuration is *cis*, they can, for steric reasons, lie only parallel to each other, and in this case their mutual anisotropic effect must result in the upfield shifts of the ring protons.

The overlapped, approximately singulet signal of the two phenyl groups in the ^{1}H NMR spectra of **4a** and **5a** is found at 7.0 and 7.1 ppm, respectively, i.e. with values shifted upfield by ~0.70 and ~0.55 ppm compared with e.g. **4c** and **5c**, proving the postulated steric structures for **4a** and **5a**.

These structures were confirmed by an investigation of the aromatic solvents induced shifts (ASIS),[10b] too. As shown in Table 2, it has been found that while the ASIS is significant with **4c** and **5c** (the difference in their chemical shifts, measured in C_6D_6 and $CDCl_3$, being 0.7 and 0.6 ppm, respectively, for the signal of the phenyls), the same effect is markedly lower for **4a** and **5a**. Considering that the parallel arrangement of the two phenyl rings in **4a** and **5a** will necessarily result in a greater shielding of the ring protons, it is evident that the solvent C_6D_6 cannot cause a further significant increase in shielding, whereas this can and does occur in the cases of **4c** and **5c**.

The configurations of the other compounds cannot be determined with the same ease. The problem is complicated by the flexibility of the thiazine ring, allowing different mutual positions of the substituents in the various conformers. (It is only the relative positions of the substituents attached to the four-membered ring which remain unaffected by the conformational change.) For this reason an attempt was made to establish the configurations of **4b–d** and **5b–c** by means of ^{13}C NMR studies.

The ^{13}C NMR data are listed in Table 3. For the assignment of the aromatic carbon signals use was made of the data of the model compounds anisole,[10c] thiophenol and dibenzylmethylamine,[11] taking into account the additivity,[10d] of the substituent effects. It is remarkable that the methylene carbons as well as C-10 and particularly C-5 are more shielded in the case of **5d** compared with the rather close values obtained for **5a** and **5c**. This can be explained by the steric compression shift[12] which increases the shielding of carbon atoms carrying sterically hindered groups. The appearance of the field effect confirms the probable configuration of

Table 3. The ^{13}C NMR chemical shifts of compounds **4a–d**, **5a**, c, d in $CDCl_3$ ($\delta_{TMS} = 0$ ppm)

Compound	C-1 (C=O)	C-2 (CH/C)	C-3 (C)	C-4 (CH_2)	C-8, 9 (OCH_3)	C-5, 6	C-7, 10	C-8, 9	C-11	C-15	C-12, 16	C-13, 17	C-14, 18
4a	168.8	71.5	71.1	43.0	56.2 56.3	121.5 122.6	112.2 113.3	148.4 149.0	138.5	132.2	126.7	127.7[x] 127.8[x]	128.2[x] 129.2[x]
4b	165.1	90.4	71.6	42.1	56.0	120.4 122.1	111.7 112.8	148.2 148.9	136.4	156.8	127.4[o] 115.7[§]	128.1[o] 129.4[§]	128.5[o] 122.4[§]
4c	164.3	68.3	71.2	42.9	56.0	120.1 121.9	111.2 112.4	148.1 148.7	136.7	−	126.8	128.4	128.9
4d	163.0	89.8	82.1	44.0	56.0	121.3 125.0	111.4 112.6	148.2 149.1	137.5	−	125.6	128.6	129.2
5a	167.9	68.5	67.2	40.1	56.1 56.6	122.5 132.3[x]	111.8 112.6	147.9 149.2	137.2	132.5[x]	127.4[+] 127.7[+]	128.3[+] 128.8[+]	
5c[*]	165.1	67.3	69.2	41.8	57.4 57.6	122.9 132.6	113.1 114.4	149.4 150.5	138.1	−	129.1[x]	129.5[x]	
5d	160.0	90.1	73.6	37.6	55.9 56.4	121.7 122.4	110.5 114.6	146.3 149.6	136.0	−	128.1[x]	128.4[x]	129.1

[*] In DMSO-d_6 solution measured data

[o] Phenyl ring in Pos. 3

[§] Phenoxy ring in Pos. 2 (R_1)

[x, +] Alternative assigment is possible (Probably: δC-10 > δC-7, except for the reversed case of 5d, and δC-5 > δC-6; δC-9 > δC-8, respectively.)

Table 4. Physical and analytical data for compounds **4a–d** and **5a, c, d**

Compound	Yield % (Method)	M. p. /C°/	Molecular Formula	Analysis							
				Calculated				Found			
				C	H	N	S	C	H	N	S
4a	93(A) 51(B)	190 - 191	$C_{24}H_{21}NO_5S$	71.44	5.25	3.47	7.95	71.64	5.37	3.41	7.27
4b	90(A) 62(B)	139 - 140	$C_{24}H_{21}NO_4S$	68.75	5.04	3.34	7.64	69.00	5.35	3.72	7.89
4c	86(A) 63(B)	145 - 146	$C_{18}H_{16}ClNO_3S$	59.74	4.46	3.87	8.86	59.42	4.63	3.47	8.49
4d	88(A)	163 - 164	$C_{18}H_{15}Cl_2NO_3S$	54.56	3.82	3.53	8.09	54.92	3.97	3.37	7.86
5a	74(A)	173 - 174	$C_{24}H_{21}NO_3S$	71.44	5.25	3.47	7.95	71.80	5.34	3.79	7.41
5c	84(A)	209 - 210	$C_{18}H_{16}ClNO_3S$	59.74	4.46	3.87	8.86	59.53	4 65	3 65	8 54
5d	89(A)	143 - 144	$C_{18}H_{15}Cl_2NO_3S$	54.56	3.82	3.53	8.09	54.64	3.71	3.42	7.76

5a suggested on the basis of ^{1}H NMR data, further, it indicates that **5a** and **5c** are of identical configuration, i.e. the phenyl ring and the chlorine atom (R_1) are in *cis* position. If the R_1 substituent were *trans* relative to the phenyl ring attached to the anellated carbon in **5a** and **5b**, the field effect would act also in these compounds, and there would be no considerable difference between the analoguous shift values of the three compounds.

No similar steric hindrance can be expected, and observed, in the case of **4d**. On the other hand, comparison of the spectrum of **4d** with the spectra of **4a, c** shows no chemical shift difference for the C–11 signal. This, in turn, indicates that the field effect is already operating also in **4a** and **4c**, and this is the reason why the chemical sifts remain essentially unaltered. Hence the ^{13}C NMR data afford evidence to show that the derivatives **4c** and **4d** also have *cis*-phenyl-R_1 configurations which has been proved for **4a** and **5a–c**, too.

It is worth mentioning that the ^{13}C NMR shift of the amide carbonyl signal is markedly decreased by α-chloro- or α,α-dichloro-substitution; also the second chlorine atom has a great effect, which is commensurable with that of the first.

EXPERIMENTAL

All m.ps are uncorrected. The IR spectra were taken with a Perkin–Elmer 577 optical grating spectrometer in KBr discs. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$ or C_6D_6 solutions with a JEOL 60-HL spectrometer (δ_{TMS} = 0 ppm). A Varian XL-100 FT spectrometer was used for obtaining the ^{13}C NMR spectra at room temperature in $CDCl_3$ or DMSO-d_6 solution, the concentration being 200 mg of the substance in 0.4 ml of solvent; the internal standard was TMS, the numbers of transients were in the order **4a, b, c, d, 5a, b, c** 47, 7.5, 25, 25, 80, 20 and 70 K.

A Preparation of **4a–d** *and* **5a- c**

Compound **1** or **2** (2.85 g; 0.01 mol) was dissolved in benzene (30 ml) and 0.01 mol of **3** was added. The mixture was refluxed, and a soln of Et_3N (1.01 g; 0.01 mol) in 30 ml benzene was added dropwise, with stirring, during 1 hr. The crystalline Et_3N.HCl was removed by filtration, the benzene soln was evaporated and then crystallised from EtOH to obtain colourless crystals (*cf* Table 4).

B Preparation of **4a–c**

Et_3N (1.01 g; 0.01 mol) was added to a soln of **1** (2.8 g; 0.01 mol) in 30 ml benzene. The mixture was refluxed, and a soln of **3** in 30 ml benzene was added by drops, with stirring, during 1 hr. The Et_3N which deposited was filtered off and the solvent evaporated. The residue was crystallised from EtOH to furnish colourless crystals (*cf* Table 4).

Splitting of **4a–c, 5a–c** *with hydrochloric acid*

The β-lactam (0.01 mol) was refluxed in anhydr ethanolic HCl (30 ml) for 2 hr. The mixture was then concentrated to 3–4 ml volume, and the yellow, crystalline hydrochloride of **1** or **2** which precipitated was filtered off. The products gave no m.p. depression in admixture with the corresponding authentic 1,3-benzothiazinium chlorides[8,9] and were identical with the latter.

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