

Augusto Colombo, Jordi Frigola, Juan Parés and Blas Andaluz

Department of Medicinal Chemistry, Laboratorios Dr. Esteve, S. A., Avda. Mare de Déu de Montserrat,
221, 08026 Barcelona, Spain

Received July 25, 1989

The synthesis, structure elucidation and chemotherapeutic activity of novel heterocyclic analogues of the cardiotropic agent Diclofurime are reported.

J. Heterocyclic Chem., **27**, 615 (1990).

A great number of oxime ethers have been reported to have interesting biological properties, such as anti-inflammatories [1], spasmolytic [2], local anesthetic [3], analgesic [4], β -adrenergic [5-7] or cardiotropic [8] characteristics, and amongst those possessing the latter activity, one of the most promising was Diclofurime [9], **5a**.

In order to better elucidate the structure-activity relationships and in search of new compounds with enhanced pharmacological activities, we were interested in substituting the furan group by five membered *N*-heterocycles such as pyrazoles or imidazoles.

The reaction between the ketones **2**, which were synthesized by methods similar to those described in the literature [10-13], and hydroxylamine hydrochloride, affords a mixture of the oximes **3** and **4**, which, in this series, were designated the *E* and *Z* isomers, respectively, except when Het is 1*H*-pyrazole-4-yl (**f**), when they were *Z* and *E* respectively (Scheme I). These isomers were separable by either fractional crystallization or chromatography.

The differences in ^1H nmr spectra of the oxime isomers were significant only in the OH signal, which was not however conclusive for determination of the stereo-

chemistry. In order to assign the structures unequivocally, selective NOE difference experiments were performed on isolated oxime isomers: when a weak irradiation on the OH signal resulted in an increase of the H6 phenyl proton signal, the configuration **3** was assigned. Configuration **4** was assigned if the increase was detected on the H4 or H5, protons of the heterocycle.

It has been reported [14] that there is no isomerization between **2a** and **3a** during alkylation at 95° in basic medium, and also that only isomer **3a** can be cyclized to **7a**. In our case the reaction works differently and **4f** is the only one not to isomerize to the **3f** as it is also the only one which does not yield the corresponding 1,2-benzisoxazole **7f**.

These oximes were generally base sensitive and their alkylation, either as separate isomers or in a mixture, under very mild conditions, affords the corresponding oxime ethers **5** and **6** and some cyclized 1,2-benzisoxazole **7**. The attempted etherification under more drastic conditions gave us only **7**.

In an attempt to obtain **6c**, we conducted the reaction between **2c** and the diethylaminoethoxyamine [15], under

SCHEME 1

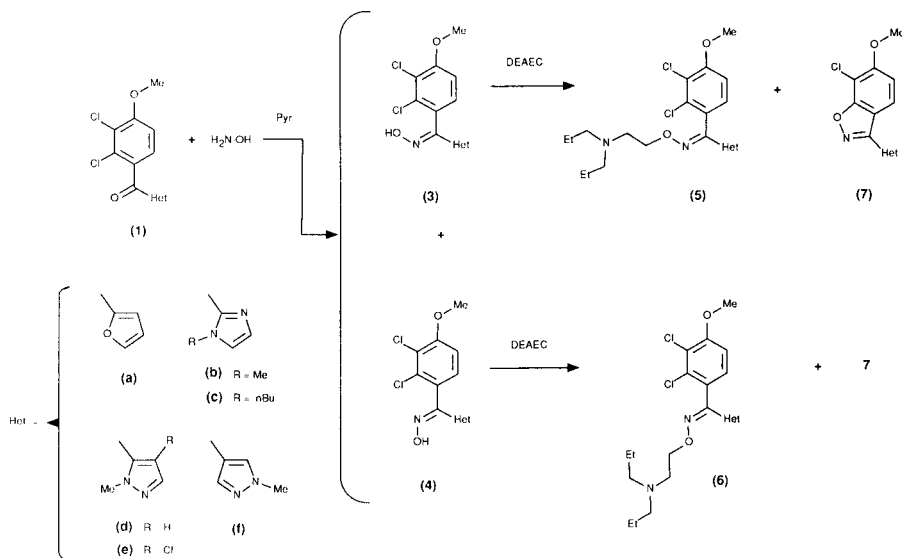


Table 1

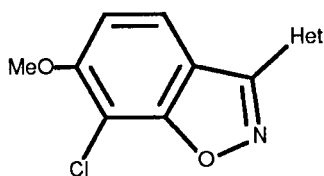
Comp.	Config.	Yield %	M.P. °C	Obtent.	Analysis %				IR (cm ⁻¹)	¹ H-NMR (DMSO-d ₆), δ, J = Hz
					Calcd./Found	C	H	N		
3b	E	21	220-2	B	48.02	3.69	14.00	23.62	2930, 1650,	3.66(s,3H,MeN); 3.93(s,3H,MeO); 6.91(s,1H,4imid); 7.25(d,1H,J=6.5,Ph); 7.55(d,1H,J=6.6,Ph); 12.26(s,1H,OH)
					47.76	3.93	13.84	23.83	1590, 1040.	
4b	Z	34	252-3	B	48.02	3.69	14.00	23.62	3120, 1595,	3.89(s,3H,MeN); 3.92(s,3H,MeO); 6.85(s,1H,4imid); 7.23(m,3H,Ph); 11.7(s,1H,OH)
					47.84	3.89	13.91	23.66	1280, 1030.	
3c	E	30	156-7	A	52.64	5.00	12.28	20.72	3125, 1600,	0.91(t,3H,J=6.4); 1.25(m,2H); 1.8(m,2H); 3.94(m,5H); 6.96(s,1H,4imid); 7.25(d,1H,J=6.5,5Ph); 7.34(s,1H,5imid); 7.52(d,1H,J=6.5,6Ph)
					52.61	4.74	11.97	20.69	1300, 1030	
4c	Z	27	183-4	A	52.64	5.00	12.28	20.72	3130, 1595,	0.85(t,3H,J=6.3); 1.25(m,2H); 1.8(m,2H); 3.93(s,3H,MeO); 4.30(m,2H); 6.89(s,1H); 7.20(m,3H); 11.66(s,1H)
					52.92	5.32	12.55	20.58	1290, 1040	
3d	E	45	190-2	B	48.02	3.69	14.00	23.62	3130, 1605,	3.81(s,3H,MeN); 3.91(s,3H,MeO); 6.07(s,1H,4Pyr); 7.19(d,1H,J=7.5,Ph); 7.22(s,1H,3Pyr); 7.45(d,1H,J=6,Ph); 12.28(s,1H)
					47.76	3.86	14.21	23.84	1300, 1050	
4d	Z	8	212-5	C	48.02	3.69	14.00	23.62	3120, 1600	3.94(s,3H,MeN); 4.05(s,3H,MeO); 5.87(s,1H,4Pyr); 7.25(b,2H); 7.35(s,1H,3Pyr); 11.72(s,1H)
					48.25	3.41	13.94	23.53	1300, 1045	
3e	E	31	202-5	A	43.08	3.01	12.65	31.78	3110, 1595,	3.82(s,3H); 3.94(s,3H); 7.30(d,1H,J=8.2); 7.50(m,2H); 12.4(s,1H)
					42.94	3.14	12.36	31.48	1295, 1040	
4e	Z	29	294-5	A	43.08	3.01	12.65	31.78	2920, 1600,	3.92(s,3H); 3.95(s,3H); 7.30(d,d,2H,J=6); 7.5(s,1H); 12.03(s,1H)
					43.23	3.27	12.82	31.57	1280, 1045	
3f	Z	40	185 ^(b)	C	48.02	3.69	14.00	23.62	3040, 1590,	3.80(s,3H); 3.92(s,3H); 7.21(d,1H,J=8.6); 7.49(d,1H,J=8.6); 7.8(s,1H); 8.20(s,1H); 10.9(s,1H)
					48.20	3.66	14.14	23.75	1290, 1030	
4f	E	45	238-40	C	48.02	3.69	14.00	23.62	3150, 1595,	3.84(s,3H); 3.94(s,3H); 7.20(d,1H,J=8.6); 7.30(d,1H,J=8.6); 7.46(s,1H); 8.05(s,1H); 11.6(s,1H)
					48.31	3.64	13.86	23.68	1300, 1040	

(b) Measured from a Mettler FP61

Table 2

Comp.	Config.	Yield %	Obtent.	Analysis %			IR (cm ⁻¹)	¹ H-NMR (DMSO-d ₆), δ, J = Hz	
				Calcd./Found	C	H			N
5b	E	35	A	54.14 54.31	6.06 5.88	14.03 14.21	17.76 17.85	2980, 1600, 1295	0.95(t,6H,Me,J=7); 2.50(q,4H,J=7); 2.75(t,2H,J=6.2); 3.70(s,3H,MeN); 3.84(s,3H,MeO); 4.27(t,2H,J=6.2); 6.87(d,1H,J=8.5); 6.91(s,1H,4imid); 7.02(s,1H,5imid); 7.54(d,1H,J=8.5)
6b	Z	47	A	54.14 54.22	6.06 6.23	14.03 14.26	17.76 17.80	2990, 1605, 1280	0.93(t,6H,Me,J=7); 2.49(q,4H,J=7); 2.73(t,2H,J=6.3); 3.85(s,3H,MeN); 3.91(s,3H,MeO); 4.23(t,2H,J=6.1); 6.90(s,1H,4imid); 6.95(d,1H,J=8.6); 7.0(s,1H,5imid); 7.20(d,1H,J=8.6)
5c	E	30	A	54.14 53.96	6.06 6.00	14.03 13.97	17.76 17.85	2990, 1595, 1290	0.98(m,9H); 1.30(m,2H); 1.75(m,2H); 2.49(q,4H,J=6.8); 3.06(t,2H,J=6.8); 3.70(t,2H,J=7.5); 3.88(s,3H); 4.16(t,2H,J=6.8); 6.85(d,1H,J=8.8); 6.9(s,1H,4imid); 7.1(s,1H,5imid); 7.50(d,1H,J=8.6)
6c	Z	56	A	54.14 54.26	6.06 6.17	14.03 14.02	17.76 17.52	2980, 1595, 1290	0.95(t,9H,J=7); 1.35(m,2H); 1.86(m,2H); 2.50(q,4H,J=7.1); 2.75(t,2H,J=6.3); 3.05(s,3H); 4.3(m,4H); 6.93(m,3H); 7.07(d,1H,J=8.6, 5Ph)
5d	E	49	A	54.14 53.88	6.06 6.29	14.03 14.17	17.76 18.01	2980, 1595, 1290	0.99(t,6H,J=7); 2.51(q,4H,J=7); 2.80(t,2H,J=6.2); 3.87(s,3H,MeN); 3.90(s,3H,MeO); 4.30(q,2H,J=6.2); 6.09(d,1H,J=1.8, 4pyr); 6.9(d,1H,J=8.6); 7.43(s,2H)
6d	Z	41	A	54.14 53.91	6.06 6.14	14.03 13.95	17.76 17.67	2990, 1600, 1290	0.96(t,6H,J=7); 2.40(q,4H,J=7); 3.90(s,3H,MeO); 4.17(s,3H,MeO); 4.3(q,2H,J=6.2); 5.90(d,1H,J=1.8,4imid); 6.9(d,1H,J=8.7, 6Ph); 7.10(d,1H,J=8.7, 5Ph); 7.35(d,1H,J=1.8, 3pyr)
5e	E	31	A	49.84 50.02	5.34 5.67	12.92 13.07	24.52 24.27	2985, 1600, 1290	0.97(t,6H,J=7); 2.54(q,4H,J=7); 2.78(t,2H,J=6.1); 3.91(s,3H); 4.0(s,3H); 4.30(t,2H,J=6.3); 6.87(d,1H,J=8.7); 7.22(d,1H,J=8.7); 7.35(s,1H)
6e	Z	52	A	49.84 49.61	5.34 5.20	12.92 12.61	24.52 24.64	2980, 1600, 1040	0.98(t,6H,J=7); 2.54(q,4H,J=7); 2.78(t,2H,J=6.1); 3.86(s,3H); 3.91(s,3H); 4.30(t,2H); 6.93(d,1H,J=8.7); 7.36(s,1H); 7.49(d,1H,J=8.7)
5f	Z	0	A	-	-	-	-	-	Not obtained
6f	E	28	A	54.14 54.22	6.06 5.92	14.03 13.82	17.76 17.70	2960, 1595, 1285	0.96(t,6H,J=7); 2.5-3.0(m,6H); 3.84(s,3H); 3.90(s,3H); 4.30(t,2H,J=6.2); 6.88(d,1H,J=8.5); 7.08(d,1H,J=8.5); 7.31(s,1H); 7.53(s,1H)

Table 3



7

Comp.	Origin	Yield %	M.P. ^(b) °C	Analysis %				IR (cm ⁻¹)	¹ H-NMR (DMSO-d ₆), δ, J = Hz
				Calcd./	Found				
				C	H	N	Cl		
7b	3b	42	225	54.66	3.82	15.93	13.45	1620, 1430,	4.0(s,6H); 7.28(s,1H,4imid); 7.40(d,1H,J=8.8, 5Ph);
	4b	45		54.49	4.10	16.09	13.27	1290	7.55(s,1H,5imid); 8.32(d,1H,J=8.8, 6Ph)
7c	3c	75	105	58.92	5.27	13.74	11.59	2950, 1620,	0.9(t,3H,J=6.7); 1.3(m,2H); 1.75(m,2H); 4.0(s,3H,
	4c	71		58.64	5.18	14.06	11.37	1290	MeO); 4.47(t,2H,J=6.7); 7.30(s,1H,4imid); 7.4(d,1H,
7d	3d	40	170	54.66	3.82	15.93	13.45	1630, 1460,	4.05(s,3H,MeO); 4.13(s,3H,MeN); 7.14(s,1H,5Pyr);
	4d	50		54.75	3.68	15.95	13.53	1295	7.4(d,1H,J=8.8, 5Ph); 7.70(s,1H,3pyr); 7.96(d,2H,J=
7e	3e	13	165	48.34	3.04	14.09	23.78	1630, 1305	3.96(s,3H,MeN); 4.0(s,3H,MeO); 7.45(d,1H,J=8.5,
	4e	7		48.26	3.15	13.83	23.92	1085	5Ph); 7.85(d,1H,J=8.5,6Ph); 7.92(s,1H,5imid)
7f	3f	80	220	54.66	3.82	15.93	13.45	1625, 1295	3.97(s,3H,MeN); 4.0(s,3H,MeO); 7.3(d,1H,J=8.8,
	4f	0		54.52	3.96	15.75	13.31	1080	5Ph); 7.95(d,1H,J=8.8, 6Ph); 8.07(s,1H,5pyr); 8.49
									(s,1H,3Pyr)

(b) From a Mettler FP61

a variety of conditions but were unable to obtain the desired compound, the ketone being recovered.

The configuration of the ethers **5** and **6** were deduced from their isolated parents *E* or *Z* and, when made from a mixture of isomers, confirmed for each separated ether by similar NOE difference experiments as were carried out in the case of the oximes.

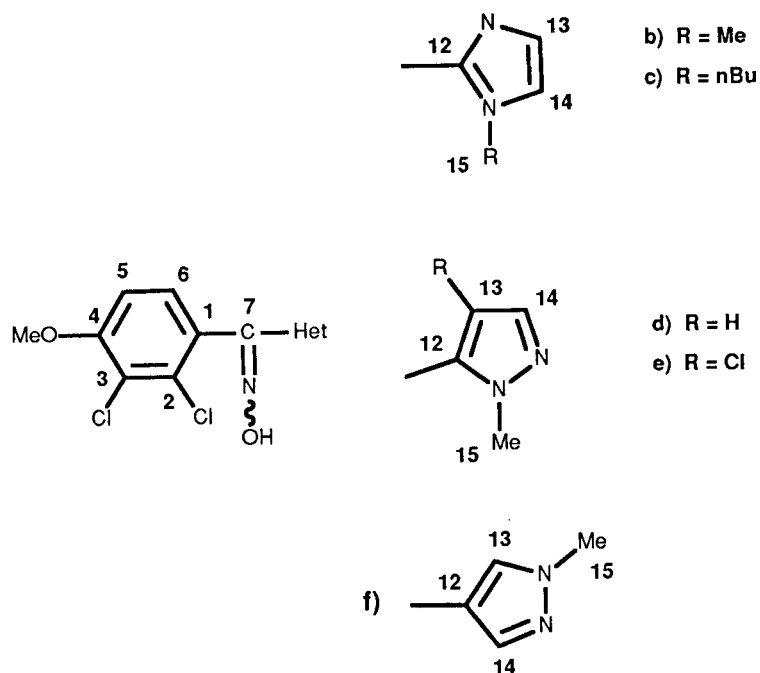
The ¹H nmr and ¹³C nmr chemical shifts and assignments are summarized in Tables 1 to 6. We may point out that, in the oxime series, carbon 1 in the *syn* isomers (normally *Z*) appears 0.6-2.3 ppm upfield to that of the *anti* isomer, in the carbon 12 the difference is 0.5-1.4 ppm, and in carbon 6 the difference is not in the same

direction. This shift is also present in the alkylated series and is similar to that of the oximes.

The ability to distinguish between *E* and *Z* isomers lies in the shielding effect of the oxime oxygen on the α-carbon when this oxygen is *syn* to said carbon [16].

The products were screened for pharmacological activities in a battery of tests, including analgesic and antipyretic effects and their activities on the central and peripheral nervous systems and on the cardiovascular system with especial reference to their incidence on calcium channels. Most of them displayed biological activities but their potencies were not sufficient to consider them as warranting further development.

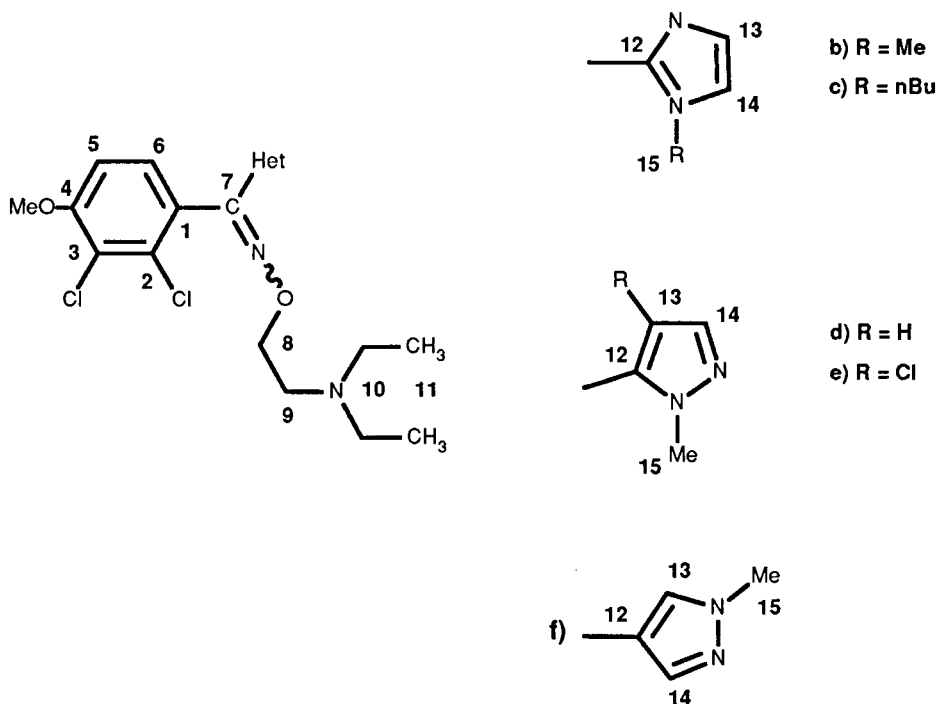
Table 4



No. Config.	3b E	4b Z	3c E	4c Z	3d E	4d Z	3e E	4e Z	3f Z	4f E
1	128.8	126.7	128.8	126.5	128.9	126.6	124.7	127.0	129.5	130.5
2	130.6	130.8	131.7	131.8	131.3	130.7	131.3	131.2	132.7	130.8
3	120.2	120.3	123.4	120.0	121.0	120.5	121.0	121.0	120.6	120.8
4	157.4	157.0	156.2	155.8	156.4	156.1	156.5	156.2	156.8	155.8
MeO	56.6	56.6	56.8	56.7	56.7	56.7	56.6	56.6	57.3	56.6
5	110.7	110.8	110.9	110.7	111.2	111.0	110.8	110.8	110.9	111.1
6	129.5	128.5	129.9	128.7	129.4	128.0	129.2	130.0	127.8	129.5
7	146.3	147.1	146.4	146.7	145.7	145.4	143.4	143.4	146.1	146.1
8	-	-	-	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-
12	140.5	141.5	140.0	140.5	135.0	137.0	133.3	131.9	114.8	114.1
13	127.8	127.6	128.4	127.8	106.6	108.4	109.4	107.8	130.3	132.7
14	121.0	123.8	120.3	123.3	137.5	137.3	136.4	136.1	137.2	139.6
15	35.3	34.9	46.6	47.0	38.3	39.3	39.0	38.8	38.2	38.1
16	-	-	31.6	32.4	-	-	-	-	-	-
17	-	-	19.4	19.1	-	-	-	-	-	-
18	-	-	13.4	13.4	-	-	-	-	-	-
Solvent	(b)	(b)	(b)	(b)	(b)	(b)	(b)	(b)	(b)	(b)

a) Cl₃CD
b) DMSO
c) T.F.A.A.

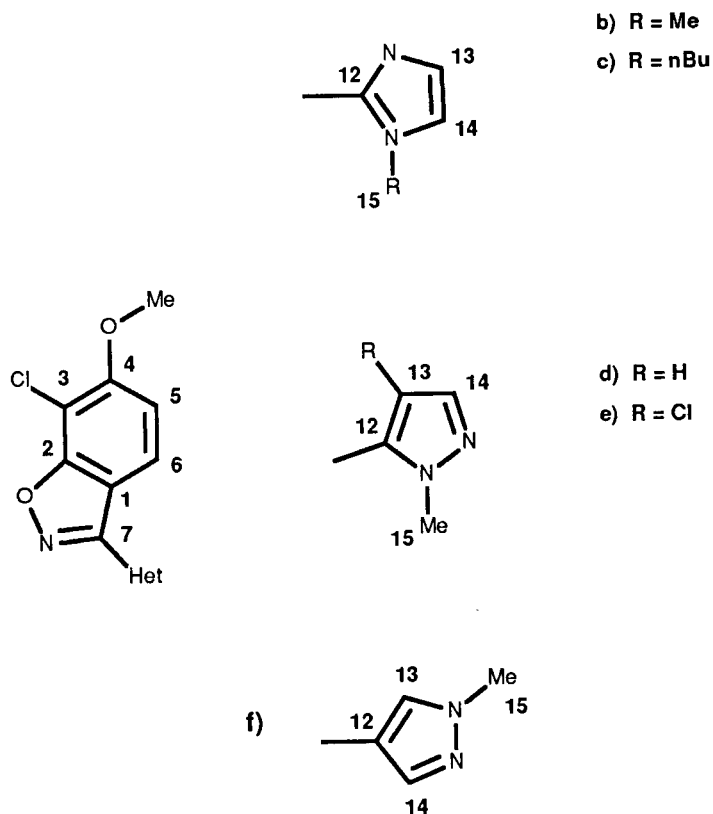
Table 5



No. Config.	5b E	6b Z	5c E	6c Z	5d E	6d Z	5e E	6e Z	5f Z	6f E
1	128.2	126.0	126.5	126.1	128.4	126.4	127.0	125.0	127.6	127.6
2	133.1	131.7	131.9	131.6	133.1	131.8	132.1	132.7	133.2	133.1
3	122.4	122.0	121.8	121.8	122.7	122.3	122.5	122.5	122.0	122.0
4	156.9	156.1	155.9	156.0	156.9	156.3	157.3	156.8	156.4	156.0
MeO	56.4	56.4	56.4	56.1	56.3	56.3	56.5	56.5	56.3	56.3
5	110.8	110.8	109.9	109.7	109.7	109.7	109.7	109.7	109.9	109.9
6	129.1	127.8	127.9	127.7	128.8	127.1	129.9	128.8	128.9	126.9
7	147.3	147.7	147.9	147.7	146.0	146.0	144.6	144.6	147.0	147.5
8	73.5	73.7	73.3	73.6	73.6	73.6	74.1	74.1	72.9	72.7
9	51.3	51.6	51.2	51.4	51.4	51.6	56.5	56.5	51.8	51.2
10	47.4	47.6	47.5	47.5	47.5	47.5	47.7	47.7	47.5	47.5
11	11.7	11.7	11.6	11.7	11.8	11.8	11.9	11.9	11.8	11.7
12	140.8	141.4	140.8	140.6	135.0	136.5	132.9	132.2	114.7	118.7
13	129.4	128.7	128.2	128.7	107.1	109.0	111.4	114.4	128.8	128.9
14	121.4	123.8	122.1	122.7	137.8	137.4	136.8	137.1	140.9	137.5
15	34.2	35.8	47.2	47.8	38.6	39.9	39.4	40.0	38.6	38.6
16	-	-	32.7	32.6	-	-	-	-	-	-
17	-	-	19.6	19.5	-	-	-	-	-	-
18	-	-	13.5	13.3	-	-	-	-	-	-
Solvent	(a)	(a)	(a)	(a)	(a)	(a)	(a)	(a)	(a)	(a)

a) Cl₃CD
b) DMSO
c) T.F.A.

Table 6



No.	7b	7c	7d	7e	7f
1	113.2	115.4	114.6	114.7	114.8
2	162.0	159.1	159.5	160.1	155.0
3	104.0	101.3	102.2	101.9	108.1
4	157.8	156.9	157.0	157.3	156.7
MeO	57.5	57.2	57.3	57.4	57.2
5	112.4	111.1	113.3	111.6	110.7
6	119.5	123.2	120.7	121.3	120.8
7	144.2	149.8	148.7	148.1	150.9
8	-	-	-	-	-
9	-	-	-	-	-
10	-	-	-	-	-
11	-	-	-	-	-
12	133.8	135.2	128.9	126.7	108.1
13	125.8	129.7	108.5	110.6	130.2
14	122.9	124.1	138.5	137.2	137.1
15	37.5	47.0	39.0	38.8	38.5
16	-	32.1	-	-	-
17	-	18.8	-	-	-
18	-	13.0	-	-	-
Solvent	(a)	(b)	(b)	(b)	(b)

a) Cl₃CD
b) DMSO
c) T.F.A.

EXPERIMENTAL

All melting points were determined with a Kofler melting point microscope or in an automatic Metler FP 61 melting point apparatus, and are uncorrected. The proton magnetic resonance spectra were obtained from a Varian AM 360 (60 MHz) or a Bruker A.M. Fourier transform spectrometer operating at 100 MHz, and the ^{13}C nmr spectra were obtained from a Bruker A.M. Fourier transform spectrometer operating at 25.1 MHz, and the chemical shifts (δ) are relative to TMS as internal standard. The infrared spectra were obtained from a Perkin-Elmer 177 grating model or with a Nicolet 5DXC Fourier transform model. Spectra were recorded for all compounds and were consistent with assigned structures. Preparative hplc was performed with a Waters Auto 500 model.

Synthesis of the Oximes **3** and **4**.

The oximes were obtained by boiling for several hours a mixture of the corresponding ketone **2** and an excess of hydroxylamine hydrochloride in pyridine and, when the reaction was complete (tlc), evaporating the excess pyridine *in vacuo*, adding ice-cold water and recrystallizing the resulting solid.

Methods of Resolution of Isomers.

A. Column chromatography, eluting with chloroform/methanol 95:5. B. Crystallization from ethanol or ethanol/water. C. Preparative hplc over silica, eluting with chloroform containing 1% ethanol, or a mixture of toluene/ether 1:1.

General Method of Synthesis of Oxime Ethers **5** and **6**.

To a vigorously stirred mixture of benzene (20 ml), TEBA (10 mg), solid potassium carbonate (0.55 g, 8 mmoles) and dimethylaminoethylchloride hydrochloride (1.1 g, 8 mmoles), was added to the oxime (3.5 mmoles), either the separate isomer *E* or *Z*, or the unseparated mixture. The stirring was continued for several days, controlling the reaction by TLC. When the reaction was complete, the mixture was filtered, washed with benzene (2 x 10 ml), the organic phase washed with water (2 x 5 ml), dried (sodium sulphate) and evaporated. The crude product was suspended in ether (50 ml), filtered, and the filtrate purified by column chromatography.

Preparation of the 1,2-Benzisoxazoles **7**.

A solution of 4 mmoles of the oxime in 20 ml of ethanol and 5 ml of 20% sodium hydroxide was refluxed for 16 hours. Evaporating the solvents, adding water and filtering, gave the 1,2-benzisoxazole, which can be recrystallized from small amounts of ethanol.

Acknowledgements.

We would like to thank Dr. F. Sanchez-Ferrando of the Facultad de Ciències, Universitat Autònoma de Barcelona, for helpful discussions.

REFERENCES AND NOTES

- [1] J. van Dijk and J. M. A. Zwagemakers, *J. Med. Chem.*, **20**, 1199 (1977).
- [2] S. Rossi, O. Pirola, A. Groppetti, F. Selva and M. L. Zappia, *Farmaco Ed. Sci.*, **19**, 688 (1964).
- [3] S. Rossi, A. Salvatori and G. Peruzzi, *Farmaco Ed. Sci.*, **34**, 486 (1979).
- [4] C. Bernhart, C. G. Wermouth, J. Cahn, M. Herald and M. G. Borzicue, *Eur. J. Med. Chem.*, **11**, 369 (1976).
- [5] B. Macchia, A. Balsamo, A. Lapucci, A. Martinelli, M. C. Breschi, F. Macchia, B. Fantoni and E. Artinotti, *J. Med. Chem.*, **28**, 153 (1985).
- [6] M. Bouzoubaa, G. Leclerc, N. Decker, J. Schwartz and G. Andermann, *J. Med. Chem.*, **27**, 1291 (1984).
- [7] G. Leclerc, N. Bieth and J. Schwartz, *J. Med. Chem.*, **23**, 620 (1980).
- [8] M. Spedding and C. Berg, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **328**, 69 (1984).
- [9] German Offen. DE 2,449,205; *Chem. Abstr.*, **83**, 97004d (1975).
- [10] G. Heinisch, W. Holzer and T. Huber, *Arch. Pharm. (Weinheim.)*, **320**, 1267 (1987).
- [11] L. A. M. Bastiaansen and E. F. Godefroi, *Synthesis*, 675 (1978).
- [12] D. Butler and H. De Wald, *J. Org. Chem.*, **36**(17), 2542 (1971).
- [13] F. Effenberger and A. Krebs, *J. Org. Chem.*, **49**(24), 4687 (1984).
- [14] J. Laforest and G. Thuillier, *J. Heterocyclic Chem.*, **14**, 793 (1977).
- [15] F. J. Villani, R. F. Tavares and C. A. Ellis, *J. Pharm. Sci.*, **58**, 138 (1969).
- [16] G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972, p 129-131.