3,3'-Diaryl-5-morpholino-4,5,4',5'-tetrahydro-4,5'-spirobi[isoxazoles]. Synthesis by Cycloaddition Reactions and Substituent Effect on the Cycloaddition Kinetics

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3-Aryl-4-methylene-5-morpholino-4,5-dihydroisoxazoles **1a-e** were synthesized; fifteen different 3,3'-diaryl-5-morpholino-4,5,4',5'-tetrahydro-4,5'-spirobi[isoxazoles] **3** were obtained by their reaction with some stable aryl nitrile oxides. The spiro-derivatives were characterized by their nmr spectra. Kinetic measurements showed that substituents on the nitrile oxide have a weak effect on the cycloaddition rate (Hammett ρ = *ca* 0.3), while substituents on the dipolarophile have no effect at all.

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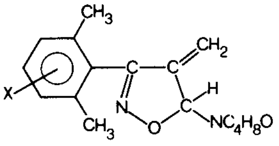
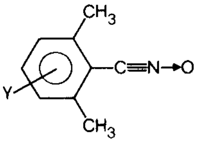
In the context of the preparation of heterocyclic compounds by employing substituted benzonitrile oxides [1,2], we report the synthesis of several 3,3'-diaryl-5-morpholino-4,5,4',5'-tetrahydro-4,5'-spirobi[isoxazoles], obtained by 1,3-cycloaddition of some stable aryl nitrile oxides to 3-aryl-4-methylene-5-morpholino-4,5-dihydroisoxazoles.

A few cases of 1,3-cycloaddition of aryl nitrile oxides to 4-methylene-isoxazolines to give spiroderivatives have been reported [3-5]. Reactions were found to be regiospecific, since only 4,5'-spirobi[isoxazolines] were obtained. In particular, Pocar *et al.* [5], by adding three different aryl nitrile oxides to 3-phenyl-4-methylene-5-morpholino-4,5-dihydroisoxazole reported in any case highly regio- and stereospecific reactions.



1



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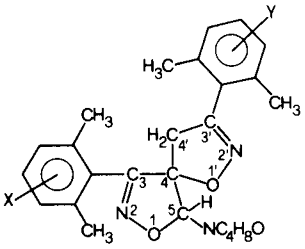


3

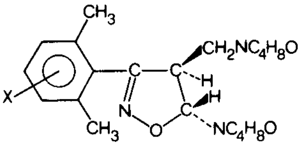
X or Y

a 4-OCH$_3$
b 4-CH$_3$
c 4-H
d 4-Br
e 3,5-Cl$_2$-4-CH$_3$

(adducts **3** are *labelled* with two letters, *e.g.* **3bc**; the former letter refers to X, the latter to Y

The aim of the present work was to study a set of reactants with variously substituted phenyl rings both on the 1,3-dipole and on the dipolarophile. To do so, isoxazolines **1a-e** and the stable nitrile oxides **2a-e** were synthesized. Fifteen out of the twentyfive possible cycloadditions to give spiroderivatives **3** were accomplished, and their products characterized. Kinetic measurements were effected on some of the reactions.

3-Aryl-4-methylene-5-morpholino-4,5-dihydroisoxazoles **1a-e** were prepared from the corresponding 3-aryl-5-morpholino-4-morpholinomethyl-4,5-dihydroisoxazoles **4a-e**. One of these (**4b**) had already been described [6].



4

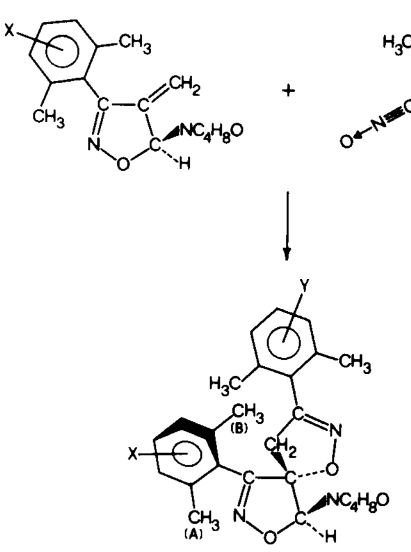
Results and Discussion.

The spirobi[isoxazolines] **3** that have been prepared (Table 1) have high melting points, in most cases above 200°. This feature is present also in other derivatives of this class, previously obtained by analogous 1,3-cycloadditions [3-5].

The structure of **3** as 4,5'-spiroderivatives is proved by the ^{1}H-nmr spectra (Table 2): the signals assigned to CH$_2$-4' could not be attributed to a methylene in the 5 position on an isoxazoline ring [3]. The lower-field (δ 3.50-3.59 ppm) and the higher-field (δ 2.92-3.07 ppm) signals compare well with those reported for similar compounds, falling in the range 3.59-3.91 and 2.77-3.42 ppm, respectively [3-5].

The configuration of some spiroadducts similar to **3** has been proved [5] to be **4** S^*, **5** S^* (as a racemate with **4** R^*, **5** R^*). Those adducts had ^{1}H-nmr signals for H-5 in the range 5.18-5.24 ppm. Since our products **3** (even when crude) showed a single signal for H-5 in the range 5.31-5.43 ppm (Table 2), it can be safely deduced that they have the above configuration and that also our cycloadditions are regio- and stereospecific (Scheme 1). The 1,3-dipole approaches the dipolarophile $>C=CH_2$ from the less hindered side of the isoxazole ring, that is *anti* to the morpholino group at the adjacent carbon.

Scheme 1



In Scheme 1 the aryl ring at C-3 of the adduct has been represented as out of the adjacent isoxazole plane, because in the ^{1}H-nmr spectra its two *o*-methyl groups were found to be non-equivalent (Table 2). One of them gives a signal at δ 2.13-2.22 ppm, the other one at 2.41-2.56 ppm. These chemical shifts can be assigned to A and B methyl groups, respectively, for the following reasons. On the basis of molecular models, the most probable rotation of the phenyl ring at C-3 with respect to the isoxazole plane seems to be of about 90°; with this orientation of phenyl ring, the shielding cone originating from the π system of the C(3′)N(2′)O(1′) group affects the A methyl group, while methyl group B (on the side of CH_2-4′) is unaffected.

The other aryl ring of the adduct is substantially free to rotate and its *o*-methyl groups appear equivalent (Table 2). The low δ values, in the range 1.81-1.90 ppm, can be justified by the shielding action of the aryl ring at C-3. An example of analogous shielding by a benzene ring is described [7] in the case of some steroidal compounds interacting with benzene as solvent.

A significant difference can be noticed also between nmr signals from *meta*-H on the two aryl rings. While the protons on the aryl at C-3′ in the case of 2,4,6-trisubstituted rings gave a singlet, the corresponding protons on the aryl at C-3 gave a multiplet, proving non-equivalent.

A parallel can be recognized between ^{1}H- and ^{13}C-nmr spectra in this respect. When the instrumental resolution made it possible to separately assign the signals from *o*-methyl on the two aryl rings, two signals (at δ around 21 ppm) could be assigned to methyl carbons on the aryl at C-3, but only one (at δ *ca* 19 ppm) to those on the aryl at C-3′ (see the spectra of **3cc**, **3cd** and **3dd** in Table 3).

Other features of the ^{13}C-nmr spectra are the following: scarcely variable signals not only from the morpholine ring, but also from C-4, C-5 and C-4′; more significant variation of the signals from C-3 and C-3′, as a function of

Table 1

Melting Points and Elemental Analyses of Products **3** [a]

Compound	Mp (°C)	Formula	Calcd. (%)			Found (%)		
			C	H	N	C	H	N
3ba	188	$C_{27}H_{33}N_3O_4$	69.9	7.2	9.1	69.7	7.0	8.9
3bb	215	$C_{27}H_{33}N_3O_3$	72.4	7.4	9.4	72.3	7.3	9.4
3bc	220	$C_{26}H_{31}N_3O_3$	72.0	7.2	9.7	72.3	7.0	9.8
3bd	220	$C_{26}H_{30}BrN_3O_3$	60.9	5.9	8.2	60.7	6.1	8.5
3be	188	$C_{27}H_{31}Cl_2N_3O_3$	62.8	6.1	8.1	63.0	6.2	8.4
3cb	216	$C_{26}H_{31}N_3O_3$	72.0	7.2	9.7	72.0	7.3	9.6
3cc	241	$C_{25}H_{29}N_3O_3$	71.6	7.0	10.0	71.3	6.9	9.9
3cd	244	$C_{25}H_{28}BrN_3O_3$	60.2	5.7	8.4	59.9	5.6	8.3
3ce	202	$C_{26}H_{29}Cl_2N_3O_3$	62.1	5.8	8.4	61.9	5.8	8.2
3db	210	$C_{26}H_{30}BrN_3O_3$	60.9	5.9	8.2	61.0	5.9	8.0
3dc	223	$C_{25}H_{28}BrN_3O_3$	60.2	5.7	8.4	60.4	5.7	8.3
3dd	232	$C_{25}H_{27}Br_2N_3O_3$	52.0	4.7	7.3	52.0	4.7	7.3
3de	182	$C_{26}H_{28}BrCl_2N_3O_3$	53.7	4.9	7.2	53.9	5.1	6.9
3ee	228	$C_{27}H_{29}Cl_4N_3O_3$	55.4	5.0	7.2	55.6	5.2	7.3

[a] Product **3aa**, mp 199°, gave low results for C, H and N, probably due to incomplete combustion, but the observed atomic ratio was around the theoretical (27:33:3).

Table 2

^{1}H-NMR Spectra of Compounds **3** in Deuteriochloroform, Reference Tetramethylsilane, δ-values, ppm [a]

Compound	CH$_2$-4' [b]	H-5 (s)	Aryl at C-3			Aryl at C-3'		
			H (m)	o-CH$_3$ (s)	X (s)	H	o-CH$_3$ (s)	Y (s)
3aa	3.53, 3.03	5.36	6.62	2.49, 2.15	3.78	6.53 (s)	1.83	3.74
3ba	3.51, 3.01	5.31	6.88	2.45, 2.13	2.27	6.51 (s)	1.81	3.72
3bb	3.55, 3.01	5.35	6.89	2.46, 2.13	2.27	6.80 (s)	1.83	2.23
3bc	3.57, 3.06	5.35	[c]	2.46, 2.13	2.27	[c]	1.86	—
3bd	3.51, 3.02	5.35	6.91	2.41, 2.13	2.27	7.13 [s]	1.83	—
3be	3.51, 3.00	5.36	6.92	2.43, 2.13	2.30	—	1.86	2.47
3cb	3.55, 3.05	5.36	7.17	2.50, 2.17	—	6.79 (s)	1.82	2.22
3cc	3.59, 3.07	5.39	[d]	2.51, 2.18	—	[d]	1.85	—
3cd	3.53, 3.03	5.38	[e]	2.49, 2.18	—	[e]	1.81	—
3ce	3.53, 3.01	5.39	7.05	2.50, 2.18	—	—	1.85	2.47
3db	3.57, 3.00	5.37	7.26	2.49, 2.14	—	6.82 (s)	1.86	2.24
3dc	3.59, 3.02	5.39	7.27	2.49, 2.16	—	7.08 (m)	1.89	—
3dd	3.56, 2.99	5.37	7.27	2.47, 2.15	—	7.16 (s)	1.86	—
3de	3.53, 2.97	5.39	7.29	2.49, 2.15	—	—	1.90	2.49
3ee	3.50, 2.92	5.43	—	2.56, 2.22	[f]	—	1.83	[f]

[a] Signals from the morpholine ring at 3.73 ±0.02 and 2.83 ±0.03 are not listed. [b] AB system. [c] 7.12-6.87 (m, both aryl groups). [d] 7.14-7.00 (m, from both aryl groups). [e] 7.16-7.13 (m, from both aryl groups). [f] 2.50-2.49 (from the two aryl groups).

Table 3

^{13}C-NMR Spectra of Compounds **3** in Deuteriochloroform, Reference Tetramethylsilane, δ-values, ppm [a]

Compound	C-3	C-4	C-5	C-3'	C-4'	Aryl	CH$_3$ on aryl		OCH$_3$
							at C-3	at C-3'	
3aa	157.1	98.5	103.3	156.6	40.6	160-113	21.2	- 19.2	55.1
3ba	158.0	98.6	103.2	156.7	39.6	160-113	20.9	- 19.2	55.1
3bb	157.1	98.8	103.4	156.7	40.6	140-124	20.9, 20.7	18.9	—
3bc	157.1	98.7	103.3	157.0	40.4	140-123	21.0	- 18.7	—
3bd	156.5	98.9	103.2	156.1	40.1	140-123	21.0, 20.7	18.8	—
3be	156.6	99.1	103.3	156.4	40.9	140-123	21.7	- 17.5	—
3cb	157.0	98.5	103.3	156.5	40.5	140-125	21.0, 20.7	18.9	—
3cc	157.0	98.7	103.4	156.5	40.4	141-128	21.1, 20.8	18.9	—
3cd	156.6	98.9	103.3	156.2	40.2	141-128	21.1, 20.8	18.8	—
3ce	156.6	99.0	103.3	156.2	40.9	141-128	21.1	- 17.4	—
3db	157.2	98.2	103.5	155.7	40.5	143-124	21.0, 20.7	18.9	—
3dc	158.0	98.3	103.6	156.7	40.7	140-113	20.2	- 19.0	—
3dd	156.3	98.7	103.6	155.6	40.3	143-124	20.8, 20.7	18.8	—
3de	157.4	98.7	103.6	156.7	40.9	147-121	23.0	- 17.5	—
3ee	156.1	98.7	103.6	155.1	40.9	137-126	20.0	- 17.2	—

[a] Signals from the morpholine ring at 66.9 ±0.1 and 48.8 ±0.1 are not listed.

the substituents on the aryl rings bound to these atoms. In the analogous spiroadducts previously prepared [5] the corresponding ^{13}C-nmr chemical shifts had similar values.

Kinetic runs were initially carried out on systems **1b** + **2e** and **1b** + **2b**, by varying the reactants concentration, with the following results (C_1°, C_2°, 10^4k/lit moles $^{-1}$s^{-1}): for **1b** + **2e** at 70.0°, 0.08, 0.01, 13.9; 0.04, 0.01, 14.2; 0.02, 0.01, 13.8; 0.007, 0.013, 14.3; for **1b** + **2b** at 60.0°, 0.08, 0.01, 4.43; 0.04, 0.01, 4.46. These results were taken as evidence that the cycloaddition is a second order reaction. Standard kinetic runs were carried out with a higher ratio C_1°/C_2° in order to speed up the reaction.

Ring-substitution on the nitrile oxides was studied by measuring the kinetics of the reaction of **1b** with the series **2a-e**. Systematic measurements at 60 and 70° (Table 4) show a progressive, although slight, increase of the kinetic coefficients from **2a** to **2e**. Hammett plots were drawn, using σ_p values (or, when required, a sum of σ_p and σ_m-values): they are fairly linear, but rather flat, showing slopes ρ equal to 0.31 ±0.05 at 60.0° and 0.33 ±0.04 at 70.0°. This indicates a scarce substituent effect for the aryl nitrile oxide.

Even weaker is the effect of substituents on the phenyl

Table 4

Kinetic Coefficients, 10^4k (lit moles $^{-1}$s^{-1}) for Reactions of **1** (*ca* 0.14 moles lit $^{-1}$) with **2** (0.01 moles lit $^{-1}$) in 1,1,2,2-Tetrachloroethane

Reaction:	**1b** + **2a**	**1b** + **2b**	**1b** + **2c**	**1b** + **2d**	**1b** + **2e**
Temp (°C)					
40.0		1.20 ±0.01			2.05 ±0.02 [a]
50.0		2.54 ±0.03			3.94 ±0.06
60.0	3.80 ±0.06	4.89 ±0.05	4.92 ±0.06	6.21 ±0.01	7.32 ±0.15
70.0	7.36 ±0.01	9.16 ±0.09	9.23 ±0.02	11.30 ±0.24	14.71 ±0.30
Reaction:	**1a** + **2a**		**1c** + **2c**	**1d** + **2d**	**1e** + **2e**
Temp (°C)					
60.0	3.73 ±0.03		4.84 ±0.03	6.06 ±0.06	8.03 ±0.12
70.0	7.23 ±0.12		9.05 ±0.02	11.08 ±0.07	14.80 ±0.07

Activation parameters:

for **1b** + **2b**, logA = 6.15 ±0.12; E_{act} = 60.4 ±0.7 kJ moles $^{-1}$; $\Delta S^{\neq}$ = −136 ±3 J moles $^{-1}$K^{-1}

for **1b** ± **2e**, log A = 6.03 ±0.30; E_{act} = 58.3 ±1.9 kJ moles^{-1}; $\Delta S^{\neq}$ = −139 ±9 J moles $^{-1}$K^{-1}

[a] In other solvents: Chloroform, 1.49 ±0.01; carbon tetrachloride, 3.32 ±0.09.

ring of the dipolarophile. This is shown by a few kinetic measurements on the reactions of nitrile oxides **2a** and **2c-e** with the isoxazolines correspondingly substituted *e.g.* **1a** + **2a**, **1c** + **2c** etc; the k-values (Table 4) are very close to those measured for the reactions of the same nitrile oxides with isoxazoline **1b**. For instance, at 60°, 10^4k = 3.80 and 3.73 lit moles $^{-1}$s^{-1} for **1b** + **2a** and **1a** + **2a**, respectively, were found. In other words, the reaction rate for a given nitrile oxide is substantially independent of the substituents on the isoxazoline. It should be considered that the aryl group at C-3 is not directly bound to a position involved in the cycloaddition, so that a weaker effect could have been expected anyway. Moreover the rotated position of such aryl group with respect to the isoxazole plane, as shown for **3** in Scheme 1, is probably present also in the transition state of the cycloaddition, further contributing to neutralize the effect of substituents by inhibiting conjugation.

In conclusion, the observed effects of substituents, transmitted through phenyl rings, are weak in the present reactions as it is the case in many 1,3-cyaloadditions [8].

In two cases (**1b** + **2b** and **1b** + **2e**) measurements were extended to four different temperatures and activation parameters were obtained by Arrhenius and Eyring plots. The results (Table 4) are in line with typical values for this class of reactions; in particular, the large negative values of $\Delta S^{\neq}$ are characteristic of concerted cycloadditions [8].

An indication of the solvent effect on the reaction is given by comparison of kinetic coefficients for **1b** + **2e**, measured at 40.0°, in chloroform (dielectric constant D = 4.80), and carbon tetrachloride (D = 2.24), besides the usual 1,1,2,2-tetrachloroethane (D = 8.08). Although a linear dependence of lnk on (D-1)/(2D + 1), as foreseen for a reaction between dipolar molecules [9], was not observed, carbon tetrachloride, which has the lowest dielectric constant, proved the best among the three solvents. This suggests that the transition state of the cycloaddition is slightly less polar than the reactant system.

EXPERIMENTAL

The ^{1}H- and ^{13}C-nmr spectra were taken by a Varian FT-80 spectrometer using deuteriochloroform as the solvent and tetramethylsilane as the internal standard.

Aromatic nitrile oxides **2a-e** were obtained as described [10].

1,3-Dimorpholinopropene [6,11].

This compound was prepared according to the method of Mannich, from acrolein and morpholine, in the presence of potassium carbonate.

3-Aryl-5-morpholino-4-morpholinomethyl-4,5-dihydroisoxazoles **4a-e**.

1,3-Dimorpholinopropene (0.05 mole) was dissolved in anhydrous benzene (50 ml) and the aryl nitrile oxide **2** (0.05 mole) was added. After stirring for 24 hours at room temperature [6], the ir band at 2280-2300 cm^{-1}, typical of nitrile oxides, had completely disappeared. The solvent was evaporated under reduced pressure and the residue was crystallized from diisopropylether. The yields were usually 35-40% (20-25%, in the case of **4e**).

Compound **4a**.

This compound had mp 175°; ^{1}H-nmr: δ 6.60 (s, Ar, 2H), 5.16 (m, H-5, 1H, $J_{4,5}$ = 4.8 Hz), 3.79 (s, OCH_3, 3H), 3.73-3.45 (m, H-4 and CH_2-O-CH_2, 9H), 2.83-2.29 (m, C-CH_2-N and CH_2-N-CH_2, 10 H), 2.25 (s, CH_3, 6H).

Anal. Calcd. for $C_{21}H_{31}N_3O_4$: C, 64.7; H, 8.0; N, 10.8. Found: C, 64.6; H, 8.0; N, 10.5.

Compound **4b**.

This compound had mp 118° (lit [6] 115-118°); ^{1}H-nmr: δ 6.87 (s, Ar, 2H), 5.16 (m, H-5, 1H, $J_{4,5}$ = 4.8 Hz), 3.78-3.46 (m, H-4 and CH_2-O-CH_2, 9H), 2.89-2.32 (m, C-CH_2-N and CH_2-N-CH_2, 10 H), 2.27 (s, *p*-CH_3, 3H), 2.24 (s, *o*-CH_3, 6H).

Compound **4c**.

This compound had mp 116°; ^{1}H-nmr: δ 7.13 (m, Ar, 3H), 5.15 (m, H-5, 1H, $J_{4\text{-}5}$ = 4.8 Hz), 3.72-3.42 (m, H-4 and CH_2-O-CH_2, 9H), 2.82-2.30 (m, C-CH_2-N and CH_2-N-CH_2, 10 H), 2.27 (s, CH_3, 6H).

Anal. Calcd. for $C_{20}H_{29}N_3O_3$: C, 66.8; H, 8.1; N, 11.7. Found: C, 66.8; H, 8.2; N, 11.7.

Compound **4d**.

This compound had mp 156°; ^{1}H-nmr: δ 7.22 (s, Ar, 2H), 5.14 (m, H-5, 1H, $J_{4,5}$ = 4.8 Hz), 3.78-3.43 (m, H-4 and CH_2-O-CH_2, 9H), 2.82-2.30 (m, C-CH_2-N and CH_2-N-CH_2, 10H), 2.25 (s, CH_3, 6H).

Anal. Calcd. for $C_{20}H_{28}BrN_3O_3$: C, 54.8; H, 6.4; N, 9.6. Found: C, 54.8; H, 6.3; N, 9.5.

Compound **4e**.

This compound had mp 142°; ^{1}H-nmr: δ 5.10 (m, H-5, 1H, $J_{4,5}$ = 5.6 Hz), 3.77-3.37 (m, H-4 and CH_2-O-CH_2, 9H), 2.82-2.34 (m, C-CH_2-N and CH_2-N-CH_2, 10 H), 2.52 (s, *p*-CH_3, 3H), 2.28 (s, *o*-CH_3, 6H).

Anal. Calcd. for $C_{21}H_{29}Cl_2N_3O_3$: C, 57.0; H, 6.6; N, 9.5. Found: C, 56.6; H, 6.5; N, 9.3.

3-Aryl-4-methylene-5-morpholino-4,5-dihydroisoxazoles **1a-e**.

They were obtained from compounds **4a-e** by reaction with methyl iodide and silver oxide [6]. The crude product was purified by column chromatography on silica gel (eluant: 6:4 ethyl acetate-benzene) and crystallization from *n*-hexane, yields 30-60%.

Compound **1a**.

This compound had mp 120°; ^{1}H-nmr: δ 6.64 (s, Ar, 2H), 5.81 (m, H-5, 1H), 5.40 d, 5.18 d, (=CH_2, each 1H), 3.80 (s, OCH_3, 3H), 3.76 (m, CH_2-O-CH_2, 4H), 2.89 (m, CH_2-N-CH_2, 4H), 2.16 (s, CH_3, 6H).

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.5; H, 7.3; N, 9.3. Found: C, 67.1; H, 7.4; N, 9.3.

Compound **1b**.

This compound had mp 90°; ^{1}H-nmr: δ 6.90 (s, Ar, 2H), 5.79 (m, H-5, 1H), 5.40 d, 5.16 d (=CH_2, each 1H), 3.71 (m, CH_2-O-CH_2, 4H), 2.92 (m, CH_2-N-CH_2, 4H), 2.28 (s, *p*-CH_3, 3H), 2.14 (s, *o*-CH_3, 6H).

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.3; H, 7.7; N, 9.8. Found: C, 71.4; H, 7.6; N, 9.7.

Compound **1c**.

This compound had mp 97°; ^{1}H-nmr: δ 7.13 (m, Ar, 3H), 5.82 (m, H-5, 1H), 5.42 d, 5.18 d (=CH_2, each 1H), 3.71 (m, CH_2-O-CH_2, 4H), 2.86 (m, CH_2-N-CH_2, 4H), 2.19 (s, CH_3, 6H).

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.6; H, 7.4; N, 10.3. Found: C, 70.7; H, 7.3; N, 10.3.

Compound **1d**.

This compound had mp 125°; ^{1}H-nmr: δ 7.26 (s, Ar, 2H), 5.82 (m, H-5, 1H), 5.43 d, 5.17 d (=CH_2, each 1H), 3.71 (m, CH_2-O-CH_2, 4H), 2.87 (m, CH_2-N-CH_2, 4H), 2.16 (s, CH_3, 6H).

Anal. Calcd. for $C_{16}H_{19}BrN_2O_2$: C, 54.7; H, 5.5; N, 8.0. Found: C, 54.5; H, 5.3; N, 8.0.

Compound **1e**.

This compound had mp 140°; ^{1}H-nmr: δ 5.86 (m, H-5, 1H), 5.42 d, 5.16 d (=CH_2, each 1H), 3.75 (m, CH_2-O-CH_2, 4H), 2.87 (m, CH_2-N-CH_2, 4H), 2.58 (s, *p*-CH_3, 3H), 2.21 (s, *o*-CH_3, 6H).

Anal. Calcd. for $C_{17}H_{20}Cl_2N_2O_2$: C, 57.5; H, 5.7; N, 8.8. Found: C, 57.9; H, 5.8; N, 8.6.

3,3'-Diaryl-5-morpholino-4,5,4',5'-tetrahydro-4,5'-spirobi[isoxazoles] **3**.

The compound **1** (3-5 mmoles) was added to the stoichiometric amount of a solution of **2** in chloroform (30 ml) and the mixture was left for several days at room temperature. After evaporation of the solvent, the residue was triturated and crystallized from diisopropylether. Yields of pure **3** were >90%. Elemental analyses and properties of spiroadducts are collected in Tables 1-3.

Kinetics.

Solutions of **1** and **2** were mixed in appropriate proportions (C_1^0 = *ca* 0.14 moles lit^{-1}; C_2^0 = 0.01 moles lit^{-1}). The mixture was quickly introduced to a thermostatted 1mm potassium bromide cell (Beckmann FH-01 variable temperature cell), positioned in an ir spectrophotometer. Temperature was constant ± 0.2°. Quantitative determinations of C_2 were made on the band at 2280-2300 cm^{-1}.

Kinetic runs were carried out up to 1-2 half-lives, and interpreted by the second-order rate equation:

$$[1/(C_1^0 - C_2^0)].\ \ln [(C_1^0 - C_2^0 + C_2) / C_2] = kt + \text{const.}$$

Most runs were carried out in 1,1,2,2-tetrachloroethane, in the range from 40 to 70°. In one case, chlorofom and carbon tetrachloride were also used as solvents.

Average results from duplicate runs are given in Table 4.

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REFERENCES AND NOTES

[1] P. Beltrame, G. Gelli and A. Loi, *J. Heterocyclic Chem.*, **20**, 1609 (1983).

[2] P. Beltrame and G. Gelli, *J. Chem. Soc., Perkin Trans. II*, 403 (1985).

[3] P. Beltrame, P. L. Beltrame, M. G. Cattania and G. Zecchi, *J. Chem. Soc., Perkin Trans. II*, 1301 (1974).

[4] G. Zecchi, *J. Org. Chem.*, **44**, 2796 (1979).

[5] M. Ballabio, P. Dalla Croce, V. Massari, D. Pocar, A. Riva and P. Trimarco, *J. Chem. Res.*, (S), 140; (M), 1317 (1983).

[6] D. Pocar, L. M. Rossi, P. Trimarco and L. Vago, *J. Heterocyclic Chem.*, **17**, 881 (1980).

[7] N. S. Bhacca and D. H. Williams, *Tetrahedron Letters*, 3127 (1964).

[8] P. Beltrame, in "Comprehensive Chemical Kinetics", Vol 9, C. H. Bamford and C. F. H. Tipper, eds, Elsevier, Amsterdam, 1973, p 129.

[9] E. S. Amis, "Kinetics of Chemical Change in Solution", MacMillan, New York, 1949, p 175.

[10] P. Beltrame, G. Gelli and A. Loi, *Nouv. J. Chim.*, **5**, 453 (1981).

[11] C. Mannich, K. Handke and K. Roth, *Chem. Ber.*, **69**, 2112 (1936).