Preparation and Addition of 3-Bromo-2-oxotetrahydro-1,3-oxazoles to Styrene and Derivatives: Some New Tetramisole Intermediates

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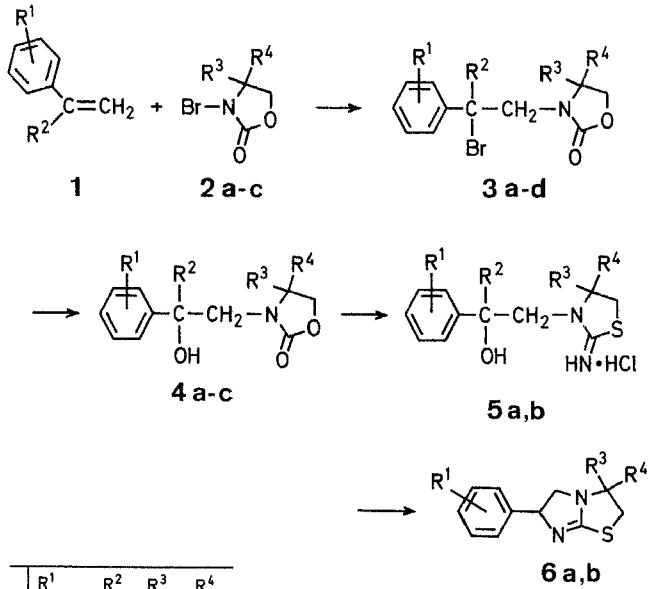
During our continuous search for a new and better process to prepare tetramisole [(±)-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*][1,3]thiazole **(6a)**], the racemate of the well-known anthelmintic levamisole[1], a new route has been found which gives rise to some new compounds and improved processes. The basis is the addition of 3-halo-2-oxazolidinones (e.g. **2**) to styrene and derivatives (e.g. **1**), Scheme **A**.

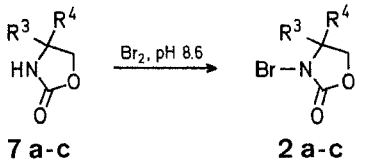


	R^1	R^2	R^3	R^4
a	H	H	H	H
b	3-O_2N	H	H	H
c	H	H	CH_3	CH_3
d	H	CH_3	CH_3	CH_3

Scheme **A**

The addition of *N*-haloamides (*N*-monohalocarbamates, *N*-dihalocarbamates, *N*-halo-sulfonamides and -phosphoramides)[2] have been known for years and have been reviewed[3]. On the other hand, the addition of *N*-halo-*N*-alkylcarbamates, especially of the heterocyclic analogues, 3-halo-2-oxazolidinones, to styrene and derivatives is, to our knowledge, not mentioned in the literature. The only examples given are additions to olefins of the non-styrene-type, and some of the authors describe the lack of addition to styrenes[4].

The 3-bromo-2-oxotetrahydro-1,3-oxazoles **2** are prepared by bromination of the 2-oxotetrahydro-1,3-oxazoles **7** in aqueous alkaline medium following an improvement of Bodor et al.'s method[6]. On maintaining the pH of the reaction mixture at 8.6, high yields are obtained (81% of **2a** compared to 24%[6]) as pH-dependent side reactions such as elimination[6], hydrolysis, and ring cleavage[5] are suppressed. The 3-chloro compounds can be prepared similarly (chloro-analogue of **2a** in 60% yield) but the 3-bromo compounds are preferred because of better yield, reactivity, and stability (Scheme **B** and Table 1).



Scheme **B**

Table 1. 3-Bromo-2-oxotetrahydro-1,3-oxazoles **2**

Product[a] No.	R^3	R^4	pH of reaction mixture	Yield [%] this work	Yield [%] Ref.[6]	m.p. [°C][b] from Ref.[6]
2a	H	H	8.6	81	24	109–111°
2a	H	H	4	55[c]	—	subl. 70°C/0.1 torr
2c	CH_3	CH_3	—	87[d]	76	118–120°

[a] All compounds have been analysed for their active bromine content by iodometric titration. They contain more than 95% active bromine.

[b] D.S.C.-(differential scanning calorimetry-)analysis on **2a** indicates a weak endothermic signal, immediately followed by a strong exothermic one at about 120°C. T.G. (thermogravimetry) showed an explosion. The decomposition temperature varies under the measurement conditions: 20°C/min: 150°C; 3°C/min: 135°C. Under isothermic conditions at 90°C, a 10% weight loss is even observed. Exposing these compounds to heat should be avoided. No melting points are measured.

[c] 25% of the starting material is recovered.

[d] In this case no α-elimination is possible.

The 3-bromo-2-oxotetrahydro-1,3-oxazoles **2** add almost quantitatively to freshly distilled styrene and derivatives **1** to give adducts **3** (Table 2). The reaction is initiated by irradiation with ordinary white light or by addition of a catalytic amount of 2,2′-azoisobutyronitrile (AIBN). With the latter, the reaction takes only a few minutes. A radical mechanism as described by Zwierzak et al.[7] is assumed to take place.

The adducts **3** are hydrolysed to the corresponding hydroxy compounds **4** by refluxing in water (Table 3). Compound **4a** is easily converted to the intermediate, 3-(2-hydroxy-2-phenylethyl)-2-iminotetrahydro-1,3-thiazole hydrochloride **(5a)**. One method is described in the experimental part. Other methods to convert the 2-oxazolidinones to 2-imino-thiazolid-

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ines are known[8,9]. Compound **5b**, the precursor of nitramisole **(6b)**, is prepared similarly. The 2-oxazolidinone ring of compound **4c** could not be cleaved. Ring closure reactions of **5a** and **5b** to tetramisole **(6a)** and nitramisole **(6b)**, respectively, are well known[10,11,12].

Table 2. 1-Aryl-1-bromo-2-(2-oxotetrahydro-1,3-oxazol-3-yl)-ethanes **3a–c**

Product	Method	Reaction Conditions temperature/time	Yield [%]	m.p. [°C]	Molecular formula[a]
3a	A	r.t./24 h	89	83–84.5°	$C_{11}H_{12}BrNO_2$ (270.1)
	B	60°C/10 min	97		
3b	A	r.t./16 h	90[b]	94.5–96.5°	$C_{11}H_{11}BrN_2O_4$ (315.1)
3c	A	r.t./19 h	78[c]	70.5–72.5°	$C_{13}H_{16}BrNO_2$ (298.2)
3d	A	r.t./21 h	—[d]	—	—

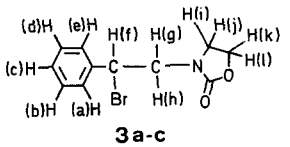
[a] Satisfactory microanalyses obtained: C ±0.08, H ±0.14, N ±0.07, Br ±0.07; exception: **3a**, C +0.41.
[b] 8% 1-(1,2-dibromoethyl)-3-nitrobenzene is also formed.
[c] 78% yield after recrystallisation from diisopropyl ether; without irradiation, the yield is only 22%.
[d] **3d** could not be isolated; the product is a mixture of 3-(2-phenyl-1-propenyl)-2-oxotetrahydro-1,3-oxazole and 3-(2-phenyl-2-propenyl)-2-oxotetrahydro-1,3-oxazole; yield: 64%.

Table 3. 1-Aryl-1-hydroxy-2-(2-oxotetrahydro-1,3-oxazol-3-yl)-ethanes **4a–c**

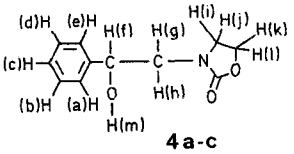
Product	Reflux time	Yield [%]	m.p. [°C]	Molecular formula[a]	
4a	1 h	71[b]	124.5–126°	$C_{11}H_{13}NO_3$	(207.2)
4b	6 h	73[c]	154–156°	$C_{11}H_{12}N_2O_5$	(252.2)
4c	45 min	78	79–81.5°	$C_{13}H_{17}NO_3$	(235.3)

[a] Satisfactory microanalyses obtained: C ±0.11, H ±0.11, N ±0.14; exception: **4a**, C −0.54.
[b] Yield after recrystallisation from 2-propanol.
[c] The pH is kept between 2 and 2.5 by adding sodium hydroxide solution.

Table 4. ^{1}H-N.M.R. Data for Compounds **3a–c** and **4a–c**



3a-c



4a-c

3-Bromo-2-oxotetrahydro-1,3-oxazole (2a):
A mixture of 2-oxotetrahydro-1,3-oxazole (**7a**; 43.54 g, 0.5 mol) and water (500 ml) is stirred. Bromine (79.9 g, 0.5 mol) is added over a 25 min period while the pH of the medium is kept at pH 8.6 by addition of 10 normal sodium hydroxide solution. After 5 min, the precipitate is filtered off, washed with water, and dried (room temperature/vacuo) to give **2a**; yield: 56.2 g; iodometric titration: 100% $Br^{\oplus}$. A second crop of product is obtained by extracting the aqueous layer with dichloromethane, drying the extracts, and evaporating them to dryness (room temperature/vacuo); yield: 11.6 g; iodometric titration: 95% $Br^{\oplus}$; total yield: 67.8 g (81%).

1-Bromo-2-(2-oxotetrahydro-1,3-oxazol-3-yl)-1-phenylethane (3a); Typical Procedures:

Method A: Freshly distilled styrene (**1**, $R^1=R^2=H$; 5.2 g, 0.05 mol) and benzene (60 ml) are stirred in a nitrogen atmosphere. Compound **2a** (8.3 g, 0.05 mol) is added, and the whole is irradiated by a 150 W lamp (white light) set about 20 cm from the vessel. Stirring and irradiation is continued for 22 h. The contents are poured into petroleum ether (250 ml), filtered, and dried; yield of **3a**: 12 g (89%).

Method B: To a suspension of 2,2'-azoisobutyronitrile (0.8 g) in benzene (100 ml) at 60°C is added compound **2a** (16.6 g, 0.1 mol), and subsequently freshly distilled styrene (10.4 g, 0.1 mol) in benzene (20 ml) is added over 5 min). After 10 min, the mixture is evaporated, the residue stirred with petroleum ether (50 ml), filtered, and dried; yield: 26.2 g (97%).

1-Hydroxy-2-(2-oxotetrahydro-1,3-oxazol-3-yl)-1-phenylethane (4a); Typical Procedure:
A mixture of **3a** (54 g, 0.2 mol) and water (200 ml) is refluxed for 1 h, cooled in ice, filtered, and the solid recrystallised from isopropanol; yield: 29.5 g (71%).

1-Hydroxy-2-(2-iminotetrahydro-1,3-thiazol-3-yl)-1-phenylethane Hydrochloride (5a); Typical Procedure:
Hydrogen chloride is bubbled into a solution of **4a** (4.15 g, 0.02 mol) in toluene (40 ml) at 100°C for 28 h. After cooling to 60°C, water (20 ml) and thiourea (2.3 g, 0.03 mol) are added, and refluxing is continued for 10 h. The hot solution is filtered, the hot filtrate saturated with sodium chloride, and cooled. The precipitate is collected by filtration, washed with water, and dried; yield: 3 g (57%); m.p. 202–204°C (Ref.[10], m.p. 201–203°C; Ref.[11], m.p. of corresponding hydrobromide 183–184.5°C).

1-Hydroxy-2-(2-iminotetrahydro-1,3-thiazol-3-yl)-1-(3-nitrophenyl)-ethane hydrochloride **(5b)** is prepared similarly; yield: 64%; m.p. 218–221°C.

We wish to thank the analytical department of Janssen Pharmaceutica, especially J. Bracke (N.M.R.), for their assistance.

Received: November 25, 1981
(Revised form: January 22, 1982)

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Product	Chemical Shifts[a] δ [ppm]												
	H(a)	H(b)	H(c)	H(d)	H(e)	H(f)	H(g)	H(h)	H(i)	H(j)	H(k)	H(l)	H(m)
3a			~7.25–7.5 (m)			5.16 (t)	4.01 (2 dd)	3.78	~3.6–3.3 (2 m)		~4.15–4.35 (m)		—
3b	8.35 (m)	—	8.23 (m)	7.61 (m)	7.85 (m)	5.27 (t)	3.94 (d)		~3.8–3.5 (2 m)		~4.3–4.4 (m)		—
3c			~7.3–7.5 (m)			5.43 (t)	3.76 (2 dd)	3.55	1.30 (s, CH_3)	0.87 (s, CH_3)	3.96 (2 d)	3.85	—
4a			~7.3–7.5 (m)			4.98 (m)	~3.35–3.70				4.28 (m)		3.16 (d)
4b	8.32 (m)	—	8.18 (m)	7.58 (m)	7.78 (m)	5.15 (m)			~3.4–3.8 (m)		4.38 (m)		
4c			~7.2–7.5 (m)			4.98 (m)	~3.25–3.35 (m)		1.22 (s, CH_3)	1.10 (s, CH_3)	4.00 (s)		4.12 (d)

[a] All N.M.R.-spectra were measured in $CDCl_3$ on a Bruker WP 200, except **4c** which was measured on a Bruker HX 60.

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