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Derivatives of 5-(Dimethylamino)-4-tosyl-1,3-oxazole-2-carbaldehyde and Its Analogs

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Abstract — Treatment of *N*-(2,2,2-trichloro-1-tosylethyl)dichloroacetamide with excess dimethylamine, piperidine, or morpholine gave substituted aminals of the oxazole series, whose facile acid hydrolysis provided 5-(dimethylamino)-4-tosyl-1,3-oxazol-2-carbaldehyde and its analogs having the piperidino and morpholino group in the 5 position of the oxazole ring. The resulting aldehydes and their aminals were condensed with phenylhydrazine, thiosemicarbazide, *N*-alkylrhodanines, and 1,3-dimethylbarbituric acid to obtain 2,5-disubstituted derivatives of 4-tosyl-1,3-oxazole.

Systematic studies of condensations of amidoalkylating agents of the general formula $CCl_3CH(Cl)\cdot NHC(O)R$ with sodium arenesulfinates resulted in the synthesis of important reagents available for further condensations [1–6]. In the present work we showed that the reaction of available *N*-(1,2,2,2-tetrachloroethyl)dichloroacetamide (**I**) with sodium *p*-toluenesulfinate gives a new S-amidoalkylation product **II** in high yield. This product proved to be a suitable starting material for the synthesis of previously unknown 2,4,5-trifunctionally substituted oxazoles (see scheme). Treatment of substrate **II** with dimethylamine, piperidine, or morpholine provides initially enamide **III** that further is involved in the transformation sequence **III** > **IV** > **V** > **VI**. The first stage of this process is a particular case of fairly general cyclocondensations of enamides like $Cl_2C{=}C(Y)NHC(O)R$ with primary and secondary amines. The range of enamides suitable for preparing 5-amino-1,3-oxazole derivatives is very broad, since Y = C(O)OAlk, CN, $P(O)(OAlk)_2$, $P(O)Ar_2$, $\overset{+}{P}Ph_3Cl^-$, SO_2Alk, SO_2Ar and other electron-acceptor groups [7].

The transformation **IV** → **VI** is made possible by the high mobility of chlorines in the dichloromethyl group of intermediates **IV**. Such a high mobility is probably associated with the effect of the nitrogen lone electron pair at C^5, that is transmitted thorough the system of multiple bonds of the oxazole ring. Similar phenomenon was also observed with analogs of compounds **IV** containing electron-acceptor substituent other than the tosyl group [8, 9].

Evidence for the formation of the final condensation products, oxazole aminals **VI**, was obtained by their transformation, via acid hydrolysis, into aldehydes **VII** that, in their turn, as shown in the scheme, were brought into trivial condensations with phenylhydrazine, thiosemicarbazide, *N*-alkylrhodanines, and 1,3-dimethylbarbituric acid. At the same time, preparative synthesis of novel 2,4,5-trisubstituted oxazoles **VIII**–**XII** is better performed with aminals **VI** that are more accessible than aldehydes **VII**. Combined spectral and chemical study showed that compounds **VIII**–**XI** are formed not only regio-, but also stereoselectively, since in most cases one of the possible stereoisomers was isolated. For unambiguous assessment of the steric structure of these isomers, further research is required.

The yields, constants, and elemental analyses of newly synthesized compounds are summarized in Table 1, and their spectral characteristics, in Table 2.

It is quite obvious that the scope of application of aldehyde oxazoles **VII** and their aminals **VI** is far from being exhausted by the condensations shown in the scheme and can be extended in near future.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument in KBr. The ^1H NMR spectra were obtained on a Varian VXR-300 instrument in DMSO-d_6, internal reference TMS.

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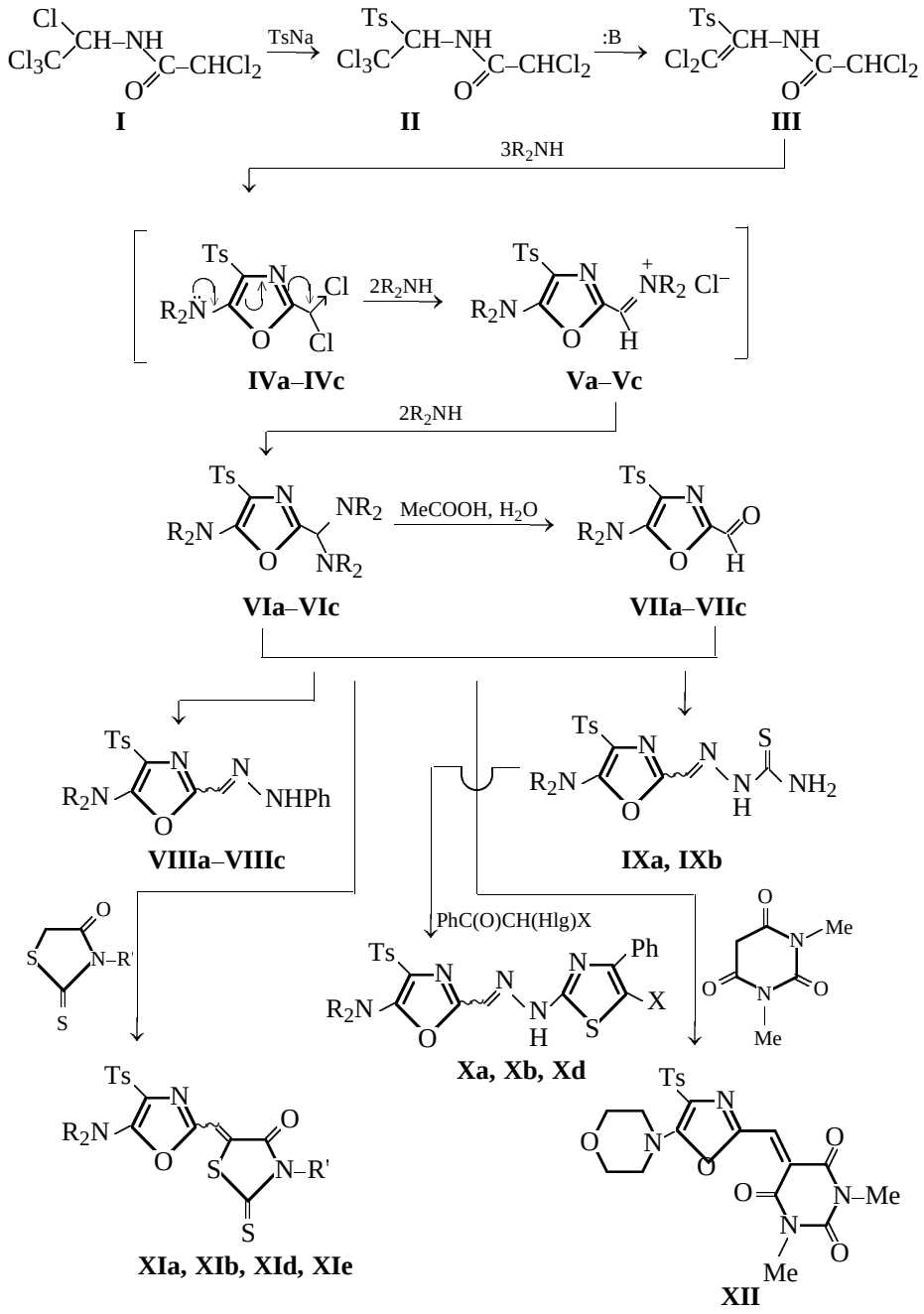

R_2N = O N (**IVa**–**XIa, Xd, XId**), N (**IVb**–**XIb, XId**), Me_2N (**IVc**–**VIIIc**); X = H (**Xa, Xb**), MeC(O)NH (**Xd**); R' = Me (**XIa, XIb**), $PhCH_2$ (**XId, XIe**); :B = $(Et)_3N$, O NH, NH, Me_2NH.

***N*-(2,2,2-Trichloroethyl-1-tosylethyl)dichloroacetamide (II).** A mixture of 0.1 mol of compound **I** [8], 0.11 mol of a thoroughly dried sodium *p*-toluenesulfinate, and 120 ml of dry acetonitrile was refluxed for 8 h, the precipitate was filtered off, the solvent was removed in a vacuum, and the residue was treated with water. Oxazole derivatives were synthesized using a crude reaction product.

***N*-(2,2-Dichloro-1-tosylethyl)dichloroacetamide (III).** Triethylamine, 0.011 mol, was added to a solution of 0.01 mol of compound **II** in 40 ml of dichloro-

Table 1. Yields, constants, and elemental analyses of compounds **II**–**XII**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)[b]	Found, %				Formula	Calculated, %			
			C	H	N	S		C	H	N	S
II	70	168–169 (EtOH–H_2O	Cl 42.60	–	3.70	7.92	$C_{11}H_{10}Cl_5NO_3S$	Cl 42.87	–	3.39	7.75
III	58	159–160 (MeCN–H_2O, 1:2)	Cl 37.83	–	3.95	8.70	$C_{11}H_9Cl_4NO_3S$	Cl 37.61	–	3.71	8.50
VIa	67	143–144 (EtOH–H_2O	55.89	6.60	11.23	6.77	$C_{23}H_{32}N_4O_6S$	56.08	6.55	11.37	6.51
VIIa	85	[c]	–	–	8.57	9.25	$C_{15}H_{16}N_2O_5S$	–	–	8.33	9.53
VIIIa	85 (90)[a]	182–183 (EtOH–) H_2O	58.80	5.13	13.28	7.43	$C_{21}H_{22}N_4O_4S$	59.14	5.20	13.14	7.52
VIIIb	72	178–179 (MeCN–H_2O, 1:2)	62.40	5.83	13.52	7.61	$C_{22}H_{24}N_4O_3S$	62.24	5.70	13.20	7.55
VIIIc	64 (74)[a]	177–178 (EtOH–H_2O	58.95	5.36	14.82	8.60	$C_{19}H_{20}N_4O_3S$	59.36	5.24	14.57	8.34
IXa	76	194–196 (DMF–EtOH, 1:1)	46.85	4.70	17.32	15.60	$C_{16}H_{19}N_5O_4S_2$	46.93	4.68	17.10	15.63
IXb	63 (68)[a]	206–207 (DMF–EtOH, 1:1)	50.15	5.23	17.30	15.76	$C_{17}H_{21}N_5O_3S_2$	50.11	5.19	17.19	15.74
Xa	83	215–216 (DMF)	56.42	4.61	13.90	12.81	$C_{24}H_{23}N_5O_4S_2$	56.57	4.55	13.74	12.58
Xb	78	213–214 (DMF)	58.95	4.91	13.96	12.85	$C_{25}H_{25}N_5O_3S_2$	59.15	4.96	13.80	12.63
Xd	70	224–227 (DMF–EtOH, 1:2)	55.32	4.57	15.01	11.40	$C_{26}H_{26}N_6O_5S_2$	55.11	4.62	14.83	11.32
XIa	75	194–196 (AcOH)	49.11	4.05	9.15	20.73	$C_{19}H_{19}N_3O_5S_3$	49.02	4.11	9.03	20.66
XIb	78 (75)[a]	158–159 (AcOH)	51.69	4.65	9.21	20.70	$C_{20}H_{21}N_3O_4S_3$	51.82	4.57	9.06	20.75
XId	82	164–164 (AcOH)	55.61	4.33	7.93	17.90	$C_{25}H_{23}N_3O_5S_3$	55.44	4.28	7.76	17.76
XIe	67	145–146 (AcOH)	57.59	4.58	8.03	17.96	$C_{26}H_{25}N_3O_4S_3$	57.86	4.67	7.79	17.82
XII	55 (63)[a]	191–192 (AcOH)	53.25	4.61	12.05	7.02	$C_{21}H_{22}N_4O_7S$	53.16	4.67	11.81	6.76

[a] Parenthesized are the yields by procedure *b* (see Experimental). [b] Compounds **VIIIa**–**VIIc, IXa, IXb, Xa, Xb**, and **XIa** melt with decomposition. [c] Thick oil.

Table 2. IR and ^{1}H NMR spectra of compounds **II, III**, and **VI**–**XII**

Comp. no.	IR spectrum, ν, cm^{-1} [a]	^{1}H NMR spectrum, δ, ppm
II	1735, 3320	2.42 s (3H, CH_3), 5.99 d (1H, CH, $^3J_{HH}$ 11 Hz), 6.12 s (1H, $CHCl_2$), 7.50 d (2H_{arom}, $^3J_{HH}$ 8.3 Hz), 7.85 d (2H_{arom}, $^3J_{HH}$ 8.3 Hz), 10.36 d (1H, NH, $^3J_{HH}$ 11 Hz)
III	1725, 3350	2.44 s (3H, CH_3), 6.96 s (1H, $CHCl_2$), 7.50 d (2H_{arom}, $^3J_{HH}$ 8.2 Hz), 7.82 d (2H_{arom}, $^3J_{HH}$ 8.2 Hz), 11.05 s (1H, NH)
VIa	[b]	2.27–2.45 m (11H, 4CH_2, CH_3), 3.49–3.70 m (16H, 8CH_2), 3.75 s (1H, CH), 7.39 d (2H arom., $^3J_{HH}$ 8.2 Hz), 7.74 d (2H_{arom}, $^3J_{HH}$ 8.2 Hz)
VIIa	1715	2.41 s (3H, CH_3), 3.60–3.79 m (8H, 4CH_2), 7.52 d (2H_{arom}, $^3J_{HH}$ 8.1 Hz), 7.87 d (2H arom., $^3J_{HH}$ 8.1 Hz), 9.75 s (1H, CH=O)
VIIIa	1620, 3300	2.41 s (3H, CH_3), 3.62–3.78 m (8H, 4CH_2), 6.80 t (1H_{arom}), 7.03 d (2H_{arom}), 7.20 t (2H_{arom}), 7.39 d (2H_{arom}, $^3J_{HH}$ 8.1 Hz), 7. 44 s (1H, CH=N), 7.76 d (2H_{arom}, $^3J_{HH}$ 8.1 Hz), 10.83 s (1H, NH)

Table 2. (Contd.)

Comp. no.	IR spectrum, ν, cm^{-1} [a]	^1H NMR spectrum, δ, ppm
VIIIb	1615, 3300	1.61–1.67 m (6H, $3CH_2$), 2.41 s (3H, CH_3), 3.55–3.59 m (4H, $2CH_2$), 6.79 t ($1H_{arom}$), 7.03 d ($2H_{arom}$), 7.20 t ($2H_{arom}$), 7.37 d ($2H_{arom}$, $^3J_{HH}$ 7.8 Hz), 7.43 s (1H, CH=N), 7.73 d ($2H_{arom}$, $^3J_{HH}$ 7.8 Hz), 10.77 s (1H, NH)
VIIIc	1630, 3300	2.40 s (3H, CH_3), 3.19 s [6H, $N(CH_3)2$], 6.78 t ($1H_{arom}$), 7.03 d ($2H_{arom}$), 7.19 t (2H arom.), 7.36 d ($2H_{arom}$, $^3J_{HH}$ 7.9 Hz), 7.45 s (1H, CH=N), 7.74 d ($2H_{arom}$, $^3J_{HH}$ 7.9 Hz), 10.72 s (1H, NH)
IXa[a]	1620, 3200–3450	2.41 s (3H, CH_3), 3.66–3.74 m (8H, $4CH_2$), [7.15 s (0.2H, CH=N), 7.67 s (0.8H, CH=N)], 7.40 d ($2H_{arom}$, $^3J_{HH}$ 8.1 Hz), 7.72 d ($2H_{arom}$, $^3J_{HH}$ 8.1 Hz), [7.57 s (0.8H, NH_2), 8.17 s (0.2H, NH_2)], [8.44 s (0.8H, NH_2), 8.76 s (0.2H, NH_2)], [11.71 s (0.8H, NH), 11.77 s (0.2H, NH)]
IXb	1610, 3200–3400	1.62–1.68 m (6H, $3CH_2$), 2.42 s (3H, CH_3), 3.60–3.66 m (4H, $2CH_2$), 7.13 s (1H, CH=N), 7.42 d ($2H_{arom}$, $^3J_{HH}$ 8.1 Hz), 7.81 d ($2H_{arom}$, $^3J_{HH}$ 8.1 Hz), 8.15 s (1H, NH_2), 8.73 s (1H, NH_2), 11.73 s (1H, NH)
Xa	[b]	2.41 s (3H, CH_3), 3.61–3.76 m (8H, $4CH_2$), 7.23–7.47 m ($6H_{arom}$), 7.64 s (1H, CH=N), 7.74–7.89 m ($4H_{arom}$), 12.48 s (1H, NH)
Xd	[b]	2.06 s (3H, $COCH_3$), 2.40 s (3H, CH_3), 3.61–3.73 m (8H, $4CH_2$), 7.43–7.50 m ($5H_{arom}$), 7.62 s (1H, CH=N), 7.71–7.82 m ($4H_{arom}$), 10.15 s [1H, NHC(O)], 12.29 s (1H, NHN=C)
XIa	1710	2.43 s (3H, CH_3), 3.38 s (3H, NCH_3), 3.65–3.76 m (8H, $4CH_2$), 7.18 s (1H, CH=), 7.44 d ($2H_{arom}$, $^3J_{HH}$ 8.2 Hz), 7.79 d ($2H_{arom}$, $^3J_{HH}$ 8.2 Hz)
XIb	1710	1.62–1.68 m (6H, $3CH_2$), 2.43 s (3H, CH_3), 3.37 s (3H, NCH_3), 3.65–3.71 m (4H, $2CH_2$), 7.17 s (1H, CH=), 7.43 d ($2H_{arom}$, $^3J_{HH}$ 8.2 Hz), 7.76 d ($2H_{arom}$, $^3J_{HH}$ 8.2 Hz)
XIc	1690	2.43 s (3H, CH_3), 3.65–3.76 m (8H, $4CH_2$), 5.19 s (2H, NCH_2C6H5), 7.22 s (1H, CH=), 7.28–7.44 m ($7H_{arom}$), 7.80 d ($2H_{arom}$, $^3J_{HH}$ 8.2 Hz)
XId	1700	1.63–1.69 m (6H, $3CH_2$), 2.42 s (3H, CH_3), 3.65–3.70 m (4H, $2CH_2$), 5.19 s (2H, $NCH_2 \cdot C_6H_5$), 7.19 s (1H, CH=), 7.28–7.42 m ($7H_{arom}$), 7.77 d ($2H_{arom}$, $^3J_{HH}$ 8.2 Hz)
XII	1620, 1670	2.42 s (3H, CH_3), 3.20 s (3H, NCH_3), 3.22 s (3H, NCH_3), 7.43 d ($2H_{arom}$, $^3J_{HH}$ 8.1 Hz), 7.51 s (1H, CH=), 7.78 d ($2H_{arom}$, $^3J_{HH}$ 8.1 Hz)

[a] Strong bands in the ranges 1600–1800 (C=N, C=O) and 3050–3600 cm^{-1} (N–H) are given. [b] Bands in the ranges 1610–1800 and 3100–3600 cm^{-1} are lacking. [c] Spectral data for a mixture of two geometric isomers (molar ratio 1:4) are given.

methane. The mixture was allowed to stand for 12 h at 20–25°C, the solvent was removed in a vacuum, and the residue was treated with water.

2-(Dimorpholinomethyl)-5-morpholino-4-tosyl-1,3-oxazole (VIa). *a*. A solution of 0.085 mol of morpholine in 10 ml of THF was added to a solution of 0.01 mol of compound **II** in 25 ml of THF. The mixture was allowed to stand for 3 days at 20–25°C, the solvent was removed in a vacuum, and the residue was treated with water.

b. A solution of 0.075 mol of morpholine in 10 ml of THF was added to a solution of 0.01 mol of compound **III** in 25 ml of THF. The mixture was allowed to stand for 3 days at 20–25°C and then worked up as described above, and the reaction product was recrystallized. Mixed sample of **VIa** obtained by procedures *a* and *b* gave no melting point depression.

2-(Dipiperidinomethyl)-5-piperidino-4-tosyl-1,3-oxazole (VIb) and 2-[bis(dimethylamino)methyl]-5-(dimethylamino)-4-tosyl-1,3-oxazole (VIc) were synthesized by the reactions of reagent **II** with excess piperidine or dimethylamine under the same conditions as for preparing compound **VIa**. As a result, aminals **VIb** and **VIc** were obtained (yield 70–75%) as pasty materials. They were used in further reactions without purification.

5-Morpholino(piperidino, dimethylamino)-4-tosyl-1,3-oxazol-2-carbaldehydes VIIa–VIIc. Water, 0.5 ml, and 0.2 ml of acetic acid were added to a solution of 0.002 mol of aminal **VIa–VIa** in 5 ml of ethanol. The mixture was heated to boiling, allowed

to stand for 24 h at 20–2°C, volatile compounds were removed in a vacuum, the residue was treated with water and diethyl ether (2.5 ml), the ether solution was dried for 12 h of sodium sulfate, and the solvent was removed in a vacuum to obtain aldehydes **VIIa**–**VIIc** as a thick yellowing buttery oily materials that, by TLC data, contained the main substance and a little admixtures. The aldehyde group in compounds **VIIa**–**VIIc** was identified by the IR spectra: $\nu_{C=O}$ 1700–1720 cm^{-1}, CH_2Cl_2).

5-Morpholino(piperidino, dimethylamino)-4-tosyl-1,3-oxazol-2-carbaldehydes VIIIa–VIIIc. *a*. Acetic acid, 1 ml, phenylhydrazine, 1 ml, and 5 ml of water were added to a solution of 0.005 mol of aminal **VIa**–**VIc** in 10 ml of ethanol. The mixture was heated to boiling, allowed to stand for 2 h at 20–25°C, and the precipitate was filtered off and washed with aqueous ethanol.

b. Phenylhydrazine, 0.2 ml, was added to a solution of 0.001 mol of aldehyde **VIIa** or **VIIc** in 3 ml of ethanol, the mixture was heated to boiling, allowed to stand for 1 h at 20–25°C, and the precipitate was filtered off. Mixed sample of **VIIIa** and two samples of **VIIIc** obtained by procedures *a* and *b* gave no melting point depression.

5-Morpholino(piperidino)-4-tosyl-1,3-oxazol-2-carbaldehyde thiosemicarbazones (IXa and IXb). *a*. A mixture of 0.005 mol of aminal **VIa** or **VIb**, 0.005 mol of thiosemicarbazide, 1 ml of acetic acid, and 15 ml of ethanol was heated under reflux for 0.5 h until precipitate formation began, after which it was left to stand for 12 h at 20–25°C, and the precipitate was filtered off.

b. A mixture of 0.002 mol of aldehyde **VIIb**, 0.002 mol of thiosemicarbazide, and 10 ml of ethanol was heated under reflux for 0.5 h until precipitate formation began, after which it was left to stand for 12 h at 20–25°C, and the precipitate was filtered off and recrystallized. Mixed sample of **IXb** obtained by procedures a and b gave no melting point depression.

5-Morpholino(piperidino)-4-tosyl-1,3-oxazol-2-carbaldehyde *N*'-(4-phenyl-1,3-thiazol-2-yl)hydrazones Xa and Xb. Bromoacetophenone, 0.002 mol, was added to a suspension of 0.002 mol of thiosemicarbazone **IXa** or **IXb** in 15 ml of ethnol. The mixture was heated under reflux for 4 h, cooled, and the precipitate was filtered off.

5-Morpholino-4-tosyl-1,3-oxazol-2-carbaldehyde *N*'-[4-(acetylamino)-1,3-thiazol-2-yl)hydrazone (Xd). *N*-(1-Chlorophenacyl)acetamide [10], 0.002 mol, was added to a solution of 0.002 of thiosemicarbazone **IXa** in 25 ml of THF. The mixture was allowed to stand for 12 h at 20–25°C, the precipitate was filtered off, washed with THF, and suspended in 15 ml of ethanol. The suspension was heated under reflux for 1 h, treated while hot with 1 ml of 25% aqueous ammonia, cooled, and the precipitate was filtered off.

3-Methyl(benzyl)-5-[5-morpholino(piperidino)-4-tosyl-1,3-oxazol-2-yl]methylenerhodanines XIa, XIb, XId, and XIe. *a*. *N*-Methyl- or *N*-benzylrhodanine, 0.005 mol, was added to a solution of 0.005 mol of aminal **VIa** or **VIb** in 10 ml of glacial acetic acid. The mixture was heated to boiling, treated with 0.1 ml of monoethanolamine, and then slowly cooled. The precipitate was filtered off and washed with acetic acid and ethanol.

b. *N*-Methylrhodanine, 0.005 mol, was added to a solution of 0.005 mol of aldehyde **VIIb** in 10 ml of acetic acid. Further treatment was performed as described in procedure *a*. Mixed sample of **XIb** obtained by procedures *a* and *b* gave no melting point depression. The ^{1}H NMR spectra of the two samples were identical.

1,3-Dimethyl-5-(5-morpholino-4-tosyl-1,3-oxazol-2-yl)methylenebarbituric acid (XII). *a*. 1,3-Dimethylbarbituric acid, 0.005 mol, and 0.1 ml of monoethanolamine were added to a solution of 0.005 mol of aminal **VIa** in 15 ml of glacial acetic acid. The mixture was heated for 1 h at 100°C, cooled, and the precipitate was filtered off.

b. 1,3-Dimethylbarbituric acid, 0.005 mol, and 0.1 ml of monoethanolamine were added to a solution of 0.005 mol of aldehyde **VIIa** in 15 ml of glacial acetic. Further treatment was performed as described in procedure *a*. The ^{1}H NMR spectra of the samples of **XII** obtained by procedures *a* and *b* were identical.

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