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Synthesis of α-Thio, α-Sulfinyl, and α-Sulfonyl-substituted Nitrosamines

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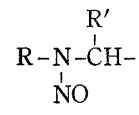
A new route to the preparation of α-alkyl (or aryl) thiosubstituted nitrosamines has been provided by nitrosation of alkylaminomethyl alkyl (or aryl) sulfides obtained simply from primary amine hydrochlorides, formaldehyde, and alkyl (or aryl) thioalcohols. By oxidation with metaperiodate and permanganate the corresponding sulfoxides and sulfones have been obtained, respectively. Compositions of the *syn* and *anti* isomers of the nitrosamines are determined by NMR technique.

Keywords——nitrosamine; metaperiodate oxidation; permanganate oxidation; sulfoxide; sulfone; *syn-anti* isomers

Nitrosamines have gained wide interest in cancer and mutagenesis research. Alkylation hypothesis of carcinogeniety requires that nitrosamines are hydroxylated enzymatically to give I (X=OH) which is a potential precursor of alkylating diazo compound.[2] The intermediates I (X=OH), which are thought to be the proximate carcinogen, have eluded isolation because of their instabilities not having appreciable lifetime. Therefore, the preparation of the closely related nitrosamines of type I (X= heteroatom-functional group) have been advanced. Up to the present, only the compounds of type I have been reported, in which R=alkyl and X=OR″,[3,4a] OCOR″[4] SR″,[5] NHCOR″,[6] and $NHCONH_2$.[7]



I

We describe here a new simple method of the synthesis of (N-nitrosoalkylamino)methyl alkyl (or aryl) sulfides I (R′=H, X=SR″) and several examples of the preparation of their derivatives, sulfoxides and sulfones. The new method relys upon a finding of the easy preparation of alkylaminomethyl alkyl (or aryl) sulfides simply from alkylamine hydrochlorides, formaldehyde and thioalcohols, and successive nitrosation leads to the nitrosamines. This route to the preparation appears more simple than the previously reported method,[5] which involves the reaction of lithiated nitrosamines with the heteroelectrophiles.

Although the reaction of secondary amines with formaldehyde and thioalcohols to yield the tertiary aminomethyl sulfides is well documented,[8] no report describing a similar fashion of the reaction of primary amines to yield secondary aminomethyl derivatives has appeared.

1) Location: *2-2-1, Oshika, Shizuoka 422, Japan.*
2) *cf.* H. Drukrey, R. Preussmann, S. Ivankovic, and D. Schmahl, *Z. Krebsforsch*, **69**, 103 (1967); P.N. Magee and J.M. Barnes, *Advan. Cancer Res.*, **10**, 169 (1967); C. Nagata and A. Imamura, *Gann*, **61**, 169 (1970).
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An accomplishment of the preparation of the compounds was previously made by the reaction of 1,3,5-trialkylhexahydrotriazines with thioalcohols in anhydrous hydrogen chloride-acetonitrile medium.[9] In contrast, we have found a very simple general method of the preparation, which was achieved by allowing primary amine hydrochlorides to react formaldehyde and thioalcohols in ethanolic medium at moderate temperature (40—45°).

Table I. Alkylaminomethyl Alkyl (or Aryl) Sulfide Hydrochlorides (1)

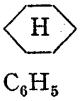
$\overset{+}{R}NH_2CH_2SR'\ Cl^-$

R	R′	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
CH_3	$CH_2C_6H_5$	81	118—119	$C_9H_{12}ClNS$	53.03 (53.06)	6.92 (6.91)	6.87 (6.79)
$C_6H_5CH_2$	$CH_2C_6H_5$	87	158—159[a]	$C_{15}H_{18}ClNS$	64.41 (64.60)	6.48 (6.45)	5.00 (4.88)
$C_6H_5CH_2CH_2$	$CH_2C_6H_5$	72	174—175	$C_{16}H_{20}ClNS$	65.40 (65.29)	6.86 (6.82)	4.77 (4.75)
$(CH_3)_2CH$	$CH_2C_6H_5$	71	159—160[b]	$C_{11}H_{18}ClNS$	57.00 (56.57)	7.83 (7.68)	6.04 (6.12)
	$CH_2C_6H_5$	76	157—159	$C_{14}H_{22}ClNS$	61.86 (61.99))	8.16 8.08)	5.15 (5.32)
CH_2=$CHCH_2$	$CH_2C_6H_5$	85	103—105	$C_{11}H_{16}ClNS$	57.50 (57.59)	7.02 (6.88)	6.10 (5.96)
$C_6H_5CH_2$	n-C_3H_7	60	143—145[c]	$C_{11}H_{18}ClNS$	57.00 (57.13)	7.83 (7.62)	6.04 (6.59)
$C_6H_5CH_2$		90	132—134	$C_{14}H_{22}ClNS$	61.86 (62.18)	8.16 (8.05)	5.15 (5.39)
$C_6H_5CH_2$	C_6H_5	75	109—111	$C_{14}H_{16}ClNS$	63.26 (62.89)	6.06 (6.08)	5.26 (5.36)
$C_6H_5CH_2$	p-$CH_3C_6H_4$	78	132—133[d]	$C_{15}H_{18}ClNS$	64.15 (63.90)	6.82 (6.54)	4.99 (5.25)

lit.[9] mp; *a*) 170—171°, *b*) 169—170°, *c*) 154—155°, *d*) 139—141°.

Table II. (N-Nitrosoalkylamino)methyl Alkyl (or Aryl) Sulfides (2)

$RNCH_2SR'$
$\quad\quad|$
$\quad\quad NO$

Compd. No.	R	R′	Yield (%)	mp or bp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	CH_3	$CH_2C_6H_5$	62	41—42	$C_9H_{12}N_2OS$	55.10 (55.29)	6.12 (6.15)	14.27 (14.34)
2b	$C_6H_5CH_2$	$CH_2C_6H_5$	67	45—46.5	$C_{15}H_{16}N_2OS$	66.15 (66.24)	5.92 (5.88)	10.28 (9.94)
2c	$C_6H_5CH_2CH_2$	$CH_2C_6H_5$	75	75—76	$C_{16}H_{18}N_2OS$	67.10 (67.45)	6.33 (6.38)	9.78 (9.79)
2d	$(CH_3)_2CH$	$CH_2C_6H_5$	60	120—121 (0.1 mmHg)	$C_{11}H_{16}N_2OS$	58.90 (59.24)	7.19 (7.14)	12.49 (12.37)
2e		$CH_2C_6H_5$	41	liq.	$C_{14}H_{20}N_2OS$	63.60 (63.91)	7.63 (7.52)	10.59 (9.01)
2f	$C_6H_5CH_2$		74	50—52	$C_{14}H_{20}N_2OS$	63.60 (63.56)	7.63 (7.62)	10.59 (10.58)
2g	$C_6H_5CH_2$	C_6H_5	58	60—61	$C_{14}H_{14}N_2OS$	65.09 (65.27)	5.46 (5.59)	10.84 (10.59)
2h	$C_6H_5CH_2$	p-$CH_3C_6H_4$	60	81—82	$C_{15}H_{16}N_2OS$	66.15 (66.23)	5.92 (5.91)	10.28 (10.37)

9) D.D. Reynolds and B.C. Cossar, *J. Heterocycl. Chem.*, **8**, 567 (1971).

$$\overset{+}{R}NH_3Cl^- + CH_2O + R'SH \xrightarrow{\text{in EtOH}} \overset{+}{R}NH_2CH_2SR'\ Cl^-$$

1

A series of alkylaminomethyl alkyl (or aryl) sulfide hydrochlorides (**1**) were synthesized by this method in good yields, as can be seen in Table I. Trials to obtain free amines failed owing to rapid decomposition of them.

The hydrochlorides (**1**) were nitrosated by sodium nitrite in aqueous medium to give the corresponding nitrosamines (**2**), as shown in Table II. Oxidation of these nitrosamines (**2**) with sodium metaperiodate in methanol and potassium permanganate in acetic acid gave the corresponding sulfoxides (**3**) and sulfones (**4**), respectively, which are listed in Table III and IV.

These nitrosamines showed all of the spectral characteristics of the nitrosamines of type I such as N-[(N-nitrosoalkylamino)methyl]amides[6] and N-[(N-nitrosoarylamino)methyl]succinimides[10] reported previously. In ultraviolet (UV) spectra they exhibited generally two absorption bands in ethanolic solution as shown in Table V; a lower intensity maximum at

Table III. (N-Nitrosoalkylamino)methyl Alkyl (or Aryl) Sulfoxides (**3**)

$$RNCH_2SR'$$
$$\underset{NO}{|}\quad\underset{O}{|}$$

Compd. No.	R	R′	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
3a	CH_3	$CH_2C_6H_5$	64	113—114	$C_9H_{12}N_2O_2S$	50.92 (51.12)	5.65 (5.66)	13.20 (13.36)
3b	$C_6H_5CH_2$	$CH_2C_6H_5$	62	100—101	$C_{15}H_{16}N_2O_2S$	62.46 (62.47)	5.60 (5.56)	9.71 (9.65)
3c	$(CH_3)_2CH$	$CH_2C_6H_5$	56	53—54	$C_{11}H_{16}N_2O_2S$	55.02 (55.02)	6.67 (6.66)	11.67 (11.61)
3d	$C_6H_5CH_2$	C_6H_5	71	89—90	$C_{14}H_{14}N_2O_2S$	61.29 (61.21)	5.14 (5.14)	10.21 (10.24)

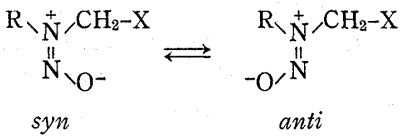
Table IV. (N-Nitrosoalkylamino)methyl Alkyl (or Aryl) Sulfones (**4**)

$$RNCH_2SO_2R'$$
$$\underset{NO}{|}$$

Compd. No.	R	R′	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
4a	CH_3	$CH_2C_6H_5$	68	73—75	$C_9H_{12}N_2O_3S$	47.35 (47.45)	5.30 (5.32)	12.27 (12.29)
4b	$C_6H_5CH_2$	$CH_2C_6H_5$	70	99—100	$C_{15}H_{16}N_2O_3S$	59.19 (58.61)	5.29 (5.16)	9.20 (8.90)
4c	$C_6H_5CH_2CH_2$	$CH_2C_6H_5$	81	118—119	$C_{16}H_{18}N_2O_3S$	60.36 (60.07)	5.65 (5.71)	8.80 (8.81)
4d	$(CH_3)_2CH$	$CH_2C_6H_5$	89	67—68	$C_{11}H_{16}N_2O_3S$	51.56 (51.90)	6.25 (6.26)	10.94 (11.08)
4e	$C_6H_5CH_2$	C_6H_5	67	82.5—84	$C_{14}H_{14}N_2O_3S$	57.92 (58.02)	4.86 (4.87)	9.65 (9.62)

10) T. Sakamoto, Y. Terao, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **25**, 731 (1977).

ca. 365 nm characteristic of N-nitroso compounds and an additional high intensity maximum or a shoulder at ca. 250 nm.



Their nuclear magnetic resonance (NMR) spectra in deuteriochloroform exhibited the two sets of signals indicating mixtures of *syn* and *anti* isomers. Each of signals could be assigned according to the knowledge obtained previously[6] from the *syn* and *anti* isomers of N-[(N-nitrosoalkylamino)methyl]amides; α-methyl, α-methylene and

Table V. IR and UV Spectral Data

Compd. No.	IR ν_{max}^{KBr} cm^{-1} (SO or SO_2)	UV λ_{max}^{EtOH} nm (log ε)	
2a		237(sh) (3.88)	354(1.98)
2b		236(sh) (3.84)	370(1.86)
2c		236(3.82)	367(2.08)
2d		237(sh) (3.84)	367(2.01)
2e		236(sh) (3.82)	368(1.80)
2f		242(3.77)	370(1.95)
2g		244(3.94)	370(1.94)
2h		245(3.94)	368(1.78)
3a	1027	250(sh) (3.83)	369(2.01)
3b	1037	253(sh) (3.75)	372(1.99)
3c	1043	254(sh) (3.67)	371(1.94)
3d	1042	242(3.86) 249(3.84)	373(2.02)
4a	1128 1320	242(3.79)	368(2.01)
4b	1137 1324	248(3.81)	372(1.95)
4c	1137 1310	248(3.77)	372(2.02)
4d	1150 1318	246(3.73)	366(1.86)
4e	1140 1320	249(3.74)	375(1.90)

sh; shoulder.

Table VI. NMR Spectral Data (δ ppm in 0.02 M $CDCl_3$ soln.)

Compd. No.	Ratio (%)		$SC\underline{H}_2C_6H_5$		$SC\underline{H}_2N$		$NC\underline{H}_2C_6H_5$		$NC\underline{H}_3$		$NCH(C\underline{H}_3)_2$		$NC\underline{H}_2C\underline{H}_2C_6H_5$	
	syn	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*	*anti*
2a		100		3.69		5.16				3.69				
2b	19	81	3.60	3.63	4.38	5.10	5.38	4.88						
2c	23	77	3.56	3.59	4.42	4.81							2.98 4.33	2.74 3.83
2d	65	35	3.79	3.69	4.42	5.02					1.46	1.27		
2e	69	31	3.80	3.71	4.46	5.08								
2f	35	65			4.46	5.12	5.43	4.92						
2g	25	75			4.72	5.40	5.29	4.92						
2h	20	80			4.59	5.23	5.19	4.83						
3b	60	40	3.95	4.10	4.72 4.24	5.08 4.95	5.63 5.53	5.01 5.02						
3c	90	10									1.49 1.46	1.15 1.12		
3d	52	48			4.92	5.07 5.05	5.48 5.42	4.71 4.18						
4a	37	63	4.18	4.29	4.82	5.28			5.05	3.24				
4b	66	34	4.14	4.28	4.59	5.03	5.56	5.03						
4c	67	33	4.09	4.20	4.64	4.89							3.10 4.61	2.76 4.02
4d	90	10	4.31	4.55	4.69	5.20					1.55	1.25		
4e	57	43			4.77	5.31	5.65	5.05						

β-methyl protons *cis* to the nitroso-oxygen resonate at higher magnetic field than the *trans* ones. Therefore an equilibrium ratio of the *syn* and *anti* isomers can be given by an intensity ratio of the corresponding signals. As clearly seen in Table VI, in a series of sulfides (**2a—e**) more branching at the α-carbon led to increase of proportion of *syn* to *anti* isomers. Similar relationship was observed in a series of sulfoxides (**3**) and sulfones (**4**), although their *syn* proportions in the equilibria were higher than those of the sulfides (**2**). Full assignment of NMR signals of **3a** and **3c** encountered difficulties because of their complicated spectra resulted from the chirality of sulfoxide.

Experimental

All melting points are uncorrected. UV spectra were recorded on a Hitachi EPS-3T spectrophotometer. Infrared (IR) spectra were obtained with a Hitachi EPI-G2 spectrophotometer. NMR spectra were taken with a Hitachi R-24 spectrometer using tetramethylsilane (TMS) as internal standard.

Alkylaminomethyl Alkyl (or Aryl) Sulfide Hydrochlorides (1) General Procedure——A series of the compounds **1** (Table I) were synthesized by the following general procedure.

A solution of 0.1 mol of primary amine hydrochloride and 9.7 g (0.12 mol) of an aqueous 37% formaldehyde in 100 ml of ethanol was warmed at 40—45°. To the solution a solution of 0.1 mol of thioalcohol in 50 ml of ethanol was dropwise added with stirring. After the addition the stirring was continued for an additional hour. Removal of ethanol under reduced pressure gave crystalline residue, which was recrystallized from ethanol.

Yields, melting points, and analytical data of the products are listed in Table I. Their IR spectra were in agreement with the structures of **1**.

(N-Nitrosoalkylamino)methyl Alkyl (or Aryl) Sulfides (2a—h) General Procedure——A solution of 3.8 g (0.055 mol) of sodium nitrite in 20 ml of water was dropwise added to a stirred mixture of 0.05 mol of **1**, 100 ml of water, and 20 ml of ether at 10—15°. After stirring for further 2 hr the ethereal layer was separated and the aqueous layer was extracted with ether. Combined ethereal solution was dried over $MgSO_4$ and concentrated. The resulting crystalline residue was recrystallized from appropriate solvent (**2a, b, g** from ether and **2c, f, h** from EtOH). The liquid product **2d** was purified by distillation under reduced pressure and **2e** by column chromatography on silica gel eluting with hexane–ether.

Yields and physical and analytical data of the products are listed in Table II. Their spectral data are shown in Tables V and VI.

(N-Nitrosoalkylamino)methyl Alkyl (or Aryl) Sulfoxides (3a—d) General Procedure——An aqueous solution of 7.1 g (0.033 mol) of sodium metaperiodate in 70 ml of water was dropwise added to a solution of 0.03 mol of **2**(**a, b, d, g**) in 100 ml of methanol with vigorous stirring at room temperature. After stirring was continued for further 5 hr, the resulting precipitate was collected by filtration, washed with cold water, and dried. The filtrate was evaporated under reduced pressure. An additional amount of the product was obtained from the residue by washing with cold water. Combined crystals were recrystallized from EtOH (**3a, b, d**) or ether (**3c**).

Yields, melting points, and analytical data of the products are listed in Table III. Their spectral data are shown in Tables V and VI.

(N-Nitrosoalkylamino)methyl Alkyl (or Aryl) Sulfones (4a—e) General Procedure——To a solution of 0.03 mol of **2**(**a—d, g**) in 50 ml of acetic acid 5.7 g (0.036 mol) of powdered potassium permanganate was added in portions with vigorous stirring over 1 hr. Stirring was continued for further 10 hr. After the remaining potassium permanganate color was quenched by addition of aqueous sodium bisulfite, the resulting precipitate was collected by filtration, washed with cold water, and dried. The filtrate was evaporated under reduced pressure. An additional amount of the product was obtained from the residue by washing with cold water. Combined crystals were recrystallized from EtOH.

Yields, melting points, and analytical data of the products are listed in Table IV. Their spectral data are shown in Tables V and VI.

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