[Chem. Pharm. Bull. 27(7)1691—1694(1979)]

UDC 547.238.04 : 547.269.1.04

Preparation of N-Alkylthiomethyl Derivatives of Hydroxylamines

Keiichi Ito and Minoru Sekiya

Shizuoka College of Pharmacy[1)]

(Received January 6, 1979)

New types of methylene compounds, N-alkylthiomethyl derivatives of N-alkyl(or aryl)hydroxylamines and N,N-bis(alkylthiomethyl)hydroxylamines, have been obtained by Mannich-type condensation using thiols, formaldehyde and hydroxylamines.

Keywords——N-alkylthiomethyl-N-methylhydroxylamine hydrochloride; N-alkylthiomethyl-N-benzylhydroxylamine; N-alkylthiomethyl-N-phenylhydroxylamine; N,N-bis(alkylthiomethyl)hydroxylamine hydrochloride; the Mannich-type condensation

Thiols are known to undergo Mannich-type condensation with formaldehyde and a primary amine[2)] (used as its hydrochloride) or secondary amine,[3)] leading to the formation of compounds containing sulfur and nitrogen linked by a methylene moiety.

$$RSH + CH_2O + R'R''NH \longrightarrow RSCH_2NR'R'' + H_2O$$

In the present paper this reaction has been extended to permit the use of hydroxylamine and its N-alkyl derivatives as the nitrogen component to provide the first preparation procedure for N-alkylthiomethyl derivatives of hydroxylamines.

Table I. Preparation of N-Alkylthiomethyl-N-alkylhydroxylamines

$$CH_3NHOH\cdot HCl \xrightarrow{RSH,\ CH_2O} RSCH_2N(CH_3)OH\cdot HCl$$

R	Yield (%)
C_3H_7	57
C_5H_{11}	75
	64
$C_6H_5CH_2$	86
CH_2CH_2	95[a)]

a) product, $HONCH_2SCH_2CH_2SCH_2NOH\cdot 2HCl$ (CH_3 on both N atoms)

$$R'NHOH \xrightarrow{RSH,\ CH_2O} RSCH_2N(R')OH$$

R	R′	Yield (%)
$C_6H_5CH_2$	$C_6H_5CH_2$	86
p-$CH_3C_6H_4$	$C_6H_5CH_2$	77
$C_6H_5CH_2$	C_6H_5	72
C_6H_5	C_6H_5	42

1) Location: *2-2-1 Oshika, Shizuoka 422, Japan.*
2) Y. Terao, K. Matsunaga, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **25**, 2964 (1977).
3) C.M. McLeod and G.M. Robinson, *J. Chem. Soc.*, **1921**, 1470; G.F. Grillot, H.R. Felton, B.R. Garett, H. Greenberg, R. Green, R. Clementi, and M. Moskowitz, *J. Am. Chem. Soc.*, **76**, 3969 (1954); I.E. Pollak, A.D. Trifunac, and G.F. Grillot, *J. Org. Chem.*, **32**, 272 (1967).

Preparation of N-alkylthiomethyl derivatives occurred readily in good yields from N-substituted hydroxylamines when either the hydrochloride of N-methylhydroxylamine or the free bases of N-benzylhydroxylamine and N-phenylhydroxylamine were allowed to react with equimolar amounts of thiol and formaldehyde in dilute ethanol at room temperature. The results of experiments with a variety of alkane- and arenethiols are summarized in Table I. Nuclear magnetic resonance (NMR) spectra of the products exhibited a singlet signal at *ca.* δ 4.5 ppm, characteristic of protons of the methylene moiety linking sulfur and nitrogen.

$$RSH + CH_2O + R'NHOH \cdot HCl \text{ (or } R''NHOH) \longrightarrow \begin{matrix} RSCH_2 \\ R' \end{matrix}\!\!>\!NOH \cdot HCl \left(\text{or } \begin{matrix} RSCH_2 \\ R'' \end{matrix}\!\!>\!NOH \right) + H_2O$$

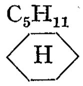
I: $R'=CH_3$; II: $R''=C_6H_5CH_2$; III: $R''=C_6H_5$

However, on similar treatment, hydroxylamine hydrochloride gave N,N-bis(alkylthiomethyl)hydroxylamines, as their hydrochlorides with alkanethiols and as the free base with benzenethiol, in good yields according to the equation given below, regardless of the use of increased molar amounts of hydroxylamine hydrochloride. By reaction with 1,2-ethanedithiol and formaldehyde, a seven-membered ring compound, tetrahydro-3-hydroxy-2H-1,5,3-dithiazepine hydrochloride, was obtained.

$$2RSH + 2CH_2O + NH_2OH \cdot HCl \longrightarrow \underset{\text{IV}}{(RSCH_2)_2NOH \cdot HCl} + 2H_2O$$

TABLE II. Preparation of N,N-Bis(alkylthiomethyl)hydroxylamine Hydrochlorides

$$2RSH + 2CH_2O + NH_2OH \cdot HCl \longrightarrow (RSCH_2)_2NOH \cdot HCl + 2H_2O$$

R	Yield (%)
C_3H_7	94
C_5H_{11}	96
	77
$C_6H_5CH_2$	90
C_6H_5	77[a]
CH_2CH_2	74[b]

a) obtained as free base.
b) product, $\begin{matrix} CH_2SCH_2 \\ | \\ CH_2SCH_2 \end{matrix}\!\!>\!NOH \cdot HCl$.

N,N-Bis(alkylthiomethyl)hydroxylamines were obtained from the hydrochlorides by treatment with potassium bicarbonate. Both sets of methylene protons of N,N-bis(alkylthiomethyl)-hydroxylamines and their hydrochlorides gave a singlet signal at *ca.* δ 4.3—4.7 ppm in their NMR spectra in every case.

The use of acetaldehyde and benzaldehyde instead of formaldehyde, or O-methylhydroxylamine hydrochloride as a hydroxylamine component gave no reaction in Mannich-type condensation under similar reaction conditions.

Experimental

All melting points are uncorrected. NMR spectra were taken with a Hitachi R-24 spectrometer (at 60 MHz) using tetramethylsilane as an internal standard. Infrared (IR) spectra were obtained with a Hitachi EPI-G2 spectrophotometer.

N-Alkylthiomethyl-N-alkylhydroxylamines (see Table I)——General Procedure: N-Alkylthiomethyl-N-methylhydroxylamine hydrochlorides (Ia—e), N-alkylthiomethyl-N-benzylhydroxylamines (IIa, b), and N-alkylthiomethyl-N-phenylhydroxylamines (IIIa, b) were prepared by the following general procedure.

To a solution of 0.04 mol of hydroxylamine derivatives in 12 ml of water (in the run with N-methylhydroxylamine hydrochloride) or EtOH (in the runs with N-benzyl- and N-phenylhydroxylamine) were added dropwise 3.8 g (0.044 mol based on CH_2O) of 35% formaline and then 0.04 mol of the thiol in 20 ml of EtOH,

with stirring at room temperature. After stirring for 2 hr, the reaction solution was concentrated under reduced pressure and crystals deposited in the resulting residue on standing in a refrigerator were collected by filtration and weighed. Recrystallization from an appropriate solvent gave a pure product in the yield listed in Table I. Melting points, analytical and NMR spectral data are summarized in Table III.

TABLE III. $RSCH_2$(R′)NOH·HCl (or $RSCH_2$(R′)NOH)

Compound No.	R	R′	Appearance (Recryst. solvent)	mp (°C)	Formula	Analysis (%) Found (Calcd.) C	H	N	NMR δ (ppm) SCH_2N
Ia[a]	C_3H_7	CH_3	Plates (Ether)	57— 59	$C_5H_{14}ClNOS$	34.53 (34.98	8.01 8.22	8.11 8.16)	4.53[d]
Ib[a]	C_5H_{11}	CH_3	Prisms (Ether)	53— 55	$C_7H_{18}ClNOS$	41.62 (42.09	8.93 9.08	7.05 7.01)	4.53[d]
Ic[a]	⟨H⟩	CH_3	Prisms (AcOEt)	78— 80	$C_8H_{18}ClNOS$	45.01 (45.38	8.52 8.57	6.64 6.62)	4.58[d]
Id[a]	$C_6H_5CH_2$	CH_3	Prisms (AcOEt)	100—102	$C_9H_{14}ClNOS$	49.24 (49.20	6.39 6.42	6.37 6.38)	4.47[d]
Ie[a,c]	CH_2CH_2	CH_3	Prisms (AcOEt)	144—146 (Decomp.)	$C_6H_{18}Cl_2N_2O_2S_2$	25.34 (25.26	6.28 6.34	9.72 9.82)	4.65[d]
IIa[b]	$C_6H_5CH_2$	$C_6H_5CH_2$	Prisms (isoPrOH)	65— 66	$C_{15}H_{17}NOS$	69.62 (69.46	6.58 6.61	5.51 5.40)	3.88[e]
IIb[b]	p-$CH_3C_6H_4$	$C_6H_5CH_2$	Prisms (isoPrOH)	60— 63	$C_{15}H_{17}NOS$	69.13 (69.46	6.59 6.61	5.35 5.40)	4.33[e]
IIIa[b]	$C_6H_5CH_2$	C_6H_5	Prisms (isoPrOH)	87— 89	$C_{14}H_{15}NOS$	68.51 (68.47	6.22 6.11	5.61 5.70)	4.53[e]
IIIb[b]	C_6H_5	C_6H_5	Needles (Petr. ether)	42— 45	$C_{13}H_{13}NOS$	67.69 (67.50	5.81 5.66	6.43 6.06)	4.98[e]

a) hydrochloride; b) free base; c) $HONCH_2SCH_2CH_2SCH_2NOH \cdot 2HCl$ (CH_3 on each S); d) measured in DMSO-d_6; e) measured in $CDCl_3$.

N,N-Bis(alkylthiomethyl)hydroxylamine Hydrochlorides (IVa—f, see Table II)——General Procedure: To a solution of 1.4 g (0.02 mol) of hydroxylamine hydrochloride in 8 ml of water were added 3.6 g (0.044 mol based on CH_2O) of 35% formaline and 0.04 mol of the thiol in 20 ml of EtOH, and the mixture was allowed to react using the procedure described above. In the runs with cyclohexanethiol and α-toluenethiol, most

TABLE IV. $(RSCH_2)_2NOH \cdot HCl$

Compound No.	R	Appearance (Recryst. solvent)	mp (°C)	Formula	Analysis (%) Found (Calcd.) C	H	N	NMR δ (ppm) in DMSO-d_6 SCH_2N
IVa	C_3H_7	Needles (Petr. ether)	45— 48	$C_8H_{20}ClNOS_2$	38.46 (38.93	8.00 8.18	6.03 5.67)	4.40
IVb	C_5H_{11}	Prisms (Petr. ether)	57— 59	$C_{12}H_{28}ClNOS_2$	47.90 (47.74	9.37 9.35	4.56 4.64)	4.38
IVc	⟨H⟩	Needles (EtOH)	125—126 (Decomp.)	$C_{14}H_{28}ClNOS_2$	51.64 (51.59	8.60 8.66	4.37 4.30)	4.33
IVd	$C_6H_5CH_2$	Plates (EtOH)	125—127	$C_{16}H_{20}ClNOS_2$	56.33 (56.20	5.87 5.90	3.93 4.10)	4.44
IVe[a]	C_6H_5	Prisms (isoPrOH)	50— 53	$C_{14}H_{15}NOS_2$	60.43 (60.64	5.39 5.42	4.97 5.05)	4.48[c]
IVf[b]	CH_2	Prisms (EtOH)	129—131 (Decomp.)	$C_4H_{10}ClNOS_2$	27.75 (27.59	5.36 5.37	7.56 7.46)	4.68

a) free base; b) $CH_2(CH_2SCH_2)_2NOH \cdot HCl$; c) in $CDCl_3$.

of the products precipitated in the reaction mixture. In the run with benzenethiol, the product was isolated as free base from the lower layer liberated from the reaction solution. In the other runs, the products were obtained by concentration of the reaction solution. Yields of the products are given in Table II. Melting points, analytical and NMR spectral data are recorded in Table IV.

As shown in the following examples, treatment of IV with aqueous $KHCO_3$ gave N,N-bis(alkylthiomethyl)hydroxylamines.

N,N-Bis(benzylthiomethyl)hydroxylamine: liquid; NMR (in DMSO-d_6) δ: 3.84 (4H, s, CCH_2S), 3.99 (4H, s, SCH_2N), 7.28 (10H, s, aromatic protons). *Anal.* Calcd. for $C_{16}H_{19}NOS_2$: C, 62.90; H, 6.28; N, 4.59. Found: C, 62.74; H, 6.22; N, 4.37.

Tetrahydro-3-hydroxy-2H-1,5,3-dithiazepine: prisms from $CHCl_3$, mp 94—95°. NMR (in DMSO-d_6) δ: 2.98 (4H, s, CH_2CH_2), 4.36 (4H, s, SCH_2N). *Anal.* Calcd. for $C_4H_9NOS_2$: C, 31.76; H, 6.01; N, 9.26. Found: C, 31.47; H, 6.00; N, 9.08.

As shown in the following examples, refluxing a chloroform solution of N,N-bis(alkylthiomethyl)hydroxylamine and acetic anhydride gave O-acetyl-N,N-bis(alkylthiomethyl)hydroxylamine.

O-Acetyl-N,N-bis(phenylthiomethyl)hydroxylamine: prisms from *n*-hexane, mp 40—42°. IR ν_{COO}^{KBr} cm^{-1}: 1754, 1210. NMR (in $CDCl_3$) δ: 1.68 (3H, s, CH_3CO), 4.61 (4H, s, SCH_2N), 7.15—7.58 (10H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{17}NO_2S_2$: C, 60.16; H, 5.37; N, 4.39. Found: C, 60.10; H, 5.36; N, 4.38.

3-Acetoxytetrahydro-2H-1,5,3-dithiazepine: needles from AcOEt, mp 137—139°. IR ν_{COO}^{KBr} cm^{-1}: 1755, 1200. NMR (in DMSO-d_6) δ: 1.99 (3H, s, CH_3CO), 2.98 (4H, s, CH_2CH_2), 4.51 (4H, s, SCH_2N). *Anal.* Calcd. for $C_6H_{11}NO_2S_2$: C, 37.28; H, 5.74; N, 7.25. Found: C, 37.28; H, 5.76; N, 7.19.

Acknowledgement We wish to thank Mr. K. Narita and the other members of the Analysis Center of this college for elementary analyses.

[Chem. Pharm. Bull. 27(7)1694—1696(1979)]

UDC 541.632.04 : 543.544.2.06

Determination of Optical Isomers of Clinofibrate by High-Performance Liquid Chromatography

HIROSHI NAKAZAWA, YOSHIAKI KANAMARU, and ATSUSHI MURANO

Institute for Biological Science, Sumitomo Chemical Co., Ltd.[1]

(Received January 16, 1979)

A method for separation and determination of optical isomers of 2,2′-(4,4′-cyclohexylidenediphenoxy)-2,2′-dimethyldibutyric acid (clinofibrate) by high-performance liquid chromatography was developed. *meso*, *d*- and *l*-isomers of clinofibrate were derivatized with D-(+)-α-methylbenzylamine to the corresponding diastereomer amides, which were separated from one another by high-performance liquid chromatography. Each isomer in clinofibrate was determined. The chromatographic conditions were as follows: column, stainless-steel two connecting columns (150 mm in length and 4 mm in i.d.) packed with LiChrosorb SI-60 (5 μm); mobile phase, *n*-hexane/isopropanol (500/3, v/v); flow rate, 1.6 ml/min; detector, UV photometer at 254 nm.

Keywords——hypolipidemic agent; clinofibrate; high-performance liquid chromatography; determination of optical isomers; diastereomer amide

2,2′-(4,4′-Cyclohexylidenediphenoxy)-2,2′-dimethyldibutyric acid, clinofibrate, is a new hypolipidemic agent[2] having the chemical formula shown in Fig. 1. This new aryloxy compound has three isomers, namely the *d*-form, *l*-form and *meso*-form, which differ in the configurations around the two asymmetric carbons in the molecule. Usually, synthesized

1) Location: *4-2-1, Takatsukasa, Takarazuka-shi, Hyogo 665, Japan.*

2) K. Toki, Y. Nakamura, K. Agatsuma, H. Nakatani, and S. Aono, *Atherosclerosis*, **18**, 101 (1973); D. Kritchevsky and S.A. Tepper, *Atherosclerosis*, **18**, 93 (1973); S. Sakamoto, K. Yamada, T. Anzai, and T. Wada, *Atherosclerosis*, **18**, 109 (1973); E. Schacht, "Topics in Current Chemistry," Springer-Verlag, Inc., New York, 1977, pp. 99—123.