TABLE I

N-ALKYL- AND N-ARALKYLAMINOETHANETHIOSULFURIC ACIDS

$RNHCH_2CH_2SSO_3H$

R	M.p., °C.	% yield[a]	Method of synthesis	Recrystn. solvent	Molecular formula	Calcd., % C	H	N	S	Found, % C	H	N	S
Methyl	163–163.5	58.4	B[b]	H_2O–EtOH	$C_3H_9NO_3S_2$	21.04	5.29	8.18	37.45	20.94	5.28	7.88	37.17
Ethyl	183–184.5 dec.	56.7	B[c]	H_2O–EtOH	$C_4H_{11}NO_3S_2$	25.93	5.96	7.56	34.61	25.64	6.25	7.31	34.46
n-Propyl	173 dec.	80.3	B[d]	H_2O	$C_5H_{13}NO_3S_2$	30.13	6.57	7.03	32.18	30.26	6.97	6.90	32.62
n-Butyl	159–160	68.7	B[e]	H_2O	$C_6H_{15}NO_3S_2$	33.78	7.09	6.57	30.06	33.74	6.85	6.49	29.78
n-Pentyl	183–184 dec.	18.3	A	H_2O	$C_7H_{17}NO_3S_2$	36.98	7.54	6.16	28.21	37.11	7.44	6.32	28.47
n-Hexyl	182 dec.	26.5	A	H_2O	$C_8H_{19}NO_3S_2$	39.80	7.93	5.80	26.57	40.04	8.15	5.76	26.51
n-Heptyl	192–194 dec.	50.0	A	H_2O	$C_9H_{21}NO_3S_2$	42.32	8.29	5.49	25.11	42.65	8.55	5.68	24.99
n-Octyl	190–190.5 dec.	46.7	A	H_2O	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.91	8.90	5.20	23.74
n-Nonyl	194 dec.	20.0	A	10% EtOH	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.62	47.06	8.95	4.84	22.88
n-Decyl	190–192 dec.	37.6	A	10% EtOH	$C_{12}H_{27}NO_3S_2$	48.45	9.15	4.71	21.56	48.74	9.22	5.21	22.22
n-Undecyl	191–193	22.8	A	30% EtOH	$C_{13}H_{29}NO_3S_2$	50.12	9.39	4.50	20.59	50.39	9.37	4.22	20.67
n-Dodecyl	196–198 dec.	39.4	A	30% EtOH	$C_{14}H_{31}NO_3S_2$	51.65	9.60	4.30	19.70	51.81	9.80	3.94	19.14
n-Tridecyl	206.5–207 dec.	28.3	A	30% EtOH	$C_{15}H_{33}NO_3S_2$	53.05	9.79	4.13	18.89	53.43	9.82	4.04	18.96
n-Tetradecyl	207.5–208.5 dec.	21.3	A	50% EtOH	$C_{16}H_{35}NO_3S_2$	54.35	9.98	3.96	18.14	54.36	10.11	4.13	18.16
n-Pentadecyl	203.5 dec.	26.6	A	50% EtOH	$C_{17}H_{37}NO_3S_2$	55.54	10.15	3.81	17.44	55.93	9.88	3.94	17.57
n-Hexadecyl	199–200 dec.	15.6	A	50% EtOH	$C_{18}H_{39}NO_3S_2$	56.65	10.30	3.67	16.80	56.84	10.17	3.85	16.70
n-Heptadecyl	197–197.5 dec.	30.5	A	60% EtOH	$C_{19}H_{41}NO_3S_2$	57.67	10.44	3.54	16.21	57.31	10.27	3.65	16.51
n-Octadecyl	190–191 dec.	14.7	A	60% EtOH	$C_{20}H_{43}NO_3S_2$	58.63	10.58	3.42	15.65	58.69	10.61	3.47	15.49
Isopropyl	189 dec.	65.3	B[c]	H_2O	$C_5H_{13}NO_3S_2$	30.13	6.57	7.03	32.18	30.23	6.65	7.09	32.57
t-Butyl	230–231 dec.	47.1	B[f]	H_2O	$C_6H_{15}NO_3S_2$	33.78	7.09	6.57	30.06	33.69	6.85	6.40	30.24
2-Heptyl	169.5–170 dec.	56.0	B	H_2O	$C_7H_{17}NO_3S_2$	42.32	8.29	5.49	25.11	42.44	8.18	5.64	25.38
2-Octyl	178–179	72.2	B[g]	MeCN	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.69	8.49	5.49	23.52
3-Octyl	124	50.0	B	H_2O	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.47	8.74	5.21	23.75
4-Octyl	117.5–118	69.8	B	H_2O	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.66	8.37	5.16	24.07
Cyclooctyl	190 dec.	64.8	B	H_2O	$C_{10}H_{21}NO_3S_2$	44.91	7.91	5.24	23.98	44.87	7.92	5.11	24.39
2-Ethyl-1-hexyl	145–146	4.9	A[h]	EtOH	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.57	8.84	5.00	23.95
Isononyl	195–197	24.0	A	H_2O	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.63	46.56	9.02	4.86	22.67
2-Nonyl	187–188	55.8	B	H_2O	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.63	46.71	8.79	4.96	22.62
3-Nonyl	141–142	29.1	B	Me_2CHOH	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.63	46.41	8.91	5.04	22.58
4-Nonyl	99	45.5	B	EtOAc	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.63	47.07	9.05	4.94	22.41
2-Decyl	189 dec.	59.2	B	50% EtOH	$C_{12}H_{27}NO_3S_2$	48.45	9.15	4.71	21.56	48.48	9.22	4.75	21.60
3-Decyl	128–130	56.0	B	EtOAc	$C_{12}H_{27}NO_3S_2$	48.45	9.15	4.71	21.56	48.72	9.26	4.37	21.44
2-Undecyl	193–194 dec.	71.1	B	45% EtOH	$C_{13}H_{29}NO_3S_2$	50.12	9.38	4.50	20.59	49.84	9.21	4.45	20.77
Benzyl	197–197.5 dec.	92.5	B[i]	H_2O	$C_9H_{13}NO_3S_2$	43.70	5.28	5.66	25.93	43.89	5.54	5.80	25.72
Phenethyl	186–186.5 dec.	14.9	A	H_2O	$C_{10}H_{15}NO_3S_2$	45.95	5.79	5.36	24.54	45.92	5.84	5.32	24.42
Phenylpropyl	173–174 dec.	29.9	A	H_2O	$C_{11}H_{17}NO_3S_2$	47.97	6.22	5.09	23.29	48.13	6.39	5.12	23.42
Phenoxyethyl	190 dec.	6.5	A[j]	H_2O	$C_{10}H_{15}NO_4S_2$	43.30	5.45	5.05	23.12	43.64	5.42	5.02	22.94

[a] Yields of thiosulfuric acids prepared by method A are based on alkyl bromides and yields of those prepared by method B are based on N-alkylaminoethyl bromide hydrobromides. [b] Reported m. p. 160° (K. Schimmelschmidt, H. Hoffmann, and E. Mundlos, *Chem. Ber.*, **96,** 38 (1963)). [c] Starting amino alcohol obtained from Eastman Organic Chemicals. [d] Because the b.p. of N-*n*-propylaminoethanol is not sufficiently different from that of 2-aminoethanol for convenient separation of the two compounds by distillation, the alcohol was prepared by treating *n*-propylamine with ethylene oxide by the method of J. H. Biel, *J. Am. Chem. Soc.*, **71,** 1306 (1949). [e] Starting amino alcohol obtained from Pennsalt Chemicals Corp. [f] Starting amino alcohol obtained from Rohm and Haas Company. [g] Starting amino alcohol obtained from Universal Oil Products Company. [h] Reaction ran 8 days. [i] Starting amino alcohol obtained from Miles Chemical Company. [j] Reaction ran 2 weeks.

N-Alkylaminoethanethiosulfuric Acids.—An equimolar mixture of sodium thiosulfate pentahydrate and an N-alkylaminoethyl bromide hydrobromide in water or water–ethanol, depending on the solubility of the latter reactant, was heated near the reflux temperature for approximately 1 hr. Completion of the reaction was indicated by failure of sulfur to precipitate from an aliquot of the solution which was acidified with mineral acid. In most instances, the Bunte salt was sufficiently water insoluble to crystallize from solution upon cooling. Solutions containing a Bunte salt which was relatively water soluble were concentrated and the product was separated from sodium bromide by crystallization. Several recrystallizations were required in order to obtain a pure, halide-free product.

2-(Trimethylammonium)ethyl Thiosulfate.—A solution of 23.7 g. (0.15 mole) of (2-chloroethyl)trimethylammonium chloride and 37.3 g. (0.15 mole) of sodium thiosulfate pentahydrate in 35 ml. of water was heated at reflux for 1 hr. On cooling, the crystalline product separated from solution. Recrystallization once from water followed by several treatments of the product with boiling methanol to remove remaining sodium bromide afforded 20.6 g. (69.1%) of 2-(trimethylammonium)ethyl thiosulfate, m.p. 267–269° dec.

Anal. Calcd. for $C_5H_{13}NO_3S_2$: C, 30.13; H, 6.57; N, 7.03; S, 32.18. Found: C, 30.11; H, 6.74; N, 7.04; S, 31.97.

Acknowledgment.—We wish to thank Dr. Thomas R. Sweeney for many helpful suggestions and Messrs. L. Hafner, J. D. White, and S. Abdou-Sabet for technical assistance.

Aminooxyacetic Acid Derivatives

ALFRED RICHARDSON, JR.

Department of Organic Research, Scientific Laboratories, The Wm. S. Merrell Company, Division of Richardson-Merrell Inc., Cincinnati, Ohio

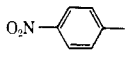
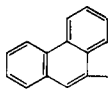
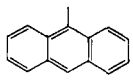
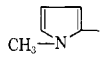
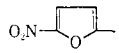
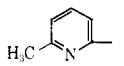
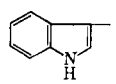
Received April 17, 1964

Aminooxyacetic acid, being a derivative of hydroxylamine, lends itself to reactions with carbonyl compounds.[1–8] Earlier work[4,5] has shown that certain oxime derivatives such as these have exhibited plant growth inhibition[4] or vitamin K activity[5]; furthermore, aminooxyacetic acid itself has been reported[8] to have antibacterial activity. The compounds described here were prepared in order that they might be investigated as poten-

(1) A. Wohl, *Bull. soc. chim. France*, **2,** 2163 (1935).
(2) M. Anchel and R. Schoenheimer, *J. Biol. Chem.*, **114,** 539 (1936).
(3) E. Borek and H. T. Clarke, *J. Am. Chem. Soc.*, **58,** 2020 (1936).
(4) M. S. Newman, W. Fones, and M. Renoll, *ibid.*, **69,** 718 (1947).
(5) D. O. Holland, British Patent 621,934 (1949); *Chem. Abstr.*, **44,** 664*b* (1950).
(6) F. Winternitz and R. Lachazette, *Bull. soc. chim. France*, 664 (1958).
(7) A. Frank and K. Riede, *Monatsh.*, **92,** 725 (1961).
(8) L. Dienes, H. J. Weinberger, and S. Madoff, *J. Bacteriol.*, **59,** 755 (1950).

TABLE I

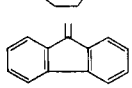
ALDOXIME ETHERS, $RCH{=}NOCH_2CO_2R'$

Compd.	R	R′	M.p., °C.	Method[a]	Yield, %	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	Solvent[b]
I		H	145–147[c]	A	41	48.22	48.53	3.59	3.77	12.49	12.66	B-PE
II		H	128.5–130.0	B	18	68.11	68.17	4.84	4.63	6.11	6.14	E-PE
III		H	208–209 dec.	B	42	73.11	73.04	4.69	4.61	5.02	4.85	E
IV		C_2H_5	69–70 69.5–70.5	D E	... 79	74.25	74.04 74.24	5.58	5.53 5.38	4.56	4.25 4.67	PE PE
V		H	141–142	C	10	50.00	50.32	4.79	4.74	16.67	16.53	Et-PE
VI		H	107–108	B	14	52.74	52.86	5.53	5.34	15.38	15.24	Et-PE
VII		H	163–164[d]	B	16	39.26	39.15	2.83	2.84	13.08	13.03	E-PE
VIII		H	129–131	B	31	45.39	45.67	3.81	3.76	7.56	7.31	Et-PE
IX		H	180–183 dec. 179–180 dec.	C B	36 56	53.33	53.66 53.42	4.47	4.48 4.41	15.55	15.15 15.34	E E
X		H	146–147	B	26	55.67	55.60	5.19	5.02	14.43	14.12	E-PE
XI		H	172–173	B	44	53.33	53.47	4.47	4.21	15.55	15.54	E
XII		H	223 dec.[e]	B	52	53.33	53.10	4.47	4.23	15.55	15.40	E
XIII		H	189–190 dec.	B	12	60.54	60.93	4.62	4.52	12.84	12.86	E-PE

[a] See Experimental. [b] Recrystallization solvents: B = benzene, E = ethanol, Et = ether, PE = petroleum ether (b. p. 60–90°). [c] Lit.[7] m.p. 144–145°. [d] Lit.[7] m.p. 165–166°. [e] Lit.[7] m.p. 218–221°.

TABLE II

KETOXIME ETHERS, $R{=}NOCH_2CO_2H$

Compd.	R	M.p., °C.	Method[a]	Yield, %	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	Solvent[b]
XIV	$C_6H_5C(CH_3)$	95.0–96.5[c]	B	54	62.17	62.53	5.74	5.66	7.25	7.23	PE
XV	$C_6H_5C(C_2H_5)$	64.5–66.0[d]	B	70	63.77	63.99	6.32	5.96	6.76	6.61	PE
XVI		85–87	A	45	53.49	53.45	7.06	7.06	8.91	8.82	PE
XVII		89–90	A	28	66.94	67.29	6.48	6.69	6.01	5.98	PE
XVIII		52–53	A	29	58.36	58.13	8.16	8.44	7.56	7.54	PE
XIX		237–239 dec.	A	35	71.14	71.17	4.38	4.63	5.53	5.56	E

[a] See Experimental. [b] Recrystallization solvents: E = ethanol, PE = petroleum ether (b.p. 60–90°). [c] Lit.[3] m.p. 97.0–97.5°. [d] Lit.[1] m.p. 58°.

tial therapeutic agents. The aldoxime ethers are listed in Table I, while the ketoxime ethers are listed in Table II. The carbonyl and imino infrared absorption bands are compiled in Table III.

Experimental

All melting points are corrected. The yields represent the quantity of analytically pure material obtained. The starting materials were purchased from various sources, except those which are mentioned below. The infrared spectra were obtained using KBr plates in a Perkin-Elmer Model 21 spectrophotometer.

Pyrrole-2-carboxaldehyde.—The method of Silverstein, *et al.*,[9] was used. There resulted a 68% yield of product which boiled at 118–120° (27–29 mm.) [lit.[9] b.p. 78° (2 mm.)], m.p. 44–45° (lit.[9] m.p. 44–45°).

N-Methylpyrrole-2-carboxaldehyde.—The method of Silverstein, *et al.*,[9] was used. A yield of 69% was obtained with the main fraction boiling at 85–88° (23 mm.) [lit.[9] b.p. 75–76° (11 mm.)].

(9) R. M. Silverstein, E. R. Ryskiewicz, C. Willard, and R. C. Koehler, *J. Org. Chem.*, **20**, 668 (1955).

TABLE III
CARBONYL AND IMINO INFRARED ABSORPTION BANDS[a-c]

Compd.	C=O, μ	C=N, μ
I	5.78, 5.85	6.17
II[d]	5.80, 5.88	...
III	5.82	6.19
IV	5.70, 5.77	6.15
V	5.73, 5.91	6.12
VI	5.76	6.17
VII	5.80	6.18
VIII	5.67, 5.74	6.22
IX	5.77	6.21
X	5.77	6.21
XI	5.83	6.16
XII	5.79	6.20
XIII	5.81	6.17
XIV	5.78, 5.84	6.16
XV	5.80, 5.85	6.19
XVI	5.66, 5.73	6.04
XVII	5.82, 5.86	6.08
XVIII	5.80, 5.86	6.16
XIX	5.82, 5.87	6.15

[a] All spectra were obtained using KBr plates. [b] The presence of two carbonyl bands indicates a mixture of monomer and dimer in the solid state. On the basis of earlier work [see L. J. Bellamy, "The Infared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958; E. J. Hartwell, R. E. Richards, and H. W. Thompson, *J. Chem. Soc.*, 1436 (1948); M. St. C. Flett, *ibid.*, 962 (1951)] the lower wave-length band has been assigned to the carbonyl absorption of the monomer while the higher wave-length band has been assigned to the carbonyl absorption of the dimer. [c] F. Mathis, *Compt. Rend.*, **232**, 505 (1961), reported that infrared absorption bands due to oxime imino groups lie in the 5.95–6.20 μ region. His studies indicated that aromatic oximes absorbed at higher wave lengths than did the aliphatic oximes. The same effect was observed in this work on oxime ethers. [d] An imino band in the 6-μ region was not observed.

5-Nitro-2-furfural.[10]—This compound was used without purification.

2-Phenylcyclopentanone.—Van Zoeren's method[11] for the synthesis of 2-(2-thienyl)cyclopentanone was employed. A 45% yield of product was obtained which boiled at 145–148° (16 mm.), $n^{23}D$ 1.5515.

Ethyl Aminooxyacetate.—The method described by Frank and Riedl[7] for the preparation of methyl aminooxyacetate was employed here. The product was an oil; yield, 53%; $n^{25}D$ 1.4267. The hydrochloride salt melted at 115–117°.

Anal. Calcd. for $C_4H_9NO_3 \cdot HCl$: C, 30.88; H, 6.48; N, 9.00. Found: C, 30.96; H, 6.29; N, 9.02.

Aminooxyacetic Acid Derivatives. Method A.—A solution of the aldehyde or ketone and 1 equiv. of aminooxyacetic acid hemihydrochloride (Eastman) was made in about 25 times its weight of 90% ethanol. To the solution was added 3.3 equiv. of sodium acetate. The mixture was stirred and refluxed for 2 hr. The solvent was then evaporated *in vacuo*. The residue was slurried in an equal volume of water and made alkaline with 10% aqueous sodium hydroxide solution. The unchanged aldehyde or ketone was removed by filtration or by extraction with ether. The aqueous phase was then made acidic to congo red indicator paper and the product was isolated by filtration or by extraction with ether and recrystallized.

Method B.—To a solution of the aldehyde or ketone and 1 equiv. of aminooxyacetic acid hemihydrochloride in 90% ethanol (as in A) was added 1 equiv. of triethylamine and the solution was refluxed for 2 hr. The solvent was removed *in vacuo*. The residue was then washed with water and recrystallized.

Method C.—Benzene was substituted for 90% ethanol as the solvent, but the procedure outlined for B was otherwise employed. The reaction mixture was heterogenous during the entire reaction period.

Method D.—Aminooxyacetic acid hemihydrochloride was allowed to react with 9-anthraldehyde (Aldrich) (12.3 g.) according to B. A yellow solid (4.2 g.) was isolated which melted at 188–190° dec., but the elemental analyses ($C_{38}H_{32}N_4O_7$), after two recrystallizations from ethanol, indicated that it was not the desired product. This material (3 g.) was refluxed for 5 hr. in 50 ml. of 1.4 *N* ethanolic hydrogen chloride. The solution was filtered and evaporated *in vacuo*. The residue was recrystallized twice from petroleum ether (b.p. 60–90°) and there resulted 1.1 g. of yellow needles which fluoresced blue, m.p. 69–70°. This material analyzed correctly as the ethyl ester of the desired product.

Method E.—A solution of the aldehyde and 1 equiv. of ethyl aminooxyacetate in about 25 times its weight of absolute ethanol was refluxed for 2 hr. The solvent was removed *in vacuo* and the residue was recrystallized.

Acknowledgments.—The author is indebted to Mrs. Janice Hall and Mr. William F. Boyd who ran the infrared spectra, and to Mr. Martin Gordon and Mr. Raymond Snider who performed the microanalyses. The author's appreciation is also extended to Mr. John Schaar who prepared the 2-phenylcyclopentanone.

(10) H. Gilman and G. F. Wright, *J. Am. Chem. Soc.*, **52**, 2550 (1930).

(11) G. J. Van Zoeren, U. S. Patent 2,520,516 (1950); *Chem. Abstr.*, **45**, 647*d* (1951).

Agents Affecting Lipid Metabolism. XII. N,N′-Disubstituted Cyclohexane-1,4-bis(methylamines)[1]

LESLIE G. HUMBER

Ayerst Research Laboratories, Montreal, Canada

Received June 5, 1964

The discovery of potent cholesterol biosynthesis inhibitory activity in compounds related to N,N′-dibenzylethylenediamine[2] has led to the synthesis of *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane, whose biological properties have already been described.[3] We wish to report here, the synthesis of this compound and of a variety of related symmetrical compounds which retain the cyclohexane-1,4-bis(methylamine) moiety. Tables I and II describe these compounds, and Tables III and IV describe intermediates used in their preparation.

Experimental[4]

Method A. N,N′-Di(2-chlorobenzylidine)cyclohexane-*trans*-1,4-bis(methylamine).—2-Chlorobenzaldehyde (28.4 g., 0.2 mole) and cyclohexane-*trans*-1,4-bis(methylamine) (14.2 g., 0.1 mole) were refluxed in benzene solution (300 ml.) until the theoretical volume of water had been collected in a Dean–Stark trap (*ca.* 3 hr.). The benzene was removed *in vacuo*, and the residue was crystallized from benzene. It had m.p. 150–154° (38.0 g.), λ_{max} 250 mμ (ε 31,300), $\nu_{max}^{CHCl_3}$ 1640 cm.$^{-1}$.

Anal. Calcd. for: $C_{22}H_{24}Cl_2N_2$: Cl, 18.31. Found: Cl, 17.92.

N,N′-Di(2-chlorobenzyl)cyclohexane-*trans*-1,4-bis(methylamine) (Table I, 4).—The above bis Schiff base (37.0 g.) was suspended in methanol (500 ml.) and sodium borohydride (7.5 g.) was added portionwise at a rate permitting gentle reflux. The mixture became homogeneous as the reduction proceeded. After refluxing for 16 hr., the methanol was removed *in vacuo* and the residue was distributed between chloroform and water. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to yield the product (35.5 g.) as a solid, m.p. 101–103° (ethanol). The dihydrochloride salt was prepared in methanol solution with methanolic hydrogen chloride. Crystallization yielded analytically pure material.

(1) For Part XI of this series see: D. Dvornik, M. Kraml, and J. F. Bagli, *J. Am. Chem. Soc.*, **86**, 2739 (1964).

(2) M. Kraml, L. G. Humber, J. Dubuc, and R. Gaudry, *J. Med. Chem.*, **7**, 500 (1964).

(3) (a) D. Dvornik, M. Kraml, J. Dubuc, and R. Gaudry, *J. Am. Chem. Soc.*, **85**, 3309 (1963); (b) C. Chappel, J. Dubuc, D. Dvornik, M. Givner, L. Humber, M. Kraml, K. Voith, and R. Gaudry, *Nature*, **201**, 497 (1964).

(4) Melting points were taken on a Thomas-Hoover apparatus and are corrected. Analyses were done by Mr. W. Turnbull and staff of our laboratories.