A mixed melting point of this acid (XX) with a sample of the acid prepared according to the directions of Adams, Miller, McGrew and Anderson[15] showed no depression.

2,7-Dimethoxynaphthalene (XXI) and 7-Methoxy-2-naphthol (XXII).—These compounds were prepared from 2,7-dihydroxynaphthalene according to the method of Fischer and Hammerschmidt.[24]

2-Hydroxy-7-methoxynaphthylglyoxylic Acid Lactone (XXIII).—This lactone was prepared from 7-methoxy-2-naphthol in the same manner as that 4-hydroxynaphthylglyoxylic acid monohydrate (I).

The orange precipitate which was obtained from the reaction was recrystallized from acetone and a 50.5% yield of the bright orange colored lactone, m.p. 199.6–200.6° (dec.) [lit. m.p. 184° (dec.) and color, brownish yellow[11]] was obtained.

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.53; neut. equiv., 228.2. Found: C, 68.23; H, 3.76; neut. equiv., 221.8.

2,7-Dimethoxynaphthylglyoxylic Acid (XIX).—2-Hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIII) was methylated in the usual manner with dimethyl sulfate.

A mixed melting point of this acid with the methylated acid prepared from 2,7-dihydroxynaphthylglyoxylic acid lactone (XVIII) showed no depression.

BETHLEHEM, PENNA.

RECEIVED JANUARY 15, 1951

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[24] O. Fischer and F. Hammerschmidt, *J. prakt. chem.*, [2] **94**, 24 (1916).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC.]

Mercurial Diuretics. IV. Methoxymercuration of Substituted Allylureas

BY R. L. ROWLAND, WENDELL L. PERRY AND SAMUEL GERSTEIN

A representative series of compounds of the general structure $R_1R_2NCONHCH_2CH(OCH_3)CH_2HgX$ has been prepared where R_1 and R_2 are alkyl, aryl, aralkyl or acyl and where X is chlorine, acetoxy or a carboxymethylmercapto group. Substitution in the propyl group has been studied by the preparation of $H_2NCONHCH_2C(CH_3)(OCH_3)CH_2HgCl$. The pharmacology of these compounds is discussed briefly.

The discovery that compounds of the structure $NH_2CONHCH_2CH(OR)CH_2HgX$ where R is an alkyl radical and X is halogen, succinimido, phthalimido, acetoxy, $-SCH_2COOH$, etc.,[1] are much more potent in the production of diuresis than the mercurial diuretics in current use has prompted investigation of compounds of related structure. Accordingly, a series of compounds of the structure $R_1R_2NCONHCH_2CH(OCH_3)CH_2HgX$ has been prepared by methoxymercuration of substituted allylureas. The acetoxymercurials formed by addition to the allyl group were converted to the chloromercurials by reaction with sodium chloride. The alkyl and aryl allylureas were synthesized by the reaction of an isocyanate with an amine. N-Allyl-N′-acetylurea and N-allyl-N′-benzoylurea were prepared both by the reaction of allylurea with acetic anhydride and with benzoyl chloride and by the reaction of allyl isocyanate with acetamide and with benzamide.

As an example of variation in the substituted propyl group of the mercurial, 3-chloromercuri-2-methoxy-2-methylpropylurea was prepared by the methoxymercuration of methallylurea.

Pharmacology.[2]—Solutions of the mercurials in dilute alkali were prepared for pharmacological evaluation. It was not possible to prepare solutions of compounds 10 and 14 of Table II.[3] N-3-Chloromercuri-2-methoxypropyl-N′-acetylurea was hydrolyzed in dilute alkaline solution to 3-chloromercuri-2-methoxypropylurea and the diuretic responses of this solution and of N-3-acetoxymercuri-2-methoxypropyl-N′-acetylurea were, accordingly, considered to be due to the hydrolysis products, 3-chloromercuri-2-methoxypropylurea and 3-acetoxymercuri- or 3-hydroxymercuri-2-methoxypropylurea, respectively. The constitution of the latter hydrolysis product was not determined but would depend upon the rate of hydrolysis of the 3-acetoxymercuri radical to the 3-hydroxymercuri radical.

Of the series, $R_1R_2NCONHCH_2CH(OCH_3)CH_2HgX$, only compounds 1 and 12 exhibited the same order of toxicity as those mercurials used clinically, *e.g.*, mercuhydrin, when the toxicity was determined as the LD_{50} at 14 days in rats; the remaining mercurials were 1.4 to 3.7 times as toxic. The degree of diuresis produced in dogs by a dosage of 0.006 millimole/kg. was, with only five exceptions, of the same order as or less than that produced by mercuhydrin. Each of the more potent diuretics, compounds 1, 2, 11, 12 and 18, effected diuresis which was three to five times that produced by the diuretics in current usage. As mentioned previously, the diuresis produced by 11 or 12 was considered to be that resulting from the hydrolysis products. Accordingly, only compounds 1 and 2, where substitution is the small methyl or ethyl radical, and compound 18 where the substituent contains another functional group, were more potent diuretics *per se*.

3-Chloromercuri-2-methoxy-2-methylpropylurea was found to be 8.5 times as toxic as mercuhydrin. Although this mercurial produced a pronounced diuresis at a dosage of 0.006 millimole/kg. in dogs, the diuretic response at 0.0015 millimole/kg. was negligible.

Experimental[4]

Substituted Allylureas.—N-Allyl-N′-phenylurea was prepared by the previously reported method from phenyl isocyanate and allylamine.[5] N-Allyl-N′-α-naphthylurea and N-allyl-N′-ethylurea were synthesized by the reaction of

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[1] R. L. Rowland, W. L. Perry, E. L. Foreman and H. L. Friedman, THIS JOURNAL, **72**, 3595 (1950).

[2] We are indebted to Mr. P. A. Nuhfer of these laboratories for the pharmacological evaluation of these mercurials.

[3] The insoluble material which was collected after attempting to prepare a solution of compound 14 in dilute aqueous alkali differed from the N-(3-chloromercuri-2-methoxypropyl)-N′-benzoylurea. Analysis of the alkali-treated material indicated the removal of a molecule of hydrochloric acid, producing a polymer of the formula $H[N(COC_6H_5)CONHCH_2CH(OCH_3)CH_2Hg]_nCl$.

[4] All melting points over 70° are corrected.

[5] F. B. Dains, THIS JOURNAL, **21**, 136 (1899).

TABLE I

ALLYL NHCONR$_1$R$_2$

NR$_1$R$_2$	Formula	Yield, %	M.p., °C.	Recryst. solv.	Nitrogen, % Calcd.	Found
NHCH$_3$[a]	$C_5H_{10}N_2O$	20	48–49	Et$_2$O	24.54	24.32
NHC$_2$H$_5$[a]	$C_6H_{12}N_2O$	20	79–80	i-Pr$_2$O	21.86	21.35
NHn-C$_3$H$_7$	$C_7H_{14}N_2O$	25	94–95	Et$_2$O	19.70	19.44
NHn-C$_4$H$_9$	$C_8H_{16}N_2O$	40	62–64	Pet. ether[e]	17.93	17.64
NHn-C$_6$H$_{13}$	$C_{10}H_{20}N_2O$	30	50–52	Pet. ether[e]	15.20	14.97
NHCH(CH$_2$)$_5$	$C_{10}H_{18}N_2O$	65	90–91	i-Pr$_2$O	15.37	15.34
NHCH$_2$C$_6$H$_5$	$C_{11}H_{14}N_2O$	50	90–91	i-Pr$_2$O	14.72	14.92
NHα-C$_{10}$H$_7$	$C_{14}H_{14}N_2O$	55	203–204	EtOH	12.38	12.60
NHCOCH$_3$[b]	$C_6H_{10}N_2O_2$	30	113–114	i-Pr$_2$O	19.71	20.05
NHCOCH$_3$[c]	$C_6H_{10}N_2O_2$	20	112–113	Dioxane	19.71	19.66
NHCOC$_6$H$_5$[b]	$C_{11}H_{12}N_2O_2$	50	130–131	EtOH–H$_2$O	13.72	13.77
NHCOC$_6$H$_5$[c]	$C_{11}H_{12}N_2O_2$	10	130–131	EtOH–H$_2$O	13.72	13.75
N(C$_2$H$_5$)$_2$	$C_8H_{16}N_2O$	65	109–110[d]	n^{20}D 1.4740	17.93	18.04
N(C$_4$H$_9$)$_2$	$C_{12}H_{24}N_2O$	30	114–118[d]	n^{20}D 1.4692	13.19	13.03
N(CH$_2$)$_5$	$C_9H_{16}N_2O$	70	88–89	i-Pr$_2$O	16.65	16.61
N(CH$_2$CH$_2$)$_2$O	$C_8H_{14}N_2O_2$	75	131–132	i-Pr$_2$O	16.46	16.65

[a] A. Cahours and A. W. Hofmann, *Ann.*, **102**, 285 (1857), reported the preparation of N-allyl-N′-methylurea and N-allyl-N′-ethylurea. The only characteristics reported were the analyses of N-allyl-N′-ethylurea. [b] By reaction of allylurea with the anhydride or acid chloride. [c] By reaction of allyl isocyanate and amide. [d] Boiling point at 1 mm. [e] Skellysolve B.

TABLE II

R$_1$R$_2$NCONHCH$_2$CH(OCH$_3$)CH$_2$HgX

No.	R$_1$R$_2$N	X	Formula	Yield, %	M.p., °C.	Recryst. solvent	Mercury, % Calcd.	Found	Nitrogen, % Calcd.	Found
1	CH$_3$NH	Cl	$C_6H_{13}N_2O_2HgCl$	25	176–177	EtOH	52.62	52.61	7.35	7.13
2	C$_2$H$_5$NH	Cl	$C_7H_{15}N_2O_2HgCl$	30	140–141	i-PrOH	50.75	50.75	7.09	6.76
3	n-C$_3$H$_7$NH	Cl	$C_8H_{17}N_2O_2HgCl$	50	119–120	i-PrOH	49.01	48.78	6.84	7.22
4	n-C$_4$H$_9$NH	Cl	$C_9H_{19}N_2O_2HgCl$	30	134–135	EtOH	47.39	47.06	6.62	6.76
5	n-C$_6$H$_{13}$NH	Cl	$C_{11}H_{23}N_2O_2HgCl$	65	112–115	C$_6$H$_6$	44.44	44.17	6.21	6.55
6	(CH$_2$)$_5$CHNH	Cl	$C_{11}H_{21}N_2O_2HgCl$	75	169–170	EtOH	44.64	44.44	6.23	5.98
7	C$_6$H$_5$CH$_2$NH	Cl	$C_{12}H_{17}N_2O_2HgCl$	65	151–152.5	EtOH	43.86	43.64	6.12	6.27
8	C$_6$H$_5$NH	OCOCH$_3$	$C_{13}H_{18}N_2O_4Hg$	40	128–130	C$_6$H$_6$	42.97	42.62	6.00	6.32
9	C$_6$H$_5$NH	Cl	$C_{11}H_{15}N_2O_2HgCl$	30	147–148	C$_6$H$_6$	45.25	44.80	6.32	6.41
10	α-C$_{10}$H$_7$NH	Cl	$C_{15}H_{17}N_2O_2HgCl$	40	192–192.5	i-PrOH	40.66	41.15	5.68	5.76
11	CH$_3$CONH	OCOCH$_3$	$C_9H_{16}N_2O_5Hg$	70	118–120	C$_6$H$_6$	46.35	46.36	6.47	6.65
12	CH$_3$CONH	Cl	$C_7H_{13}N_2O_3HgCl$	70	186–187	EtOH	49.02	48.64	6.85	6.94
13	C$_6$H$_5$CONH	OCOCH$_3$	$C_{14}H_{18}N_2O_5Hg$	80	128–129	C$_6$H$_6$	40.53	40.25	5.66	5.78
14	C$_6$H$_5$CONH	Cl	$C_{12}H_{15}N_2O_3HgCl$	70	154–155	EtOH	42.56	42.82	5.94	5.94
15	C$_6$H$_5$CONH	SCH$_2$COOH	$C_{14}H_{18}N_2O_5HgS$	80	101–102		38.07	37.80	5.32	5.53
16	(C$_4$H$_9$)$_2$N	Cl	$C_{13}H_{27}N_2O_2HgCl$	35	67–68	Pet. ether[a]	41.84	41.34	5.84	5.94
17	(CH$_2$)$_5$N	Cl	$C_{10}H_{19}N_2O_2HgCl$	55	118–119	i-Pr$_2$O	46.08	45.85	6.44	6.47
18	O(CH$_2$CH$_2$)$_2$N	Cl	$C_9H_{17}N_2O_3HgCl$	40	111.5–112	EtOH	45.87	45.83	6.41	6.58

[a] Skellysolve B.

allylamine with the requisite isocyanate while the remainder of the N-allyl-N′-alkylureas and N-allyl-N′,N′-dialkylureas were obtained from the reaction of allyl isocyanate with the corresponding amines.

N-Allyl-N′-acetylurea (a) From Acetic Anhydride and Allylurea.—A mixture of 50 g. (0.50 mole) of allylurea and 51 g. (0.50 mole) of acetic anhydride was heated for three hours in an oil-bath maintained at 85°. After the mixture stood at room temperature for 20 hours, the precipitate was collected and crystallized from isopropyl ether.

(b) From **Acetamide and Allyl Isocyanate.**[6]—A mixture of 3.5 g. (0.06 mole) of acetamide, 5.0 g. (0.06 mole) of allyl isocyanate and 25 ml. of anhydrous toluene was heated under reflux for 24 hours. The solid which separated on cooling was crystallized from dioxane.

N-Allyl-N′-benzoylurea (a) From Allylurea and Benzoyl Chloride.—A mixture of 20 g. (0.20 mole) of allylurea, 14 g. (0.10 mole) of benzoyl chloride and 100 cc. of anhydrous toluene was heated for 24 hours in an oil-bath maintained at 90°. After the mixture was cooled, the product was collected by filtration.

(b) From **Benzamide and Allyl Isocyanate.**—The procedure was identical with that described above for the preparation of N-allyl-N′-acetylurea. The N-allyl-N′-substituted ureas are listed in Table I.

Methallylurea.—An aqueous solution of methallylamine[7] neutralized with sulfuric acid was allowed to react with sodium cyanate. The product after crystallization from ethyl acetate was isolated in 55% yield and melted at 119–120°.

Anal. Calcd. for $C_5H_{10}N_2O$: N, 24.54. Found: N, 24.37.

Addition of Mercuric Acetate and Methyl Alcohol to Substituted Ureas.—The addition is illustrated by the reaction of N-allyl-N′-acetylurea with mercuric acetate in methyl alcohol. To a refluxing solution of 10 g. (0.07 mole) of the substituted urea in 100 ml. of methyl alcohol was added a hot solution of 22 g. (0.07 mole) of mercuric acetate and 4.2 g. of glacial acetic acid in 240 ml. of methyl alcohol. The mixture was heated under reflux for two hours. To one-half of the reaction mixture was added an aqueous solution of 2 g. of sodium chloride. The precipitated chloromercurial was crystallized from ethyl alcohol or acetone.

The second half of the addition reaction mixture was concentrated to dryness at room temperature. The residue,

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[6] P. F. Wiley, THIS JOURNAL, **71**, 1310 (1949).

[7] The authors gratefully acknowledge the generous gift of methallylamine from the Shell Development Company, Emeryville, California.

presumed to be the acetoxymercurial, was crystallized from benzene.

In those preparations in which addition of sodium chloride to the reaction mixture did not result in formation of a precipitate, the solutions were concentrated to dryness at room temperature. These residues were then crystallized from suitable solvents as indicated in Table II which lists the mercurials prepared from substituted allylureas.

The N-(3-carboxymethylmercaptomercuri-2-methoxypropyl)-N′-benzoyl urea was prepared by reaction of the chloromercuri compound with thioglycolic acid in the presence of alkali as reported previously for similar compounds.[1]

Methoxymercuration of Methallylurea.—Methallylurea was mercurated similarly and the chloromercurial was prepared by addition of sodium chloride. The product after washing with water was crystallized from ethyl alcohol. The crystallized product, obtained in 55% yield, melted at 172.5–173°.

Anal. Calcd. for $C_6H_{13}N_2O_2HgCl$: Hg, 52.62; N, 7.35. Found: Hg, 52.24; N, 7.39.

Reaction of N-(3-Chloromercuri-2-methoxypropyl)-N′-benzoylurea with Dilute Alkali.—A mixture of 3.3 g. (0.007 mole) of N-(3-chloromercuri-2-methoxypropyl)-N′-benzoylurea, 30 ml. of water and 3 ml. of 10% sodium hydroxide was allowed to stand at room temperature with occasional agitation for one week. The solid was collected and washed by suspension in 50 ml. of 1% sodium hydroxide solution. The insoluble material weighed 2.9 g. (90%) and decomposed at 205–207°.

Anal. Calcd. for $(C_{12}H_{14}N_2O_3Hg)_{15}HCl$: Hg, 45.87; Cl, 0.57. Found: Hg, 45.57; Cl, 0.43.

Hydrolysis of N-(3-Chloromercuri-2-methoxypropyl)-N′-acetylurea.—A mixture of 1.0 g. (0.0024 mole) of N-(3-chloromercuri-2-methoxypropyl)-N′-acetylurea, 2.0 g. (0.005 mole) of 10% sodium hydroxide and 17 ml. of water was allowed to stand one week. To the solution was added 3.0 ml. of glacial acetic acid and after 20 hours the precipitate was collected. The product weighed 0.33 g. (35%) and melted at 152–153°. Mixed melting points with 3-chloromercuri-2-methoxypropylurea and with N-(3-chloromercuri-2-methoxypropyl)-N′-acetylurea were 152–153° and 142–152°, respectively.

MILWAUKEE, WIS. RECEIVED FEBRUARY 9, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH, AND MELLON INSTITUTE]

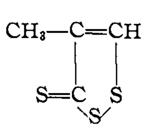
Some New Alkyl 1,2-Dithia-4-cyclopentene-3-thiones[1a]

BY RODERICK S. SPINDT,[1b] DONALD R. STEVENS[1b] AND W. E. BALDWIN[1c]

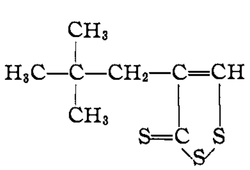
Isobutylene and diisobutylene were sulfurized with elemental sulfur to give orange crystalline compounds, $C_4H_4S_3$ and $C_8H_{12}S_3$. There were two isomers of the latter. The structures of these were determined by physical and chemical approaches. Most significant were the results obtained on alkaline hydrolysis, which gave characteristic degradation products. It was concluded that the compounds are derivatives of 1,2-dithia-4-cyclopentene-3-thione.

During a study of the reaction of sulfur with diisobutylene (a mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene) an orange-colored crystalline material was isolated, from which there were obtained by fractional crystallization two isomeric compounds, each having the empirical formula $C_8H_{12}S_3$. The reaction of sulfur with isobutylene produced another orange-colored crystalline compound possessing the empirical formula $C_4H_4S_3$.

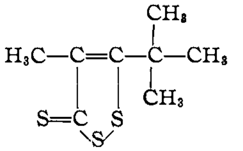
Evidence is presented in this paper to support the following structures for these compounds[2]



I



II



III

PHYSICAL PROPERTIES

	I	II	III
M.p., °C.	40.5–41.5	86.5–87.3	80.5–81.3
B.p., °C. (mm.)	110–112 (1.7)	159 (1.7)	175 (5)
d^{20}_4	1.466 ± 0.015	1.177 ± 0.018	1.359 ± 0.014

The compounds are soluble in the common organic solvents, particularly chloroform, ether and carbon disulfide, but are almost insoluble in water. They are quite soluble in concentrated inorganic acids, from which they can be recovered by dilution with water.

All three show some of the characteristics of many other organic sulfur compounds, forming methiodides with methyl iodide and yielding addition products with mercuric chloride. They are readily oxidized or reduced. They do not give a positive test for the sulfhydryl group.

Lüttringhaus, Konig and Böttcher[3] reported the preparation and characterization of a similar group of compounds obtained by treating sulfur with a number of aromatic-substituted olefins, such as 1-phenyl-1-propene, 1-phenyl-2-propene, 2-phenylpropene, etc. They gave evidence for the same ring system reported here, and described the preparation of the parent compound, $C_3H_2S_3$, by reaction of sulfur with propylene.

Other workers in this field who produced sulfur compounds of the same type are Gaudin and Pottier,[4] working with anethole; Lozac'h,[5] with

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[1] (a) Part of a thesis submitted to the Graduate School of the University of Pittsburgh by R. S. Spindt in partial fulfillment of the requirements for the degree of Doctor of Philosophy; (b) Gulf Research & Development Company's Multiple Fellowship at Mellon Institute; (c) University of Pittsburgh.

[2] Compound I was first produced by Donald R. Stevens and Arthur C. Whitaker, and II and III were first produced by Donald R. Stevens and William C. Starnes at Gulf Research & Development Co. Laboratories, Harmarville, Pa.

[3] B. Böttcher and A. Lüttringhaus, *Ann.*, **557**, 89 (1947); A. Lüttringhaus, H. B. Konig and B. Böttcher, *ibid.*, **560**, 201 (1947).

[4] O. Gaudin and R. Pottier, *Compt. rend.*, **224**, 479 (1947).

[5] N. Lozac'h, *Bull. soc. chim. France*, 840 (1949).