1,4-Thiapyrone Hydrochloride (VIII).—This compound, as prepared by the addition of dry hydrogen chloride to the thiapyrone in dry benzene, melted at 125–135°. Arndt and Bekir[7a] reported that the salt melted indefinitely around 135°, and gave no analysis. Sublimation of our sample at 80° (1 mm.) did not improve the m.p., but the analysis was reasonably satisfactory.

Anal. Calcd. for C_6H_5ClOS: C, 40.40; H, 3.39. Found: C, 40.85; H, 3.52.

3-Carboxamido-1,4-thiapyrone (VII).—The 3-carbomethoxy compound V (0.30 g.) was shaken with 3 ml. of concentrated aqueous ammonia. Precipitation of the amide occurred practically simultaneously with the disappearance of the ester. A white solid (0.22 g.) was obtained, m.p. 195.5–197°. Recrystallization from 95% ethanol–ethyl acetate yielded 0.20 g., m.p. 198–198.5°. Further recrystallization did not change the melting point.

Anal. Calcd. for $C_6H_5NO_2S$: C, 46.44; H, 3.25. Found: C, 46.59; H, 3.29.

3-Nitroso-3-carbomethoxytetrahydro-1,4-thiapyrone (XIII).—A solution of 1.38 g. of sodium nitrite in 3 ml. of cold water was added dropwise with swirling to a solution of 3.0 g. of the tetrahydro ester XI in 5 ml. of acetic acid in an ice-bath. An immediate dark blue color developed. Toward the end of the addition an oily solid separated and the color of the solution changed to pale orange. After an additional hr. in the ice-bath, the mixture was filtered and washed with water, yielding 1.60 g. of a white solid, m.p. 96.5–97.5° dec. The solid was insoluble in organic solvents in the cold, but dissolved in warm solvents with the development of a transient, pale blue color. No solid could be recovered on cooling. The nitroso compound became oily and discolored on standing for several weeks, and an odor was apparent resembling that of the starting material XI.

The preparation was repeated, and the solid, after washing copiously with water and 95% ethanol, was dried *in vacuo* over phosphorus pentoxide.

Anal. Calcd. for $C_7H_9NO_4S$: C, 41.37; H, 4.47. Found: C, 41.51; H, 4.63.

Various attempts to hydrolyze the nitroso compound with mineral acid yielded no tractable product. However, it slowly dissolved in cold 10% sodium hydroxide to give a pale amber solution. The cooled solution was acidified with concentrated hydrochloric acid, extracted with ether and the dried ether extracts (anhydrous sodium sulfate), were evaporated, leaving an amber oil which solidified on scratching to yield 1.16 g. from 1.71 g. of XIII of a discolored solid, m.p. 118–126° dec. Several recrystallizations from ethyl acetate–benzene (decolorized with Nuchar) raised the melting point to 128–128.5° dec. The analysis was not in accord with that of the expected β-carbomethoxy-β-oximino-β′-carboxydiethyl sulfide but could be accounted for as that of a mixture of the monoester and the dicarboxylic acid. This is not unreasonable in view of the ease of hydrolysis of pyruvic esters.

Anal. Calcd. for $C_7H_{11}O_5NS$: C, 37.99; H, 5.01. Calcd. for $C_6H_9O_5NS$: C, 34.77; H, 4.38. Found: C, 35.50; H, 4.60.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Mercurial Diuretics[1]

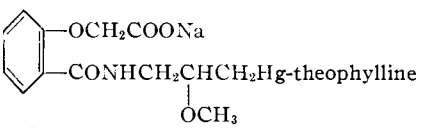
BY L. H. WERNER AND C. R. SCHOLZ

RECEIVED OCTOBER 17, 1953

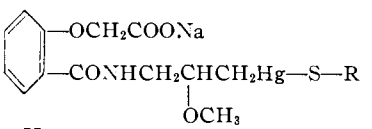
Various mercaptans were combined with 3-hydroxymercuri-2-hydroxypropylcarbamylnicotinic acid sodium salt. A number of mercurated compounds of different structures were prepared and combined with 1-thiosorbitol. The substances were tested for diuretic effect and toxicity.

Organic mercurial diuretics of the type now in general use were introduced in 1924 (Salyrgan) and have since established their place in medicine. More recently, the investigations of Farah[2] and Lehman[3] have shown that replacement of the theophylline moiety of the mercurial diuretic I by a suitable substituted thiol as in II reduces the cardiac toxicity and also the irritation at the site of injection without loss of diuretic potency.

The first part of this investigation was concerned with the structural requirements of the thiol for maximal detoxification. Various thiols were combined with 3-hydroxymercuri-2-hydroxypropyl carbamyl nicotinic acid sodium salt[4] (Table I) and tested for toxicity by our Division of Macrobiology.[5] The compounds were prepared by dissolving the mercurated acid in water containing one equivalent of sodium hydroxide and adding a concentrated aqueous or alcoholic solution of the



I



II

thiol. The mercaptomercuri compound was precipitated by the addition of acetone, filtered off and dried. Further purification was difficult as the compounds were only soluble in water and showed no tendency to crystallize. The amorphous compounds, especially the mercaptomercuri derivatives containing thiosorbitol, were in general hygroscopic and retained solvent very tenaciously. This led in some cases (Tables I–IV) to poor agreement of the analytical with the calculated values. Reprecipitation of the mercaptomercuri compounds had little effect or led to decomposition, as did also attempts to remove retained solvent by vigorous drying *in vacuo*. The analytical values of the intermediate acetoxymercuri and hydroxymercuri compounds are given as an indication of their purity.

(1) Presented before the XIIth International Congress of Pure and Applied Chemistry, Section of Medicinal Chemistry, Sept. 10–13, 1951, New York, N. Y.

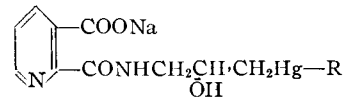
(2) W. K. Long and A. Farah, *Science*, **104**, 220 (1946); *J. Pharm. Exptl. Therap.*, **88**, 388 (1946).

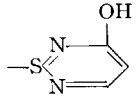
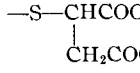
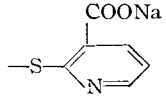
(3) R. A. Lehman, *Proc. Soc. Expti. Biol. and Med.*, **64**, 428 (1947).

(4) M. Hartmann and L. Panizzon, U. S. Patent 2,136,501; 2,136,503, Nov. 15, 1938.

(5) A. J. Plummer, W. Reitze and F. F. Yonkman, *Federation Proc.*, **11**, Part I, 383 (1952).

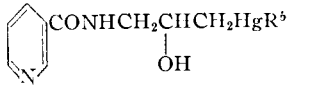
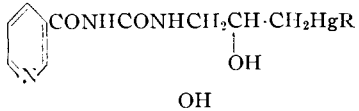
TABLE I



No.	R	M.p. dec., °C.	Empirical formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Mercury, % Calcd.	Mercury, % Found
1	$-SC_2H_5$	100–150	$C_{12}H_{15}HgN_2NaO_4S$	5.5	5.4	6.3	6.2	39.6	39.0
2	$-SCH_2C_6H_5$	105–160	$C_{17}H_{17}HgN_2NaO_4S$	4.9	5.0	5.6	5.8	35.3	35.4
3	$-S-C_6H_4-o-CH_3$	115–160	$C_{17}H_{17}HgN_2NaO_4S$	4.9	5.2	5.6	5.7	35.3	35.3
4		112–155	$C_{14}H_{13}HgN_4NaO_5S\cdot H_2O$	9.5	9.1	5.4	5.0	34.0	33.7
5	$-SCH_2COONa$[a]	110	$C_{12}H_{12}HgN_2Na_2O_6S\cdot H_2O$	4.9	4.5	5.5	5.7	34.8	34.2
6		105–115	$C_{14}H_{13}HgN_2Na_3O_8S$	4.4	4.3	5.0	5.4	31.4	30.6
7	$-S-C_6H_4-o-COONa$	130–215	$C_{17}H_{14}HgN_2Na_2O_6S$	4.5	4.4	5.2	5.1	32.3	32.6
8	 [b]	138–172	$C_{16}H_{14}HgN_2Na_2O_6S\cdot(2H_2O)$	6.4	6.0	4.9	4.7	30.5	30.0
9	$-SCH_2CH_2OH$	85–90	$C_{12}H_{15}HgN_2NaO_5S$	5.1	5.4	5.9	6.0	36.7	36.3
10	$-SCH_2CHOHCH_2OH$	74–78	$C_{13}H_{17}HgN_2NaO_6S$	5.1	4.8	5.8	5.9	36.3	35.6
11	$-SCH_2(CHOH)_3CH_2OH$[c] (D-xylo)	90–100	$C_{15}H_{21}HgN_2NaO_8S$	4.6	4.4			32.7	31.4
12	$-SCH_2(CHOH)_4CH_2OH$[c] (D-gluco)	79	$C_{16}H_{23}HgN_2NaO_9S + CH_3COCH_3$	4.0	3.9	4.6	4.8	28.6	28.3
13	$-SCH_2(CHOH)_4CH_2OH$[c] (D-manno)	64	$C_{16}H_{23}HgN_2NaO_9S + CH_3COCH_3$	4.0	4.1			28.6	28.8

[a] Prepared by Dr. A. Shabica and co-workers. [b] Reference 12. [c] Reference 13.

TABLE II

No.	Mercurial	R[a]	M.p. dec. °C.	Empirical formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Mercury, % Calcd.	Mercury, % Found
14		OAc	163	$C_{11}H_{14}HgN_2O_4$	6.4	6.3			45.7	45.5
		TS	111–120	$C_{15}H_{24}HgN_2O_7S$	4.9	4.9			34.8	33.7
15		OAc	145–155	$C_{12}H_{15}HgN_3O_5$	8.7	8.6			41.6	41.4
		TS	63–70	$C_{16}H_{25}HgN_3O_8S$	6.8	6.7			32.4	32.5
16	$C_2H_5OCONHCH_2CHCH_2Hg-R$[c]	OAc	80-87	$C_8H_{15}HgNO_5$	3.4	3.3			49.4	49.7
		TS	84	$C_{12}H_{25}HgNO_8S$	2.6	2.6	5.9	6.3	36.9	36.6

17	$C_2H_5CONHCONHCH_2CHCH_2Hg—R^d$ (OH)	OH	71–78	$C_7H_{14}HgN_2O_5$	6.8	6.8		49.3	49.3
		TS	126–130	$C_{13}H_{26}HgN_2O_9S$	4.8	4.9		34.2	34.3
18	$CO—NCH_2CHCH_2Hg—R^e$ (OH)	OH	190–220	$C_7H_{10}HgN_2O_5$	7.0	7.2		49.8	50.4
	$CO—NCH_2CHCH_2Hg—R^e$ (TS)	TS	50–56	$C_{13}H_{21}HgN_2NaO_9S$	4.6	4.5	5.3	33.2	33.2
19	$NH_2CONHCH_2CHCH_2Hg—R^f$ (OAc)	OAc	120–121	$C_7H_{14}HgN_2O_4$	7.2	7.2		51.3	50.8
	$NH_2CONHCH_2CHCH_2Hg—R^f$ (TS)	TS	Foam	$C_{11}H_{24}HgN_2O_7S + CH_3COCH_3$			5.5	34.2	33.6
20	$NH_2CONHCH_2CHCH_2HgR$ (OAc)	OAc	155	$C_8H_{15}HgN_3O_5$	9.7	9.8		46.2	45.2
	$NH_2CONHCH_2CHCH_2HgR$ (TS)	TS	55	$C_{12}H_{23}HgN_3O_8S + CH_3COCH_3$	6.7	6.1	5.1	31.8	32.9
21	$NCH_2CONHCH_2CHCH_2HgR^g$ (OH)	OH	135	$C_{10}H_{20}HgN_2O_3 \cdot {}^1/_2H_2SO_4$	6.0	5.7		43.0	43.1
	$NCH_2CONHCH_2CHCH_2HgR^g$ (TS)	TS	60	$C_{16}H_{32}HgN_2O_7S \cdot {}^1/_2H_2SO_4 + CH_3COCH_3$	4.0	3.8	6.8	7.5	28.5	28.1

[a] TS = 1-thiosorbitol, OAc = $OOCCH_3$. [b] M. Hartmann and L. Panizzon, U. S. Patents 2,136,501, 2,136,503, November 15, 1938. [c] K. Miescher and K. Hoffmann, U. S. Patent 2,156,598, May 2, 1939. [d] The intermediate acetoxymercuri compound was treated with 2 *N* NaOH in methanol solution which precipitated the hydroxymercuri derivative. [e] The acidic nature of the parabanic acid moiety leads to an inner salt which was formulated as the hydroxymercuri compound. [f] Reference 7. [g] Based on the analytical results this compound was written as the hydroxymercuri derivative.

These figures are also given for the intermediate compounds 19, 22, 23, 24, 25 and 30, although they are not new (Tables I–IV).

The lower figure of the melting point or decomposition range refers to the temperature at which the compound softened, and the higher figure, to the temperature at which decomposition had taken place and a brown or black melt was obtained.

Animal studies indicated that the polyhydroxyalkylthiols were highly effective in reducing the toxicity; of these, 1-thiosorbitol appeared most promising.

Having established the detoxifying action of 1-thiosorbitol, the effect on toxicity of variation of the mercurated moiety of the compound was investigated. The mercurial diuretics in common use today are characterized by structure III, being mercurated monoallyl amides of dicarboxylic acids.

$$NaO_2C—R—CONHCH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_2Hg—R^1$$

III, R^1 = theophylline or thioglycolic acid
R = divalent radical

Recently a number of mercurial diuretics have been reported which do not conform to this structure, such as Mercumatilin[6] (IV), in which the mercurated side chain is attached to the rest of the molecule by a carbon-to-carbon bond, and the compounds prepared by Rowland, *et al.*,[7] by mercuration of 1-allylurea and substituted 1-allylureas (V).

R′ and R″ = H, alkyl, aralkyl, aryl, acyl
X = acetoxy, Cl

The second series of mercurated compounds prepared in this work contained the characteristic R—$CONHCH_2CHOR^2CH_2Hg—R^1$ (R^2 = H, CH_3) structure but lacked the carboxyl group (Table II). The compounds of the third series (Table III) all have a carboxyl group and in most instances the mercury is attached to the rest of the molecule through an allyl amide radical. On the other hand, the compounds of the fourth series (Table IV) do not contain the carboxyl moiety, but rely on a polyhydroxyalkyl chain to solubilize the compound. With the exception of compounds no. 31-33, which are thiophene derivatives, they contain the typical mercurated alkyl amide grouping.

All of the compounds were mercurated with mercuric acetate. In the case of the olefins, addition to the double bond took place.

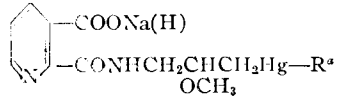
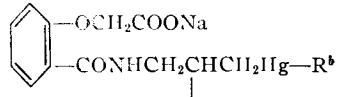
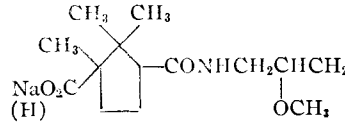
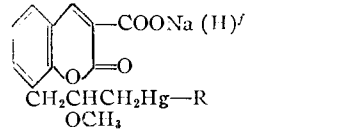
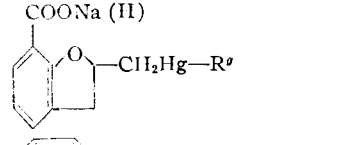
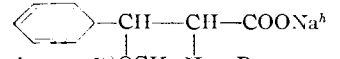
$$R—CH=CH_2 + Hg(OOCCH_3)_2 + R'OH \longrightarrow RCH(OR')—CH_2HgOOCCH_3 + CH_3COOH$$

R′ = alkyl, H

(6) H. Blumberg, A. Schlesinger and S. M. Gordon, *J. Pharm. Exptl. Therap.*, **105**, 336 (1952).

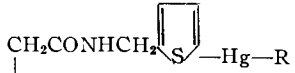
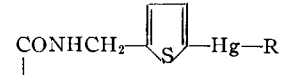
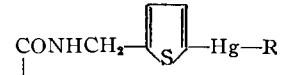
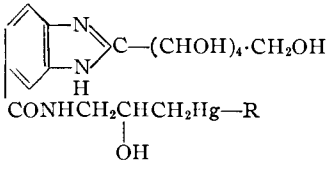
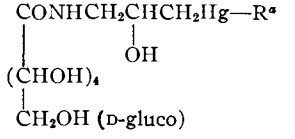
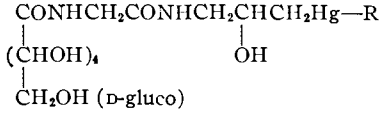
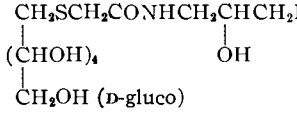
(7) R. L. Rowland, W. L. Perry, E. L. Foreman and H. L. Friedman, THIS JOURNAL, **72**, 3595 (1950); R. L. Rowland, W. L. Perry and S. Gerstein, *ibid.*, **73**, 3691 (1951).

TABLE III

No.	Mercurial	R	M.p. dec., °C.	Empirical formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Mercury, % Calcd.	Mercury, % Found
22	 —COONa(H) —CONHCH$_2$CHCH$_2$Hg—R[a] OCH$_3$	OH	185–190	$C_{11}H_{14}HgN_2O_5$	6.2	6.1			44.1	44.0
		TS	70–80	$C_{17}H_{25}HgN_2NaO_9S$ + CH_3COCH_3	3.9	4.0			28.0	27.2
23	 —OCH$_2$COONa —CONHCH$_2$CHCH$_2$Hg—R[b] OCH$_3$	—	195	$C_{13}H_{15}HgNO_5$					43.1	42.8
	(forms inner salt)	TS	65	$C_{19}H_{28}HgNNaO_{10}S$ + CH_3COCH_3					27.0	26.5
24	 —CONHCH$_2$CHCH$_2$Hg—R[c] OCH$_3$	OH	175	$C_{14}H_{25}HgNO_5$					41.1	41.4
	(H)	TS	58	$C_{20}H_{36}HgNNaO_9S$ + CH_3COCH_3					26.8	26.7
25	(H)NaOOCCH$_2$CH$_2$CONHCO[d]	OH	180–185	$C_9H_{16}HgN_2O_6$	6.2	6.6			44.7	44.6
	R—HgCH$_2$CHCH$_2$NH OCH$_3$	TS	90–95	$C_{15}H_{27}HgN_2NaO_{10}S$	4.3	3.8	4.9	5.7	30.8	28.0
26	CONHCH$_2$CHCH$_2$Hg—R[e] (CHOH)$_4$ OH	OH	175	$C_9H_{17}HgNO_9$	2.9	3.2			41.5	42.9
				$C_9H_{15}HgNO_8$ (lactone)	3.0				43.1	
	COONa (H) (D-galacto)	TS	150	$C_{15}H_{28}HgNNaO_{13}S$ Freeze dried	2.0	1.9	4.7	5.3	29.2	27.8
27	CONHCH$_2$CHCH$_2$Hg—R (CHOH)$_2$ OH	OH	202	$C_7H_{13}HgNO_7$	3.3	3.4			47.3	48.1
	COONa (H)	TS	Foam	$C_{13}H_{24}HgNNaO_{11}S$	2.2	2.0	5.1	5.2	32.0	29.1
28	 —COONa (H)[f] CH$_2$CHCH$_2$Hg—R OCH$_3$	OH	197	$C_{14}H_{14}HgO_6$					41.9	42.6
		TS	69	$C_{20}H_{25}HgNaO_{10}S$			4.7	4.7	29.4	29.4
29	 COONa (H) —CH$_2$Hg—R[g]	OH	210–215	$C_{10}H_{10}HgO_4$					50.8	50.6
		TS	Foam Freeze-dried	$C_{16}H_{21}HgNaO_8S$			5.4	5.6	33.6	30.4
30	 —CH—CH—COONa[h]	—	180–185	$C_{10}H_{10}HgO_3$					53.0	52.5
	(forms inner salt) OCH$_3$ Hg—R	TS	90–100	$C_{16}H_{23}HgNaO_8S$			5.4	5.8	33.5	31.5

[a] Reference 4. Mercuration, however, carried out in methanol, followed by treatment with dil. sodium hydroxide. [b] Bios report, 766, page 132 (British Intelligence Objectives Sub-committee). [c] N. M. Molnar, U. S. Patent 2,117,901, May 17, 1938. [d] E. Geiger, L. Vargha and L. Richter, U. S. Patent 2,208,941, July 23, 1940. [e] D. L. Tabern, U. S. Patent 2,163,296, June 20, 1939; 2,084,626, June 22, 1937. [f] Buu-Hoi, R. Royer, J. J. Jouin, J. Lecocq and D. Guettier, *Bull. soc. chim. Fr.*, 128 (1947). [g] L. Claisen, *Ber.*, 45, 3157 (1912), see also L. E. Mills and R. Adams, THIS JOURNAL, 45, 1842 (1923). [h] W. Schrauth, W. Schoeller and R. Struensee, *Ber.*, 43, 695 (1910), and 44, 1048 (1911).

TABLE IV

No.	Mercurial	R	M.p. dec., °C.	Empirical formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Mercury, % Calcd.	Mercury, % Found
31		—	200–230	$C_9H_9HgNO_3S$	3.4	3.4			48.7	48.4
		TS	Foam	$C_{15}H_{22}HgNNaO_8S_2$ Freeze dried	2.2	2.1	10.1	9.7	31.7	30.0
32		OH	204	$C_{11}H_{15}HgNO_8S$	2.7	2.7			38.4	38.8
		TS	130	$C_{17}H_{26}HgNNaO_{12}S_2$	1.9	1.6	8.9	8.4	27.7	27.3
33		OAc	172–174	$C_{13}H_{19}HgNO_8S$	2.6	2.6			36.5	35.7
		TS	98–105	$C_{17}H_{29}HgNO_{11}S_2$					29.1	27.3
34		OAc	150	$C_{18}H_{25}HgN_3O_9$	6.7	6.7			31.9	31.8
		TS	115–118	$C_{22}H_{35}HgN_3O_{12}S$ Freeze dried	5.5	5.0	4.2	4.8	26.2	22.6
35		OAc	80–100	$C_{11}H_{21}HgNO_9$	2.7	2.8			39.2	37.7
		TS	Foam	$C_{15}H_{31}HgNO_{12}S$	2.0	2.1	4.6	4.9	30.9	29.2
36		OAc	75–85	$C_{13}H_{24}HgN_2O_{10}$	4.9	5.1			35.3	36.3
		TS	Foam	$C_{17}H_{34}HgN_2O_{13}S$ Freeze dried	4.0	3.7	4.5	4.9	28.4	24.8
37		OAc	Amorph.	$C_{13}H_{25}HgNO_9S$	2.4	2.4			35.1	33.4
		TS	55–70	$C_{17}H_{35}HgNO_{12}S_2$	2.0	1.6			28.2	26.8

[a] D. L. Tabern, U. S. Patent 2,163,296, June 20, 1939; 2,084,626, June 22, 1937.

The reaction was carried out at room temperature in aqueous or alcoholic solution. In general, methanol was used; in such case R′ is CH_3. In the N-(2-alkoxy-3-hydroxymercuripropyl)-barbital series, according to Halpern,[8] these methoxy derivatives have been found to be less toxic than those with higher alkoxy groups. A direct comparison with N-(2-hydroxy-3-hydroxymercuripropyl)-barbital was not made. The addition of mercuric salts to olefins has been reviewed in detail by Chatt.[9] In Tables II-IV references are given either for the preparation of the corresponding olefin or for the mercurated derivative. For the compounds not reported in the literature, details are given in the Experimental part.

The thiophene derivatives were mercurated in aqueous solution with mercuric acetate. The mercuration of thiophene has been thoroughly investigated and has been summarized by Hartough.[10] The α-positions in thiophene are attacked first, and when, as in our compounds (no. 31–33), the 2-position is occupied, it may be assumed that substitution takes place in the 5-position. The products formed by mercuration of the olefin or thiophene derivatives were obtained as acetoxymercuri or, in the case that the starting material contained a free carboxyl group, as hydroxymercuri compounds. These intermediates were then combined in aqueous solution with one equivalent of 1-thiosorbitol. Compounds having an acidic group were neutralized by the addition of one equivalent of sodium hydroxide.

Pharmacology.—Toxicological studies indicated that the polyhydroxyalkyl mercaptans were the most effective of the thiols tested in reducing the cardiac toxicity of mercurials. These investigations also showed that of the mercurials listed in Tables II–IV those which conformed to the structure $NaO_2C–R–CONHCH_2–CH(OCH_3)CH_2Hg–SCH_2(CHOH)_4CH_2OH$ (D-gluco) exhibited the lowest cardiac and renal toxicity when compared on a molar basis. This work will be reported in detail by our Division of Macrobiology.

Experimental[11]

A. Combinations of 3-Hydroxymercuri-2-hydroxypropylcarbamylnicotinic Acid Sodium Salt with Thiols. General Procedure.—Ten millimoles (4.40 g.) of 3-hydroxymercuri-2-hydroxypropylcarbamylnicotinic acid[4] was dissolved in 10 cc. of *N* sodium hydroxide. An equivalent amount of thiol was dissolved in water (hydroxythiols), alcohol (*e.g.*, thiocresol) or *N* sodium hydroxide (mercaptocarboxylic acids) and combined with the mercurated intermediate. The product was precipitated by addition of 100 cc. of acetone, triturated repeatedly with fresh acetone and dried *in vacuo*. In general the products were somewhat hygroscopic and had a pronounced tendency to retain solvent. The presence of acetone in a number of compounds could be shown by dissolving a sample in water and distilling the acetone off in a stream of nitrogen. It was then isolated as the 2,4-dinitrophenylhydrazone, m.p. 124°.

The thiols used were commercially available with the exception of 2-mercaptonicotinic acid,[12] 1-thioxylitol and 1-thiomannitol,[13] the latter two were obtained as sirups by catalytic reduction of D-xylose and D-mannose, respectively, in the presence of sulfur and purified *via* the cuprosalt. Chromatography of the purified 1-thiomannitol on alumina in methanol solution yielded crystalline material, m.p. 88–92°.

Anal. Calcd. for $C_5H_{12}O_4S$: C, 35.7; H, 7.2. Found: C, 35.6; H, 7.3. Calcd. for $C_6H_{14}O_5S$: C, 36.4; H, 7.1; S, 16.2. Found: C, 37.1; H, 7.0; S, 16.3.

B. Preparation of Other Mercurials and Combination with 1-Thiosorbitol. Intermediates. 1-Nicotinoyl-3-allylurea.—A suspension of 36.9 g. of nicotinic acid in 150 cc. of toluene and 25 cc. of thionyl chloride was refluxed for 3 hours, 50 cc. of solvent was then distilled off *in vacuo* to remove excess thionyl chloride. On addition of 30 g. of allylurea and vigorous agitation, the reaction mixture solidified. Treatment with water, separation of the toluene layer and neutralization of the aqueous phase with potassium carbonate yielded 1-nicotinoyl-3-allylurea, m.p. 117–120° (38.8 g.) after recrystallization from water; hydrochloride, m.p. 192–195°.

Anal. Calcd. for $C_{10}H_{11}N_3O_2 \cdot HCl$: Cl, 14.7. Found: Cl, 14.7.

Ethyl γ-Allylallophanate.—A mixture of 11.0 g. of allylurea and 5.5 g. of chloroethyl carbonate was heated for 4 hours to 80–90°. After cooling, water was added, the allophanate separated and was recrystallized from water; yield 2.62 g., m.p. 64–66°.

Anal. Calcd. for $C_7H_{12}N_2O_3$: N, 16.3. Found: N, 16.0.

1-Allylparabanic Acid.—Following the general procedure of Biltz and Topp[14] 6.4 g. of oxalyl chloride, 120 cc. of ether and 5.0 g. of 1-allylurea were combined and refluxed for 4 hours. A precipitate formed which was filtered off and recrystallized from water; yield 4.73 g., m.p. 142–145°.

Anal. Calcd. for $C_6H_6N_2O_3$: N, 18.2. Found: N, 18.1.

Hydantoic Acid N-Allyl Amide.—Methyl hydantoate[15] (13.2 g.) was treated with 32 cc. of allylamine by warming gently until a clear solution was obtained. On cooling, the allyl amide crystallized. The product (14.4 g.) was filtered off and recrystallized from water, m.p. 172–176°.

Anal. Calcd. for $C_6H_{11}N_3O_2$: N, 26.7. Found: N, 26.7.

1-Piperidineacetic Acid Allyl Amide.—A solution of 10.0 g. of α-chloro-N-allylacetamide[16] in 10 cc. of benzene was added dropwise to 15 g. of piperidine in 60 cc. of benzene. After refluxing for 1 hour the solution was filtered, concentrated and the residue distilled *in vacuo;* yield 10.8 g., b.p. 115–116° (14 mm.).

Anal. Calcd. for $C_{10}H_{18}N_2O$: N, 15.4. Found: N, 15.5.

D-Tartaric Acid Monoallyl Amide.—To 43 g. of diacetyl-D-tartaric acid anhydride[17] dissolved in 120 cc. of ethyl acetate, 30 cc. of allylamine, dissolved in 60 cc. of ethyl acetate was added dropwise with cooling. The precipitate was filtered off and dissolved in water; acidification yielded 2,3-diacetyl-D-tartaric acid monoallyl amide, m.p. 154–157°. The acetyl groups were removed by adding to 18.2 g. of diacetyl-D-tartaric acid monoallyl amide 10-cc. portions of 2 *N* sodium hydroxide until the solution remained alkaline to phenolphthalein. This required 90 cc. (calcd. 100 cc.) of 2 *N* sodium hydroxide. The solution was acidified with 2 *N* hydrochloric acid, concentrated *in vacuo* and the product extracted from the residue with anhyd. ethanol. Evaporation to dryness and treatment of the residue with ethyl acetate gave 9.4 g. of D-tartaric acid monoallyl amide, m.p. 142–145°.

Anal. Calcd. for $C_7H_{11}NO_5$: N, 7.4. Found: N, 7.3.

Succinic Acid Mono-α-thenyl Amide.—To a solution of 3.0 g. of α-thenylamine[18,19] in 10 cc. of ethanol, 2.5 g. of

(8) A. Halpern, J. W. Jones and E. G. Gross, *J. Am. Pharm. Assoc., Sci. Ed.*, **37**, 333 (1948).

(9) J. Chatt, *Chem. Revs.*, **48**, 7 (1951).

(10) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 444.

(11) All melting points are uncorrected and were taken by the capillary tube method in an aluminum block. We wish to thank Mr. M. E. Walsh for technical assistance and Mr. Louis Dorfman and his associates for the analytical data.

(12) O. Seide, *Ber.*, **57**, 1802 (1924); E. Sucharda and Cz. Troszkiewiczowna, *Roczniki Chem.*, **12**, 493 (1932), *Chem. Zentr.*, **103**, II, 3400 (1932).

(13) M. W. Farlow, M. Hunt, C. M. Langkammerer, W. A. Lazier, W. J. Peppel and F. K. Signaigo, THIS JOURNAL, **70**, 1392 (1948).

(14) H. Biltz and E. Topp, *Ber.*, **46**, 1387 (1913).

(15) O. Rosen, *Acta Chem. Scand.*, **4**, 687 (1950).

(16) C. Harries and I. Petersen, *Ber.*, **43**, 634 (1910).

(17) A. Wohl and C. Oesterlin, *ibid.*, **34**, 1139 (1901).

(18) K. B. Wiberg and H. F. McShane, *Org. Syntheses*, **29**, 31 (1949).

(19) K. B. Wiberg, *ibid.*, **29**, 87 (1949); H. D. Hartough, "Thiophene and its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 252.

succinic acid anhydride was added. The succinic anhydride dissolved and the product crystallized on standing; yield 3.4 g., m.p. 133–135°.

Anal. Calcd. for $C_9H_{11}NO_3S$: N, 6.6. Found: N, 6.5.

Mucic Acid Mono-α-thenyl Amide.—To 2.88 g. of sirupy mucic acid monolactone[20] 3.4 g. of α-thenylamine was added with cooling, followed by 5 cc. of ethanol. After standing overnight, the product was filtered off, dissolved in water and the acid precipitated with concd. hydrochloric acid. After recrystallization from water, the mucic acid thenyl amide melted at 197–200°.

Anal. Calcd. for $C_{11}H_{15}NO_7S$: C, 43.3; H, 4.9; N, 4.6. Found: C, 43.2; H, 4.7; N, 4.8.

Gluconic Acid α-Thenyl Amide.—To a solution of 3.5 g. of α-thenylamine in 7 cc. of ethanol, 4.7 g. of gluconolactone was added. The reaction mixture warmed up and solidified, then 10 cc. of ethanol was added. After standing overnight the product was filtered off and recrystallized from methanol; yield 5.9 g., m.p. 170–172°.

Anal. Calcd. for $C_{11}H_{17}NO_6S$: N, 4.8. Found: N, 4.8.

Allyl Amide of 2-(D-Glucopentahydroxyamyl)-5-benzimidazolecarboxylic Acid.—By refluxing 19.5 g. of 3-nitro-4-formamidobenzoic acid[21] with 60 cc. of thionyl chloride for 90 min., and then cooling, the acid chloride was obtained crystalline from the reaction mixture. It was filtered off and washed with benzene; yield 15.9 g., m.p. 104–107°. A solution of 8.0 g. of allylamine in 30 cc. of benzene was added dropwise with stirring to 15.9 g. of 3-nitro-4-formamidobenzoyl chloride dissolved in 350 cc. of benzene. A precipitate formed which was filtered off. On concentrating the reaction mixture a second crop was obtained. The material was recrystallized from ethanol, and apparently consisted of a mixture of the 4-formamido- and 4-amino-3-nitrobenzoic acid allyl amide. This material (11.3 g.) was dissolved in 150 cc. of ethanol, heated to boiling and 25 cc. of 2 *N* sodium hydroxide was then added. On cooling, 4-amino-3-nitrobenzoic acid allyl amide crystallized. Recrystallization from ethanol gave 11.0 g., m.p. 200–203°.

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: N, 19.0. Found: N, 19.0.

Hydrogenation of 20.0 g. of 4-amino-3-nitrobenzoic acid allyl amide with Raney nickel in 250 cc. of ethanol, followed by recrystallization of the product from ethyl acetate gave 17.0 g. of 3,4-diaminobenzoic acid allyl amide, m.p. 125–126°. Following the procedure of Link, *et al.*,[22] 4.6 g. of gluconic acid lactone, 5.0 g. of 3,4-diaminobenzoic acid allyl amide, 15 cc. of water, 4 cc. of ethanol and 2.6 cc. of concd. hydrochloric acid were combined. The reaction mixture was warmed gently until a solution was obtained, then heated to 135° for 2 hours. On working up, the allyl amide of 2-(D-glucopentahydroxyamyl)-5-benzimidazolecarboxylic acid, m.p. 230–232°, was obtained.

Anal. Calcd. for $C_{16}H_{21}N_3O_6$: N, 12.0. Found: N, 11.8.

N-Allylglycylgluconamide.—Glycinallyl amide[16] (1.3 g.) prepared according to Sheehan's[23] method was shaken with 1.62 g. of δ-gluconolactone in 5 cc. of ethanol; yield 2.25 g., m.p. 161–163°.

Anal. Calcd. for $C_{11}H_{20}N_2O_7$: N, 9.6. Found: N, 9.5.

D-Glucopentahydroxyhexylmercaptoacetic Acid N-Allyl Amide.—To a mixture of 36 g. of 1-thiosorbitol (80% pure) dissolved in 120 cc. of water and 12.6 g. of KOH in 60 cc. of water, 29.83 g. of α-chloro-N-allylacetamide[16] was added dropwise with stirring under N_2. Stirring was continued until the test for –SH groups (sodium nitroprusside) was negative. The reaction mixture was neutralized with hydrochloric acid and concentrated *in vacuo*. The residue was extracted with methanol and the potassium chloride filtered off. Evaporation of the filtrate to dryness and treatment with acetone gave a crystalline product which was recrystallized three times from ethanol; yield 25.2 g., m.p. 103–105°.

Anal. Calcd. for $C_{11}H_{21}NO_6S$: C, 44.7; H, 7.2. Found: C, 44.7; H, 7.2.

Mercuration. General Procedure.—The olefin or thiophene derivative was dissolved in water or methanol, respectively, and an equivalent amount of mercuric acetate as a 20% (w./v.) aqueous or 6% (w./v.) methanolic solution added. In some cases (compounds 18, 25, 27, 28, 31, 32, 33) the mercurated intermediates precipitated and were filtered off. If no precipitate formed after 16 hours, the solution was evaporated to dryness at room temperature. The residue was then treated with methanol, acetone or ethyl acetate to induce crystallization; some products, however, could be obtained only as an amorphous powder.

Combination with 1-Thiosorbitol. General Procedure.—Mercurials with an acidic group were combined with 1-thiosorbitol according to the procedure given above for 3-hydroxymercuri-2-hydroxypropylcarbamylnicotinic acid. Other mercurials: 10 mmoles of substance was dissolved or suspended in 10 cc. of water; 10 mmoles of 1-thiosorbitol dissolved in 5 cc. of water was added. The mercaptomercuri compound was then isolated either by precipitation as an amorphous solid with acetone, or by freeze drying the aqueous solution. Methanol, ethanol or dioxane can also be used as precipitant.

(20) E. Fischer, *Ber.*, **24**, 2136 (1891).

(21) A. Zehra, *ibid.*, **23**, 3625 (1890).

(22) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940); *J. Org. Chem.*, **5**, 637 (1940).

(23) J. C. Sheehan and V. S. Frank, THIS JOURNAL, **71**, 1856 (1949).

SUMMIT, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF PURE CHEMISTRY, UNIVERSITY COLLEGE OF SCIENCE & TECHNOLOGY]

Alkaloids of *Glycosmis pentaphylla* (Retz.) DC. Part I

BY A. CHATTERJEE AND S. GHOSH MAJUMDAR

RECEIVED JULY 16, 1953

From *Glycosmis pentaphylla* (Retz.) DC., three different alkaloids have been isolated: skimmianine, m.p. 175–176°, $C_{14}H_{13}O_4N$; glycosminine, m.p. 225–227°; and glycosine, m.p. 155–156°, $C_{16}H_{14}N_2O$. A complete assignment of the structure for the alkaloid glycosine as 2-benzylidene-1-methyl-4-quinazolone has been possible from studies of its infrared and ultraviolet absorption spectra, from the hydrolysis characteristics of the base and its ozonolysis and from the oxidation experiments of the alkaloid with periodic acid as well as with neutral potassium permanganate in acetone.

Glycosmis pentaphylla (Retz.) DC., commonly known in India as tooth brush plant, belongs to the family *Rutaceae* which is well-known for its varied therapeutically active constituents. Chemical investigation of this plant was first undertaken by Dutta[1] who isolated from this species a neutral compound glycosmin, $C_{22}H_{26}O_{10}$, m.p. 169°, which has been shown to be identical with veratroyl salicin. Recently Chakravarti and Chakravarti[2–4] have shown that *G. pentaphylla* (later identified as *Glycosmis arborea*)[3b] contains two different alka-

(1) S. B. Dutta, *Proc. Acad. Sci., United Province Agra and Oudh, India*, 56 (1935).

(2) R. N. Chakravarti and S. C. Chakravarti, *Proc. Indian Sci. Cong.*, Part III, 79 (1951).

(3) (a) *Ibid.*, 100 (1952); (b) R. N. Chakravarti and S. C. Chakravarti, *J. Proc. Inst. Chemist (India)*, **24**, 96 (1952).

(4) (Mrs.) D. Chakravarti, R. N. Chakravarti and S. C. Chakravarti, *Science and Culture*, **18**, 533 (1953).