[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

New Mercurial Diuretics[1]

BY HARRY L. YALE

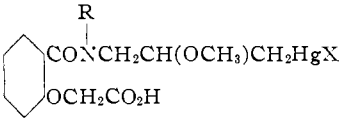
RECEIVED MARCH 21, 1957

Seven new mercurials have been synthesized for evaluation as diuretics. In part, their unique structural features are that they possess either a $-CON(CH_2CH{=}CH_2)CH_2CH(OCH_3)CH_2HgX$ or a $-CON[CH_2CH(OCH_3)CH_2HgX]_2$ group, where X is O_2CCH_3, OH, Cl, Br or SCH_2CO_2H.

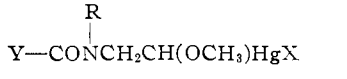
Mercurial diuretics form a comprehensive and well established treatment for the edema caused by congestive heart failure. A review of the types of mercury compounds presently in use[2] indicates that the functional grouping common to nearly all is $-CONHCH_2CH(OCH_3)CH_2HgX$ (where X is a halogen, hydroxyl or $-SCH_2CO_2H$ group).

As part of a program on diuretics, seven new mercurials have been synthesized. In part, their unique structural features are that they possess either a $-CON(CH_2CH{=}CH_2)CH_2CH(OCH_3)CH_2HgX$ or a $-CON[CH_2CH(OCH_3)CH_2HgX]_2$ group; these represent new classes of mercury compounds since derivatives of these types have not been described previously.

The seven new mercurials are shown below.



I, R = $CH_2CH(OCH_3)CH_2HgX$, *ortho* compound
II, R = $CH_2CH{=}CH_2$, *para* compound



III, Y = 4-carboxycyclohexyl, R = H
IV, Y = NH_2, R = $CH_2CH(OCH_3)CH_2HgX$
V, Y = H_2NCONH, R = $CH_2CH(OCH_3)CH_2HgX$
VI, Y = H_2NCONH, R = H
VII, $H_2NCONHCONHCH_2CH(HgX)CH_2OCH_3$
[X = O_2CCH_3, OH, Cl, Br or SCH_2CO_2H]

Compounds represented by I were prepared by the following sequence of reactions: *o*-acetoxybenzoyl chloride and diallylamine gave a 72% yield of *o*-acetoxy-N,N-diallylbenzamide; the latter compound with 5% aqueous sodium hydroxide at room temperature gave essentially a quantitative yield of N,N-diallyl-*o*-hydroxybenzamide, and this with chloroacetic acid gave the desired product, [*o*-(diallylcarbamoyl)-phenoxy]-acetic acid in about 50% yield; approximately 50% of the N,N-diallyl-*o*-hydroxybenzamide was always recovered. [*o*-(Diallylcarbamoyl)-phenoxy]-acetic acid and two moles of mercuric acetate in methanol gave {*o*-{bis - [3 - (acetoxymercuri) - 2 - methoxypropyl]-carbamoyl}-phenoxy}-acetic acid which was then converted to the **bis-(chloromercuri), bis-(hydroxymercuri) and bis-(carboxymethylmercaptomercuri) derivatives.**

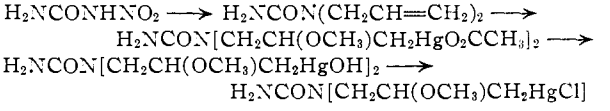
(1) Presented before the Division of Medicinal Chemistry at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 16–21, 1956.

(2) One of the more recent reviews on diuretics is found in Goodman and Gilman, "The Pharmacological Bases of Therapeutics," 2nd ed., The Macmillan Co., New York, N. Y., 1955, pp. 840-868.

Compounds of the type represented by II were obtained by a sequence of reactions identical with those used in the preparation of compound I. Surprisingly, although a number of attempts were made, the reaction of [*p*-(diallylcarbamoyl)-phenoxy]-acetic acid with two moles of mercuric acetate did not give a homogeneous dimercurated derivative; consequently, a reaction was carried out with one mole of mercuric acetate which gave homogeneous **monoacetoxymercuri and monochloromercuri derivatives.**

Compound III was obtained by a series of reactions starting with dimethyl hexahydroterephthalate. By conventional procedures, this compound gave hexahydroterephthalic acid methyl ester in 75% yield; only small amounts of *trans*-hexahydroterephthalic acid were formed as a by-product. The ester-acid and thionyl chloride gave the ester-acyl chloride in 90% yield and this with allylamine gave the ester-monoallyl amide in 75% yield; saponification could be effected at only the ester linkage to give hexahydroterephthalic acid monoallyl amide in 75% yield, and the latter compound was converted to the **acetoxymercuri and di-sodium (carboxymethylmercaptomercuri) derivatives.**

Compounds represented by IV were prepared by the series of reactions



1,1-Diallylurea, not previously described, was prepared in essentially quantitative yield by the reaction of nitrourea and diallylamine at 100°. The intermediate **bis-(acetoxymercuri) and bis-(hydroxymercuri) derivatives** were prepared but were not isolated, in view of their great solubility in the reaction media; the final product, 1,1-bis-(3-chloromercuri-2-methoxypropyl)-urea was obtained as a crystalline solid.

Nitrobiuret was converted in similar fashion through the new intermediate, 1,1-diallylbiuret, into 1,1-bis-(3-chloromercuri-2-methoxypropyl)-biuret (compounds of type V) which was obtained as a crystalline product.

The synthesis of compounds represented by VI followed the pattern established with IV and V. 1-Allylbiuret, a new intermediate prepared from nitrobiuret and allylamine, and mercuric acetate in methanol gave 1-(3-acetoxymercuri-2-methoxypropyl)-biuret, and the latter compound, in turn, was converted to the **3-chloromercuri- and 3-bromomercuri-derivatives.**

Addition of mercuric acetate in methanol across

the double bond of an unsymmetrically substituted olefin should lead to two isomeric products. The first, and thus far the only, report of the separation and characterization of two such isomeric products was in the reaction of N-allylphthalimide with (a) mercuric acetate in methanol and (b) a mixture of mercuric acetate and mercuric chloride in methanol.[3]

The reaction of 1-allylbiuret with a mixture of mercuric acetate and mercuric chloride in methanol has also led to the isolation of two isomeric products: 1-(3-chloromercuri-2-methoxypropyl)-biuret in 67% yield and 1-(2-chloromercuri-3-methoxypropyl)-biuret (VII) in 16% yield. These isomeric structures are tentatively assigned, largely on the basis of the relative yields obtained.[3]

Pharmacological Evaluation.—These compounds were screened for diuretic activity by Dr. J. J. Piala of the Division of Pharmacology of the Squibb Institute for Medical Research. All of the compounds showed activity in the dog by the intravenous route. Compounds of the type represented by VI were also highly active by the oral route. The details of the pharmacological evaluation will be published elsewhere.

Experimental Part

All melting points are uncorrected.

Compound I.—To a stirred, ice-cooled solution of 50 g. (0.25 mole) of *o*-acetoxybenzoyl chloride[4] and 25 g. (0.25 mole) of N-methylmorpholine in 500 ml. of dry benzene was added dropwise 25 g. (0.25 mole) of diallylamine in 200 ml. of dry benzene. The mixture was allowed to stand at room temperature for 3 days and was filtered. The filtrate was concentrated and the residue distilled to give 46.7 g. (72% yield) of **o-acetoxy-N,N-diallylbenzamide**, b.p. 160–177° (2 mm.). *Anal.* Calcd. for $C_{15}H_{17}NO_3$: N, 5.40. Found: N, 5.58.[5] A mixture of *o*-acetoxy-N,N-diallylbenzamide, 46.7 g. (0.18 mole), and 14.4 g. (0.36 mole) of sodium hydroxide in 290 ml. of water was kept at room temperature. Solution occurred within five minutes. After 1 hr., the mixture was acidified with 10% aqueous hydrochloric acid to give an essentially quantitative yield of **N,N-diallyl-o-hydroxybenzamide**, m.p. 92–93°, after recrystallization from 50% ethanol. *Anal.* Calcd. for $C_{13}H_{15}NO_2$: N, 6.45. Found: N, 6.63. N,N-Diallyl-*o*-hydroxybenzamide, 21.8 g. (0.1 mole), was dissolved in a solution of 7 g. (0.1 mole) of 85% potassium hydroxide in 200 ml. of water; to this solution was added another solution made up of 9.5 g. (0.1 mole) of chloroacetic acid, 7 g. of 85% potassium hydroxide and 200 ml. of water. The mixture was heated under reflux for 48 hr., cooled and treated with an excess of carbon dioxide. The solid (unreacted N,N-diallyl-*o*-hydroxybenzamide) which separated was removed, and the filtrate was acidified with 20% hydrochloric acid. The oil which separated was extracted into ether, the ether extracts were dried and concentrated to give 15.4 g. (56% yield) of crude [*o*-(diallylcarbamoyl)-phenoxy]-acetic acid as a viscous oil. *Anal.* Calcd. for $C_{15}H_{17}NO_4$: N, 5.09. Found: N, 5.88. To 16.5 g. (0.06 mole) of [*o*-(diallylcarbamoyl)-phenoxy]-acetic acid in 200 ml. of methanol was added a solution of 38.4 g. (0.12 mole) of mercuric acetate in 250 ml. of methanol. The solution was kept at room temperature for 24 hr., then while stirring, was treated dropwise with a solution of 7 g. (0.12 mole) of sodium chloride in 70 ml. of water. The colorless crystalline product separated directly. The yield of **{o-{N,N-bis-[3-(chloromercuri)-2-methoxypropyl]-carbamoyl}-phenoxy}-acetic acid** which sintered at 90° and melted at 140° with decomposition was 35 g. (86%).

Anal. Calcd. for $C_{17}H_{23}Cl_2NO_6Hg_2$: N, 1.73; Cl, 8.76. Found: N, 1.99; Cl, 8.75.

{o-{N,N-Bis-[3-carboxymethylmercaptomercuri-2-methoxypropyl]-carbamoyl}-phenoxy}-acetic Acid.—To a suspension of 4.05 g. (0.005 mole) of the above chloromercuri derivative, 5 ml. of *N* sodium hydroxide solution and 200 ml. of water was added 1.3 g. of 70% thioglycolic acid in 20 ml. of *N* sodium hydroxide solution. The solid went into solution rapidly. The mixture was allowed to stand overnight, clarified with Hyflo and the filtrate acidified with 7.5 ml. of glacial acetic acid. A solid separated directly. The solid was filtered and dried *in vacuo*. The yield of white powder was 2.4 g. (41%). The product turns yellow gradually and then melts with decomposition at 155–160°.

Anal. Calcd. for $C_{21}H_{29}NO_{10}S_2Hg_2$: N, 1.52; S, 6.96. Found: N, 1.30; S, 7.43.

The trisodium salt of this compound was also prepared by an alternate procedure. When 400 ml. of a methanol solution of the bis-(3-acetoxymercuri) derivative prepared as above was poured into 2 liters of water, the **bis-(3-hydroxymercuri) derivative** separated as a gelatinous solid. This was collected by centrifuging and desiccated. *Anal.* Calcd. for $C_{17}H_{25}NO_8Hg_2$: N, 1.81. Found: N, 2.28. The bis-(3-hydroxymercuri) derivative, 1.0 g. (0.0014 mole), 1.4 ml. of *N* sodium hydroxide solution and 250 ml. of water was stirred until a clear solution formed and the solution was treated with a solution of 0.35 g. (0.0028 mole) of 71% thioglycolic acid in 2.8 ml. of *N* sodium hydroxide solution. The clear solution was kept overnight and lyophilized. The trisodium salt was obtained as a yellow amorphous solid.

Anal. Calcd. for $C_{21}H_{26}NO_{10}S_2Hg_2Na_3$: N, 1.42; Na, 6.99; S, 6.49. Found: N, 1.70; Na, 7.25; S, 6.26.

Compound II.—To 231.2 g. (1.18 moles) of *p*-acetoxybenzoyl chloride,[6] 118 g. of N-methylmorpholine and 730 ml. of dry benzene, with stirring and ice-cooling, was added 118 g. of diallylamine in 200 ml. of dry benzene. The mixture was then kept at room temperature for several days, filtered and the filtrate concentrated from the steam-bath. The residual oil crystallized. Recrystallization from heptane gave 251 g. (85% yield) of **p-acetoxy-N,N-diallylbenzamide**, m.p. 68–70°. *Anal.* Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.34; H, 6.58; N, 5.35. A mixture of *p*-acetoxy-N,N-diallylbenzamide, 26 g. (0.1 mole), and 8 g. (0.2 mole) of sodium hydroxide in 150 ml. of water was heated to 80–90°; at this temperature a homogeneous solution formed. The solution was allowed to cool and was acidified with acetic acid. The solid which separated was filtered, dried and recrystallized from benzene to give an essentially quantitative yield of **N,N-diallyl-p-hydroxybenzamide**, m.p. 138–140°. *Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.86; H, 6.80; N, 6.74. A mixture of 125.5 g. (0.58 mole) of N,N-diallyl-*p*-hydroxybenzamide, 56 g. (0.59 mole) of chloroacetic acid, a solution of 78 g. (1.2 moles) of 85% potassium hydroxide in 1 l. of 95% ethanol and few crystals of potassium iodide was refluxed for 24 hr., the alcohol was distilled and the residue worked up as above with the ortho derivative to give 98.4 g. (62% yield) of **[p-(diallylcarbamoyl)-phenoxy]-acetic acid**, m.p. 71–75°. An analytical sample from water melted at 75–77°. *Anal.* Calcd. for $C_{15}H_{17}NO_4$: C, 65.43; H, 6.23; N, 5.09. Found: C, 65.37; H, 6.23; N, 5.09. To 34 g. (0.11 mole) of mercuric acetate, 4 ml. of acetic acid and 100 ml. of methanol at the boiling point, with stirring, was added 29.5 g. (0.107 mole) of [*p*-(diallylcarbamoyl)-phenoxy]-acetic acid in 150 ml. of methanol. The solution became cloudy and a viscous oil separated. The mixture was heated under reflux for 18 hr. To the refluxing mixture was then added 7.4 g. of sodium chloride in 80 ml. of water, dropwise. The mixture was allowed to cool and the solvents were allowed to evaporate at room temperature. The residual oil was washed with water, methyl ethyl ketone and ether; the oil remaining insoluble after the successive washes solidified on desiccation. The yield of **p-N-allyl-N-[3-(chloromercuri)-2-methoxypropyl]-carbamoylphenoxyacetic acid**, m.p. 129–130° dec., was 21 g. (39%).

Anal. Calcd. for $C_{16}H_{20}ClNO_5Hg$: N, 2.58; Cl, 6.54; Hg, 36.96. Found: N, 2.38; Cl, 6.18; Hg, 38.82.

(3) D. E. Pearson, M. V. Sigal and R. H. Krug, *J. Org. Chem.*, **15**, 1048 (1950).

(4) J. McConnan and A. W. Titherley, *J. Chem. Soc.*, **89**, 1318 (1906).

(5) The microanalyses were carried out by Mr. J. F. Alicino and his associates.

(6) W. H. Linnell and I. M. Roushdi, *Quart. J. Pharm. Pharmacol.*, **14**, 270 (1941).

Compound III.—To 40 g. (0.2 mole) of dimethyl hexahydroterephthalate[7] in 600 ml. of methanol was added slowly with stirring, 13.2 g. (0.2 mole) of 85% potassium hydroxide in 200 ml. of methanol. The clear solution was heated under reflux for 3 hr. and concentrated from the steam-bath. The residue was partitioned between 300 ml. of ether and 200 ml. of water, the water layer was separated, acidified with 20% aqueous hydrochloric acid and cooled. The crude solid which separated was filtered and dried; it weighed 28 g. (75% yield), m.p. 90–110°. An analytical sample was prepared by extracting the crude product with carbon tetrachloride. The carbon tetrachloride insoluble material melted at 306° and was apparently *trans*-hexahydroterephthalic acid.[8] The carbon tetrachloride extracts were concentrated to dryness and the residue recrystallized from water to give a pure sample of **hexahydroterephthalic acid monomethyl ester**, m.p. 112–114°. *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.87; H, 7.30. A mixture of 27.5 g. of the crude half-ester and 34.5 g. of purified thionyl chloride was allowed to stand overnight, was refluxed 3 hr. and distilled to give 28.5 g. of crude **hexahydroterephthalic acid monomethyl ester monoacid chloride**, b.p. 105–109° (3 mm.). This material was apparently contaminated with some hexahydroterephthaloyl chloride. *Anal.* Calcd. for $C_9H_{13}ClO_3$: Cl, 17.33. Found: Cl, 20.10. To an ice-cold mixture of 28.1 g. (0.14 mole) of the above acid chloride, 100 ml. of dry benzene and 14 g. of N-methylmorpholine was added dropwise 8.0 g. (0.14 mole) of allylamine in 50 ml. of dry benzene. After standing overnight, the mixture was stirred and heated under reflux for 0.5 hr., cooled and filtered. The filtrate was concentrated and distilled to give **hexahydroterephthalic acid monoallyl amide monomethyl ester**, b.p. 160–165° (2 mm.). On standing, the distillate crystallized; after one recrystallization from heptane it melted at 118°. The yield was 17 g. (75%). *Anal.* Calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.22; H, 8.74; N, 6.10. A solution of 17 g. (0.076 mole) of the ester in 200 ml. of methanol was treated dropwise with 5 g. (0.075 mole) of 85% potassium hydroxide in 50 ml. of methanol with stirring during 0.5 hr. The mixture was then refluxed 2 hr. and concentrated from the steam-bath. The residue was cooled, dissolved in 100 ml. of water and acidified while cold with 20% aqueous hydrochloric acid. The solid which separated was filtered and recrystallized from water. The yield of **hexahydroterephthalic acid monoallyl amide** was 12 g. (75%), m.p. 214–216°. *Anal.* Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.67; H, 8.21; N, 6.51. To 2.11 g. (0.01 mole) of the acid amide in 10 ml. of methanol was added a warm solution of 3.18 g. (0.01 mole) of mercuric acetate in 40 ml. of methanol. A solid separated immediately which was filtered and washed with boiling methanol. The yield was 3.15 g. (63%) of a white microcrystalline powder, m.p. 205° dec. It was insoluble in all of the common solvents. *Anal.* Calcd. for $C_{14}H_{23}NO_6Hg$: N, 2.79. Found: N, 2.87. This solid, 3.05 g. (0.006 mole), was suspended in 50 ml. of water, and 6.1 ml. of 0.996 *N* aqueous sodium hydroxide was added. A clear solution was formed; 0.7 g. of 71% thioglycolic acid and 6.1 ml. of 0.996 *N* sodium hydroxide was added, the mixture was allowed to stand overnight and was lyophilized. The **N-(3-carboxymethylmercaptomercuri-2-methoxypropyl)-hexahydroterephthalic acid monoamide disodium salt** was obtained as a pale yellow solid.

Anal. Calcd. for $C_{14}H_{21}NO_6SHgNa_2$: N, 2.42; S, 5.54; Na, 7.96; Hg, 34.71. Found: N, 2.04; S, 5.38; Na, 6.77; Hg, 36.6.

Compound IV.—A mixture of 7.5 g. (0.07 mole) of nitrourea,[9] 8 g. (0.08 mole) of diallylamine and 50 ml. of water were heated 4 hr. at 100° in a sealed tube. The cooled tube was opened, the reaction mixture was transferred to a flask and concentrated *in vacuo* from the steam-bath. Recrystallization from Skellysolve E gave essentially quantitative yield of 1,1-**diallylurea**, m.p. 60–62°. *Anal.* Calcd. for $C_7H_{12}N_2O$: C, 59.97; H, 8.63; N, 19.99. Found: C, 60.16; H, 8.51; N, 20.03. To 22 g. (0.07 mole) of mercuric acetate in 300 ml. of methanol and 5 ml. of glacial acetic acid, at the boiling point and with stirring, was added dropwise a solution of 4.82 g. (0.035 mole) of 1,1-diallylurea in 300 ml. of methanol. Subsequently, the mixture was heated under reflux for 24 hr. No separation of solid occurred during the heating or cooling periods. The mixture was concentrated to give an oil. When a solution of 2.4 g. of sodium hydroxide in 25 ml. of water was stirred with the oil, there was evidence of a reaction but no solid separated. The solution was evaporated to dryness *in vacuo* over phosphorus pentoxide and gave the **bis-(3-hydroxymercuri) derivative** as a friable solid. This solid was dissolved in 100 ml. of water, the solution was decolorized with Darco and the filtrate was treated, dropwise, with 12 ml. of a 20% aqueous solution of sodium chloride. A white crystalline solid separated directly. The solid was filtered and dried; it was insoluble in the common solvents. The yield was 14 g. (60%) of 1,1-**bis-(3-chloromercuri-2-methoxypropyl)-urea** which sinters at 80° and melts at 130°.

Anal. Calcd. for $C_9H_{18}Cl_2O_3Hg_2$: N, 4.16; Cl, 10.51. Found: N, 4.23; Cl, 10.12.

Compound V.—A mixture of 14.8 g. (0.1 mole) of nitrobiuret,[10] 11 g. (0.11 mole) of diallylamine and 50 ml. of water in a sealed tube was heated for 5 hr. at 100°. A solid product was present in the cooled tube. This was filtered and dried; it weighed 4 g. (22% yield), m.p. 85–87°. Recrystallization from Skellysolve E gave 1,1-**diallylbiuret**, m.p. 94–95°. *Anal.* Calcd. for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.26; H, 7.04; N, 23.07. To a refluxing solution of 12.1 g. (0.04 mole) of mercuric acetate, 125 ml. of methanol and 5 ml. of acetic acid was added 3.5 g. (0.02 mole) of 1,1-diallylbiuret. The clear solution was heated under reflux for 18 hr. and the solvents removed *in vacuo* at room temperature. Even after prolonged desiccation, the residual oil did not crystallize. This oil was dissolved in 50 ml. of warm methanol and the methanol solution was treated slowly, with stirring, with a solution of 2.23 g. of sodium chloride in 25 ml. of water. A solid product separated directly. The reaction mixture was warmed until solution occurred and the solution allowed to cool. The crystalline solid was filtered and dried. It weighed 14 g., sintered at 50° and melted with decomposition at 85°. A recrystallization from methanol–water (2:1) gave 1,1-**bis-(3-chloromercuri-2-methoxypropyl)-biuret**, sinters at 90° and melts with decomposition at 117°. The yield was 12 g. (86%).

Anal. Calcd. for $C_{10}H_{19}Cl_2N_3O_4Hg_2$: N, 5.86; Cl, 9.89. Found: N, 5.72; Cl, 9.63.

Compound VI.—A mixture of 14.8 g. (0.1 mole) of nitrobiuret, 6.3 g. (0.11 mole) of redistilled allylamine and 50 ml. of water was heated 5 hr. at 100° in a sealed tube. The product crystallized in the cooled tube; it was filtered, dried and recrystallized from benzene to give 6.5 g. (46%) of 1-**allylbiuret**, m.p. 145–146°. *Anal.* Calcd. for $C_5H_9N_3O_2$: C, 41.96; H, 6.34; N, 29.36. Found: C, 42.49; H, 5.88; N, 29.69. To a stirred and refluxing solution of 28 g. (0.088 mole) of mercuric acetate, 5 ml. of acetic acid and 70 ml. of methanol was added, dropwise, 12.5 g. (0.088 mole) of 1-allylbiuret in 125 ml. of methanol. The mixture was heated under reflux for 18 hr.; no product separated during the heating period or on cooling. The solvents were evaporated at room temperature. The residual oil when triturated repeatedly with methyl ethyl ketone became granular. The solid could not be recrystallized. The 1-(3-**acetoxymercuri-2-methoxypropyl)-biuret** thus obtained melted with decomposition at 128–130°. The yield was 25 g. (66%). *Anal.* Calcd. for $C_8H_{15}N_3O_5Hg$: N, 9.69; CH_3O, 7.15. Found: N, 10.15; CH_3O, 7.78. To 24.35 g. (0.055 mole) of the above **acetoxymercuri derivative** dissolved in 200 ml. of warm methanol was added 3.25 g. (0.055 mole) of sodium chloride in 35 ml. of water. **The chloride** began to separate quickly as a crystalline solid. The cooled mixture was filtered to give 22 g. (98%) of product, m.p. 175–177° dec. A recrystallization from 95% ethanol gave 18 g. of 1-(**3-chloromercuri-2-methoxypropyl**)-**biuret**, m.p. 177–179° dec. *Anal.* Calcd. for $C_6H_{12}ClN_3O_3Hg$: N, 10.24; Cl, 8.64; Hg, 48.90. Found: N, 10.44; Cl, 8.37; Hg, 48.94.

(7) P. C. Guha and G. D. Hazra, *J. Indian Inst. Sci.*, **22A**, 263 (1939).

(8) W. H. Mills and G. H. Keats, *J. Chem. Soc.*, 1373 (1935), report m.p. of 312–313° for *trans*-hexahydroterephthalic acid.

(9) T. L. Davis and K. C. Blanchard, THIS JOURNAL, **51**, 1790 (1929).

(10) T. L. Davis and K. C. Blanchard, *ibid.*, **51**, 1801 (1929).

1-(3-Bromomercuri-2-methoxypropyl)-biuret was similarly prepared; it melted at 180–182° after recrystallization from water. *Anal.* Calcd. for $C_6H_{12}BrN_3O_3Hg$: N, 9.24. Found: N, 9.45.

Compound VII.—A suspension of 15.9 g. (0.05 mole) of mercuric acetate and 13.6 g. (0.05 mole) of mercuric chloride in 150 ml. of methanol was added to a boiling solution of 14.3 g. (0.1 mole) of 1-allylbiuret in 100 ml. of methanol. A solid separated directly but redissolved when the mixture was heated to reflux temperature. The boiling solution, which had been clear for about 1 hr., began to deposit a crystalline product. The mixture was refluxed for a tota of 3 hr., cooled and filtered. The air-dried solid weighed 44 g. (100% yield), m.p. 172–174° dec. One recrystallization from water gave 29 g. (67% yield) of 1-(3-chloromercuri-2-methoxypropyl)-biuret, m.p. 175–177° dec. alone or mixed with the sample of preparation described above. The aqueous filtrate from the above recrystallization slowly deposited a crystalline solid. This was filtered and air-dried; it weighed 7 g. (16% yield), m.p. 144° dec. Recrystallization from acetonitrile gave 1-(2-chloromercuri-3-methoxypropyl)-biuret, m.p. 153–155° dec. A mixed m.p. (equal portions) of the two isomers was 150–165° dec. *Anal.* Calcd. for $C_6H_{12}ClN_3O_3Hg$: N, 10.24; Cl, 8.64. Found: N, 10.66; Cl, 8.42.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM APPLIED SCIENCE DEPARTMENT, UNIVERSITY OF CINCINNATI]

The Selenium Catalyzed *cis–trans* Isomerization of 9-Octadecenoic (Oleic–Elaidic) Acids

BY J. D. FITZPATRICK[1] AND MILTON ORCHIN

RECEIVED NOVEMBER 16, 1956

The selenium-catalyzed elaidinization of oleic acid proceeds *via* π-complex formation between oleic acid and selenium, resulting in the solution of the selenium. At reaction temperature, this complex undergoes isomerization, but concomitantly there is a further reaction to a different species in which the selenium is catalytically inactive and in which the substrate has combined irreversibly with selenium in some type of different σ-complex or compound. At any particular initial concentration of selenium, the pseudo first-order rate equation for a reversible reaction holds. The full rate equation is most accurately expressed as rate $= k_1[\text{Oleic}][\text{Se}_0]^{1/3} - k_2[\text{Elaidic}][\text{Se}_0]^{1/3}$. The mechanism for the isomerization is proposed as given in the text. The rate of the reverse isomerization of elaidic to oleic acid is slower than the elaidinization. The requirement of having a particular species of selenium is demonstrated. The high temperatures are probably required for the dissociation of polyatomic selenium. The generality of π- and σ-complexing with unsaturated compounds is established and the analogy between the reaction of selenium and that of oxygen with olefinic compounds is suggested.

Introduction

One of the most simple and effective methods to achieve the isomerization of oleic acid to its *trans* isomer, elaidic acid, is to treat it at elevated temperatures in the presence of elemental selenium, a reaction first described by Bertram.[2] Accordingly, when a sample of elaidic acid was required in this Laboratory, a commercial (90%) oleic acid was treated by the selenium procedure. After isolation of the elaidic acid, it was noted that during its distillation, some reverse isomerization to oleic acid occurred. This chance observation led us to suspect that a soluble form of selenium might have been responsible for the original isomerization as well and that the selenium-catalyzed isomerization is in reality a rare and hitherto unrecognized example of homogeneous catalysis.

In an elaboration of the reaction, Bertram[3] had studied its kinetics and concluded that the conversion was termolecular. Aside from the dubious validity of the kinetic treatment,[4] the facts that neither the dependence on catalyst concentration nor the fate of the catalyst had been studied further prompted us to re-investigate the reaction.

Experimental

Preparation of Pure Acids. Oleic Acid.—Approximately 6.6 liters of a virgin olive oil was transesterified with methanol and the methyl esters carefully fractionated. About 2.8 liters of esters, b.p. 197–199° (9.5 mm.), was collected and saponified, and the recovered crude oleic acid was further purified by two low temperature crystallizations from acetone containing 10 volume per cent. of water.[5] The final product (1900 g.) was estimated to be better than 99% pure oleic acid (iodine no., neut. equiv., m.p.). The acid was sealed *in vacuo* in small, Pyrex, low-actinic bottles.

Elaidic Acid. Oleic–elaidic acid mixtures secured from various experiments with selenium were combined and crystallized from acetone containing 10 volume per cent. of water. A second crystallization combined with carbon treatment gave pure elaidic acid, m.p. 44.0–44.8°. Heating a sample of this material at 200° for 1 hr. under nitrogen did not change its melting point.

Analytical Procedure.—A satisfactorily accurate method for analyzing 1-ml. samples of the acid mixture from a 100-g. charge was developed which involved a micro-modification of the Cc12–41 AOCS Official Titre or freezing-point method.

In place of the standard titer tube which contains approximately 20 ml. of material, a small 3″ × 3/8″ test-tube was employed. Into this small test-tube there was fitted a copper–constantan thermocouple and a small stirrer. The thermocouple wires led to a cold junction (ice-water) and thence to a d.c. millivoltmeter having a range of 0 to 1.0 millivolt with a scale that made readings to 0.001 m.v. possible.

For the determination, a 1-ml. sample is placed in the sample tube and the bath temperature adjusted to about 10° below the expected titer point. The sample is stirred with the wire loop stirrer until clouding appears. At this point, stirring is discontinued. The needle of the millivoltmeter rises along the scale as solidification proceeds and finally reaches a maximum and then begins to drop. The maximum is the microtiter in millivolts. The readings are reproducible to within 0.002 millivolt corresponding to 0.1 to 0.2°. The composition of the mixture can be read from a plot of microtiter *versus* composition, Fig. 1, which was constructed from the determination of the titer points of samples of known composition using the pure oleic acid as prepared above and a sample of pure elaidic acid (courtesy Eastern Regional Laboratory, Department of Agriculture).

Isomerization Experiments. Apparatus.—The apparatus employed for the isomerization reactions consisted of a 1-l. 3-neck flask mounted with a condenser, stirrer and thermometer. A capillary tube was sealed onto the flask near the center neck. This permitted the insertion of a hypodermic

(1) Taken in part from this author's Ph.D. thesis.
(2) S. H. Bertram, *Chem. Weekblad*, **33**, 3 (1936).
(3) S. H. Bertram, *ibid.*, **33**, 637 (1936).
(4) J. Stuurman, *ibid.*, **33**, 700 (1936).
(5) J. B. Brown and G. J. Shinowara, THIS JOURNAL, **59**, 6 (1937).