[Contribution from the Chemical Research Division of Lakeside Laboratories, Inc.]

Mercurial Diuretics. III. Mercuration of Allylacetic Acid and Related Compounds

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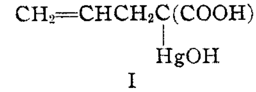
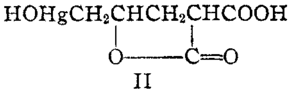
In the course of a study of the diuretic properties of the products obtained by addition of mercuric acetate to olefins, the mercurations of allylacetic acid and allyldiphenylacetic acid were accomplished. On the basis of the analytical results, the products from these γ,δ-unsaturated acids are considered to be of similar structure. Mercurated allyldiphenylacetic acid was converted, by reaction with bromine, to α,α-diphenyl-δ-bromo-γ-valerolactone, indicating that the mercuration product is a δ-chloromercuri-γ-valerolactone.

The formation of a complex between mercuric sulfate and allylacetic acid has been reported,[1] but the product was not isolated. The only mercurial which has been isolated and studied from the mercuration of γ,δ-unsaturated acids is that from allylmalonic acid.[2] This mercuration product was postulated to be the anhydride of compound I.



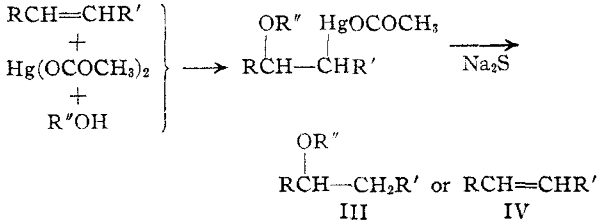
$CH_2{=}CHCH_2C(COOH)_2$ with HgOH below the C

I

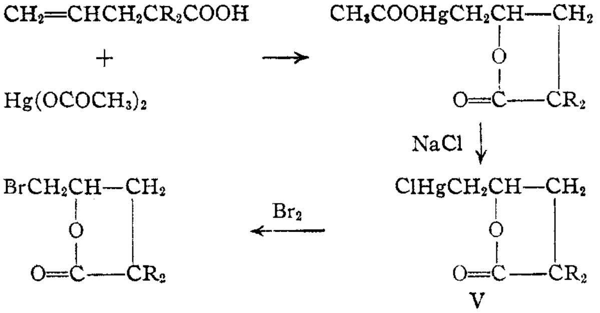


II

This structure was assigned on the basis of the formation of allylmalonic acid by the reaction of hydrogen sulfide with an alkaline solution of the mercuration product. Structures such as the anhydride of the γ-lactone, II, or of the corresponding δ-lactone were rejected since it was postulated that these lactones on reaction with hydrogen sulfide in sodium hydroxide would form the α-carboxyvalerolactones. Of the mercurials obtained by addition to an olefinic double bond, however, only those obtained by the mercuration of α,β-unsaturated acids or esters (R′ = COOH) have been converted by sodium sulfide to the corresponding alcohol or ether (III, R″ = H or alkyl) from which the mercury has been removed. Other mercurials of the olefin-addition type may react with sodium sulfide to form the olefin (IV) from which the mercurial was derived.[3]



In the course of a study of a diversity of organic mercurials as potential diuretics, allylacetic acid and allyldiphenylacetic acid were mercurated in methyl alcohol. The mercuration products were converted to the chloromercurials by reaction with sodium chloride. In both cases analyses of the product agreed with a molecular formula of $C_5H_6O_2$-$HgClR_2$ (V, R = H or C_6H_5), indicating that a methoxy group had not been added. The chloromercurial obtained *via* the mercuration of allyldiphenylacetic acid was allowed to react with bromine in chloroform, producing α,α-diphenyl-δ-bromo-γ-valerolactone identical with that formed by reaction of allyldiphenylacetic acid with bromine. The most reasonable formula for V, R = C_6H_5 would accordingly be α,α-diphenyl-δ-chloromercuri-γ-valerolactone.[4] The chloromercurial obtained from allylacetic acid has been assumed to be δ-chloromercuri-γ-valerolactone (V, R = H) on the basis of analyses.



The formation of the lactone rather than the methoxymercuration product is similar to the formation of 2-substituted mercurimethyl-2,3-dihydrobenzofuran by the reaction of mercuric salts with *o*-allylphenol in alcohol.[5] This latter reaction is of interest in that it can be accomplished using mercuric chloride or mercuric sulfate whereas methoxymercuration is successful with mercuric salts of mineral acids only in the presence of alkali. Similarly, α,α-diphenyl-δ-chloromercuri-γ-valerolactone is produced in good yield by the reaction of allyldiphenylacetic acid with mercuric chloride in methyl alcohol.

The remarkable stability of 2-chloromercurimethyl-2,3-dihydrobenzofuran (VI) toward mineral acids[5] and the similarity of the structures of V and VI suggested an investigation of the stability of V in the presence of mineral acid. This problem is under investigation and will be reported in the future.

From the reaction of hydrogen sulfide with a suspension of α,α-diphenyl-δ-chloromercuri-γ-valerolactone (V, R = C_6H_5) in aqueous alkali, allyldiphenylacetic acid was isolated in good yield, indicating that a lactone of type V will react with sodium hydroxide and hydrogen sulfide to form the corresponding olefin from which it was derived and suggesting that compound II would react with so-

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[1] E. Billmann and A. Hoff, *Rec. trav. chim.*, **36**, 289 (1916).

[2] E. Billman and A. Hoff, *ibid.*, **36**, 306 (1916).

[3] F. C. Whitmore, "Organic Compounds of Mercury," (Chemical Catalog Co.), Reinhold Publishing Corp., New York, N. Y., 1921, pp. 53-55; L. E. Mills and R. Adams, This Journal, **45**, 1842 (1923)

[4] The possibility that the mercurial possesses a δ-lactone structure has not been unequivocally eliminated since if hydrogen bromide were present as a contaminant of the bromine, the δ-lactone could presumably by converted to allyldiphenylacetic acid, which would subsequently react with bromine to form α,α-diphenyl-δ-bromo-γ-valerolactone. The γ-lactone structure is favored over the δ-lactone structure on the basis of the preferred formation of γ-lactones and the occurrence of methoxymercuration in accordance with Markownikoff's rule as noted by Pearson, Sigal and Krug, *J. Org. Chem.*, **15**, 1048 (1950).

[5] R. Adams, F. L. Roman and W. N. Sperry, This Journal, **44**, 1781 (1922)

dium sulfide to form allylmalonic acid. Accordingly, the product isolated by Biilmann and Hoff from mercuration of allylmalonic acid could reasonably be the anhydride of II.

Pharmacology.—γ-Chloromercuri-γ-valerolactone (V, R = H) would appear on the basis of preliminary studies to be less effective as a diuretic in dogs at a dosage of 0.006 millimole/kg. than, and three to four times as toxic as, the clinical mercurial diuretics when the toxicity is based on the LD_{50}, 14 days in rats following single intravenous dosage.[6] α,α-Diphenyl-γ-chloromercuri-α-valerolactone (V, R = C_6H_5) was not evaluated pharmacologically since a satisfactory aqueous solution could not be prepared.

Experimental[7]

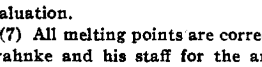
δ-Chloromercuri-γ-valerolactone (V, R = H).—A mixture of 10 g. (0.10 mole) of γ-pentenoic acid, 32 g. (0.10 mole) of mercuric acetate and 350 ml. of methyl alcohol was allowed to stand at room temperature for 2 days. The insoluble material was removed by filtration and an aqueous solution containing 9.0 g. (0.16 mole) of sodium chloride was added to the filtrate. A minute amount of solid was removed by filtration and the filtrate was concentrated at room temperature. The viscous residue, after washing with a small amount of water, was crystallized from ethyl alcohol. The crystallized material weighed 5.0 g. (15%) and melted at 81–82°.

Anal. Calcd. for $C_5H_7O_2HgCl$: Hg, 59.85; Cl, 10.58. Found: Hg, 59.75; Cl, 11.01.

The isolation of reaction products was hindered by the difficulty of inducing crystallization. The low yield might indicate the formation of some δ-chloromercuri-γ-methoxyvaleric acid.

Mercuration of Allyldiphenylacetic Acid with Mercuric Acetate in Methyl Alcohol.—A mixture of 5.0 g. (0.02 mole) of allyldiphenylacetic acid,[8] 6.3 g. (0.02 mole) of mercuric acetate, 2 ml. of acetic acid and 175 ml. of methyl alcohol was heated under reflux for sixteen hours. The insoluble material was removed by filtration and a solution of 2.5 g. (0.04 mole) of sodium chloride in 15 ml. of water was added to the filtrate. After crystallization of the precipitate from ethyl alcohol, the product weighed 5.4 g. (55%) and melted at 202–203°.

Anal. Calcd. for $C_{17}H_{15}O_2HgCl$: Hg, 41.16; Cl, 7.27. Found: Hg, 40.79; Cl, 7.55.

When the mercuration was accomplished using only 40% of the methyl alcohol used in the preceding procedure, a precipitate of the acetoxymercurial compound,  $\underset{\text{CO}\text{———}\text{O}}{(C_6H_5)_2\text{-}C\text{—}CH_2CHCH_2HgOCOCH_3}$ separated in close to quantitative yield. After crystallization from isopropyl alcohol, the product melted at 159–161°.

Anal. Calcd. for $C_{19}H_{18}O_4Hg$: Hg, 39.26. Found: Hg, 38.66.

The crude product was converted quantitatively to the chloromercuri compound (V, R = C_6H_5) by reaction with sodium chloride.

Mercuration of Allyldiphenylacetic Acid with Mercuric Chloride in Methyl Alcohol.—A solution of 1.1 g. (0.004 mole) of mercuric chloride in 100 ml. of methyl alcohol was added to 1.0 g. (0.004 mole) of allyldiphenylacetic acid in 30 ml. of methyl alcohol. After 1 hour, the solution was concentrated to dryness at room temperature. The residue was washed with 100 ml. of cold water and with 20 ml. of hot water and then crystallized from 200 ml. of ethyl alcohol. The crystalline product weighed 1.0 g. (50%) and melted at 203–204°. The melting point was not depressed by mixture with the chloromercurial produced *via* mercuration with mercuric acetate in methyl alcohol.

Mercuration of Allyldiphenylacetic Acid with Mercuric Acetate in Water.—A solution of 2.5 g. (0.008 mole) of mercuric acetate in 100 ml. of water was added to a mixture of 2.0 g. (0.008 mole) of allyldiphenylacetic acid, 2.7 ml. of 10% sodium hydroxide and 100 ml. of water. The mixture was warmed gently and then allowed to stand overnight. The mother liquors were removed by decantation and to the suspension of the solid material in 150 ml. of methyl alcohol was added a solution of 3.0 g. of sodium chloride in 20 ml. of water. After the mixture was heated gently for 10 minutes, it was cooled and the solid material was collected by filtration. After crystallization from ethyl alcohol, the product weighed 2.0 g. (50%) and melted at 202–203° with no depression of melting point upon admixture with the chloromercurial obtained *via* mercuration with mercuric acetate in methyl alcohol.

Reaction of α,α-Diphenyl-δ-chloromercuri-γ-valerolactone with Bromine.—To 1.5 g. of the mercurial obtained by the mercuration of allyldiphenylacetic acid in 50 ml. of chloroform was added gradually in sunlight a solution of 0.5 g. of bromine in 12 ml. of chloroform. The white precipitate was removed by filtration and the filtrate was concentrated to dryness at room temperature. The residue was dissolved in ether and the ethereal solution was washed with two 15-ml. portions of an aqueous solution, of which each portion contained 3 g. of sodium bromide. The ethereal solution was then concentrated to dryness, and the residue was crystallized from ethyl alcohol. The white crystals weighed 0.8 g. (80%) and melted at 88–89° (cor.). No depression of melting point was noted in a mixed melting point determination with α,α-diphenyl-δ-bromo-γ-valerolactone, prepared by the reaction of allyldiphenylacetic acid with bromine according to the method of Craig and Witt.[9]

Reaction of α,α-Diphenyl-δ-chloromercuri-γ-valerolactone with Sodium Sulfide.—Hydrogen sulfide was added to a suspension of 3.0 g. (0.006 mole) of α,α-diphenyl-δ-chloromercuri-γ-valerolactone in 40 ml. of 2.5% sodium hydroxide solution. To the black reaction mixture was added 30 ml. of 6% acetic acid. The solid was collected, washed with water and the organic material was extracted from the mercuric sulfide with 50 ml. of ethyl ether. The residue from the concentration of the ethereal extract weighed 1.0 g. (65%), melted at 142.5–143.5° and exhibited no depression of melting point with allyldiphenylacetic acid.

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[6] We are indebted to Mr. P. A. Nuhfer for the pharmacological evaluation.

[7] All melting points are corrected. We are indebted to Mr. H. C. Krahnke and his staff for the analyses. Determination of mercury was accomplished by precipitation as mercuric sulfide from hydrochloric acid solution.

[8] Generously suppiled by General Mills, Inc., Minneapolis, Minn.

[9] P. N. Craig and I. N. Witt, THIS JOURNAL, 72, 4925 (1950).