[Contribution from the Dept. of Chemistry, University of Toronto]

METHOXYMERCURATION OF THE CINNAMIC ACIDS

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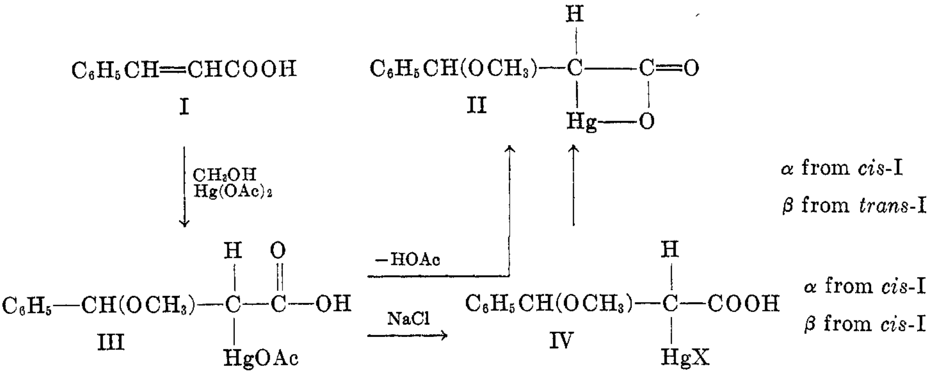
cis-Cinnamic acid (I) was hydroxymercurated by Biilman (1) while Schrauth, Schoeller, and Struensee (2) methoxymercurated *trans*-cinnamic acid (I) and obtained the analogous diastereomer, β-3-methoxy-3-phenyl-anhydro-2-hydroxymercuripropanoic acid (II).

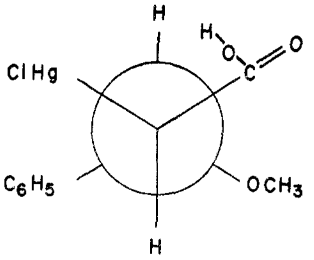


These authors were unable to specify whether the anhydro product (II) was formed during the process of oxymercuration or subsequent to it. We have now found, by isolation of β-2-chloromercuri-3-methoxy-3-phenylpropanoic acid (IV, X = Cl, which evidently derived from the acetoxymercurial, III), that anhydromercurial formation occurs subsequent to the initial oxymercuration of *trans*-cinnamic acid. This isolation has been accomplished by drowning the reaction system in dilute aqueous sodium chloride just when the precipitation of the anhydromercurial begins to occur. Evidently at this point the acetoxymercurial (III) begins to lose acetic acid, thus to be converted to II.

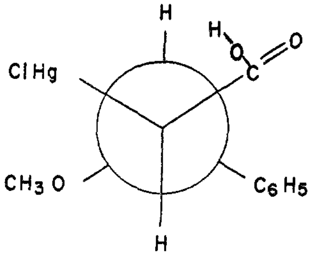
The β-3-methoxy-3-phenyl-2-chloromercuripropanoic acid (IV, X = Cl) does not precipitate from the aqueous sodium chloride solution but must be extracted from it with chloroform. The crystals which slowly form in this extract contain chloroform in a 1:1 ratio. The chloroform-free mercurial may be obtained by dissolving in an excess of alkali either the β-anhydromercurial or the crystals of IV which contain chloroform, and then carefully acidifying with the calculated amount of dilute hydrochloric acid. An excess of sodium chloride seems to be necessary because an alkaline solution of IV precipitates only the β-anhydromercurial (II) when it is acidified with dilute sulfuric acid.

On the other hand an alkaline solution of the β-anhydromercurial (II), which contains only one equivalent of sodium bromide, may be acidified by dilute sulfuric acid to yield β-3-methoxy-3-phenyl-2-bromomercuripropanoic acid (IV, X = Br). This acidification must be carried out rapidly. Indeed when we acidify slowly we obtain a mixture of anhydromercurial (II) and *trans*-cinnamic acid which melts at about 160–166°. This is approximately the melting point reported for IV (X = Br) by Schrauth and Geller (3), whereas the compound we designate as IV (X = Br) melts at 85°. Our bromomercurial is quite unstable, and cannot be purified for analysis because it reverts to the anhydromercurial (II) in any medium from which it can be crystallized.

Indeed the β-chloromercurial (IV, X = Cl) is sufficiently unstable that it can be crystallized to analytical purity only from chloroform with which it forms the 1:1 solvate. Solution in solvents like methanol convert it at once to the β-anhydromercurial (II). This behavior is in significant contrast to that observed for the α-3-methoxy-3-phenyl-2-chloromercuripropanoic acid (IV, X = Cl). This diastereomer may be obtained by acidification with hydrochloric acid on an alkaline solution of the α-anhydromercurial (II) which we have prepared by methoxymercuration of *cis*-cinnamic acid. This α-IV is much more stable than the β-isomer, and may be boiled with hot methanol without loss of hydrogen chloride. If, in consideration of this contrast, one represents these diastereomeric chloromercurials by Newman's description (4), the conformations most favorable for elimination of hydrogen chloride are Va and Vb.



Va



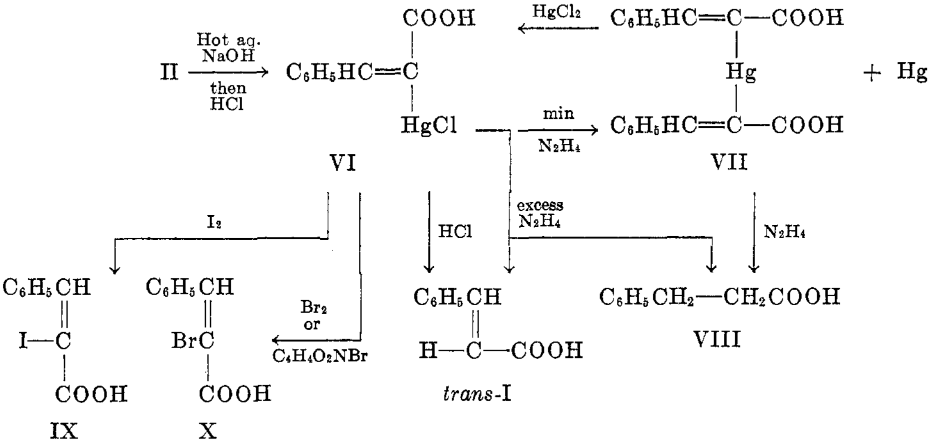
Vb

Insofar as steric hindrance is involved the conformation Vb ought to be most favorable since phenyl but not methoxyl ought to be oriented as far as possible from the mercuri linkage. Upon this basis the β-diastereomer would be assigned structure Vb.

For the first time we have been able to eliminate the elements of methanol from methoxymercurials. When either of the anhydromercurials (α or β-II) is boiled in hot alkali for several hours the sole product, in good yield, is 2-chloromercuri-3-phenylpropenoic acid (VI). Because treatment with hot alkali would be expected to cause diastereomeric isomerization due to hydrogen on the carbon atom *vicinal* to the carboxyl group, we have made no attempt to ascertain which of the two diastereomers loses methanol with greater ease. This information also is lacking from consideration of the geometric configuration of VI. We have as yet been unable to decarboxylate the acid so as to compare the resulting styrylmercurial with the one which already is known (5).

However only a single pure 2-bromo-3-phenylpropenoic acid (X) (6) is obtained by treatment of VI with bromine or bromosuccinimide. Also only one 2-iodo-3-

phenylpropenoic acid (IX) (7) is obtained by treatment with iodine. Both of these acids are thought to be *trans* with respect to the phenyl and carboxyl groups. Furthermore treatment of VI with hydrochloric acid leads to *trans*-cinnamic acid. On the basis of this equivocal evidence one may tentatively consider the carboxyl group in VI to be *trans* to the phenyl group.



Despite the fact that reduction of mercurials by hydrazine hydrate is thought to proceed *via* radical interchange wherein structural configuration is lost (8), treatment of VI with a small amount of this reducing agent gives a mixture of the same geoisomer of VI which is reduced and also 2-mercury-bis-3-phenylpropenoic acid. Since this bis-mercurial may be reconverted to VI by treatment with mercuric chloride its geometric configuration also is identical (8).

Evidence that the hydrazine reduction of VI proceeds *via* a radical mechanism is afforded by the observation that an excess of the reducing agent (which leaves cinnamic acid unchanged) converts VI to a mixture of 3-phenylpropanoic acid (VIII) and cinnamic acid (I), although only 3-phenylpropanoic acid is obtained when the bis-mercurial (VII) is treated with excess hydrazine hydrate.

EXPERIMENTAL

Melting points have been corrected against reliable standards. The x-ray reflections are reported as the strongest powder lines using Cu $K\alpha$ radiation (Ni filtered) and relative intensities $[I/I_1]$.

β-3-Methoxy-3-phenyl-anhydro-2-hydroxymercuripropanoic acid (II). A solution of 7.4 g. (0.05 mole) of *trans*-cinnamic acid (m.p. 133°) in 30 ml. of methanol was added to a solution of 15.9 g. (0.05 mole) of mercuric acetate in methanol. The mercuric cinnamate which was precipitated by admixture of these solutions was found to be capable of converting cyclohexene into 2-methoxycyclohexylmercuric salts. However this mercuric cinnamate was dissolved by boiling the methanolic suspension for ten minutes. After one day the new precipitate of anhydro-mercurial (16.1 g., 85%) was filtered off, m.p. 204–206° (decomp.), x-ray pattern [10] 16.3; [4] 12.0; [2] 9.6; [1] 17.5, 14.7, 13.9.

Anal. Calc'd for $C_{10}H_{10}HgO_3$: C, 31.6; H, 2.66.
Found: C, 31.2; H, 2.67.

β-2-Chloromercuri-3-methoxy-3-phenylpropanoic acid (IV, X = Cl). Eighteen minutes after the solution of mercuric cinnamate was prepared in hot methanol identical with that described above, the anhydromercurial began to precipitate and the system was quickly filtered into 350 ml. of 10% aqueous sodium chloride. The clear solution was extracted with ten 25-ml. portions of chloroform. When this extract was vacuum-evaporated to 20% of the original volume the crystals of chloromercurial and chloroform (1:1) separated, 6.0 g. (27%), m.p. 83–89° (decomp.). The filtrate, evaporated further, yielded 4.25 g. (58%) of impure *trans*-cinnamic acid, m.p. 124–127°. Treatment of the chloroform-extracted aqueous liquor with alkali precipitated 5.15 g. (48%) of mercuric oxide.

The impure chloromercurial was crystallized from hot chloroform (32 ml./g., 84% recovery), m.p. 89–91° (decomp.). The melting point was not improved by further crystallization. X-ray diffr. [10] 7.89, 6.50, 4.29; [9] 4.98, 363. The distillate collected by heating in a vacuum contained chloroform (9).

Anal. Calc'd for $C_{11}H_{12}Cl_4HgO_3$: C, 25.2; H, 2.36; Cl, 25.1.

Found: C, 24.8; H, 2.36; Cl, 24.5.

When this compound was dissolved in one equivalent of alkali and precipitation was effected by cautious acidification with 1:20 hydrochloric acid, the chloromercurial, m.p. 100–102° (decomp.), was obtained without chloroform of solvation. It could be converted to the solvate by crystallization from chloroform, but when 0.5 g. was dissolved in hot methanol or ethanol (10 ml./g.), the solution precipitated 0.12 g. of impure β-anhydromercurial (m.p. 186–188°) after several minutes, and the mother liquor became *p*H 3.6. The identity of the anhydromercurial was established by mixture melting point (203–205°, decomp.) after it was crystallized from 1:4 benzene-ethanol (42 ml./g.).

The β-chloromercurial (IV) could also be obtained by dissolving the β-anhydromercurial (II, 0.2 g., 0.005 mole) in 5 ml. of 1% aqueous sodium hydroxide, then adding 0.3 ml. of saturated aqueous sodium chloride, chilling, and acidifying cautiously with 1:20 hydrochloric acid until precipitation was complete. This chloromercurial (0.12 g., 54%) melted at 99–101° (decomp.). Only cinnamic acid was obtained if an excess of hydrochloric acid was used. Acidification with sulfuric rather than hydrochloric acid regenerated the anhydromercurial, or cinnamic acid if an excess was used.

β-2-Bromomercuri-3-methoxy-3-phenylpropanoic acid (IV, X = Br). No matter how gradually a cold alkaline solution of the β-anhydromercurial (II) was neutralized with 1:20 hydrobromic acid, the substance was converted to *trans*-cinnamic acid. However if 0.378 g. (0.001 mole) of the β-anhydromercurial was dissolved in 5 ml. of 1% aqueous sodium hydroxide containing 0.103 g. (0.001 mole) of sodium bromide and this cold solution was acidified rapidly with dilute sulfuric acid, a gum was precipitated, 0.29 g. (63%), which gradually solidified, m.p. 68–85° (decomp.). This bromomercurial could not be purified for analysis but it was characterized by conversion to the acetoxymercurial with silver acetate in chloroform, followed by treatment with aqueous sodium chloride to form the β-chloromercurial (IV, X = Cl).

α-3-Methoxy-3-phenyl-anhydro-2-hydroxymercuripropanoic acid (II). A mixture of 0.162 g. (0.0011 mole) of *cis*-cinnamic acid (m.p. 68°) and 0.348 g. (0.0011 mole) of mercuric acetate in 4 ml. of methanol was boiled under reflux until both solids had dissolved. After three hours the anhydromercurial which precipitated subsequently was filtered off, 0.42 g. (100%), m.p. 202–204° (decomp.), x-ray pattern: [10] 13.1; [1] 6.9, 6.6, 4.1, 3.9.

Anal. Calc'd for $C_{10}H_{10}HgO_3$: C, 31.6; H, 2.66.

Found: C, 31.7; H, 2.79.

α-2-Chloromercuri-3-methoxy-3-phenylpropanoic acid (IV, X = Cl). The α-anhydromercurial (II, 0.10 g., 0.00026 mole) was dissolved in 5 ml. of 0.3% aqueous sodium hydroxide, then 3.5% hydrochloric acid was added to this solution until precipitation was complete. This α-chloromercurial (0.10 g., 91%), m.p. 179–181° (decomp.), was dissolved in 1 ml. of hot methanol in which it was stable. The system made turbid with water was chilled, 0.08 g. (80%), m.p. 179.6–181° (decomp.); x-ray diffr. [10] 4.02; [9] 6.32; [8] 5.79, 5.40; [5] 4.55.

Anal. Calc'd for $C_{10}H_{11}ClHgO_3$: C, 28.9; H, 2.65.

Found: C, 29.1; H, 2.89.

2-Chloromercuri-3-phenylpropenoic acid (VI). A solution of 7.60 g. (0.02 mole) of either α- or β-3-methoxy-3-phenylanhydro-2-hydroxymercuripropanoic acid (II) in 80 ml. of 10% aqueous sodium hydroxide was boiled under reflux for six hours, then cooled and filtered into an excess of cold 12% hydrochloric acid. The 2-chloromercuri-3-phenylpropenoic acid which was precipitated (5.23 g., 68%) melted at 193–197° (decomp.). It was crystallized (76% recovery) from hot ethanol (10 ml./g.), m.p. 207–209°; x-ray pattern: [10] 10.2; [9] 5.05; [7] 8.54.

Anal. Calc'd for $C_9H_7ClHgO_2$: C, 28.2; H, 1.84.
Found: C, 28.2; H, 1.85.

When this compound (VI) was boiled with 18% hydrochloric acid it was converted to *trans*-cinnamic acid. It could be oxidized in 82% yield to benzoic acid by treatment with hot aqueous alkaline potassium permanganate.

2-Bromo-3-phenylpropenoic acid (X). To a chilled and stirred suspension of 0.19 g. (0.0005 mole) of 2-chloromercuri-3-phenylpropenoic acid (VI) in 5 ml. of absolute ethanol was added 0.08 g. (0.0005 mole) of bromine. After 20 minutes the colorless solution was poured into 10 ml. of 10% aqueous sodium bromide. After evaporation of the ethanol, 0.12 g. (93%) of 2-bromo-3-phenylpropenoic acid, m.p. 129–130°, was obtained. A mixture melting point with authentic material (6) (m.p. 131°) was not depressed.

The same acid was obtained in 79% yield by boiling the chloromercuriphenylpropenoic acid with one equivalent of *N*-bromosuccinimide in carbon tetrachloride for 28 hours.

3-Phenyl-2-iodopropenoic acid (IX). A mixture of 0.19 g. (0.0005 mole) of α-chloromercuriphenylpropenoic acid and 0.12 g. (0.0005 mole) of iodine in 5 ml. of dry methanol was stirred for 18 hours, then poured into 15 ml. of 13% aqueous sodium chloride. Ether extraction removed 0.13 g. (90%) of impure iodophenylpropenoic acid (IX), m.p. 149–150°. After four crystallizations from benzene (5 ml./g., 54% recovery) the melting point was raised to that of an authentic specimen (162°) and no depression of mixture melting point was observed.

2-Mercury-bis-3-phenylpropenoic acid (VII). To a solution of 1.91 g. (0.005 mole) of 2-chloromercuri-3-phenylpropenoic acid in 60 ml. of 2% aqueous sodium hydroxide solution was added 0.10 g. (0.0016 mole) of 85% hydrazine hydrate. After 40 hours on the steam-bath this system was cooled, filtered to remove 0.43 g. (43%) of metallic mercury, and acidified with dilute hydrochloric acid. The precipitate, weighing 1.14 g. (m.p. 178–190°), was extracted with 30 ml. of boiling methanol for five minutes, leaving 0.35 g. (29%) of insoluble bis-mercurial, m.p. 199–201° (decomp.). This melting point was not raised by crystallization from dioxane; x-ray pattern: [10] 14.2, 2.37; [7] 6.23, 2.07; [6] 6.32, 3.29.

Anal. Calc'd for $C_{18}H_{14}HgO_4$: C, 43.7; H, 2.85.
Found: C, 44.1; H, 3.04.

The methanolic extract yielded 0.73 g. (38%) of 2-chloromercuri-3-phenylpropenoic acid, m.p. 202–206° (decomp.), when it was evaporated to dryness. This product was identified by mixture melting point after it was purified by crystallization. The same acid (m.p. 206–207°, decomp.) was obtained in 83% yield (0.45 g.) as crystals from the cooled solution when 0.35 g. (0.0007 mole) of the bis-mercurial was boiled for 90 minutes with 10 ml. of methanol containing 0.19 g. (0.0007 mole) of mercuric chloride.

When 0.20 g. (0.0004 mole) of the bis-mercurial (VII) was dissolved in 5 ml. of 2% aqueous sodium hydroxide and 1 ml. (0.016 mole) of 85% $N_2H_4 \cdot H_2O$ was added, the system precipitated mercury during eight hours on the steam-bath. The filtered, cooled system was acidified with hydrochloric acid and thrice extracted with 5-ml. portions of diethyl ether. Evaporation of the etherous extract left 0.09 g. (75%) of 3-phenylpropanoic acid, m.p. 43–48°. The substance was characterized by a mixture melting point after it was purified (m.p. 48.5°) by crystallization from petroleum ether (b.p. 60–70°) (6 ml./g., 55% recovery).

Reduction of 2-chloromercuri-3-phenylpropenoic acid (VII) *with excess hydrazine hydrate.* A solution containing 1.91 g. (0.005 mole) of VII, 1.2 g. of sodium hydroxide, and 6 ml. (0.096 mole) of 85% hydrazine hydrate in 60 ml. of water was heated by a steam-bath for 22 hours, then filtered to remove 0.98 g. (98%) of metallic mercury. Acidification of the cooled filtrate yielded 0.12 g. (16%) of *trans*-cinnamic acid, m.p. 129–131°, (authenticated by mixture melting point) after crystallization from petroleum ether (b.p. 60–70°). The mother liquor, extracted with three 20-ml. portions of ether, yielded 0.41 g. (55%), m.p. 41–46°, of impure 3-phenylpropanoic acid which was characterized by mixture melting point after purification from petroleum ether (75% recovery).

SUMMARY

1. The formation of β-3-methoxy-3-phenyl-anhydro-2-hydroxymercuripropanoic acid has been shown to occur subsequent to the methoxymercuration of *trans*-cinnamic acid which yields, initially, β-3-methoxy-3-phenyl-2-acetoxymercuripropanoic acid.

2. Both α- and β-2-chloromercuri-3-methoxy-3-phenylpropanoic acids have been prepared. The α-acid has been found to be more stable than the β-diastereomer.

3. Long reflux of alkaline solutions of the α- or β-3-methoxy-3-phenyl-anhydro-2-hydroxymercuripropanoic acid causes elimination of methanol. The product, 2-chloromercuri-3-phenylpropenoic acid after treatment with hydrochloric acid, has been characterized by replacement of the mercuri linkage with bromine or iodine. Also it has been characterized as 2-mercury-bis-3-phenylpropenoic acid having the same geometrical configuration.

TORONTO 5, CANADA

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