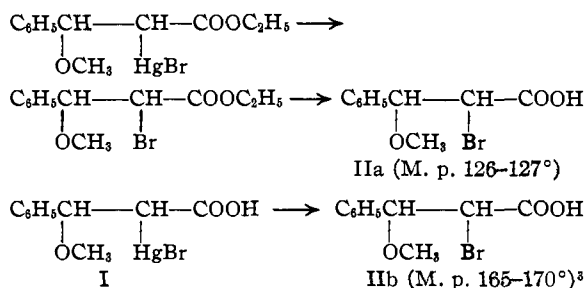


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The α -Bromo- β -methoxy- β -phenylpropionic Acids¹

BY EDWARD J. VAN LOON AND HERBERT E. CARTER

The synthesis of α -amino- β -hydroxy acids is complicated by the fact that most of them contain two asymmetric carbon atoms and hence exist in two racemic forms which are usually difficult to separate. A further difficulty is introduced by the fact that an α -halogen- β -hydroxy acid when treated with ammonia is converted into a glycidic acid which adds ammonia, usually yielding an α -hydroxy- β -amino acid as the main product. If the amination method is to be used, therefore, the hydrogen of the β -hydroxyl must be replaced by a group not readily removed under the conditions of amination. For this purpose an alkyl group seems most suitable. Therefore when we became interested in synthesizing *dl*-threonine we considered various methods of preparing α -halogen- β -alkoxy acids with particular reference to the possibility of obtaining each racemic form independently of the other. In this connection the work of Schrauth and Geller² on the mercuriation of cinnamic acid and its esters seemed to offer a promising lead. The following equation shows the important points.



Thus Schrauth and Geller obtained the two racemic bromo acids by separate reactions each of which yielded a single form. It was decided, therefore, to repeat the work, amplify it in certain particulars and, if possible, apply the results to other unsaturated acids and esters.

In attempting to duplicate the previous work, several discrepancies were found. In the mercuriation of cinnamic acid the addition product began to separate immediately. (Schrauth and

Geller obtained a clear solution even after twelve hours.) At the end of twelve hours a white crystalline substance having the correct mercury content for anhydro- α -hydroxymercuri- β -methoxy- β -phenylpropionic acid (Ia) had precipitated almost quantitatively. This was quite soluble in chloroform and only very slightly soluble in aqueous potassium bromide. It was rather surprising, therefore, to discover that a sample which had remained in contact with the mother liquor for a week was completely insoluble in chloroform and readily soluble in aqueous potassium bromide. This second substance (Ib) had a variable mercury content which was always lower than that of Ia. A possible explanation of this behavior is that Ia in contact with the mother liquor polymerized to an intermolecular salt of the structure

$\text{AcO} \left[\begin{array}{c} \text{C}_6\text{H}_5 \\ | \\ \text{CH-OCH}_3 \\ | \\ \text{CH-C} \begin{array}{c} // \\ \text{O} \end{array} \text{O} \end{array} \right]_x \text{H}$ whose size is limited by the increasing insolubility of the polymer as the molecular weight goes up. The insolubility of Ib in organic solvents makes it difficult to obtain conclusive evidence concerning its structure. From a practical standpoint this discovery is valuable since the ready solubility of Ib in aqueous potassium bromide greatly simplifies the preparation of α -bromomercuri- β -methoxy- β -phenylpropionic acid (I).

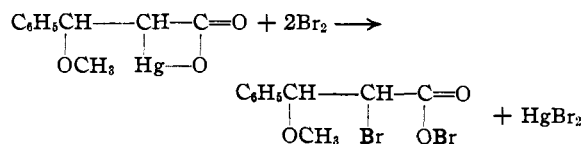
The bromination of I, Ia, and Ib was studied under several different conditions. Contrary to the results previously reported a mixture of the two racemic bromo acids was obtained in every case, although the relative amounts of the two forms were altered somewhat by variation in the temperature and type of light to which the reaction was exposed. It is interesting to note that Ia and Ib took up almost two moles of bromine per mole. Since Bockemüller⁴ has shown that mercury salts of organic acids react with bromine yielding acyl hypobromites, it seems probable that the reaction proceeded as shown in the equation. Attempts to isolate the hypobromite were unsuccessful due to the instability of the compound.

(1) Presented at the Pittsburgh meeting of the American Chemical Society, September 8, 1936.

(2) Schrauth and Geller, *Ber.*, **55**, 2783 (1922).

(3) Conant and Jackson [*THIS JOURNAL*, **46**, 1727 (1924)] reported that this form when pure melts at 182-183°.

(4) Bockemüller and Hoffmann, *Ann.*, **519**, 165 (1935).



In seeking other methods of carrying out the bromination, it was discovered that a solution of Ib in aqueous potassium bromide rapidly absorbed bromine giving an excellent yield of the bromo acid melting at 126–127° (IIa). Fractional crystallization of this material disclosed, however, that it was not homogeneous but contained some IIb. After laborious fractionation from benzene and ethyl acetate, pure IIa melting sharply at 139–140° was obtained. Later a simple method of separating the two forms was afforded by the discovery that the sodium salt of IIb is almost quantitatively insoluble in an aqueous sodium carbonate solution whereas the sodium salt of IIa is quite soluble.

These results indicate that a single racemic form of the bromo acid cannot be obtained by this method. However, the bromination of the potassium salt of I does furnish a remarkably simple method of synthesizing a mixture of the bromo acids. This reaction has been utilized with satisfactory results in the synthesis of *dl*-threonine from crotonic acid.⁵

Experimental

Mercuration of Cinnamic Acid.—A solution of 148 g. of pure cinnamic acid⁶ in 600 cc. of hot methyl alcohol was added to a solution of 320 g. of mercuric acetate in 2 liters of hot methyl alcohol. A thick precipitate formed immediately and dissolved on heating. When the hot solution was allowed to cool, a fine white solid began to separate and, at the end of twelve hours, the reaction was practically complete. The solid was filtered and washed several times with methyl alcohol. The yield was 370 g. The compound (Ia) decomposed at 210–211° and was soluble in chloroform but not in other organic solvents. It dissolved only slightly in aqueous potassium bromide.

Anal. Calcd. for C₁₀H₁₀O₃Hg: Hg, 52.99. Found: Hg, 52.81.

When Ia was allowed to stand in the mother liquor for five to six days a second substance (Ib) was formed. This compound was insoluble in all common organic solvents, decomposed at 210–212° and gave consistently lower mercury analyses than Ia.

Anal. Calcd. for C₁₀H₁₀O₃Hg: Hg, 52.99. Found: Hg, 51.53, 51.46, 50.19.

Ib dissolved readily in aqueous potassium bromide and was always used in preparing I.

(5) West and Carter, *J. Biol. Chem.*, **119**, 103 (1937).

(6) If a crude cinnamic acid obtained from Antoine Chiris was used without purification, the mercuration product obtained was always insoluble in aqueous potassium bromide.

The variation in solubility of the addition product with the time of mercuration is shown in Table I.

TABLE I

Time of mercuration, days	% soluble in 5 volumes of CHCl ₃	% soluble in 5 volumes of 10% aq. KBr
1	95–98	5–10
2	60–70	60–70
3	45–55	70–80
4	10–15	85–90
5	5–10	90–95
6	0–3	98–100

α -Bromomercuri- β -methoxy- β -phenylpropionic Acid (I).

—Two hundred grams of Ib was dissolved in a solution of 60 g. of potassium bromide in 1500 cc. of water. After filtration, the solution was acidified with 65 g. of glacial acetic acid, precipitating a heavy gum. On standing this material crystallized and was removed by filtration, washed with water and methyl alcohol, and dried. The bromomercuri acid thus obtained was practically pure and melted with decomposition at 118–120°. (Schrauth and Geller reported a melting point of 160–166°.) I is insoluble in the common organic solvents.

Bromination of Ia and Ib.—The brominations were carried out under several different conditions of solvent (chloroform and ethyl acetate), light (sunlight, diffuse daylight, dark), and temperature (0, 35, 60°). The product obtained in each case was a mixture of IIa and IIb melting between 120 and 140°. The brominations proceeded more rapidly at higher temperatures and in the presence of sunlight. A typical run is described below.

One-tenth mole of Ia or Ib was suspended in 200 cc. of ethyl acetate at room temperature and 32 g. of bromine was added as it was utilized. After an initial lag the reaction proceeded rapidly with the evolution of heat. After the bromination was complete, a slight amount of bromine was removed with aqueous sodium bisulfite. The ethyl acetate solution was then extracted with two 300-cc. portions of saturated sodium bicarbonate. The extracts were combined, washed with ether and acidified, precipitating a crude mixture of IIa and IIb containing some dibromocinnamic acid. The material was dissolved in 10 volumes of 10% sodium carbonate solution and warmed on the steam-bath for fifteen minutes to destroy the dibromocinnamic acid. On cooling the solution in an icebox overnight, the sodium salt of IIb precipitated in a nearly pure form. From this material was obtained 4–5 g. of pure IIb. The filtrate yielded 14–15 g. of IIa melting at 132–136° and still containing a very small amount of IIb which was removed by recrystallization from benzene or ethyl acetate. Pure IIa melts at 139–140°. If a solution of IIa in ethyl acetate is allowed to evaporate slowly at room temperature, beautiful hexagonal crystals of almost a centimeter in diameter are obtained.

Bromination of I.—Several different conditions of bromination were tried. The best yield of IIb was obtained by carrying out the reaction in boiling ethyl acetate. One mole of the bromo-mercuri acid (I) took up almost one mole of bromine. The solution was worked up as described for Ia and Ib yielding 90–105 g. of pure IIb and 70–80 g. of IIa.

Bromination of Potassium Salt of I.—One mole of Ib was dissolved in a solution of 180 g. of potassium bromide in 1500 cc. of water. The solution was cooled in an ice-bath and exposed to direct sunlight. A solution of 160 g. of bromine and 180 g. of potassium bromide in 600 cc. of water was added as it was utilized. The solution was acidified with 40% hydrobromic acid yielding a crude bromo acid mixture which was purified by heating with a 10% solution of sodium carbonate. The solution was cooled and acidified giving 170–190 g. of a bromo acid melting at 126–127°.

This material was dissolved in 10 volumes of 10% sodium carbonate solution and cooled overnight in an icebox. The precipitate yielded 15–18 g. of IIb and the filtrate 100–125 g. of impure IIa melting at 132–136°. This was re-

crystallized from 3 volumes of ethyl acetate giving pure IIa melting at 139–140°.

Summary

1. Cinnamic acid in methyl alcohol solutions reacts with mercuric acetate giving a product whose composition and properties vary with the length of time of mercuration.

2. The bromination of the mercuration products under various conditions yields a mixture of the two diastereomeric α -bromo- β -methoxy- β -phenylpropionic acids.

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Sulfur Studies. XIV. Some Derivatives of Certain Higher Mercaptans

BY DAN FORE, JR., AND R. W. BOST

Very little work has been done on mercaptans and derived sulfur compounds of a molecular weight greater than that of the decyl series. Noller and Gordon¹ prepared the four *n*-aliphatic mercaptans from undecyl through myristyl. Collin, Hilditch, and others² synthesized dodecyl, hexadecyl, and octadecyl mercaptans and the corresponding *n*-disulfides. In the present work the *n*-disulfides from dodecyl through nonadecyl (excepting pentadecyl), the lead salts of the parent thio alcohols, the corresponding 2,4-dinitrophenyl thioethers, and a few of the dinitrophenylalkyl sulfones were prepared. The starting point for the synthesis in each particular series was the appropriate alcohol, of which lauryl, myristyl, palmityl, and stearyl were kindly furnished in quantity by the du Pont Company. Access to the odd numbered carbon atom alcohols was had through treatment of the next lower alkylmagnesium bromide with polymerized formaldehyde.

The procedure for the preparation of the bromides was essentially that outlined in "Organic Syntheses."³ The yields ranged from 58 to 70%. Tri-, hepta- and nonadecyl alcohols were prepared by the method of Courtot⁴ in yields of 62, 48 and 50%, respectively.

The Mercaptans and Lead Mercaptides.—The mercaptans were prepared from the bromides by

the interaction with potassium hydrosulfide in absolute alcohol. It was found convenient to convert the crude mercaptans directly to the lead salts without preliminary purification. The crude product was precipitated from the hot reaction mixture by the addition of cold water and ice, and the mercaptan was removed by filtration or in a separatory funnel. After a thorough washing with water to remove any potassium hydrosulfide, the product was dissolved in boiling ethyl alcohol and enough alcoholic lead acetate added to ensure the complete precipitation of the yellow lead derivative. Following an hour's digestion, the precipitate was filtered hot, washed with cold water, and then with successive portions of hot acetone and boiling ether until no more soluble material could be extracted. Since the free mercaptans were oxidized with the greatest ease by air, it was found best to store the dried mercaptides as such in tightly stoppered bottles.

The melting points of the lead mercaptides are given below. They were analyzed for lead by fuming down with sulfuric acid and then digesting

TABLE I
LEAD MERCAPTIDES

Lead salt	M. p., °C.		% Lead	
	Darkens	Melts	Calcd.	Found
Tridecyl	97	100	32.4	33.0
Tetradecyl	99	104–105	31.1	31.8
Hexadecyl	99	106–107	28.7	29.1
Heptadecyl	100	108–109	27.6	27.7
Octadecyl	106	110–111	26.6	27.1
Nonadecyl	108	112–114	25.7	26.2

(1) Noller and Gordon, *THIS JOURNAL*, **55**, 1090 (1933).

(2) Collin, Hilditch, Marsh and McLeod, *J. Soc. Chem. Ind.*, **52T**, 272 (1933).

(3) *Org. Syntheses*, **15**, 24, 35 (1935).

(4) Courtot, "Le Magnesium en Chimie organique," 1926, p. 158.