

PREPARATION OF ALDEHYDES AND KETONES

The experimental procedure for the preparation of aldehydes and ketones has been already described (7) except for the inclusion of the following: before extraction with ether, the reaction mixture was heated to 50° for one-half hour in order to expel dissolved nitrogen and decompose excess diazotizes sulfanilic acid. This operation facilitates the extraction procedure.

LITERATURE CITED

- (1) Busignies, M.G., *Comp. rend.* **149**, 349 (1909).
- (2) Fecht, H., *Ber.* **40**, 3902 (1907).

- (3) Hurd, C., Webb, C., "Organic Syntheses," Vol. I, p. 217 Wiley, N. Y., 1941.
- (4) Pfeiffer, P., Blank, H., *J. prakt. Chem.* **153**, 242 (1939).
- (5) Sachs, F., Sachs, L., *Ber.* **38**, 511 (1906).
- (6) Sisti, A.J., Burgmaster, J., Fudim, M., *J. Org. Chem.* **27**, 279 (1962).
- (7) Stiles, M., Sisti, A.J., *Ibid.*, **25**, 1691 (1960).

RECEIVED for review April 24, 1963. Accepted September 25, 1963.

3,4,5-Trimethoxymandelic Acid

ALFONSO R. GENNARO, NORTON NEFF¹, and G. VICTOR ROSSI
Philadelphia College of Pharmacy and Science, Philadelphia 4, Pa.

DURING THE INVESTIGATION of the metabolic fate of mescaline, it became necessary to prepare 3,4,5-trimethoxymandelic acid (III) tagged with C-14 in the carboxyl group. The synthesis of this compound is reported herein. No published information concerning this material is available.

Classical methods of hydrolysis of the cyanohydrin formed from 3,4,5-trimethoxybenzaldehyde and potassium cyanide failed to yield the desired product. Alkaline hydrolysis gave a good yield of 3,4,5-trimethoxybenzoic acid, while acid hydrolysis afforded a red, intractable material. The compound was successfully synthesized by acetylation of the cyanohydrin and hydrolysis of the cyanoester (3), and by forming the imino ether from the cyanohydrin and subsequent hydrolysis of the ethyl ester (1). In the preparation of the radioactive material, using C-14 labelled potassium cyanide to form the cyanohydrin, the former synthesis was employed.

Using the method of Rapoport (2), a portion of the radioactive 3,4,5-trimethoxymandelonitrile was converted to carboxyl labelled 3,4,5-trimethoxyphenylacetic acid.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3,4,5-Trimethoxymandelonitrile (I) (2). A solution of 13.4 grams (0.13 mole) of sodium bisulfite in 50 ml. of water was added to 19.6 grams (0.1 mole) of 3,4,5-trimethoxybenzaldehyde in a beaker and the mixture stirred for 10 minutes, whereupon the contents solidified. Sufficient water was added to form a paste, the beaker placed in an ice bath, 150 ml. of ether added, and stirring continued for an additional 10 minutes. The lumps of addition product were broken up with a stirring rod, a cold solution of 11.7 grams (0.24 mole) of potassium cyanide in 30 ml. of water was added in one portion and the mixture stirred rapidly for one hour. An additional 20 ml. of ether and 1.4 grams of sodium bisulfite were added and stirring was continued for 30 minutes. After the ether layer was separated, the aqueous solution was extracted with two 25-ml.

portions of ether, the ether extracts were combined and washed with two 25-ml. portions of 20% sodium bisulfite solution and two 25-ml. portions of ice water. The ether solution was chilled in ice, dried with sodium sulfate and the solvent removed in vacuo to give 19 grams (90%) of (I), m.p. 99–100° [ref. (2), m.p. 99.6–100.8° C.] This material was used without further purification in subsequent syntheses.

α -Acetoxy-3,4,5-trimethoxyphenylacetone nitrile (II) (3). To 8 grams (0.036 mole) of (I), previously dried at 60° for 3 hours in a vacuum oven, was added a mixture of 8 ml. of dry pyridine and 20 ml. of acetic anhydride with cooling. The mixture was allowed to stand overnight. To the red solution was added 100 ml. of water and 100 ml. of ether. The separated aqueous layer was extracted with 25 ml. of ether, and the combined ethereal extracts were washed with two 25-ml. portions of water, two 25-ml. portions of 5% sodium bicarbonate solution, and finally with water. The ether solution was dried with sodium sulfate and filtered. The filtrate was shaken with 0.5 gram of activated charcoal, filtered, and the solvent removed under vacuum. Recrystallization of the residue from ethanol-water gave 7.2 gram (90%) of (II), m.p. 68°; b.p. 178–82° at 4 mm. of Hg pressure.

Anal. Calcd. for C₁₃H₁₅NO₅: C, 58.85; H, 5.70. Found: C, 59.33; H, 5.60.

3,4,5-Trimethoxymandelic acid (III). Dry hydrogen chloride was bubbled through a solution of 5.6 grams (0.025 mole) of (II) in 50 ml. of anhydrous methanol for 30 minutes at 15°. The reaction vessel was protected with a silica gel drying tube. After standing at room temperature for two hours, the excess solvent was removed under water pump vacuum, 75 ml. of water added, the mixture stirred for two hours, 6 grams of sodium hydroxide pellets added, and stirring continued for one hour. Upon acidification with 6N hydrochloric acid and saturation with sodium chloride, the solution was extracted with five 25-ml. portions of ethyl acetate. The extract was dried with sodium sulfate and the solvent removed under vacuum. Recrystallization of the crystalline residue from chloroform-petroleum ether gave 5.0 grams of (III), m.p. 121–121.5°.

Anal. Calcd. for C₁₁H₁₃O₆: C, 54.54; H, 5.82; neutralization equivalent 242. Found: C, 54.23, 54.74; H, 5.85, 5.78; neutral. equiv. 245.

¹Present address: National Institute of Health, Bethesda, Md.

Ethyl 3,4,5-trimethoxymandelate (IV) (7). A solution of 3 grams (0.0134 mole) of (I) (vacuum dried) in 20 ml. of anhydrous ethanol was saturated with dry hydrogen chloride at 0-5° and refrigerated (4°) over night. Excess solvent was removed from the purple semi-solid mass at the water pump and 50 ml. of water added. Solid barium carbonate was added in excess to neutralize the acid, the mixture kept for 2 hours in the dark, filtered, and the filtrate extracted with four 30-ml. portions of ethyl acetate, using the first two portions of solvent to extract also the filter cake. The combined extracts were dried with sodium sulfate, and the solvent was removed under vacuum to give a yellow oil which crystallized slowly on standing. Recrystallization from ethanol-water gave 1.91 grams (53%) of (IV), m.p. 83-5°.

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.22; H, 6.20.

3,4,5-Trimethoxymandelic acid (III) by hydrolysis of the ethyl ester, (IV). A mixture of 1 gram (0.0037 mole) of (IV) and 20 ml. of 5% sodium hydroxide solution was refluxed for one hour, cooled, acidified with 6*N* hydrochloric acid, saturated with sodium chloride, and extracted with five

25-ml. portions of ethyl acetate. Isolation as previously described gave 0.74 gram (81%) of (III), m.p. 120-121°. Mixed m.p. and infrared spectra indicated that this compound was identical with (III) obtained through the acetoxynitrile, (II).

3,4,5-Trimethoxyphenylacetic acid (V). Using the method of Rapoport (2), (I), labelled with C-14 on the nitrile group, was easily reduced with tin (II) chloride to (V), m.p. 117-18° (lit. m.p. 117-118°), labelled in the carboxyl group.

LITERATURE CITED

- (1) LaManna, A., Ghislandi, V., *Gazz. Chim. Ital.* **89**, 1231 (1959); LaManna, A., Campiglio, A., Pagani, G., *Farmaco (Pavia) Ed. Sci.* **15**, 9 (1960).
- (2) Rapoport, H., Williams, A.R., Cisney, M.E., *J. Am. Chem. Soc.* **73**, 1414 (1951).
- (3) Recondo, E.F., Rinderknight, H., *J. Org. Chem.* **25**, 2248 (1960).

RECEIVED for review April 18, 1963. Accepted September 13, 1963. This work was supported by National Institutes of Health Grant MY-5325.

Some Ethers and Amino-Derivatives of *s*-Triazine

GERHARD F. L. EHLERS, GERARD A. LOUGHRAN, JAMES D. RAY¹
and EDWARD M. HAGERMAN²

Air Force Materials Laboratory, Research and Technology Division,
Wright-Patterson Air Force Base, O.

A number of methyl- and phenyl- substituted phenoxy- and amino-derivatives of *s*-triazines have been prepared by reaction of the corresponding chloro-derivatives with phenol and with amines in the melt and in solution.

A NUMBER of new methyl- and phenyl- substituted phenoxy- and amino-derivatives of *s*-triazines have been prepared, Table I. The phenoxy-derivatives were obtained by heating the corresponding chlorotriazines with equivalent amounts of phenol over a period of several hours. The anilino-derivatives resulted from refluxing the chlorotriazines with excess of aniline in a solvent, such as dioxane or benzene, and separating the reaction product from the aniline hydrochloride formed. The methyl- and ethyl-aminotriazines were prepared by introducing an excess of methyl- and ethylamine gas into benzene solutions of chlorotriazines at controlled temperatures.

¹ Present address: University of Dayton Research Institute, Dayton, Ohio.

² Present address: U.S. Army Chemical Center, Aberdeen, Maryland.

Several dimers, trimers and tetramers were obtained from the melt reaction of chlorotriazines with anilino-triazines under nitrogen at temperatures of 200° to 220° C. over several hours. One of these (Compound 12) has also been prepared in solution (diphenylether as solvent).

The trimers and tetramers were subjected to thermogravimetric analysis under nitrogen ($\Delta T = 150^\circ \text{C./hour}$). As Figure 1 shows, breakdown begins to occur in the range of 350° to 460° C., the compounds containing methyl groups being less stable than those without. The dimer (Compound 11) was subjected to a decomposition study in a high pressure isotenoscope (Monsanto Chemical Company under Air Force contract.) The value found for a decomposition of approximately 1% per hour was 382° C.

RECEIVED for review December 11, 1962. Accepted May 13, 1963.