with concomitant electronic redistribution, then gives IV.

Experimental Section[8]

The preparation of the 1-alkyl-2-aryl-5-chloroimidazoles will be exemplified by the synthesis of IVa.

N-Benzyloxamic Acid Ethyl Ester.—A solution of 107 g (1.0 mole) of benzylamine in 200 ml of alcohol was added dropwise and with stirring to a solution of 157 g (1.20 moles) of diethyl oxalate in 100 ml of alcohol at 0–5°. Upon completion of the addition, the mixture was stirred for another hour, whereupon solvent was removed *in vacuo*. Vacuum distillation of the residue yielded 170 g of product, bp 150–155° (0.2 mm). The distillate solidified upon rubbing with petroleum ether and melted at 47–48°.

N-Benzyl-N′-methyloxamide (IIIa).—A solution of 103.5 g (0.50 mole) of N-benzyloxamic acid ethyl ester in 250 ml of alcohol was added dropwise to 300 ml of 35% aqueous methylamine. The product precipitated out immediately and was isolated by filtration after 3 hr: yield 82 g, 86%; mp 184–185°.

1-Methyl-2-phenyl-5-chloroimidazole (IVa).—To a stirred slurry of 192 g (1.0 mole) of IIIa in 600 ml of phosphorus oxychloride was added over a 10-min period 436 g (2.10 moles) of phosphorus pentachloride. Some cooling was necessary. The mixture was subsequently refluxed for 2 hr. Solvent (600 ml) was then removed at atmospheric pressure, whereupon xylene was alternatively added and distilled off, thereby removing the last traces of phosphorus oxychloride. To the cooled mixture, containing *ca.* 200 ml of xylene, was added 1 l. of water. The aqueous phase was drawn off, and the organic phase was extracted once more with dilute hydrochloric acid. Basification of the combined aqueous phases gave crude, solid product which was filtered off. It was dissolved in the minimum amount of boiling heptane, separated from adhering water, and allowed to crystallize, giving 143 g (75%) of stout needles, mp 106–107°.

Registry No.—N-Benzyloxamic acid ethyl ester, 7142-72-5; IIIa, 7666-51-5; IVa, 7666-52-6; $C_{11}H_{12}ClNO_3$ (*p*), 6951-43-5; $C_{11}H_{12}ClNO_3$ (*o*), 6621-71-2; $C_{10}H_{12}N_2O_3$, 3262-95-1; $C_{13}H_{18}N_2O_3$, 7666-55-9; $C_{10}H_{11}ClN_2O_2$ (*p*), 7666-56-0; $C_{10}H_{11}ClN_2O_2$ (*o*), 7666-57-1; $C_9H_{11}N_3O_2$, 7666-58-2; $C_{10}H_9ClN_2 \cdot HCl$, 7666-59-3; $C_{10}H_8Cl_2N_2 \cdot HCl$, 7631-11-0; $C_{10}H_8Cl_2N_2$, 7666-60-6; $C_{10}H_8Cl_2N_2 \cdot HCl$, 7666-61-7; $C_9H_8ClN_3$, 7631-12-1; $C_{13}H_{15}ClN_2O \cdot HCl$, 7666-62-8.

Acknowledgment.—The authors are indebted to the "Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" for financial support of this program. The reported analyses were performed by Messrs. A. Sels and W. Verkest. Special thanks are due to Mr. J. Loomans for ultraviolet measurements and interpretations.

(8) Melting points were taken on a Fisher-Johns block.

A New Synthesis of 3-Mercapto-2-(mercaptomethyl)propionic Acid by Phosphorothioate Hydrolysis[1]

JAMES R. PIPER AND THOMAS P. JOHNSTON

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received October 7, 1966

Interest in asparagus juice component 3-mercapto-2-(mercaptomethyl)propionic acid[2a] (**3**) earlier prompted its synthesis from 3-iodo-2-(iodomethyl)propionic acid by two groups of investigators. Corse and Jansen obtained **3** by reduction of 3-(benzylthio)-2-[(benzylthio)methyl]propionic acid with sodium in liquid ammonia, basic hydrolysis of the corresponding bis(isothiuronium) derivative having failed.[2b] Schotte and Ström later obtained **3** by reduction of its cyclic disulfide, 1,2-dithiolane-4-carboxylic acid, with zinc powder in aqueous ammonia. Preparation of the cyclic disulfide involved oxidation of a crude preparation of **3** obtained by hydrolysis of the corresponding bis(acetylthio) derivative.[3]

In a search for a reaction sequence that could be easily applied to the preparation of sizable amounts of **3**, we made use of a recently described method in which the acid-labile S-substituted phosphorothioic acid function served as a precursor to the thiol group. In the earlier application, S,S′-1,4-diamino-1,4-cyclohexylenedimethylenebis(phosphorothioic acid) was converted through treatment with phosphoric acid to 1,4-diamino-1,4-cyclohexanedimethanethiol diphosphate, phosphoric acid hydrolysis being used to avoid introduction of a second anion and thereby simplify isolation of the resultant aminothiol salt.[4] Extension of this method to the preparation of **3** involved treatment of the sodium salt of 3-bromo-2-(bromomethyl)-propionic acid[5] (**1**) with 2 molar equiv of trisodium phosphorothioate[6a] in aqueous solution followed by *in situ* hydrochloric acid hydrolysis of the intermediate salt **2**; pure **3** was thus obtained in 50% yield.

$$(BrCH_2)_2CHCOOH \xrightarrow[2.\ 2Na_3SPO_3]{1.\ NaHCO_3} (Na_2O_3PSCH_2)_2CHCOONa \xrightarrow[\text{hydrolysis}]{HCl} (HSCH_2)_2CHCOOH$$

1 — **2** (not isolated) — **3**

Although acid hydrolysis of S-substituted phosphorothioic acids to the corresponding thiols has been used by Åkerfeldt as a precondition for iodometric assay of sulfur in such compounds,[6b] it has not heretofore been developed as a preparative method. The relative efficacy afforded by this method in the examples discussed here, particularly in the synthesis of **3**, suggests that it may be generally useful.

Experimental Section

3-Bromo-2-(bromomethyl)propionic acid (**1**) was prepared by the procedure of Ferris.[5] Recrystallization of the crude product from cyclohexane (instead of water as used by Ferris) afforded pure **1** in excellent recovery.

Trisodium Phosphorothioate.—The hydrolysis (NaOH) of freshly distilled thiophosphoryl chloride was carried out on the same scale and in essentially the same manner as described by Åkerfeldt;[6a] some additional details are noteworthy. The rapidly stirred mixture was carefully maintained at 75–85° until all the $PSCl_3$ had just disappeared (about 40 min required). The solution was immediately chilled until crystals began separating, and the mixture was refrigerated overnight. Following recrystallization and dehydration as described by Åkerfeldt, the product was dried at 100° *in vacuo* for 30 min.

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

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(5) A. F. Ferris, *J. Org. Chem.*, **20**, 780 (1955).

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3-Mercapto-2-(mercaptomethyl)propionic Acid (3).—3-Bromo-2-(bromomethyl)propionic acid (1, 18.0 g, 73.2 mmoles) was dissolved in a cold (0–5°), stirred solution of $NaHCO_3$ (6.15 g, 73.2 mmoles) in water (100 ml). The solution was allowed to warm to 25°, and Na_3SPO_3 (26.4 g, 0.147 mole) was added in portions during 15 min with the temperature maintained at less than 35°. Stirring at 25–30° was continued for 5 hr. (All Na_3SPO_3 dissolved during the first hour.) After the solution had been refrigerated overnight, the apparatus was purged with N_2, concentrated hydrochloric acid (38 ml) was added, and the solution was heated at 90–95° for 10 min while **3** separated as a colorless oil. The stirred mixture, still under N_2, was chilled (ice–water bath) and seeded.[7] Rapid crystallization ensued, and the solid was collected (under N_2) and dried *in vacuo* (NaOH pellets). The filtrate was extracted three times with ether (100-ml portions). Evaporation of the dried ($MgSO_4$) ether solution left a viscous oil (2.8 g), which was combined with the dried solid (8.3 g) filtered from the reaction mixture. The crude material was extracted three times with boiling cyclohexane (250-ml portions), and the combined cyclohexane extract was filtered while hot. The filtrate was concentrated under reduced pressure (water pump, rotary evaporator) to about 100 ml. The concentrated mixture, from which **3** had separated as an oil, was seeded; and the oil crystallized readily. The collected and dried solid, mp 53–60°, amounted to 58% yield (6.49 g) of partially purified **3**. Concentration of the filtrate gave a small additional amount (1.00 g) of lower melting material. The two crops were combined and sublimed *in vacuo* (0.1–0.3 mm, bath temperature 45–50°) in an apparatus in which seed crystals of **3** had been implanted on the collection surface. The crystalline solid removed from the collection surface was stirred briefly with cyclohexane (100 ml), collected under N_2, and dried *in vacuo* to give pure **3**: mp 58–61°,[8] 50% yield (5.58 g); σ^{KBr} (major bands) 2575 (SH), 1705 (CO), 1430, 1355, 1305, 1285, 1240, 1190, 920, 640 cm^{-1}.

Anal.[9] Calcd for $C_4H_8O_2S_2$: C, 31.56; H, 5.30; S, 42.13. Found: C, 31.61; H, 5.36; S, 42.57.

Registry No.—**3**, 7634-96-0.

Acknowledgment.—The authors appreciate the technical assistance of Mr. Carl R. Stringfellow, Jr.

(7) A sample of **3** with mp 57–60°[8] was obtained from a small-scale, trial run. Isolation involved extraction with ether, short-path distillation *in vacuo*, and recrystallization of partially crystallized distillate from cyclohexane.

(8) Reported melting points for **3** are 60–61°[2b] and 57–60°.[3]

(9) Thiol assay by the iodometric method is apparently not applicable to **3**; erratic, high results were obtained.

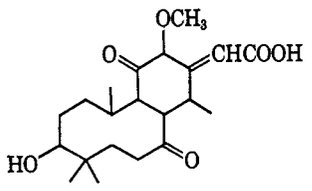
Identity of Cryptophlamic Acid with Erythrophlamic Acid[1]

WALTER J. GENSLER, CYNTHIA L. DEYRUP, JAMES M. ALLISON, CHRISTOS D. GATSONIS, AND BERNARD M. TURSCH

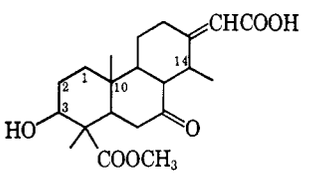
Department of Chemistry, Boston University, Boston, Massachusetts

Received November 7, 1966

Cryptophlamic acid (I)[2] is the name assigned to an acid derived from a mixture of *Erythrophleum* alkaloids. We believe that cryptophlamic acid is the same as erythrophlamic acid (II)[3–5] and that both the name and the proposed structure I should be dropped from the literature.



I



II

Cryptophlamic acid was obtained[2] from "erythrophleine sulfate,"[6] a commercial mixture of sulfate salts of the total alkaloids from *Erythrophleum guineense*. We have now shown that erythrophlamic acid (II) can be isolated from the same starting material by following a procedure similar to the one used for cryptophlamic acid (I). The physical properties of the erythrophlamic acid isolated from "erythrophleine," the properties recorded in the literature for erythrophlamic acid, and the properties given for cryptophlamic acid[2] correspond closely. The same is true of a series of derivatives. Comparison of the pertinent data (see the Experimental Section) will suggest strongly that cryptophlamic acid is, in fact, erythrophlamic acid.

Two results complicated the identification. In the cryptophlamic series, ozonolysis of methyl cryptophlamate (VII) is described as giving rise to product VIII (mp 165–167°). In the revised erythrophlamic formulation, this material should be the tricyclic diketone IV; yet, it is clearly not the same as the tricyclic diketone (mp 211–212°) of the same structure previously obtained from the ozonolysis of methyl erythrophlamate.[4] In our hands, ozonolysis of methyl erythrophlamate (III) gave tricyclic diketone IV (mp 167–168°), the same as that found in the cryptophlamic series and again different from that expected for the erythrophlamic series. The problem was resolved when the lower melting material turned out to be an epimer of the higher melting form. Exposure to alkali transformed the 167–168° compound (IV) to the 211–212° compound (V). Evidently, compound V described before[4] had isomerized during its isolation. Similar inversions have been encountered in closely related structures.[7]

The action of phosphorus pentachloride on ozonolysis product VIII = IV presented another problem. Structure VIII in the cryptophlamic formulation carried a *gem*-dimethyl grouping next to secondary hydroxyl. Phosphorus pentachloride would be expected to dehydrate and rearrange this system to the isopropylidene system as in IX;[8] ozonolysis would then give compound X. When this recognized two-stage sequence was applied to the cryptophlamic ozonolysis product, anticipated product X, mp 201–203°, was actually obtained.[2] This result was disconcerting, since rationalization of the transformation on the basis of erythrophlamic formulation IV would be difficult. Accordingly, the process was reexamined, with

(1) This work was supported by the National Heart Institute, U. S. Public Health Service, under Grant HE-04141.

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