Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.3; H, 4.9. Found: C, 53.5; H, 4.9.

(b) More Vigorous Oxidations.—Using the same quantities as in (a), the solution was refluxed for twenty minutes, an additional 2 cc. of nitric acid was added and refluxing continued for one and one-half hours. After cooling in ice, the solution was filtered (without dilution) through sintered glass and the solid washed with concentrated nitric acid. No crystalline material was isolated from the filtrate. The colorless solid (376 mg., m. p. 151–163°) was recrystallized from ethanol to give 203 mg. (30%) of 3,5-dimethyl-2,4-dinitroanisole as colorless rods, m. p. 170.5–172°. Evaporation of the filtrate and recrystallization of the residue from petroleum ether–acetone gave 103 mg. (15%) of colorless needles of 2,6-dimethyl-3-nitroanisic acid, m. p. 189.5–190°.

Oxidation of the methyl ether (400 mg.) with 3 cc. of concentrated nitric acid and 8 cc. of water at 190° for twenty-four hours in a sealed tube gave a clear solution from which no crystalline material could be isolated. With one-half this amount of nitric acid and water, considerable carbonaceous material was formed.

Preparation of 3,5-Dimethyl-4-(and 2)-nitroanisole.—3,5-Xylenol was mono-nitrated and the two isomers were separated according to the procedure of Adams and Stewart.[13]

The nitrophenols were methylated by an adaptation of the procedure of Rowe, *et al.*,[12] which was satisfactory on a small scale. 3,5-Dimethyl-4-nitroanisole was obtained as thin nearly colorless needles from dilute alcohol, m. p. 50–52° (reported[12] 53°). 3,5-Dimethyl-2-nitroanisole, however, was obtained as a low melting crystallographic modification from dilute methanol as nearly colorless prismatic needles melting at 35–35.5°. Steam distillation of the material and recrystallization from methanol gave the known form melting at 43–44°.[12,13] When a melt of the lower form was seeded with the higher it solidified and remelted at 43–44°.

Summary

5-Methoxybenzene-1,2,3-tricarboxylic acid was prepared by permanganate oxidation of 2,6-dimethyl-4-methoxybenzaldehyde. The products resulting from treatment of this intermediate with nitric acid also were investigated.

(13) Adams and Stewart, THIS JOURNAL, **63**, 2861 (1941).

MADISON 6, WISCONSIN RECEIVED JANUARY 26, 1946

NOTES

Preparation of a Filaricide. *p*-[bis-(Carboxymethylmercapto)-arsino]-benzamide[1]

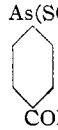
BY THOMAS H. MAREN

The screening of a large number of metal-organic and organic compounds against the filarial parasites, *Dirofilaria immitis* and *Litomosoides carinii*, of the dog and the cotton rat, respectively, revealed that phenyl arsenoxides as a class were outstandingly lethal to these organisms. Of twenty representative arsenoxides generously supplied by Dr. Harry Eagle,[2] the most favorable chemotherapeutic index was shown by *p*-arsenosobenzamide (I). Because of its low solubility in water, this compound was unsuitable for intravenous administration, and it became necessary to synthesize a compound which would retain the therapeutic activity of the parent and yet be adequately soluble for injection.

The condensation of *p*-arsenosobenzamide (I) and thioglycolic acid yields a thioarsenite, *p*-[bis-(carboxymethylmercapto)-arsino]-benzamide (II) whose disodium salt has the desired characteristics. This reaction was previously investigated by Gough and King.[3] In an attempt to make a particularly pure product on a larger scale, their method has been modified in several respects. The high As value found for their product suggests that 1–2% of unreacted *p*-arsenosobenzamide (I) may have been present. Introduction of a filtration step before crystallization of the final product (II) has eliminated the possibility of this type of contamination. Further changes in the proportions and manipulative procedure were made to prevent formation by hydrolysis of *p*-arsenosobenzoic acid (III) or its thioarsenite (IV). Since there is no nitrogen in III and IV, the nitrogen assay of the final product is a critical indication of the presence of these compounds. Since they are particularly toxic,[4] it is important to prevent their formation. Gough and King[3] did not report nitrogen values but it has been found that low nitrogen in the final product (indicating the presence of III or IV) is associated with overheating or recrystallization from aqueous solutions. In the present procedure these have been avoided, and both nitrogen and arsenic conform closely to the theoretical value for II.

Since properties of the thioarsenite (II) and its disodium salt have not been described previously, some of these are given below together with the revised method of synthesis.

II $As(SCH_2COOH)_2$



$CONH_2$

Preparation of *p*-[Bis-(carboxymethylmercapto)-arsino]-benzamide (II).—In a typical experiment 11.45 g. (0.05 mole) of *p*-arsenosobenzamide (I) was suspended in 150

(1) This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and The Johns Hopkins University.

(2) Venereal Disease Research and Postgraduate Training Center, U. S. Public Health Service, Johns Hopkins Hospital, Baltimore, Maryland.

(3) Gough and King, *J. Chem. Soc.*, 669 (1930).

(4) Eagle, Hogan, Doak and Steinman, *Public Health Reports*, **59**, 765 (1944).

ml. of water. An excess (15.2 ml.) of thioglycolic acid[5] was added and the mixture was heated to 100° with rapid stirring. When the solution became almost clear, it was filtered rapidly while very hot. The filtrate was allowed to cool, and a copious crystalline precipitate formed immediately. The precipitate was filtered off and washed with three portions of 50 ml. of cold water. It was then dried to constant weight at 40° and then in a vacuum desiccator; yield was 18.8 g., 98%; m. p., 158–162°.

Anal. Calcd. for $C_{11}H_{12}O_5NS_2As$; N, 3.71; As, 19.85; neut. eq., 184.5. Found: N, 3.63; As, 19.75; neut. eq., 185.7.

The acid (II) is insoluble in cold water but soluble in water above 90°. It is sparingly soluble in cold ethanol and methanol, and very soluble in these solvents when warm. It is insoluble in warm isopropyl ether. The acid dissociation constant is $pK_a = 4$, which is similar to that of thioglycolic acid. A potentiometric titration of the acid showed that the disodium salt is stoichiometrically formed in solution at *p*H 7–8.

For therapeutic purposes II is used in the form of an aqueous solution prepared by dissolving the acid in sufficient 0.2 *N* sodium hydroxide to yield a solution of *p*H 7. A 2% solution, formed in this way and sterilized by filtration, is stable in sealed amber ampules at room temperature for at least six months. In practice it has been useful to include, for each liter of solution, 72 ml. of *M*/15 Na_2HPO_4 and 48 ml. KH_2PO_4 to maintain the *p*H value. Both unbuffered and buffered solutions have been used successfully for intravenous therapy in dogs.

(5) Attention must be given to the purity of $HSCH_2COOH$. It should be water-white, spec. grav. 1.32, and distilled at 105–109° under 13–16 mm. pressure. The acid used in this Laboratory was purchased according to these specifications from Wallace Laboratories, New Brunswick, New Jersey.

DEPARTMENT OF PARASITOLOGY
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Solid Esters of Cellosolves and Carbitols

BY DAVID C. O'DONNELL AND RICHARD J. CAREY[1,2]

Many derivatives of the alcohol-ethers of the cellosolve and carbitol type have been prepared by various methods,[3] but these have not usually been easily obtained solids of characteristic melting points. We have therefore now prepared nine esters of these alcohol-ethers with 3,4,5-triiodobenzoic acid. The alcohol-ethers were generously supplied by the Carbide and Carbon Chemical Corporation and were simply fractionated except for the methyl and ethyl carbitols which were purified by the method of Seikel.[4] The acid chloride of the 3,4,5-triiodobenzoic acid was prepared by the method of Klemme and Hunter[5] and proved to be quite stable, a sample of it kept in a stoppered vial melting unchanged after two years.

Procedure.—To 1 g. of the acid chloride in a 10-cm. test-tube 0.5 cc. of the alcohol-ether was added and the mixture was heated gently over a micro burner until the evolution of hydrogen chloride ceased. This usually required from three to five minutes. The molten mass was then poured into 20 cc. of a 20% solution of alcohol to which cracked ice had been added. Some of the compounds solidified instantly and those that came down as oils changed to solids in a few minutes without further manipulation. All of the esters can be recrystallized from 95% alcohol, but 50% alcohol is a better recrystallizing solvent for the esters obtained from methyl and butyl carbitols. One recrystallization is frequently enough to give a pure compound, but two may be needed. The esters precipitate in granular form, with the exception of the isopropyl cellosolve derivative which comes down in the form of fine needles. The melting points were taken with Anschutz thermometers, but are not corrected.

TABLE I

ESTERS OF 3,4,5-TRIODOBENZOIC ACID

Cellosolve or carbitol used	M. p., °C.	Yield, %	Formula	Iodine, % Calcd.	Found
Methyl cellosolve	152.0–152.3	54.2	$C_{10}H_9O_3I_3$	68.26	68.47
Cellosolve	127.7–128.2	74.3	$C_{11}H_{11}O_3I_3$	66.58	67.11
Isopropyl cellosolve	79.5– 80.0	47.7	$C_{12}H_{13}O_3I_3$	64.99	65.45
Butyl cellosolve	85.0– 85.5	37.1	$C_{13}H_{15}O_3I_3$	63.46	63.93
Phenyl cellosolve	144.9–145.3	71.7	$C_{15}H_{11}O_3I_3$	61.41	61.60
Benzyl cellosolve	103.5–104.0	65.6	$C_{16}H_{13}O_3I_3$	60.06	60.61
Methyl carbitol	82.0– 82.5	39.7	$C_{12}H_{13}O_3I_3$	63.26	63.25
Ethyl carbitol	75.5– 76.5	42.0	$C_{13}H_{15}O_3I_3$	61.81	62.20
Butyl carbitol	53.8– 54.5	37.1	$C_{16}H_{19}O_3I_3$	59.11	58.99

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(1) Taken for the most part from a thesis submitted by Richard J. Carey in partial fulfilment for the M.S. degree.

(2) Present address: Compo Shoe Machinery Corporation, Boston, Mass.

(3) Mason and Manning, THIS JOURNAL, **62**, 1635–1640, 3136–3139 (1940).

(4) Seikel, *Ind. Eng. Chem., Anal. Ed.*, **13**, 388–389 (1941).

(5) Klemme and Hunter, *J. Org. Chem.*, **5**, 508–511 (1940).

Catalytic Acetylation of Steroid Compounds

BY BRADLEY WHITMAN AND ERWIN SCHWENK

Based on the work of Conant and Bramann,[1] we have found that acetylations may be carried out rapidly at room temperature if a trace of anhydrous perchloric acid is used to catalyze the reaction.

Procedure.—One gram of the substance to be acetylated is added to a mixture of 10 cc. of glacial acetic acid and 3 cc. of acetic anhydride. The mixture is cooled to 18° and 0.1 cc. of 5 *N* anhydrous perchloric acid added. The temperature is kept below 35° with external cooling. After standing for thirty minutes, the reaction mixture is cooled to 18° and sufficient ice added to destroy the excess acetic anhydride. The reaction mixture is worked up by pouring into water and filtering the precipitate.

This procedure has been used successfully on a great variety of bile acids and their derivatives. The yields are excellent and the physical constants are in agreement with those in the literature. When the diphenyl carbinols encountered in the Barbier–Wieland[2] degradation of the side-chain of 3,12-dihydroxycholanic and similar acids are acetylated by this method, the 3,12-diacetoxydiphenylethylenes are obtained; water splitting takes place even under the mild conditions of this reaction.

In the course of this work, three cases of polymorphism were encountered. 3(α)-12(β)-Diacetoxy-*nor*-cholanic acid and 3(α)-12(β)-diacetoxy-*bis-nor*-cholanic acid may be obtained in high melting forms by recrystallization from ether–petroleum ether and in low melting forms by salting out the ammonium salts and regenerating the free acids.

(1) Conant and Bramann, THIS JOURNAL, **50**, 2305 (1928).

(2) (a) Barbier and Locquin, *Compt. rend.*, **156**, 1433 (1933); (b) Wieland, Schlichting and Jacobi, *Z. physiol. Chem.*, **161**, 80 (1926).