The phenylhydrazide of this ester was prepared as follows: 0.248 g. of the substance was dissolved in 3 cc. of methyl alcohol and the solution refluxed with 1.5 cc. of phenylhydrazine for four hours. On cooling in the ice-box, a few crystals separated. Ether was added to the mixture, when the compound separated as a colorless powder. The phenylhydrazide crystallized from alcohol in colorless glistening plates, m. p. 236°.

Anal. Calcd. for $C_{13}H_{13}ON_4Cl$: N, 20.25. Found: N, 20.41, 20.29.

Summary

Ethyl 2-methyl-6-oxypyrimidine-5-acetate has been synthesized, and from it the corresponding acid has been obtained. Treatment of the ester with hydrazine resulted in the hydrazide of the acid; treatment with concentrated ammonia gave the amide.

The hydrazide has been degraded to the amine containing one less carbon atom. From the amine the corresponding alcohol has been prepared.

The ester gave with phosphorus oxychloride the corresponding 6-chloro derivative, from which the phenylhydrazide was obtained.

NEW YORK, N. Y. RECEIVED JUNE 29, 1937

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Meta Arsenated Phenoxyethanols

BY STEPHEN B. BINKLEY[1] AND CLIFF S. HAMILTON

The fact that certain para arsenated phenoxyalkanols possess considerable therapeutic value suggested a study of the corresponding meta derivatives. Although the para derivatives[2] were prepared by condensing *p*-hydroxyphenylarsonic acid with chlorohydrins, attempts to prepare meta derivatives[3] by this method were unsuccessful. In the case of the ortho and para arsenated phenoxyalkanols the orientation is definitely known. However, in the case of the meta compounds the nitro group may enter any one of three positions, -2, -4, or -6, with reference to the arsono group if it is assumed that the alkoxy group exerts a stronger directive influence than the weakly meta-directing arsono group. This investigation deals with the preparation of, and the orientation of, the nitro group in β-3-arsonophenoxyethanol.

β-3-Arsonophenoxyethanol was prepared by condensing ethylene chlorohydrin with *m*-nitrophenol, reducing to the corresponding amine, and replacing the amino group by the arsono group by means of the Bart[4] reaction.

Nitration of the sodium salt of β-3-arsonophenoxyethanol at 0° for three hours with 3 molecular proportions of fuming nitric acid (sp. gr. 1.50) gave a mixture of isomeric compounds containing one nuclear nitro group with the alcoholic hydroxyl group esterified.

The mixture of nitro-3-arsonophenoxyethyl nitrates was hydrolyzed with 3 *N* hydrochloric acid to yield β-2-nitro-3-arsonophenoxyethanol and β-6-nitro-3-arsonophenoxyethanol which were separated by fractional crystallization, the former being less soluble than the latter.

Refluxing the isomeric nitro compounds with 6 *N* sodium hydroxide gave the corresponding nitro-3-hydroxyphenylarsonic acids.

3-β-Hydroxyethoxyphenylarsenious oxide, the 2- and 4-nitro derivatives, and 2-nitro-3-hydroxyphenylarsenious oxide were prepared from the corresponding arsonic acids by reduction with sulfurous acid employing hydriodic acid as a catalyst.

The 2- and 4-nitro-3-β-hydroxyethoxyphenylarsenious oxides were converted to the corresponding chloromercuri compounds by refluxing in glacial acetic acid with mercuric acetate and precipitating with sodium chloride or calcium chloride.

The β-2- and 6-nitro-3-chloromercuriphenoxyethanols were converted to β-2-nitrophenoxyethanol[5] by refluxing with dilute hydrochloric acid, which was in turn converted to *o*-nitrophenol showing that the nitro group in each of the isomeric nitro compounds was ortho to the ether linkage. Attempts to replace the chloromercuri group in these compounds with bromine or iodine gave polyhalogenated compounds.

2-Nitro-3-chloromercuriphenol gave *o*-nitrophenol when treated with dilute hydrochloric acid,

(1) Parke, Davis and Company Fellow.

(2) Sweet and Hamilton, THIS JOURNAL, **56**, 2409 (1934); Stevinson and Hamilton, *ibid.*, **57**, 1600 (1935).

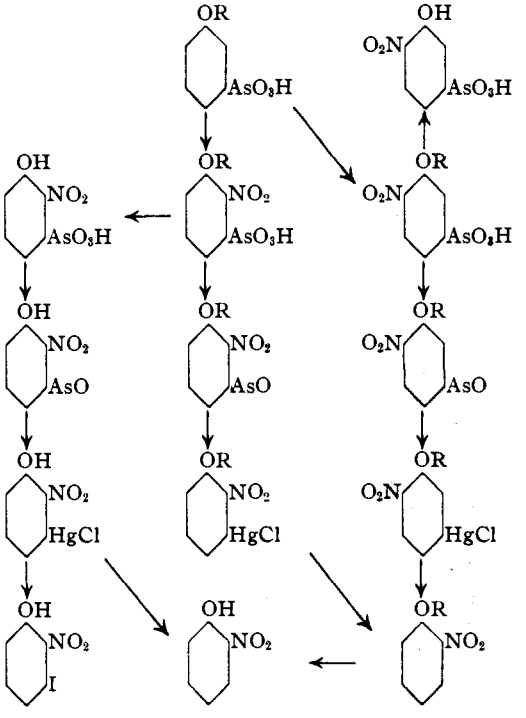
(3) Unpublished work, Chemical Laboratory, University of Nebraska.

(4) Bart, *Ann.*, **429**, 55 (1922).

(5) Boyd and Marle, *J. Chem. Soc.*, **105**, 2117 (1914).

and 2-nitro-3-iodophenol[6] when treated with iodine, showing definitely that the less soluble isomer was β-2-nitro-3-arsonophenoxyethanol and that the more soluble isomer was β-6-nitro-3-arsonophenoxyethanol. As a check 3-hydroxy-4-nitrophenylarsonic acid was prepared by the method described by Balaban.[7] Its properties checked those of the 4-nitro-3-hydroxyphenylarsonic acid prepared by cleaving the ether linkage.

The complete proof of structure is represented by the following series of reactions



Although the three possible nitro-3-hydroxyphenylarsonic acids have been prepared, they have been so briefly characterized or their physical constants are such that they do not readily lend themselves as reference compounds. The replacement of arsenic by mercury which in turn can be replaced by hydrogen or halogen gives derivatives which have been well characterized.

Experimental

β-3-Nitrophenoxyethanol.[5]—A solution of 13.5 g. (1 mol. eq.) of *m*-nitrophenol and 13.5 cc. (2 mol. eq.) of ethylene chlorohydrin in 100 cc. of 2 *N* sodium hydroxide was refluxed for four hours, during which time the product separated as a heavy oil which solidified on cooling. The product was purified by recrystallization from ethyl acetate; m. p. 88°.

(6) Hodgson and Moore, *J. Chem. Soc.*, 633 (1927).

(7) Balaban, *ibid.*, 809 (1928).

β-3-Aminophenoxyethanol.—Eighteen and one-half grams of β-3-nitrophenoxyethanol dissolved in 50 cc. of tech. methanol was reduced with molecular hydrogen at 30 pounds (2 atm.) pressure in the presence of Raney[8] catalyst. After the reduction was complete the catalyst was filtered off, the solvent removed by distillation, and the amine purified by distillation under reduced pressure.

β-3-Arsonophenoxyethanol and its Sodium Salt.—One-tenth mole of β-3-aminophenoxyethanol in a mixture of 24 cc. of concentrated hydrochloric acid, 500 cc. of water, and 100 g. of ice was diazotized with 7 g. of sodium nitrite dissolved in 100 cc. of water; time twenty minutes; temp. 5°. The cold diazonium solution was added slowly with stirring to a mixture of 17 g. of sodium arsenite dissolved in 700 cc. of water, 500 g. of cracked ice, 28 cc. of 6 *N* sodium hydroxide, and 0.5 g. of copper sulfate in 10 cc. of water. After stirring for an hour the mixture was filtered, evaporated to 200 cc., acidified to litmus paper, charcoaled, acidified to Congo red paper, and evaporated to dryness. The residue was extracted with 150 cc. of isopropyl alcohol in 50-cc. portions, 50 cc. of water added to the extract, the alcohol removed by evaporation, the solution neutralized to litmus paper, and added slowly with stirring to cold acetone, precipitating the crude sodium salt. The free acid was obtained by dissolving the sodium salt in 50 cc. of water and acidifying to Congo red paper. The product was purified by recrystallization from water.

The sodium salt was prepared by neutralizing a solution of the acid to litmus paper and adding the solution slowly to cold acetone.

Nitration of β-3-Arsonophenoxyethanol.—The monosodium salt of β-3-arsonophenoxyethanol (20 g.) was stirred with 60 cc. of nitric acid (sp. gr. 1.50) for three hours; temp. 0°. The mixture of β-nitro-3-arsonophenoxyethyl nitrates was precipitated by pouring into 500 cc. of ice water.

β-2- and 6-Nitro-3-arsonophenoxyethanol.—The mixture of β-nitro-3-arsonophenoxyethyl nitrates (20 g.) was hydrolyzed by refluxing for two hours with 75 cc. of 3 *N* hydrochloric acid. On filtering and cooling the solution β-2-nitro-3-arsonophenoxyethanol separated and was purified by recrystallization from water. When the filtrate was made just acid to Congo red paper, evaporated until salt started to separate, and cooled β-6-nitro-3-arsonophenoxyethanol separated and was purified by recrystallization from water.

2- and 4-Nitro-3-hydroxyphenylarsonic Acids.—β-2-Nitro-3-arsonophenoxyethanol (5 g.) was refluxed for one hour with 15 cc. of 6 *N* sodium hydroxide. When the solution was acidified to Congo red paper with dilute hydrochloric acid, filtered and cooled, 2-nitro-3-hydroxyphenylarsonic acid separated.

By the same method β-6-nitro-3-arsonophenoxyethanol gave 4-nitro-3-hydroxyphenylarsonic acid.

3-β-Hydroxyethoxyphenylarsenious Oxide, the 2- and 4-Nitro Derivatives, and 2-Nitro-3-hydroxyphenylarsenious Oxide.—The four arsenious oxides were prepared from the corresponding arsonic acids by reduction with sulfurous acid, employing hydriodic acid as a catalyst. They were purified by dissolving in 2 *N* sodium hydroxide and precipitating at 0° with dilute hydrochloric acid.

(8) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

TABLE I

	Name	Crystalline form	Yield	M. p., °C.	Formula	As Analysis[a] % calcd.	% found
1	β-3-Aminophenoxyethanol	White needles	95	52	$C_8H_{11}O_2N$	N, 9.15	9.05
2	β-3-Arsonophenoxyethanol	Plates	53	110	$C_8H_{11}O_5As$	28.62	28.73
3	Sodium salt 2	White granules	92	...	$C_8H_{10}O_5AsNa$[b]	26.41	26.31
4	3-β-Hydroxy ethoxyphenylarsenious oxide	Amorphous powder	55	...	$C_8H_9O_3As$	32.86	32.65
5	Mixture β-nitro-3-arsonophenoxyethyl nitrates	White needles	70	...	$C_8H_9O_9N_2As$	21.30	21.25
6	β-2-Nitro-3-arsonophenoxyethanol	Yellow plates	50	>270	$C_8H_{10}O_7NAs$	24.43	24.36
7	β-6-Nitro-3-arsonophenoxyethanol	Irregular yellow prisms	30	164	$C_8H_{10}O_7NAs$	24.43	24.35
8	2-Nitro-3-β-hydroxyethoxyphenylarsenious oxide	Yellow amorphous powder	87	>270	$C_8H_8O_5NAs$	27.45	27.63
9	4-Nitro-3-β-hydroxyethoxyphenylarsenious oxide	Yellow amorphous powder	85	>270	$C_8H_8O_5NAs$	27.45	27.54
10	4-Nitro-3-hydroxyphenylarsonic acid	Yellow plates	60	>270	$C_6H_6O_6NAs$	28.51	28.62
11	2-Nitro-3-hydroxyphenylarsonic acid	Yellow plates	40	208(dec.)	$C_6H_6O_6NAs$	28.51	28.41
12	2-Nitro-3-hydroxyphenylarsenious oxide	Yellow powder	87	220–223(dec.)	$C_6H_4O_4NAs$	32.75	32.63

[a] See Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930). [b] Gained two molecules of water of hydration when left exposed to the air for forty-eight hours.

TABLE II

	Name	Yield, %	M. p., °C.	Formula	Hg Analysis %[a] Calcd.	Found
1	3-Chloromercuri-2-nitrophenol	75	212–214	$C_6H_4O_3NHgCl$	53.6	53.4
2	β-3-Chloromercuri-2-nitrophenoxyethanol	80	150–152	$C_8H_8O_4NHgCl$	48.0	47.4
3	β-3-Chloromercuri-6-nitrophenoxyethanol	80	147–149	$C_8H_8O_4NHgCl$	48.0	48.7

[a] Determined by heating sample for fifteen minutes with 2 cc. of concd. hydrobromic acid and 2 cc. of 95% ethyl alcohol, diluting to 50 cc. with 50% ethyl alcohol and precipitating as mercuric sulfide.

β-2- and 4-Nitro-3-chloromercuriphenoxyethanols, and 3-Chloromercuri-2-nitrophenol.—2-Nitro-β-3-hydroxyethoxyphenylarsenious oxide (3 g.) and mercuric acetate (6 g.) suspended in 50 cc. of glacial acetic acid was refluxed for six hours. The solution was filtered, diluted with 4 volumes of water and the chloromercuri compound precipitated by the addition of 2 g. of sodium chloride. The product was purified by dissolving in acetone and precipitating by the addition of water.

β-3-Chloromercuri-4-nitrophenoxyethanol prepared by the same method was purified by dissolving in 15 cc. of methylcellosolve, adding an equal volume of ether, filtering, evaporating off the ether and precipitating the product by the addition of water.

3-Chloromercuri-2-nitrophenol prepared by the same method was purified by dissolving in ethyl alcohol and precipitating by the addition of water.

Two grams of β-3-chloromercuri-2-nitrophenoxyethanol refluxed for thirty minutes with 10 cc. of 3 *N* hydrochloric acid gave β-2-nitrophenoxyethanol which was converted to *o*-nitrophenol by refluxing with 10 cc. of 6 *N* sodium hydroxide for one hour.

β-3-Chloromercuri-6-nitrophenoxyethanol treated by the same method gave the same products.

When 2 g. of 3-chloromercuri-2-nitrophenol was refluxed for thirty minutes with 10 cc. of 6 *N* hydrochloric acid *o*-nitrophenol was obtained. On dissolving 3 g. of 3-chloromercuri-2-nitrophenol in an equivalent amount of dilute sodium hydroxide and adding a potassium iodide solution of iodine until iodine was no longer absorbed, 3-iodo-2-nitrophenol was obtained.

Summary

β-3-Arsonophenoxyethanol was prepared by condensing ethylene chlorohydrin with *m*-nitrophenol, reducing to the corresponding amine, and replacing the amino group with the arsono group be means of the Bart reaction. Nitration gave a mixture of β-nitro-3-arsonophenoxyethyl nitrates from which β-2- and 6-nitro-3-arsonophenoxyethanol were prepared by hydrolysis with dilute hydrochloric acid.

The structure of the nitro compounds was determined by cleaving the ether linkage with sodium hydroxide and by replacement of the arsenious oxide group by the chloromercuri group, with subsequent replacement of the latter by hydrogen or halogen. From β-2-nitro-3-arsonophenoxyethanol were derived 2-nitro-3-hydroxyphenylarsonic acid, *o*-nitrophenol, and 3-iodo-2-

nitrophenol while β-6-nitro-3-arsonophenoxyethanol gave 3-hydroxy-4-nitrophenylarsonic acid and *o*-nitrophenol.

LINCOLN, NEBRASKA RECEIVED JULY 6, 1937

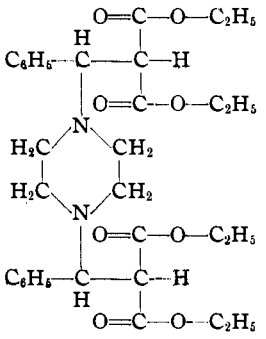
[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. X. Reactions with Unsaturated Esters. Part 2[1]

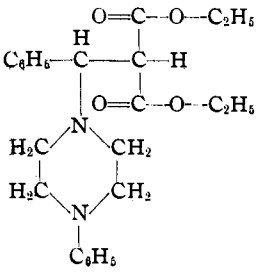
BY J. P. BAIN AND C. B. POLLARD

In the first paper[2] of this series, the addition of piperazine to esters of maleic and fumaric acids was reported. Further work in this field by the present authors has led to a study of the reactions of piperazine and monophenylpiperazine with a number of arylidene malonic esters. Other investigators have reported the addition of aniline,[3] phenylhydrazine,[4] piperidine[5] and other primary and secondary amines to benzalmalonic ester. The reactions proceed as expected with addition of the amine to the conjugate system.

Piperazine and benzalmalonic ester yielded tetraethyl (α,α′-diphenyl-1,4-piperazylene-dimethylene)-dimalonate (I). Monophenylpiperazine and benzalmalonic ester yielded diethyl α-(4-phenyl-1-piperazyl)-benzylmalonate (II).



(I)



(II)

The desired products may be formed in two ways: (a) the addition of the secondary amine to the arylidene malonic ester in alcoholic solution, and (b) addition of the secondary amine to the aromatic aldehyde and malonic ester in alcoholic solution. Heating is not necessary but serves to complete the reaction in a shorter time.

Arylidene malonic esters may be prepared by heating a mixture of aromatic aldehyde and malonic ester with a trace of an amine as a catalyst. It is probable that in the alternative procedure the secondary amine catalyzes the formation of the arylidene malonic ester and then adds to the conjugate system. On mixing equivalent quantities of piperazine, an aromatic aldehyde, and cyanoacetic ester, good yields of the arylidene cyanoacetic ester were obtained but no addition products were detected.

On refluxing (I) with a slight excess of alcoholic potassium hydroxide, long needles of a nitrogen-free potassium salt were obtained. This was surprising as another investigator[4,5] obtained the expected potassium salts from his amine addition products with benzalmalonic ester. The potassium salt was identified tentatively as potassium α-ethoxybenzylmalonate,[6] which would be formed by splitting out piperazine, adding alcohol to the conjugate system, and hydrolyzing. Piperazine was recovered in good yield from the mother liquor.

Acid hydrolysis of (I) with 3 *N* hydrochloric acid yielded piperazine hydrochloride and benzalmalonic ester which on prolonged hydrolysis yielded benzaldehyde and malonic acid. From one hydrolysis a small amount of cinnamic acid was identified.

The stability of (I) is also shown by hydrogenolysis experiments. Dibenzylpiperazine and malonic ester are produced by cleavage of the C–C bond and benzylmalonic ester and piperazine are produced by cleavage of the C–N bond. Toluene might be produced by simultaneous cleavage of the two bonds in the same molecule, but has not been identified as yet.

Experimental

Materials.—Piperazine hexahydrate, aldehydes and malonic ester were purchased from Eastman Kodak Co. The arylidene malonic esters were prepared by the method of Knoevenagel.[7] N-Monophenylpiperazine was prepared by the method of Pollard and MacDowell.[8]

(1) Presented at the Chapel Hill meeting of the American Chemical Society, April 14, 1937.

(2) Pollard, Bain and Adelson, THIS JOURNAL, **57**, 199 (1935).

(3) Blank, *Ber.*, **28**, 145 (1895).

(4) Goldstein, *ibid.*, **28**, 1450 (1895).

(5) Goldstein, *ibid.*, **29**, 813 (1896).

(6) Claisen and Crismer, *Ann.*, **218**, 141 (1883).

(7) Knoevenagel, *Ber.*, **31**, 2585 (1898).

(8) Pollard and MacDowell, THIS JOURNAL, **56**, 2199 (1934).