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An Anomalous Reaction of 2-Nitro-4-arsonophenyl Ethers

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There have been several attempts to prepare 2-aminophenoxyacetic acids and acetamides, particularly the parent compounds[1,2,3] and their 4-arsono- derivatives.[4,5] It was found that reduction of 2-nitrophenoxyacetic acids, hydrolysis of 2-acetaminophenoxyacetic acids and amides and reduction of 2-nitrophenoxyacetate esters all resulted in the formation of 1,4,2-benzoxazines. While 2-acetamino-4-arsonophenoxyacetamide underwent ring closure on hydrolysis of the acetyl group,[4] the conditions used to effect the hydrolysis may have been responsible for the simultaneous loss of the amide group and spontaneous cyclization. To obviate this possibility, the reaction of methyl 2-arsono-4-nitrophenoxyacetate[5] with ammonia and amines and subsequent reduction of the nitro group catalytically under extremely mild conditions was investigated.

Methyl 4-arsono-2-nitrophenoxyacetate reacted with alcoholic and aqueous ammonia at room temperature to yield the expected amide but reaction with ethanolamine, diethanolamine, morpholine and ethylenediamine resulted in compounds containing more nitrogen and arsenic than predicted on the basis of simple aminolysis of the ester. The reaction product was identified as 3-nitro-4-β-hydroxyethylaminobenzenearsonic acid, identical with the product described by Maclay and Hamilton,[6] obtained from 3-nitro-4-chlorobenzenearsonic acid and ethanolamine. Further investigations showed the reaction to be quite general. 4-Arsono-2-nitrophenoxyacetic acid, 3-nitro-4-β-hydroxyethoxybenzenearsonic acid and 3-nitro-4-methoxybenzenearsonic acid also yielded the same product when mixed with an excess of amine, with or without solvent, at room temperature and at 80°. 3-Nitro-4-hydroxybenzenearsonic acid also formed the same products but with greater difficulty.

The ortho nitro group is insufficient to explain the activation.[7] While 2,4-dinitroanisole and the analogous phenetole[8,9,10,11,12] are cleaved at the ether group by amines to give substituted dinitro anilines, the conditions employed imply that the 2-nitro-4-arsonophenyl ethers are split as readily as the 2,4-dinitrophenyl ethers. From studies of the influence of the arsono group on the reactivity of nuclear halogen[6,13-18] the order of activation for chloro- or bromobenzene was found to be 4-arsono-2-nitro- > 2-arsono-4-nitro- > 2-arsono-4-carboxy- = 2-arsono-4-cyano- = 2-arsono > the inactive combinations; 2-arsono-4-amino-, 2-arsono-4-hydroxy- and 4-arsono- for the replacement of halogen by amines and phenols. None of these combinations equaled the 2,4-dinitro- substitution in activation. Similarly, in 3-chloro-4-nitro- and 3-amino-2-nitrobenzenearsonic acids, the halogen and amine groups are removed on boiling in strong alkali.[19,20] These previous studies all indicate that the nitro group is more electronegative than the arsono group. In comparison with such data, the activating influence of the arsono group was unexpectedly great in our study. It is possible that the formation of the amine salts of the arsonic acids led to a coördination complex having different coulombic properties from those of the arsono group.

Reduction of 4-arsono-2-nitrophenoxyacetamide in neutral aqueous solution with hydrogen and Raney nickel catalyst yielded 6-arsono-3-hydroxy-1,4,2-benzoxazine. Apparently, the cyclization reaction is sufficiently vigorous to displace the amide group.

Experimental

4-Arsono-2-nitrophenoxyacetic acid prepared by the method of Christiansen[21] was converted to its methyl ester by the method of Sweet and Hamilton.[5]

2-Nitro-4-arsonophenoxyacetamide.—Methyl 2-nitro-4-arsonophenoxyacetate (0.1 mole) was dissolved in 500 ml. of alcoholic ammonia (9 *N*) with external cooling. The solution was placed in a pressure bottle and allowed to stand at room temperature for three days. The solvent and excess ammonia were removed *in vacuo* and the residue dissolved in water with a slight amount of sodium hydroxide, filtered, and the product separated from the filtrate by acidification to congo red paper. It was recrystallized from hot water as pale yellow needles. The same product was obtained by dissolving 0.1 mole of the ester in 180 ml. of concentrated aqueous ammonia, allowing to stand twenty-four hours, acidifying to congo red paper and separating as before.

Reaction of 2-Nitro-4-arsonophenyl Ethers with Substituted Amines.—The best procedure proved to be the reaction of the ether (0.1 mole) with an excess of the amine (1 mole) at 80° for two to six hours. The reaction mixture was then poured into 500 ml. of alcohol and 500 ml. of

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TABLE I

Reactants: X (NO₂)	Amine	Product: Y (NO₂)	Yield, %	Empirical formula	Analyses,[a] % As Calcd.	As Found	N Calcd.	N Found
—OCH_2COOCH_3	Alcoholic NH_3	—OCH_2CONH_2	72	$C_8H_9AsN_2O_7$	23.40	23.36	8.75	8.76
—OCH_2COOCH_3	Aqueous NH_3	—OCH_2CONH_2	61			23.30		8.70
—OCH_2COOCH_3	$H_2NCH_2CH_2OH$	—$NHCH_2CH_2OH$	76	$C_8H_{11}AsN_2O_6$	24.47	24.50	9.15	9.06
—OCH_2COOH	$H_2NCH_2CH_2OH$	—$NHCH_2CH_2OH$	56			24.42		8.96
—OCH_2CH_2OH	$H_2NCH_2CH_2OH$	—$NHCH_2CH_2OH$	42			24.60		9.10
—OCH_3	$H_2NCH_2CH_2OH$	—$NHCH_2CH_2OH$	67			24.50		...
—OH	$H_2NCH_2CH_2OH$	—$NHCH_2CH_2OH$	24			24.37		...
—OCH_2COOCH_3	$H_2NCH_2CH_2NH_2$ (excess)	—$NHCH_2CH_2NH_2$	37	$C_8H_{12}AsN_3O_5$	24.55	24.59	13.73	13.95
—OCH_2COOCH_3	$HN(CH_2CH_2OH)_2$	—$N(CH_2CH_2OH)_2$	55	$C_{10}H_{15}AsN_2O_7$	21.39	21.15		
—OCH_2COOCH_3	HNC_4H_8O	—NC_4H_8O	46	$C_{10}H_{13}AsN_2O_6$	22.55	22.50		

[a] The authors wish to thank A. W. Spang and C. S. Chamberlain (dec.) for the analytical determinations.

ether added slowly. The amine salts of the arsonic acids crystallized and were filtered off, dissolved in water, and the free acids caused to crystallize by acidification to congo red paper.

Summary

1. 2-Nitro-4-arsonophenyl ethers reacted with aliphatic primary and secondary amines to yield 2-nitro-4-arsonoanilines.

2. Methyl 2-nitro-4-arsonophenoxyacetate reacted with ammonia to yield the corresponding acetamide.

3. Reduction of 2-nitro-4-arsonophenoxyacetamide with hydrogen, using Raney catalyst, in neutral solution resulted in elimination of the amide and formation of 6-arsono-3-hydroxy-1,4,2-benzoxazine.

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Some Naphthalene Analogs of Desoxycorticosterone

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The object of the present investigation was the preparation of simple naphthalene analogs of desoxycorticosterone, especially by conversion of 6-methoxy-1-naphthoic acid, available by condensation of anisole with furoic acid,[4] into hydroxymethyl ketone derivatives.

Spurred by the discovery of the high estrogenic activity of synthetic analogs of estradiol and estrone, such as diethylstilbestrol and hexestrol, a number of investigators have explored the synthesis and testing of analogs of cortical hormones. Linnell and Roushdi[5] reported slight activity for hydroxymethyl phenyl ketone and appreciable activity for 3-(4′-hydroxyphenyl)-4-(3′-hydroxyacetylphenyl)-3-hexene. A number of other hydroxyacetyl compounds were devoid of activity.[5,6,7,8] These have included 1-hydroxyacetylnaphthalene,[5] 1-hydroxyacetyldecahydronaphthalene[8] and 7-methoxy-1-hydroxyacetylnaphthalene.[7]

We have prepared 4- and 6-acetoxy-1-acetoxyacetylnaphthalene (X and VI) and they showed no significant activity.[9] 6-Methoxy-1-acetoxyacetyl-1,2,3,4-tetrahydronaphthalene (III) was prepared and characterized but found too unstable for physiological testing.

The procedures used for the preparation of these compounds are outlined below.

Long and Burger[8] had previously reported experiments on the hydrogenation of I and IV. In every instance, any conditions which lead to hydrogenation also lead to simultaneous removal of the oxygen function at carbon 6. We had hoped the primary chemical reduction of the ring holding the carboxyl group might permit reduction of the other ring without removal of the oxygen. Unfortunately, this hope was not realized. Hydrogenation of IV, either at low temperature and pressure with Adams platinum oxide catalyst or at higher temperatures and pressure with Raney nickel, yielded only the desoxy acid VIII. Attempts to hydrogenate the methoxy acid II with either of these catalysts were entirely unsuccessful; starting material was recovered unchanged.

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(9) These compounds were tested in adrenalectomized rats through the courtesy of Eli Lilly and Company. Daily doses of 0.25 mg. subcutaneously failed to prolong survival significantly.