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The Preparation of Phenylarsenoxides. III. Derivatives of Carboxy- and Sulfophenylarsenoxides

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In order to study the influence of acid substituents and their derivatives on the toxicity and treponemicidal activity (*T. pallidum*) of phenylarsenoxides, a series of monosubstituted compounds has been prepared in which carboxyl or sulfonic acid groups were either extended on side chains, or blocked, as by ester or amide formation.

As indicated in Table I, most of the amides and esters were prepared by condensation of the appropriate amine or alcohol with benzoyl- or sulfonylchloride dichloroarsines, following the procedure of Gough and King,[1a] and Fourneau and Ochslin.[1b] Ethylenediamine and diethanolamine, however, failed to give the desired amides. With *p*-aminoacetanilide and *p*-aminobenzamide condensation was effected in pyridine solution.

The remaining arsenoxides were prepared by sulfur dioxide reduction of the corresponding arsonic acids in the usual manner.

Phenylarsenoxides containing an amide group showed less tendency to occur in the hydrated form than the corresponding acids, although several amides were obtained in both forms, depending on the method used for isolation. Thus, although *p*-arsenosobenzenesulfonamide was obtained on crystallization from dilute phosphoric acid following the procedure of Oneto and Way,[2] it precipitated as the hydrate when an alkaline solution was acidified. Similarly *p*-arsenosobenzamide and *p*-arsenosohippuric acid, prepared by the procedures of Gough and King,[1a] and Hugounenq and Morel[3] were converted to the arsonoso form by slow crystallization from saturated aqueous solutions.

TABLE I

ARSENOXIDES FORMED BY THE CONDENSATION OF BENZOYL- AND SULFONYLCHLORIDE DICHLOROARSINES WITH AMINES AND ALCOHOLS

Compound R = Arsenoso	Formula	As analyses, % Calcd.	As analyses, % Found	N analyses, % Calcd.	N analyses, % Found
p-R-N,N-dimethylbenzamide	$C_9H_{10}O_2NAs$	31.4	31.2		
p-R-N,N-diethylbenzamide	$C_{11}H_{14}O_2NAs$	28.1	28.3		
p-R-N-benzylbenzamide	$C_{14}H_{12}O_2NAs$	24.9	24.8	4.7	4.7
p'-Acetamido-*p*-R-benzanilide	$C_{15}H_{13}O_3N_2As$	21.8	21.9	8.1	8.1
p-R-N-α-pyridylbenzamide	$C_{12}H_9O_2N_2As$	26.0	26.0	9.7	9.4
p-R-N-methylbenzenesulfonamide	$C_7H_8O_3NSAs$	28.7	28.6		
p-R-N-ethylbenzenesulfonamide	$C_8H_{10}O_3NSAs$	27.2	27.2		
p-R-N-β-hydroxyethylbenzenesulfonamide	$C_8H_{12}O_5NSAs$	24.2	24.2		
p-R-phenylacetamide	$C_8H_8O_2NAs$	33.3	33.3		
p-R-phenylbutyramide[a]	$C_{10}H_{12}O_2NAs$	29.6	28.7	5.5	5.3
p-R-cinnamamide	$C_9H_8O_2NAs$	31.6	31.3	5.9	5.9
Ethyl *m*-R-benzoate	$C_9H_9O_5As$	31.2	30.9		
R = Arsonoso, $(HO)_2As$-					
o-R-benzamide[b]	$C_7H_8O_5NAs$	32.7	32.7		
p-R-benzanilide	$C_{13}H_{12}O_5NAs$	24.6	24.5	4.6	4.7
p-R-*p'*-carbamylbenzanilide	$C_{14}H_{13}O_4N_2As$	21.5	21.4	8.0	7.7
p-R-hippuric acid	$C_9H_{10}O_6NAs$	26.1	25.8	4.9	4.8
o-R-benzenesulfonamide[b]	$C_6H_8O_4NSAs$	28.3	28.0	5.3	5.4
p-R-N,N-dimethylbenzenesulfonamide	$C_8H_{12}O_4NSAs$	25.6	25.3		
p-R-N,N-diethylbenzenesulfonamide	$C_{10}H_{16}O_4NSAs$	23.3	23.2		

[a] Obtained as a gum which could not be successfully purified. [b] These amides were unique in that they hydrolyzed in cold dilute alkaline solution.

Those arsonic acids which are new compounds or which were prepared by a new procedure are listed in Table III.

The *p*-arsonophenylmethylsulfone was obtained in the theoretical yield by the oxidation of the corresponding sulfide with 30% hydrogen peroxide.

(1) (a) Gough and King, *J. Chem. Soc.*, 669 (1930); (b) Fourneau and Ochslin, *Bull. soc. chim.*, [4] **11**, 909 (1912).

(2) Oneto and Way, THIS JOURNAL, **61**, 2105 (1939).

(3) Hugounenq and Morel, *J. pharm. Chim.*, [7] **7**, 383 (1913).

TABLE II

ARSENOXIDES PREPARED BY REDUCTION OF THE CORRESPONDING ARSONIC ACIDS

Compound R = Arsenoso	Formula	As analyses, % Calcd.	Found
p-R-phenylacetic acid	$C_8H_7O_3As$	33.2	33.0
p-R-phenylpropionic acid	$C_9H_9O_3As$	31.2	30.7
p-R-phenylbutyric acid	$C_{10}H_{11}O_3As$	29.5	29.6
m-R-benzenesulfonamide	$C_6H_6O_3NSAs$	30.3	30.4
p-R-N-α-pyridylbenzenesulfonamide[a]	$C_{11}H_9O_3N_2SAs$	23.1	23.0
p-R-N-thiazylbenzenesulfonamide[b]	$C_9H_7O_3N_2S_2As$	22.7	22.6
p-R-phenoxyacetic acid	$C_8H_7O_4As$	31.0	31.2
Methyl *p*-R-phenoxyacetate[c]	$C_9H_9O_4As$	29.3	28.6
p-R-succanilic acid[d]	$C_{10}H_{10}O_4NAs$	26.5	26.4
p-R-succanilamide[e]	$C_{10}H_{11}O_3N_2As$	26.6	26.6
R = Arsonoso			
p-R-cinnamic acid	$C_9H_9O_4As$	29.3	29.3
p-R-benzenesulfonamide	$C_6H_8O_4NSAs$	28.3	28.1
p-R-phenylmethylsulfone	$C_7H_9O_4SAs$	28.4	28.5
p-R-phenylcarbamide[f]	$C_7H_9O_3N_2As$	30.7	30.6
p-R-phenoxyacetamide	$C_8H_{10}O_4NAs$	28.9	28.9

[a] Calcd.: N, 8.7. Found: N, 8.8. [b] Calcd.: N, 8.5. Found: N, 8.5. [c] Decomposed on standing at −25°. [d] Calcd.: N, 4.9. Found: N, 4.7. [e] Calcd.: N, 9.9. Found: N, 9.4. The arsonic acids corresponding to this compound and the one preceding were prepared according to Morgan and Walton, *J. Chem. Soc.*, 615 (1931). [f] Prepared by the reduction of "Carbarsone" (sodium *p*-carbamidophenylarsonate).

TABLE III

Compound R = Arsono	Yield, %	Crystalline form	Formula	As analyses, % Calcd.	Found
p-R-phenylmethylsulfone[a]	100	Plates	$C_7H_9O_5SAs$	26.7	26.9
p-R-phenylpropionic acid	69	Prisms	$C_9H_{11}O_5As$	27.5	27.4
p-R-phenylbutyric acid[b]	75	Amorphous powder	$C_{10}H_{13}O_5As$	26.0	26.3
p-R-phenylmethylsulfide[a]	50	Needles	$C_7H_9O_3SAs$	30.2	30.4
p-R-N-α-pyridylbenzenesulfonamide[c]	25	Prisms	$C_{11}H_{11}O_5N_2SAs$	20.9	21.1
p-R-N-thiazylbenzenesulfonamide[d]	55	Cubes	$C_9H_9O_5N_2S_2As$	20.7	20.7
p-R-phenylacetic acid[e]	35	Hexagonal plates	$C_8H_9O_5As$	28.8	29.2
p-R-cinnamic acid	30	Needles	$C_9H_9O_5As$	27.5	27.4

[a] The procedure used was the same as that of Cherline and Iacoubovitch, *Bull. soc. chim.*, [5] **1**, 1367 (1934), for the analogous ethyl compounds. [b] M. p. 125.5–126.5°. [c] Calcd.: N, 7.8. Found: N, 7.8. Prepared from 2-sulfanilamidopyridine (sulfapyridine). [d] Calcd.: N, 7.7. Found: N, 8.0. Prepared from 2-sulfanilamidothiazole (sulfathiazole). [e] Isolated through the magnesium salt, m. p. 190–192°. The customary Bart procedure gives a 20% yield, Robertson and Stieglitz, THIS JOURNAL, **43**, 179 (1921).

p-Arsonophenylpropionic acid was prepared by the catalytic reduction of *p*-arsonocinnamic acid, using Raney catalyst, instead of by the Bart reaction employed by Walton.[4] The customary Bart procedure with *p*-aminophenylbutyric acid was used for the preparation of *p*-arsonophenylbutyric acid. The remaining five arsonic acids were prepared by the Scheller modification of the Bart reaction.[5] In the case of the *p*-arsonocinnamic acid the reaction mixture contained an oil, insoluble in hot water and hence easily separated from the arsonic acid. From its properties this oil appeared to be a dichloroarsine, possibly formed by the addition of arsenous chloride to the double bond. The exact structure of the compound was not determined.

(4) Walton, *J. Chem. Soc.*, 156 (1939).

(5) Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 229 (1927); Doak, THIS JOURNAL, **62**, 167 (1940).

Summary

A series of monosubstituted arsonic acids and phenylarsenoxides has been prepared in which carboxyl and sulfonic acid groups were extended on side chains or blocked, as by amide or ester formation.

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