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Arylaminoheterocycles. IV. Arsenicals of Anilinopyrimidines

BY C. K. BANKS AND JOHN CONTROULIS

The unusual trypanocidal properties of the arsenical derivatives of anilinotriazines[1,2] suggested that the arsenic derivatives of other anilinoheterocycles might also be of interest. Because of the similarity in structure between the triazine and pyrimidine nuclei, the arsonoanilinopyrimidines and their related trivalent arsenic analogs were investigated. In a previous paper[3] the reaction of 4-aminobenzenearsonic acid with 2-amino-4-chloropyrimidine in aqueous acid suspension was demonstrated. Recently a number of arsonoanilinopyrimidines were reported by Andres and Hamilton,[4] who used the same general method of preparation. In addition to these compounds, we were particularly interested in the arsenoso derivatives of these and other similar arsonic acids.

The arsonic acids were prepared by refluxing a mixture of the appropriate aminobenzenearsonic acid with the desired halopyrimidine in aqueous suspension or solution containing a trace of hydrochloric acid, as described in previous publications.[1,3,5] In no instance was it necessary to use a mixture of water and polar organic solvent.[3,4] The arsonic acids obtained were converted to their sodium salts, arsenoso and dithioarsenoso derivatives by previously described methods.[1] The compounds prepared are listed in Table I and their toxicity and trypanocidal effect listed in Table II. The phenoxy analog of one of the anilino compounds was prepared by treating 4-hydroxybenzenearsonic acid with 2-amino-4-chloropyrimidine in cellosolve with potassium carbonate.

TABLE I

Compound	% Yield	Formula	% Arsenic[a] Calcd.	Found
2-Amino-4-X-anilinopyrimidine, X =				
4′-Arsono-	87	$C_{10}H_{11}AsN_4O_3$	24.15	24.18
hydrochloride	93	$C_{10}H_{12}AsClN_4O_3$	21.61	21.50
disodium salt	95	$C_{10}H_9AsN_4Na_2O_3$	21.15	20.99
4′-Arsenoso-	72	$C_{10}H_9AsN_4O$	27.13	27.02
4′-Dichloroarsenoso-, hydrochloride	89	$C_{10}H_{10}AsCl_3N_4$	20.38	20.12
4′-Di-(carboxymethylenethio)-arsenoso-, disodium salt	67	$C_{14}H_{13}AsN_4Na_2O_4S_2$	15.40	15.12
4′-Arsono-3′-hydroxy-	82	$C_{10}H_{11}AsN_4O_4$	22.97	22.83
disodium	86	$C_{10}H_9AsN_4Na_2O_4$	20.24	20.58
4′-Arsenoso-3′-hydroxy-	46	$C_{10}H_9AsN_4O_2$	25.65	25.35
5′-Arsono-2′-hydroxy-	78	$C_{10}H_{11}AsN_4O_4$	22.97	22.86
disodium	87	$C_{10}H_9AsN_4Na_2O_4$	20.24	19.96
5′-Arsenoso-2′-hydroxy-	78	$C_{10}H_9AsN_4O_2$	25.65	25.78
5′-Dichloroarsenoso-2′-hydroxy-, hydrochloride	72	$C_{10}H_{10}AsCl_3N_4O$	19.53	19.59
5′-Arsono-2′-β-hydroxyethoxy-	75	$C_{12}H_{15}AsN_4O_5$	20.23	20.19
disodium	87	$C_{12}H_{13}AsN_4Na_2O_5$	18.08	17.93
5′-Dichloroarsenoso-2′-β-hydroxyethoxy-, hydrochloride	79	$C_{12}H_{14}AsCl_3N_4O_2$	17.51	17.26
Miscellaneous Pyrimidines				
4-Amino-2-(4′-arsonoanilino)-pyrimidine	91	$C_{10}H_{11}AsN_4O_3$	24.15	23.98
4-Amino-2-(4′-dichloroarsenosoanilino)-pyrimidine hydrochloride	93	$C_{10}H_{10}AsCl_3N_4$	20.38	20.60
2-Amino-4-(4′-arsonophenoxy)-pyrimidine	50	$C_{10}H_{10}AsN_3O_4$	24.08	24.00
disodium	82	$C_{10}H_9AsN_3Na_2O_4$	21.10	21.16

[a] Thanks are due Arthur W. Spang, Margaret McCarthy Ledyard and Clara Johnston for the analytical work reported in this paper.

Experimental

4-Aminobenzenearsonic acid was prepared by recrystallizing commercial *p*-arsanilic acid (containing less than 0.1% ortho isomer) from hot water. 4-Amino-2-hydroxybenzenearsonic acid and 3-amino-4-β-hydroxyethoxybenzenearsonic acid were prepared by previously published methods.[6,7] 3-Amino-4-hydroxybenzenearsonic acid, as the hydrochloride, was available as a commercial intermediate. We are indebted to the Calco Division of American Cyanamid Co. for a generous supply of 2-

(1) Banks, Gruhzit, Tillitson and Controulis, THIS JOURNAL, **66**, 1771 (1944).

(2) Friedheim, *ibid.*, **66**, 1775 (1944); *Schweiz. med. Wochschr.*, **5**, 116 (1941); *Ann. inst. Pasteur*, **65**, 108 (1940).

(3) Banks, THIS JOURNAL, **66**, 1127 (1944).

(4) Andres and Hamilton, *ibid.*, **67**, 946 (1945).

(5) Banks, *ibid.*, **66**, 1131 (1944).

(6) Banks and Hamilton, *ibid.*, **62**, 3142 (1940).

(7) Sweet and Hamilton, *ibid.*, **56**, 2409 (1934).

TABLE II

TOXICITY AND TRYPANOCIDAL EFFECT[a]

	Compound	LD50-Rats I. V.- mg./kg.	Trypanocidal effect M. Th. D. mg./kg.	M. C. D. mg./kg.	Th. I.	C. I.
	Comparison compounds					
1	Atoxyl[b]	335	100	250	3.4	1.3
2	Tryparsamide[c]	4000	200	1000	20	4
3	Melarsen[d]	2000	30	60	67	33
4	Melarsen oxide[e]	17.5	0.10	0.50	175	35
	Pyrimidines					
5	2-Amino-4-(4'-arsonoanilino)-, disodium	275	17.5	45	15	6
6	2-Amino-4-(5'-arsono-2'-hydroxyanilino)-, disodium	60	20	>120	3	0
7	2-Amino-4-(5'-arsono-2'-β-hydroxyethoxyanilino)-, disodium	185	100	>200	1.8	0
8	2-Amino-4-(4'-arsono-3'-hydroxyanilino)-, disodium	80	4	25	20	3
9	4-Amino-2-(4'-arsonoanilino)-, disodium	400	80	100	5	4
10	2-Amino-4-(4'-arsonophenoxy)-	275	50	>80	5.5	..
11	2-Amino-4-(4'-arsenosoanilino)-	12	0.3	4	30	3
12	2-Amino-4-(4'-dichloroarsenosoanilino)-, hydrochloride	17.5	0.5	2	35	8.8
13	2-Amino-4-[4'-di-(carboxymethylenethio)arsenosoanilino]-, disodium	17.5	0.8	5	22	3.5
14	4-Amino-2-[4'-dichloroarsenosoanilino)-, hydrochloride	12	1.4	5	8.5	2.4
15	2-Amino-4-(5'-arsenoso-2'-hydroxyanilino)-	9.6	1	>3	9.6	..

[a] The methods used for this study are described in a previous paper.[1] [b] Atoxyl is sodium 4-aminobenzenearsonate. [c] Tryparsamide is sodium 4-arsonophenylglycineamide. [d] Melarsen is sesquisodium 2-(4'-arsonoanilino)-4,6-diamino-*s*-triazine. [e] Melarsen oxide is 2-(4'-arsenosoanilino)-4,6-diamino-*s*-triazine.

amino-4-chloropyrimidine. 4-Amino-2-chloropyrimidine was prepared by the method of Hilbert and Johnson.[8]

All of the new anilinopyrimidine compounds were prepared by previously described methods for the triazine compounds,[1] substituting the appropriate pyrimidine for triazine. All were white solids with no melting point under 300° or with a non-reproducible decomposition point.

2-Amino-4-(4'-arsonophenoxy)-pyrimidine.—4-Hydroxybenzenearsonic acid (109 g.), anhydrous potassium carbonate (70 g.) and cellosolve (1 liter) were refluxed with 2-amino-4-chloropyrimidine (70 g.) for four hours. The cellosolve was removed by vacuum distillation and the residue treated with water (500 ml.) and 10 *N* sodium hydroxide (60 ml.). The insoluble residue was filtered off and the filtrate was acidified with hydrochloric acid until just basic to congo red paper. This solution was treated with charcoal (Darco), filtered and the filtrate acidified until definitely acid to congo red paper. The crude product crystallized as a yellow solid, which was purified by dissolving in hot water, treating with charcoal (Nuchar), filtering and cooling the filtrate. The product crystallized in white needles, m. p. 227–228°. The yield was 76 g. or 50% of the theoretical.

Toxicity and Trypanocidal Effect

The toxicity and trypanocidal effect against *Trypanosoma equiperdum* infections in white rats were determined by Dr. O. M. Gruhzit.[1] The results are summarized in Table II. It can be seen that pentavalent compounds 5, 8 and 9 are superior to atoxyl and equal or superior to tryparsamide in experimental infections. Similarly, trivalent compounds derived from 5, 12, 13 and 14, although very toxic, are correspondingly active. None of the pyrimidine arsenicals is comparable to Melarsen or Melarsen Oxide (3 and 4) in trypanocidal activity.

Summary

A number of arsenicals of anilinopyrimidines have been prepared by the condensation of halopyrimidines with arsonoanilines in acid solution. The trypanocidal activity of these compounds against *T. equiperdum* infections in rats was inferior to that of the previously published arsenicals of anilinotriazines.

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(8) Hilbert and Johnson, THIS JOURNAL, **52**, 1152 (1930).