then brown again. After refluxing for one hour, water was added, and the aqueous layer, after washing with ether, was acidified with dilute sulfuric acid. The pale yellow solid obtained in 85% yield was twice recrystallized from glacial acetic acid, m. p. 171°.

On standing the aldehyde deepens in color and becomes diminishingly soluble in aqueous alkali.

For the purposes of characterization, the acetate was prepared by the addition of acetic anhydride to a solution of the aldehyde in aqueous potassium hydroxide. It was recrystallized from a benzene–ligroin mixture, m. p. 219°.

Anal. Calcd. for $C_{16}H_{10}O_2Br_2$: C, 48.76; H, 2.56. Found: C, 49.69; H, 2.69.

2,7-Dibromo-9-fluorenylcarbinol.—To aluminum isopropoxide, prepared from 1 g. of aluminum, was added 9.5 g. of 2,7-dibromo-9-formylfluorene in 25 cc. of isopropanol. The mixture was distilled through a Vigreux column, holding the vapor temperature at 60° for about five hours, after which the remaining alcohol was removed under reduced pressure. The residue was treated with 6 *N* sulfuric acid, and the solid product was then separated by filtration. Extraction of the solid with hot alcohol, followed by precipitation from the alcoholic extract on the addition of water, yielded 5.5 g. (58%) of material which, after three recrystallizations from ligroin, melted at 154°.

Anal. Calcd. for $C_{14}H_{10}OBr_2$: C, 47.50; H, 2.85. Found: C, 47.61, H, 3.37.

The carbinol formed an acetate readily on boiling with acetic anhydride and sodium acetate, m. p. 190° (from alcohol).

2,7-Dibromophenanthrene.—One gram of 2,7-dibromo-9-fluorenylcarbinol was refluxed for thirty minutes with 1 g. of phosphorus pentoxide and 25 cc. of xylene. The xylene layer was decanted and the xylene was removed by distillation. Recrystallization of the residual solid from a xylene–ligroin mixture yielded 0.1 g. of colorless crystals, m. p. 205° (lit.[2] m. p. 2,7-dibromophenanthrene, 202°). Oxidation of the product with chromic acid in glacial acetic acid yielded 2,7-dibromophenanthraquinone, m. p. 321° (lit.[2] m. p. 323°).

(2) Schmidt and Mezger, *Ber.*, **40**, 4560 (1907).

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Amide-Substituted Phenylarsine Oxides and Their Derivatives: A Group of Compounds of Possible Utility in the Treatment of Syphilis

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We have previously found[1] that strongly acidic substituent groups introduced into phenylarsine oxide regularly caused a striking decrease in direct treponemicidal activity against *T. pallidum*, without a commensurate decrease in toxicity. The potential therapeutic utility of these compounds was therefore even less than that of the simple unsubstituted phenylarsine oxide. However, when the acidic group was blocked, as in ethyl or methyl esters, or as in the sulfone and phenone compounds, the treponemicidal activity was largely restored, and the ratio of treponemicidal activity: toxicity was increased as much as fourteen-fold, in several cases significantly exceeding that of the parent compound.

In the light of that finding, a series of phenylarsine oxides was prepared in which an acidic substituent group had been blocked by amide formation.[2,3] The majority of these amides have proved to be actively treponemicidal and relatively low in toxicity (first section of Table I). The ratio of treponemicidal activity: toxicity, which may be taken as a rough measure of potential therapeutic utility, was usually 2 to 6 times as favorable as that of the parent phenylarsine oxide, due primarily to the uniformly low toxicity of these compounds. As will be discussed in a following paper, some of these compounds have shown a chemotherapeutic index in the treatment of rabbit syphilis equal to or exceeding that of mapharsen, and on that basis are of potential value in the treatment and prophylaxis of syphilis. The favorable effect of amide-substitution has been so regular as to suggest that further study may disclose other related compounds of greater therapeutic utility than any of those here described.

The favorable effect of amide substituents on the toxicity of phenylarsine oxide was observed whether that amide group was attached directly to the benzene ring, as in the case of 3- and 4-$CONH_2$ and -SO_2NH_2 compounds, or through some intermediate linkages (*cf.* first section, Table I). Moreover, the integrity of the amide group was usually essential for the favorable activity: toxicity ratio: When either or both of the amide hydrogens were substituted, the compound usually developed properties apparently determined by the new terminal substituent (*cf.* 2nd and 3rd sections, Table I). Although treponemicidal activity was usually increased by such substitution, toxicity was increased to an even greater degree, giving a less favorable ratio. In this group of compounds, the activity and toxicity of the compound had thus reverted toward that of the simple unsubstituted phenylarsine oxide, or of phenylarsine oxides with such indifferent sub-

(1) H. Eagle, R. B. Hogan, G. O. Doak and H. G. Steinman, *J. Pharmacol.*, **70**, 221 (1940).

(2) G. O. Doak, H. G. Steinman and H. Eagle, THIS JOURNAL, **62**, 3012 (1940).

(3) G. O. Doak, H. G. Steinman and H. Eagle, in preparation.

TABLE I

THE TOXICITY AND TREPONEMICIDAL ACTIVITY OF AMIDE-SUBSTITUTED PHENYLARSINE OXIDES AND THEIR DERIVATIVES

R-C_6H_4AsO or R-$C_6H_4As(OH)_2$	Ref.	Relative treponemicidal activity per mole	Relative toxicity per mole	Ratio of treponemicidal activity to toxicity
Phenylarsine oxide (reference compound)		100	100	1
3-NH_2-4-OH (mapharsen)		38	6.94	5.5
3-$CONH_2$	*a*	41	9.8	4.1
4-$CONH_2$	*a*	45	9.6	4.6
3-SO_2NH_2	*b*	21	6.1	3.5
4-SO_2NH_2	*b*	29	4.8	6.1
4-$NHCONH_2$	*b*	38	8.1	4.7
4-$NHCH_2CONH_2$	*c*	22	4.5	4.8
4-OCH_2CONH_2	*b*	52	9.0	5.7
4-$CH{=}CHCONH_2$	*b*	43	9.7	4.4
4-CH_2CONH_2	*b*	20	8.6	2.3
4-$(CH_2)_3CONH_2$	*b*	33	13.5	2.4
4-$NHCO(CH)_2CONH_2$	*b*	25	9.0	2.7
4-$CONHCH_2CONH_2$	*d*	24	3.9	6.1
4-$CONHCONH_2$	*d*	34	6.4	5.2
4-$CH_2CONHCH_2CONH_2$	*d*	11	3.4	3.2
4-$SO_2NHCH_2CONH_2$	*d*	17	3.5	5.1
4-$CONHCH_2CH_2CONH_2$	*d*	13	3.2	4.1
4-SO_2NHCH_3	*b*	72	18.0	4.0
4-$SO_2N(CH_3)_2$	*b*	112	93	1.2
4-$SO_2NHC_2H_5$	*b*	72	32	2.3
4-$SO_2N(C_2H_5)_2$	*b*	101	134	0.74
4-$SO_2NHC_2H_4OH$	*b*	23	4.3	5.3
4-$CONHCH_3$	*a*	54	15	3.6
4-$CON(CH_3)_2$	*b*	48	19	2.5
4-$CONHC_2H_5$	*a*	59	26	2.3
4-$CON(C_2H_5)_2$	*b*	53	64	0.84
4-$CONHC_6H_5$	*b*	97	101	.96
4-$CONHCH_2C_6H_5$	*b*	79	80	.98
4-$CONHC_5H_4N$	*b*	74	116	.64
4-$C(=NH)OC_2H_5$	*e*	68	87	.78
4-$CONHCH_2COOH$	*b*	0.7	15.7	.44
4-$CONHC_6H_4NHCOCH_3$-(4′)	*b*	9	2.0	4.5
4-$CONHC_2H_4OH$	*a*	25	4.8	5.2
4-$CONHCONHC_2H_4OH$	*d*	30	5.0	6.5
4-$CONHCH_2CHOHCH_2OH$	*f*	14	3.7	3.72
3-NHCONH-(4)	*g*	20	6.9	2.93
4-$CONHCH_2CN$	*h*	27	4.5	6

[a] Gough and King, *J. Chem. Soc.*, 669 (1930). [b] Doak, Eagle and Steinman, THIS JOURNAL, **62**, 3012 (1940). [c] Cohen, King and Strangways, *J. Chem. Soc.*, 2505 (1932). [d] Doak, Steinman and Eagle, Abstracts, 105th Meeting, American Chemical Society, Detroit, Michigan, 1943. Experimental details for the preparation of these compounds will be published in a separate paper. [e] *Anal.* Calcd. for $C_9H_{12}O_3NAs$: As, 29.2; N, 5.45. Found: As, 29.8; N, 5.61. Experimental details for the preparation of this compound will be published in a separate paper. [f] *Anal.* Calcd. for $C_{10}H_{12}O_4NAs$: As, 26.3; N, 4.92. Found: As, 26.6; N, 4.56. Experimental details of this compound will be published in a separate paper. [g] Doak, Steinman and Eagle, THIS JOURNAL, **63**, 99 (1941). [h] *Anal.* Calcd. for $C_9H_7O_2N_2As$: As, 30.0; N, 11.2. Found: As, 30.0; N, 11.1. Experimental details of this compound will be published in a separate paper.

stituents as $-CH_3$, $-Cl$, or $-OCH_3$ groups.[4]

Exceptions to this unfavorable effect of blocking the amide group were the acetanilide (*p*-$CONHC_6H_4NHCOCH_3$), nitrile (*p*-$CONHCH_2CN$), and alcohol (*p*-$CONHCONHC_2H_4OH$, *p*-$CONHCH_2CHOHCH_2OH$, *p*-$CONHC_2H_4OH$, and *p*-$SO_2NHC_2H_4OH$) derivatives, with indices essentially the same as that of the parent amides.

(4) H. Eagle, G. O. Doak, R. B. Hogan and H. G. Steinman, *J. Pharmacol.*, **70**, 211 (1940).

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