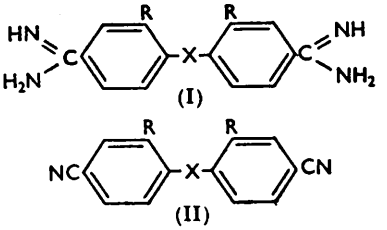
316. *The Search for Chemotherapeutic Amidines. Part XIII.* αω-Di-p-amidinophenoxy-alkenes and -alkynes.*

By J. N. Ashley and R. D. MacDonald.

Some αω-di-*p*-amidinophenoxy-alkenes and -alkynes and their nuclear-substituted derivatives have been prepared for comparison with the saturated analogues. They are of no interest as trypanocides.

Although some αω-di-*p*-amidinophenoxyalkanes [1] and their nuclear-substituted derivatives [2] were prepared some years ago, no unsaturated representatives of this class have been described. In continuation therefore of a systematic investigation into the effect on trypanocidal activity of varying the link X in aromatic diamidines of type (I) we have now synthesised a series of diamidines of type (I*a*—*i*). These are considerably less active against *Trypanosoma rhodesiense* than are the saturated analogues. Most are inactive against *T. congolense*; only 1 : 4-di-*p*-amidinophenoxybut-2-yne (I*a*) had a curative action with a chemotherapeutic ratio (LD_{50}/CD_{50}) in mice of approx. 2. The antibacterial activity *in vitro* of some of the compounds was of the same order as that of "Dibromopropamidine" (I; X = O·[CH$_2$]$_3$·O, R = Br).



(I)

(II)

(*a*) X = O·C·CH$_2$≡C·CH$_2$·O; R = H
(*b*) X = O·CH$_2$C≡C·CH$_2$·O; R = Me
(*c*) X = O·CH$_2$·C≡C·CH$_2$·O; R = Cl
(*d*) X = O·CH$_2$·C≡C·CH$_2$·O; R = Br
(*e*) X = O·CH$_2$·C≡C·C≡C·CH$_2$·O; R = H
(*f*) X = *trans*-O·CH$_2$·CH=CH·CH$_2$·O; R = H
(*g*) X = *cis*-O·CH$_2$·CH=CH·CH$_2$·O; R = H
(*h*) X = *trans*-O·CH$_2$·CH=CH·CH$_2$·O; R = Cl
(*i*) X = *cis*-O·CH$_2$·CH=CH·CH$_2$·O; R = Cl

In most cases the diamidines were prepared by the method of Ashley *et al.*[1] which involved the conversion of the dinitriles (II) into the di-imidoates and thence into the diamidines. The latter were isolated as dihydrochlorides or as the more soluble dimethanesulphonates or di-isethionates. The two diamidines in the *cis*-but-2-ene series were prepared by catalytic hydrogenation of the corresponding but-2-yne compounds.

The αω-di-*p*-cyanophenoxy-alkenes and -alkynes were prepared by condensation of the αω-dichloro- or -dibromo-alkene or -alkyne with the sodium or potassium salt of the appropriate cyanophenol. 2-Chloro- and 2-bromo-4-cyanophenol were prepared by

* Part XII, *J.*, 1956, 368.

[1] Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103.
[2] Berg and Newbery, *J.*, 1949, 642.

chlorination and bromination, respectively, of *p*-cyanophenol in chloroform.[2] 4-Cyano-2-methylphenol was first described by Paschen [3] who prepared it from 4-formyl-2-methylphenol by converting the formyl group into the oxime and thence by dehydration with acetic anydride into the nitrile. A better preparative method used in the present work involved the conversion of 4-bromo-2-methylphenyl acetate (obtained by successive bromination and acetylation of *o*-cresol) into the 4-cyano-compound by treatment with cuprous cyanide in pyridine with subsequent hydrolysis of the acetoxy-group.

The appropriate dihalogeno-alkenes and -alkynes were prepared by known methods.

Experimental

*4-Bromo-2-methylphenyl Acetate.**—Concentrated sulphuric acid (2·9 c.c.) was added, in one portion, with stirring to 4-bromo-2-methylphenol [4] (498 g.) dissolved in acetic anhydride (325 c.c.). The temperature rose to 75—80° and the solution was then refluxed for 2 hr. After the solution was cooled to 20°, ether (800 c.c.) was added, and the solution was washed successively with water, 2N-sodium carbonate, and water. The *4-bromo-2-methylphenyl acetate* was obtained as a colourless oil (562 g., 93·5%), b. p. 132°/12 mm. (Found: C, 47·4; H, 4·1; Br, 34·6. $C_9H_9O_2Br$ requires C, 47·2; H, 3·9; Br, 34·9%).

4-Cyano-2-methylphenyl Acetate.†—Cuprous cyanide (145 g.) was added, with stirring, during 30 min. to dry pyridine (100 c.c.) at 90°. The reaction was exothermic and the internal temperature rose to 140° (bath-temp., 110—115°). The thick brown mixture was stirred for a further 10 min. and 4-bromo-2-methylphenyl acetate (275 g.) was added. The bath-temperature was raised quickly to 200°; an exothermic reaction occurred and the mixture was then heated (bath-temp. 228—230°) for 3 hr. After being cooled somewhat the reaction mixture was distilled, the bath-temperature being slowly raised to 300° during 45 min. The pale yellow distillate, b. p. 60—170°/20—30 mm., was poured on ice (300 g.), and concentrated hydrochloric acid was added until the mixture was acid to litmus. The white crystalline cyano-compound (177 g., 84%) was filtered off, washed with water, and dried; it had m. p. 75—76°.

4-Cyano-2-methylphenol.†—This was prepared by hot alkaline hydrolysis of the acetate and was obtained (87%) as a white solid, m. p. 93—95°, b. p. 180—182°/12 mm.

Dihalogeno-alkenes and -alkynes.—1 : 4-Dichlorobut-2-yne (70%), b. p. 52—52·5°/10 mm. (Johnson [5] gives b. p. 68—69°/17 mm.), 1 : 4-dibromobut-2-yne [5] (85%), and 1 : 6-dibromohexa-2 : 4-diyne (79%), m. p. 18—19° (Armitage and Whiting [6] give m. p. 16—18°), were prepared by the recorded methods, but the two dibromo-compounds were not distilled. *trans*-1 : 4-Dibromobut-2-ene was prepared essentially as described by Valette.[7] The *cis*-dibromide (54%), b. p. 33·5—34·0°/0·8 mm. (Valette [7] gives b. p. 82°/16 mm.) [from *cis*-1 : 4-dihydroxybut-2-ene [5] (82%), b. p. 128—130°/15 mm.], was heated, with a trace of iodine, at 130—140° for 1 hr.; on cooling, the *trans*-isomer crystallised; it formed colourless plates, m. p. 52—53·5°, from light petroleum (b. p. 40—60°).

αω-Di-p-cyanophenoxy-alkenes and -alkynes.—These *dinitriles* are recorded in Table 1. Three general methods of preparation were used:

(*A*) An alcoholic solution of the cyanophenol (2·2 mol.) followed by 1 : 4-dibromobut-2-yne (1 mol.) was added to a solution of sodium (2·2 atom-equivs.) in dry ethanol (20 c.c. per g. of sodium). The mixture was refluxed overnight and then cooled and filtered. The residue was washed with water and recrystallised from a suitable solvent.

(*B*) 1 : 6-Dibromohexa-2 : 4-diyne (22 g.) was added to a stirred suspension of sodium hydrogen carbonate (17·2 g.) in a solution of *p*-cyanophenol (24·3 g.) in acetone (100 c.c.). The mixture was refluxed, with stirring, overnight, then cooled and filtered. The residue was washed with water and crystallised from acetic acid.

(*C*) 1 : 4-Dichlorobut-2-yne (1 mol.) was added to the cyanophenol (2·2 mol.) dissolved in a solution of potassium hydroxide (2·2 mol.) in alcohol (30 c.c./g.). The mixture was refluxed

* These preparations were carried out by Mr. S. S. Berg.

[3] Pashen, *Ber.*, 1891, **24**, 3671.
[4] Claus and Jackson, *J. prakt. Chem.*, 1888, **38**, 324.
[5] Johnson, *J.*, 1946, 1009.
[6] Armitage and Whiting, *J.*, 1952, 2005.
[7] Valette, *Ann. Chim.* (*France*), 1948, **3**, 644.

overnight and was then cooled and filtered. The residue was washed with water and crystallised from a suitable solvent.

TABLE 1. *Dinitriles.*

Subst.	Method	Yield (%)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
II*a*	*A* [a]	60	159—161°	74·7	4·4	9·65	$C_{18}H_{12}O_2N_2$	75·0	4·2	9·7
II*b*	*A* [a]	40	166—167	76·2	5·2	8·9	$C_{20}H_{16}O_2N_2$	75·9	5·1	8·9
II*c*	*C* [b]	54	224—226	60·9	3·4	7·9	$C_{18}H_{10}O_2N_2Cl_2$ [c]	60·5	2·8	7·8
II*d*	*C* [b]	50	220—222	48·6	2·6	6·4	$C_{18}H_{10}O_2N_2Br_2$ [d]	48·4	2·2	6·3
II*e*	*B* [a]	49	195—197	77·0	4·2	8·8	$C_{20}H_{12}O_2N_2$	76·95	3·85	9·0
II*f*	*A* [a]	70	204—206	75·0	5·05	9·6	$C_{18}H_{14}O_2N_2$ [e]	74·5	4·8	9·65
II*h*	*C* [a]	61	207—209	60·1	3·6	7·7	$C_{18}H_{12}O_2N_2Cl_2$	60·2	3·4	7·8

[a] Cryst. from acetic acid. [b] Cryst. from pyridine. [c] Found: Cl, 19·9. Required: Cl, 19·9%. [d] Found: Br, 35·7. Required: Br, 35·9%. [e] Found: Cl, 19·5. Required: Cl, 19·8%.

TABLE 2. *Diamidines.*

Subst.	Alcohol (and diluent) used in preparation of di-imidoate	Solvent for crystn.	M. p.
I*a*	EtOH [a] ($CHCl_3$)	MeOH–$COMe_2$	245—247°
I*b*	EtOH [a] ($CHCl_3$)	MeOH	308—310 [b]
I*c*	EtOH (dioxan)	MeOH–Et_2O	243—245
I*d*	EtOH	MeOH	253—255
I*e*	EtOH	Dil. HO·$[CH_2]_2$·SO_3H	272—274 [c]
I*f*	EtOH	Dil. Me·SO_3H	274—276
I*g*	—	MeOH	232—234
I*h*	HO·$[CH_2]_2$·OEt	MeOH	236—238
I*i*	—	—	218—220

Subst.	Formula	Found (%) followed by required (%) C	H	N	Halogen or S
I*a*	$C_{18}H_{18}O_2N_4,2HCl,2H_2O$ [d]	50·5	5·5	13·0	16·5 (Cl)
		50·1	5·6	13·0	16·5
I*b*	$C_{20}H_{22}O_2N_4,2MeSO_3H$	48·75	5·8	10·2	11·9 (S)
		48·7	5·5	10·3	11·8
I*c*	$C_{18}H_{16}O_2N_4Cl_2,2HO·[CH_2]_2·SO_3H,0·5H_2O$ [e]	40·15	4·5	8·25	10·85 (Cl)
		40·4	4·4	8·6	10·8
I*d*	$C_{18}H_{16}O_2N_4Br_2,2HO·[CH_2]_2·SO_3H$	36·0	3·6	7·5	21·9 (Br)
		36·1	3·8	7·7	21·85
I*e*	$C_{20}H_{18}O_2N_4,2HO·[CH_2]_2·SO_3H$	48·2	5·2	9·3	10·7 (S)
		48·2	5·0	9·35	10·7
I*f*	$C_{18}H_{20}O_2N_4,2Me·SO_3H$	46·8	5·7	10·8	12·3 (S)
		46·6	5·4	10·85	12·4
I*g*	$C_{18}H_{20}O_2N_4,2Me·SO_3H$	46·3	5·7	10·75	11·9 (S)
		46·6	5·4	10·85	12·4
I*h*	$C_{18}H_{18}O_2N_4Cl_2,2HO·[CH_2]_2·SO_3H$	40·6	5·0	8·4	11·1 (Cl)
		40·8	4·7	8·7	11·0
I*i*	$C_{18}H_{18}O_2N_4Cl_2,2HO·[CH_2]_2·SO_3H$	40·5	4·9	8·6	10·9 (Cl)
		40·8	4·7	8·7	11·0

[a] In these preparations the dinitriles were in solution when the mixture was saturated with HCl. In the other cases the dinitriles were present in suspension. [b] Found: H_2O, 8·5. Required: H_2O, 8·35%. [c] Decomp. [d] Found: H_2O, 1·5. Required: H_2O, 1·4%.

Preparation of Diamidines.—The dinitriles were suspended or dissolved in the appropriate alcohol (often in presence of a diluent), and the mixture was saturated with hydrogen chloride while being kept at 0—10°. The di-imidoate dihydrochlorides were gradually formed and after several days were filtered off, dried in a vacuum at room temperature, and added to saturated alcoholic ammonia (10 c.c./g. of solid) and the mixture was heated at 50—60° for 5—6 hr. The *diamidines* which are recorded in Table 2 were isolated by standard procedures.

cis-1 : 4-*Di*-p-*amidinophenoxybut*-2-*ene* (I*g*).—1 : 4-Di-*p*-amidinophenoxybut-2-yne dihydrochloride in methanol was hydrogenated in presence of 10% w/w palladium–calcium carbonate at room temperature. The uptake of hydrogen was stopped when 1 mol. had been absorbed.

The catalyst was then filtered off, and after removal of the solvent the diamidine dihydrochloride was converted into the dimethanesulphonate (70%) which was crystallised from methanol.

cis-1 : 4-*Di*-(4-*amidino*-2-*chlorophenoxy*)*but*-2-*ene* (I*i*).—This was prepared similarly; after hydrogenation, most of the solvent was evaporated and the gummy dihydrochloride, which was precipitated by addition of acetone, was obtained as a white powder after trituration with acetone.

The authors thank Dr. H. J. Barber, F.R.I.C., for his interest, Mrs. R. Stone, B.Sc., and Mr. W. A. Freeman for the biological tests, Mr. S. Bance, B.Sc., A.R.I.C., for the semimicroanalyses, and the Directors of May & Baker Ltd. for permission to publish these results.

THE RESEARCH LABORATORIES, MAY & BAKER, LTD.,
DAGENHAM, ESSEX.

[*Received, November 30th,* 1956.]