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

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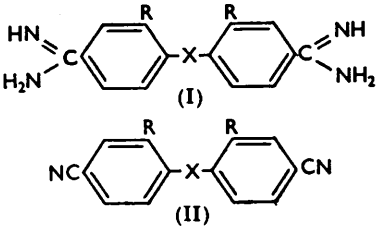
Some αω-di-*p*-amidinophenoxy-alkenes and -alkynes and their nuclear-substituted derivatives have been prepared for comparison with the saturated analogues. They are of no interest as trypanocides.

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* | $C_{18}H_{16}O_2N_4Cl_2,2HO·[CH_2]_2·SO_3H$ | 40·6 | 5·0 | 8·4 | 11·1 (Cl) |
| | | 40·8 | 4·7 | 8·7 | 11·0 |
| I*i* | $C_{18}H_{16}O_2N_4Cl_2,2HO·[CH_2]_2·SO_3H$ | 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.

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