241. *Some Aryl Di-β-amidinoethyl Ethers.*

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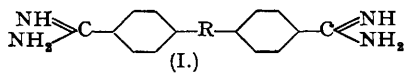
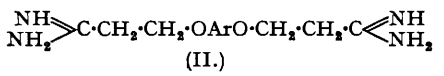
Several dihydric phenols have been condensed with vinyl cyanide and the resulting di-β-cyanoethyl ethers converted into the corresponding diamidines (II), *via* the di-γ-imino-γ-propoxyethyl ethers. In most cases the latter compounds readily underwent alcoholysis to β-carbethoxyethyl ethers.

Since the discovery of the trypanocidal action of certain aliphatic diamines, diamidines, diguanidines, and di*iso*thioureas of the type of synthalin, many aromatic diamidines of the general skeleton (I) have been prepared and examined (see, for example, Ashley *et al.*, *J.*, 1942, 103); these include diamidines where R is an aliphatic chain, a chain including O, NH, hydroxyl, keto or other groupings, or an ethylenic linkage (Fulton and Yorke, *Ann. Trop. Med.*, 1943, **37**, 48). The main feature common to all the effective structures is the



(I.)



(II.)

separation of the basic groupings by a chain, which may be continued through aromatic rings, of considerable length. As a number of phenols were being cyanoethylated in another connection, it was thought worth while to convert the derivatives of dihydric phenols into the corresponding diamidines; these would thus bear resemblance to compounds of both the synthalin and the propamidine type, and the distance between the amidine groupings could be controlled by the use of appropriately orientated phenols.

The cyanoethylation of a few phenols had been previously described in the patent literature (F.P. 833,734; D.R.P. 670,357); the method consisted in the interaction of phenols and vinyl cyanide in presence of metallic sodium. In the present work this catalyst proved troublesome as it resulted in undue polymerisation, and trimethylbenzylammonium hydroxide had a similar disadvantage. Using sodium methoxide, however, 1 : 2-, 1 : 3-, and 1 : 4-*di*-β-*cyanoethoxybenzene*, 2 : 6- and 2 : 7-*di*-β-*cyanoethoxynaphthalene*, and 4 : 4′-*di*-β-*cyanoethoxydiphenyl* as well as β-*cyanoethyl phenyl ether* were prepared. Similar condensations with *iso*propenyl cyanide could not be effected.

Keeping the dicyanides in chloroform or dioxan (cf. King and Wright, *J.*, 1939, 253) containing excess of ethanol and hydrogen chloride (cf. Ashley *et al.*, *loc. cit.*) afforded the corresponding *iminoethers* which were smoothly converted into the *esters* in boiling ethanol; indeed, 1 : 2-di-β-cyanoethoxybenzene was converted directly into the ester and in this case the iminoether was not isolated. Only tarry mixtures resulted from the action of liquid ammonia or 8—10% alcoholic ammonia on the iminoethers but 1 : 3- and 1 : 4-*di*-β-*amidinoethoxybenzene*, 2 : 6-*di*-β-*amidinoethoxynaphthalene*, and 4 : 4′-*di*-β-*amidinoethoxydiphenyl*, eventually in the form of their tartrates, were obtained by the action of 50% ethanolic ammonia.

Experimental.

Aryl β-Cyanoethyl Ethers.—The general method consisted in heating vinyl cyanide with the phenol and sodium or sodium methoxide under pressure, recovering excess of vinyl cyanide by distillation under reduced pressure, and treating the residue with aqueous sodium hydroxide; the product then crystallised. *β-Cyanoethyl phenyl ether* (yield, 70%) from phenol (18·8 g.), sodium (0·2 g.), and vinyl cyanide (14 g.) at 130—140° for 5 hours, separated from *cyclo*hexane in prisms, m. p. 61—62° (Found: N, 9·5. C_9H_9ON requires N, 9·5%). Vinyl cyanide (30 g.), catechol (10 g.), and sodium methoxide (0·6 g.) at 85° for 24 hours gave 1 : 2-*di*-β-*cyanoethoxybenzene* (4·8 g.) which separated from ethanol in long needles, m. p. 123° (Found: C, 66·2; H, 5·4; N, 12·9. $C_{12}H_{12}O_2N_2$ requires C, 66·6; H, 5·6; N, 12·95%). The following were similarly obtained: 1 : 3-*Di*-β-*cyanoethoxybenzene* (Found: C, 66·4; H, 5·6; N, 12·95%) (yield, 53%), and 1 : 4-*di*-β-*cyanoethoxybenzene* (Found: C, 66·3; H, 5·4; N, 12·7%) (yield, 50%) which crystallised from ethanol in needles, m. p. 112° and 140—141° respectively; 4 : 4′-*di*-β-*cyanoethoxydiphenyl* (yield, 47%), from 4 : 4′-dihydroxydiphenyl (30 g.), sodium methoxide (2 g.) and vinyl cyanide (200 g.), which separated from acetic acid in leaflets, m. p. 188—189° (Found: C, 74·0; H, 5·6; N, 9·7. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%); 2 : 6-*di*-β-*cyanoethoxynaphthalene* which crystallised from dioxan in long needles, m. p. 194° (Found: C, 71·7; H, 5·3; N, 10·2. $C_{16}H_{14}O_2N_2$ requires C, 72·1; H, 5·3; N, 10·5%); 2 : 7-*di*-β-*cyanoethoxynaphthalene* which separated from ethanol in leaflets, m. p. 153° (Found: N, 10·6%).

Aryl γ-Imino-γ-propoxyethyl Ethers.—The following was a typical preparation though the optimum reaction time differed in other instances: 1 : 4-Di-β-cyanoethoxybenzene (4 g.) was suspended in dioxan (50 c.c.) containing ethanol

(6 c.c.) and kept for 2 days at 0° after saturation with hydrogen chloride. Precipitation of the iminoether hydrochloride was completed by adding ether (100 c.c.). 1 : 4-*Di-γ-ethoxy-γ-iminopropoxybenzene hydrochloride* (7 g.) separated from a mixture of acetic acid and ether in small prisms, m. p. 205—207° (Found : N, 7·3. $C_{16}H_{26}O_4N_2Cl_2$ requires N, 7·35%). The following were prepared similarly : 1 : 3-*Di-γ-ethoxy-γ-iminopropoxybenzene hydrochloride* (yield theoretical) which formed small prisms from a mixture of acetic acid and ether, m. p. 125—135° (decomp.) depending on rate of heating (Found : N, 7·3%); 4 : 4′-*di-γ-ethoxy-γ-iminopropoxydiphenyl hydrochloride* (reaction time, 1 week) which separated in crystalline form from a mixture of acetic acid and ether (Found : N, 6·05. $C_{22}H_{30}O_4N_2Cl_2$ requires N, 6·1%); 2 : 6-*di-γ-ethoxy-γ-iminopropoxynaphthalene hydrochloride* (reaction time, 2 weeks; yield theoretical) which formed prisms, m. p. 220—222° (slight decomp.), from acetic acid (Found : N, 6·5. $C_{20}H_{28}O_4N_2Cl_2$ requires N, 6·5%); 2 : 7-*di-γ-ethoxy-γ-iminopropoxynaphthalene hydrochloride* which separated from a mixture of acetic acid and ether in prisms, m. p. 240° (decomp.) (Found : N, 6·6%).

Aryl β-Carbethoxyethyl Ethers.—1 : 4-Di-β-ethoxy-β-iminoethoxybenzene hydrochloride (0·5 g.) was refluxed for 30 mins. with ethanol (15 c.c.), the solution concentrated and diluted with water (20 c.c.); a nitrogen-free crystalline mass was precipitated (yield theoretical). 1 : 4-*Di-β-carbethoxyethoxybenzene* separated from ligroin in silky needles, m. p. 59—61° (Found : C, 62·2; H, 7·2. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1%). 1 : 3-*Di-β-carbethoxyethoxybenzene*, prepared in analogous manner (yield, 60%), formed silky needles, m. p. 43—44°, from ligroin (Found : C, 62·3; H, 6·9%); 2 : 6-*di-β-carbethoxyethoxynaphthalene*, prepared similarly, separated from ethanol in needles, m. p. 122—124° (Found : C, 66·3; H, 6·8. $C_{20}H_{24}O_6$ requires C, 66·6; H, 6·7%). Attempts to convert the cyanide from catechol into the iminoether by the method described above gave only an impure hydrochloride which on refluxing with ethanol, concentrating the solution, and adding water gave the pure *N*-free ester; 1 : 2-*di-β-carbethoxyethoxybenzene* crystallised from ligroin in fragile needles, m. p. 47—48° (Found : C, 61·9; H, 7·2. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1%).

Aryl β-Amidinoethyl Ethers.—A typical preparation was carried out as described. 1 : 4-Di-β-ethoxy-β-iminoethoxybenzene hydrochloride (7·5 g.) was shaken with ethanol (20 c.c.) and liquid ammonia (20 c.c.) at room temp. for 3 hours and then at 40—50° for 2 hours (autoclave). Most of the ammonia was removed under reduced pressure and the amidine hydrochloride contaminated with ammonium chloride allowed to crystallise after dilution of the residue with ethanol; more of the free base was obtained by concentrating the mother liquor, removing ammonium chloride, and again diluting with ethanol. The hydrochloride was dissolved in the minimum of water, the free base liberated with cold aqueous potassium carbonate, the whole evaporated under reduced pressure and the solid extracted with ethanol. Concentration of the extract and addition of alcoholic tartaric acid gave the deliquescent crystalline tartrate which was collected and washed with ethanol. 1 : 4-*Di-β-amidinoethoxybenzene tartrate* had m. p. 148—150° (decomp.) and could not be recrystallised unchanged (Found : N, 13·7. $C_{16}H_{24}O_8N_4$ requires N, 14·0%). The following were obtained similarly : 1 : 3-*di-β-amidinoethoxybenzene tartrate*, m. p. 110° (decomp.) (Found : N, 13·6%); 4 : 4′-*di-β-amidinoethoxydiphenyl tartrate*, m. p. 200° (Found : N, 14·4. $C_{20}H_{28}O_8N_4$ requires N, 14·0%); 2 : 7-*di-β-amidinoethoxynaphthalene tartrate*, m. p. 217° (decomp.) (Found : N, 12·7. $C_{20}H_{26}O_8N_4$ requires N, 12·5%).

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