20. *A Chemotherapeutic Comparison of the Trypanocidal Action of Some Aromatic Diamidines.*

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A study has been made of the relationship between chemical constitution and trypanocidal activity of a number of aromatic amidines. The greatest activity was shown by compounds of the type $NH_2 \cdot C(:NH) \cdot C_6H_4 \cdot X \cdot C_6H_4 \cdot C(:NH) \cdot NH_2$, in which X is a simple aliphatic chain in which one or more of the CH_2 groups are replaced by oxygen, or is an ethylenic linkage as in the stilbenes. The preparation of diamidino-compounds from the corresponding nitriles is discussed, and the synthesis of a number of such compounds and of the required nitriles described.

The direct trypanocidal action of synthalin {decamethylenediguanidine dihydrochloride, $NH_2 \cdot C(:NH) \cdot NH \cdot [CH_2]_{10} \cdot NH \cdot C(:NH) \cdot NH_2, 2HCl$} was first demonstrated by Lourie and Yorke (*Ann. Trop. Med. Parasit.*, 1937, **31**, 435), following the observations of Jancsó and Jancsó (*Z. Immunitätsforsch.*, 1935, **86**, 1) and of Artagaveytia-Allende (*ibid.*, 1936, **89**, 21) that this compound, when injected into mice infected with various pathogenic trypanosomes, exerted a curative action. This, however, they attributed to its hypoglycæmic properties rather than to any direct action on the trypanosome. Later, King, Lourie, and Yorke (*Lancet*, 1937, **233**, 136) prepared and examined a number of compounds, more or less closely related to synthalin, and found that symmetrical diamidinoalkanes showed an even greater trypanocidal action than that of the corresponding guanidine derivatives, the most active being 1 : 11-diamidinoundecane dihydrochloride, $NH_2 \cdot C(:NH) \cdot [CH_2]_{11} \cdot C(:NH) \cdot NH_2, 2HCl$.

This discovery of the trypanocidal action of the diamidino-compounds opened up a new field of investigation, and its extension to the aromatic compounds was undertaken by the present authors, in the hope that such compounds would more readily lend themselves to a study of the effects of substitution, and so to products of increased trypanocidal action and possible therapeutic application. To this end, a preliminary *in vivo* examination of the trypanocidal action of a number of such compounds was undertaken, and the present publication deals with their preparation and their comparative trypanocidal activity. The wider investigation of the more active of these compounds was undertaken by Prof. Yorke and his collaborators, in which it was shown that the most active trypanocidal compounds were the 4 : 4′-diamidino-derivatives of stilbene, of diphenoxypentane and of diphenoxypropane. These were also found to be active against leishmania and babesia infections. Against the latter 4 : 4′-diamidinodiphenyl ether was also found to be effective (Lourie and Yorke, *Ann. Trop. Med. Parasitol.*, 1939, **33**, 289; Warrington Yorke, *Trans. Roy. Soc. Trop. Med. Hygiene*, 1940, **33**, 463).

Clinical trials of certain of these compounds for the treatment of trypanosomiasis are in progress under the direction of the Therapeutic Trials Committee of the Medical Research Council. 4 : 4′-Diamidinostilbene and 4 : 4′-diamidinodiphenoxypentane have been successfully employed for the treatment of Mediterranean kala azar (Kirk and Sati, *Ann. Trop. Med. Parasitol.*, 1940, **34**, 82; Kirk and MacDonald, *ibid.*, 1940, **34**, 131) and of Indian kala azar (Adams and Yorke, *ibid.*, 1939, **33**, 323; 1940, **34**, 173). The more active compounds also give some promise of being useful in the treatment of babesia and other infections in cattle and domestic animals.

The starting point of the investigation was 4 : 4′-diamidinodiphenylmethane, $NH_2 \cdot C(:NH) \cdot C_6H_4 \cdot CH_2 \cdot C_6H_4 \cdot C(:NH) \cdot NH_2$, a symmetrical aromatic diamidine of approximately the same molecular complexity as 1 : 11-diamidinoundecane. As was expected, this compound exhibited definite *in vivo* trypanocidal activity, which was, however, of a lower order than that of the aliphatic diamidine. Many lines of development from this point suggested themselves and of these we mention the following : effect of nuclear substitution, of increasing the length of the hydrocarbon chain, of substituting hetero-atoms in the chain, of partly oxidised linkages, of unsaturated linkages, of substitution in the amidine groups, of the position of the amidine groups symmetrically or otherwise. It was obvious that all these lines could not be explored fully and, in seeking preliminary indications of these effects, we were naturally guided by considerations of accessibility of the compounds. Later, as methods were developed, it became possible to fill in some of the gaps in our schemes, and we drew certain inferences which enabled us to concentrate the work into fewer and more promising channels. Definite conclusions on any one point would only be justified on data from many more compounds than we have examined, but we give the deductions we have made, and the evidence on which they are based, in the following comparative tables, in which Am = $NH_2 \cdot C(:NH) \cdot$, R = $\cdot C_6H_4 \cdot$, M.T.D. = maximum tolerated dose (mice), M.E.D. = minimum effective dose, *i.e.*, the smallest dose which, when injected into infected mice, caused the complete disappearance of the try-

panosomes from the peripheral blood stream within 72 hours, M.C.D. = minimum curative dose, *i.e.*, the minimum single dose which caused the complete disappearance of the trypanosomes from the blood stream for a period of at least 28 days. The doses are in all cases given in mg./g. Ratio = M.T.D./M.C.D. Where the substituent amidine groups are other than 4 : 4′ in the aromatic nucleus, the position is given in parentheses. I = Intravenous, S = subcutaneous injection. These tables relate only to the effect on *T. equiperdum*, but the activity of some of these compounds on *T. rhodesiense* and *T. brucei* has also been examined and found to be of the same order.

TABLE I.

Homology of mononuclear diamidines.

Substance.		M.T.D.	M.E.D.	M.C.D.	Ratio.
Am·R·Am		—	No trypanocidal activity		—
Am·R·CH_2·Am	I	0·016	0·005	Not curative	—
Am·CH_2·R·CH_2·Am		—	No trypanocidal action		—

Products of this type show little or no activity.

TABLE II.

Homology in hydrocarbon chain linking binuclear amidines.

Am·R·R·Am	I	0·03	0·015	Not curative	—
Am·R·CH_2·R·Am	I	0·016	0·005	,,	—
Am·R·CHPh·R·Am		—	No trypanocidal action		—
Am·R·[CH_2]$_2$·R·Am	I	0·015	0·001	0·005	3
	S	0·07	0·001	0·005	14
Am·R·[CH_2]$_3$·R·Am	I	0·02	0·0025	0·01	2
	S	0·10	0·0025	0·02	5
Am·R·CH:CH·R·Am	I	0·025	0·005	0·01	2·5
	S	0·125	0·005	0·01	12·5
Am·R·CH:CH·CH:CH·R·Am	I	0·03	No trypanocidal action		—
	S	0·1	0·02	0·04	2·5

Maximum activity is shown by a chain containing two carbon atoms. The investigation of this series is being extended.

TABLE III.

Replacement of one CH_2 *group by another bivalent linkage.*

Am·R·CH_2·R·Am	I	0·016	0·005	Not curative	—
Am·R·O·R·Am	I	0·025	0·0075	0·0175	1·5
Am·R·S·R·Am	I	0·02	0·01	Not curative	—
Am·R·SO_2·R·Am		—	No trypanocidal action		—
Am·R·NH·R·Am	I	0·04	0·01	0·04	1
	S	0·08	0·005	0·02	4
Am·R·CH_2·CH_2·R·Am	I	0·015	0·001	0·005	3
	S	0·07	0·001	0·005	14
Am·R·CH_2·O·R·Am	I	0·015	0·0025	0·01	1·5
	S	0·07	0·0025	0·005	14
Am·R·CH_2·NH·R·Am	I	0·015	0·0025	Not curative	—
	S	0·01	0·0025	,,	—
Am·R·CH_2·CH_2·CH_2·R·Am	I	0·02	0·0025	0·01	2
	S	0·10	0·0025	0·02	5
Am·R·CH_2·CH_2·O·R·Am	I	0·015	0·0025	0·015	1
	S	0·08	0·0025	0·005	16
Am·R·CH_2·O·CH_2·R·Am	I	0·015	0·0005	0·0075	2
	S	0·10	0·001	0·01	10
Am·R·CH_2·S·CH_2·R·Am	I	0·02	0·01	Not curative	—
Am·R·CH_2·NH·CH_2·R·Am	I	0·025	No trypanocidal action		—
	S	0·06	0·04	Not curative	—

Replacement of CH_2 by O results in slightly enhanced activity, by NH in a diminution, and by S in a practical disappearance of activity.

TABLE IV.

Homology in chain containing one ether linkage.

Am·R·O·R·Am	I	0·025	0·0075	0·0175	1·5
Am·R·CH_2·O·R·Am	I	0·015	0·0025	0·01	1·5
	S	0·07	0·0025	0·005	14
Am·R·CH_2·CH_2·O·R·Am	I	0·015	0·0025	0·015	1
	S	0·08	0·0025	0·005	16
Am·R·CH_2·O·CH_2·R·Am	I	0·015	0·0005	0·0075	2
	S	0·10	0·001	0·01	10

Homology in this series has no marked effect on trypanocidal activity.

TABLE V.

Homology in chain containing two ether linkages.

Substance.		M.T.D.	M.E.D.	M.C.D.	Ratio.
Am·R·O·CH_2·O·R·Am	I	0·015	0·0025	Not curative	—
	S	0·08	0·0025	0·04	2
Am·R·O·[CH_2]$_2$·O·R·Am	I	0·03	0·0025	0·015	2
	S	0·07	0·0025	0·05	1·4
Am·R·O·[CH_2]$_3$·O·R·Am	I	0·04	0·0025	0·005	8
	S	0·08	0·0025	0·005	16
Am·R·O·[CH_2]$_4$·O·R·Am	I	0·025	0·004	Not curative	—
	S	0·04	0·01	0·02	2
Am·R·O·[CH_2]$_5$·O·R·Am	I	0·02	0·0012	0·0025	8
	S	0·1	0·0025	0·005	20
Am·R·O·[CH_2]$_6$·O·R·Am	I	0·017	0·0012	0·006	3
	S	0·1	0·0012	0·01	10
Am·R·O·[CH_2]$_7$·O·R·Am	I	0·007	0·0016	Not curative	—
	S	0·03	0·001	0·01	3
Am·R·O·[CH_2]$_{10}$·O·R·Am	I	0·02	0·005	Not curative	—
	S	0·1	0·005	0·075	1·3
Am·R·O·CH_2·R·CH_2·O·R·Am	I	0·08	0·06	Not curative	—
	S	0·1	No trypanocidal action		—
Am·R·CH_2·O·R·O·CH_2·R·Am	I	0·015	No trypanocidal action		—
	S	0·1	0·04	Not curative	—

Maximum activity appears with chains of 3 and 5 carbon atoms.

TABLE VI.

Replacement of one CH_2 *by* CH(OH) *or by* CO.

Am·R·CH_2·R·Am	I	0·016	0·005	Not curative	—
Am·R·CH(OH)·R·Am		—	No trypanocidal action		—
Am·R·CO·R·Am		—	,,	,,	—
Am·R·CH_2·CH_2·R·Am	I	0·015	0·001	0·005	3
	S	0·07	0·001	0·005	14
Am·R·CH_2·CO·R·Am	I	0·02	0·01	Not curative	—
	S	0·1	0·02	,,	—
Am·R·CH_2·NH·R·Am	I	0·015	0·0025	,,	—
	S	0·08	0·0025	,,	—
Am·R·CO·NH·R·Am		—	No trypanocidal action		—

Replacement of CH_2 by CH(OH) or by CO diminishes the activity.

TABLE VII.

Substitution in the amidine groups.

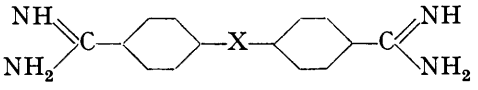
Am·R·R·Am	I	0·03	0·015	Not curative	—
*MeAm·R·R·AmMe	I	0·02	0·01	0·015	1·3
†Et_2Am·R·R·AmEt_2		—	No trypanocidal action		—
†PhAm·R·R·AmPh		—	,,	,,	—
Am·R·O·R·Am	I	0·025	0·0075	0·0175	1·5
*MeAm·R·O·R·AmMe	I	0·025	No trypanocidal action		—
Am·R·CH:CH·R·Am	I	0·025	0·005	0·01	2·5
	S	0·125	0·005	0·01	12·5
†NHPh·Am·R·CH:CH·R·Am·NHPh		—	No trypanocidal action		—

* In this formula MeAm indicates the structure NHMe·C(:NH). Formulæ marked † should be similarly interpreted.

Substitution in the amidine group is unfavourable to activity.

The last compound in Table XI is the only one of any noteworthy activity and this type of amidine is being examined further.

The general inference we draw from all data so far available is that the most active trypanocidal compounds are of the type



where X is a simple alkane chain in which one or more of the CH_2 groups are replaced by oxygen, or is an ethylenic linkage as in the stilbenes.

The method of preparation of the amidines included in the foregoing tables was essentially that of Pinner (" Die Imido Äther ") which involves the conversion of the nitriles into the imino-ethers and thence into the amidines. The best conditions for the two stages do not seem to have been discussed.

TABLE VIII.

Variation in the position of the amidine groups.

Substance.		M.T.D.	M.E.D.	M.C.D.	Ratio.
Am·R·CH_2·O·R·Am	I	0·015	0·0025	0·01	1·5
	S	0·07	0·0025	0·005	14
Am·R·CH_2·O·R·Am(3′)	I	0·03	0·0025	0·01	3
	S	0·1	0·0025	0·04	2·5
Am·R·CH:CH·R·Am	I	0·025	0·005	0·01	2·5
	S	0·125	0·005	0·01	12·5
Am·R·CH:CH·R·Am(3′)	I	0·015	0·005	0·01	1·5
	S	0·08	0·0025	0·04	2
Am·R·O·$[CH_2]_3$·O·R·Am	I	0·04	0·0025	0·005	8
	S	0·08	0·0025	0·005	16
Am(3)·R·O·$[CH_2]_3$·O·R·Am(3′)	I	0·03	0·0025	0·01	3
	S	0·1	0·0025	0·02	5
Am·R·O·$[CH_2]_5$·O·R·Am	I	0·02	0·00125	0·0025	8
	S	0·1	0·0025	0·005	20
Am(3)·R·O·$[CH_2]_5$·O·R·Am(3′)	I	0·025	0·0025	0·015	1·6
	S	0·08	0·005	0·01	8

3′ : 4-Diamidines appear to differ little from the corresponding 4 : 4′-compounds, but the 3 : 3′-compounds are definitely less active.

TABLE IX.

Monoamidines of similar structure to some active diamidines.

Am·R·O·R	—	No trypanocidal action		—
Am·CH_2·R·NH_2	—	,,	,,	—
Am·R·R·CN(2)	—	,,	,,	—
Am·R·CH:CHR	—	,,	,,	—
Am·R·CH:CH·R·NH_2(4)	—	,,	,,	—

Two amidine groups are needed for activity.

TABLE X.

Compounds in which one or both of the amidine groups are aliphatic in character.

Am·R·CH_2·O·CH_2·R·Am	I	0·015	0·0005	0·0075	2
	S	0·10	0·001	0·01	10
Am·CH_2·R·O·CH_2R·Am	I	0·01	0·0025	Not curative	—
	S	0·05	0·0025	0·05	1
Am·R·CH_2·CH_2·R·Am	I	0·015	0·001	0·005	3
	S	0·07	0·001	0·005	14
Am·CH_2·R·R·CH_2·Am	I	0·02	No trypanocidal action		—
	S	0·04	0·04	Not curative	—

Amidines in which the amidine group is aliphatic in character are markedly less active than those with the corresponding length of chain in which both amidine groups are aromatic.

TABLE XI.

Diamidines with miscellaneous linkages.

Am·R·N:N·R·Am		—	No trypanocidal action		—
Am·R·S·S·R·Am		—	,,	,,	—
Am·R·SO_2·NH·R·Am		—	,,	,,	—
Am·R·NH·CO·NH·R·Am	I	0·02	0·005	Not curative	—
	S	0·06	0·02	,,	—
Am·R·CH:CH·CO·R·Am		—	No trypanocidal action		—
Am·R·CH:CH·CH:CH·R·Am	I	0·03	,,	,,	—
	S	0·1	0·02	0·04	2·5
Am·R·O·CH_2·O·CH_2·O·R·Am	I	0·08	0·06	Not curative	—
	S	0·1	No trypanocidal action		—
Am·R·O·CH_2·CH_2·NH·R·Am	I	0·02	0·00125	0·01	2
	S	0·06	0·00125	0·01	6

Pinner states (*op. cit.*, p. 3) that the reaction R·CN + EtOH + HCl = R·C(NH)·OEt,HCl proceeds best with practically the theoretical quantities of the three reactants, but he is not quite consistent, since, for β-naphthimino-ether, he uses 1·7 molecules of alcohol and 1 molecule of hydrogen chloride (p. 72) and for *p*-toluimino-ether he uses 1 molecule of alcohol and saturates the solution with hydrogen chloride (p. 61). Earlier (p. 53—4) he says, in connection with benzimino-ether, that with 2 molecules of hydrogen chloride an unstable chloride of the type R·CCl(OR′)·NH_2,HCl is formed. This he regards as undesirable for various reasons and mentions that, on standing, it may decompose more or less completely into

ammonium chloride and esters. Pyman (J., 1930, 400) uses equimolecular quantities of alcohol and nitrile and saturates the solution with hydrogen chloride. H. King (private communication) uses 2 molecules of alcohol for each nitrile group and saturates with hydrogen chloride. In our experience with aromatic dinitriles 2 molecules of alcohol is the minimum quantity for a complete conversion into imino-ether hydrochloride, and we prefer to use 2·5—3 molecules. As most of the aromatic dinitriles are sparingly soluble in alcohol, we have used diluents in which the nitriles have some solubility, and of these chloroform, benzene, and nitrobenzene have proved useful. In certain cases a very considerable excess of alcohol served. King (J., 1939, 254) suggested the use of dioxan. The general procedure was to suspend the powdered nitriles in dry diluent with 2·5—3 molecules of absolute ethyl alcohol, saturate the liquid with hydrogen chloride at 0—5°, and keep it for 7—10 days at room temperature. The imino-ether hydrochlorides usually separated more or less completely, but in some cases it was found necessary to precipitate them by addition of light petroleum. Removal of the excess of hydrogen chloride (pump) as suggested by King was also a useful technique in some cases where the hygroscopic character of the crude imino-ether hydrochlorides rendered their isolation undesirable. No evidence was found for the existence of unstable chlorides such as were formulated by Pinner, but in the case of cyanophenyl cyanobenzyl ether the product approximated in composition to a trihydrochloride, the third molecule of hydrogen chloride possibly being associated with the ether oxygen atom.

The conversion of the imino-ether hydrochloride into amidine hydrochloride may not be as simple as is suggested by the equation

$$R{\cdot}C(OEt){:}NH,HCl + NH_3 = R{\cdot}C(NH_2){:}NH,HCl + EtOH$$

It seems to have been assumed that the reaction takes place between excess of ammonia and the imino-ether base liberated from its hydrochloride, but Knorr (*Ber.*, 1917, **50**, 229) claims to have demonstrated that it takes place between the free imino-ether and ammonium chloride and that the excess of ammonia plays no part in it. We have found, however, that benziminoether base, for example, does yield benzamidine base with alcoholic ammonia. In considering the optimum conditions for the conversion of the imino-ether hydrochlorides into the amidines the decomposition of imino-ether hydrochlorides by alcohol according to the equation

$$R{\cdot}C(OEt){:}NH,HCl + 2EtOH = NH_4Cl + R{\cdot}C(OEt)_3$$

(Reither and Hess, *Ber.*, 1907, **40**, 3020) must not be overlooked. In our experience it is necessary to use a large excess (10 molecules of ammonia per imino-ether group) of 10% absolute alcoholic ammonia to avoid the formation of traces of non-basic by-products (cf. acetamidine, *Org. Syntheses*, I—X, p. 5). It seems probable that the chief function of this excess is to displace the equilibrium

$$R{\cdot}C(OEt){:}NH,HCl + NH_3 \rightleftharpoons R{\cdot}C(OEt){:}NH + NH_4Cl$$

as far as possible in favour of ammonium chloride and imino-ether base, the latter being much more stable to alcohol than is the imino-ether hydrochloride.

The amidines generally presented no especial difficulties in isolation and purification, the hydrochloride being the salt most commonly used. In some cases the free base was more readily obtained and was therefore used in preliminary tests. Some of the hydrochlorides formed hydrates which could not be dehydrated without decomposition.

Few of the dinitriles required in these investigations have been described before and, indeed, the literature on the types in question is relatively scanty. We found early in this work that the Sandmeyer method was generally unsuitable for the preparation of any but relatively small quantities of dinitriles, so wherever possible we preferred the synthesis from two mononitriles. In the cases given in the table in the experimental section, however, we had to employ the Sandmeyer reaction, and we would call attention to the very simple but practical technique which we evolved for isolating these dinitriles, and which we describe in the experimental section. Of these nitriles a few require further comment.

4 : 4′-Dicyanobenzophenone was described by Brömme (*Ber.*, 1887, **20**, 521) as having been obtained by distillation of calcium 4-cyanobenzoate and having m. p. 204°, a method which, in our hands, gave traces only of this product. The Sandmeyer method on 4 : 4′-diaminobenzophenone gave a product, m. p. 162°, which was authentic 4 : 4′-*dicyanobenzophenone*, so the constitution of Brömme's product is obscure. The Sandmeyer reaction applied to 4 : 4′-diaminobenzhydrol yielded only traces of 4 : 4′-dicyanobenzophenone, but reduction of the latter with amalgamated aluminium gave the required 4 : 4′-*dicyanobenzhydrol*.

Since the completion of this work 4 : 4′-dicyanostilbene has been described by Lamb and White

(J., 1939, 1256), but the product obtained by them was probably impure. In our experience a purer product is obtained after vacuum sublimation of the crude reaction product.

3 : 4′-Diaminostilbene, required for 3 : 4′-*dicyanostilbene*, was obtained from the dinitro-compound by reduction with stannous chloride, which gave higher yields than the mixture of acetic and hydrochloric acids and zinc powder used by Harrison (J., 1926, 1236).

4-Nitrocinnamaldehyde (Fecht, *Ber.*, 1907, **40**, 2898), condensed with sodium 4-nitrophenylacetate in presence of acetic anhydride, gave 4 : 4′-*dinitro-αδ-diphenylbutadiene-α-carboxylic acid*, which was reduced to the corresponding diamine. The crude dinitrile obtained from this lost carbon dioxide during vacuum sublimation to yield 4 : 4′-*dicyano-αδ-diphenylbutadiene*.

4 : 4′-Diaminoazobenzene was readily obtained by reduction of the dinitro-compound with sodium sulphide. Previous methods described are reduction of 4-nitro-4′-aminoazobenzene (Noelting and Binder, *Ber.*, 1887, **20**, 3016) and hydrolysis of the mono- and di-acetamido-compounds (Wietzki, *Ber.*, 1884, **17**, 345; Minter, *Amer. Chem. J.*, 1883—1884, **5**, 283).

4 : 4′-Dicyano-αβ-diphenylethane has been isolated by Kattwinkel and Wolffenstein (*Ber.*, 1901, **34**, 2423; 1904, **37**, 3221) as a product of the oxidation of 4-toluonitrile by persulphates, but repetition of these experiments showed that the amounts formed were so small as to be impractical for the present purposes. Attempts to apply various methods, used for the preparation of diphenylethane or of 4 : 4′-dinitrodiphenylethane from benzyl chloride or 4-nitrobenzyl chloride, to 4-cyanobenzyl chloride, bromide, or iodide all failed. Diphenylethane itself can be obtained in excellent yields from benzyl chloride by the action of magnesium (Reichstein and Oppenauer, *Helv. Chim. Acta*, 1933, **16**, 1373), which is preferable to sodium (*J. Soc. Chem. Ind.*, 1936, 347T), as the latter reaction is less readily controlled and gives rise to by-products. The nitration of this to pure 4 : 4′-dinitrodiphenylethane is claimed (*J. Amer. Chem, Soc.*, 1930, **52**, 5040), but we were unable to obtain a pure product and resorted to the older method due to Roser (D.R.-P. 29,381; *Ber.*, 1887, **20**, 351, R) in which 4-nitrobenzyl chloride is reduced with alkaline stannite.

The yield of dinitrile obtained by the Sandmeyer reaction on 4 : 4′-diaminodiphenylethane was too small to be of practical utility. The 4 : 4′-dialdehyde has been prepared by Reichstein and Oppenauer (*loc. cit.*), and the complete series of reactions involved in the preparation of a nitrile from a hydrocarbon by this method is RH ⟶ R·CH_2Cl ⟶ R·CH_2·OAc ⟶ R·CH_2·OH ⟶ R·CHO ⟶ R·CH:NOH ⟶ R·CN. Although six stages are involved, the reactions are smooth except the first. The reagent used for the chloromethylation by Reichstein and Oppenauer is the solution obtained by saturating 40% formaldehyde with hydrogen chloride. This does largely consist of dichlorodimethyl ether, which is the active agent in the condensation, but it contains other substances which appear to polymerise and render the isolation of the pure chloromethyl compounds difficult. Better results were obtained by using pure dichlorodimethyl ether (Descude, *Centr.*, 1904, I, 1642). Since this work was done recent publications (*Compt. rend.*, 1939, **208**, 818; *Bull Soc. chim.*, 1939, **6**, 1025) on chloromethylation suggest an improved technique which should prove useful.

4 : 4′-*Dicyano-αγ-diphenylpropane* was prepared by the same series of reactions from the hydrocarbon. Attempts to reduce 4 : 4′-*dicyanobenzylideneacetophenone*, prepared by condensation of 4-cyanobenzaldehyde with 4-cyanoacetophenone, by hydrogen and palladium as applied to the unsubstituted substance (Straus and Grindal, *Annalen*, 1924, **439**, 279) failed.

Certain mononitriles, required for the synthesis of dinitriles with hetero-linkages, were prepared in considerable quantity. 4-Aminobenzonitrile has been prepared by reduction of the corresponding nitro-compound, but we preferred to convert 4-acetamidobenzaldehyde into the oxime, which on dehydration yielded 4-acetamidobenzonitrile, readily hydrolysed to the free amine by acid hydrolysis. 4-Hydroxybenzonitrile was prepared by the Sandmeyer method from 4-aminophenol, and 4-cyanobenzyl chloride by chlorination of 4-toluonitrile (Mellinghoff, *Ber.*, 1889, **22**, 3208).

4-Cyanobenzyl chloride with 4-hydroxybenzonitrile yielded 4-*cyanophenyl* 4-*cyanobenzyl ether* and with 3-hydroxybenzonitrile 3-*cyanophenyl* 4-*cyanobenzyl ether*. Similarly with 4-aminobenzonitrile 4 : 4′-*dicyanobenzylaniline* was obtained. Quinol and 2 molecules of 4-cyanobenzyl chloride gave 1 : 4-bis-(4′-cyanobenzyloxy)benzene, $C_6H_4(O{\cdot}CH_2{\cdot}C_6H_4{\cdot}CN)_2$. The 4 : 4′-dicyanodiphenoxyalkanes,

$$CN{\cdot}C_6H_4{\cdot}O{\cdot}[CH_2]_n{\cdot}O{\cdot}C_6H_4{\cdot}CN$$

were prepared by condensation of the appropriate αω-dibromoalkane with sodium 4-cyanophenoxide; *p*-xylylene dibromide yielded ωω′-bis-(4′-cyanophenoxy)-*p*-xylene, $C_6H_4(CH_2{\cdot}O{\cdot}C_6H_4{\cdot}CN)_2$. By use of an excess of the alkylene dibromide the ω-bromoalkoxybenzonitriles may be obtained (cf. *Org. Syntheses*, I—X, p. 425) and 4-cyano-β-phenoxyethyl bromide gave 4 : 4′-*dicyano-β-phenoxyethylaniline* on condensation with 4-aminobenzonitrile. The hydrolysis of 4-cyanobenzyl chloride has been carried out by Banse

(*Ber.*, 1894, **27**, 2170), who described a product, m. p. 134°, as 4-cyanobenzyl alcohol. It has now been shown that this is 4-carbamidobenzyl alcohol and the true 4-*cyanobenzyl alcohol* has been obtained in excellent yield by a slight modification of Banse's procedure.

More drastic hydrolysis of 4-cyanobenzyl chloride with potassium hydroxide yields an acid, $C_{16}H_{14}O_5$, which Günther (*Ber.*, 1890, **23**, 1061) assumed, without much evidence, to be 4 : 4′-dicarboxydibenzyl ether. This acid has now been converted through the *acid chloride* and *amide* into the *dinitrile*, which was identical with the product obtained in small yields by condensing 4-cyanobenzyl alcohol with 4-cyanobenzyl chloride. Attempts to prepare this dinitrile from 4-cyanobenzyl alcohol by Meisenheimer's method (*Ber.*, 1908, **41**, 1421) for dibenzyl ether failed.

4-Cyanobenzaldehyde has been prepared by boiling 4-cyanobenzyl chloride with copper nitrate solution (Reinglass, *Ber.*, 1891, **24**, 2421; Moses, *Ber.*, 1900, **33**, 3624), but in our hands this method gave mixtures of alcohol, aldehyde, and acid. More recently (*J. Amer. Chem. Soc.*, 1936, **58**, 561) 2-cyanobenzaldehyde has been prepared from 2-cyanobenzylidene dibromide and silver nitrate in 50% yield only. We have found that nitrogen tetroxide in chloroform solution [an excellent method due to Cohen (J., 1897, **71**, 1050), which deserves to be more widely known] gives almost quantitative yields of the aldehyde from cyanobenzyl alcohol.

The considerable literature on the benzoin condensation did not suggest that an aldehyde such as 4-cyanobenzaldehyde would give the benzoin. The aldehyde reacted vigorously to give 4 : 4′-*dicyanodeoxybenzoin*. There does not appear to be any precedent for this in the literature, but it is well known that benzoins are readily converted into the deoxybenzoins by mild reducing agents, and it seemed possible that the benzoin might have been formed first and reduced rapidly by unconverted aldehyde. However, the yield of deoxybenzoin was practically the same after a few minutes as after 1 hour's boiling, a fact which would preclude that explanation. Some 4-cyanobenzoic acid was isolated, the amount being about half that required by the equation $3R{\cdot}CHO = R{\cdot}CO_2H + R{\cdot}CO{\cdot}CH_2R$.

4 : 4′-*Dicyanobenzanilide* was obtained in the usual way from 4-*cyanobenzoyl chloride* and 4-aminobenzonitrile, and 4 : 4′-*dicyanobenzenesulphonanilide* similarly from 4-cyanobenzenesulphonyl chloride (Remsen, Hartman, and Muchenfuss, *Amer. Chem. J.*, 1896, **18**, 158).

The projected scheme for the preparation of 4-cyanophenyl 4-cyano-β-phenylethyl ether was to condense 4-nitro-β-phenylethyl bromide with 4-hydroxybenzonitrile to give 4-cyanophenyl 4-nitro-β-phenylethyl ether, which on reduction to the amino-compound, followed by a Sandmeyer reaction, should have given the required dicyano-ether. The condensation, however, gave traces only of the required ether and attempts to nitrate 4-cyanophenyl β-phenylethyl ether led to a dinitro-compound, probably 2-*nitro*-4-*cyanophenyl* 4-*nitro*-β-*phenylethyl ether*.

4-Nitro-β-phenylethyl bromide was smoothly reduced by hydrogen in presence of platinum oxide to 4-*amino*-β-*phenylethyl bromide*, which gave 4-*cyano*-β-*phenylethyl bromide* by the Sandmeyer method. The condensation of this with 4-hydroxybenzonitrile gave small yields of 4-*cyanophenyl* 4-*cyano*-β-*phenylethyl ether*.

Attempts to prepare 4 : 4′-dicyanodiphenylamine from 4-bromobenzonitrile and 4-aminobenzonitrile failed entirely and the following method was evolved. N-4-*Cyanophenylbenziminochloride*, prepared from 4-cyano-*N*-benzoylaniline, gave with sodium 4-cyanophenoxide N-4-*cyanophenylbenzimino*-4′-*cyanophenyl ether*, $CN{\cdot}C_6H_4{\cdot}N{:}CPh{\cdot}O{\cdot}C_6H_4{\cdot}CN$, which on rearrangement (cf. Chapman, J., 1925, **127**, 1992) yielded 4 : 4′-*dicyano*-N-*benzoyldiphenylamine*.

It was expected that removal of the benzoyl group would be effected during the preparation of the amidine *via* the imino-ether, but the amidine was in fact obtained with only small amounts of 4 : 4′-diamidinodiphenylamine, separated by means of its sparingly soluble *acid sulphate*. The amidine $NBz[C_6H_4{\cdot}C(:NH){\cdot}NH_2]_2$ decomposed smoothly at its melting point, giving excellent yields of 4 : 4′-*dicyanodiphenylamine* and benzamide, conveniently separated by sublimation. The sparing solubility of 4 : 4′-dicyano-*N*-benzoyldiphenylamine made the direct removal of the benzoyl group difficult, but sodium hydroxide in boiling ethylene glycol was a suitable hydrolytic agent for this substance.

Chemotherapeutic studies in the amidine series are being continued.

Experimental.

Amidines.—The general procedure has been outlined already and has been followed for the amidines for which the data have been summarised in the following table. In certain other cases the details are given. Two of the amidines included in the tables have been described : 1 : 4-diamidinobenzene ((Luckenbach, *Ber.*, 1884, **17**, 1436) and ωω′-diamidino-*p*-xylene (Glock, *Ber.*, 1888, **21**, 2660). The preparation of the compounds marked * has been described in detail in Brit. Pat. 507,565 and of that marked † in Brit. Pat. 510,097.

Compound.	Solvent.	Crystalline form.	M. p.	Formula.	Found, %.	Required.
4-*Aminophenylacetamidine dihydrochloride*	Alcohol	Plates	270°	$C_8H_{11}N_3,2HCl$	Cl, 31·7	32·0
4-*Amidinomethylbenzamidine dihydrochloride*	Methyl alcohol–acetone	Tetrahedra	280—285 (decomp.)	$C_9H_{12}N_4,2HCl$	Cl, 27·5	28·5
*4 : 4′-Diamidinodiphenyl dihydrochloride	Water	Slender needles	—	$C_{14}H_{14}N_4,2HCl$	N, 17·2 Cl, 22·6	18·0 22·8
4 : 4′-*Dimethylamidinodiphenyl dihydrochloride*	Alcohol–acetone	White prisms	—	$C_{15}H_{18}N_4,2HCl$	N, 16·9	16·5
4 : 4′-*Di*-N-*diethylamidinodiphenyl dihydrochloride*	Methyl alcohol–ether	Microcryst. powder	—	$C_{22}H_{30}N_4,2HCl$	N, 13·4	13·2
4 : 4′-*Di*-N-*phenylamidinodiphenyl dihydrochloride*	Water	Fine needles	—	$C_{26}H_{22}N_4,2HCl$	N, 11·8	12·1
*4 : 4′-Diamidinodiphenylmethane dihydrochloride	Alcohol–acetone	Slender prisms	—	$C_{15}H_{16}N_4,2HCl$	N, 15·6	15·5
4 : 4′-*Diamidinotriphenylmethane dihydrochloride*	,,	Microcryst. powder	—	$C_{21}H_{20}N_4,2HCl$	Cl, 18·1	17·7
4 : 4′-*Diamidinomethyldiphenyl dihydrochloride*	,,	Hexagonal plates	—	$C_{16}H_{18}N_4,2HCl$	N, 16·5	16·5
4-*Amidino*-2′-*cyanodiphenyl*	Water	Slender prisms	160—161	$C_{14}H_{11}N_3$	N, 18·4	19·0
*4 : 4′-Diamidinodiphenylethane dihydrochloride	5N-HCl	Small prisms	—	$C_{16}H_{18}N_4,2HCl,\frac{1}{2}H_2O$	N, 15·9 H_2O, 2·6	16·1 2·6
4 : 4′-*Diamidinodiphenylpropane dihydrochloride*	,,	Feathery needles	—	$C_{17}H_{20}N_4,2HCl$	N, 15·3	15·85
4 : 4′-*Diamidinobenzophenone dihydrochloride*	Methyl alcohol–ether		300	$C_{15}H_{14}ON_4,2HCl$	N, 15·9	16·4
4 : 4′-*Diamidinobenzhydrol dihydrochloride*	Methyl alcohol–ether	Microcrystalline	212	$C_{15}H_{16}ON_4,2HCl,3H_2O$	N, 14·0 Cl, 18·0	14·2 18·0
†4 : 4′-Diamidinostilbene dihydrochloride	Water	Needles	300	$C_{16}H_{16}N_4,2HCl,2H_2O$ $C_{16}H_{16}N_4,2HCl$ (dried at 100°)	N, 14·8 N, 16·4	15·0 16·6
4 : 4′-*Diamidinostilbene dimethanesulphonate*	,,	Long rods	—	$C_{16}H_{16}N_4,2CH_3{\cdot}SO_3H$	N, 12·3	12·3
3 : 4′-*Diamidinostilbene dihydrochloride*	Acetone–water	Clusters of prisms	300	$C_{16}H_{16}N_4,2HCl$	N, 16·2	16·6
4 : 4′-*Diamidino-αδ-diphenylbutadiene dihydrochloride*	Dil. HCl	Pale yellow prisms	—	$C_{18}H_{18}N_4,2HCl$	N, 14·9	15·4
4-*Amidinostilbene hydrochloride*	,,	Colourless plates	225—226	$C_{15}H_{15}N_3,HCl,H_2O$	N, 10·1	10·1
4-*Nitro*-4′-*amidinostilbene hydrochloride*	Acetic acid–HCl	Long yellow plates	300	$C_{15}H_{13}O_2N_3,HCl$	N, 13·9	13·8
4-*Amino*-4′-*amidinostilbene dihydrochloride*	,,	Plates	300	$C_{15}H_{15}N_3,2HCl$	N, 13·8	13·6
4 : 4′-*Diamidinobenzylideneacetophenone dihydrochloride*	Dil. HCl	Orange microcryst.	—	$C_{17}H_{16}ON_4,2HCl$	N, 15·5	15·3
4 : 4′-*Diamidinodeoxybenzoin dihydrochloride*	70% Alcohol	Small prisms	280—282	$C_{16}H_{15}ON_4,2HCl,1\frac{1}{2}H_2O$	N, 14·6 H_2O, 6·6	14·7 7·1
4-*Amidinodiphenyl ether*	Water	Hexagonal plates	126—127	$C_{13}H_{12}ON_2$	Equiv., 213	212
*4 : 4′-Diamidinodiphenyl ether	,,	Irregular plates	215—216	$C_{14}H_{14}ON_4$	N, 22·0	22·0
4 : 4′-Diamidinodiphenyl ether dihydrochloride	2N-HCl	Slender needles	—	$C_{14}H_{14}ON_4,2HCl,2H_2O$	N, 15·4 Cl, 19·4	15·4 19·55
*4 : 4′-*Diamidinodiphenyl sulphide*	Water	Spear-shaped plates	209—210 (decomp.)	$C_{14}H_{14}N_4S$	N, 20·2	20·7
4 : 4′-*Diamidinodiphenylsulphone dihydrochloride*	Methyl alcohol–ether	Colourless prisms	290 (decomp.)	$C_{14}H_{14}O_2N_4S,2HCl$	N, 14·9	14·9
*4-Amidinophenyl 4-amidinobenzyl ether	Water	Flat prisms	232—233	$C_{15}H_{15}ON_3$	N, 20·5	20·9
4-*Amidinophenyl* 4-*amidinobenzyl ether dihydrochloride*	Methyl alcohol–acetone	Heavy prisms	—	$C_{15}H_{15}ON_3,2HCl$	N, 16·3	16·4
3-*Amidinophenyl* 4-*amidinobenzyl ether dihydrochloride*	Alcohol	Slender prisms	—	$C_{15}H_{16}ON_4,2HCl,\frac{1}{2}H_2O$	N, 16·0 15·9	16·0 —
4-*Amidinomethylphenyl* 4-*amidinobenzyl ether*	Water	Diamond-shaped plates	182	$C_{16}H_{18}ON_4$	N, 19·6	19·9
*4 : 4′-Diamidinobenzylaniline dihydrochloride	Alcohol–acetone		296	$C_{15}H_{17}N_5,2HCl,H_2O$	N, 19·65 H_2O, 4·25	19·55 5·0
*4 : 4′-Diamidinodibenzylamine trihydrochloride	Conc. HCl	Prisms	—	$C_{16}H_{19}N_5,3HCl$	N, 17·8 Cl, 27·3	17·9 27·3
4 : 4′-*Diamidinodibenzyl ether*	Water	Pearly leaflets	195 (decomp.)	$C_{16}H_{18}ON_4$	N, 20·0	19·9
4 : 4′-*Diamidinodibenzyl ether dihydrochloride*	Aqueous alcohol–acetone	Long prisms	—	$C_{16}H_{18}ON_4,2HCl,H_2O$	N, 14·9 H_2O, 4·9	15·0 4·8
*4 : 4′-Diamidinodibenzyl sulphide	Aqueous alcohol	Colourless needles	198—199 (decomp.)	$C_{16}H_{18}N_4S$	N, 18·4	18·8
4-*Amidinophenyl* 4-*amidino*-β-*phenylethyl ether dihydrochloride*	Aqueous alcohol–acetone	Dense prisms	—	$C_{16}H_{18}ON_4,2HCl,H_2O$	N, 14·7	15·0
4 : 4′-*Diamidinodiphenoxymethane dihydrochloride*	Water	Colourless prisms	249 (decomp.)	$C_{15}H_{16}O_2N_4,2HCl$	N, 15·7	15·7
*4 : 4′-Diamidino-αβ-diphenoxyethane	,,	,, ,,	234—235 (decomp.)	$C_{16}H_{18}O_2N_4$	N, 18·9	18·9
4 : 4′-*Diamidino-αβ-diphenoxyethane dihydrochloride*	,,	Colourless needles	297	$C_{16}H_{18}O_2N_4,2HCl,H_2O$	N, 14·4 Cl, 18·4	14·4 18·3
*4 : 4′-Diamidino-αγ-diphenoxypropane dihydrochloride	Dil. HCl Alcohol	Fine needles Prisms	292 300	$C_{17}H_{20}O_2N_4,2HCl,H_2O$ $C_{17}H_{20}O_2N_4,2HCl$	N, 13·9 N, 14·2	13·9 14·5
3 : 3′-*Diamidino-αγ-diphenoxypropane dihydrochloride*	Alcohol–acetone	Fine needles	202—204 (decomp.)	$C_{17}H_{20}O_2N_4,2HCl$	N, 14·2	14·5
4 : 4′-*Diamidino-αδ-diphenoxybutane dihydrochloride*	Dil. HCl	Thin plates	259—261	$C_{18}H_{22}O_2N_4,2HCl,2H_2O$	N, 12·8 H_2O, 8·5	12·8 8·3
*4 : 4′-Diamidino-αε-diphenoxypentane	Water	Colourless plates	186 (decomp.)	$C_{19}H_{24}O_2N_4$	N, 16·5	16·5
4 : 4′-*Diamidino-αε-diphenoxypentane dihydrochloride*	Dil. HCl Alcohol	Fine needles Colourless prisms	233—234 (decomp.)	$C_{19}H_{24}O_2N_4,2HCl,2H_2O$	N, 12·5	12·5
4 : 4′-*Diamidino-αε-diphenoxypentane dimethanesulphonate*	90% Alcohol	Heavy prisms	—	$C_{19}H_{24}O_2N_4,2CH_3{\cdot}SO_3H$	N, 10·4	10·5
3 : 3′-*Diamidino-αε-diphenoxypentane dihydrochloride*	Dil. HCl	Matted needles	—	$C_{19}H_{24}O_2N_4,2HCl,2H_2O$	N, 12·3	12·5
4 : 4′-*Diamidino-aζ-diphenoxyhexane-dihydrochloride*	,,	Prisms	246—247 (decomp.)	$C_{20}H_{24}O_2N_4,2HCl,2H_2O$	N, 12·1 H_2O, 7·6	12·1 7·8
4 : 4′-*Diamidino-aη-diphenoxyheptane*	Water	Colourless powder	175—177 (decomp.)	$C_{21}H_{28}O_2N_4$	N, 15·2	15·2
4 : 4′-*Diamidino-aη-diphenoxyheptane dihydrochloride*	Dil. HCl Alcohol–acetone	Fibrous needles Rhombs	245—246 (decomp.)	$C_{21}H_{28}O_2N_4,2HCl,2H_2O$	N, 11·6	11·7
*4 : 4′-Diamidino-aκ-diphenoxydecane dihydrochloride	Water	Prisms	254	$C_{24}H_{34}O_2N_4,2HCl$	N, 11·4	11·6
ωω′-*Di*-(4′-*amidinophenoxy*)*xylene dihydrochloride*	,,	,,	—	$C_{22}H_{22}O_2N_4,2HCl,H_2O$	N, 12·0	12·0

Compound.	Solvent.	Crystalline form.	M. p.	Formula.		Found, %.	Required.
1 : 4-*Di*-(4′-*amidinobenzyloxy*)*benzene dihydrochloride*	Water	Slender prisms	—	$C_{22}H_{22}O_2N_4,2HCl,2H_2O$	N,	11·2	11·6
4 : 4′-*Diamidinodiphenoxydimethyl ether*	90% Alcohol		Indefinite	$C_{16}H_{18}O_2N_4$	N,	17·4	17·8
4 : 4′-*Diamidinodiphenoxydimethyl ether dihydrochloride*	Absolute alcohol–ether		—	$C_{16}H_{18}O_2N_4,2HCl$	N,	14·6	14·5
4 : 4′-*Diamidinoazobenzene dihydrochloride*	Dil. HCl	Red plates or rods	>300	$C_{14}H_{14}N_6,2HCl,H_2O$	N,	23·8	23·5
4 : 4′-*Diamidinodiphenyl disulphide dihydrochloride*	,,	Prisms	>300	$C_{14}H_{14}N_4S_2,2HCl,2H_2O$	N,	14·35	14·25
4 : 4′-*Diamidinobenzanilide*	Water	Microcryst.	245—250 (decomp.)	$C_{15}H_{15}ON_3$	N,	23·5	24·9
4 : 4′-*Diamidinobenzenesulphonanilide dihydrochloride*	Dil. HCl	Octohedra	239	$C_{14}H_{16}O_2N_3S,2HCl,4H_2O$	N,	15·3	15·1
					Cl,	15·6	15·3
4 : 4′-*Diamidinodiphenylurea dimethanesulphonate*	Methyl alcohol	Prisms	—	$C_{15}H_{16}ON_4,2CH_3{\cdot}SO_3H,H_2O$	N,	16·6	16·6
*4 : 4′-Diamidino-β-phenoxyethylaniline	Water	,,	204 (decomp.)	$C_{16}H_{11}ON_3$	N,	24·0	24·0
*4 : 4′-Diamidino-β-phenoxyethylaniline dihydrochloride	Dil. HCl	,,	296—297	$C_{16}H_{11}ON_3,2HCl,2H_2O$	N,	17·8	17·6
					Cl,	17·6	17·5
4 : 4′-*Diamidino*-N-*benzoyldiphenylamine*	Water	Colourless prisms	194 (decomp.)	$C_{21}H_{19}ON_3,2·5H_2O$	N,	17·0	17·4
					H_2O,	10·4	11·2
4 : 4′-*Diamidinodiphenylamine sulphate*	Dil. H_2SO_4	Deep orange rhombs	—	$C_{14}H_{15}N_3,1·5H_2SO_4$	N,	17·7	17·5
4 : 4′-*Diamidinodiphenylamine dihydrochloride*	Alcohol		—	$C_{14}H_{15}N_3,2HCl,H_2O$	N,	20·2	20·3

The following dinitriles were prepared by methods given in the literature: Terephthalonitrile (*Annalen*, 1876, **180**, 89); 4-cyanophenylacetonitrile (*Ber.*, 1887, **20**, 3209); ωω′-dicyano-*p*-xylene (*Ber.*, 1888, **21**, 2659); 4 : 4′-dicyanodiphenyl (J., 1920, **117**, 1149); 2 : 4′-dicyanodiphenyl (*Ber.*, 1889, **22**, 3018); 4 : 4′-dicyanodiphenylmethane (*Ber.*, 1894, **27**, 2325); 4 : 4′-dicyanomethyldiphenyl (*Ber.*, 1933, **66**, 1475); 4 : 4′-dicyanodiphenyl disulphide (J., 1930, 1102); 4 : 4′-dicyanodibenzyl sulphide (*J. Amer. Chem. Soc.*, 1927, **49**, 2552); 4 : 4′-dicyanodiphenylurea (*ibid.*, 1921, **43**, 696); 4 : 4′-dicyanodibenzylamine (*Ber.*, 1900, **32**, 2629).

Dinitriles by the Sandmeyer Method.—The general procedure is that described in Organic Syntheses (Coll. Vol. I—IX, p. 500) with the difference that benzene is not used during the decomposition of the diazocyanide, and the cuprocyanide solution is maintained at temperatures varying with the diamine from 40° to 90° (there seems to be no general principle as to the optimum temperature for a given class of compound). The crude product, usually a dark, brittle, coke-like mass containing varying amounts of copper and weighing about the same as the original diamine employed, is dried and sublimed. The very simple technique employed is so marked an improvement on the conventional methods of extraction and repeated crystallisation as to merit some description.

The apparatus consists of a copper or gun-metal heating block approximately 70 × 60 × 60 mm., bored to take a 25 mm. test-tube and a thermometer. A short rod screwed into one side enables the block to be held in an ordinary boss and a retort stand at any desired angle. The sublimation is carried out in a 25 × 125 mm. Pyrex glass tube closed by a rubber stopper carrying a short length of 2 mm. bore glass tubing for connection to the vacuum pump; no cooling is needed. The tube is charged with the crude product (usually about 5 g.), followed by a loose asbestos plug. When the tube is inserted in the block, this plug should be a few mm. inside. The sublimations are carried out generally at 0·1—1 mm. pressure and at temperatures a little above or below the melting point. The nitriles usually form a hard crystalline crust in the tube a few mm. outside the block and are then almost invariably pure after one crystallisation. This process, used also for certain nitriles obtained by methods in which some amide may be formed, readily gives a sharp separation owing to the much greater volatility of the nitriles.

4 : 4′-*Dicyanotriphenylmethane*, m. p. 134—145°, was obtained in 5% yield from the diamine (Found: C, 85·4; H, 4·7; N, 9·35. $C_{21}H_{14}N_2$ requires C, 85·7; H, 4·8; N, 9·5%).

4 : 4′-*Dicyanobenzophenone*, obtained in 60% yield from the diamine, had m. p. 162° after crystallisation from acetic acid (Found: C, 77·9; H, 3·4; N, 12·05. $C_{15}H_8ON_2$ requires C, 77·6; H, 3·4; N, 12·05%). The *phenylhydrazone* formed yellow prisms from alcohol, m. p. 242—243° (Found: N, 17·2. $C_{21}H_{14}N_4$ requires N, 17·4%).

4 : 4′-*Dicyanobenzhydrol.*—4 : 4′-Dicyanobenzophenone (2 g.), suspended in ethyl alcohol (200 c.c.) containing ammonia, was treated with amalgamated aluminium foil (10 g.) under reflux, with occasional shaking, for 2 hours. The mixture was cooled, the liquid filtered, and the residue extracted with ethyl alcohol. The combined filtrate and extracts were evaporated to dryness, and the residue extracted with cold methyl alcohol (50 c.c.). The solution was again evaporated, and the residue crystallised from 50% acetic acid, yielding 0·65 g., m. p. 158—159° (Found: C, 76·9; H, 4·4; N, 12·0; *M*, Rast, 222. $C_{15}H_{10}ON_2$ requires C, 77·0; H, 4·3; N, 12·0%; *M*, 234).

4 : 4′-*Dicyanostilbene* (45% yield) crystallised from nitrobenzene in almost white prisms, m. p. 282° (Found: N, 12·1. $C_{16}H_{10}N_2$ requires N, 12·2%).

αβ-*Bis*-(4-*phenylbenzamidrazino*)*ethylene.*—The di-imino-ether obtained from 4 : 4′-dicyanostilbene (6 g.) was heated at 50° for 4 hours with a solution of phenylhydrazine (15 c.c.) in absolute alcohol (100 c.c.). The solid product obtained on cooling was washed with alcohol and acetone and boiled with water (4·5 l.). The solution was filtered, and hydrochloric acid (100 c.c., *d* 1·16) added to the filtrate. The product was recrystallised from water, the *dihydrochloride* (4 g.) separating in long cream-coloured needles, m. p. above 300° (Found:

N, 16·3; Cl, 13·3. $C_{28}H_{26}N_6$,2HCl requires N, 16·2; Cl, 13·7%). The *base* crystallised from dilute acetone in clusters of brown needles, m. p. 261—262° (decomp.) (Found: N, 18·5. $C_{28}H_{26}N_6$ requires N, 18·8%).

3 : 4′-*Diaminostilbene.*—A mixture of 3 : 4′-dinitrostilbene (2·7 g.), stannous chloride (cryst., 17 g.), glacial acetic acid (10 c.c.), and hydrochloric acid (20 c.c., *d* 1·16) was heated to boiling. The stannichloride which separated on cooling was decomposed with sodium hydroxide, and the diamine crystallised from aqueous alcohol. Yield 1·2 g., m. p. 153°.

3 : 4′-*Dicyanostilbene* (yield, 26%) crystallised from glacial acetic acid in yellow needles, m. p. 137—138° (Found: N, 11·9. $C_{16}H_{10}N_2$ requires N, 12·2%).

4 : 4′-*Dinitro-αδ-diphenylbutadiene-α-carboxylic Acid.*—A mixture of sodium 4-nitrophenylacetate (38 g.) and 4-nitrocinnamaldehyde (30 g.), heated to 140—150°, was treated gradually with acetic anhydride (30 c.c.) and heated at 150° for 2 hours. Acetic anhydride (10 c.c.) was then added, and heating continued at 160° for a further 2 hours. The cold mixture was treated with water and left for 12 hours. The solid obtained after filtration was exhaustively extracted with boiling 0·5N-sodium carbonate, and the *acid* (24 g.) precipitated by boiling dilute hydrochloric acid. It crystallised from alcohol in squat yellowish-brown prisms, decomp. 295—300° (Found: N, 8·3. $C_{17}H_{12}O_6N_2$ requires N, 8·2%).

4 : 4′-*Dicyano-αδ-diphenylbutadiene.*—The dinitro-compound (10 g.) was heated with a solution of crystallised stannous chloride (50 g.) in hydrochloric acid (50 c.c., *d* 1·16) and glacial acetic acid (50 c.c.). After the vigorous reaction abated, the mixture was diluted, and tin removed as sulphide. Evaporation of the filtrate left the diaminocarboxylic acid dihydrochloride as a colourless solid (yield, 60%), which was tetrazotised without further purification. The crude product was sublimed at 250—260°/1—2 mm. The sublimate of 4 : 4′-*dicyano-αδ-diphenylbutadiene* crystallised from acetic acid in almost colourless, long plates or prisms, m. p. 260—261° (decomp.). Yield, 8% (Found: N, 10·85. $C_{18}H_{12}N_2$ requires N, 10·9%).

4-*Cyanostilbene*, obtained in 16% yield from 4-aminostilbene (Pfeiffer and Sergiewskaja, *Ber.*, 1911, **44**, 1110), crystallised from 80% acetic acid in fine needles, m. p. 114° (Found: N, 6·45. $C_{15}H_{11}N$ requires N, 6·8%).

4-*Nitro*-4′-*acetamidostilbene.*—A mixture of 4-nitrophenylacetic acid (45 g.), 4-acetamidobenzaldehyde (40 g.), and piperidine (12 c.c.) was heated under reflux at 160° for 6 hours. The cooled melt was ground with alcohol and washed thoroughly with alcohol and ether, the crude product (26 g.) being used in the next reaction. It crystallised from pyridine in yellow plates, m. p. 255° (Found: N, 10·3. $C_{16}H_{14}O_3N_2$ requires N, 9·9%).

4-*Nitro*-4′-*aminostilbene.*—The acetyl compound (10 g.) was refluxed with alcohol (100 c.c.) and hydrochloric acid (100 c.c., *d* 1·16) for 2 hours. When cool, the yellow hydrochloride was filtered off, and suspended in water, and the base (7·9 g.) liberated with sodium carbonate. It crystallised from pyridine in deep red plates, m. p. 245° (Strakosch, *Ber.*, 1873, **6**, 329, gives m. p. 229—230°).

4-*Nitro*-4′-*cyanostilbene* (yield, 31%) crystallised from glacial acetic acid in yellow needles, m. p. 247—249° (Found: N, 11·2. $C_{15}H_{10}O_2N_2$ requires N, 11·2%).

4-*Amino*-4′-*amidinostilbene.*—A hot solution of stannous chloride (6 g.) in hydrochloric acid (6 c.c., *d* 1·16) was added to a boiling solution of 4-nitro-4′-amidinostilbene hydrochloride (2 g.) in a mixture of glacial acetic acid (25 c.c.) and hydrochloric acid (10 c.c., *d* 1·16). The yellow stannichloride, which quickly separated, was cooled, collected, and dissolved in water. The free base was liberated by 50% sodium hydroxide solution (15 c.c.). The washed base was dissolved in cold glacial acetic acid and precipitated as the dihydrochloride by addition of concentrated hydrochloric acid (yield, 54%).

4 : 4′-*Diaminoazobenzene.*—A mixture of 4 : 4′-dinitroazobenzene (10 g.), crystallised sodium sulphide (100 g.), water (100 c.c.), and alcohol (300 c.c.) was refluxed for ½ hour. The hot liquid was filtered, and the diamine which separated was recrystallised from alcohol. Yield 3·2 g., m. p. 245—246°.

4 : 4′-*Dicyanoazobenzene* (yield, 45%) crystallised from glacial acetic acid in deep maroon needles, m. p. 270° (Found: N, 24·25. $C_{14}H_8N_4$ requires N, 24·1%).

4 : 4′-*Dicyanodiphenylethane.*—Diphenylethane-4 : 4′-dialdehyde (Reichstein and Oppenauer, *loc. cit.*) was converted into the oxime in the usual way, and this was boiled for 2 hours with 10 parts of acetic anhydride. Sufficient water was added to convert the acetic anhydride into acetic acid; the required dinitrile crystallised. Yield, 74%. The overall yield of dinitrile for the five stages from the dichloromethyl compound was 40%.

αγ-Diphenylpropane.—Dibenzyl ketone, b. p. 178—182°/10—11 mm., prepared by distillation of calcium phenylacetate in 500 g. lots in a steel retort, followed by fractionation of the distillate (yield, 60%), was reduced by the Clemmensen method to the hydrocarbon, b. p. 155—160°/9—10 mm. Yield, 70%. The higher-boiling fractions were returned to the next reduction. In this way 1 kg. of calcium salt gave 300 g. of pure αγ-diphenylpropane. The hydrocarbon was submitted to the same series of reactions as for αβ-diphenylethane. Chloromethylation gave a small yield of 4 : 4′-*dichloromethyl-αγ-diphenylpropane*, m. p. 103—106° (Found: Cl, 25·0. $C_{17}H_{18}Cl_2$ requires Cl, 24·2%). This was converted successively into 4 : 4′-*dihydroxymethyl-αγ-diphenylpropane*, m. p. 118—122° (Found: C, 79·4; H, 7·65. $C_{17}H_{20}O_2$ requires C, 79·6; H, 7·87%), the 4 : 4′-dialdehyde (oil), 4 : 4′-dialdoxime (m. p. 125—127°), and finally 4 : 4′-*dicyano-αγ-diphenylpropane*. This formed white prisms from alcohol, m. p. 94—95° (Found: N, 11·0. $C_{17}H_{14}N_2$ requires N, 11·4%). The overall yield from the dichloromethyl compound was 35%.

4 : 4′-*Dicyanobenzylideneacetophenone*.—4-Cyanobenzaldehyde (2·6 g.) and 4-cyanoacetophenone (2·9 g.) were boiled in absolute alcohol containing piperidine (0·2 g.) for 3 hours. The product which crystallised on cooling (2·6 g.; yield 60%) was recrystallised from glacial acetic acid, forming pale yellow, fibrous needles, m. p. 216—217° (Found : N, 11·0. $C_{17}H_{10}ON_2$ required N, 10·85%). Other condensing agents such as sodium hydroxide or sodium ethoxide gave red gums from which no satisfactory product was isolated.

4 : 4′-*Dicyanodiphenyl Ether*.—(*a*) The Sandmeyer method gave 50% of sublimed material. (*b*) In the Ullmann method, sodium 4-cyanophenoxide dried at 120° (7 g.), mixed with excess of 4-bromobenzonitrile (20 g.) and copper powder (0·1 g.), was heated to gentle ebullition (250—270°) for 3½ hours. The cooled melt was ground and washed thoroughly, first with ether and then with water. Yield 4·1 g. (37%), m. p. 178—180°. The *dinitrile* crystallised readily from alcohol (50 vols.), glacial acetic acid or pyridine (3 vols.); m. p. 180° (Found : N, 12·8. $C_{14}H_8ON_2$ requires N, 12·7%).

4 : 4′-*Dicyanodiphenyl sulphide*, similarly prepared by Sandmeyer method, formed pale yellow prisms from alcohol, m. p. 133—134° (Found : N, 12·0. $C_{14}H_8N_2S$ requires N, 11·9%).

4 : 4′-*Dicyanodiphenylsulphone*.—4 : 4′-Dicarboxydiphenylsulphone (Michael and Adair, *Ber.*, 1878, **11**, 121) was converted *via* the acid chloride into the *diamide*, m. p. >300°. Yield, 80% (Found : N, 9·4. $C_{14}H_{12}O_4N_2S$ requires N, 9·3%). The diamide was heated over a naked flame with twice its weight of phosphoric oxide until it became dark brown and sticky. The melt was extracted with 2N-sodium carbonate, and the residue crystallised from glacial acetic acid, forming faintly yellow prisms, m. p. 232—233°, identical with the product prepared from 4 : 4′-diaminodiphenylsulphone by the Sandmeyer reaction (Found : N, 10·5. $C_{14}H_8O_2N_2S$ requires N, 10·45%).

4-*Cyanodiphenyl Ether*.—4-Bromobenzonitrile (9·1 g.), boiled for 6 hours with excess of phenol (20 g.) containing potassium hydroxide (3·5 g.), gave a mixture of the required nitrile and the corresponding amide, which were separated by sublimation at 100°/0·1 mm. The nitrile, which sublimed, had m. p. 43—45° (Found : N, 7·25. $C_{13}H_9ON$ requires N, 7·2%). The residual *amide*, crystallised from 40% alcohol, had m. p. 164—165° (Found : N, 6·4. $C_{13}H_{11}O_2N$ requires N, 6·6%).

4-*Aminobenzonitrile*.—The dried ethereal extract of 4-aminobenzaldehyde obtained from 4-nitrotoluene (270 g.) (Geigy, D.R.-P. 86,874; Hodgson and Beard, J., 1927, 20) was treated with acetic anhydride (300 c.c.) and left overnight. The crude 4-acetamidobenzaldehyde (170 g., m. p. 149—150°) which separated was converted into the oxime (175 g.) (Gabriel and Herzberg, *Ber.*, 1883, **16**, 2004). The crude oxime, after drying at 100°, was boiled for 1 hour with acetic anhydride (150 c.c.). After stirring into ice-water (1 l.), the solution was neutralised; the resulting 4-acetamidobenzonitrile was collected and added to boiling 2N-hydrochloric acid (1,200 c.c.) and boiling was continued for 5 minutes after complete solution. The solution was then cooled in ice and neutralised, and the light yellow 4-aminobenzonitrile collected, washed, and dried in a vacuum. Yield 91 g., m. p. 82—84°. Acetylation of the aqueous mother-liquor with acetic anhydride gave a recovery of 4-acetamidobenzonitrile (about 16 g.). The total yield is thus 80%, calculated on 4-acetamidobenzaldehyde.

4-*Hydroxybenzonitrile*.—The Sandmeyer reaction on *p*-aminophenol is best carried out with the cuprocyanide solution at 90—95° (H. King, private communication). The most convenient method of isolation on a large scale is as follows. The acidified reaction mixture was saturated with sodium chloride, and the crude hydroxybenzonitrile collected. The wet product was extracted with ether (the solubility of the purified nitrile is approximately 40% in ether at room temperatures but only 2% in benzene), the extract washed with a little water after separation from any tarry matter, dried, and evaporated, and the residual nitrile distilled under reduced pressure. B. p. 148°/1 mm. Yield, 65—70%. The amount of nitrile remaining in the aqueous solution after salting out was approximately 5% of the total, a quantity which obviously did not merit recovery by ether extraction.

4-*Cyanophenyl* 4-*Cyanobenzyl Ether*.—To 4-hydroxybenzonitrile (24 g.), dissolved in alcohol (100 c.c.), was added a solution of sodium ethoxide (4·6 g. of sodium in 100 c.c. of alcohol), followed by 4-cyanobenzyl chloride (35 g.). The solution was refluxed for 3 hours. The mixture of salt and *dinitrile*, which separated on cooling, was washed with cold alcohol and then with water. The product at this stage was pure and needed no further crystallisation. Yield 42·2 g. (90%); m. p. 167—168° (Found : N, 12·1. $C_{15}H_{10}ON_2$ requires N, 11·95%).

3-*Cyanophenyl* 4-*cyanobenzyl ether*, obtained similarly from 3-hydroxybenzonitrile and 4-cyanobenzyl chloride, formed fine needles from alcohol, m. p. 97—98° (Found : N, 12·0. $C_{15}H_{10}ON_2$ requires N, 11·95%).

ω-*Cyano*-p-*tolyl* 4-*cyanobenzyl ether*, prepared from 4-hydroxyphenylacetonitrile and 4-cyanobenzyl chloride, and separated from a small amount of amide formed in the condensation by the sublimation process, formed short prisms from alcohol, m. p. 92° (Found : N, 11·3. $C_{16}H_{12}ON_2$ requires N, 11·3%).

4 : 4′-*Dicyano*-αω-*diphenoxyalkanes*.—The same general procedure was adopted throughout this series, minor variations such as volume of alcohol and time of boiling being introduced as required. For the first member of the series methylene iodide was used; in all other cases the alkylene dibromide was employed. The nitriles were well-defined crystalline solids, alcohol or acetic acid being the most convenient solvents for recrystallisation. The following details for 4 : 4′-dicyano-αγ-diphenoxypropane are typical. To a suspension of 4-hydroxybenzonitrile (48 g.) in ethyl alcohol (200 c.c.) was added a solution of sodium ethoxide (9·2 g. of sodium in 200 c.c. of alcohol), and to the resulting solution of sodium 4-cyanophenoxide was added trimethylene bromide (40 g.). The solution was refluxed for 16 hours and then cooled with stirring. The mixture of sodium

bromide and dicyano-compound was collected and washed with alcohol and then with water until free from sodium bromide. In most cases the dinitriles at this stage were sufficiently pure for conversion into the amidines. Alcoholic sodium hydroxide may be substituted for sodium ethoxide solution.

4 : 4′-*Dicyanodiphenoxymethane* (yield, 30%) formed needles from acetic acid, m. p. 148° (Found : N, 11·2. $C_{15}H_{10}O_2N_2$ requires N, 11·2%).

4 : 4′-*Dicyano-αβ-diphenoxyethane* (yield, 55%) formed prisms from acetic acid, m. p. 197° (Found : N, 10·6. $C_{16}H_{12}O_2N_2$ requires N, 10·6%).

4 : 4′-*Dicyano-αγ-diphenoxypropane* (yield 83%) crystallised from acetic acid in prisms, m. p. 188° (Found : N, 10·1. $C_{17}H_{14}O_2N_2$ requires N, 10·1%).

4 : 4′-*Dicyano-αδ-diphenoxybutane* (yield, 60%) formed prisms from acetic acid, m. p. 168—169° (Found : N, 9·75. $C_{18}H_{16}O_2N_2$ requires N, 9·6%).

4 : 4′-*Dicyano-αε-diphenoxypentane* (yield, 78%) separated from alcohol in needles, m. p. 114—114·5° (Found : N, 9·1. $C_{19}H_{18}O_2N_2$ requires N, 9·1%).

4 : 4′-*Dicyano-αζ-diphenoxyhexane* (yield, 70%) formed prisms from acetic acid, m. p. 147° (Found : N, 8·9. $C_{20}H_{20}O_2N_2$ requires N, 8·8%).

4 : 4′-*Dicyano-αη-diphenoxyheptane* (yield, 55%) formed rhombohedra from acetic acid, m. p. 107° (Found : N, 8·5. $C_{21}H_{22}O_2N_2$ requires N, 8·4%).

4 : 4′-*Dicyano-ακ-diphenoxydecane* (yield, 30%) formed needles from alcohol, m. p. 123° (Found : N, 7·4. $C_{24}H_{28}O_2N_2$ requires N, 7·4%).

1 : 4-*Di*-(4′-*cyanobenzyloxy*)*benzene* (yield, 83%) had m. p. 170—171° (Found : N, 8·0. $C_{22}H_{16}O_2N_2$ requires N, 8·2%).

ωω′-*Di*-(4′-*cyanophenoxy*)-p-*xylene* (yield, 60%) formed prisms from acetic acid, m. p. 215—216° (Found : N, 8·1. $C_{22}H_{16}O_2N_2$ requires N, 8·2%).

β-4-*Cyanophenoxyethyl Bromide*.—Ethylene dibromide (30 g.), 4-hydroxybenzonitrile (11·9 g.), sodium hydroxide (4 g.), and water (60 c.c.) were refluxed for 6 hours. After cooling, the oil was extracted with ether, filtered from a little 4 : 4′-dicyano-αβ-diphenoxyethane, washed with dilute sodium hydroxide solution, and dried. After removal of ether the residual oil was stirred with light petroleum (b. p. 60—80°). The solid obtained crystallised from alcohol in white needles, m. p. 59°. Yield, 45% (Found : N, 6·2. C_9H_8ONBr requires N, 6·2%).

4 : 4′-*Dicyano-β-phenoxyethylaniline*.—β-4-Cyanophenoxyethyl bromide (11 g.) and 4-aminobenzonitrile (11·7 g.) were heated together for 1 hour at 130—140°. After cooling, the mass was ground with water and then with alcohol. The residue crystallised from 60% acetic acid in pale yellow prisms, m. p. 163°. Yield, 35% (Found : N, 15·9. $C_{16}H_{13}ON_3$ requires N, 16·0%).

4-*Cyanobenzyl Alcohol*.—When the hydrolysis of 4-cyanobenzyl chloride by potassium carbonate solution was carried out according to Banse (*loc. cit.*), a low-melting solid, liquid in contact with water, always accompanied the product, m. p. 134°, described by Banse as the nitrile. Further examination showed that the low-melting solid was the nitrile, which on further hydrolysis gave the amide, m. p. 134—135°. If the period of hydrolysis was shortened to 2½ hours instead of the 4 hours of Banse, the yield of 4-cyanobenzyl alcohol, isolated by ether extraction and purified by vacuum distillation, was 85%. B. p. 203°/53 mm., m. p. 41—42° (Found : C, 71·9; H, 5·8; N, 10·5; *M*, ebullioscopic in benzene, 144, 147. Calc. for C_8H_7ON : C, 72·1; H, 5·3; N, 10·5%; *M*, 133). The *phenylurethane* had m. p. 112—113° (Found : N, 11·2. $C_{15}H_{12}O_2N_2$ requires N, 11·2%), and 4-*carbamidobenzyl alcohol*, m. p. 134—135° (Found : C, 63·1; H, 5·7; N, 9·4. $C_8H_9O_2N$ requires C, 63·5; H, 6·0; N, 9·3%).

4 : 4′-*Dicyanodibenzyl Ether*.—(*a*) 4-Cyanobenzyl chloride (40 g.) was boiled with potassium hydroxide solution (80 g. in 160 c.c. of water) until it had dissolved (about 3 hours). The potassium salt of 4 : 4′-dicarboxydibenzyl ether which separated on cooling was collected and dissolved in hot water, and the acid precipitated by hydrochloric acid. Yield 15 g., m. p. 272—274° (cf. Günther, *loc. cit.*). The mother-liquor from the potassium salt yielded on acidification a mixture of the above acid and 4-hydroxymethylbenzoic acid, from which 3·5 g. of the latter, m. p. 175—182°, were separated by crystallisation from hot water. The dicarboxylic acid was ground with twice its weight of phosphorus pentachloride until reaction set in and was then left for ½ hour. The mass was then ground with ice, and the crude acid chloride separated and added to 20 vols. of aqueous ammonia (*d* 0·880). After ½ hour's stirring, the *diamide* was removed. Yield, 80%. It formed plates or prisms from glacial acetic acid, m. p. 241° (Found : N, 9·8. $C_{16}H_{16}O_3N_2$ requires N, 9·85%). The crude diamide was converted into the dinitrile by boiling for ½ hour with an equal weight of phosphorus pentachloride in xylene (10 vols.). The crude product was precipitated by addition of light petroleum and was crystallised from alcohol. Yield, 37%. The product was identical with that from method (*b*).

(*b*) 4-Cyanobenzyl alcohol (2·4 g.), dissolved in absolute ethyl alcohol (5 c.c.), was treated with sodium ethoxide (0·4 g. of sodium in 8 c.c. of alcohol). The excess of alcohol was removed under reduced pressure and to the jelly of the sodium derivative was added 4-cyanobenzyl chloride (2·7 g.). The mixture was heated at 95—100° for 1 hour with stirring. The melt was ground with water and ether (10 c.c. of each), and the required *ether* collected. It formed hexagonal plates from alcohol, m. p. 97—98°. Yield, 0·95 g. (21%) (Found : N, 11·5. $C_{16}H_{12}ON_2$ requires N, 11·3%).

4-*Cyanobenzaldehyde*.—4-Cyanobenzyl alcohol (10 g.) in chloroform (60 c.c.) was treated at 0° with a solution of nitrogen tetroxide (10 g.) in dry chloroform (30 c.c.) and kept at room temperature in a sealed flask for 2 days. The excess of the oxides of nitrogen was removed in a vacuum, and the chloroform washed with dilute sodium carbonate solution and then with water. After drying and removal of chloroform the aldehyde (8—9 g.) was obtained in practically pure condition, m. p. 94—95°. A small amount of 4-cyanobenzoic acid was obtained by acidifying the alkaline wash liquors.

Benzoin Condensation of 4-*Cyanobenzaldehyde*.—A solution of 4-cyanobenzaldehyde (5 g.) in alcohol (10 c.c.) was treated with a solution of potassium cyanide (1 g.) in water (2 c.c.). Reaction was immediate and the solution darkened. After boiling under reflux for 1 hour, the crystalline 4 : 4′-*dicyanodeoxybenzoin* which separated was removed and washed with alcohol. Yield, 1·8—2·0 g. (40%). It formed irregular plates from glacial acetic acid or heavy prisms from acetone, m. p. 219—220° (Found : C, 77·9; H, 4·3; N, 11·3; *M*, ebullioscopic in benzene, 264. $C_{16}H_{10}ON_2$ requires C, 78·0; H, 4·1; N, 11·4%; *M*, 246). Variation in time of boiling produced little variation in yield. Dilution of the alcoholic mother-liquors yielded a viscous gum which slowly hardened. The only product isolated from this was 4-cyanobenzoic acid (0·3 g.).

4-*Cyanobenzoyl Chloride*.—A mixture of 4-cyanobenzoic acid (3·3 g.) with thionyl chloride (8 c.c.) was heated for 1 hour on the steam-bath. The excess of thionyl chloride was removed in a vacuum, and the residual oil ground with ice-water. The moist solid was at once dissolved in benzene and the solution was dried, filtered, and concentrated to small bulk; addition of light petroleum gave 2 g. of crystalline *acid chloride*, m. p. 65° (Found : N, 8·95. C_8H_4ONCl requires N, 9·25%). Phosphorus pentachloride was unsatisfactory for this preparation, as it gave appreciable quantities of the acid anhydride.

4 : 4′-*Dicyanobenzanilide*.—Molecular proportions of 4-cyanobenzoyl chloride and 4-aminobenzonitrile in pyridine solution yielded, after the usual procedure, the required *anilide* in 85% yield. It formed colourless prisms from pyridine, m. p. 259—261° (Found : C, 73·0; H, 3·5; N, 16·9. $C_{15}H_9ON_3$ requires C, 73·0; H, 3·7; N, 17·0%).

4 : 4′-*Dicyanobenzenesulphonanilide*, prepared by condensing 4-cyanobenzenesulphonyl chloride and *p*-aminobenzonitrile in dry pyridine and repeatedly crystallised from 50% acetic acid, formed prisms, m. p. 201—202° (Found : N, 15·0. $C_{14}H_9O_2N_3S$ requires N, 14·8%).

β-*Phenylethyl Bromide*.—The following simple procedure gave excellent results. β-Phenylethyl alcohol (technical) was distilled with 2 vols. of hydrobromic acid (50% w/v) at the rate of 80—100 c.c. per hour. At first water and phenylethyl bromide collected and the upper aqueous layer was rejected. When the temperature of the vapour reached 124° the phenylethyl bromide became the upper layer and the lower layer of constant-boiling hydrobromic acid was returned to the distillation flask at convenient intervals. A continuous separator can be fitted, but it is an unnecessary elaboration unless large-scale operations are in progress. When all the bromide had distilled, it was separated, washed, dried, and redistilled, b. p. 94—95°/12—13 mm. Yield, 90%.

4-*Cyanophenyl* β-*phenylethyl ether*, obtained by condensation of β-phenylethyl bromide with sodium 4-cyanophenoxide in the usual way (yield, 20%), formed plates from alcohol, m. p. 64° (Found : N, 6·55. $C_{15}H_{13}ON$ requires N, 6·3%). Nitration in concentrated sulphuric acid at −5° gave 3-nitro-4-hydroxybenzonitrile, m. p. 143° (Found : N, 16·8. Calc. : N, 16·7%). Nitration in nitric acid (*d* 1·5) at −10° to 0° gave almost theoretical yields of 2-*nitro*-4-*cyanophenyl* 4(?)-*nitro*-β-*phenylethyl ether*, which formed prisms from acetic acid, m. p. 185—186° (Found : N, 13·5. $C_{15}H_{11}O_5N_3$ requires N, 13·4%). Heating of this ether for ½ hour at 90° in concentrated sulphuric acid produced fission of the ether linkage and 3-nitro-4-hydroxybenzoic acid (yield, 42%) was isolated. Other attempts to achieve mononitration failed.

All attempts to condense 4-nitro-β-phenylethyl bromide with 4-hydroxybenzonitrile gave impracticably small yields of ether.

4-*Amino*-β-*phenylethyl Bromide*.—(*a*) 4-Nitro-β-phenylethyl bromide (9·6 g.) in ethyl alcohol (100 c.c.) containing 10N-hydrochloric acid (4 c.c.) and platinum oxide catalyst (Adams) (0·2 g.) was reduced with hydrogen at 50 lb. pressure at room temperature. After removal of catalyst and concentration of the solution the required *hydrochloride* was obtained by addition of ether. Yield, 9·2 g. (95%). It crystallised from absolute alcohol in prisms, m. p. 212—213° (Found : N, 5·9. $C_8H_{10}NBr,HCl$ requires N, 5·8%). The sulphate was much less soluble in water, and formed plates from dilute sulphuric acid.

(*b*) 4-Nitro-β-phenylethyl bromide (4·6 g.) was added to a solution of stannous chloride (14 g.) in hydrochloric acid (20 c.c., *d* 1·16) and warmed for a short time at 80—90° until all the oil had disappeared. The solution was cooled and filtered from a trace of unchanged material which separated, and the stannichloride was then crystallised by the addition of 3—4 vols. of 10N-hydrochloric acid. The product was removed, dissolved in water, made alkaline with excess of sodium hydroxide at 0—5° and rapidly extracted with ether. The extract was washed, dried, and treated with alcoholic hydrogen chloride. The hydrochloride so obtained was identical with that from (*a*). Yield, 55%.

4-*Cyano*-β-*phenylethyl Bromide*.—The Sandmeyer reaction on the above amine was carried out at 20—30° in presence of benzene. The benzene layer and extracts were washed, dried, and distilled. The fraction, b. p. 135—140°/2 mm., was collected. Yield, 40%. The *nitrile* crystallised from 30 vols. of light petroleum (b. p. 40—60°) in long slender prisms, m. p. 53° (Found : N, 6·5; Br, 37·5. C_9H_8NBr requires N, 6·7; Br, 38·0%). This product and the amine have an irritant action on the skin.

4-*Cyanophenyl* 4-*cyano*-β-*phenylethyl ether*, obtained in 10—12% yield by condensation of the preceding nitrile with 4-hydroxybenzonitrile, formed colourless prisms from alcohol, m. p. 129—130° (Found : N, 11·1. $C_{16}H_{12}ON_2$ requires N, 11·3%).

N-4-*Cyanophenylbenziminochloride*.—*N*-Benzoyl-4-cyanoaniline (32 g.) was ground with phosphorus pentachloride (33 g.) and heated for 1 hour at 120°. The phosphorus oxychloride was removed by distillation at 25 mm. pressure, the residual syrup dissolved in cold benzene (40 c.c.) and the solution filtered from a little impurity and distilled. Benzene and a little phosphorus pentachloride were removed and the *product* was collected at 194—198°/3 mm. Yield, 27 g. (76%). It crystallised from light petroleum (b. p. 60—80°) in fine prisms, m. p. 88—89° (Found : N, 11·8. $C_{14}H_9N_2Cl$ requires N, 11·65%).

N-4-*Cyanophenylbenzimino*-4′-*cyanophenyl Ether*.—The iminochloride (27 g.) was dissolved in dry ether (200 c.c.), added to a cold solution of sodium 4-cyanophenoxide (sodium, 2·7 g.), and kept overnight. The mixture of sodium chloride and the *ether* was collected and washed with alcohol and then with water. Yield, 32 g. (82%). The product was pure, m. p. 155° (Found : N, 13·1. $C_{21}H_{13}ON_3$ requires N, 13·0%). Rearrangement to N-*benzoyl*-4 : 4′-*dicyanodiphenylamine* took place smoothly when the iminoether was heated for 1¼ hours at 280—300°. The product formed heavy rhombic crystals, m. p. 219°, from 15 vols. of acetic acid (Found : N, 13·0. $C_{21}H_{13}ON_3$ requires N, 13·0%).

4 : 4′-*Diamidinodiphenylamine dihydrochloride* was obtained from the corresponding dinitrile. This was pale yellow, neutral, and readily soluble in water (Found : N, 20·2, 20·4. $C_{14}H_{15}N_5,2HCl,H_2O$ requires N, 20·3%). Its solution with excess of 2N-sulphuric acid gave heavy, deep orange rhombs of the sparingly soluble *acid sulphate* (Found : N, 17·7. $C_{14}H_{15}N_5,1\frac{1}{2}H_2SO_4$ requires N, 17·5%).

4 : 4′-*Diamidino*-N-*benzoyldiphenylamine*.—The aqueous solution of crude amidine hydrochloride obtained in the usual preparation from the corresponding dinitrile was treated with an excess of 2N-sulphuric acid to remove any dibenzoylated amidine as the sparingly soluble sulphate (see above). The acid mother-liquor yielded the *N*-benzoylated *base* on precipitation with alkali, a small intermediate fraction of less basic matter being removed first. This formed colourless flat prisms which retained water of crystallisation after drying in a vacuum; m. p. 194° (decomp.) (Found : N, 17·0; loss at 100—110°/1—2 mm., 10·4. $C_{21}H_{19}ON_5,2\frac{1}{2}H_2O$ requires N, 17·4; H_2O, 11·2%). When the anhydrous amidine (107 mg.) was heated at 180—200°, and the product sublimed, benzamide (30 mg., 82%), m. p. 127—128°, was collected first and then 4 : 4′-dicyanodiphenylamine (50 mg., 76%), m. p. 240—246°.

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