822. *Aryl-2-halogenoalkylamines. Part X.* The Preparation of Some Derivatives of 1-Aryl-3 : 4-dihalogenopyrrolidines and 1 : 4-Bis-arylamino-2 : 3-dihalogenobutanes.*

By J. J. Roberts and W. C. J. Ross.

The preparation of 1-aryl-3 : 4-dihalogenopyrrolidines (I; X = halogen) and 1 : 4-di(arylamino)-2 : 3-dihalogenobutanes (II; X = halogen) and some related compounds has been examined. Although it has not proved possible to obtain the halogen compounds without substituents in the aromatic ring two 3 : 4-dibromopyrrolidines, probably the 1-(2 : 4 : 6-tribromophenyl) and 1-(3 : 5-dibromo-2 : 4 : 6-trimethylphenyl) derivatives and also 2 : 3-dibromo-1 : 4-di-(2 : 4 : 6-trimethylanilino)butane have been prepared. The *cis*- and the *trans*-isomers of (I; R = Ph, X = O·SO_2·C_6H_4Me) and the DL- and the *meso*-isomer of (II; R = Ph, R′ = Me, X = O·SO_2·C_6H_4Me) have been obtained. The rates of hydrolysis in aqueous acetone of these derivatives have been determined.

It has been shown (Ross, *J.*, 1949, 183; Kon and Roberts, *J.*, 1950, 978) that a large number of di-2-halogenoalkylarylamines possess a powerful cytotoxic activity and inhibit the growth of transplanted animal tumours; also that such compounds are mutagenic (Bird, *Nature*, 1950, **165**, 491) and carcinogenic (Haddow, unpublished). In all the compounds tested so far the two reactive halogen atoms were attached to flexible alkyl chains, and in their reactions with biological material attachments could occur at sites very close together (for example, with a single amino-group; Davis and Ross, *J.*, 1949, 2831) or in the case of the compounds prepared by Kon and Roberts (*loc. cit.*) at sites separated by as much as 18 Å. In connection with the hypothesis that the dihalogeno-alkylamines produce their characteristic biological effects by means of a cross-linking alkylation reaction (Goldacre, Loveless, and Ross, *Nature*, 1949, 163, 667) it was of interest

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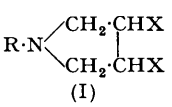
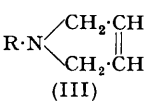
to prepare compounds in which the alkylating centres were situated at a known and fixed distance apart.

This paper describes attempts to prepare two such types of compound : the pyrrolidine derivatives (I; X = halogen) and 1 : 4-bisarylamino-2 : 3-dihalogenobutanes (II; X = halogen). Two routes to each of these derivatives were examined; in the first the corresponding diol (I or II; X = OH) was the intermediate and in the second the pyrroline (III) or the butene (IV).


(I)

$RR'N\cdot CH_2\cdot CHX\cdot CHX\cdot CH_2\cdot NRR'$
(II)
$RR'N\cdot CH_2\cdot CH{:}CH\cdot CH_2\cdot NRR'$
(IV)


(III)

Compounds (I) via *Dihydroxypyrrolidines.*—Przybytek (*Ber.*, 1884, **17**, 1091) studied the reaction between aniline and *meso*-1 : 4-dichlorobutane-2 : 3-diol and claimed to have obtained 1 : 4-dianilinobutane-2 : 3-diol (II; R = Ph, R′ = H, X = OH). A low yield of this diol has now been obtained when DL-1 : 4-dibromobutane-2 : 3-diol is heated in benzene with aniline but heating *meso*- or DL-1 : 4-dichloro- or DL-1 : 4-dibromobutane-2 : 3-diol with three or four equivalents of aniline without solvent gives *cis*- or *trans*-3 : 4-dihydroxy-1-phenylpyrrolidine (I; R = Ph, X = OH). Since it has been claimed (G.P. 805,522; *Chem. Abs.*, 1952, **46**, 1049) that vacuum-distillation of 1 : 4-dianilinobutane-2 : 3-diol (m. p. 111—112°; apparently prepared from aniline and butadiene diepoxide) gives 3 : 4-dihydroxy-1-phenylpyrrolidine, butanediols may be intermediates in the reaction in absence of solvent, being converted into pyrrolidine derivatives at the higher temperature attained. The *cis*- and *trans*-dihydroxypyrrolidines are also obtained when methylaniline is heated with either of the dichlorohydrins, probably by decomposition of a quaternary pyrrolidine salt formed as intermediate.

Attempts to convert these diols into the dichloro-derivatives by phosphorus oxychloride alone or with phosphorus pentachloride failed (contrast Ross, *loc. cit.*), and no dibromo-compound could be isolated after heating of the diols with ethyl bromoacetate and triphenyl phosphite (cf. Landauer and Rydon, *Chem. and Ind.*, 1951, 313) or after treatment of the diacetates with saturated aqueous hydrobromic acid for four days (contrast Wilson and Lucas, *J. Amer. Chem. Soc.*, 1936, **58**, 2396). It was, however, possible to prepare the di-*p*-toluenesulphonates. Reaction with sodium iodide in acetone (the *cis*-compound reacts at approximately twice the rate of the *trans*-derivative at 110°) gave only an unidentified product in poor yield.

Since *NN*-di-2-toluene-*p*-sulphonyloxyethylaniline inhibits tumour growth, having properties very similar to those of *NN*-dihalogenoethylanilines (Timmis, 27th Annual Report of the British Empire Cancer Campaign, p. 43) the toluene-*p*-sulphonates (I; X = $O\cdot SO_2\cdot C_6H_4Me$) were deemed adequate for testing of the cytotoxic potentialities of structure (I).

Compounds (I) via *Pyrrolines.*—Reduction of 3 : 6-dihydro-2-phenyl-1 : 2-oxazine (Arbuzov, *Doklady Akad. Nauk. S.S.S.R.*, 1948, **60**, 993) yields a product which when distilled in steam (Arbuzov, *ibid.*, 1948, **63**, 531) or dehydrated with phosphoric acid (Wichterle and Vogel, *Coll. Czech. Chem. Comm.*, 1949, **14**, 209), affords phenylpyrroline (III; R = Ph). The preparation of 1-phenyl-Δ^3-pyrroline by reaction of 1 : 4-dibromobut-2-ene with aniline appears to have been considered by von Braun and Lemke (*Ber.*, 1922, **55**, 3536) but they did not obtain sufficient of the base for characterisation or analysis. It is now found that the phenyl-Δ^3-pyrroline may be conveniently prepared by condensing *cis*-1 : 4-dibromobut-2-ene with aniline in hot benzene.

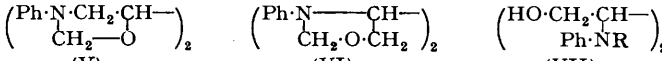
Bromination of (III; R = Ph) with two equivalents of bromine in chloroform solution or when dissolved in aqueous hydrobromic acid gave a monobromo-derivative, which is 1-*p*-bromophenyl-Δ^3-pyrroline since it is also obtained by the reaction of *cis*-1 : 4-dibromobut-2-ene with *p*-bromoaniline. With a large excess of bromine this product yielded a pentabromide provisionally formulated as 3 : 4-dibromo-1-(2 : 4 : 6-tribromophenyl)- and pyrrolidine. In an attempt to avoid bromination of the aromatic ring, 1-*p*-methoxyphenyl-(2 : 4 : 6-trimethylphenyl)-Δ^3-pyrroline were prepared and brominated, but the only

identifiable product was a tetrabromo-compound from the mesidine derivative—probably 3 : 4-dibromo-1-(3 : 5-dibromo-2 : 4 : 6-trimethylphenyl)pyrrolidine. The formation of 3 : 5-dibromo-compounds from mesidine derivatives has been reported by Adams and Dankert (*J. Amer. Chem. Soc.*, 1940, **62**, 2191).

Compounds (II) via *Butanediols.*—From aniline and *meso*-1 : 2-3 : 4-diepoxybutane Przybytek (*loc. cit.*) obtained 1 : 4-dianilinobutane-2 : 3-diol (II; R = Ph, R′ = H, X = OH); he confirmed its identity by analysis of the dihydrochloride, but gave no melting points. It is now found that aniline and DL-1 : 2-3 : 4-diepoxybutane give *dl*-1 : 4-dianilinobutane-2 : 3-diol, m. p. 109° (dipicrate, m. p. 185°). Methylaniline similarly gives DL-1 : 4-di-*N*-(methylanilino)butane-2 : 3-diol, m. p. 102·5° (II; R = Ph, R′ = Me, X = OH) (dipicrate, m. p. 191°; diacetate, m. p. 133°) which is also readily obtained by methylating the diol, m. p. 109°, with methyl iodide. The diol, m. p. 109°, reacts with formaldehyde to yield a dioxazolidine derivative (V), m. p. 184—186°.

When aniline reacts with the 1 : 2-3 : 4-diepoxybutane obtained by epoxidation of 3 : 4-epoxybut-1-ene with perbenzoic acid (Everett and Kon, *J.*, 1950, 3131), the resultant DL-diol, m. p. 109°, already described, is accompanied by an approximately equal amount of an isomer, m. p. 163° (dipicrate, m. p. 180°; forming a dioxazolidine, m. p. 176·5°) which is almost certainly *meso*-1 : 4-dianilinobutane-2 : 3-diol formed from the *meso*-diepoxide in the mixture. Methylaniline similarly gives the diol, m. p. 102·5°, described above and the *meso*-isomer, m. p. 77° (dipicrate, m. p. 184°; diacetate, m. p. 115°).

The view that neither of the diols is a 1 : 4-diol formed by the opening of the epoxide rings in 1 : 2-3 : 4-diepoxybutane at the non-terminal carbon atoms is supported by the similar rates of hydrolysis of their ditoluene-*p*-sulphonates (see below) and by formation of a third isomeric diol, m. p. 116° [dioxazolidine derivative (VI), m. p. 152°] by the reaction of DL-2 : 3-dibromobutane-1 : 4-diol with aniline.



(V) (VI) (VII)

In contrast with the ease with which the 2 : 3-diols are methylated it has not been possible to methylate the 1 : 4-diol (VII; R = H), and methylaniline does not react with the 2 : 3-dibromide. Formation of (VII; R = Me) would be expected to be difficult for steric reasons. The difference supports the view that the diols formed from diepoxybutane and an aromatic base are 2 : 3-diols.

As in the case of the dihydroxypyrrolidines, the butane-2 : 3-diols could not be converted into halogen derivatives, and the ditoluene-*p*-sulphonates were submitted to biological testing.

Compounds (II) via *Butenes.*—Substituted 1 : 4-diaminobut-2-enes have been prepared by the reaction of 1 : 4-dibromobut-2-ene with alkyl- or aryl-amines. For example, Willstätter and Wirth (*Ber.*, 1913, **46**, 535) obtained *NNN′N′*-tetramethyl-1 : 4-diaminobut-2-ene from dimethylamine and von Braun and Lemke (*loc. cit.*) prepared 1 : 4-dianilinobut-2-ene from aniline. *NNN′N*-Tetraethyl-1 : 4-diaminobut-2-ene (IV; R = R′ = Et) and 1 : 4-dipiperidino- and 1 : 4-dimorpholino-but-2-ene have now been synthesised for the study of the bromination of the ethylenic double bond: 1 : 4-Dianilino- (IV; R = Ph, R′ = H), 1 : 4-bis-*N*-methylanilino- (IV; R = Ph, R′ = Me), 1 : 4-bis-*N*-ethylanilino- (IV; R = Ph, R′ = Et), 1 : 4-di-*p*-anisidino- (IV; R = *p*-MeO·C_6H_4, R′ = H), and 1 : 4-di-(2 : 4 : 6-trimethylanilino)-but-2-ene have also been prepared as potential intermediates by allowing the appropriate arylamine to react with *trans*-1 : 4-dichloro- or *trans*-1 : 4-dibromo-but-2-ene.

Bromination of 1 : 4-dipiperidinobut-2-ene afforded the 2 : 3-dibromo-compound, isolated as the dihydrobromide, but 1 : 4-dimorpholinobut-2-ene yielded only the dihydrobromide of the original butene. Only polymeric products were obtained by the action of bromine on *NNN′N′*-tetraethyl-1 : 4-diaminobut-2-ene.

The greater susceptibility of the aromatic ring to attack by bromine, compared with the ethylenic bond—already noted for the arylpyrrolines (above)—was further manifest in formation of 1 : 4-di-*p*-bromoanilino- and 1 : 4-di-(*p*-bromo-*N*-methylanilino)-but-2-ene

(also obtained from *p*-bromo-*N*-methylaniline and *trans*-1 : 4-dichlorobutene) when the corresponding amines were brominated. The only compound of the required structure obtained was 2 : 3-dibromo-1 : 4-di-(2 : 4 : 6-trimethylanilino)butane (II; R = 2 : 4 : 6-$C_6H_2Me_3$, R′ = H, X = Br); this is being tested biologically.

In view of the correlation between the chemical reactivity of the "aromatic nitrogen mustards" and their biological activity (Ross, "Advances in Cancer Research," Vol. I, Academic Press, 1952), the hydrolysis rates of some of the new compounds are recorded in the annexed Table.

No.	Compound †		% Hydrolysed in 50% acetone at 66°
1	$[NPhMe\cdot CH_2\cdot CH(OTs)\cdot]_2$	*meso*	60% in 30 min.
2	,,	DL	62% in 30 min.
3	(I; R = Ph, X = OTs)	*cis*	<1% in 120 min.
4	,,	*trans*	,,
5	(I; R = 2 : 4 : 6-$C_6H_2Br_3$, X = Br)		<1% in 180 min.
6	(I; R = 2 : 4 : 6 : 3 : 5-$C_6Me_3Br_2$, X = Me)		<1% in 240 min.
7	$Ph\cdot N(CH_2\cdot CH_2\cdot OTs)_2$ *		100% in 30 min.
8	$[Ph\cdot N(CH_2\cdot CH_2\cdot OTs)\cdot CH_2\cdot]_2$		,,
9	$Me\cdot SO_2\cdot O\cdot[CH_2]_n\cdot O\cdot SO_2\cdot Me$	$n = 2$ *	<1% in 120 min.
10	,,	$n = 3$ *	3·5% in 120 min.
11	,,	$n = 4$ *	13% in 120 min.
12	,,	$n = 6$ *	11% in 120 min.
13	$(TsO\cdot CHMe\cdot)_2$		<1% in 120 min.
14	$CH_2(CHMe\cdot OTs)_2$		5% in 30 min.
15	$([CH_2]_5>N\cdot CH_2\cdot CHBr\cdot)_2$		40% in 30 min.
16	$(2 : 4 : 6\text{-}C_6H_2Me_3\cdot NH\cdot CH_2\cdot CHBr\cdot)_2$		52% in 30 min.; 100% in 360 min.

* Kindly made available by Mr. G. M. Timmis of this Institute. † OTs = $\cdot O\cdot SO_2\cdot C_6H_4Me$-*p*.

Foster and Hammett (*J. Amer. Chem. Soc.*, 1946, **68**, 1736) found that the rate of hydrolysis of the ditoluene-*p*-sulphonate of ethylene glycol in aqueous dioxan was about one-twentieth of that of ethyl toluene-*p*-sulphonate. They indicated that the low reactivity could be ascribed to the mutual interaction of the two sulphonyloxy-groups. The relative hydrolysis rates for the toluene-*p*-sulphonates (13 and 14) and the series of methanesulphonates (9—12, Table 1) shows that this deactivating effect decreases as the distance between the sulphonyloxy-groups increases.

The substitution of methylanilino-groups for hydrogen in the terminal methyl groups of compound (13) to give compounds (1) and (2) clearly accelerates hydrolysis. That there is still some retardation due to the proximity of the sulphonyloxy-groups is evident from the rapid hydrolysis of compounds (7) and (8) in which the ester groups are β to the nitrogen atom: these compounds are derivatives of primary alcohols and would be expected to hydrolyse somewhat more slowly than derivatives of unhindered secondary alcohols (compare the relative reactivities of 2-chloroethyl- and 2-chloropropyl-arylamines, Everett and Ross, *J.*, 1949, 1972).

The similar rates of hydrolysis of the two butane derivatives (1) and (2) supports their formulation as *meso*- and DL-isomers of 2 : 3-diols: a sulphonic ester of the 1 : 4-diol (VII) would be derived from a primary unhindered alcohol and would certainly be expected to hydrolyse as fast as compounds (7) and (8).

The nitrogen atom in the β-position to the sulphonyloxy-groups or the bromine atoms in the pyrrolidines (3, 4, 5, and 6) has not the same effect on the hydrolysis rates as is observed in the butane derivatives. This can only be partly due to the fact that there is a single nitrogen atom available for activating both ester groups—compare the hydrolysis rate of *N*-2-chloroethyl-*N*-ethylaniline which is approximately three times that of *NN*-di-2-chloroethylaniline (Ross, *loc. cit.*). The main reason for the lowered reactivity compared with (1) and (2) is probably the restriction imposed by the cyclic pyrrolidine structure on the approach of the activating nitrogen atom to the ester oxygen atom of the toluene-*p*-sulphonyloxy-group or to the bromine atom. Models show that such approach is relatively easy in the butane derivatives.

The hydrolysis rate of the dibromobutane (16) is also slower than would have been expected for an isolated secondary 2-bromoethylamine, thus showing again the retarding influence of the adjacent halogen atom. The fact that the two bromine atoms are

eliminated under these mild conditions supports the formulation of the compound as 2 : 3-dibromo-1 : 4-di-(2 : 4 : 6-trimethylanilino)butane rather than as a compound containing the bromine atoms in the aromatic ring.

Preliminary biological examination indicates that none of the vicinal diesters now described is effective as a tumour-growth inhibitor; in some cases this could have been due to the relatively low chemical reactivity but the biological inactivity in other cases suggests that such close proximity of the alkylating centres does not favour cytotoxic activity.

Experimental

cis-3 : 4-*Dihydroxy*-1-*phenylpyrrolidine*.—(*a*) *meso*-1 : 4-Dichlorobutane-2 : 3-diol (4·5 g.; Owen, *J.*, 1949, 243) and aniline (9 ml.) were heated at 100° for 4 hours. The product was ground with water, and the solid collected by filtration. The *diol* (3·5 g.) remaining after further washing with water and finally with a little ether crystallised from benzene–light petroleum (b. p. 60—80°) as fine needles, m. p. 158·5° (Found : C, 67·3; H, 7·6. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%).

(*b*) *meso*-1 : 4-Dichlorobutane-2 : 3-diol (1·6 g.) and methylaniline (4·7 g.) were heated at 100° for 5 hours and finally at 130° for one hour. The product, isolated as above, had m. p. 158·5°, undepressed by admixture with *cis*-3 : 4-dihydroxy-1-phenylpyrrolidine prepared by method (*a*).

The diol with acetic anhydride afforded the *diacetate*, m. p. 110·5°, flattened needles from aqueous acetone (Found : C, 63·9; H, 6·5. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5%).

cis-3 : 4-*Ditoluene*-p-*sulphonyloxy*-1-*phenylpyrrolidine*.—Toluene-*p*-sulphonyl chloride (2·6 g.) was added during 15 minutes to an ice-cooled solution of the diol (1 g.) in dry pyridine (4 ml.). The clear solution was then allowed to warm to room temperature. Next day the mixture was diluted with water and the *ditoluene*-p-*sulphonate* (2·8 g.) was filtered off. It formed fine needles, m. p. 162—164°, from aqueous acetone (Found : C, 59·4; H, 5·5. $C_{24}H_{25}O_6NS_2$ requires C, 59·1; H, 5·2%).

trans-3 : 4-*Dihydroxy*-1-*phenylpyrrolidine*.—(*a*) Aniline (4 ml.) and DL-1 : 4-dichlorobutane-2 : 3-diol (1·6 g., Owen, *loc. cit.*) were heated at 100° for 4 hours and then at 140° for 2 hours. The cooled mixture was diluted with water and extracted with benzene. The washed and dried (Na_2SO_4) extract was passsed down a column of activated alumina and the column was eluted with fresh benzene and finally with methanol which removed trans-3 : 4-*dihydroxy*-1-*phenylpyrrolidine* (1 g.), m. p. 123·5—124·5°, prisms from benzene–light petroleum (b. p. 40—60°) (Found : C, 66·7; H, 7·3. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%).

(*b*) The same diol was obtained when methylaniline (4 ml.) was heated with DL-1 : 4-dichlorobutane-2 : 3-diol (1·6 g.) under the same condition.

The *diacetate* formed plates, m. p. 88·5°, from aqueous methanol (Found : C, 64·1; H, 6·6. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5%). The *di*-p-*toluenesulphonate*, m. p. 153—154°, separated from aqueous acetone (Found : C, 59·1; H, 5·5. $C_{24}H_{25}O_6NS_2$ requires C, 59·1; H, 5·2%).

Reaction of the Above Ditoluene-p-*sulphonates with Sodium Iodide*.—The ditoluene-*p*-sulphonate (0·5 g.) was heated at 110° with sodium iodide (1 g.) in acetone (8 ml.). The extent of reaction was determined by weighing the precipitated sodium toluene-*p*-sulphonate. After 10 hours' heating the *cis*-compound yielded 320 mg. of the salt and after 15 hours 380 mg. (theor. 380 mg.). In 10 hours only 180 mg. had separated in the case of the *trans*-compound.

1-*Phenyl*-Δ^3-*pyrroline*.—*cis*-1 : 4-Dibromobut-2-ene (21·5 g.) and aniline (27 g.) in benzene (80 ml.) were heated under reflux for 1 hour. The cooled solution was washed several times with water, dried (Na_2SO_4), and evaporated. 1-Phenyl-Δ^3-pyrroline (6 g.) formed prisms, m. p. 100—101°, from methanol (Found : C, 82·4; H, 8·0. Calc. for $C_{10}H_{11}N$: C, 82·7; H, 7·6%). Arbuzov (*Doklady Akad. Nauk. S.S.S.R.*, 1948, **63**, 531) gives m. p. 101—102°.

Bromination. (*a*) Bromine (1·1 g.) in carbon tetrachloride (10 ml.) was added during 30 minutes to a stirred solution of the pyrroline (1 g.) in carbon tetrachloride (40 ml.). The *bromo*-compound which separated crystallised from aqueous methanol as plates, m. p. 126—126·5° (Found : C, 53·2; H, 4·7; N, 5·9; Br, 34·6. $C_{10}H_{10}NBr$ requires C, 53·6; H, 4·5; N, 6·3; Br, 35·6%).

cis-1 : 4-Dibromobut-2-ene (2·1 g.), *p*-bromoaniline (1·7 g.), sodium carbonate (1·5 g.), and benzene (5 ml.) were heated under reflux for 2 hours, then diluted with benzene, washed with water, dried, and evaporated, yielding a residue which crystallised from light petroleum (b. p. 60—80°) as plates, m. p. 126° undepressed by admixture with the monobromide.

(*b*) Bromine (0·64 g.) was added to the pyrroline (0·58 g.) in 48% hydrobromic acid (10 ml.).

Next day the solution was neutralised with ammonia and extracted with ether. The ethereal solution contained the monobromide, m. p. 126°.

(*c*) Bromine (1·95 g.) in chloroform (25 ml.) was added during 10 minutes to a vigorously stirred solution of the phenylpyrroline (0·58 g.) in chloroform (10 ml.). Two days later the chloroform solution was washed with 2N-ammonia, then with water, and dried (Na_2SO_4). The *pentabromide*, obtained on evaporation, formed fine needles (from pentane), m. p. 79° (Found : N, 3·0; Br, 72·4. $C_{10}H_8NBr_5$ requires N, 2·6; Br, 72·9%). The same compound was obtained similarly from the monobromo-derivative.

1-p-*Methoxyphenyl-*Δ^3*-pyrroline.*—*cis*-1 : 4-Dibromobut-2-ene (4·3 g.), *p*-anisidine (2·5 g.), sodium carbonate (2·2 g.), sodium iodide (0·1 g.), and benzene (20 ml.) were heated on a steam-bath for 4 hours. The solution was washed with water and extracted three times with 2N-hydrochloric acid. The combined extracts were decolorised with charcoal, neutralised with ammonia, and re-extracted with ether. Evaporation of the dried (K_2CO_3) ethereal solution yielded the *pyrroline* which crystallised from benzene–pentane as plates, m. p. 118° (Found : C, 75·6; H, 7·2. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5%).

1-*Mesityl-*Δ^3*-pyrroline.*—*cis*-1 : 4-Dibromobut-2-ene (6·7 g.), mesidine (4·2 g.), anhydrous sodium carbonate (4 g.), and sodium iodide (0·1 g.) in benzene (30 ml.) were heated under reflux for 4 hours. The solution was washed several times with water, dried (Na_2SO_4), and distilled. The fraction of b. p. 90—100°/2 mm. (1·5 g.) was the required pyrroline, characterised as *hydrobromide*, needles (from benzene), m. p. 190—191° (Found : C, 58·4; H, 6·6. $C_{13}H_{17}N,HBr$ requires C, 58·2; H, 6·8%).

Bromination. The pyrroline (1·5 g.) in carbon tetrachloride (20 ml.) was treated with bromine (3 g.) in carbon tetrachloride (40 ml.). After 2 hours at room temperature the solvent and excess of bromine were removed under reduced pressure. The *tetrabromo*-compound formed prisms, m. p. 178—179·5°, from light petroleum (b. p. 60—80°) (Found : C, 31·1; H, 2·0; N, 2·9; Br, 63·9. $C_{13}H_{15}NBr_4$ requires C, 30·9; H, 3·0; N, 2·8; Br, 63·3%).

The pyrroline hydrobromide gave the same product (m. p. and mixed m. p.).

meso- *and* DL-1 : 4-*Dianilinobutane*-2 : 3-*diol.*—1 : 2-3 : 4-Diepoxybutane (2 g.; Everett and Kon, *J.*, 1950, 3131) and aniline (5 ml.) in benzene (10 ml.) were heated under reflux for 4 hours. The solid (3·8 g.) which separated was collected by filtration, washed with a little benzene, and crystallised twice from ethanol. meso-1 : 4-*Dianilinobutane*-2 : 3-*diol* formed prisms, m. p. 163° (Found : C, 71·0; H, 7·5. $C_{16}H_{20}O_2N_2$ requires C, 70·6; H, 7·4%).

The *dipicrate* formed red prisms (from ethanol), m. p. 179—180° (Found : C, 45·8; H, 3·8. $C_{28}H_{26}O_{16}N_8$ requires C, 46·0; H, 3·6%).

The diol (0·5 g.) was shaken for 1 hour with 40% formaldehyde solution (20 ml.). The dried ethereal extract of this mixture yielded meso-3 : 3′-*diphenyldi*(*oxazolidin*-5-*yl*), m. p. 174—176·5°, plates from methanol (Found : C, 72·9; H, 7·1. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·9%).

Chromatography of the benzene liquors obtained after the separation of the *meso*-diol on activated alumina, and development with benzene and then chloroform, left material on the column which was eluted with methanol and finally crystallised from benzene–light petroleum (b. p. 40—60°). DL-1 : 4-*Dianilinobutane*-2 : 3-*diol* formed plates, m. p. 109—110° (Found : C, 70·4; H, 7·5%). Its *dipicrate*, m. p. 183—185°, formed red prisms from ethanol (Found : C, 45·9; H, 3·8%), and the *di*(*oxazolidine*) derivative formed small prisms (from methanol), m. p. 184—186° (Found : C, 73·4; H, 7·2%).

The same DL-diol, m. p. and mixed m. p. 110°, was obtained when aniline (4·5 g.) and pure DL-1 : 2-3 : 4-diepoxybutane (1·7 g.; b. p. 56—58°/25 mm., m. p. 2—4°; prepared from DL-2 : 3-dibromobutane-1 : 4-diol essentially by the method of Prevost, *Compt. rend.*, 1926, **183**, 1292) in benzene (8 ml.) were heated under reflux for 4 hours.

meso- *and* DL-1 : 4-*Di*-N-*methylanilinobutane*-2 : 3-*diol.*—1 : 2-3 : 4-Diepoxybutane (6 g.; Everett and Kon, *loc. cit.*), methylaniline (18 ml.), and benzene (20 ml.) were heated under reflux for 12 hours. Dilution of the cooled solution with light petroleum (b. p. 40—60°) precipitated DL-1 : 4-*bis*-N-*methylanilinobutane*-2 : 3-*diol* (4·9 g.) which formed fine needles, m. p. 102—102·5°, from benzene–light petroleum (b. p. 40—60°) (Found : C, 72·3; H, 8·4. $C_{18}H_{24}O_2N_2$ requires C, 72·0; H, 8·1%).

The DL-diol was also obtained by similarly condensing pure DL-diepoxybutane with methylaniline. The diol formed a *dipicrate*, m. p. 190—191°, yellow prisms from ethanol (Found : C, 47·8; H, 4·4. $C_{30}H_{30}O_{16}N_8$ requires C, 47·5; H, 4·0%), and a *diacetate* (acetic anhydride in warm pyridine), stout prisms, m. p. 132·5—133·5°, from methanol (Found : C, 68·8; H, 7·6. $C_{22}H_{28}O_4N_2$ requires C, 68·7; H, 7·3%).

The mother-liquors from the original precipitation of the DL-diol were diluted with benzene

(300 ml.) and passed through a column of activated alumina (150 g.). Continued washing with benzene slowly eluted meso-1 : 4-*bis*-N-*methylanilinobutane*-2 : 3-*diol* (5·8 g.) which formed needles, m. p. 76·5—77° from benzene–light petroleum (b. p. 40—60°) (Found : C, 72·2; H, 8·2%). The *meso*-diol formed a *dipicrate*, m. p. 184°, prisms from acetone (Found : C, 47·8; H, 4·3%), and a *diacetate*, m. p. 114—115·5°, thick prisms from methanol (Found : C, 68·7; H, 7·3%).

Methylation of meso- *and* DL-1 : 4-*Dianilinobutane*-2 : 3-*diol*.—Methyl iodide (4 g.) in ethanol (10 ml.) was added to the diol (0·5 g.) in boiling ethanol (25 ml.) and heating was continued for 1½ hours. The excess of the methyl iodide and solvent were removed by distillation and an ethereal solution of the residue was washed with dilute aqueous sodium hydroxide, dried, and evaporated. The oily product from the *meso*-diol gave a picrate, m. p. 184°, and from the DL-diol a picrate, m. p. 190°, was obtained. From the recrystallised picrates the same *meso*- and DL-1 : 4-di-*N*-methylanilinobutane-2 : 3-diols were regenerated which had been obtained directly from methylaniline.

Ditoluene-p-*sulphonates of* meso- *and* DL-1 : 4-*Di*-N-*methylanilinobutane*-2 : 3-*diols*.—Toluene-*p*-sulphonyl chloride (2 g.) was added during 15 minutes to a stirred, ice-cooled solution of the diol (1·5 g.) in dry pyridine (5 ml.). After being kept at room temperature overnight the mixture was poured on ice and extracted with chloroform. The residue obtained when this extract was washed with 2N-sodium hydroxide, dried, and evaporated solidified on trituration with ether–methanol. The *ditoluene*-p-*sulphonate* of the *meso*-diol formed a micro-crystalline powder [from benzene–light petroleum (b. p. 60—80°], m. p. 142—143° (Found : C, 63·5; H, 6·3. $C_{32}H_{36}O_6N_2S_2$ requires C, 63·2; H, 6·0%), and of the DL-diol formed small prisms, m. p. 145—146° (depressed to 130° by admixture with the derivative from the *meso*-diol) (Found : C, 63·7; H, 6·3%).

DL-2 : 3-*Dianilinobutane*-1 : 4-*diol*.—DL-2 : 3-Dibromobutane-1 : 4-diol (2·5 g.) and aniline (5 ml.) were heated at 110° for 4 hours. The mixture was shaken with benzene and water, and the dried benzene layer was evaporated, giving a residue which crystallised from benzene–light petroleum (b. p. 40—60°). DL-2 : 3-*Dianilinobutane*-1 : 4-*diol* formed plates, m. p. 115—116° (Found : C, 70·6; H, 7·5. $C_{16}H_{20}O_2N_2$ requires C, 70·6; H, 7·4%). When this diol was treated with aqueous formaldehyde as previously described DL-3 : 3′-*diphenyldi*(*oxazolidin*-4-*yl*), m. p. 151—152°, needles from methanol, was obtained (Found : C, 73·1; H, 7·0. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·9%).

trans-1 : 4-*Dipiperidinobut*-2-*ene*.—Piperidine (16 g.) was added during 15 minutes to a cooled solution of *trans*-1 : 4-dichlorobut-2-ene (5 g.) in benzene (25 ml.). The product was diluted with chloroform and washed with water. Evaporation of the dried chloroform layer gave an oil (5·3 g., 58%) which formed a *dipicrate*, m. p. 191—193°, yellow needles from water (Found : C, 45·8; H, 4·7. $C_{26}H_{32}O_{14}N_8$ requires C, 45·9; H, 4·7%).

By a similar method morpholine afforded trans-1 : 4-*dimorpholinobut*-2-*ene* (63% yield), m. p. 90—91·5°, prisms from pentane (Found : C, 63·5; H, 10·0. $C_{12}H_{22}O_2N_2$ requires C, 63·7; H, 9·8%).

When diethylamine and the *trans*-dichloride were allowed to react a fraction, b. p. 125°/36 mm., 65—75°/4 mm. (45% yield), forming a dipicrate, m. p. 154°, needles from acetone–ethanol (Found : C, 44·1; H, 5·3. Calc. for $C_{24}H_{32}O_{16}N_8$: C, 43·9; H, 4·9%), was obtained. Amundsen, Mayer, Pitts, and Malentacchi (*J. Amer. Chem. Soc.*, 1951, **73**, 2118) give b. p. 113°/20 mm. for the free base and m. p. 154—155·5° for the dipicrate.

trans-1 : 4-*Di*-N-*methylanilinobut*-2-*ene*.—*trans*-1 : 4-Dichlorobut-2-ene (5 g.) and methylaniline (17·5 g.) were heated at 100° for 4 hours. Water was then added and the mixture extracted with ether. Evaporation of the washed and dried (K_2CO_3) extract gave a residue which crystallised from methanol. The trans-*diamine* formed small prisms (6·1 g., 57%), m. p. 77—78·5° (Found : C, 80·7; H, 8·2. $C_{18}H_{22}N_2$ requires C, 81·1; H, 8·3%).

trans-1 : 4-*Di*-N-*ethylanilinobut*-2-*ene*, m. p. 73—73·5°, prisms from methanol (Found : C, 81·5; H, 9·0. $C_{20}H_{26}N_2$ requires C, 81·6; H, 8·9%), was similarly prepared from ethylaniline (yield, 51%).

A poor yield of *trans*-1 : 4-dianilinobut-2-ene, b. p. 174—176°/0·4 mm. (Found : C, 80·1; H, 7·7. Calc. for $C_{16}H_{18}N_2$: C, 80·6; H, 7·6%), was obtained from aniline. von Braun and Lemke (*loc. cit.*) record b. p. 235—245°/14 mm. for this base.

trans-1 : 4-*Di*-(2 : 4 : 6-*trimethylanilino*)*but*-2-*ene*.—A mixture of mesidine (6·8 g.), *trans*-1 : 4-dibromobut-2-ene (5·4 g.), anhydrous sodium carbonate (5 g.), and sodium iodide (0·1 g.) in benzene (50 ml.) was heated for 2 hours on a steam-bath. The benzene solution was then washed with water and extracted with dilute hydrochloric acid. After decolorisation with charcoal the acid extract was neutralised with ammonia and shaken with ether. Evaporation of the dried

(K_2CO_3) ethereal solution gave a residue which crystallised from aqueous methanol or pentane. trans-1 : 4-*Di*-(2 : 4 : 6-*trimethylanilino*)*but*-2-*ene* formed diamond-shaped crystals, m. p. 100·5—102·5° (36%) (Found : C, 82·0; H, 9·3. $C_{22}H_{30}N_2$ requires C, 81·9; H, 9·4%).

A 59% yield of trans-1 : 4-*di*-p-*anisidinobut*-2-*ene*, m. p. 124·5—125·5°, plates from benzene–pentane (Found : C, 72·7, 72·8; H, 7·7, 7·6. $C_{22}H_{18}O_2N_2$ requires C, 72·5; H, 7·4%), was similarly obtained.

Although *p*-bromoaniline gave no identifiable product when treated with the dibromobutene, *p*-bromo-*N*-methylaniline readily gives a 62% yield of *trans*-1 : 4-di-(*p*-bromo-*N*-methylanilino)-but-2-ene, m. p. 118°, prisms from light petroleum (b. p. 60—80°), not depressed by admixture with the product obtained by brominating *trans*-1 : 4-bis-*N*-methylanilinobut-2-ene (see below).

Bromination of trans-1 : 4-*Dipiperidinobut*-2-*ene*.—Bromine (3·6 g.) in chloroform (20 ml.) was added during ½ hour to a stirred solution of the dipiperidinobutene (2·2 g.) in chloroform (40 ml.). The solvent and excess of bromine were removed under reduced pressure and the semi-solid residue crystallised from methanol. 2 : 3-*Dibromo*-1 : 4-*dipiperidinobutane-dihydrobromide*, m. p. 262° (decomp.), formed small prisms (Found : C, 30·6; H, 4·8. $C_{14}H_{26}N_2Br_2,2HBr$ requires C, 30·9; H, 5·2%).

Bromination of trans-1 : 4-*Dianilinobut*-2-*ene*.—Bromine (1·6 g.) in chloroform (40 ml.) was added during 1 hour to a solution of the dianilinobutene (2·4 g.) in chloroform (40 ml.) at −20°. The mixture was allowed to come slowly to room temperature and 3 days later the dihydrobromide (2·4 g.), m. p. 208—209° (decomp.), was collected by filtration. trans-1 : 4-*Di*-p-*bromoanilinobut*-2-*ene* formed prisms, m. p. 134—136°, from benzene–pentane (Found : C, 48·6; H, 4·2. $C_{16}H_{16}N_2Br_2$ requires C, 48·5; H, 4·1%).

Similar bromination of the methylanilinobutene, m. p. 77—78·5°, afforded a hydrobromide, m. p. 172—173° (decomp.), from which trans-1 : 4-*di*-(p-*bromo*-N-*methylanilino*)*but*-2-*ene*, m. p. 114°, prisms from light petroleum (b. p. 60—80°), was obtained (Found : C, 51·3; H, 4·9. $C_{18}H_{20}N_2Br_2$ requires C, 51·0; H, 4·8%).

2 : 3-*Dibromo*-1 : 4-*di*-(2 : 4 : 6-*trimethylanilino*)*butane*.—When the trimethylanilinobutene (1·5 g.; m. p. 102·5°) was brominated as above, a hydrobromide (3 g.), m. p. 210—212°, separated. The free base proved to be the required 2 : 3-*dibromobutane* derivative, m. p. 152—153° (slow heating), 162° (rapid heating), fine needles from light petroleum (b. p. 40—60°) (Found: C, 54·4; H, 6·5; Br, 33·5. $C_{22}H_{30}N_2Br_2$ requires C, 54·8; H, 6·2; Br, 33·2%).

NN′-*Diphenyl*-NN′-*di*-(2-*toluene*-p-*sulphonyloxyethyl*)*ethylenediamine*.—A solution of *NN′*-di-2-hydroxyethyl-*NN′*-diphenylethylenediamine (30 g.) (Kon and Roberts, *J.*, 1950, 978) in dry pyridine (200 ml.) was cooled to 0° and toluene-*p*-sulphonyl chloride (36 g.) was added during ½ hour. The solution was allowed to warm to room temperature and next day was poured into water, and the precipitated *ditoluene*-p-*sulphonate* was filtered off and washed with dilute hydrochloric acid followed by iced water. The ester formed prisms from benzene, m. p. 154—156° (Found : C, 63·4; H, 5·9. $C_{32}H_{36}O_6N_2S_2$ requires C, 63·1; H, 6·0%).

Hydrolysis Rates of the 1 : 2-*Diesters*.—The hydrolysis rates in 50% aqueous acetone at 66° were determined as described by Ross (*J.*, 1949, 183).

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