595. *Aryl-2-halogenoalkylamines. Part V. The Preparation of* 1 : 4-*Disubstituted Piperazines by the Reaction of Di-2-halogenoalkylamines with Primary Amines.*

By W. Davis and W. C. J. Ross.

1 : 4-Disubstituted piperazines are conveniently prepared by the reaction of di-2-halogenoalkylamines with primary amines in aqueous acetone solution. A number of unsymmetrically 1 : 4-disubstituted piperazines has been prepared from *NN*-di-2-chloroethyl-*p*-anisidine and β-naphthyldi-2-chloroethylamine.

A number of methods are available for the preparation of symmetrically 1 : 4-disubstituted piperazines: *e.g.*, (*a*) Hofmann (*Jahresber.*, 1858, 352; 1859, 387) prepared 1 : 4-diethyl- and 1 : 4-diphenyl-piperazine by the interaction of 1 : 2-dibromoethane with ethylamine and aniline respectively; (*b*) Hofmann (*loc. cit.*) also prepared the diethyl derivative by the direct alkylation of piperazine with ethyl iodide; and (*c*) Thorpe and Wood (*J.*, 1913, **103**, 1608) obtained 1 : 4-diphenylpiperazine by the action of 1 : 2-dibromoethane on 1 : 2-bismethylanilinoethane.

Unsymmetrically substituted dialkylpiperazines have been obtained by the successive alkylation of piperazine with different halides. The monosubstituted piperazines required by this method are not always easy to obtain but satisfactory experimental procedures have been worked out in a number of cases (Baltzly, Buck, Lorz, and Schon, *J. Amer. Chem. Soc.*, 1944, **66**, 263; Wellcome Foundation Ltd., B.P. 578,342). This method cannot be used to prepare aryl-substituted piperazines.

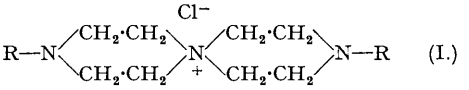
1-Phenyl-4-alkylpiperazines have been prepared by Prelog and Stephan (*Coll. Czech. Chem. Comm.*, 1935, **7**, 93) by the prolonged heating of alkyldi-2-chloroethylamines, or preferably -2-bromoethylamines, with aniline in alcoholic solution. Cerkovnikov and Stern (*Archiv Kemi*, 1946, **18**, 12) obtained 4-phenyl-1-*p*-methoxyphenyl- and -1-*p*-diethylaminophenyl-piperazine by heating *NN*-di-2-bromoethylaniline with *p*-anisidine and *NN*-diethyl-*p*-phenylenediamine respectively in sealed tubes at 130°.

The study of the reactions of aryldi-2-halogenoalkylamines with primary amines in aqueous solutions (Ross, preceding paper) suggested that 1 : 4-disubstituted piperazines could be obtained by use of conditions much milder than those employed by Cerkovnikov and Stern (*loc. cit.*). Accordingly *NN*-di-2-chloroethyl-*p*-anisidine and β-naphthyldi-2-chloroethylamine were allowed to react in 50% acetone solution with a variety of arylamines and in each case the piperazine derivative was readily obtained. In each instance where a known compound was prepared a purer product of higher melting point resulted by the present method. The procedure can also be applied to the preparation of 1-aryl-4-alkyl-substituted piperazines. The yields of the piperazine

derivatives varied between 40% and 70%, generally being higher with the more basic amines. A list of the compounds prepared in the present work is given in the table.

1-Aryl-4-alkylpiperazines form stable mono- and di-picrates, but the diaryl derivatives form picrates which have a marked tendency to dissociate on recrystallisation and it is not always possible to purify them. Monomethiodides are readily obtained by the action of methyl iodide on 1-aryl-4-alkylpiperazines, the nitrogen atom carrying the alkyl group being involved (compare the preceding paper), whilst the diaryl derivatives do not react under mild conditions.

When an attempt was made to prepare 1-*p*-methoxyphenylpiperazine by allowing *NN*-di-2-chloroethyl-*p*-anisidine to react with an aqueous acetone solution of ammonia, the main product of the reaction was N′N″-*di*-p-*methoxyphenyl*-N-spiro*dipiperazinium chloride* (I; R = MeO·C_6H_4), the monosubstituted piperazine which is first formed reacting with a second molecule of chloroethylamine. Similarly β-naphthyldi-2-chloroethylamine affords N′N″-*di*-β-*naphthyl*-N-spiro*dipiperazinium chloride* (I; R = $C_{10}H_7$).



(I.)

The two isomers of β-naphthyldi-2-chloropropylamine (Everett and Ross, this vol., p. 1972) react with *p*-anisidine to give stereoisomeric 1-p-*methoxyphenyl*-4-β-*naphthyl*-2 : 6-*dimethylpiperazines*. The configuration of the chloropropylamines has not yet been established but the *meso*-form would be expected to give the *cis*-isomer of the piperazine.

Prelog and Stephan (*loc. cit.*) found that better yields of piperazine were obtained, by their procedure, with bromo- than with chloro-ethylamines. This is to be expected since the method, using a non-aqueous medium, relies on a bimolecular (S_N2) type of reaction and it is known that in these circumstances bromo-compounds are the more reactive (compare the difference in the ease of replacement of the halogen by iodine when sodium iodide in dry acetone solution is used; Part III). The method now described relies on an S_N1 type of reaction (see preceding paper) and chloroalkylamines, which are more readily obtained in good yields (Parts I and II), can be employed. Since the reaction proceeds at a rate proportional to the rate of ionisation of the halide, shorter times of reaction are required if bromo- or iodo-alkylamines are used, but as the conditions are very mild the final yields of piperazines are not lowered if the more slowly reacting chloroalkylamines are used.

Experimental.

Preparation of 1 : 4-*Diarylpiperazines*.—(*a*) *NN*-Di-2-chloroethyl-*p*-anisidine (1 g., 4 millimols.) and the arylamine (12 millimols.) dissolved in 50% acetone (200 ml.) were heated under reflux for 2 hours. In most cases crystals of the piperazine derivative separated from the hot solution during this period. After removal of the acetone, the cooled mixture was filtered and the product was crystallised from acetone or methanol. A further small quantity of piperazine could be obtained by basifying the original aqueous mother-liquor, extracting it with benzene, and then passing the dried extract through a column of activated alumina. Early eluates contained the piperazine, any unreacted amine being more strongly adsorbed. The yield of piperazine from *p*-toluidine was 65%, and from *p*-anisidine 75%.

(*b*) β-Naphthyldi-2-chloroethylamine (1·07 g., 4 millimols.) and the arylamine (12 millimols.) dissolved in 50% acetone (400 ml.) were heated under reflux for 6 hours, and the products were isolated exactly as above. The yields of piperazine were as follows: from aniline, 41% (after 6 or 24 hours); from *p*-toluidine, 58%; and from *p*-anisidine, 63%.

Preparation of 1-*Aryl*-4-*alkylpiperazines*.—The conditions were exactly as above, but with use of alkylamines; however, in these cases, since no piperazine separated during either the heating or the subsequent cooling, the acetone was removed by distillation and the mixture was treated with an excess of aqueous sodium hydroxide. The solution was saturated with sodium chloride and then extracted with benzene. The dried extract was allowed to percolate through a column of alumina and the piperazine derivative, which was recovered from the early eluates, was crystallised from light petroleum. Ethylenediamine reacted in a manner similar to that of monoamines, the products being di(arylpiperazino)ethanes.

Formation of Monomethiodides of 1-*Aryl*-4-*alkylpiperazines*.—The piperazine (1 millimol.) and methyl iodide (2 millimols.) dissolved in benzene (10 ml.) were heated on a steam-bath for 10 minutes. The crystalline solid which separated was filtered off, washed with ether, and crystallised from methanol. Under these conditions the diarylpiperazines did not react.

Reaction of NN-*Di*-2-*chloroethyl*-p-*anisidine and* β-*Naphthyldi*-2-*chloroethylamine with Ammonia*.—A solution of *NN*-di-2-chloroethyl-*p*-anisidine (3 g.) in 50% acetone (200 ml.) was heated under reflux for 2 hours while a solution of aqueous ammonia (*d* 0·88; 15 ml.) was gradually added. After the removal of the acetone the solution was saturated with sodium chloride. The crystalline precipitate which formed was collected and recrystallised from ethanol. Sword-shaped needles of N′N″-*di*-p-*methoxyphenyl*-N-spiro*dipiperazinium chloride*, m. p. 280—285° (decomp.), were obtained (Found: C, 65·4; H, 7·4. $C_{22}H_{30}O_2N_3Cl$ requires C, 65·4; H, 7·5%. 10·6 Ml. of 0·1N-silver nitrate were required to titrate the ionic chlorine in 428 mg. of the halide; calc., 10·6 ml.).

Piperazine derivative.	M. p.	Crystal form.	S.	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.
1-p-*Methoxyphenyl*-4-*methyl*-	69°	Flattened needles	D	$C_{12}H_{18}ON_2$	69·7	8·8	69·9	8·8
,, ,, *dipicrate*	200 *	Prisms	A, C	$C_{24}H_{24}O_{15}N_8$	N, 17·3		N, 16·9	
,, ,, *monomethiodide*	220	Plates	A	$C_{13}H_{21}ON_2I$	44·6	6·1	44·8	6·1
1-p-*Methoxyphenyl*-4-*ethyl*-	66	Plates	D	$C_{13}H_{20}ON_2$	70·6	9·1	70·9	9·2
,, ,, *dipicrate*	189 *	Needles	A, C	$C_{25}H_{26}O_{15}N_8$	44·5	4·1	44·3	3·9
1-p-*Methoxyphenyl*-4-2′-*hydroxyethyl*-	88	Flattened needles	E	$C_{13}H_{20}O_2N_2$	66·3	8·6	66·1	8·5
,, ,, *dihydrate*	60	Needles	G	$C_{13}H_{24}O_4N_2$	57·5	8·9	57·4	8·9
,, ,, *monopicrate*	90	Orange needles	A	$C_{19}H_{23}O_9N_5$	49·0	4·9	49·1	5·0
,, ,, *dipicrate*	178	Yellow plates	C	$C_{25}H_{26}O_{16}M_8$	43·6	3·7	43·5	3·8
,, ,, *monomethiodide*	161	Plates	A	$C_{14}H_{23}O_2N_2I$	I, 33·2		I, 33·6	
1-p-*Methoxyphenyl*-4-*allyl*-	59	Plates	H	$C_{14}H_{20}ON_2$	72·5	8·9	72·5	8·6
,, ,, *monopicrate*	144	Red prisms	A	$C_{20}H_{23}O_8N_5$	51·8	5·1	52·1	5·0
,, ,, *dipicrate*	190 *	Yellow plates	A, C	$C_{26}H_{26}O_{15}N_8$	45·5	4·0	45·2	3·8
1-p-*Methoxyphenyl*-4-cyclo*hexyl*-	125	Prismatic needles	E	$C_{17}H_{26}ON_2$	74·3	9·6	74·5	9·6
,, ,, *dipicrate*	185 *	Plates	A, C	$C_{29}H_{32}O_{15}N_8$	47·9	4·4	47·5	4·4
,, ,, *monomethiodide* [1]	165—167	Plates	A	$C_{18}H_{29}ON_2I$	I, 30·3		I, 30·5	
1-Phenyl-4-*p*-methoxyphenyl [2]	168	Large plates	C	$C_{17}H_{20}ON_2$	76·0	7·6	76·2	7·5
,, ,, *dipicrate*	175	Fine needles	A, C	$C_{29}H_{26}O_{15}N_8$	48·0	3·7	47·9	3·6
1-p-*Methoxyphenyl*-4-p-*tolyl*-	171	Plates	C	$C_{18}H_{22}ON_2$	76·7	8·2	76·6	7·9
1 : 4-Di-*p*-methoxyphenyl- [3]	239	Small prisms	I	$C_{18}H_{22}O_2N_2$	72·6	7·5	72·5	7·4
1-p-*Methoxyphenyl*-4-α-*naphthyl*-	170	Plates	B, C	$C_{21}H_{22}ON_2$	79·3	7·1	79·2	7·0
1-p-*Methoxyphenyl*-4-β-*naphthyl*- [4]	190	Prismatic needles	C	$C_{21}H_{22}ON_2$	79·2	7·0	79·2	7·0
,, ,, *dipicrate*	172	Needles	A, C	$C_{33}H_{28}O_{15}N_8$	51·3	3·8	51·0	3·6
1-β-*Naphthyl*-4-*methyl*-	94	Diamond shaped plates	D	$C_{15}H_{18}N_2$	80·0	8·0	79·7	8·0
,, ,, *dipicrate*	158	Short needles	C	$C_{27}H_{24}O_{14}N_8$	N, 16·6		N, 16·4	
1-β-*Naphthyl*-4-*ethyl*-	75	Short needles	D	$C_{16}H_{20}N_2$	80·1	8·5	80·0	8·4
,, ,, *dipicrate*	169	Needles	C	$C_{28}H_{26}O_{14}N_8$	48·5	4·0	48·2	3·8
1-β-*Naphthyl*-4-2′-*hydroxyethyl*-	135	Fine needles	C	$C_{16}H_{20}ON_2$	75·1	8·0	75·0	7·9
,, ,, *dipicrate*	147	Short needles	C	$C_{28}H_{26}O_{15}N_8$	N, 16·2		N, 15·7	
1-β-*Naphthyl*-4-*allyl*-	71	Plates	C	$C_{17}H_{20}N_2$	80·7	8·1	80·9	8·0
,, ,, *dipicrate*	176	Fine needles	A, C	$C_{29}H_{26}O_{14}N_8$	49·1	3·9	49·0	3·7
1-β-*Naphthyl*-4-cyclo*hexyl*-	149	Prismatic needles	C	$C_{20}H_{26}N_2$	81·8	9·2	81·6	8·9
,, ,, *dipicrate*	181	Diamond shaped plates	A	$C_{32}H_{32}O_{14}N_8$	51·5	4·6	51·1	4·3
1-*Phenyl*-4-β-*naphthyl*-	164	Flattened needles	C	$C_{20}H_{20}N_2$	83·1	7·2	83·3	7·0
,, ,, *monopicrate*	191	Orange rhombs	C, F	$C_{26}H_{23}O_7N_5$	60·2	4·4	60·4	4·5
1-p-*Tolyl*-4-β-*naphthyl*-	159	Flattened rhombs	C	$C_{21}H_{22}N_2$	83·9	7·3	83·5	7·3
,, ,, *dipicrate*	163	Needles	A, C	$C_{33}H_{28}O_{14}N_8$	N, 15·0		N, 14·7	
1-β-*Naphthyl*-4-α-*naphthyl*-	200·5	Prismatic needles	C	$C_{24}H_{22}N_2$	85·4	6·5	85·3	6·6
1 : 4-Di-β-naphthyl- [5]	238	Plates	F	$C_{24}H_{22}N_2$	85·4	6·6	85·3	6·6
1 : 2-*Di*-(4-β-*naphthylpiperazino*)*ethane*	243	Fine needles	A, F	$C_{30}H_{34}N_4$	79·7	7·8	80·0	7·6
1 : 2-*Di*-(4-p-*methoxyphenylpiperazino*)*ethane*	176	Prismatic needles	C	$C_{24}H_{34}O_2N_4$	70·4	8·4	70·3	8·4
,, ,, *tetrapicrate*	224 *	Small prisms	C	$C_{48}H_{46}O_{30}N_{16}$	N, 16·7		N, 16·9	

Solvents (S) used for crystallisation were: A methanol; B ethanol; C, acetone; D, light petroleum (b. p. 40—60°); E, light petroleum (b. p. 60—80°); F, chloroform; G, water; H, ether; I, acetic acid. * With decomp.

[1] The compound melts at 165—167° if slowly heated, but at 140° if heating is rapid. [2] Cerkovnikov and Stern (*loc. cit.*) give m. p. 164—165°. [3] Bischoff (*Ber.*, 1889, **22**, 1782) gives m. p. 233°. [4] This compound has been made by the reaction (i) of *NN*-di-2-chloroethyl-*p*-anisidine with β-naphthylamine or (ii) of β-naphthyldi-2-chloroethylamine with *p*-anisidine. [5] Bischoff and Hausdorfer (*Ber.*, 1890, **23**, 1984) give m. p. 228°.

N'N''-*Di*-β-*naphthyl*-N-spiro*piperazinium chloride* was isolated from an experiment in which β-naphthyldi-2-chloroethylamine (1·0 g.) dissolved in 50% acetone (400 ml.) was heated under reflux for 6 hours with the gradual addition of aqueous ammonia (15 ml.). The halide formed broad, flattened needles, m. p. 305° (decomp.), when crystallised from ethanol (Found: C, 75·4; H, 7·1. $C_{28}H_{30}N_3Cl$ requires C, 75·7; H, 6·8%. 5·9 Ml. of 0·1N-silver nitrate were required to titrate the ionic chlorine in 261 mg. of the halide; calc., 5·9 ml.).

1-p-*Methoxyphenyl*-4-β-*naphthyl*-2 : 6-*dimethylpiperazines*.—β-Naphthyldi-2-chloropropylamine (1·5 g. of the isomer, m. p. 102°, or of the isomer, m. p. 82°) and *p*-anisidine (5 g.) dissolved in 50% acetone (100 ml.) were heated under reflux for 1 hour. It is necessary to employ a much higher concentration of arylamine than is used for the chloroethylamines in order to obtain a reasonable yield of piperazine, since the chloropropylamine has more tendency to undergo simple hydrolysis than to react with the amine if the amine concentration is low (compare the lower competition factor of anions towards 2-chloropropylamines discussed in Part II). The *piperazine* derivatives were isolated in the usual way after removal of most of the excess of anisidine by a steam-distillation. The derivative from the high-melting isomer formed plates (from acetone–methanol), m. p. 141°, which dissolved in acetone to give a solution which exhibited a blue fluorescence in daylight (Found: 79·9; H, 7·8. $C_{23}H_{26}ON_2$ requires C, 79·7; H, 7·6%). The compound obtained from the low-melting isomer was more difficult to purify and even after several crystallisations from methanol formed plates of somewhat indefinite m. p., ranging from 127° to 131° (Found: C, 80·3; H, 7·8%).

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THE CHESTER BEATTY RESEARCH INSTITUTE,
FULHAM ROAD, LONDON, S.W.3.

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