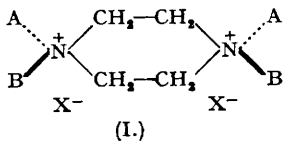
219. *Geometrically Isomeric Piperazine Derivatives Containing Two Quaternary Nitrogen Atoms.*

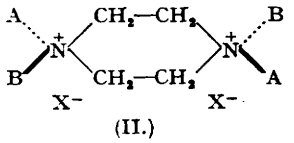
By W. E. Hanby and H. N. Rydon.

A number of diquaternary salts of *NN'*-dimethylpiperazine have been obtained in *cis*- and *trans*-stereoisomeric forms. This is the first recorded case of geometrical isomerism arising from the configuration of substituent groups about two nitrogen atoms forming part of a ring and thus completes the stereochemical series of which the other members are the hexahydroterephthalic acids and the geometrically isomeric 4-substituted piperidinium salts of Mills, Parkin, and Ward (*J.*, 1927, 2613).

Diquaternary piperazinium salts bearing two dissimilar groups on each of the nitrogen atoms would be expected to exist in the *cis*- and *trans*-stereoisomeric forms (I) and (II). The preparation of many such piperazinium salts is on record (*e.g.*, Strömholm, *Ber.*, **1903**, **36**, 144; Pyman, *J.*, 1908, **93**, 1804; Franchimont and Kramer, *Rec. trav. chim.*, 1912, **31**, 51; Kaufmann and Dürst, *Ber.*, 1917, **50**, 1636) but in none of these instances was more than one isomer obtained; in this paper we describe the preparation and properties of a number of stereoisomerides of this type.



(I.)



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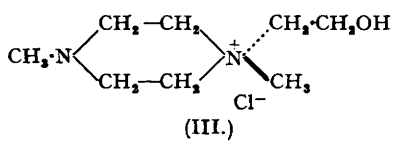

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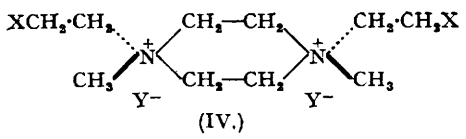
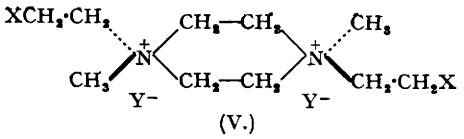


(IV.)



(V.)

Ethylene chlorohydrin and *NN'*-dimethylpiperazine react at 100° to form both the monoquaternary salt, N-β-*hydroxyethyl*-NN'-*dimethylpiperazinium chloride* (III), and the desired diquaternary salt, NN'-*di*-(β-*hydroxyethyl*)-NN'-*dimethylpiperazinium dichloride* (IV and V; X = OH, Y = Cl), the former predominating except when the reaction is very prolonged. Two forms of the diquaternary salt were readily isolated from the reaction product; these two substances, shown by analysis to be isomeric, differ in m. p. although they show no depression of m. p. on admixture; they give different picrates and differ markedly in solubility. There can be no doubt that they are the expected geometrical isomers (IV and V; X = OH, Y = Cl); the *X*-ray results (quoted below) on derivatives show that the higher melting, less soluble compound has the *trans*-configuration (V).

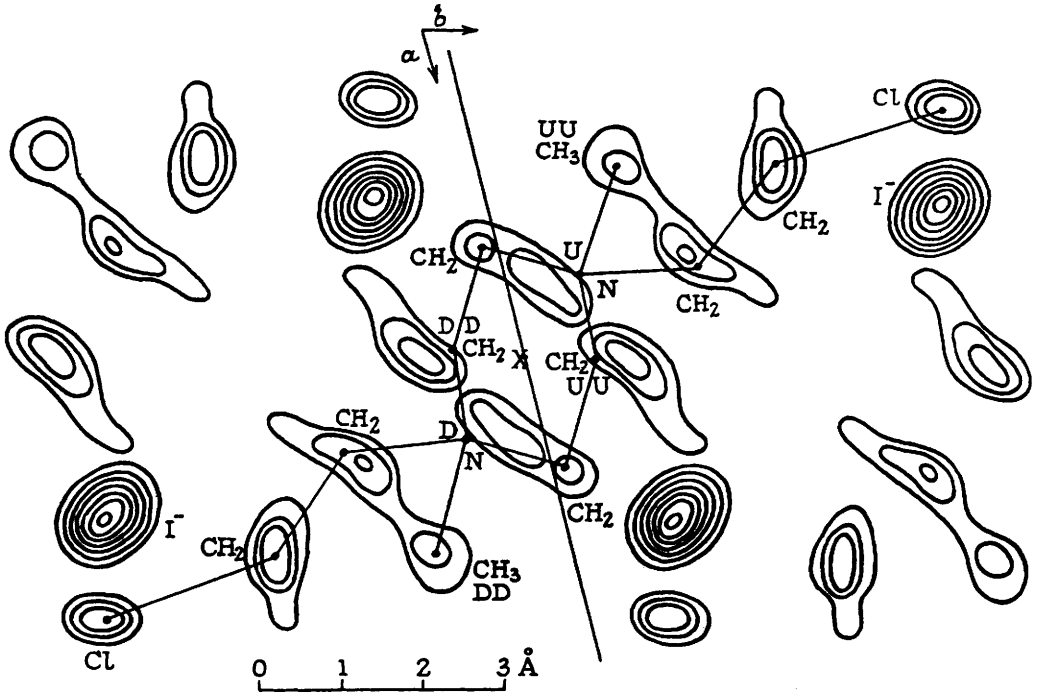
These two stereoisomerides show marked differences in the reactivity of the hydroxyl groups, the *trans*-compound being the less reactive in this respect. Thus, the *trans*-compound was recovered unchanged after prolonged heating with acetyl chloride, alone or in the presence of pyridine, whereas the *cis*-compound was readily acetylated by heating with acetyl chloride alone. Similarly the *cis*-isomer gave the corresponding *dichloro-dichloride* (IV; X = Y = Cl) by simple refluxing with thionyl chloride, a process which left the *trans*-isomer unchanged; the latter could, however, be converted into the trans-*dichloro-dichloride* (V; X = Y = Cl) by heating with thionyl chloride in the presence of pyridine. The two stereoisomeric dichloro-dichlorides were characterised as their picrates and were also converted, for the purpose of the *X*-ray work, into the rather sparingly soluble *di-iodides* (IV and V; X = Cl, Y = I). In addition to yielding these markedly different derivatives the two dichloro-dichlorides also differ in that the *cis*-isomer crystallises from water as a stable hemihydrate whereas the *trans*-isomer crystallises in the anhydrous state from the same solvent. No success attended a number of attempts to bring about the interconversion of this pair of stereoisomerides.

The properties of the various pairs of stereoisomerides obtained in the course of the present work are summarized in the following table:

Stereoisomeric Piperazinium Salts, (IV) and (V).

X.	Y.	Configuration.	M. p.	Relative solubility.	Other properties.	Dipicrate.
OH	Cl	*cis*	241°	More soluble	Deliquescent. OH group readily replaced.	Pale yellow needles, m. p. 220°.
		trans	246—247	Less soluble	Not deliquescent. OH group relatively unreactive.	Orange prismatic needles, m. p. 248—249°.
OAc	Cl	*cis*	229	—	—	Yellow needles, m. p. 188°.
		trans	Not obtained.			
Cl	Cl	*cis*	328	More soluble	Hemihydrate from water.	Golden leaflets or needles, m. p. 207°.
		trans	327—328	Less soluble	Anhydrous from water.	Orange needles, m. p. 225°.
	I	*cis*	238	More soluble	Photosensitive.	As above.
		trans	Indefinite	Less soluble	Not photosensitive.	

The *X*-ray crystallographic investigation of the dichloro-dichlorides (IV and V; X = Y = Cl) and the dichloro-di-iodides (IV and V; X = Cl, Y = I) was kindly undertaken by Mr. H. M. Powell of the Department of



Electron-density map for trans-NN'-*di*-(*β-chloroethyl*)-NN'-*dimethylpiperazinium di-iodide* (V; X = Cl, Y = I).

(*All the atoms may be taken as roughly in the plane of the paper except those marked* U, D, *which are respectively somewhat up and down out of the plane of the paper and those marked* UU *and* DD, *which are further above and below than* U, D.)

Chemical Crystallography, Oxford University, whose preliminary report is quoted in the experimental section. His results leave no doubt that the photo-insensitive dichloro-di-iodide is in fact the *trans*-isomer; this is clearly apparent from the electron density map shown. The configurations of the other compounds follow from this without ambiguity. The usual correlation between low melting point, high solubility and *cis*-configuration holds in the present series.

Although diastereoisomeric open-chain diquaternary ammonium salts have previously been obtained in *meso*- and racemic forms (Wedekind and Wedekind, *Ber.*, 1910, **43**, 2707; Wedekind and Goost, *ibid.*, 1916, **49**, 942) the present work appears to constitute the first recorded case of geometrical isomerism due to the disposition of groups about two nitrogen atoms forming part of a ring. As such it satisfactorily completes the stereochemical series of which the other members are the *cis*- and *trans*-hexahydroterephthalic acids, in which two carbon atoms are involved in the stereoisomerism, and the 4-substituted piperidinium salts of Mills, Parkin, and Ward (*J.*, 1927, 2613), whose stereoisomerism is due to the configuration of groups about one carbon and one nitrogen atom. Among sulphur compounds the closest analogues of our compounds are the *cis*- and *trans*-forms of dithian dioxide obtained by Bell and Bennett (*J.*, 1927, 1798).

Although the monoquaternary salt (III) could theoretically exist in two stereoisomeric forms (cf. the piperidine derivatives of Mills *et al.*, *loc. cit.*) no evidence was obtained of the existence of more than one form of

this compound. This negative result is, of course, only to be expected in view of the known stereochemical lability of tervalent nitrogen.

Experimental.

NN'-*Di*-(*β-hydroxyethyl*)-NN'-*dimethylpiperazinium Dichlorides*.—*NN'*-Dimethylpiperazine (11 g.; Forsee and Pollard, *J. Amer. Chem. Soc.*, 1935, **57**, 1788) was heated on the water-bath with dry ethylene chlorohydrin (31 g.) for 18 hrs. After cooling, the deposited solid (5·2 g.; m. p. 239—240°) was filtered off and crystallised from aqueous alcohol, yielding trans-NN'-*di*-(*β-hydroxyethyl*)-NN-*dimethylpiperazinium dichloride* (V; X = OH, Y = Cl) in leaflets, m. p. 246—247° (decomp.) (Found: C, 43·4; H, 8·9; N, 10·7; Cl, 26·5. $C_{10}H_{24}O_2N_2Cl_4$ requires C, 43·6; H, 8·7; N, 10·2; Cl, 25·8%). The *dipicrate* crystallised from dilute alcohol in small orange prismatic needles, m. p. 248—249° (Found: C, 40·2; H, 4·45; N, 17·5. $C_{22}H_{28}O_{16}N_8$ requires C, 40·0; H, 4·25; N, 17·0%).

Acetone was added to the reaction product after this *trans*-dihydroxy-dichloride had been separated; the precipitated solid was crystallised from aqueous alcohol yielding the deliquescent cis-NN'-*di*-(*β-hydroxyethyl*)-NN'-*dimethylpiperazinium dichloride* (IV; X = OH, Y = Cl), m. p. 241° not depressed on admixture with the *trans*-isomer (Found: C, 43·4; H, 9·0; Cl, 25·6. $C_{10}H_{24}O_2N_2Cl_4$ requires C, 43·6; H, 8·7; Cl, 25·8%). The *dipicrate* crystallised from water in pale yellow needles, m. p. 220° (Found: C, 40·0; H, 4·4. $C_{22}H_{28}O_{16}N_8$ requires C, 40·0; H, 4·25%).

Evaporation of the reaction liquor after removal of the two dihydroxy-dichlorides left an oil which crystallised on rubbing with acetone. The solid (6·5 g.; m. p. 135—150°) was twice crystallised from methanol–acetone yielding N-*β-hydroxyethyl*-NN'-*dimethylpiperazinium chloride* (III) as very hygroscopic prisms, m. p. 162° (Found: C, 49·3; H, 10·0; N, 14·0; Cl, 18·8. $C_8H_{19}ON_2Cl$ requires C, 49·35; H, 9·8; N, 14·4; Cl, 18·25%).

Acetylation.—The *cis*-dihydroxy-dichloride (IV; X = OH, Y = Cl) (0·5 g.) was refluxed for 10 hrs. with acetyl chloride (5 c.c.). After removal of excess acetyl chloride, the hygroscopic product was crystallised from methanol–acetone, yielding *cis*-NN'-*di*-(*β-acetoxyethyl*)-NN'-*dimethylpiperazinium dichloride* (IV; X = OAc, Y = Cl), m. p. 229° (Found: C, 46·8; H, 8·0; Cl, 20·0. $C_{14}H_{28}O_4N_2Cl_2$ requires C, 46·75; H, 7·8; Cl, 19·8%). The *dipicrate* crystallised from water in flat needles, m. p. 188° (Found: C, 41·9; H, 4·4. $C_{26}H_{32}O_{18}N_8$ requires C, 41·9; H, 4·3%).

The *trans*-dihydroxy-dichloride was recovered unchanged after prolonged refluxing with acetyl chloride, alone or in the presence of pyridine.

NN'-*Di*-(*β-chloroethyl*)-NN'-*dimethylpiperazinium Dichlorides*.—The *cis*-dihydroxy-dichloride (IV; X = OH, Y = Cl) (0·5 g.) was refluxed on the water-bath for 4 hrs. with thionyl chloride (5 c.c.). The cooled reaction product was treated with acetone and filtered; crystallisation of the solid from aqueous acetone yielded cis-NN'-*di*-(*β-chloroethyl*)-NN'-*dimethylpiperazinium dichloride* (IV; X = Y = Cl), m. p. 328° (decomp.) (Found: C, 37·3; H, 7·45. $C_{10}H_{22}N_2Cl_4,\frac{1}{2}H_2O$ requires C, 37·4; H, 7·2%. Found in material dried under reduced pressure and over P_2O_5 at 100°: C, 38·7; H, 7·05; Cl′, 22·3. $C_{10}H_{22}N_2Cl_4$ requires C, 38·5; H, 7·05; Cl′, 22·75%). The *dipicrate* crystallised from water in golden leaflets or needles, m. p. 207° (Found: C, 38·0; H, 4·0; N, 16·2; Cl, 10·4. $C_{22}H_{26}O_{14}N_8Cl_2$ requires C, 37·9; H, 3·7; N, 16·1; Cl, 10·2%).

The *trans*-dihydroxy-dichloride (V; X = OH, Y = Cl) (1 g.) was heated on the water-bath for 5 hrs. with thionyl chloride (5 g.) and pyridine (0·6 g.). The reaction product was warmed with chloroform and filtered while hot; the solid, after washing with chloroform, was crystallised from aqueous acetone yielding trans-NN'-*di*-(*β-chloroethyl*)-NN'-*dimethylpiperazinium dichloride* (V; X = Y = Cl), m. p. 327—328°, not depressed on admixture with the *cis*-isomer (Found: C, 38·7; H, 6·7; Cl, 45·0. $C_{10}H_{22}N_2Cl_4$ requires C, 38·5; H, 7·05; Cl, 45·5%). The *dipicrate* crystallised from water in orange needles, m. p. 225° (Found: C, 37·5; H, 3·8; N, 15·8; Cl, 10·4.. $C_{22}H_{26}O_{14}N_8Cl_2$ requires C, 37·8; H, 3·7; N, 16·1; Cl, 10·2%). The *trans*-dihydroxy-dichloride remained unchanged after long refluxing with thionyl chloride in the absence of added tertiary base.

NN'-*Di*-(*β-chloroethyl*)-NN'-*dimethylpiperazinium di-iodides* were precipitated in almost quantitative yield when concentrated aqueous solutions of the corresponding dichlorides were treated with an excess of aqueous potassium iodide. The cis-*di-iodide* (IV; X = Cl, Y = I) crystallised from water in minute photosensitive leaflets, m. p. 238° (Found: C, 24·4; H, 4·3. $C_{10}H_{22}N_2Cl_2I_2$ requires C, 24·25; H, 4·4%). The *trans*-di-iodide (V; X = Cl, Y = I) crystallised from water in leaflets having no definite m. p. (Found: C, 24·4; H, 4·0%).

X-Ray Investigation.—Mr. H. M. Powell reports as follows:—"Both the *trans*-chloride and -iodide crystallise well; both substances form anorthic crystals and are closely related in crystal structure judged by similarities in their *X*-ray diffraction patterns.

The unit cell constants are:

Chloride (V; X = Y = Cl).

$a_0 = 7·7$ A.; $b_0 = 6·7$ A.; $c_0 = 7·3$ A.
$\alpha = 96° 54'$; $\beta = 99°$; $\gamma = 80° 4'$.

Iodide (V; X = Cl, Y = I).

$a_0 = 8·1$ A.; $b_0 = 7·25$ A.; $c_0 = 7·37$ A.
$\alpha = 109° 30'$; $\beta = 105° 30'$; $\gamma = 72° 20'$.

Patterson Fourier analysis carried out on the iodide permits the location of the iodine atoms in the unit cell and the observed intensities of *X*-ray reflections may be used in combination with phases for the structure factors, calculated by considering the iodine atom contributions alone, to derive the electron density map. This is a first approximation only and a small number of observations had to be omitted, through uncertainties, at this stage. Nevertheless the projection shows a complete set of lower peaks and gives a good approximation for the general lay-out of the rest of the structure. The cation lies at a centre of symmetry and must therefore have the *trans*-configuration. An approximate representation of the space arrangement may be obtained by building up a model on the projection shown as plan.

The *cis*-forms do not crystallise well. It has been possible to get crystals large enough to distinguish something of their form microscopically. They are probably monoclinic and appear always to be twinned in a complex manner. The prospects for a complete structure determination do not seem good."

We are much indebted to Mr. H. M. Powell of the Department of Chemical Crystallography, University Museum, Oxford, for carrying out the X-ray work and for allowing us to quote his findings, and to the Director General of Scientific Research and Development, Ministry of Supply, for permission to publish this paper.

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