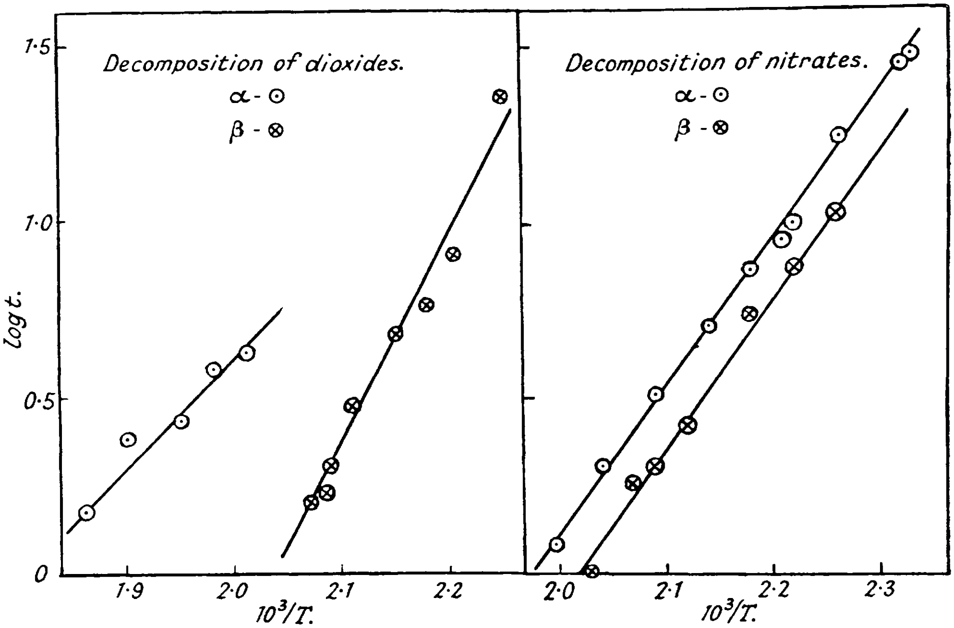
49. *Geometrical Isomerism of the Dioxides of Diphenylpiperazine.*

By G. M. Bennett and (Mrs.) Erika Glynn.

Diphenylpiperazine is oxidised by hydrogen peroxide to two isomeric di-*N*-oxides. The α-isomeride crystallises as an efflorescent octahydrate and a stable dihydrate which loses its water in a vacuum. The β-isomeride, formed in a proportion of about 1 in 10, is much the more soluble in water. It is isolated in the form $B,H_2O_2,2H_2O$, stable in a vacuum. The salts of these dioxides are usually anhydrous, free from hydrogen peroxide, and of the composition $B,2HX$. The isomeric hydrochlorides, nitrates, and picrates have been characterised and also the oxalate, sulphate, perchlorate, ferrocyanide, platinichloride and aurichloride of the α-dioxide. All these substances explode when heated, and the times required for explosion at various temperatures have been studied. The stability of its complex with hydrogen peroxide indicates that the β-isomeride has the *cis*-configuration.

Di-*N*-oxides of suitable diamines should exist in diastereoisomeric or *cis-trans*-forms analogous to those of the dithian dioxides (Bell and Bennett, *J.*, 1927, 1788). In order to demonstrate this the oxidation of 1 : 4-diphenylpiperazine has been examined. Hydrogen peroxide in acetone or glacial acetic acid yielded as the main product the *α-dioxide*, crystallising magnificently from warm water as the *octahydrate*, which, however, rapidly effloresces to the *dihydrate* stable in air. Both hydrates lose their water in a vacuum to give the hygroscopic anhydrous *dioxide*.



From the mother-liquor of the α-dioxide a small quantity of a much more soluble β-*dioxide* was isolated which was found on analysis to have the composition β-dioxide,$H_2O_2,2H_2O$. The presence of hydrogen peroxide was also confirmed by direct tests. These crystals are stable in air and lose neither water nor hydrogen peroxide when kept in a vacuum. Both dioxides are readily reduced to the parent diphenylpiperazine.

The two dioxides give salts which are generally anhydrous and contain no hydrogen peroxide. Pairs of isomeric *hydrochlorides*, *nitrates*, and *picrates* were characterised and in addition the *sulphate*, *oxalate*, *perchlorate*, *ferrocyanide*, *platinichloride*, and *aurichloride* of the α-dioxide.

The two dioxides and all their salts decompose explosively when heated. A study of the temperatures of decomposition showed that for each substance explosion occurred after a particular time (t secs.) of heating at a given temperature (T °K.) where $\log_{10} t = a/T - b$, a and b being constants for the substance. This relationship is illustrated in the figure for observations with the α- and the β-nitrate and with the two dioxides (α-dioxide dihydrate and hydrated β-dioxide–hydrogen peroxide complex). The constants a and b for all the compounds studied are in the table.

Substance.	$10^{-3}a$.	b.	Temperature (° c.) (calc.) for $t = 1$ sec.
α-Oxalate	6·6	11·8	289°
α-Hydrochloride	5·7	10·6	268
α-Aurichloride	4·8	10·6	182
α-Nitrate	4·2	8·3	234
β-Nitrate	4·2	8·5	224
α-Picrate	6·5	13·5	221
β-Picrate	5·8	12·2	207
α-Dioxide dihydrate	3·2	5·8	281
β-Dioxide complex	5·8	12·0	210

It is noticeable that the values of a (slopes of the curves in the figure) are similar for the pairs of isomerides. This is not so for the two dioxides, but the compounds actually examined were in this case not isomeric since only the β-specimen contained combined hydrogen peroxide.

This type of behaviour has been reported more than once before, for example for the decomposition of lead styphnate (Hales, *Trans. Faraday Soc.*, 1933, **29**, 544) and of barium azide (Hervey, *ibid.*, p. 653). The former author records some variation in times before detonation with the size of the crystals. Our specimens were all finely powdered.

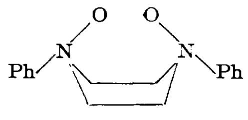
These observations help in characterising the compounds examined and, in the absence of melting points, provide clear evidence of the individuality of the pairs of isomerides studied.

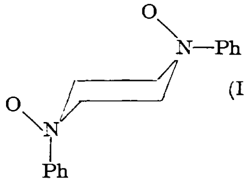
The α-dioxide and its salts are all somewhat more stable than their β-isomerides. The α-dioxide is more sparingly soluble in water (by a factor of the order of 100 : 1) than the β-dioxide, but in 95·6% alcohol the converse is true and the solubilities at 25° were α- 9·1 and β- 1·16% by weight.

Although the α-dioxide forms stable salts of the composition B,2HX, its aqueous solutions are not alkaline but have a pH between 6 and 7. Moreover measurably more N/10-sodium hydroxide is needed to change the colour of phenolphthalein in its presence than in pure water. A similar faintly acidic character was observed by Polonovski, Boulanger, and Taghavi (*Atti del X° Congresso Internazionale di Chimica, Roma,* 15—21, Maggio, 1938, XVI, **3**, 303) with dimethylpiperazine dioxide. The formula suggested by these authors for a negative ion produced by the union of an amine oxide and a hydroxyl ion is, however, electronically unsound and we doubt whether the effect under consideration can be explained in terms of normal bonding.

The tenacity with which the molecule of hydrogen peroxide is retained by the β-dioxide is remarkable and may be regarded as significant in connexion with the question of configuration. General considerations such as stability, as indicated by temperatures of decomposition, and solubility in water would suggest that the α-dioxide has the *trans*-configuration. The stable retention of hydrogen peroxide might be due to the attachment of the peroxide molecule by hydrogen bonds simultaneously to both amine oxide oxygen atoms, and this would be expected to be possible in a *cis*- but not in a *trans*-form of the piperazine dioxide. A study of molecular models supports this view. For this purpose we have assumed the following interatomic distances: CH_2-CH_2 1·54; CH_2-N 1·47; $\overset{+}{N}-\overset{-}{O}$ 1·36 A. (compare Sutton, *J.*, 1945, 146). If all the angles in the piperazine ring are taken as tetrahedral, the ring must be puckered and there are several distinct arrangements for each of the *cis*- and *trans*-forms of the dioxide (actually 5 *cis* and 4 *trans*). In the various arrangements of the *trans*-form the distance between the two

(I.)

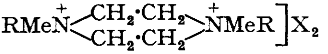




(II.)

oxygen atoms is of the order 4—5 A., but in every case the bulky phenyl group or the atoms of the ring are interposed making any bridging by the hydrogen peroxide molecule improbable. On the other hand no such obstruction arises in the various arrangements of the *cis*-dioxide. In one of these (I) the oxygen atoms are less than 2 A. apart (calculated on the above-mentioned assumptions, 1·61 A.), but this particular arrangement would presumably have low stability owing to the close approach of the mutually repellent fields of the two amine oxide groups. The other possible arrangements of the *cis*-dioxide have oxygen atoms at a distance of the order 4—5 A., for example (II) (calculated distance, 4·35 A.). In considering the possible attachment of hydrogen peroxide the *X*-ray examination of the crystal structure of the urea–hydrogen peroxide compound by Lu, Hughes, and Giguère (*J. Amer. Chem. Soc.*, 1941, **63**, 1507) is relevant. These authors concluded that the crystal is an assemblage of urea and hydrogen peroxide molecules held together by hydrogen bonds, the hydrogen peroxide molecule retaining the configuration calculated for it by Penney and Sutherland (*Trans. Faraday Soc.*, 1934, **30**, 898) in which the O–H bonds are at 101·5° to the O–O bond but lie in two planes inclined at 106° to each other. A trial with models, taking the O–O distance in hydrogen peroxide to be 1·47 A. (Giguère and Schomaker, *J. Amer. Chem. Soc.*, 1943, **65**, 2025) shows that this hydrogen peroxide molecule can in fact be fitted, with only slight distortion of the angles, to bridge the two oxygen atoms of the *cis*-dioxide in the arrangement (II) with hydrogen bond distances of the order 2·7 A. We therefore conclude that the stability of the hydrogen peroxide complex is strong evidence that the β-dioxide has the *cis*-configuration.

It is evident that the dioxide of dimethylpiperazine should similarly occur in *cis*- and *trans*-forms. Although this substance was described by Polonovski, Boulanger, and Taghavi (*loc. cit.*) no such isomerism was reported. Yet their paper does contain indications of the existence of two forms, and the point requires re-investigation.

While this work was in progress the geometrical isomerism of some diquaternary salts of dimethylpiperazine of the type  $\left[\mathrm{RMe}\overset{+}{\mathrm{N}}{<}^{\mathrm{CH_2{\cdot}CH_2}}_{\mathrm{CH_2{\cdot}CH_2}}{>}\overset{+}{\mathrm{N}}\mathrm{MeR}\right]\mathrm{X_2}$ was described by Hanby and Rydon (*J.*, 1945, 833). These are analogous to the isomerides described in this paper.

EXPERIMENTAL.

Analyses.—Determinations of carbon, hydrogen, and nitrogen were made by Messrs. Weiler and Strauss. Determinations of peroxidic oxygen were carried out by the method recently described by one of us (Glynn, *Analyst*, 1947, **72**, 248). Explosion temperatures given below are calculated temperatures at which explosion occurs after 1 second.

Oxidation of 1 : 4-*Diphenylpiperazine.*—A mixture of the base (20 g.) dissolved in glacial acetic acid (300 ml.) with hydrogen peroxide (120 g. of 30% aqueous) was kept at 50—70° for 16 hours. The resulting dark red solution gave a copious precipitate of the α-dioxide when neutralised with 10N-sodium hydroxide, but in order to isolate the whole of the products with a minimum contamination with inorganic matter the solution was diluted and evaporated several times at 60° and finally kept over sodium hydroxide in a desiccator until all the acetic acid had been removed. The crude product had a peroxidic oxygen content of 6·8%. This was dissolved in water (500 ml.) at 60°, and the solution on cooling deposited crystals of the hydrated α-dioxide (15 g.). After 2 further crystallisations from water the *diphenylpiperazine α-dioxide octahydrate* was obtained in large well-formed crystals (Found : peroxidic O, 7·78, 7·68%).

Evaporation of the original mother-liquors yielded further small crops of crude α-dioxide, and the solution was finally taken to dryness in a desiccator over potassium hydroxide. A brown oily residue was left which gradually became crystalline (Found, in the crude product: peroxidic O, 13·2, 12·1%). This material was extracted with rectified alcohol, some insoluble inorganic matter being rejected, and after repeated crystallisation from 95% ethanol (charcoal) the β-dioxide was obtained.

Diphenylpiperazine α-Dioxide.—The large crystals from warm water are the octahydrate which effloresces rapidly in air (Found : C, 47·3; H, 8·0; N, 6·8. $C_{16}H_{18}O_2N_2,7{\cdot}7H_2O$ requires C, 47·2; H, 8·3; N, 6·9%. A freshly prepared specimen gave peroxidic O, 7·76; loss over P_4O_{10}, 34·9. $C_{16}H_{18}O_2N_2,8H_2O$ requires peroxidic O, 7·73; H_2O, 34·8%). This substance is sparingly soluble in cold water but more readily soluble in alcohol. 60 Ml. of a 0·16M-solution required 0·26 ml. of N/10-sodium hydroxide for titration with phenolphthalein as indicator, as compared with one drop in a similar volume of pure water.

This octahydrate crystallises magnificently in the orthorhombic system with $a : b : c$ = 0·5639 : 1 : 0·7067. The habit is prismatic with the form *q*(011) elongated along the *c* axis, the prisms being terminated by the form *m*(110). Barker classification angles: *cr*(001) : (101) = 51°25′; *am*(100) : (110) = 29°25′; and *bq*(010) : (011) = 54°45′. The extinction is straight on the prism faces and one optic axis emerges nearly perpendicular to *m*.

The anhydrous *diphenylpiperazine α-dioxide* is obtained as a white hygroscopic powder by dehydrating the octahydrate *in vacuo* over phosphoric anhydride (Found : C, 69·8; H, 6·9. $C_{16}H_{18}O_2N_2$ requires C, 71·1; H, 6·5%). Exposed to the atmosphere this substance absorbs water (2 mols.) smoothly in 2 hours without any intermediate break in the process. The *dihydrate* so obtained is also formed by the efflorescence of the octahydrate in air (Found : C, 62·7; H, 7·25; N, 9·4; peroxidic O, 10·2%. $C_{16}H_{18}O_2N_2,2H_2O$ requires C, 62·7; H, 7·25; N, 9·2; peroxidic O, 10·4%). It is quite stable in air and is obtained in well-formed crystals when any of the forms of the α-dioxide is recrystallised from 95% ethanol. It explodes at 281° (corr.). Its solubility in 95·6% alcohol at 25° is 9·15 wt.-% of anhydrous dioxide.

The crystals of dihydrate belong to the holohedral class of the monoclinic system with $a : b : c$ = 2·041 : 1 : 1·500 and β = 87°4′. The habit is usually tabular with *c*(001) large, *a*(100) absent or small, and the pyramid faces *o*(111) and *p*($\bar{1}$11) prominent. Barker classification angles: *cr*(001) : (101) = 35°15′; *ra*(101) : (100) = 51°49′; *am*(100) : (110) = 63°52′ and *bq*(010) : (011) = 33°43′. The extinction on *c* is diagonal.

Reduced in aqueous hydrochloric acid with zinc dust the α-dioxide dihydrate yields the parent diphenylpiperazine base.

The *dihydrochloride* forms a colourless crystalline powder readily soluble in cold water but sparingly in alcohol and exploding at 268° (corr.) (Found : C, 55·1 ; H, 5·5 ; N, 8·7 ; HCl by titration, 21·4. $C_{16}H_{20}O_2N_2Cl_2$ requires C, 55·1 ; H, 5·8 ; N, 8·2 ; HCl, 21·3%). The *sulphate* is a white microcrystalline powder sparingly soluble in cold water or alcohol (Found : C, 52·1 ; H, 5·4 ; H_2SO_4 by titration, 26·9. $C_{16}H_{20}O_6N_2S$ requires C, 52·3 ; H, 5·4 ; H_2SO_4, 26·6%). The *dipicrate* crystallises from alcohol in yellow needles with a straight extinction, sparingly soluble in alcohol but more so in water, and exploding at 221° (corr.) (Found : C, 46·2 ; H, 3·4 ; N, 15·0. $C_{28}H_{24}O_{16}N_8$ requires C, 46·2 ; H, 3·3 ; N, 15·4%). The *dinitrate* is a white powder consisting of microscopic prismatic crystals having a high double refraction and an oblique extinction. It is sparingly soluble in water and explodes at 234° (corr.) (Found : C, 48·3 ; H, 4·7 ; N, 15·3. $C_{16}H_{20}O_8N_4$ requires C, 48·5 ; H, 5·1 ; N, 14·2%). The *oxalate* is a white microcrystalline powder sparingly soluble in cold water and exploding at 289° (corr.) (Found : C, 59·4 ; H, 5·5. $C_{18}H_{20}O_6N_2$ requires C, 59·8 ; H, 5·6%). The *monoperchlorate* was obtained, even in presence of an excess of perchloric acid, as a sparingly soluble microcrystalline powder exploding with a bright flash when heated (Found : C, 51·0 ; H, 4·8 ; N, 7·6 ; $HClO_4$ by titration, 27·5. $C_{16}H_{19}O_6N_2Cl$ requires C, 51·8 ; H, 5·2 ; N, 7·6 ; $HClO_4$, 27·1%). The *platinichloride* is a yellow sparingly soluble precipitate (Found : Pt, 28·6. $C_{16}H_{20}O_2N_2Cl$ Pt requires Pt, 28·7%). The *aurichloride* was obtained as a sparingly soluble yellow precipitate when gold chloride solution was added to the aqueous solution of the α-dioxide whether neutral or acid. It decomposes explosively at 182° (corr.) (Found : C, 31·4 ; H, 3·3 ; Cl, 22·2 ; Au, 32·9, 32·2. $C_{16}H_{19}O_2N_2Cl_4Au$ requires C, 31·5 ; H, 3·1 ; Cl, 23·2 ; Au, 32·3%). On the other hand, when the solution of the α-dioxide was added to an excess of gold chloride in aqueous hydrochloric acid, the precipitate, although very little different in composition (Found : Au, 31·7%), was extremely explosive, detonating on scratching or on heating to 90°. For analysis it was moistened and treated with sulphur dioxide, then dried, and ignited. The *ferrocyanide* forms sparingly soluble yellow needles with a straight extinction, which appear to be a dihydrate (Found : C, 56·7 ; H, 5·6 ; N, 17·9. $C_{38}H_{44}N_{10}O_6Fe$ requires C, 57·5 ; H, 5·7 ; N, 17·7%).

Diphenylpiperazine β-Dioxide.—The substance isolated from the final mother-liquors of the crystallisation of the crude dioxides crystallised from water in tufts of hair-like crystals or bunches of radiating prismatic needles and proved to be a *dihydrated hydrogen peroxide complex* of the β-dioxide (Found : C, 56·4, 56·7 ; H, 6·5, 6·7 ; N, 8·0. $C_{16}H_{24}O_6N_2$ requires C, 56·5 ; H, 7·1 ; N, 8·2%. A tetrahydrate of the β-dioxide would require C, 56·4 ; H, 7·7 ; N, 8·2%). This substance is many times as soluble in water as the α-isomeride. 95·6% Alcohol at 25° dissolves 1·16 wt.-% of it. It explodes at 210° (corr.) and remains unchanged when kept *in vacuo* over phosphoric anhydride.

The presence of molecular hydrogen peroxide in this compound was confirmed by direct tests. The material available being insufficient for repeated precise reductometric analysis by our usual procedure, two experiments were made as follows. (*a*) 10 Mg. each of the α-dioxide dihydrate and the β-dioxide complex were separately distilled with aqueous 1% sulphuric acid. The distillate from the β-specimen gave a positive reaction for peroxide with iodide and starch whereas that from the α-dioxide did not. (*b*) 10 Mg. each of the α-dioxide dihydrate and of the β-dioxide complex were separately dissolved in aqueous sulphuric acid (5 ml. of 2N.) in a stream of nitrogen, and 1 ml. of 5% potassium iodide and 1 ml. of 1% starch solution added to each. The β-dioxide complex gave an instantaneous blue colour; the α-dioxide developed a blue colour when kept. Both were then very slowly titrated with N/10-thiosulphate. The α-dioxide required 1·40 ml., the β-dioxide complex 2·15 ml. of thiosulphate solution. The latter thus has a content of total peroxidic oxygen 50% higher than the former corresponding to the presence of one mol. of hydrogen peroxide in the latter.

The β-dioxide complex was reduced by zinc dust in acid solution to the parent diphenylpiperazine.

The following salts of the β-dioxide were prepared : the *dipicrate*, small yellow needles with a high double refraction and a straight extinction, which explode at 207° (corr.) (Found : C, 46·1 ; H, 3·4 ; N, 15·2. $C_{28}H_{24}O_{14}N_8$ requires C, 46·2 ; H, 3·3 ; N, 15·4%) ; the *dihydrochloride*, a white microcrystalline powder (Found : C, 55·4 ; H, 6·1 ; N, 7·7. $C_{16}H_{20}O_2N_2Cl_2$ requires C, 55·1 ; H, 5·8 ; N, 8·2%) ; the *dinitrate*, colourless thin plates, rhomb-shaped or elongated with oblique ends, having low double refraction and an oblique extinction, which explode at 224° (corr.) (Found : C, 48·2 ; H, 5·3. $C_{16}H_{20}O_8N_4$ requires C, 48·5 ; H, 5·1%). The β-dioxide also yields an aurichloride, a sulphate, and a perchlorate more soluble in alcohol than the α-salts.

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