LXXVI.—*A Contribution to the Stereochemistry of Tervalent Nitrogen.*

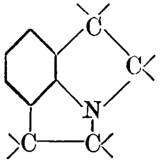
By JOSEPH GILBERT JACKSON and JAMES KENNER.

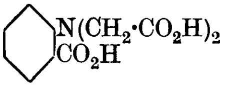
ALTHOUGH the Hantzsch–Werner hypothesis has been fully substantiated through the researches of Mills and his collaborators as a means of explaining the isomerism of the oximes and similar compounds, its application to compounds in which three separate groups are attached to the nitrogen atom has been much less successful. It is unnecessary to refer in detail to the earlier work, since this has been critically reviewed by Meisenheimer (*Ber.*, 1923, **56**, 1353; 1924, **57**, 1715, 1744; *Annalen*, 1924, **438**, 217), to whom we owe valuable contributions to the subject. At the present time, the evidence in favour of a non-planar configuration of compounds of tervalent nitrogen is to be seen in the dipolarity of the ammonia molecule, which confers on it the capacity of participation in metal-ammine formation (compare Magnus, *Z. anorg. Chem.*, 1922, **124**, 289; Hund, *Z. Physik*, 1925, **31**, 82); the existence of quinuclidine (compare Meisenheimer, *Annalen*, 1920, **420**, 190); a difference in the readiness with which the two forms of 4 : 5-dimethoxy-4 : 5-dihydroglyoxalone are converted into 5-methoxy-4 : 5-diphenyl*iso*glyoxalone (Biltz, *Annalen*, 1909, **368**, 156; *Naturwiss.*, 1926, **29**, 1678); the work of Moore (P., 1914, **30**, 183); and the isomerism of methyl*iso*pelletierine with *dl*-methylconhydrinone (Hess, *Ber.*, 1919, **52**, 1622; 1920, **53**, 129; Hess and Grace, *Annalen*, 1925, **441**, 101). But, apart from this last instance, the search for isomerides demanded by a non-planar configuration has been unsuccessful, and it would therefore appear that in general the non-planar readily passes into a planar form, from which the original or its enantiomorph may be regenerated, or else that the normal configuration is plane (compare Meisenheimer, *Ber.*, 1924, **57**, 1747).

Before, however, such conclusions can be accepted, it is desirable that the negative results on which they rest should be supplemented by positive evidence. This would be supplied by the preparation of a compound in the molecule of which a nitrogen atom is common to two ring structures, which are at the same time plane and coplanar. Since, so far as we know, there is no evidence available which renders doubtful the plane configuration of five-membered ring structures, it would appear that these conditions would be fulfilled by a structure of type (I), if Kekulé's formula for benzene and its derivatives be accepted.

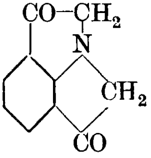
The validity of the latter provision, however, requires examination, since the evidence of crystal structure indicates the possibility that the benzene nucleus may not always be plane. It was therefore desirable, before proceeding to work in the direction indicated on nitrogen compounds, to examine the behaviour of a compound, otherwise analogous, but containing in place of the nitrogen atom that of an element of which the stereochemical relationships are known to be closely similar to those postulated for nitrogen by the Hantzsch–Werner hypothesis. Since, then, anthranilodiacetic acid (II) appeared from the literature to be readily accessible, and the conditions suitable for the formation of the indoxylic ring structure, on which (III) is based, are well known, β-phenylglutaric acid (IV) was selected as its analogue for preliminary work.

(I.)



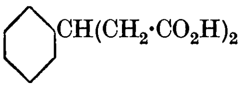


(II.)

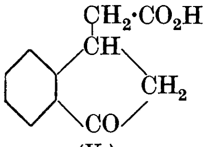


(III.)

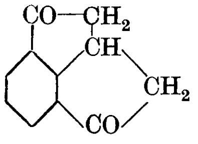
β-Phenylglutaric acid was easily converted under the influence of sulphuric acid into 1-*ketohydrindene*-3-*acetic acid* (V), but a careful search for any non-acidic, ketonic product, such as (VI), was unsuccessful. Similarly β-*phenylglutaryl chloride* underwent only



(IV.)

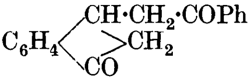


(V.)



(VI.)

partial internal condensation under the influence of aluminium chloride. In the first experiments on this reaction, the light petroleum used as solvent was not purified, so that a ketonic product corresponding in composition to ω-3-*hydrindonylacetophenone* (VII) was also isolated.

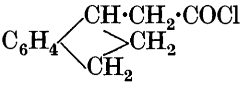


$$C_6H_4{<}\begin{matrix}CH\cdot CH_2\cdot COPh\\ CO\end{matrix}{>}CH_2$$

(VII.)

$C_6H_5\cdot CH(CH_2\cdot COPh)_2$

(VIII.)



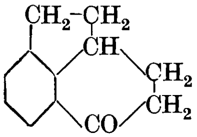
$$C_6H_4{<}\begin{matrix}CH\cdot CH_2\cdot COCl\\ CH_2\end{matrix}{>}CH_2$$

(IX.)

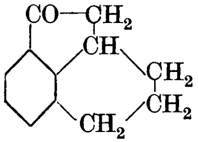
Its nature was demonstrated by its absence from among the products of reaction when aromatic components were removed from the solvent, and by its reappearance when benzene was added to the mixture employed. The formation of (VII) rather than αγε-triphenylpentane-αε-dione (VIII) under these conditions is an interesting illustration of the usual tendency towards intra- rather than inter-molecular condensation, and throws into stronger relief the significance of the failure to obtain (VI).

These results accord with the earlier observation by von Braun, Danziger, and Kohler that α-hydrindylacetyl chloride (IX) cannot be made to undergo internal condensation and, it may be noted, the combined results supply direct evidence against Sachse's benzene formula, according to which the ring system of (VI) is almost free from strain.

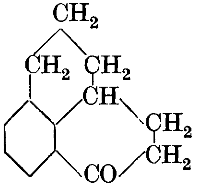
On the other hand, the results are in accord with the Kekulé formula and support, although possibly they do not finally demonstrate, the truth of the suggestion that two five-membered rings associated with a benzene nucleus in the manner contemplated must be coplanar. In regard to these rings, it was recognised that, for the present purpose, current views in regard to the configuration of saturated ring structures make it necessary to limit the number of atoms composing the ring to five. Experimental confirmation of this has recently been supplied by von Braun and Reutter, who were able to prepare the ketones (X), (XI), and (XII) by the Friedel–Crafts reaction (*Ber.*, 1926, **59**, 1922).*



(X.)



(XI.)



(XII.)

The fact that these compounds can be prepared serves at least to weaken any objection to the test here proposed, based on a possible difference in readiness of condensation between the 1 : 2- and the 1 : 6-positions in the benzene nucleus when the two are to be operative simultaneously (compare Marckwald, *Ber.*, 1890, **23**, 1015; *Annalen*, 1893, **274**, 331; 1894, **279**, 1).

A more serious defect lies in the fact that a valency angle of 120° in the case of a nitrogen atom might be sufficiently great to inhibit the possibility of forming the ring system (III). Possibly for this reason, although it was found possible to prepare *indoxylacetic acid*,†

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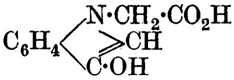
* In view of von Braun and Reutter's work, it is necessary to point out that this work was completed in 1924, that all the considerations here advanced were embodied in a thesis presented by one of us (J. G. J.) in that year for the degree of Doctor of Philosophy in the University of Sheffield, and that models and specimens thereof were on view at the British Empire Exhibition at Wembley in 1924.

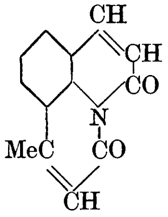
† During the performance of this portion of the work I was unable to exercise any supervision. The careful work involved is therefore to be credited to my collaborator.—J. K.



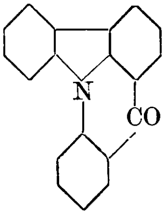
$$C_6H_4\begin{array}{l}\diagup N\cdot CH_2\cdot CO_2H \\ \diagdown\!\!\!> CH \\ \diagdown C\cdot OH\end{array}$$

(XIII), after suitable revision of the procedure described in D.R.-P. 128955 (Friedlaender, " Fortschritte der Teerfarbenfabrikation," VI, p. 559), no satisfactory evidence of the formation of (III) could be obtained. In certain circumstances, detailed in the experimental portion of this paper, small quantities of a compound of the desired composition were obtained, but the conditions were such as to make it necessary to regard this result as not entirely conclusive.

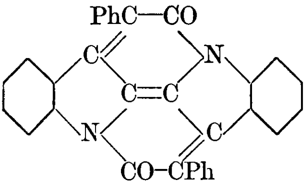
Although the outcome of the experimental work now described is thus in some respects indefinite, we venture to think that the mode of approaching the main problem on which it is based is not without value; for, if the benzene nucleus be regarded as a guide in the manner discussed, a scrutiny of the following formulæ of compounds described in the literature indicated under them will show it to be difficult to escape the conclusion that, if their respective constitutions have been correctly assigned, a plane distribution of groups round the nitrogen atom is probable.



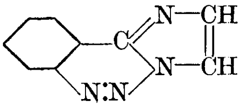
Reissert, *Ber.*, 1892, **25**, 108.



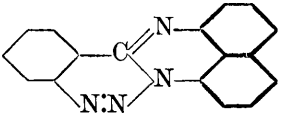
Eckert, Seidel, and Endler, *J. pr. Chem.*, 1922, **104**, 85.



Posner and Pyl, *Ber.*, 1923, **56**, 31; D.R.-P. 260243 (Friedlaender, *op. cit.*, XI, p. 293).

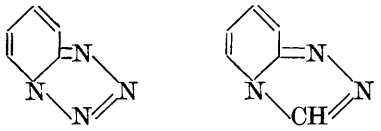


Balaban and King, J., 1925, **127**, 2704.

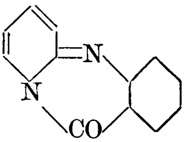


Sachse and Steiner, *Ber.*, 1909, **42**, 367.

If the same assumption be permissible in regard to the pyridine nucleus, the following compounds also should have plane configurations:



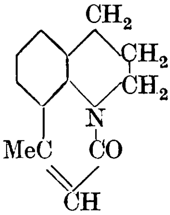
Marckwald and Rudszik, *Ber.*, 1903, **36**, 1111.



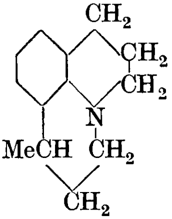
Seide, *Annalen*, 1924, **440**, 311.

In order, however, that a final conclusion may be reached it will be necessary to apply the usual tests for the asymmetry which would accompany non-planar configurations in any of these cases.

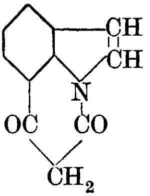
The considerations mentioned in connexion with the results of von Braun and Reutter indicate that the existence of the following compounds is less conclusive in respect of the question under discussion :



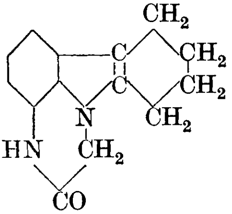
Reissert, *Ber.*, 1891, **24**, 841.



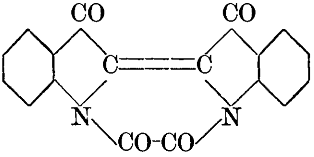
Reissert, *Ber.*, 1892, **25**, 118; Pinkus, *ibid.*, p. 2798; von Braun and Neumann, *ibid.*, 1919, **52**, 2015.



Bamberger and Steinitzki, *Ber.*, 1893, **26**, 1300; von Braun and others, *ibid.*, 1918, **51**, 1215.



Perkin and Riley, J., 1923, **123**, 2400.



Friedlaender and Sandes, *Ber.*, 1924, **57**, 641.

EXPERIMENTAL.

β-Phenylglutaric acid was prepared by hydrolysis of ethyl β-phenylpropane-ααγ-tricarboxylate with hydrobromic acid (b. p. 125°). The crude material (yield, 90% : Avery and Bouton, *Amer. Chem. J.*, 1898, **20**, 512, obtained only 70%), after crystallisation from dilute hydrochloric acid, gave a 75% yield of pure material, m. p. 139°.

1-*Ketohydrindene*-3-*acetic acid* (V) was produced when β-phenylglutaric acid (40 g.) was added rapidly, but in portions, to sulphuric acid (480 g.) at 150°. Immediate addition of the solution to cold water (2500 c.c.) caused the condensation product (30 g.) to separate in octagonal plates, completely soluble in sodium carbonate solution. Similarly, the material (1 g.) recovered by extraction of the mother-liquor with ether contained no purely ketonic substance. After crystallisation from benzene, the acid melted at 151° (Found :

C, 69·6; H, 5·2; equiv., 190. $C_{11}H_{10}O_3$ requires C, 69·6; H, 5·2%; equiv., 190).

The *semicarbazone* (Found: N, 17·0; equiv., 248. $C_{12}H_{13}O_3N_3$ requires N, 17·0%; equiv., 247) formed colourless, irregular prisms, m. p. 268° (decomp.). The *methyl* ester separated from benzene in large, hexagonal tablets, m. p. 65° (Found: C, 71·2; H, 6·0. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%), and furnished a *semicarbazone*, m. p. 152° (Found: N, 16·5. $C_{13}H_{13}O_3N_3$ requires N, 16·1%), and a 2-iso*nitroso*-derivative, m. p. 167° (decomp.) (Found: N, 6·2. $C_{12}H_{11}O_4N$ requires N, 6·0%). The last compound was prepared by adding hydrochloric acid (*d* 1·17; 0·5 c.c.) to a solution of the ester (3·2 g.) and freshly prepared amyl nitrite (2·5 g.) in methyl alcohol (102 c.c.) at 40°, and maintaining this temperature for 3 hours after the initial vigorous reaction had subsided.

The *ethyl* ester, a viscous liquid, b. p. 194—200°/13 mm. (Found: C, 72·0; H, 6·4. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%), similarly yielded a *semicarbazone*, m. p. 131—132° (Found: N, 15·2. $C_{14}H_{17}O_3N_3$ requires N, 15·2%), and a 2-iso*nitroso*-derivative, prisms, m. p. 193° (decomp.) (Found: N, 6·1. $C_{13}H_{13}O_4N$ requires N, 5·7%). When either the acid or the methyl ester was treated in ethyl-alcoholic solution with amyl nitrite and hydrochloric acid, the respective products melted at 192° (decomp.) (Found: N, 5·8, 5·9%) and at 193° (decomp.) (Found: N, 5·7%), and neither depressed the melting point of the derivative just described.

β-Phenylglutaryl Chloride.—The action of thionyl chloride, phosphorus pentachloride, or phosphorus trichloride upon the acid under the usual conditions led to the formation either of the well-known anhydride, m. p. 105° (Avery and Bouton, *loc. cit.*, p. 513; Vorländer, *Annalen*, 1901, **320**, 85), or of charred material, from which nothing definite could be isolated. An intimate mixture of the sodium salt (25 g.) with phosphorus pentachloride (40 g.) was therefore gently warmed for ½ hour after the initial reaction had subsided. The crude chloride (11 g.), b. p. 170—190°/15 mm., slowly deposited large plates, which melted at 46° after crystallisation from a mixture of carefully dried benzene and light petroleum. Owing to the facility with which the compound is converted into the anhydride, even on exposure to the atmosphere, the results of analysis were less satisfactory than usual (Found: Cl, 27·7; equiv., 62·5. $C_{11}H_{10}O_2Cl_2$ requires Cl, 28·9%; equiv., 61·2).

Action of Aluminium Chloride upon β-Phenylglutaryl Chloride.—Aluminium chloride (12 g.) was added to a solution of the crude chloride (9 g.) in light petroleum (100 c.c., b. p. 70—90°), which had been freed from aromatic compounds by treatment with nitrating acid, and finally the mixture was warmed until the evolution of hydrogen chloride ceased. After the residue had been treated with ice, the light petroleum was volatilised in steam and shown not to have carried with it any of the products of reaction. These were extracted from the aqueous liquor by means of ether, and ketohydrindeneacetic acid (3·1 g.) was removed from the extract by means of sodium carbonate solution and identified in the usual manner with that already described. The non-acidic material (1·1 g.) in the ethereal extract was a black tar, from which a gummy distillate (0·5 g.) was obtained by distillation under reduced pressure. No ketonic constituents could be detected in this by means of semicarbazide acetate.

When unpurified light petroleum was employed in an otherwise similar experiment, a ketonic substance was isolated. This was identical with that obtained when a mixture of purified light petroleum (90 c.c.) with benzene (3·2 g.) was employed as solvent. Under these conditions ketohydrindeneacetic acid (1 g.) and non-acidic material (2 g.) were obtained. The latter, after distillation under reduced pressure and crystallisation from benzene–light petroleum, furnished yellowish, hexagonal plates (1·15 g.), m. p. 78°. Its composition was in accord with the formula of ω-3-*hydrindonylacetophenone* (VII) (Found: C, 81·8, 82·1; H, 5·7, 5·5; *M*, ebullioscopic in benzene, 266. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%; *M*, 250). The *disemicarbazone*, hexagonal prisms, m. p. 233° (decomp.) (Found: N, 23·4. $C_{19}H_{20}O_2N_6$ requires N, 23·0%), and the *dioxime*, colourless prisms, m. p. 179° after dehydration (Found: Loss in weight at 130°, 8·5. $C_{17}H_{16}O_2N_2,1\frac{1}{2}H_2O$ requires H_2O, 8·8%. Found in the dried material: N, 10·0. $C_{17}H_{16}O_2N_2$ requires N, 10·0%), were prepared.

Anthranilodiacetic Acid (II).—The conditions of preparation described in D.R.-P. 128955 (Friedlaender, *op. cit.*, VI, p. 559) result in the formation of a large quantity of phenylglycine-*o*-carboxylic acid and only a small quantity of the desired acid. Vorländer and Mumme's method (*Ber.*, 1900, **33**, 3182) also is not very efficacious. Eventually a mixture of crystallised sodium carbonate (200 g.), water (1000 c.c.), anthranilic acid (60 g.), and chloroacetic acid (100 g.) was boiled for 8 hours, alkalinity being just maintained by suitable addition of sodium carbonate. Finally, the cooled deep green liquid was treated with 50% sulphuric acid (70 c.c.). The precipitate, together with the small amount obtained from the liquor after the addition of more acid (30 c.c.), furnished pure anthranilodiacetic acid (50 g.), m. p. 216° (decomp.) after crystallisation from water (400 c.c.). The material (40 g.) contained in the liquor from this crystallisation was chiefly phenylglycine-*o*-carboxylic acid, which was treated with more sodium chloroacetate.

The acid crystallised from water in colourless, octagonal plates, m. p. 216° (decomp.) (Vorländer and Mumme, *loc. cit.*, give 212°) [Found : equiv., 87. Calc. for $C_8H_8N(CO_2H)_3$: equiv., 84], and its solution in water or alcohol was not fluorescent. The blue fluorescence mentioned in D.R.-P. 128955 is due to phenylglycine-*o*-carboxylic acid, as are also the deep yellowish-brown colour of the acid there described and the dark red coloration it develops in not too dilute alcoholic solution on treatment with ferric chloride. Phenylglycine-*o*-carboxylic acid melts at 215° (decomp.), and a mixture of the two acids at about 200°.

Indoxylacetic Acid (XIII).—This acid is not obtainable by the process described in D.R.-P. 128955. In order to prepare it, anthranilodiacetic acid (16 g.) and a solution of sodium hydroxide (30 g.) in water (25 c.c.) were heated together with constant stirring. Apart from evolution of steam, no change occurred at 150°. At 200°, a few drops of water were added to facilitate disintegration of the hard lumps of material, and when this was complete and the mass of a uniform brown colour and of the consistency of clay, the mixture was allowed to cool. The solution of the cold melt (45 g.) in hot water (80 c.c.) furnished the crude acid on acidification with 50% sulphuric acid (60 c.c.). By crystallisation from hot water (100 c.c.), the pure acid (10 g.) was obtained in radiate clusters of monohydrated, hexagonal plates, which appeared green in the mass but yellow under the microscope (Found : loss in weight at 80°, 8·3. $C_{10}H_9O_3N,H_2O$ requires H_2O, 8·6%). The anhydrous acid melted at 165° (decomp.) (Found : C, 62·8, 63·2; H, 4·9, 5·0; N, 7·3. $C_{10}H_9O_3N$ requires C, 62·8; H, 4·7; N, 7·3%).

O-*Methylindoxylacetic Acid.*—A solution of indoxylacetic acid (5 g.) in 20% aqueous sodium hydroxide (6 c.c.) was gradually treated with methyl sulphate (8 g.) and a further quantity of alkali (14 c.c.). After being shaken for 3 days, the homogeneous light brown liquid yielded on acidification a reddish oil, which slowly solidified, and crystallised from aqueous methyl alcohol in monohydrated, colourless, hexagonal prisms (3·5 g.) (Found : loss in weight at 80°, 8·2, 8·4. $C_{11}H_{11}O_3N,H_2O$ requires H_2O, 8·1%), sparingly soluble in water, but easily soluble in sodium carbonate solution and in methyl and ethyl alcohols. The anhydrous acid melted at 141—142° and contained one methoxyl group [Found : C, 64·4; H, 5·5; N, 7·1; OMe, 15·5; equiv., 206. $C_9H_7N(OMe)\cdot CO_2H$ requires C, 64·4; H, 5·5; N, 6·8; OMe, 15·1%; equiv., 206].

Fusion of Sodium Indoxylactetate with Sodamide.—The sodium salt for this purpose was prepared as already described, with the exception that no water was added at 200°, but the mixture was thoroughly stirred and maintained at 200—210° for 2 minutes. In order to prevent further reaction, the yellow, powdery mass was then quickly spread in a thin layer.

The interaction between this material and sodamide is very violent and the following procedure was finally adopted to secure some control of the reaction, and permit the use of sufficient condensing agent. Sodamide (40 g.) was melted and cooled until solidification commenced at about 150°. The crude salt (50—60 g.) from two of the fusions described above was then gradually added with continuous stirring. Finally, the temperature was carefully raised to 180—200°; then in spite of continuous stirring and cooling with cold water, a vigorous reaction occurred, accompanied by a strong odour of carbylamine and a further rise of temperature to 250°. When the main reaction had subsided and the temperature had been maintained at 220° for a further half-hour, the product was dissolved in hot water (200 c.c.) and acidified with 50% sulphuric acid (120 c.c.). In case the desired product, like indoxyl itself (compare Vorländer and Dresche, *Ber.*, 1902, **35**, 1701), might be unstable in presence of air, the tarry precipitate was dissolved in 20% sodium hydroxide solution (50 c.c.) and treated with methyl sulphate (20 c.c.). By repeated extraction with ether, a small quantity of material was obtained which crystallised from water in colourless needles (0·6 g.), m. p. 163°. Although this product could not be isolated unless the methylation process was carried out, its composition, remarkably enough, agreed with that of the compound sought in the experiment (Found: C, 63·8, 63·5, 63·1; H, 5·3, 5·5, 5·4; N, 14·7; *M*, by Rast's method, 210. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%; *M*, 190).

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