CLII.—*Piperidine as a General Reagent for the Determination of the Constitution of Halogenonitro-compounds. The Nitration of 4 : 4′-Dihalogenodiphenylmethane and -s-diphenylethane.*

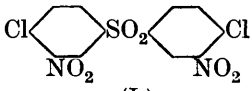
By Raymond James Wood Le Fèvre and Eustace Ebenezer Turner.

In this paper are described a number of piperidino-compounds the preparations and properties of which have led us to the conclusion that, as a reagent for reactive halogen atoms, piperidine is superior to alcoholic ammonia, aromatic amines, alkali alkyloxides, etc. The advantages contributing to this superiority include the following : (1) The substituted phenylpiperidines produced are as a rule highly crystalline. (2) Piperidine appears to react much more readily than most bases with mobile halogen atoms. (3) The interaction of piperidine and halogeno-compounds is generally characterised by the absence of by-products, whereas with hydrazines and alkali alkyloxides, for example, a mixture of products is usually obtained (compare Brand, *J. pr. Chem.*, 1903, **67**, 145; Lobry de Bruyn, *Rec. trav. chim.*, 1890, **9**, 203).

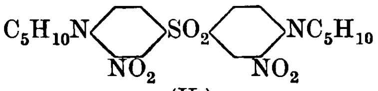
A few isolated piperidine compounds have been described in the past, notably by Lellmann and by Borsche. Lellmann was, however, not concerned with piperidine as a reagent, and Borsche, in employing piperidine, uses a method which in our hands has given most unsatisfactory yields (see Experimental).

Some examples follow illustrating the use of piperidine as a general reagent for reactive halogen atoms present in a number of compounds of known constitution.

The constitution (I) of the product of nitrating 4 : 4′-dichlorodiphenylsulphone was established by Ullmann and Korselt (*Ber.*, 1907, **40**, 643), using aniline and ammonia as reagents for reactive chlorine. Piperidine readily converts (I) into 3 : 3′-*dinitro*-4 : 4′-*dipiperidinodiphenylsulphone* (II).



(I.)



(II.)

Similarly, 2 : 5-dibromonitrobenzene is converted by piperidine into 4-*bromo*-2-*nitropiperidinobenzene*. In the case of 2 : 4-dichloronitrobenzene both halogens rapidly react with piperidine to give 1-*nitro*-2 : 4-*dipiperidinobenzene*.

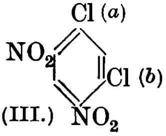
3 : 4-Dichloronitrobenzene would be expected to react once only

with piperidine and does so to give 2-*chloro*-4-*nitropiperidinobenzene.* 2 : 4 : 5-Trichloronitrobenzene, however, gives 4 : 5-*dichloro*-1-*nitro*-2-*piperidinobenzene* and not 5-chloro-1-nitro-2 : 4-dipiperidinobenzene, a fact which may be attributed to the combined steric and deactivating effects of the 5- on the 4-chlorine atom. The constitution of the product is proved below.

On the other hand, the introduction of a third group, *e.g.*, carboxyl or carbethoxyl, which by itself has feeble activating effect, produces a very marked exaltation of reactivity when its effect supports that of the nitro-group. Thus, towards piperidine, ethyl 2-chloro-5-nitrobenzoate, 4-chloro-3-nitrobenzoic acid, and 2 : 4-dichloronitrobenzene react apparently with the same vigour as does 1-chloro-2 : 4-dinitrobenzene.

The binuclear halogenonitro-compounds mentioned in this paper are all further examples of the same fact, *i.e.*, they react much more rapidly and completely than does either *o*- or *p*-chloronitrobenzene. Similarly, Borsche and Exss (*Ber.*, 1923, **46**, 2353) obtained quantitative results showing that 4-chloro-3-nitroazobenzene was intermediate between 1-chloro-2-nitro- and 1-chloro-2 : 4-dinitro-benzene in degree of reactivity.

The investigation of 1 : 3-dichloro-4 : 6-dinitrobenzene by previous workers has already raised many interesting points. Thus, Borsche and Bahr (*Annalen*, 1913, **402**, 81) considered that in this compound (III) one chlorine atom (*a*) is less reactive than the other (*b*).



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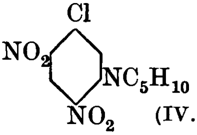

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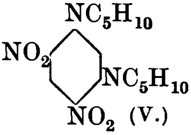
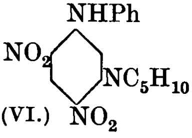


(V.)

The evidence for this assertion, apart from a very general reference to the work of " Nietzki and others " on the interaction of amines with this compound, consisted in the facts that ethyl sodio-malonate and -acetoacetate each reacted with only one chlorine atom, and that a second similar group was introduced only with difficulty. In the same paper there is described the compound (IV), and we therefore expected to find that the dichlorodinitrobenzene would, even under conditions sufficing to effect the conversion, *e.g.*, of 2 : 4-dichloronitrobenzene into 1-nitro-2 : 4-dipiperidinobenzene, give mainly (IV) and that the corresponding *dipiperidino*-compound (V) would be obtainable only with difficulty. Actually the reverse was the case. Borsche and Bahr's compound (IV) was certainly obtainable if care were exercised, but in presence of a slight excess of piperidine there occurred rapid formation of (V), which is very readily obtainable by warming the dichlorodinitrobenzene with enough piperidine to dissolve it. Moreover, the chlorine atom in (IV) is sufficiently mobile to react rapidly with aniline to give 4 : 6-*dinitro*-3-*anilino*-1-*piperidinobenzene* (VI).

Kenner (J., 1914, **105**, 2717) and Davies and Hickox (J., 1922, **121**, 2640) also have criticised some of Borsche's conclusions in connexion with other work on 1 : 3-dichloro-4 : 6-dinitrobenzene. Similarly, we are unable to agree with Hodgson (*J. Soc. Dyers and Col.*, 1926, 42) that the existence of two forms of 1-chloro-3-bromo-4 : 6-dinitrobenzene is capable of satisfactory explanation only by means of Borsche's conceptions, since at least six halogenonitrobenzenes, including 1 : 3-dibromo-4 : 6-dinitrobenzene (Jackson and Cohol, *Amer. Chem. J.*, 1903, **26**, 4), have been found to exhibit polymorphism.

1 : 3 : 5-Tribromo-2 : 4-dinitrobenzene is readily converted by two mols. of piperidine into a compound which we regard as 1 : 3-*dibromo*-2 : 4-*dinitro*-5-*piperidinobenzene* (VII), since (Borsche and Rantscheff, *Annalen*, 1911, **379**, 152) the halogen atom in 2-chloro-1 : 3-dinitrobenzene is less reactive than that in 1-chloro-2 : 4-dinitrobenzene. Excess of piperidine converts the original tribromo-compound with violence into 2 : 4-dinitro-1 : 3 : 5-tripiperidinobenzene (VIII), a compound obtained by Borsche and Trautner (*Annalen*, 1926, **447**, 1) from 1 : 3 : 5-trichloro-2 : 4-dinitrobenzene. These authors report the m. p. as 147—148°, but it actually melts 30° higher, and it is possible that this affords another illustration of the unsatisfactory nature of Borsche's method of using piperidine (see Experimental).



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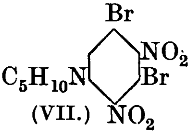

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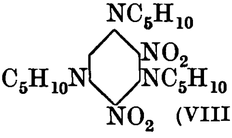
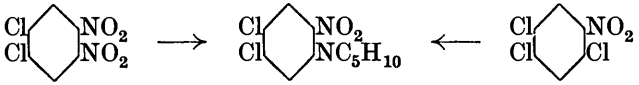


(VIII.)

The possibility of a reaction occurring owing to the activating effect of an ortho-para- on a meta-orienting substituent in the *m*-position to it, which has been observed in a few instances, *e.g.*, Tiemann (*Ber.*, 1891, **24**, 709), Kenner and others (J., since 1914), and Morgan (J., 1920, **117**, 784; 1921, **119**, 1537), has not been overlooked. It seems, however, that when there is no great crowding of groups, particularly nitro-groups, evidence based on the removal of halogen is trustworthy, *i.e.*, in general, only that halogen is labile which is in the *o*- or *p*-position to the nitro-group.

A reaction of piperidine with a compound having a labile nitro-group has been utilised to prove the constitution of the product obtained from 2 : 4 : 5-trichloro-1-nitrobenzene and piperidine.

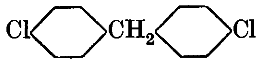


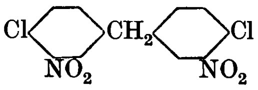
Thus, 1 : 2-dichloro-4 : 5-dinitrobenzene reacts readily with piperidine to give 4 : 5-dichloro-2-nitropiperidinobenzene, a nitro-group being replaced by a piperidino-group.

4 : 4′-Dichlorodiphenylmethane (IX) on nitration gave mainly 4 : 4′-*dichloro*-3 : 3′-*dinitrodiphenylmethane* (X), the constitution of which follows from its conversion, by piperidine, into 3 : 3′-*dinitro*-4 : 4′-*dipiperidinodiphenylmethane.*

The nitration of 4 : 4′-dibromo-*s*-diphenylethane (XI) was far from quantitative, but a nitro-derivative was isolated with a m. p. ascribed in the literature to 4 : 4′-dibromo- ? : ?-dinitro-*s*-diphenylethane, and therefore evidently the main, or most readily isolable, product of the nitration. Since piperidine converted this compound into a *dipiperidino*-compound, it is clearly 4 : 4′-*dibromo*-3 : 3′-*dinitro*-s-*diphenylethane* (XII).

(IX.)





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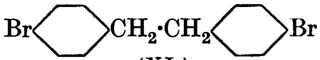

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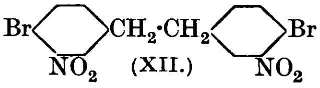


(XII.)

EXPERIMENTAL.

General Method of Preparation of Piperidino-derivatives.—Except where otherwise stated, these derivatives were prepared by gently boiling, for 3 minutes, the halogenonitro-compound with that amount of piperidine which effects complete solution. In cases where interaction was violent, a solvent such as alcohol was also used. As a rule, reaction was accompanied by the appearance of a bright red colour, the cooled product usually setting to a crystalline magma of piperidine hydrohalide. Water was added, and frequently solidification then ensued. Two methods of inducing crystallisation were particularly effective in cases of delayed solidification due to the presence of a trace of water or of unchanged halogen-compound : (*a*) The oily piperidino-derivative was dissolved in benzene, and the solution left over anhydrous sodium sulphate for a few minutes. Evaporation of the filtered solvent followed by desiccation in a vacuum, in most cases caused solidification. (*b*) In other cases, the oily derivative was warmed with dilute mineral acid, and the liquid was cooled, filtered, and basified. These two methods are referred to below as treatments (*a*) and (*b*) respectively.

3 : 3′-*Dinitro*-4 : 4′-*dipiperidinodiphenylsulphone* (II).—4 : 4′-Dichloro-3 : 3′-dinitrodiphenylsulphone gave a yellow coloration with cold piperidine and reacted violently with the latter on warming. The crude product was solid, was only slightly soluble in carbon tetrachloride, chloroform, benzene, or toluene, but was more soluble in acetone and methyl alcohol. It separated from methylated spirit in long, yellow needles, m. p. 183·5° (Found : N, 11·9. $C_{22}H_{26}O_6N_4S$ requires N, 11·8%).

4-*Bromo*-2-*nitropiperidinobenzene*.—The oily product of the interaction of 2 : 5-dibromonitrobenzene did not solidify after treatment (*a*), but did so after treatment (*b*). It separated from alcohol in deep red prisms, m. p. 48—49° (Found : Br, 28·1. $C_{11}H_{13}O_2N_2Br$ requires Br, 28·1%).

1-*Nitro*-2 : 4-*dipiperidinobenzene*.—The product of interaction of 2 : 4-dichloronitrobenzene and piperidine solidified after treatment (*a*). The crude piperidino-derivative was a mass of red-orange needles, m. p. 63—64°. When the solution in alcohol was cooled, there was a sudden deposition of radiating bunches of hexagonal leaflets, m. p. 67—68° (Found : N, 14·8. $C_{16}H_{23}O_2N_3$ requires N, 14·5%).

2-*Chloro*-4-*nitropiperidinobenzene*.—3 : 4-Dichloronitrobenzene and piperidine gave a yellow solution in the cold, and reacted vigorously on warming. Treatment (*b*) was necessary to induce solidification and then crystallisation from aqueous alcohol gave small, lemon-yellow plates, m. p. 47—48° (Found : N, 12·4; Cl, 14·9. $C_{11}H_{13}O_2N_2Cl$ requires N, 11·6; Cl, 14·8%).

4 : 5-*Dichloro*-1-*nitro*-2-*piperidinobenzene*.—2 : 4 : 5-Trichloronitrobenzene reacted with piperidine to give an oil which solidified only after treatment (*a*). It then separated from alcohol in red prisms, m. p. 64—65° (Found : Cl, 25·9. $C_{11}H_{12}O_2N_2Cl_2$ requires Cl, 25·8%).

5-*Nitro*-2-*piperidinobenzoic Acid and the Corresponding Ethyl Ester*.—*o*-Chlorobenzoic acid (55 g.) was added to 300 g. of nitric acid (*d* 1·5), and the resulting solution, after being left for 10 minutes, was poured on ice. The crude nitro-acid (42·5 g.) melted at 163—164°, whereas Hübner, for the pure acid, gives 165° (*Annalen*, 1884, **222**, 195).

The 2-chloro-5-nitrobenzoic acid reacted readily with piperidine to give the *piperidino-acid*, m. p. 201—202°, and when heated with alcohol and concentrated sulphuric acid gave the ethyl ester as a pale yellow oil, b. p. 190—191°/16 mm., solidifying at about 25°. Ethyl 2-chloro-5-nitrobenzoate reacted vigorously with piperidine without the application of heat. Treatment (*a*) led to the solidification of *ethyl* 5-*nitro*-2-*piperidinobenzoate*, which separated from aqueous alcohol in bright yellow, rectangular plates, m. p. 78—79° (Found : N, 10·2. $C_{14}H_{18}O_4N_2$ requires N, 10·1%).

3-*Nitro*-4-*piperidinobenzoic Acid.*—Addition of the diazo-solution prepared from *p*-chloroaniline (hydrochloric acid) to a solution of potassium cuprocyanide gave a 45% yield of almost pure *p*-chlorobenzonitrile. Nitration of the latter with nitric acid (*d* 1·5) at 5° gave a crude 4-chloro-3-nitrobenzonitrile, m. p. about 94°. Crystallisation from alcohol gave a product melting at 100—101°, as recorded by Claus and Kurz (*J. pr. Chem.*, 1888, **37**, 197), who obtained the nitrile from 4-chloro-3-nitroaniline by the diazo-process.

The nitrile was converted by piperidine into 3-nitro-4-piperidinobenzonitrile, m. p. 110—111° (compare Borsche, Stackmann, and Makaroff-Semljanski, *Ber.*, 1916, **49**, 2222), and by boiling 70% sulphuric acid into 4-chloro-3-nitrobenzoic acid. The latter reacted with piperidine quite as readily as did 2-chloro-5-nitrobenzoic acid, and the product (m. p. 202—203°) was evidently identical with that obtained by the last-mentioned authors by hydrolysing 3-nitro-4-piperidinobenzonitrile, the latter being obtained by them from 4-bromo-3-nitrobenzonitrile and piperidine.

Ethyl 3-*nitro*-4-*piperidinobenzoate* was obtained by esterification of the corresponding acid, with alcohol and sulphuric acid, as a red, viscous syrup (Found : N, 10·0. $C_{14}H_{18}O_4N_2$ requires N, 10·1%).

Behaviour of Piperidine towards o-*Chlorobenzoic Acid.*—(*a*) The acid was recovered unchanged after being heated for 6 hours with piperidine at the b. p. of the mixture. (*b*) The acid was heated with anhydrous potassium carbonate and piperidine in the presence of a little copper bronze. It was converted into salicylic acid.

4 : 6-*Dinitro*-1 : 3-*dipiperidinobenzene* (V).—Since 1 : 3-dichloro-4 : 6-dinitrobenzene reacted explosively in the cold, it was dissolved in pyridine and excess of piperidine added slowly, with external cooling. The dark brown, crystalline paste was filtered off; the solid so obtained separated from glacial acetic acid in dark yellow leaflets, m. p. 130—131° (Found : N, 16·9. $C_{16}H_{22}O_4N_4$ requires N, 16·8%).

3-*Chloro*-4 : 6-*dinitropiperidinobenzene* (IV).—A solution of 3·6 g. of piperidine in 15 c.c. of alcohol was added, slowly and with shaking, to a solution of 4 g. of 1 : 3-dichloro-4 : 6-dinitrobenzene in 50 c.c. of alcohol. The mixture was gently boiled for 10 minutes and then diluted with water, and the resulting yellow product was washed and crystallised thrice from alcohol. It then had m. p. 119° (compare Borsche and Bahr, *loc. cit.*).

4 : 6-*Dinitro*-3-*anilino*-1-*piperidinobenzene* (VI).—The previous

compound was heated with excess of aniline for 3 minutes, and the cooled solution was then poured into excess of dilute hydrochloric acid. The resulting black, brittle, solid product, after two crystallisations from glacial acetic acid, formed bright yellowish-green plates, m. p. 148—148·5° (Found : N, 16·6. $C_{17}H_{18}O_4N_4$ requires N, 16·4%).

Action of Piperidine on 1 : 3 : 5-*Tribromo*-2 : 4-*dinitrobenzene.*—(*a*) To a solution of 4 g. (1 mol.) of tribromodinitrobenzene in 25 c.c. of boiling chloroform were added 2·2 c.c. (2·25 mols.) of piperidine dissolved in 10 c.c. of chloroform. The solution was then boiled for a further 2 minutes, the chloroform removed by evaporation, and the residue extracted with water. The residue, on crystallisation from alcohol, gave 1 : 3-*dibromo*-2 : 4-*dinitro*-5-*piperidinobenzene* (VII) in yellow plates, m. p. 125—126° (Found : Br, 39·0. $C_{11}H_{11}O_4N_3Br_2$ requires Br, 39·1%).

(*b*) With 4·3 c.c. of piperidine and 4 g. of the tribromo-compound, under the above conditions, a mixture was obtained.

(*c*) When the tribromo-compound was treated with excess of piperidine a violent reaction at once set in, and even with careful cooling it was found difficult to prevent some *actual charring* in the centres of the masses formed. Addition of water, filtration, and crystallisation from alcohol led to yellow needles of 2 : 4-dinitro-1 : 3 : 5-tripiperidinobenzene (VIII), m. p. 177—178° (Found : N, 16·5. $C_{21}H_{31}O_4N_5$ requires N, 16·8%).

1 : 2-*Dichloro*-4 : 5-*dinitrobenzene.*—The preparation of this substance from *o*-dichlorobenzene by the method described by Hartley and Cohen (J., 1904, **85**, 867) is very tedious, since even after two lengthy nitration processes the product is a mixture. We have found it more convenient to nitrate *o*-dichlorobenzene, separate the 3 : 4-isomeride—a comparatively simple matter—and nitrate it. 3 : 4-Dichloronitrobenzene (10 g.) was dissolved in 60 c.c. of nitric acid (*d* 1·5), and 40 c.c. of fuming sulphuric acid (20% SO_3) were added. The solution was heated for 2 hours at 100°, then cooled and poured into water. The solid precipitated, after being twice crystallised from dilute acetic acid, gave the dinitro-compound, m. p. 109—110° (Hartley and Cohen give 104° ; Nietzki and Konwaldt, *Ber.*, 1904, **37**, 3892, give 114°).

Action of Piperidine on 1 : 2-*Dichloro*-4 : 5-*dinitrobenzene.*—This chloronitro-compound reacted in the cold with piperidine. The reaction was completed by boiling for a few minutes, and the resulting solution was treated with water. The red oil precipitated was washed with very dilute hydrochloric acid and then with water. Crystals, m. p. 62—64°, separated on inoculation of an alcoholic solution with solid obtained as above from trichloronitrobenzene.

The two products were identical. The unidirectional nature of the reaction just described is perhaps worth comment. Aniline and other primary bases give products which are much less easily isolated.

4 : 4'-*Dichlorodiphenylmethane*.—Montagne (*Rec. trav. chim.*, 1906, **25**, 390, 412) had previously obtained this substance by reducing 4 : 4'-dichlorobenzophenone, but we have obtained it more conveniently as follows: 4 : 4'-Diaminodiphenylmethane (25 g.) was dissolved in 150 c.c. of concentrated hydrochloric acid with the addition of 150 c.c. of water. The suspension (obtained on cooling) was diazotised with 17 g. of sodium nitrite dissolved in 40 c.c. of water, ice being added at intervals to keep the temperature at 0°. The resulting clear solution (about 600 c.c.) was poured into a cooled solution of cuprous chloride in hydrochloric acid (made from 150 g. of copper sulphate pentahydrate). A biscuit-coloured copper compound separated, which decomposed when the mixture was warmed at 100° for 0·5 hour. The brown oil formed was extracted with benzene, and isolated by distillation under reduced pressure; 15 g. of dichloro-compound, b. p. 186—190°/18 mm., m. p. 55—56° (after one crystallisation from alcohol), were then obtained.

4 : 4'-*Dichloro*-3 : 3'-*dinitrodiphenylmethane* (X).—The dichloro-compound was added to eight times its weight of water-cooled nitric acid (*d* 1·5). After a few minutes, when crystals began to separate, the mixture was poured into excess of water. The precipitated solid was slightly soluble in light petroleum (b. p. 80—100°) and in acetone, but more soluble in benzene, chloroform, and alcohol. It separated from glacial acetic acid in white plates, m. p. 198—199° (Found: Cl, 21·6. $C_{13}H_8O_4N_2Cl_2$ requires Cl, 21·7%).

The dinitro-compound reacted normally with piperidine to give 3 : 3'-*dinitro*-4 : 4'-*dipiperidinodiphenylmethane*, which, after being crystallised first from glacial acetic acid and then from alcohol, melted at 183—184° (Found: N, 13·4. $C_{23}H_{28}O_4N_4$ requires N, 13·2%).

4 : 4'-*Dibromo*-3 : 3'-*dinitro*-s-*diphenylethane* (XII).—4 : 4'-Dibromo-*s*-diphenylethane, m. p. 114°, prepared by the direct bromination of *s*-diphenylethane (compare Stelling and Fittig, *Annalen*, 1866, **137**, 267) was added to 15 parts of water-cooled nitric acid (*d* 1·5). The solution was warmed gently for 15 minutes, cooled, and poured into water. The resulting gummy precipitate, when dry, separated from benzene with m. p. 155—160°. Two further crystallisations gave small, yellowish-white crystals, m. p. 204°, the figure given by Stelling and Fittig.

The dinitro-compound was converted by piperidine into a product which separated from glacial acetic acid in orange-yellow, microscopic needles, m. p. 235—240°, with previous shrinking (Found: N, 13·0. $C_{24}H_{30}O_4N_4$ requires N, 12·8%).

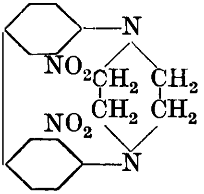
The Use of Sodium Acetate in the Preparation of Piperidino-compounds.—Borsche and his co-workers (*loc. cit.*) prepared a number of piperidino-compounds by heating 1 mol. of halogenonitro-compound with 1 mol. of piperidine hydrochloride (per 1 atom of reactive halogen) and excess of sodium acetate in alcoholic solution. Using this method with *p*-chloronitrobenzene, only a 36% yield has been obtained by us, whereas with 2·5 mols. of piperidine at 100°, almost theoretical conversion is effected.

Again, 4-chloro-3-nitrobenzonitrile gave only a 40% yield of piperidino-compound by Borsche's method, whilst almost theoretical yields were obtained by using piperidine alone at 100°.

1 : 4-*Di*-op-*dinitrophenylpiperazine.*—Piperazine (1 mol. of the hexahydrate) was heated with 3 mols. of 1-chloro-2 : 4-dinitrobenzene. At the b. p. of the mixture, sudden interaction occurred, and the previous two layers became an orange paste. After extraction with boiling alcohol and hot water, a product remained which was sparingly soluble in hot or cold glacial acetic acid, pyridine, acetone, or chloroform. It separated from nitrobenzene in orange-red needles, decomp. with effervescence at about 240° (Found : N, 20·3. $C_{16}H_{14}O_8N_6$ requires N, 20·1%).

1 : 4-*Di*-oop-*trinitrophenylpiperazine* (1 : 4-*dipicrylpiperazine*), prepared similarly, crystallised from nitrobenzene in orange needles, not melting at 260° (Found : N, 22·2. $C_{16}H_{12}O_{12}N_8$ requires N, 22·0%).

Interaction of Piperazine with 4 : 4′-*Dibromo*-3 : 3′-*dinitrodiphenyl.*—These two substances might conceivably interact to give a compound of the following structure (see, however, Le Fèvre and Turner, J., 1926, 2476) :



A solution of 1 g. of dibromodinitrodiphenyl and 0·5 g. of piperazine hexahydrate in 30 c.c. of pyridine was boiled for 2 hours, and then evaporated to a small bulk. The reddish-orange *powder* which separated on cooling, after crystallisation from pyridine, melted at about 215° (Found : N, 14·0. $C_{16}H_{15}O_4N_4Br$ requires N, 13·8%).

The substitution of benzidine for piperazine in the last experiment gave brown *needles*, from pyridine, m. p. 251° (Found : N, 10·8. $C_{24}H_{17}O_4N_4Br$ requires N, 11·1%).

In neither case, therefore, is a " Kaufler " compound formed.

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