117. *New Syntheses of Heterocyclic Compounds. Part VI. Triazafluorenes and Azaphenazines from 4-Chloro-3 : 5-dinitropyridine.*

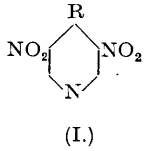
By V. A. Petrow and J. Saper.

N-(3′ : 5′-*Dinitro*-4′-*pyridyl*)-2-*aminopyridine* (II), prepared by interaction of 4-chloro-3 : 5-dinitropyridine (I; R = Cl) and 2-aminopyridine, has been found to lose readily the elements of nitrous acid to furnish a new base, 1-*nitro*-3 : 9 : 12-*triazafluorene* (III; R = NO_2). Reduction gave the *amino*-derivative (III; R = NH_2), which furnished 13-*hydroxy*-3 : 12-*diaza*-12 : 13-*dihydrocarbazole*-1 : 9-*diazole* (IV) on diazotisation.

Condensation of phenyl-*o*-phenylenediamine with (I; R = Cl) gave N-(3 : 5-*dinitro*-4-*pyridyl*)-N′-*phenyl*-*o*-*phenylenediamine* (V; R = Ph), converted by loss of the elements of nitrous acid into 1-*nitro*-5-*phenyldihydro*-3-*azaphenazine* (VI), and passing on reduction into 1-*amino*-5-*phenyl*-3-*azaphenazonium chloride* (VII; R = NH_2).

In Parts III and IV of this series (Petrow and Rewald, *J.*, 1945, 313, 591) it was shown that 4-chloro-3 : 5-dinitropyridine (I; R = Cl) could, like picryl chloride, be used in the synthesis of phenoxazines and phenthiazines. We now record an extension of the synthetical uses of this reagent to include the preparation of the hitherto unknown 3 : 9 : 12-triazafluorenes and 5-phenyl-3-azaphenazines.

In an attempt to prepare new bases of the pyridine series of potential chemotherapeutic interest, Morgan and Stewart (*Chem. and Ind.*, 1937, 670) studied the ring closure of picryl-2-aminopyridine. They found that removal of the elements of nitrous acid readily took place on heating in a suitable diluent to give a new base to which they assigned the constitution of a 1 : 3-dinitro-9 : 12-diazafluorene [4 : 6-dinitropyrido(1′ : 2′ : 1 : 2)-benziminazole]. They pointed out in a subsequent communication (*J.*, 1938, 1292) that, although this reaction could theoretically give rise to a dinitro-α-carboline, yet such a formulation was inconsistent with the observations that (*a*) picryl-2-amino-3-methylpyridine, the structure of which precluded the formation of a carboline, behaved in an exactly similar way, and (*b*) reduction followed by deamination gave a new base which was not identical but isomeric with the known α-carboline. Further work showed that picryl chloride could be replaced by the technically available 1-chloro-2 : 4-dinitrobenzene (*J.*, 1939, 1057), provided that somewhat more drastic methods of ring closure were employed.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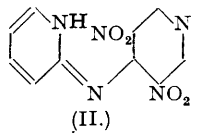
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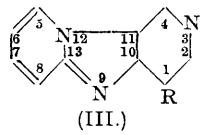
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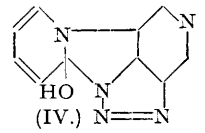
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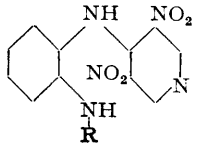
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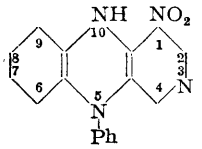
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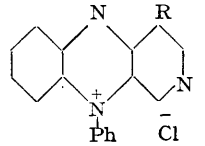
(VII.)

We now find that (I; R = Cl) undergoes ready condensation with 2-aminopyridine in benzene solution in the presence of sodium acetate to give N-(3′ : 5′-*dinitro*-4′-*pyridyl*)-2-*aminopyridine* (II) (shown as the imino-form). Pyrolysis of this compound in quinoline leads to the facile removal of the elements of nitrous acid followed by separation of a new base, $C_{10}H_6O_2N_4$, to which we have assigned the constitution of a 1-*nitro*-3 : 9 : 12-*triazafluorene* (III; R = NO_2). Attempts to confirm this structure by a similar condensation of 2-amino-3-methylpyridine with (I; R = Cl), as used by Morgan and Stewart (1938, *loc. cit.*) in the case of the simpler diazafluorenes, and thus exclude the alternative diazacarbazole formulation for our product, were unsuccessful for reasons outlined below.

Reduction of (III; R = NO_2) gave 1-*amino*-3 : 9 : 12-*triazafluorene* (III; R = NH_2), characterised by an *acetyl* derivative. The latter gave only a *monomethiodide*. The behaviour of (III; R = NH_2) with nitrous acid showed certain points of interest. In acid solution the normal diazonium salt was presumably formed as evidenced by the formation of a red dyestuff on coupling with alkaline 2-naphthol. When an acid solution of the diazonium salt was heated for a few minutes, however, a rearrangement occurred leading to the formation of an isomeric compound, for which we tentatively propose the structure of a 13-*hydroxy*-3 : 12-*diaza*-12 : 13-*dihydrocarbazole*-1 : 9-*diazole* (IV). Our evidence for structure (IV) is the presence in the product of a free hydroxyl group (Zerewitinoff determination) which is evidently of a tertiary character, as the compound was recovered unchanged after prolonged boiling with acetic anhydride.

Attempts to extend the above reactions to 2-amino-3-methylpyridine, 2-aminoquinoline, and 9-aminophenanthridine proved unsuccessful. In contrast to the ready formation of (II), the yellow products in all three cases appeared to be the molecular addition *complexes* of the bases with 3 : 5-dinitro-4-hydroxypyridine (I; R = OH). The same compounds were also obtained by direct addition of (I; R = OH) to boiling solutions of the bases in suitable solvents, although, when prepared in this way, their decomposition points differed slightly from those of the products formed *via* the chloro-compound (I; R = Cl). The bases were regenerated from the complexes by treatment with dilute acetic acid, followed by removal of the insoluble 3 : 5-dinitro-4-hydroxypyridine and basification of the filtrate, or by warming with a slight excess of caustic alkali, in which (I; R = OH) is readily soluble. Thus in properties and appearance these complexes resemble the picrates.

Now Ullmann and Bruck (*Ber.*, 1908, **41**, 3938) have shown that 2 : 4-dinitronaphthyl 1-*p*-toluenesulphonate resembles picryl chloride in its reaction with *o*-aminophenol to give a phenoxazine derivative. We therefore attempted the preparation of 3 : 5-dinitropyridyl 4-*p*-toluenesulphonate (I; R = $O{\cdot}SO_2{\cdot}C_7H_7$) in the hope that the interaction of such a derivative with 2-aminopyridine, for example, would furnish an alternative route to compounds of type (II). When 3 : 5-dinitro-4-hydroxypyridine (I; R = OH) was treated with *p*-toluenesulphonyl chloride in diethylaniline solution on the water-bath, however, a sulphur-free product was obtained giving consistent analytical figures for $C_{10}H_4O_9N_6$. There appears to be little doubt that this compound is the unknown *di-(3 : 5-dinitro-4-pyridyl) ether*, as, in common with the *o*- and *p*-nitrophenyl alkyl ethers, it underwent ready hydrolysis on treatment with alkalis to furnish (I; R = OH). Again, nitroethers such as trinitroanisole can be used like picryl chloride in the synthesis of phenoxazines (Misslin and Bau, *Helv. Chim. Acta*, 1919, **2**, 295). 4-Chloro-3 : 5-dinitropyridine (I; R = Cl) has been shown in earlier communications (Petrow and Rewald, *loc. cit.*) to give 1-nitro-3-azaphenoxazine with *o*-aminophenol, and 1-nitro-3-azaphenthiazine with *o*-aminothiophenol. We now find that di-(3 : 5-dinitro-4-pyridyl) ether can be equally well employed in these reactions. Condensation of the ether with 2-aminopyridine, however, failed to give (II), the product being the addition complex of the base with 3 : 5-dinitro-4-hydroxypyridine (I; R = OH).

Removal of the elements of nitrous acid from the picryl derivatives of *o*-phenylenediamine was first achieved by Kehrmann and Messinger (*Ber.*, 1893, **26**, 2372), who found that picrylmethyl-*o*-phenylenediamine passed smoothly on warming with alkali into *N*-methyldihydrodinitrophenazine, whilst phenylpicryl-*o*-phenylenediamine gave *N*-phenyldihydrodinitrophenazine. The reduction of the latter compound was subsequently investigated by Kehrmann (*Ber.*, 1899, **32**, 2607; cf. Kehrmann and Kramer, *Ber.*, 1900, **33**, 3074) who found that, when alcoholic stannous chloride was employed, *iso*phenosafranine was obtained. The parent compound of the series, dinitrodihydrophenazine, was obtained by Leemann and Grandmougin (*Ber.*, 1908, **41**, 1308; cf. Kehrmann and Messinger, *loc. cit.*) from *o*-phenylenediamine. A further extension of the reaction was made by Kehrmann and Effront (*Helv. Chim. Acta*, 1921, **4**, 517) who showed that 1-chloro-2 : 6-dinitrobenzene could be equally well employed in these reactions.

We successfully condensed 4-chloro-3 : 5-dinitropyridine (I; R = Cl) with *o*-phenylenediamine, obtaining N-(3 : 5-*dinitro*-4-*pyridyl*)-o-*phenylenediamine* (V; R = H) in excellent yield, but all attempts at ring closure of this compound failed. Prolonged heating with one molecular proportion of alkali led only to profound decomposition. Pyrolysis in neutral solvents led to the formation of brown amorphous products, a result no doubt connected with the instability of dihydrophenazines in the presence of oxidising agents. In contrast to these results, facile removal of the elements of nitrous acid readily occurred when N-(3 : 5-*dinitro*-4-*pyridyl*)-N′-*phenyl*-o-*phenylenediamine* (V; R = Ph), obtained from phenyl-*o*-phenylenediamine, was heated with one molecular proportion of alkali, giving 1-*nitro*-5-*phenyldihydro*-3-*azaphenazine* (VI) in 60% yield. Pyrolysis of (V; R = Ph) in boiling quinoline on one occasion gave 65% of (VI), but in general the yields by this method were very low. Reduction of (VI) gave 1-*amino*-5-*phenyl*-3-*azaphenazonium chloride* (VII; R = NH_2), characterised by its well-defined *acetyl* derivative (VII; R = NHAc). The formation of the phenylaminophenazonium salts by reduction of the *N*-phenylnitrodihydrophenazines is a well-established reaction, *viz.*, the preparation of *iso*phenosafranine referred to above.

Biological examination of 1-amino-3 : 9 : 12-triazafluorene (III; R = NH_2) kindly undertaken at our request by Mr. R. H. Thorpe (Wellcome Physiological Research Laboratories, on behalf of the Therapeutic Research Corporation of Great Britain, Ltd.) has shown that this substance is a convulsant poison. The L.D.$_{50}$ for intravenous injection in mice was about 60 mg./kg. In the anæsthetised dog the compound caused a fall in blood pressure equivalent to about 25 mm. of mercury followed by recovery in about three minutes. After the injection of 3 mg./kg. of morphine the blood pressure fell by about 25 mm. and an injection of 5 mg./kg. of (III; R = NH_2) caused a transient increase lasting a minute or so. A further similar dose gave a rise of blood pressure of 40 mm. of mercury, but the duration of the effect was very short. Dr. R. Wien and Dr. J. Harrison (Biological Division, May and Baker Ltd., on behalf of the Therapeutic Research Corporation of Great Britain, Ltd.) have kindly examined 1-amino-5-phenylphenazonium chloride (VII; R = NH_2). The L.D.$_{50}$ in mice was 20 mg./kg. for intravenous injections and 25 mg./kg. for subcutaneous injections. The compound was inactive against *Staph. aureus*, *B. coli*, *Ps. aeruginosa* (*pyocyanea*), *T. equiperdum*, and *T. congolense*.

Experimental.

M. ps. are corrected. Microanalyses and Zerewitinoff determination are by Drs. Weiler and Strauss, Oxford.

N-(3′ : 5′-*Dinitro*-4′-*pyridyl*)-2-*aminopyridine* (II).—3 : 5-Dinitro-4-hydroxypyridine (18·5 g.), phosphorus pentachloride (34 g.), and a little phosphorus oxychloride were heated under reflux for 1 hour at 160°. Excess of phosphorus

halides was removed under reduced pressure on the water-bath, and to the cooled product 2-aminopyridine (15 g.) in dry benzene (*ca.* 40 ml.) was added with shaking. The mixture was warmed gently on the water-bath for 2 minutes, and sodium acetate (12 g.) followed by benzene (100 ml.) added. The mixture was heated for 10 minutes under reflux. The filtrate on cooling deposited N-(3′ : 5′-*dinitro*-4′-*pyridyl*)-2-*aminopyridine*, lemon-yellow plates from alcohol, m. p. 184—185° (Found : C, 46·2; H, 2·9; N, 26·7. $C_{10}H_7O_4N_5$ requires C, 46·2; H, 2·7; N, 26·8%). Yield, 5·1 g. (20%).

1-*Nitro*-3 : 9 : 12-*triazafluorene* (III; R = NO_2).—*N*-(3′ : 5′-Dinitro-4′-pyridyl)-2-aminopyridine (5 g.) and redistilled quinoline (10 ml.) were heated under reflux for 10 minutes. Evolution of oxides of nitrogen took place followed by sudden separation of 1-*nitro*-3 : 9 : 12-*triazafluorene*, light yellow needles from nitrobenzene, m. p. 319° (Found : C, 56·3; H, 2·9; N, 26·2. $C_{10}H_6O_2N_4$ requires C, 56·1; H, 2·8; N, 26·2%). Yield, 3 g. (75%).

1-*Acetamido*-3 : 9 : 12-*triazafluorene* (III; R = NHAc).—Finely powdered 1-nitro-3 : 9 : 12-triazafluorene (2 g.), reduced iron (3 g.), ethanol (7 ml.), water (3 ml.), and concentrated hydrochloric acid (0·5 ml.) were heated under reflux for 2 hours. The filtrate and washings were concentrated until crystallisation commenced. The product (1 g.), after two crystallisations from aqueous ethanol (charcoal), was heated under reflux with acetic anhydride (7 ml.) for 30 minutes. 1-*Acetamido*-3 : 9 : 12-*triazafluorene* formed white needles from aqueous ethanol, m. p. 264—265° (Found : C, 63·6; H, 4·4; N, 25·0. $C_{12}H_{10}ON_4$ requires C, 63·7; H, 4·4; N, 24·8%). Yield, 700 mg. (33%). The *methiodide*, prepared from the methosulphate formed by adding methyl sulphate (650 mg.) to a hot solution of the base (1 g.) in nitrobenzene (5 ml.), formed light yellow hexagonal rods from water, m. p. 311° (decomp.) (Found : I, 33·9. $C_{13}H_{13}ON_4I$ requires I, 34·5%).

1-*Amino*-3 : 9 : 12-*triazafluorene* (III; R = NH_2), obtained by heating the acetamido-compound (2 g.) with 2N-hydrochloric acid (50 ml.) for 1½ hours, formed light yellow needles from aqueous methanol, m. p. 256—257° (Found : C, 65·0; H, 4·4; N, 30·0. $C_{10}H_8N_4$ requires C, 65·2; H, 4·4; N, 30·4%).

13-*Hydroxy*-3 : 12-*diaza*-12 : 13-*dihydrocarbazole*-1 : 9-*diazole* (IV).—1-Amino-3 : 9 : 12-triazafluorene (1·8 g.) dissolved in 2N-hydrochloric acid (50 ml.) was gradually treated at −5° with an ice-cold solution of sodium nitrite (800 mg.). After 20 minutes at 0° the solution was boiled for 5 minutes, cooled, made alkaline with sodium hydroxide solution, and the product precipitated by the passage of carbon dioxide. Recrystallisation of the brown powder from aqueous acetic acid gave 13-*hydroxy*-3 : 12-*diaza*-12 : 13-*dihydrocarbazole*-1 : 9-*diazole*, felted white needles, m. p. 314° (decomp.) (Found : C, 56·1; H, 3·2; N, 33·0; active hydrogen (Zerewitinoff), 0·41. $C_{10}H_7ON_5$ requires C, 56·3; H, 3·3; N, 32·9%; active hydrogen, 0·47%).

3 : 5-*Dinitro*-4-*hydroxypyridine Addition Complexes*.—Method (*A*) consisted in treating a boiling solution of the base in benzene or xylene with an equivalent amount of recrystallised 4-chloro-3 : 5-dinitropyridine (cf. Petrow and Rewald, *loc. cit.*) followed by addition of finely powdered anhydrous sodium acetate. After 30 minutes' refluxing the complex was isolated by filtration followed by extraction of the insoluble residues with pyridine or nitrobenzene. Method (*B*) involved the addition of the very finely powdered dinitrohydroxypyridine to a boiling solution of the base in benzene or xylene. After 30 minutes under reflux the mixture was filtered and the *complex* purified by crystallisation from pyridine or spirit.

From 2-aminopyridine : (*B*) gave yellow felted needles, m. p. 224° (Found : C, 43·0; H, 3·3; N, 24·8. $C_{10}H_9O_5N_5$ requires C, 43·0; H, 3·2; N, 25·1%). From 2-amino-3-methylpyridine : (*A*) gave light yellow needles, m. p. 261° (decomp.) (Found : N, 23·6. $C_{11}H_{11}O_5N_5$ requires N, 23·9%). (*B*) gave m. p. 259° (decomp.) (Found : C, 45·1; H, 3·5; N, 23·9. $C_{11}H_{11}O_5N_5$ requires C, 45·0; H, 3·8; N, 23·9%). From 2-aminoquinoline : (*A*) gave light yellow needles, m. p. 269° (decomp.) (Found : C, 51·1; H, 3·3; N, 21·5. $C_{14}H_{11}O_5N_5$ requires C, 51·1; H, 3·3; N, 21·3%). (*B*) gave m. p. 269° (decomp.) (Found : N, 21·7%). From 9-aminophenanthridine : (*A*) gave light yellow needles, m. p. 259—260° (Found : C, 56·8; H, 3·6; N, 18·2. $C_{18}H_{13}O_5N_5$ requires C, 57·0; H, 3·4; N, 18·5%). (*B*) gave m. p. 267° (Found : N, 18·7%). Complexes prepared by the two methods gave no depression of m. ps. in admixture.

Di-(3 : 5-*dinitro*-4-*pyridyl*) *Ether*.—Finely powdered 3 : 5-dinitro-4-hydroxypyridine (2 g.) and *p*-toluenesulphonyl chloride (2 g.) suspended in redistilled diethylaniline (8 ml.) were warmed on the water-bath for 10 minutes. Spirit (30 ml.) was immediately added and, after allowing to cool, the brown crystalline powder collected and crystallised from ethanol–acetone. *Di*-(3 : 5-*dinitro*-4-*pyridyl*) *ether* formed light brown needles, m. p. 288° (decomp.) (Found : C, 34·3; H, 1·2; N, 24·0. $C_{10}H_4O_9N_6$ requires C, 34·1; H, 1·1; N, 23·9%). Yield, 1·5 g. (80%). When the ether was hydrolysed by heating under reflux with aqueous sodium hydroxide, followed by precipitation with acetic acid and crystallisation from hot water, characteristic plates of 3 : 5-dinitro-4-hydroxypyridine were obtained (Found : N, 22·7. Calc. for $C_5H_3O_5N_3$: N, 22·8%).

5-*Nitro*-3-*azaphenoxazine*.—Di-(3 : 5-dinitro-4-pyridyl) ether (1 g.) and *o*-aminophenol (1 g.) in spirit (20 ml.) were heated under reflux for 10 minutes. Excess of ammonia (*d*, 0·880) was then added and the heating continued for a further 20 minutes. After allowing to cool, the 5-nitro-3-azaphenoxazine was collected. It formed deep red crystals, m. p. 209—210° (Found : N, 18·8. Calc. for $C_{11}H_7O_3N_3$: N, 18·3%), not depressed in admixture with an authentic specimen (Part III, *loc. cit.*).

5-*Nitro*-3-*azaphenthiazine*.—Di-(3 : 5-dinitro-4-pyridyl) ether (1·5 g.) and *o*-aminothiophenol zinc double salt (1·5 g.), suspended in ethanol (30 ml.), were treated with concentrated sulphuric acid (1 ml.). The mixture was heated under reflux until evolution of oxides of nitrogen had ceased (*ca.* 1½ hours). The resulting solution was treated at the boiling point with 33% aqueous sodium hydroxide solution until the appearance of a permanent purple coloration, and then poured into water (200 ml.). On cooling, the product was collected and crystallised from ethanol. 5-Nitro-3-azaphenthiazine formed purple plates, m. p. 143—144° (Found : N, 17·5. Calc. for $C_{11}H_7O_2N_3S$: N, 17·1%), not depressed in admixture with an authentic specimen (Part IV, *loc. cit.*).

N-(3 : 5-*Dinitro*-4-*pyridyl*)-o-*phenylenediamine* (V; R = H).—Recrystallised 4-chloro-3 : 5-dinitropyridine, prepared from (I; R = OH; 10 g.), was added to *o*-phenylenediamine (2 g.) and anhydrous sodium acetate (5 g.) in boiling benzene (70 ml.). After 30 minutes under reflux the mixture was cooled and the solids were collected and thoroughly extracted with boiling water and cold dilute aqueous sodium hydroxide solution. N-(3 : 5-*Dinitro*-4-*pyridyl*)-o-*phenylenediamine* formed red hexagonal plates from aqueous pyridine, m. p. 222° (decomp.) (Found : C, 48·6; H, 3·4; N, 25·4. $C_{11}H_9O_4N_5$ requires C, 48·0; H, 3·3; N, 25·4%). Yield, 4·3 g. (85%).

N-(3 : 5-*Dinitro*-4-*pyridyl*)-N′-*phenyl*-o-*phenylenediamine* (V; R = Ph).—Recrystallised 4-chloro-3 : 5-dinitropyridine (*ca.* 6 g., prepared from 18·5 g. of the hydroxy-compound) was added to boiling phenyl-*o*-phenylenediamine (7·2 g.) anhydrous sodium acetate (10 g.), and benzene (100 ml.). After 15 minutes the hot mixture was filtered. N-(3 : 5-*Dinitro*-4-*pyridyl*)-N′-*phenyl*-o-*phenylenediamine* separated on cooling; bright red prisms from ethanol, m. p. 180—182° (decomp.) (Found : C, 58·0; H, 3·9; N, 20·0. $C_{17}H_{13}O_4N_5$ requires C, 58·1; H, 3·7; N, 19·9%). Yield, 9 g. (66%).

1-*Nitro*-5-*phenyl*-5 : 10-*dihydro*-3-*azaphenazine* (VI).—(a) *N*-(3 : 5-Dinitro-4-pyridyl)-*N*′-phenyl-*o*-phenylenediamine (3 g.) and redistilled quinoline (9 ml.) were heated under reflux for 5 minutes. Oxides of nitrogen were evolved. The quinoline was removed in steam and the solid crystalline residue crystallised from benzene. 1-*Nitro*-5-*phenyl*-5 : 10-*dihydro*-3-*azaphenazine* formed dark violet prisms, m. p. 247—247·5° (Found : C, 67·0; H, 4·2; N, 18·3. $C_{17}H_{12}O_2N_4$ requires C, 67·1; H, 4·0; N, 18·4%). Yield, 1·7 g. (65%). (b) To a boiling suspension of finely powdered *N*-(3 : 5-dinitro-4-pyridyl)-*N*′-phenyl-*o*-phenylenediamine (2 g.) in ethanol (75 ml.) an ethanolic solution of potassium hydroxide

(300 mg.) was slowly added and the heating continued for a further 2 hours. After allowing to cool, the product was collected and crystallised from benzene, m. p. 247—247·5° (Found: N, 18·0), not depressed in admixture with the compound obtained by method (a). Yield, 1 g. (60%).

1-*Amino-5-phenyl-3-azaphenazonium Chloride* (VII; R = NH_2).—Finely powdered 1-nitro-5-phenyl-5 : 10-dihydro-3-azaphenazine (2 g.), reduced iron (5 g.), methanol (15 ml.), water (4 ml.), and ferric chloride (3 g.) were heated under reflux for 1¾ hours. On concentration of the filtrate and washings 1-*amino-5-phenyl-3-azaphenazonium chloride* separated; bronze plates from methanol, m. p. >310° (Found: C, 66·1; H, 4·7; N, 18·5; Cl, 11·8. $C_{17}H_{13}N_4Cl$ requires C, 66·1; H, 4·2; N, 18·2; Cl, 11·5%). Yield, 1 g. (44%).

1-*Acetamido-5-phenyl-3-azaphenazonium chloride* (VII; R = NHAc), red prisms, m. p. 275° (decomp.) (Found: C, 65·1; H, 4·7; N, 16·3; Cl, 10·1. $C_{19}H_{15}ON_4Cl$ requires C, 65·0; H, 4·3; N, 16·0; Cl, 10·1%), was prepared by heating the amino-compound (1 g.) with acetic anhydride (10 ml.) for 15 minutes under reflux. After allowing to cool the purple solids were collected and crystallised (charcoal) from ethanol.

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QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E. 1. [*Received, January 10th*, 1946.]