393. *Reactions of Methazonic Acid. Part III.* A Novel Reaction of 3-Aminolepidine.*

By D. W. Ockenden and K. Schofield.

3-Aminolepidine reacted with two mols. of nitrous acid to give 1 : 2 : 3 : 9-tetra-azaphenanthrene 3-oxide, converted by acid into 3-azidoquinoline-4-aldehyde. The latter when heated gave quinolino(3′ : 4′-3 : 4)sydnone. Diazotisation of the amine in dilute acid produced some 3*H*-1 : 2 : 6-triaza-4 : 5-benzindene.† In concentrated hydrochloric acid the initial reaction between 3-aminolepidine and nitrous acid produced a deep violet colour, not observed in sulphuric acid of similar concentration. 3-Amino-6-chlorolepidine gave similar reactions.

The *N*-nitroso-derivative of 3-acetamidolepidine was converted by hot benzene into 3*H*-1 : 2 : 6-triaza-4 : 5-benzindene.

Various ultra-violet absorption spectra are recorded.

Recently, Schofield and Theobald (*J.*, 1950, 395) described the diazotisation of 3-aminolepidine (I; R = H) and the coupling of the diazonium salt with pyridine. The diazotisation in concentrated hydrochloric acid gave a violet diazonium solution, and the reaction was stated to be complicated. In contrast, Eiter and Nagy (*Sitzungsber. Oesterr. Akad. Wiss.*, Abt., II*b*, 1949, **158**, 607), who diazotised the amine in 2N-sulphuric acid, evidently did not observe a violet diazonium solution, and isolated the alkali-soluble triazabenzindene (II; R = H), m. p. 224°. We now present the results of a re-examination of this diazotisation.

Both Eiter and Nagy and Schofield and Theobald prepared 3-aminolepidine by reducing the nitro-compound, obtained from *o*-aminoacetophenone and methazonic acid, with stannous chloride, but whereas the former authors isolated the amine as a hemihydrate, m. p. 90—91° after melting at 40° and re-solidifying, the latter described a hydrate, m. p. 72—73°. It was therefore necessary to establish that these different workers had the same compound in hand. Repetition of the reduction as described by the Austrian authors gave an amine, m. p. 96—98°, but this was converted into the monohydrate, m. p. 72—73° by crystallisation from aqueous ethanol (Eiter and Nagy used ether–light petroleum). Catalytic reduction of 3-nitrolepidine in methanol, with palladium–charcoal, gave a high yield of an amine which at first behaved like that of Eiter and Nagy, but when crystallised and seeded also gave the monohydrate. It is clear therefore that the amines previously reported differed only in their degree of hydration.

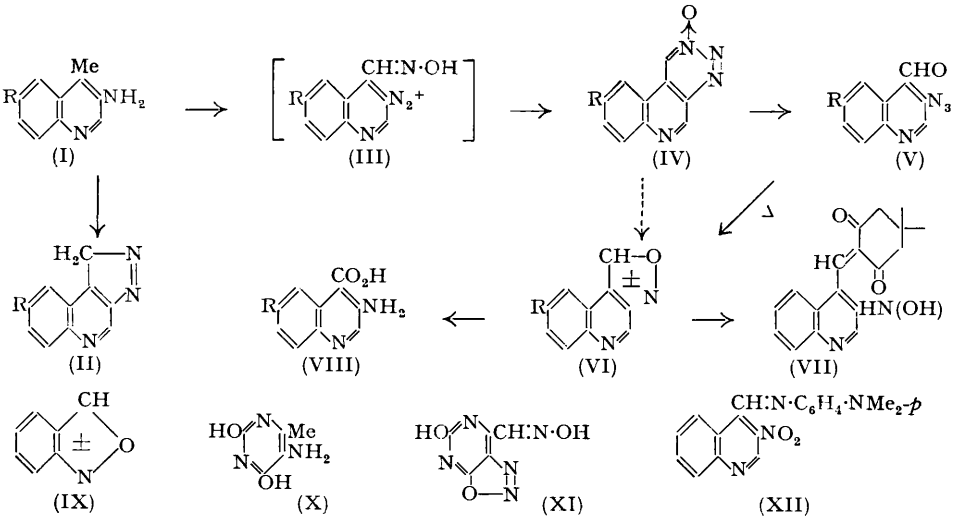
Schofield and Theobald (*loc. cit.*) noticed that the violet solution formed by diazotising 3-aminolepidine in concentrated hydrochloric acid rapidly deposited a brown solid (A). In repeating this work we were unable to improve the low yields of 3-pyridyl-lepidines obtained by the method previously described, and found (A) to be the major product of the diazotisation, its formation being accompanied by fading of the violet colour of the solution. If (A) was left in contact with the acid solution from which it had separated it slowly dissolved, and in our first experiment by basification of the resulting solution a new substance (C) was isolated. Subsequently, this result could not be reproduced, basification of the solution produced by dissolution of (A) always providing a different compound (B). (C) was a base, m. p. 117—118°, for which analysis indicated the formula $C_{10}H_6ON_2$, or, less likely, $C_{10}H_8ON_2$. The latter would correspond to 3-aminoquinoline-4-aldehyde, whilst the most obvious structure with the former composition would be the quinolino*iso*-oxazole (VI; R = H). That the latter is the correct structure is proved by the following facts. The compound could not be acetylated or benzoylated, but with nitrous acid it gave a diazonium solution capable of coupling with β-naphthol; with dimedone it did not give the usual type of aldehyde derivative, but the additive compound (VII; R = H); warm dilute alkali converted (C) into 3-aminocinchoninic acid (VIII; R = H). Analogies for each of these reactions are available in the behaviour of anthranil (IX) (Morton, " The

* Part II, *J.*, 1950, 395.

† See footnote on p. 1918.

Chemistry of Heterocyclic Compounds," McGraw-Hill, New York, 1946, pp. 425 *et seq.*). Although a compound of this type does not appear to have been treated with dimedone before, anthranil undergoes a similar addition reaction with another carbonyl reagent, *viz.*, hydroxylamine (*op. cit.*).

The substance (B), $C_{10}H_6ON_4$, was basic and melted with decomposition at 135°; when cooled, the melt solidified and then had m. p. 117—118°. It seemed likely that (B) lost nitrogen at its m. p., being converted into (C). This was proved by the fact that the conversion could be effected by boiling a solution of (B) in dioxan, the method finally adopted for preparing (C). These facts suggested that (B) was 3-azidoquinoline-4-aldehyde (V; R = H), a deduction supported by the preparation of the 2 : 4-dinitrophenylhydrazone.



The parent compound (A), being insoluble in most solvents, was difficult to purify. Early and unreproducible attempts to crystallise it from acetic acid or dioxan merely produced (C), with the liberation of nitrogen, but after crystallisation [m. p. 216° (decomp.)] from pyridine, it was found to be isomeric with (B). The only possible structure for (A) is that of the tetra-azaphenanthrene 3-oxide (IV; R = H). This attribution would imply that 2 mols. of nitrous acid react initially with 3-aminolepidine, and support is given to this by the formation of (A) in almost quantitative yield by the use of this quantity of reagent.

The reaction with nitrous acid of the methyl group in 3-diazolepidine was unexpected, such reactions, though common with the analogously activated groups in methyl ketones, being rare in heterocyclic systems. 5-Amino-6-methyluracil (X) gives with nitrous acid the oxime (XI) (Rose, *J.*, 1952, 3448), and the 2-methyl group of 2 : 3 : 3-trimethylindolenine is similarly nitrosated (Plancher, *Ber.*, 1898, **31**, 1496). 3-Aminoquinaldine, on the other hand, appears to be diazotised normally (Lawson, Perkin, and Robinson, *J.*, 1924, **125**, 626; Bargellini and Berlingozzi, *Gazzetta*, 1923, **53**, 3), although the description given by Stark and Hoffmann (*Ber.*, 1913, **46**, 2697) suggests that this case might deserve re-examination. 3-Nitrolepidine did not react with nitrous acid.

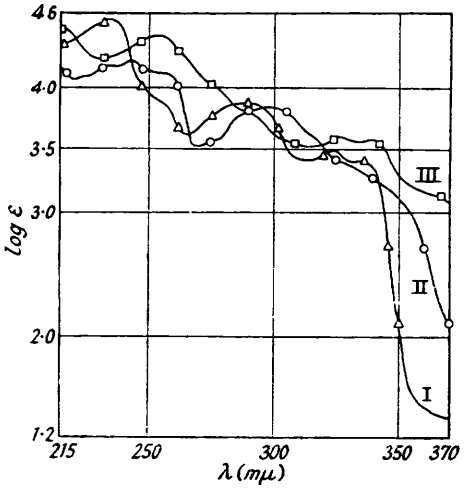
The precursor of (IV; R = H) must be the oxime (III; R = H), and the sequence (III ⟶ IV ⟶ V ⟶ VI) closely parallels that occurring when *o*-aminoaceto- or *o*-aminobenzo-phenone oxime is diazotised (Meisenheimer, Senn, and Zimmermann, *Ber.*, 1927, **60**, 1736).

The intense violet colour of the solution formed immediately upon diazotisation of 3-aminolepidine in concentrated hydrochloric acid remains unexplained. Experiment showed that in N- or 2N-hydrochloric acid the diazonium solution was pale yellow, and the precipitate of (IV; R = H) redissolved either very slowly or not at all at these acid concentrations. With 5N-acid the solution was dark orange and deposited no solid. At 6N

the colour was dark red, and at greater concentrations violet, these solutions all depositing (IV; R = H), which was slowly redissolved, as described. By carrying out diazotisations in solutions ranging from N- to 8N-hydrochloric acid and leaving the precipitated solid in contact with the mother-liquors overnight, it was possible to collect undissolved (IV; R = H) in amounts which decreased as acid concentration increased, and by basifying the mother-liquors to isolate (V; R = H), except with N-hydrochloric acid, in which case the triazabenzindene (II; R = H) was obtained.

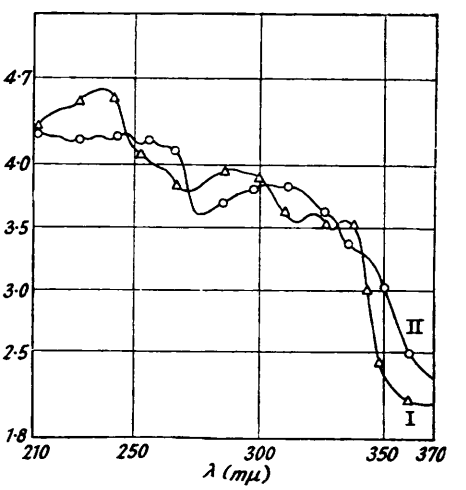
Although we could not isolate (II; R = H) in the way described by Eiter and Nagy (*loc. cit.*), the substance was obtained by diazotising the amine in N-sulphuric acid and, after removal of the small amount of (IV; R = H) still remaining after 12 hours, neutralising the solution. Again the use of more concentrated acid facilitated the transformation of (IV; R = H), and from 5N- and 8N-sulphuric acid the triazabenzindene (II; R = H) was contaminated with 3-azidoquinoline-4-aldehyde. The diazonium solution in N-sulphuric acid was yellow, and light orange and orange respectively in 5N- and 8N-acid. Violet solutions were not encountered when sulphuric acid was used.

FIG. 1.



(I) 3H-1 : 2 : 6-*Triaza*-4 : 5-*benzindene*.
(II) *Quinolino*(3′ : 4′-3 : 4)*isooxazole*.
(III) 3-*Azidoquinoline*-4-*aldehyde*.
(*In absolute alcohol.*)

FIG. 2.



(I) 2′-*Chloro*-3H-1 : 2 : 6-*triaza*-4 : 5-*benzindene*.
(II) 6′-*Chloroquinolino*(3′ : 4′-3 : 4)*isooxazole*.
(*In absolute alcohol.*)

Roughly similar observations were made with 3-amino-6-chlorolepidine (I; R = Cl) (Schofield and Theobald, *loc. cit.*). On diazotisation in both 2N-hydrochloric acid and -sulphuric acid, (IV; R = Cl) was precipitated, and from the reaction solution the chlorotriazabenzindene (II; R = Cl) was isolated. Again the use of 2 mols. of sodium nitrite gave (IV; R = Cl) in superior yield. The diazonium solutions in these cases were pale yellow, and even in concentrated hydrochloric acid became only light orange. In this last case the *N*-oxide (IV; R = Cl) redissolved when left in contact with the reaction solution, and the base (VI; R = Cl) was isolated on neutralisation. In this series the azide was not encountered. The quinolino*iso*oxazole (VI; R = Cl) was characterised by conversion into 3-amino-6-chlorocinchoninic acid (VIII; R = Cl).

Recently, Adams and Hey (*J.*, 1951, 1521) converted 3-acetamido-1 : 2-dimethyl-4-quinolone into 1-methylpyrazolo(4′ : 5′-2 : 3)-4-quinolone by heating its *N*-nitroso-derivative in benzene. Similarly we converted 3-acetamidolepidine by means of nitrosyl chloride in acetic anhydride into the *N*-nitroso-derivative, and transformed the latter into (II; R = H) identical with the compound described above. We were unable to prepare the *N*-nitroso-derivative of 3-acetamido-6-chlorolepidine.

The ultra-violet absorption spectra of (II; R = H and Cl), (VI; R = H and Cl), and

(V; R = H) are recorded in Figs. 1 and 2. The spectra of the analogous compounds are clearly similar, but the chlorine atom produces a bathochromic shift.

Early in this work we prepared the anil (XII) from 3-nitrolepidine and *p*-nitrosodimethylaniline, as a possible source of 3-nitroquinoline-4-aldehyde.

Experimental

3-Aminolepidine.—3-Nitrolepidine (0·5 g.), palladium–charcoal (0·2 g.), and methanol (100 c.c.) were shaken with hydrogen. Reduction was complete in 120 min., and filtration and concentration gave the amine (0·48 g.), melting like that described by Eiter and Nagy (*loc. cit.*). Recrystallisation from aqueous alcohol, with seeding, gave the monohydrate, m. p. 72—73°.

1 : 2 : 3 : 9-Tetra-azaphenanthrene 3-Oxide.—3-Aminolepidine (0·25 g.) in concentrated hydrochloric acid (25 c.c.) and water (10 c.c.) was treated at 0° with sodium nitrite (0·25 g.) in water (2 c.c.). The product [0·26 g., 84%; m. p. 205° (decomp.)] began to separate immediately and was collected when the violet colour had faded (about 5 min.). The *3-oxide* formed small, dark brown crystals, m. p. 216° (decomp.) (Found: C, 61·3; H, 3·3; N, 27·8. $C_{10}H_6ON_4$ requires C, 60·6; H, 3·1; N, 28·3%), from pyridine.

With the amine (2·0 g.), concentrated hydrochloric acid (20 c.c.), water (18 c.c.), and sodium nitrite (0·9 g.) the purple colour was also developed and 1·1 g. of product were obtained. A solution of the amine (0·2 g.), dilute hydrochloric acid (5 c.c.), and water (5 c.c.), when treated at 0° with sodium nitrite (0·09 g.) in water (1 c.c.), gave a yellow solution which slowly became red-brown and overnight deposited the *N*-oxide (0·09 g.). The mother-liquor when basified gave 3-azidoquinoline-4-aldehyde (0·02 g.) (see below).

3-Azidoquinoline-4-aldehyde.—3-Aminolepidine (1 g.), concentrated hydrochloric acid (10 c.c.), and water (5 c.c.) were treated at 0° with sodium nitrite (0·45 g.) in water (5 c.c.). The initially violet solution quickly deposited solid and became red-brown. On being kept overnight at 0° the precipitate redissolved, and the solution was filtered and basified. The product (0·75 g.) crystallised from acetone, giving orange-brown needles of *3-azidoquinoline-4-aldehyde*, m. p. 135° (decomp.) (Found: C, 60·3; H, 3·1; N, 28·6. $C_{10}H_6ON_4$ requires C, 60·6; H, 3·0; N, 28·3%). Its *2 : 4-dinitrophenylhydrazone* exhibited polymorphism: as obtained initially, the orange solid had m. p. 255—260° (decomp.), but crystallisation from benzene containing a trace of pyridine gave small orange needles, m. p. 160° (decomp.) (Found: C, 51·3; H, 2·9; N, 28·6. $C_{16}H_{10}O_4N_8$ requires C, 50·8; H, 2·7; N, 29·6%).

Quinolino(3′ : 4′-3 : 4)isooxazole.—On one occasion only was this compound isolated instead of the azide from an experiment similar to that described above; subsequently, even when the acid reaction solution containing the azide was kept for several days before being basified, the azide was always recovered. 3-Azidoquinoline-4-aldehyde (0·6 g.) and dioxan (30 c.c.) were refluxed for 4 hr., and the solvent was then removed *in vacuo*. The residue when crystallised from aqueous alcohol gave *quinolino(3′ : 4′-3 : 4)isooxazole* (0·35 g.), fawn-coloured leaflets, m. p. 117—118° (Found: C, 70·2; H, 3·4; N, 16·9. $C_{10}H_6ON_2$ requires C, 70·6; H, 3·6; N, 16·5%). The *iso*oxazole and dimedone in aqueous ethanol gave a derivative, *4-(2 : 6-diketo-4 : 4-dimethylcyclohexylidenemethyl)-3-hydroxyaminoquinoline*, which crystallised from the same solvent in orange leaflets, m. p. 145—146° (Found: C, 69·7; H, 5·8; N, 8·6. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·8; N, 9·0%).

3-Aminocinchoninic Acid.—The *iso*oxazole (0·03 g.) and 2N-sodium hydroxide (3 c.c.) were kept at 95° for 2 hr. The resulting clear yellow solution was made faintly acid (Congo-red) with sulphuric acid (2N), one drop of ammonia added, and the solution slowly evaporated. Orange-yellow needles [0·02 g.; m. p. 230° (decomp.)] separated which gave no mixed m. p. depression with authentic 3-aminocinchoninic acid.

3-Aminocinchoninic acid was first obtained by Colonna (*Boll. sci. Fac. Ind. Bologna*, 1941, 89) who reduced 3-nitrocinchoninic acid with iron and acetic acid. We found this procedure very inconvenient and obtained the amine as follows. 3-Nitrocinchoninic acid (1 g.), water (80 c.c.), sodium hydroxide (0·2 g.), and palladium–charcoal (0·25 g.) were shaken with hydrogen. Reduction was complete in 1 hr. and the filtered solution was concentrated to half volume. Careful neutralisation with 2N-sulphuric acid precipitated 3-aminocinchoninic acid (0·86 g., 100%), m. p. 230—232° (decomp.).

*3H-1 : 2 : 6-Triaza-4 : 5-benzindene.**—(i) 3-Aminolepidine (0·5 g.) in sulphuric acid (10 c.c.; 2N) was diazotised at 0° with sodium nitrite (0·25 g.) in water (2 c.c.). From the pale

* The symbol *3H* indicates the position of the " indicated " (" extra ") hydrogen atom as in (II), but we do not wish to be committed to this particular location of this atom.

yellow diazonium solution a solid separated, and after the addition of iced water (10 c.c.) it (tetrazaphenanthrene oxide, 0·13 g.) was collected. The filtrate was basified with ammonia and the precipitate (0·33 g.; m. p. 210—212°) was crystallised from benzene–pyridine. 3*H*-1 : 2 : 6-Triaza-4 : 5-benzindene formed small fawn-coloured crystals, m. p. 219—220° (Found : C, 71·8; H, 4·5; N, 23·8. Calc. for $C_{10}H_7N_3$: C, 71·0; H, 4·4; N, 24·8%). Eiter and Nagy (*loc. cit.*) gave m. p. 224°.

(ii) When 3-aminolepidine (0·5 g.) and acetic anhydride (10 c.c.) were kept at 95% for 1 hr., and the solvent was then removed, 3-acetamidolepidine (0·6 g.; m. p. 200—204°) suitable for further use was obtained. Eiter and Nagy (*loc. cit.*) gave m. p. 206°. The amide (0·2 g.), acetic acid (2 c.c.), acetic anhydride (1 c.c.), anhydrous potassium acetate (0·1 g.), and phosphoric oxide (0·05 g.) were treated at 0° with nitrosyl chloride (0·2 c.c.) in acetic anhydride (0·8 c.c.). The mixture was kept at 0° for 1 hr., with occasional shaking, poured on ice, and basified with sodium carbonate solution. The greenish gum which separated was taken up in benzene and the dry (Na_2SO_4) extract was refluxed for 3 hr. By concentration (charcoal) of the filtered solution the triazabenzindene (0·11 g.) was obtained, having m. p. 218—220° alone and mixed with the compound above.

6-*Chloro*-1 : 2 : 3 : 9-*tetra-azaphenanthrene* 3-*Oxide*.—The hydrochloride suspension from 3-amino-6-chlorolepidine (1 g.), concentrated hydrochloric acid (10 c.c.) and water (5 c.c.) was treated at 0° with sodium nitrite (0·8 g.) in water (5 c.c.). The solution became yellow, then orange-red, and deposited a pale yellow solid. Iced water (25 c.c.) was added, and after 12 hr. at 0° the precipitate [1·14 g.; m. p. 180—185° (decomp.)] was collected. 6-*Chloro*-1 : 2 : 3 : 9-*tetra-azaphenanthrene* 3-*oxide* crystallised from benzene containing a trace of pyridine as light brown prisms, m. p. 220° (decomp.) (Found: C, 52·1; H, 2·6; N, 21·1. $C_{10}H_5ON_4Cl$ requires C, 51·6; H, 2·2; N, 24·1%). This may be impure (cf. analysis) but its structure is not in doubt.

6′-*Chloroquinolino*(3′ : 4′-3 : 4)iso*oxazole*.—Although this compound was formed when 3-amino-6-chlorolepidine was diazotised in concentrated hydrochloric acid and the initial precipitate was allowed to redissolve overnight in the reaction liquor, the sydnone was best prepared as follows. The pure chloro-oxide (0·5 g.) and concentrated hydrochloric acid (20 c.c.) were left together for 12 hr., and the resulting solution was basified with ammonia. The precipitate (0·43 g.) gave yellow needles of 6′-*chloroquinolino*(3′ : 4′-3 : 4)iso*oxazole*, m. p. 202—204° (Found: C, 58·7; H, 2·8; N, 14·3. $C_{10}H_5ON_2Cl$ requires C, 58·7; H, 2·5; N, 13·7%), from benzene–light petroleum (b. p. 60—80°).

The chloro-*iso*oxazole (0·1 g.) was converted by aqueous sodium hydroxide by the method previously described into 3-*amino*-6-*chlorocinchoninic acid* (0·1 g.), small yellow flakes, m. p. 263—264° (decomp.) (Found : C, 54·7; H, 3·4. $C_{10}H_7O_2N_2Cl$ requires C, 53·9; H, 3·2%), from alcohol.

2′-*Chloro*-3H-1 : 2 : 6-*triaza*-4 : 5-*benzindene*.—The hydrochloride suspension from 3-amino-6-chlorolepidine (0·2 g.) and hydrochloric acid (5 c.c.; 2N) was treated at 0° with sodium nitrite (0·08 g.) in water (1 c.c.). The solution, yellow at first, became orange and deposited a solid. Iced water (5 c.c.) was added, and after 12 hr. at 0° the *N*-oxide (0·11 g.) was removed. Basification of the mother-liquor gave the *chlorotriazabenzindene* (0·1 g.); it separated from benzene–pyridine as small, lemon-yellow needles, m. p. 283—285° (Found : C, 58·8; H, 3·0. $C_{10}H_6N_3Cl$ requires C, 58·9; H, 3·0%). A similar experiment in sulphuric acid (5 c.c.; 2N) gave the *N*-oxide (0·18 g.) and very impure chlorotriazabenzindene (0·02 g.).

3-*Acetamido*-6-*chlorolepidine*.—Prepared as described for 3-acetamidolepidine, this *compound* gave small needles, m. p. 233—235° (Found : C, 61·2; H, 4·4. $C_{12}H_{11}ON_2Cl$ requires C, 61·4; H, 4·7%), from dilute alcohol.

Reaction of 3-*Nitrolepidine with* p-*Nitrosodimethylaniline*.—3-Nitrolepidine (0·3 g.), *p*-nitrosodimethylaniline (0·24 g., 1 mol.), and anhydrous sodium carbonate (0·03 g.) were refluxed in alcohol (20 c.c.) for 8 hr. The brown solution was concentrated, and the product (0·12 g.; m. p. 146—156°) collected. The *anil* crystallised from alcohol as small grey-black crystals, m. p. 155—157° (Found : C, 67·2; H, 4·8. $C_{18}H_{16}O_2N_4$ requires C, 67·5; H, 5·0%).

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