The Reaction between NN-*Di-2′-chloroalkyl-2-naphthylamines and 4-Amino-5-nitrosopyrimidines.*

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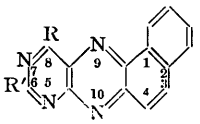
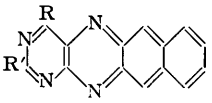
The reaction between 2 : 4 : 6-triamino-5-nitrosopyrimidine and *NN*-di-2′-chloroethyl- or *NN*-di-2′-chloropropyl-2-naphthylamine in acetic acid in the presence of anhydrous sodium acetate yields 6 : 8-diamino-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = R′ = NH_2), which is also, and better, obtained by fusion of 2 : 4 : 6-triamino-5-nitrosopyrimidine with 2-naphthol at 150°. 4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine and *NN*-di-2′-chloroethyl-2-naphthylamine yield (I; R = NH_2, R′ = MeS). In efforts to elucidate the course of this reaction, it has been shown that trimethyl-2-naphthylammonium iodide, in the presence of both 4-amino-5-nitrosopyrimidines mentioned and anhydrous sodium acetate, yields 3 : 4-6 : 7-dibenzacridine methiodide (IV), whereas triethyl-2-naphthylammonium iodide yields triethyl-2-naphthylammonium periodide with triaminonitrosopyrimidine.

In some exploratory attempts to synthesise heterocyclic systems which have analogies with the pteridine series and might possess antifolic acid or antifolinic acid (anticitrovorum factor, antileucovorin) activity, it was observed that 2 : 4 : 6-triamino-5-nitrosopyrimidine reacted with the biologically active aromatic nitrogen "mustard," *NN*-di-2′-chloroethyl-2-naphthylamine (Ross, *J.*, 1949, 183), in glacial acetic acid solution in the presence of anhydrous sodium acetate to yield a sparingly soluble, yellow, high-melting solid (A), exhibiting a very intense yellowish-green fluorescence in solution in glacial acetic acid. Analysis characterised it as $C_{14}H_{10}N_6$ although, at first, the existence of hydrates tenaciously holding water complicated the results. 4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine and the same aromatic amine gave a very small yield of an analogous compound, $C_{15}H_{11}N_5S$. This type of reaction did not take place when a number of substituted *NN*-di-2′-chloroethylanilines were employed; but *NN*-di-2′-chloropropyl-2-naphthylamine (Everett and Ross, *J.*, 1949, 1972) and 2 : 4 : 6-triamino-5-nitrosopyrimidine gave the same yellow product (A). This surprising result implied that the di-2-chloroalkyl group was not involved in the final product, while the formulæ of the products and the dependence on the nature of the aryl substituent of the aromatic amine suggested that the naphthalene moiety was somehow united with the pyrimidine molecule. Consequently the di-2-chloroalkylamino-group must be ejected during the reaction.

From these considerations the structures (I; R = R′ = NH_2) and (I; R = NH_2, R′ = MeS) were proposed for the products (A; $C_{14}H_{10}N_6$) and $C_{15}H_{11}N_5S$; structure (II) is much less likely since the 2-dialkylamino-group will probably activate position 1 of the naphthalene molecule and the colour of (A) is much lighter than that of the linear benzalloxazine (Ross, *J.*, 1948, 219).

Compounds of structure (I) have been recorded (Kühling, *Ber.*, 1891, **24**, 2363, 3031; Kuhn and Cook, *Ber.*, 1937, **70**, 761; Ross, *loc. cit.*) but all were obtained by condensation of a 1 : 2-diaminonaphthalene with alloxan or of a 1 : 2-naphthaquinone with a 4 : 5-diaminopyrimidine, neither of these routes yielding an unambiguously orientated product. Where one of the azine nitrogen atoms (9 or 10) is substituted, *e.g.*, by a sugar residue or

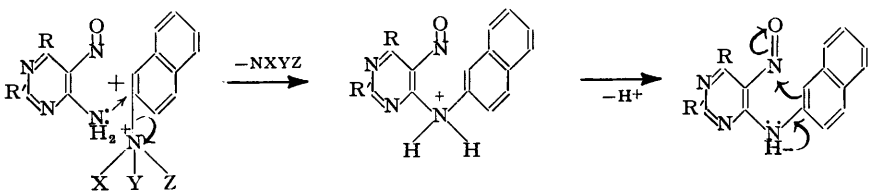
(I)   (II)

alkyl group (Karrer and Quibell, *Helv. Chim. Acta*, 1936, **19**, 1034; Lettré and Fernholz, *Ber.*, 1940, **73**, 436; Ross, *loc cit.*) then, of course, an unambiguously orientated benz*iso*-alloxazine is formed. It appeared probable that the product (A) consisted of one isomer only, *viz.*, that shown.

In an effort to obtain compounds of structure (I) in high yield a study was made of the conditions of the reaction. Alkaline catalysis by sodium 2-ethoxyethoxide in 2-ethoxyethanol, or by anhydrous potassium carbonate in the same solvent failed to bring about the reaction at all, as did heating the components in glacial acetic acid alone. The maximum yield was obtained when two mols. of aromatic amine were used together with two of sodium acetate for one of the triaminonitrosopyrimidine.

In view of the poor yields which this reaction afforded, an examination was made of the methods of synthesis available for the related 1 : 2-benzophenazine series. That due to Ullmann and Ankersmit (*Ber.*, 1905, **38**, 1811), in which a 2 : 4-diaminoazobenzene derivative (chrysoidine) was fused with 2-naphthol, seemed promising; and by regarding 2-naphthol as the enol of a cyclic ketone, a still closer analogy may be found in the unambiguous synthesis of 6 : 7-unsymmetrically substituted pteridines by the reaction of 4-amino-5-nitrosopyrimidines with α-keto-methylene compounds described by one of us (*Nature*, 1949, **164**, 139; and unpublished work). Accordingly, 2 : 4 : 6-triamino-5-nitrosopyrimidine was fused at 150° with 2-naphthol: the product (I; R = R′ = NH_2) was isolated from the melt in nearly quantitative yield.

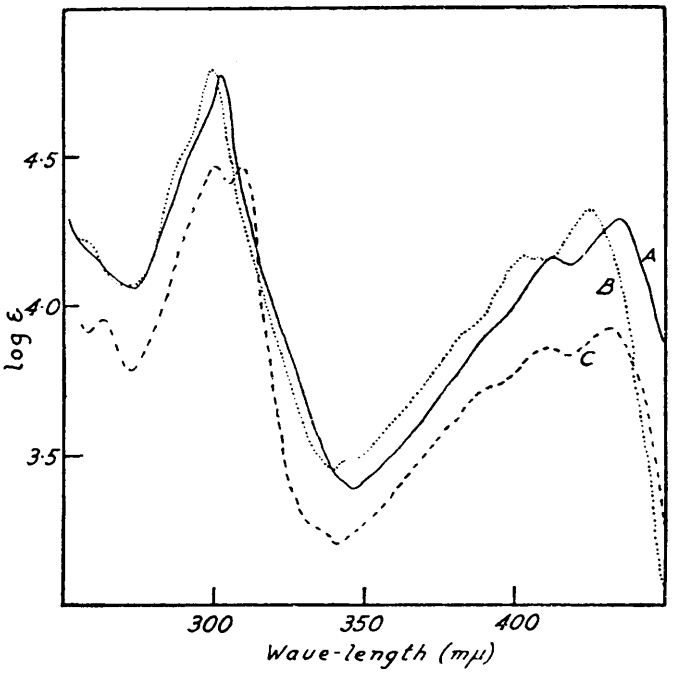
In considering the course of the reaction it was thought initially that its extremely weak basicity was responsible for the ejection of the di-2-chloroalkylamino-group from the naphthalene molecule; but using the corresponding weakly basic alcohol, *NN*-di-2′-hydroxyethyl-2-naphthylamine, we were unable to isolate any trace of compound (I; R = R′ = NH_2). Attempts to cause non-basic or weakly basic derivatives of 2-naphthylamine, *viz.*, *NN*-di-2′-acetoxyethyl-2-naphthylamine, 2-acetamidonaphthalene, or *N*-benzylidene-2-naphthylamine, to react with 2 : 4 : 6-triamino-5-nitrosopyrimidine failed, as did that with 2-naphthylamine hydrochloride. Thus no reaction occurred in the absence of halogen. This suggested that either inter- or intra-molecular quaternisation of the chloro-amine was necessary, the former being the more likely as the maximum yield of (I; R = R′ = NH_2,



or R = NH_2, R′ = MeS) occurred when two molecular proportions of the amine were taken.

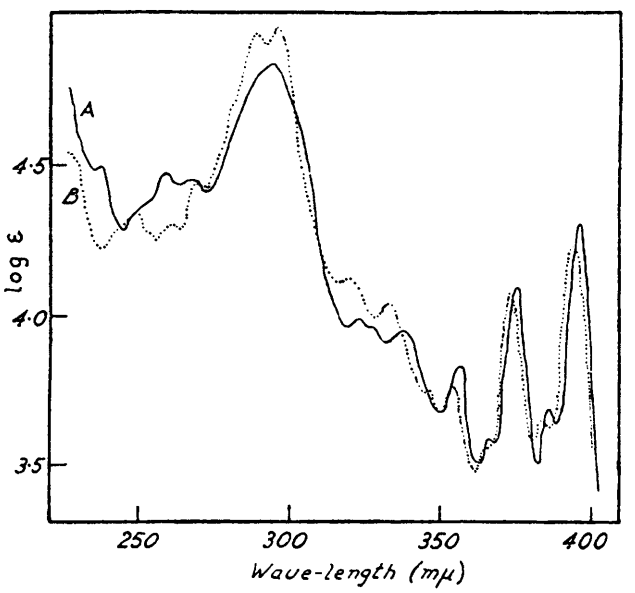
All attempts to isolate a quaternary salt of the aromatic nitrogen mustards have so far failed (Everett and Ross, *loc. cit.*) and we were unable to form the methiodide of *NN*-di-2′-hydroxyethyl-2-naphthylamine. Assuming, however, that quaternisation did occur to a slight extent in solution—and Ross and his co-workers do not exclude entirely the transitory

FIG. 1. *Ultra-violet absorption spectra.*



A, 3 : 4-6 : 7-*Dibenzacridine methoidide*.
B, 3 : 4-6 : 7-*Dibenzacridine*.
C, 1 : 2-6 : 7-*Dibenzacridine*.
(*Solvent:* 4·5% *formic acid for A;* 36% *formic acid for B and C*).

FIG. 2. *Ultra-violet absorption spectra.*

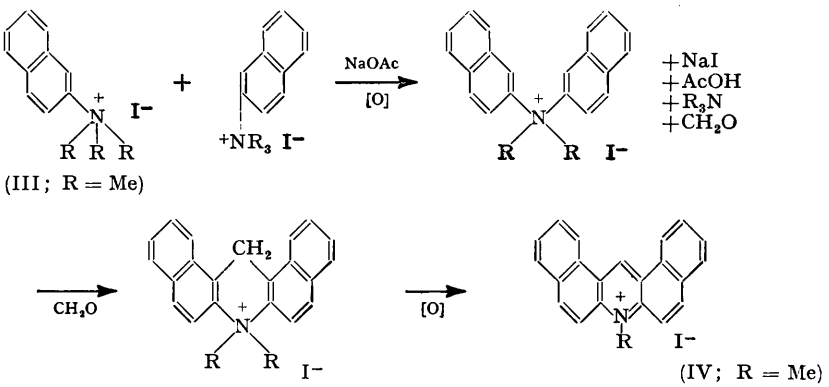


A, 3 : 4-6 : 7-*Dibenzacridine*.
B, 1 : 2-6 : 7-*Dibenzacridine*.
(*Solvent:* 95% *ethanol*).

existence of such compounds in solution—it is conceivable that under the influence of the sodium acetate, acting as a base in acetic acid, loss of the quaternary group as a tertiary alkylamine would occur, leaving a deficiency of electrons at position 2 of the naphthyl residue, which could then initiate the reaction as shown.

In the absence of quaternary salt derived from the chloro-amine, trimethyl-2-naphthylammonium iodide (III; R = Me) was chosen as a model. This reacts with 2 : 4 : 6-triamino-5-nitrosopyrimidine in hot glacial acetic acid in the presence of anhydrous sodium acetate more slowly than does *NN*-di-2'-chloroethyl-2-naphthylamine to yield an orange-yellow highly crystalline product in small amount. This product, which possessed a fluorescence reminiscent of that of (I; R = R' = NH_2), appeared to a be quaternary salt: although for some reason unknown the ordinary qualitative tests did not reveal the presence of iodine, iodide ion was present in the eluate when a dilute solution of the compound in aqueous acetone was allowed to percolate down a column of Amberlite IR-120. The same product was obtained from trimethyl-2-naphthylammonium iodide and 4 : 6-diamino-2-methylthio-5-nitrosopyrimidine, so that in this case it was very unlikely that the nitrosopyrimidine moiety was incorporated in the final product. Analysis indicated the formula $C_{22}H_{16}NI$ and the ultra-violet absorption spectrum was suggestive of an acridine system. Comparison with 1 : 2-6 : 7- and 3 : 4-6 : 7-dibenzacridine (Figs. 1 and 2) indicated the latter ring system, and the product was then identified as 3 : 4-6 : 7-dibenzacridine methiodide (IV) (Morgan, *J.*, 1898, **73**, 548).

This formation of an acridinium salt directly from the quaternary salt of an aromatic amine appears to be unique and we suggest that it is brought about by the oxidative action of the nitroso-compound which causes the union of two molecules of (III; R = Me) with concurrent formation of formaldehyde, which then provides the bridging carbon atom 5. The suggested mechanism is as illustrated.



An attempt to generalise this reaction, by oxidising (III; R = Me) to (IV) by means of chromic acid in acetic acid, failed: much iodine was formed by preferential oxidation of the iodide ion, and no other product was isolated.

It was thought that, whereas methyl groups might be readily lost as formaldehyde, it would be less likely that an ethyl group would be eliminated oxidatively as acetaldehyde. Moreover, triethyl-2-naphthylammonium iodide (III; R = Et) is a closer model for the suggested quaternary derivative from the chloro-amine. 2 : 4 : 6-Triamino-5-nitrosopyrimidine was accordingly treated with (III; R = Et) under the conditions obtaining earlier, but again no trace of (I; R = R' = NH_2) was found. Instead, triethyl-2-naphthylammonium tri-iodide was formed in good yield; this was independently synthesised from the iodide (III; R = Et) and one molecular proportion of iodine in aqueous ethanol.

A final attempt was made to obviate the complicating ease of oxidation of the iodide anion by treating 2 : 4 : 6-triamino-5-nitrosopyrimidine with triethyl-2-naphthylammonium chloride, a still closer analogy to the quaternary salt which we conjecture to be formed

from the chloro-amine but lacking 2′-chloro-substituents. However, prolonged heating did not cause any reaction.

In conclusion, the condensation of the chloro-amine to give the tetra-azabenzanthracene remains unique, and our suggested reaction mechanism for it, although plausible, remains tentative and unsubstantiated.

Experimental

M p.s were determined in an electrically heated copper block. Some of the analyses were done by Mr. F. Oliver, Imperial College of Science and Technology, S.W.7. Fluorescence observations were made in ultra-violet light from a Hanovia lamp, and ultra-violet absorption spectra were determined with a Unicam photoelectric spectrophotometer, Model SP. 500.

6 : 8-*Diamino*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (I; R = R′ = NH_2).—(a) *Reaction of* NN-*di*-2′-*chloroethyl*-2-*naphthylamine with* 2 : 4 : 6-*triamino*-5-*nitrosopyrimidine*. A mixture of *NN*-di-2′-chloroethyl-2-naphthylamine (16·2 g.), 2 : 4 : 6-triamino-5-nitrosopyrimidine (4·5 g.), and anhydrous sodium acetate (5·1 g.) in glacial acetic acid (60 ml.) was refluxed for 2 hr. during which the insoluble nitroso-compound was slowly replaced by a yellow precipitate. This was collected, extracted with hot water to remove traces of unchanged nitroso-compound, and crystallised several times from 80% formic acid, in which it appeared to be converted into a *formate*, pale yellow felted needles, m. p. >400° (Found: C, 57·4, 57·3; H, 4·2, 3·9; N, 27·4. $C_{14}H_{10}N_6$,H·CO_2H requires C, 58·5; H, 3·9; N, 27·3%). Consequently a hot solution in 80% formic acid was filtered into an excess of hot dilute aqueous ammonia, and the golden-yellow precipitate of 6 : 8-*diamino*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (I; R = R′ = NH_2), m. p. >400°, was washed with hot water, ethanol, and ether in succession and dried at 100°/0·1 mm. (Found: C, 62·8; H, 3·9; N, 31·8. $C_{14}H_{10}N_6$,$\frac{1}{4}H_2O$ requires C, 63·0; H, 3·9; N, 31·5. Found, on a sample dried at 150° in a high vacuum immediately before analysis: C, 63·6; H, 4·1; N, 31·9. $C_{14}H_{10}N_6$ requires C, 64·1; H, 3·8; N, 32·05%). Ultra-violet absorption max. in 4·5% formic acid solution: 281 (log ε 4·26), 291 (log ε 4·28), 302 (log ε 4·32), and 413 mμ (log ε 4·18). In dilute solution in glacial acetic acid the compound exhibited an intense yellow-green fluorescence. It gave a cherry-red colour in concentrated sulphuric acid. The *diacetamido*-derivative formed primrose-yellow needles, m. p. 322° (decomp.), from glacial acetic acid (Found: C, 61·8; H, 4·2; N, 23·6. $C_{18}H_{14}O_2N_6$,$\frac{1}{4}H_2O$ requires C, 61·6; H, 4·1; N, 24·0%).

(b) *Reaction of* NN-*di*-2′-*chloropropyl*-2-*naphthylamine with* 2 : 4 : 6-*triamino*-5-*nitrosopyrimidine*. *NN*-Di-2′-chloropropyl-2-naphthylamine (2·96 g.), 2 : 4 : 6-triamino-5-nitrosopyrimidine (0·8 g.), and anhydrous sodium acetate (0·8 g.) were refluxed in glacial acetic acid (10 ml.) for 2 hr. The yellow precipitate, worked up as in (a), was a *hydrated* base, m. p. >400° (Found: C, 60·6, 60·8; H, 4·2, 4·15; N, 30·7. $C_{14}H_{10}N_6$,$\frac{3}{4}H_2O$ requires C, 61·0; H, 4·2; N, 30·5%). Ultra-violet absorption max. in 4·5% formic acid solution: 281 (log ε 4·26), 291 (log ε 4·27), 302 (log ε 4·32), and 413 mμ (log ε 4·18).

(c) *Reaction of* 2-*naphthol with* 2 : 4 : 6-*triamino*-5-*nitrosopyrimidine*. 2-Naphthol (4·5 g.) was melted and 2 : 4 : 6-triamino-5-nitrosopyrimidine (1·54 g.) was stirred into it when the internal temperature was 130°. The temperature was held at 150° with intermittent stirring for 2 hr. The melt was cooled and extracted with ether, and the insoluble residue (2·56 g.) was thoroughly washed with ethanol and ether. Recrystallisation from 80% formic acid followed by a treatment with dilute ammonia afforded the tetra-aza-1 : 2-benzanthracene (I; R = R′ = NH_2), identified by the ultra-violet absorption in 4·5% formic acid solution: $\lambda_{max.}$ 281 (log ε 4·25), 291 (log ε 4·28), 302 (log ε 4·31), and 413 mμ (log ε 4·16).

8-*Amino*-6-*methylthio*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (I; R = NH_2, R′ = MeS).—*NN*-Di-2′-chloroethyl-2-naphthylamine (2·7 g.), 4 : 6-diamino-2-methylthio-5-nitrosopyrimidine (0·9 g.), and anhydrous sodium acetate (0·9 g.) in glacial acetic acid (20 ml.) were refluxed for 2 hr. and the solid obtained after cooling and collection was triturated with water, yielding a green solid (0·7 g.). Unchanged nitroso-compound was removed by extraction with boiling water (7 × 50 ml.), and the insoluble residue purified by crystallisation from 2-ethoxyethanol. The *tetra-aza*-1 : 2-*benzanthracene* (I; R = NH_2, R′ = MeS) formed greenish-yellow leaflets with a strong golden lustre, m. p. 330° (decomp.) (Found, in a sample dried at 140° in a high vacuum: C, 61·9; H, 4·2; N, 24·1. $C_{15}H_{11}N_5S$ requires C, 61·5; H, 3·8; N, 23·9%). The compound gives a cherry-red colour with concentrated sulphuric acid and exhibits an intense yellow-green fluorescence in glacial acetic acid.

3 : 4-6 : 7-*Dibenzacridine Methiodide* (IV).—(a) *Reaction of trimethyl*-2-*naphthylammonium*

iodide with 2 : 4 : 6-*triamino-5-nitrosopyrimidine.* 2 : 4 : 6-Triamino-5-nitrosopyrimidine (1·54 g.), trimethyl-2-naphthylammonium iodide (6·26 g.), and anhydrous sodium acetate (1·64 g.) were refluxed in glacial acetic acid (30 ml.). After 1 hr. precipitation of orange crystals began and the mixture was filtered hot after 5 hr. The orange solid (2·18 g.) so obtained was dissolved in hot aqueous-ethanolic sodium hydroxide, and the solution filtered and acidified with acetic acid, yielding a precipitate (1·29 g.). This was then further purified by crystallisation from 80% formic acid and finally from 50% formic acid, to yield lustrous orange-yellow prisms, m. p. 284° (decomp.), undepressed on admixture with 3 : 4-6 : 7-dibenzacridine methiodide [Morgan, *loc. cit.*, gives m. p. 262—264° (decomp.)] (Found : C, 62·5, 63·0; H, 3·8, 3·95; N, 3·3, 3·6; I, 29·6; NMe, 6·9. Calc. for $C_{22}H_{16}NI$: C, 62·7; H, 3·8; N, 3·3; I, 30·1; NMe, 6·9%. A Rast determination could not be carried out owing to the insolubility of the compound in camphor). Ultra-violet absorption spectrum max. in 4·5% formic acid : 302 (log ε 4·78), 412 (log ε 4·16), and 434 mμ (log ε 4·29).

(b) *Reaction of trimethyl-2-naphthylammonium iodide with* 4 : 6-*diamino-2-methylthio-5-nitroso-pyrimidine.* Trimethyl-2-naphthylammonium iodide (3·13 g.) in glacial acetic acid (20 ml.) with 4 : 6-diamino-2-methylthio-5-nitrosopyrimidine (0·92 g.) and anhydrous sodium acetate (0·82 g.), treated as in (a), gave the same orange-yellow prisms (0·55 g., crude) m. p. and mixed m. p. 284° (decomp.) (Found : C, 62·3; H, 3·7%), having the recorded ultra-violet absorption max. in 4·5% formic acid. Addition of ether to the mother-liquors from the reaction gave a buff precipitate, which was boiled with aqueous-ethanolic sodium hydroxide; the resulting pale orange solution was filtered and acidified with acetic acid. No precipitate was obtained but the addition of saturated ethanolic picric acid afforded a *picrate*, yellow needles (from ethanol), m. p. 195°, undepressed on admixture with authentic trimethyl-2-naphthylammonium picrate (Ingham, *J.*, 1927, 1972) (Found : C, 55·4; H, 4·4. $C_{19}H_{18}O_7N_4$ requires C, 55·1; H, 4·4%).

Triethyl-2-naphthylammonium Periodide.—(*a*) Triethyl-2-naphthylammonium iodide (0·5 g.) was dissolved in a mixture of water (20 ml.) and ethanol (5 ml.). Iodine solution (29·25 ml. of 0·965 × 0·1N-iodine) was added and the dark red precipitate (yield quantitative) was collected after thorough chilling. When crystallised from ethanol, the *tri-iodide* formed dark red needles with a steely-blue lustre, m. p. 99° (Found : C, 31·9; H, 3·9; N, 2·3; I, 63·2. $C_{16}H_{22}NI_3$ requires C, 31·7; H, 3·6; N, 2·3; I, 62·5%). The tri-iodide, in hot water, yields the characteristic blue colour with starch solution.

(*b*) Triethyl-2-naphthylammonium iodide (3·55 g.) was heated with a suspension of 2 : 4 : 6-triamino-5-nitrosopyrimidine (0·78 g.) and anhydrous sodium acetate (0·82 g.) in glacial acetic acid (20 ml.). The precipitate of greenish-brown iridescent needles (1·5 g.) was collected after 4 hr. and crystallised from 80% formic acid, yielding the tri-iodide as dark red needles with a blue sheen, m. p. and mixed m. p. 98—99°. The mother-liquors afforded only dark oils.

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