Xanthones and Thioxanthones. Part VI. The Preparation and Properties of 9-Thia-3-aza-anthrone.*

By S. KRUGER and FREDERICK G. MANN.

[Reprint Order No. 6223.]

The preparation of 9-thia-3-aza-anthrone (which completes the series of the four isomeric 9-thia-aza-anthrones) and of certain derivatives is described. 9-Oxa-3-aza-anthrone has been synthesised, but only in low yield. The 9-thia-compound and its methochloride are ineffective as schistosomicides.

THE synthesis and properties of 9-oxa-1-aza-, 9-thia-1-aza-, 9-thia-2-aza-, and 9-thia-4-aza-anthrone have been described in Parts III—V.* We have now prepared 9-thia-3-aza-anthrone (V), which is the remaining isomer in this thia-series.

The general method adopted for the synthesis of the above 1-aza-, 2-aza- and 4-aza-anthrones consisted essentially in the introduction first of the carboxylic acid group and then of the SPh group into the appropriate positions in the pyridine nucleus: the acid was then converted into the acid chloride, which was condensed with the phenyl residue to give

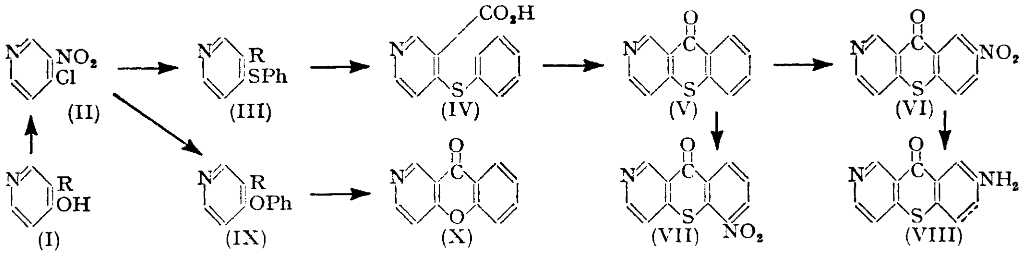
---

* Parts III—V, *J.*, 1951, 761; 1952, 2057; 1954, 3905.

the desired 9-thia-aza-anthrone. Syntheses on these lines, introducing first either the carboxy- or the cyano-group into the pyridine ring, uniformly failed in the 3-aza-series.

Consequently, 4-hydroxypyridine was nitrated, to give 4-hydroxy-3-nitropyridine (I; R = NO$_2$), which in turn gave 4-chloro-3-nitropyridine (II). A cold equimolecular mixture of this with thiophenol, when carefully warmed to *ca.* 20°, underwent a sudden and violent reaction with complete solidification but no loss of hydrogen chloride. This product melted at *ca.* 190° with vigorous evolution of hydrogen chloride, forming 3-nitro-4-pyridyl phenyl sulphide (III; R = NO$_2$) which on reduction gave the 3-amino-sulphide (III; R = NH$_2$) and then, by diazotisation and treatment with potassium iodide, 3-iodo-4-pyridyl phenyl sulphide (III; R = I).

It is noteworthy that 3-cyano-4-pyridyl phenyl sulphide (III; R = CN) was obtained by treating the diazotised amino-compound with potassium cuprocyanide and by heating the iodo-compound with an excess of dry cuprous cyanide: in both cases the yield was very low, and all attempts to hydrolyse the nitrile to the required 3-carboxy-4-pyridyl phenyl sulphide (IV) caused extensive decomposition.



The preparation of a Grignard reagent from the 3-iodo-sulphide (III; R = I) could not be satisfactorily achieved, for the sulphide is insoluble in diethyl ether, and in di-*n*-amyl ether solution it rapidly coats the magnesium with a white insoluble film which prevents further reaction. Gilman and Spatz (*J. Amer. Chem. Soc.*, 1940, **62**, 446) have shown that halogenopyridines can be converted by *n*-butyl-lithium into lithiopyridines if a low temperature and a short reaction time are employed: otherwise butylation of the pyridine ring may occur. For example, they converted 3-bromoquinoline into the lithio-derivative at —35° using a metalation time of 15 minutes: Murray, Foreman, and Langham (*ibid.*, 1948, **70**, 1037), using 3-bromopyridine, reduced the metalation time to 5 minutes.

We have briefly investigated the yield of the acid (IV) obtained when the iodo-sulphide (III; R = I) and *n*-butyl-lithium are allowed to react in toluene at various temperatures and for various times, the product being then treated with an excess of solid carbon dioxide. When a metalation time of 5 minutes was employed, the yields of acid at —25°, —30°, —35°, —37·5°, —40°, and —45° were 53, 62, 68, 72, 68, and 55% respectively: when the metalation was carried out at —40°, the yields of acid using a metalation time of 3·5, 5, and 6 minutes were 60, 68, and 58% respectively. Using the optimum conditions, *i.e.*, metalation at —38° for 5 minutes, we have thus obtained the acid in 73% yield.

The acid (IV) was converted into the acid chloride with thionyl chloride, and then cyclised in nitrobenzene, by using aluminium chloride, to 9-thia-3-aza-anthrone (V).

9-Thia-3-aza-anthrone (V), when heated with methyl toluene-*p*-sulphonate, readily undergoes quaternisation, and the methiodide and methochloride have thus been obtained. Attempts to oxidise the anthrone (V) to the sulphone failed, only intractable yellow oils being obtained: this result contrasts markedly with the ready and mild oxidation of the three isomeric 9-thia-aza-anthrones to their sulphones.

The nitration of the anthrone (V) gave one mononitro-derivative, m. p. 335°, in 66% yield, and an isomer, m. p. *ca.* 225°, in 17% yield: there is little doubt that these compounds are the 6- and the 8-nitro-derivatives (VI and VII) respectively, for nitration would occur more readily in the position *para* to the sulphur atom than in that *ortho* to this atom (cf. the corresponding products in the 2- and 4-aza-series). The very pale yellow 6-nitro-derivative (VI) on reduction gave the orange-yellow 6-amino-9-thia-3-aza-anthrone (VIII).

It is noteworthy that the 6-amino-derivatives of the 2- and 4-aza-anthrones are deep red, and evidence was adduced (Part IV) that this intense colour was due in each case to the contribution of a quadruply charged form in which the primary amine group and the sulphur atom become positively charged and the oxygen and the pyridyl nitrogen atom negatively charged : this is supported by the less intense colour of the 6-amino-derivative (VIII), which cannot show this extensive charge separation.

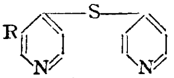
In earlier attempts to introduce the cyano-group into the pyridine ring before reaction with thiophenol, 4-hydroxy-3-nitropyridine (I; $R = NO_2$) was converted in turn into 3-amino-4-hydroxypyridine (I; $R = NH_2$) and 4-hydroxy-3-iodopyridine (I; $R = I$). Neither the amino- nor the iodo-compound could be converted into 3-cyano-4-hydroxypyridine (I; $R = CN$). Furthermore, many attempts using a variety of conditions to convert 4-hydroxynicotinic acid into 4-chloronicotinic acid (on the lines of our earlier syntheses) failed, the hydroxy-acid being either unchanged or, under more vigorous conditions, completely decomposed. Failure also attended the use, in the model experiments, of ethyl 4-chloro-2 : 6-dimethylnicotinate, which can be readily prepared from ethyl aminocrotonate (Michaelis and Arend, *Ber.*, 1901, **34**, 2284), for this chloro-group is unreactive and could not be condensed with thiophenol under various conditions.

9-Oxa-3-aza-anthrone (X) has also been prepared, but the synthetic route remains unsatisfactory. 4-Chloro-3-nitropyridine (II) condensed smoothly with phenol to give 3-nitro-4-pyridyl phenyl ether (IX; $R = NO_2$); reduction then gave the 3-amino-derivative (IX; $R = NH_2$), which was converted into the 3-iodo-derivative (IX; $R = I$). The great instability of this iodo-derivative, even at room temperature, alone or in toluene solution, made the preparation of a lithio-derivative impracticable, and the synthetic route analogous to that employed for the thia-anthrone (V) had to be abandoned. The 3-amino-derivative (IX; $R = NH_2$) was therefore converted into 3-cyano-4-pyridyl phenyl ether (IX; $R = CN$), but the yield was very low, and all attempts to hydrolyse the nitrile to the acid caused decomposition. The cyano-derivative (IX; $R = CN$) when heated with sulphuric acid at 110° gave the carbamoyl derivative (IX; $R = CO{\cdot}NH_2$) but at 195° gave the required 9-oxa-3-aza-anthrone (X), both in very low yield, possibly owing to the formation of water-soluble sulphonated phenoxy-derivatives. A detailed investigation of the properties of the anthrone (X) could not therefore be undertaken.

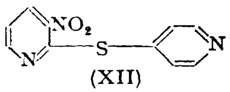
This conversion of an aromatic nitrile into a cyclic ketone is unusual, but Schaarschmidt (*Annalen*, 1915, **409**, 59) has shown that 1-cyano-2-*p*-tolylthioanthraquinone when heated with sulphuric acid undergoes a similar cyclisation to the corresponding thioxanthone.

Ultraviolet absorption data for 9-oxa-1-aza- and 9-oxa-3-aza-anthrone and the four isomeric 9-thia-aza-anthrones and various derivatives are given on p. 2761 and briefly discussed.

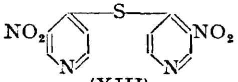
Certain pyridine derivatives prepared as intermediates for possible syntheses of 9-thia-diaza-anthrones, having the nitrogen atoms in different rings, are now recorded. 4-Chloro-3-nitropyridine (II) reacted with pyridine-4-thiol in boiling ethanol to give 3-nitro-4 : 4'-dipyridyl sulphide (XI; $R = NO_2$), but in acetone containing potassium carbonate to give 4 : 4'-dipyridyl sulphide (XI; $R = H$). The result recalls that of King and Ware (*J.*, 1939, 875), who found that pyridine-4-thiol reacted with bromine to give 4 : 4'-dipyridyl disulphide, but anomalously with chlorine to give the sulphide (XI; $R = H$). We find that the thiol reacted normally with 2-chloro-3-nitropyridine to give 3-nitro-2-pyridyl 4-pyridyl sulphide (XII). 3-Nitropyridine-4-thiol reacted with 4-chloro-3-nitropyridine (II) to form both di-3-nitro-4-pyridyl sulphide (XIII) and (in greater yield) the corresponding disulphide. Finally, a mixture of the pyridine (II) and 4-hydroxypyridine in boiling concentrated absolute ethanol solution gave 4-hydroxy-3-nitropyridine (I; $R = NO_2$) in 61% yield, a result which could hardly be due to simple hydrolysis. These reactions



(XI)



(XII)



(XIII)

warrant further investigation, particularly as only the main products were isolated in the above brief investigation.

Tests kindly undertaken by Mr. O. D. Standen at the Wellcome Laboratories of Tropical Medicine have shown that 9-thia-3-aza-anthrone (V) and its methochloride have no significant effect on schistosomiasis infections (cf. Part V). The introduction of the nitrogen atom into the four possible positions in the thioxanthone molecule has thus been without effect for this purpose.

EXPERIMENTAL

4-*Hydroxy*-3-*nitropyridine* (I; R = NO_2).—Pyridine was converted into 4-hydroxypyridine nitrate (Koenigs and Greiner, *Ber.*, 1931, **64**, 1049; Leis and Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 79). The nitrate (282 g.) was added to a mixture of fuming nitric acid (*d* 1·5) (570 g.) and 20% oleum (570 g.) which was warmed gently and, after the initial reaction had subsided, boiled for 1 hr. The cold mixture was poured with stirring into water (2 l.) and partly neutralised with ammonia. The precipitated yellow 4-hydroxy-3-nitropyridine (I; R = NO_2), when collected, washed, and dried (219 g., 88%), had m. p. 278—279°, and was sufficiently pure for the next stage: it crystallised readily from water (cf. Bremer, *Annalen*, 1937, **529**, 294). Koenigs and Fulde (*Ber.*, 1927, **60**, 2108) give m. p. 280—281°.

4-*Chloro*-3-*nitropyridine* (II).—Phosphorus oxychloride (9 c.c.) was added to an intimate mixture of the powdered hydroxy-pyridine (I; R = NO_2) (90 g.) and phosphorus pentachloride (150 g.), which was then heated in an oil-bath (120—130°) to ensure gentle boiling. When hydrogen chloride evolution ceased (*ca.* 3 hr.), distillation first removed the oxychloride at atmospheric pressure, and then gave the chloro-pyridine (II), a pale yellow liquid (83 g., 82%), b. p. 158°/25 mm., which solidified on cooling. Reitmann (*Med. u. Chem. Abh. med.-chem. Forschungstätten I.G. Farbenind.*, 1934, **2**, 384; *Chem. Zentr.*, 1934, I, 3597) gives m. p. 45°, b. p. 95°/5 mm. The compound, which is lachrymatory and a strong skin-irritant, is stable if kept dry in a refrigerator.

3-*Nitro*-4-*pyridyl Phenyl Sulphide* (III; R = NO_2).—The chloro-pyridine (II) (3·1 g.) and thiophenol (2·1 g., 1 mol.) were mixed at *ca.* 10° and then cautiously warmed to *ca.* 20°; a violent exothermic reaction occurred and the mass solidified. This product melted at 185—190° with hydrogen chloride evolution, and was kept at 190—195° for 1 hr. until this decomposition was complete. The brown residual oil solidified on cooling, and when recrystallised from benzene and then aqueous ethanol furnished the *sulphide* (III; R = NO_2), yellow crystals, m. p. 86° (4·5 g.) (Found: C, 57·3; H, 3·6; N, 12·2. $C_{11}H_8O_2N_2S$ requires C, 56·9; H, 3·5; N, 12·1%).

3-*Amino*-4-*pyridyl Phenyl Sulphide* (III; R = NH_2).—Granulated tin (27 g.) was added to a suspension of the sulphide (III; R = NO_2) (22·8 g.) in concentrated hydrochloric acid (100 c.c.). On cautious heating, a vigorous reaction occurred, and the mixture was then heated on a water-bath for 30 min. The clear solution was strongly basified and the precipitated brown solid, when collected, washed, dried, and recrystallised from light petroleum (b. p. 60—80°), gave the *sulphide* (III; R = NH_2), cream-coloured needles, m. p. 107·5—108° (11·5 g., 58%) (Found: C, 65·3; H, 4·75; N, 13·6. $C_{11}H_{10}N_2S$ requires C, 65·3; H, 4·95; N, 13·8%).

3-*Iodo*-4-*pyridyl Phenyl Sulphide* (III; R = I).—A diazotised solution of the sulphide (III; R = NH_2) (8 g.) was added dropwise to an excess of potassium iodide in water at 75°. The deposited heavy brown oil, when collected, washed in turn with sodium hydroxide and thiosulphate solutions, and distilled, gave the sulphide (III; R = I) as a pale brown viscous syrup, b. p. 149°/0·03 mm. (slight decomp.) (8·9 g., 72%).

For characterisation, a sample was dissolved in an excess of warm aqueous 60% perchloric acid, which on cooling deposited the *perchlorate*, pale yellow leaflets, m. p. 189·5°, from water (Found: C, 32·2; H, 2·0; N, 3·5. $C_{11}H_8NIS,HClO_4$ requires C, 31·9; H, 2·2; N, 3·4%).

Aqueous chloroplatinic acid, when added to a suspension of another sample in concentrated hydrochloric acid, gave a yellow granular precipitate, m. p. 292° (decomp.), which, when recrystallised from ethanol–epichlorohydrin, apparently underwent co-ordination with reduction to bivalent platinum, forming *bis*-(3-*iodo*-4-*pyridyl phenyl sulphide*)*dichloroplatinum*, pale yellow rods, m. p. 164° (decomp.) (Found: C, 29·7; H, 2·0; N, 2·9; Pt, 22·0. $C_{22}H_{16}N_2Cl_2I_2S_2Pt$ requires C, 29·6; H, 1·8; N, 3·1; Pt, 21·9%).

3-*Cyano*-4-*pyridyl Phenyl Sulphide* (III; R = CN).—(*A*) A diazotised solution of the amine (III; R = NH_2) (2·5 g.) was added dropwise to a solution of cuprous cyanide in aqueous potassium cyanide at 75°. The brown precipitate was collected from the cooled mixture, dried, and extracted with boiling ethanol. Evaporation of the filtered extract gave a dark brown gum, which, after repeated crystallisation from light petroleum (b. p. 60—80°), furnished the ***nitrile*** (III; R = CN), pale yellow crystals, m. p. 63—63·5° (0·45 g., 17%) (Found: C, 67·9; H, 3·7; N, 12·9. $C_{12}H_8N_2S$ requires C, 67·9; H, 3·8; N, 13·2%).

(*B*) An intimate mixture of the iodo-sulphide (III; R = I) (1 g.) and cuprous cyanide (3 g.), on heating, underwent no apparent change until 200°, when it darkened considerably. Extraction with boiling ethanol and recrystallisation as in (*A*) gave the nitrile (III; R = CN), m. p. and mixed m. p. 63°. The yield was very low.

The nitrile was unaffected when its suspension in 5% aqueous sodium hydroxide was boiled under reflux for 5 hr. Its solution in ethanolic potassium hydroxide, when boiled for 1 hr., evolved ammonia and then contained thiophenol. A mixture of the nitrile with concentrated hydrochloric acid or 90% sulphuric acid, when heated at 100° for 3 hr., liberated thiophenol, but the mixture yielded only a small amount of the unchanged nitrile.

3-*Carboxy*-4-*pyridyl Phenyl Sulphide* (IV).—(*a*) To prepare the solution of *n*-butyl-lithium, fine strips of very thin lithium foil (4 g.) and glass beads were added to a solution of *n*-butyl chloride (18·4 g.) in anhydrous toluene (200 c.c.) under nitrogen. The mixture was shaken for 24 hr., and then filtered under nitrogen pressure through a sintered glass funnel containing freshly heated "Hyflo Supercel." The concentration of the filtrate (which was stored under nitrogen) was determined by titration with standard acid. The yield was 64—69%. (*b*) A pre-cooled solution of the iodo-sulphide (III; R = I) (2·5 g.) in anhydrous toluene (10 c.c.) was rapidly added to the butyl-lithium solution (1·1 mols. of solute) which had been placed under nitrogen in a flask fitted with a mercury seal, and had been very vigorously stirred whilst being cooled to −38°. After 5 min., finely powdered carbon dioxide (*ca.* 5 g.) was added, and the stirring continued for 10 min. more. The mixture was poured into water, and the aqueous layer separated and treated with acetic acid until it attained pH 4. The precipitated yellow ***acid*** (IV) (1·45 g., 73%), when washed and dried, was sufficiently pure for the next stage: a sample, recrystallised in turn from ethanol and acetic acid, formed cream-coloured crystals, m. p. 236° (Found: C, 62·0; H, 4·05; N, 5·9. $C_{12}H_9O_2NS$ required C, 62·3; H, 3·9; N, 6·05%).

If the above acidification was carried out with 5N-hydrochloric acid, the ***hydrochloride*** of the acid was precipitated; it formed colourless crystals, m. p. 275° (decomp.), from ethanol (Found: C, 53·5; H, 3·6; N, 5·4. $C_{12}H_9O_2NS,HCl$ requires C, 53·8; H, 3·7; N, 5·2%).

Toluene was employed as a solvent in the above preparation because the iodo-sulphide (III; R = I) is insoluble in ether and light petroleum, and the use of benzene (cf. Ziegler and Colonius, *Annalen*, 1930, **479**, 135) was obviously precluded.

A sample of the acid (IV) was heated at 250° until effervescence ceased. The homogeneous melt, on cooling, formed an oil which did not solidify but, when treated with picric acid (both in ethanolic solution), gave ***phenyl 4-pyridyl sulphide picrate***, yellow needles, m. p. 165°, from water (Found: C, 49·05; H, 3·05; N, 13·7. $C_{11}H_9NS,C_6H_3O_7N_3$ requires C, 49·0; H, 2·9; N, 13·5%).

9-*Thia*-3-*aza-anthrone* (V).—A mixture of the acid (IV) (9·1 g.) and thionyl chloride (30 c.c.) was boiled under reflux for 1 hr., the excess of chloride removed under reduced pressure, and the residue dissolved in dry nitrobenzene (50 c.c.), to which powdered aluminium chloride (13·5 g.) was then added. The mixture was heated at 100° for 3 hr., carefully poured on ice, and the nitrobenzene removed with steam. The filtered solution, when cooled and strongly basified with aqueous sodium hydroxide, deposited the ***anthrone*** (V) (7·45 g., 89%), which, when sublimed in a vacuum or crystallised from ethanol, formed colourless needles, m. p. 181° (Found: C, 67·7; H, 3·6; N, 6·75. $C_{12}H_7ONS$ requires C, 67·6; H, 3·3; N, 6·6%).

Quaternary salts. A mixture of the anthrone (V) (2 g.) and methyl toluene-*p*-sulphonate was heated at 170° for 4 hr., cooled, and repeatedly extracted with ether. An aqueous solution of the residue, when filtered and treated with an excess of aqueous potassium iodide, deposited the ***methiodide*** (2·5 g., 75%), yellow needles, m. p. 279·5—280°, from water (Found: C, 44·2; H, 3·0; N, 4·05. $C_{13}H_{10}ONIS$ requires C, 43·95; H, 2·85; N, 3·95%).

An excess of freshly prepared silver chloride was added to a solution of the methiodide (1 g.) in hot methanol (300 c.c.), which was boiled under reflux for 1 hr. whilst protected from the light. The hot mixture was filtered, the residue was washed with hot methanol, and the combined filtrate and washings were evaporated to small bulk, cooled, and diluted with a small volume of ether. The precipitated ***methochloride monohydrate*** (0·39 g., 49%), when recrystallised from methanol–ether, had m. p. 261·5° (efferv.) (Found: C, 55·4; H, 4·4; N, 4·9. $C_{13}H_{10}ONClS,H_2O$ requires C, 55·4; H, 4·25; N, 5·0%). The salt dissociates at its m. p. giving a residue of the pure anthrone (V), m. p. and mixed m. p. 180—181°.

Attempted oxidation. A suspension of the finely powdered anthrone (V) (1 g.) in acetic acid

(20 c.c.) was diluted with 30% hydrogen peroxide (4 c.c.) and kept at 70° for 5 hr. The addition of water precipitated unchanged anthrone (0·320 g.), and the only other product isolated was a water-soluble yellow oil which could not be purified. Closely similar results were obtained when this oxidation was performed at 90° for 2 hr., or at 20° for 2 or 14 days, and when the oxidation was attempted using chromic acid in acetic or in 10N-sulphuric acid, or potassium permanganate in acetone.

Nitration.—A mixture of the anthrone (1 g.), powdered sodium nitrate (0·5 g.), and sulphuric acid (100 c.c.) was kept at 35—40° with stirring for 10 min., and then poured on ice and neutralised with ammonia. The yellow precipitate was collected, washed, dried, and repeatedly extracted with boiling ethanol. The insoluble residue (0·80 g., 66%), when recrystallised from acetic acid, gave 6-*nitro*-9-*thia*-3-*aza-anthrone* (VI), very pale yellow needles, m. p. 355° (Found : C, 55·85; H, 2·25; N, 11·3. $C_{12}H_6O_3N_2S$ requires C, 55·8; H, 2·3; N, 10·8%); it sublimed fairly readily at *ca.* 230°/0·002 mm.

The ethanolic extracts on evaporation gave the crude 8-*nitro*-isomer (VII) (0·20 g., 16·5%), which was recrystallised from a minimum of ethanol so that the least soluble portion was discarded : after sublimation it melted rather indefinitely at 225° (Found : C, 55·6; H, 2·2; N, 11·1. $C_{12}H_6O_3N_2S$ requires C, 55·8; H, 2·3; N, 10·8%). The indefinite m. p. may indicate slight contamination by the 6-nitro-isomer, but there was insufficient material for further crystallisation : the infrared spectra of the two isomers were too similar to permit detection of a very small proportion of (VI) in (VII).

Stannous chloride (1·5 g.) was added to a solution of the 6-nitro-derivative (VI) (0·55 g.) in concentrated hydrochloric acid (10 c.c.), which was then kept at 60° for 1 hr. The cold mixture was strongly basified and the precipitated 6-*amino*-9-*thia*-3-*aza-anthrone* (VIII) was collected, washed, dried, and heated at 225—230°/0·0005 mm., subliming very slowly to form orange-yellow prisms (0·42 g., 86%), m. p. 272—273° (Found : C, 63·9; H, 3·6; N, 12·7. $C_{12}H_8ON_2S$ requires C, 63·2; H, 3·5; N, 12·3%). Resublimation or recrystallisation from ethanol did not change the m. p.

3-*Iodo*-4-*hydroxypyridine* (I; R = I).—(*a*) Iron " pin-dust " (20 g.) was added in small portions to a warm stirred suspension of 4-hydroxy-3-nitropyridine (I; R = NO_2) (20 g.) in water (100 c.c.) containing concentrated hydrochloric acid (1 c.c.). When the main reaction had subsided, more pin-dust (30 g.) was added, and the mixture was heated for 30 min. on the water-bath, filtered hot, treated with an excess of hydrochloric acid, and evaporated to small bulk. The solution, on cooling, deposited crystalline 3-amino-4-hydroxypyridine hydrochloride (17·5 g., 84%) (cf. Crowe, *J.*, 1925, **127**, 2028). The free base readily decomposes, forming a coloured resin.

(*b*) A diazotised solution of this hydrochloride (7·8 g.) was added to an excess of aqueous potassium iodide, which was then gently warmed until effervescence ceased. The filtered solution, when neutralised with sodium hydrogen carbonate, deposited the *iodo*-compound (I; R = I) (3·25 g., 28%), colourless leaflets, m. p. 299—300° (decomp.), from water (Found : C, 27·6; H, 1·65; N, 6·35. C_5H_4ONI requires C, 27·2; H, 1·8; N, 6·3%).

3-*Nitro*-4-*pyridyl Phenyl Ether* (IX; R = NO_2).—A mixture of 4-chloro-3-nitropyridine (II) (7·2 g.) and phenol (15 g., 3·5 mols.) was heated under reflux until evolution of hydrogen chloride ceased (*ca.* 1 hr.), and was then cooled and poured into an excess of sodium hydroxide solution. The precipitated material solidified and, when collected, washed and recrystallised from aqueous ethanol or light petroleum (b. p. 40—60°), gave the colourless *nitro-ether* (IX; R = NO_2) (8·7 g., 89%), m. p. 74° (Found : C, 61·4; H, 3·9; N, 13·2. $C_{11}H_8O_3N_2$ requires C, 61·1; H, 3·7; N, 13·0%).

3-*Amino*-4-*pyridyl Phenyl Ether* (IX; R = NH_2).—Granulated tin (10·5 g.) was added to a solution of the ether (IX; R = NO_2) (6 g.) in concentrated hydrochloric acid (30 c.c.), which when gently warmed deposited a sticky cream-coloured solid : at *ca.* 35° a violent reaction ensued, and strong external cooling was applied. When the reaction subsided, the clear pale brown solution was heated at 100° for 1 hr., cooled, strongly basified, and repeatedly extracted with ether. The united extracts on distillation gave the amino-ether (IX; R = NH_2) as a pale yellow viscous syrup (4 g., 78%), b. p. 138°/0·2 mm., 145°/0·5 mm., which could not be obtained solid. In ethanol, it gave a *picrate*, yellow needles, m. p. 230°, from much ethanol (Found : C, 49·2 ; H, 2·8; N, 17·1. $C_{11}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 49·1; H, 3·1; N, 16·9%).

3-*Iodo*-4-*pyridyl Phenyl Ether* (IX; R = I).—The amino-ether (IX; R = NH_2) (23·7 g.) was diazotised, excess of nitrous acid removed with urea, and the solution then added as usual to aqueous potassium iodide. The heavy dark brown oil, when distilled in nitrogen, gave the iodo-ether (IX; R = I) (28 g., 75%) as a viscous brown syrup, b. p. 134°/0·03 mm. The syrup, alone or in toluene solution, rapidly deposited a solid, which on crystallisation from ethyl acetate gave bronze-coloured leaflets, m. p. 155°: they were not identified, but may have been a *polyiodide* [Found: C, 27·2; H, 1·9; N, 3·1. $(C_{11}H_8ONI)_2I_3$ requires C, 27·1; H, 1·6; N, 2·9%].

The freshly prepared iodo-ether in ethanol solution, when added to aqueous chloroplatinic acid, gave a yellow precipitate insoluble in the common solvents: recrystallisation from epichlorohydrin caused co-ordination with the formation of *bis-(3-iodo-4-pyridyl phenyl ether)-tetrachloroplatinum*, yellow plates, m. p. 249° (dependent on rate of heating, considerable darkening at *ca.* 220°) (Found: C, 28·6; H, 2·1; N, 3·1; Pt, 21·0. $C_{22}H_{18}O_2N_2Cl_4I_2Pt$ requires C, 28·4; H, 1·75; N, 3·0; Pt, 21·0%).

3-*Cyano-4-pyridyl Phenyl Ether* (IX; R = CN).—The amino-ether (IX; R = NH_2) (2·8 g.), when diazotised and added to aqueous potassium cuprocyanide, gave the *nitrile* (IX; R = CN), which after sublimation at 100°/0·2 mm. and recrystallisation from ethanol formed colourless crystals (0·6 g., 21%), m. p. 104—105° (Found: C, 73·8; H, 4·4; N, 14·5. $C_{12}H_8ON_2$ requires C, 73·5; H, 4·2; N, 14·3%).

A suspension of this nitrile in 6N-hydrochloric acid, when boiled under reflux for 6 hr., gave a strong odour of phenol, but no other product could be isolated. A solution of the nitrile in ethanolic potassium hydroxide, when similarly boiled for 3 hr., evolved ammonia and gave an intractable dark resinous product.

3-*Carbamoyl-4-pyridyl Phenyl Ether* (IX; R = $CO{\cdot}NH_2$).—A mixture of the nitrile (0·2 g.) and 95% sulphuric acid (2 c.c.) was heated at 110° for 90 min., cooled, diluted, and treated with an excess of aqueous ammonia. The precipitated *amide* (IX; R = $CO{\cdot}NH_2$), when sublimed at 160°/0·005 mm., formed a colourless micro-crystalline powder (35 mg., 16%), m. p. 196° (Found: C, 67·6; H, 5·0; N, 12·6. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%).

9-*Oxa-3-aza-anthrone* (X).—The above mixture of nitrile and sulphuric acid was heated at 195° for 30 min., and the dark-brown reaction mixture, treated as before, deposited the *anthrone* (X), which after repeated sublimation at 160°/0·005 mm. formed white needles (20 mg., 10%), m. p. 184·5° (Found: C, 72·4; H, 3·8; N, 7·3. $C_{12}H_7O_2N$ requires C, 73·1; H, 3·6; N, 7·1%). A similar result was obtained when the mixture was heated at 165—170° for 3·5 hr.

Ultraviolet Absorption Spectra.—All were determined (see Table) in ethanol containing 5% of water except those marked *, which were determined in water. The λ values (in mμ) are followed by the ε values in parentheses.

Xanthone	$\lambda_{max.}$	238 (38,700)	260 (11,900)	287 (4260)	336 (6300); $\lambda_{infl.}$ 232—233 (34,900)		
	$\lambda_{min.}$	212 (8390)	251 (8390)	281 (3860)	298 (930)		
Anthrone							
9-Oxa-1-aza-	$\lambda_{max.}$	226 (28,400)	276 (10,100)	282 (13,000)	332 (8000)		
	$\lambda_{min.}$	254 (6200)	277 (10,000)	298 (1640)			
9-Oxa-3-aza-	$\lambda_{max.}$	232—234 (40,000)		324 (5400);	$\lambda_{infl.}$ 254—256 (11,990)		
	$\lambda_{min.}$	214 (17,100)		288 (1300)			
Thioxanthone	$\lambda_{max.}$	214 (5900)	219 (7400)	257 (18,900)	286 (2330)	299 (1590)	379 (2990)
	$\lambda_{min.}$	216 (5790)	225 (2690)	285 (2320)	295 (2450)	314 (166)	
Anthrone							
9-Thia-1-aza-	$\lambda_{max.}$	227 (25,800)	239 (24,000)	254 (34,350)	375 (6200)		
	$\lambda_{min.}$	220 (23,900)	235 (23,200)	242 (23,200)	309 (470)		
9-Thia-2-aza-	$\lambda_{max.}$	222 (17,000)	228 (16,800)	247 (19,900)	270 (16,900)	294 (6370)	304 (5870) 392 (6280)
	$\lambda_{min.}$	226 (16,600)	236 (13,700)	256 (14,200)	288 (5630)	300 (5360)	322 (240)
9-Thia-3-aza-	$\lambda_{max.}$	247 (31,800)	289 (8790)	299 (9400)	364 (5220)		
	$\lambda_{min.}$	230 (17,800)	283 (8500)	293 (8580)	318 (990)		
9-Thia-4-aza-	$\lambda_{max.}$	216 (11,900)	258 (37,300)	382–383 (5760)			
	$\lambda_{min.}$	222 (8300)	314 (390)				
9-Thia-1-aza-	$\lambda_{max.}$	258 (14,800)	282 (16,000)	376 (5540)			
methiodide *	$\lambda_{min.}$	249 (12,300)	267 (12,600)	330 (100)			
9-Thia-2-aza-	$\lambda_{max.}$	232 (31,000)	244 (18,300)	250 (17,200)	288 (11,600)	306 (9100)	420 (5060)
methochloride	$\lambda_{min.}$	240 (17,800)	249 (17,000)	270 (8160)	302 (9050)	344 (300)	
9-Thia-3-aza-	$\lambda_{max.}$	234 (30,800)	276 (11,200)	335 (13,000);	$\lambda_{infl.}$ 270—273 (11,100)		
methochloride *	$\lambda_{min.}$	224 (24,200)	263 (10,900)	303 (4100)			
9-Thia-4-aza-	$\lambda_{max.}$	219 (18,700)	250 (13,000)	271 (28,500)	407—408 (2870)		
methochloride	$\lambda_{min.}$	232 (10,200)	254 (11,900)	340 (410)			
6-Amino-9-thia-	$\lambda_{max.}$	212 (18,200)	258 (35,200)	332 (7280)	424—429 (3370)		
3-aza	$\lambda_{min.}$	220 (13,700)	311 (5470)	375 (1370)			

It will be seen that all the spectra have a general similarity. They can however be separated into two main groups. Xanthone and 9-oxa-1-aza- and 9-oxa-3-aza-anthrone form one group, in which there is usually a strong band in the 230-mμ, two weak contiguous bands at 260—280 mμ, and a marked band in the 335-mμ region. Thioxanthone and the four 9-thia-aza-anthrones form a second group, having usually one or two weak bands in the 220-mμ, a strong band in the 250—260-mμ, two weak bands in the 295—305-mμ, and a weak broad band in the 380-mμ region. The quaternary methohalides of the four 9-thia-aza-anthrones give absorption curves intermediate between the above two main types.

3-*Nitro*-4 : 4'-*dipyridyl Sulphide* (XI; R = NO_2).—Pyridine-4-thiol was prepared by King and Ware's method (*loc. cit.*). A solution of 4-chloro-3-nitropyridine (II) (3 g.) and the thiol (2 g., 1 mol.) in ethanol (50 c.c.) was boiled under reflux for 3 hr., then evaporated, and the residue treated with aqueous sodium hydroxide and extracted with ether. The dried extract was evaporated and the residue, when recrystallised from ether and then sublimed at 110°/0·01 mm., furnished the *sulphide* (XI; R = NO_2) (3·2 g., 77%), pale yellow needles, m. p. 112° (Found: C, 51·4; H, 3·2; N, 17·7. $C_{10}H_7O_2N_3S$ requires C, 51·5; H, 3·0; N, 18·0%).

The above experiment was repeated, the ethanol being replaced by acetone (50 c.c.) containing dry potassium carbonate (2·2 g.). The residue from the ether extract, when sublimed at 60°/0·005 mm. and then recrystallised from light petroleum (b. p. 40—60°), afforded 4 : 4'-dipyridyl sulphide (XI; R = H), (0·51 g.), pale cream crystals, m. p. 68° (Found: C, 64·1; H, 4·4; N, 14·9. Calc. for $C_{10}H_8N_2S$: C, 63·8; H, 4·3; N, 14·9%). King and Ware (*loc. cit.*) give m. p. 71°.

Stannous chloride (1·05 g.) was added to a solution of the nitro-sulphide (XI; R = NO_2) (0·5 g.) in concentrated hydrochloric acid (10 c.c.), which was then heated at 60° for 1 hr., cooled, and strongly basified. The precipitate, when washed, dried, and sublimed at 140°/0·004 mm., afforded 3-*amino*-4 : 4'-*dipyridyl sulphide* (XI; R = NH_2), colourless crystals, m. p. 138° (Found: C, 58·8; H, 4·8; N, 21·0. $C_{10}H_9N_3S$ requires C, 59·1; H, 4·45; N, 20·7%).

3-*Nitro*-2-*pyridyl* 4-*Pyridyl Sulphide* (XII).—A solution of 2-chloro-3-nitropyridine (0·40 g.) and the thiol (0·27 g., 1 mol.) in ethanol (10 c.c.) was boiled under reflux for 3 hr., and the solvent removed. The residue, when basified with aqueous sodium hydroxide solution, washed, and repeatedly sublimed at 145°/0·002 mm., afforded the *sulphide* (XII), yellow prisms (0·36 g., 63%), m. p. 144—145° (Found: C, 51·2; H, 2·9; N, 18·4. $C_{10}H_7O_2N_3S$ requires C, 51·5; H, 3·0; N, 18·0%).

3-*Nitropyridine*-4-*thiol*.—A solution of potassium hydroxide (7 g.) in methanol (40 c.c.) was saturated with hydrogen sulphide and rapidly added to one of 4-chloro-3-nitropyridine (9·10 g.) in methanol (100 c.c.). Heat was evolved and the solution became dark red. It was heated on a water-bath for 5 min., and the solvent removed under reduced pressure. A solution of the residue in water was acidified with acetic acid, and the precipitate, when recrystallised from ethanol, gave the above *thiol* (6·9 g., 70%), orange-yellow needles, m. p. 153° (effervescence) in a preheated bath (Found: C, 38·8; H, 2·35; N, 17·8. $C_5H_4O_2N_2S$ requires C, 38·5; H, 2·55; N, 17·95%). On slow heating, the substance melted indefinitely at 190—210°.

A solution of 4-chloro-3-nitropyridine (2 g.) and the thiol (2 g., 1 mol.) in ethanol (50 c.c.) was boiled under reflux for 90 min., a yellow deposit increasing steadily after the first 20 min. The solvent was removed, and the residue extracted first with aqueous sodium carbonate and then with boiling ethanol. The ethanolic extract on evaporation gave *di*-3-*nitro*-4-*pyridyl sulphide* (XIII), which after recrystallisation from a minimum of ethanol and then sublimation at 135—140°/0·0005 mm. formed yellow crystals (0·40 g., 11%), m. p. 129—130° (Found: C, 42·8; H, 2·0; N, 20·1. $C_{10}H_6O_4N_4S$ requires C, 43·1; H, 2·1; N, 20·1%).

The residue from the ethanol extraction was heated at 200°/0·001 mm., a yellow sublimate (0·9 g.) being slowly deposited, which had m. p. 210° after crystallisation from acetic acid (Found: C, 38·4; H, 2·5; N, 17·5%). The unsublimed residue (0·6 g.), recrystallised from ethyl acetate (charcoal), afforded *di*-3-*nitro*-4-*pyridyl disulphide*, colourless crystals, m. p. 235° from room-temperature, 240° when immersed at 230° (Found: C, 38·9; H, 2·1; N, 18·0. $C_{10}H_6O_4N_4S_2$ requires C, 38·7; H, 1·9; N, 18·1%). The identity of the yellow sublimate remains uncertain. Its composition is almost identical with that of the original thiol, from which it differs in its insolubility in ethanol. It is possible that it is the isomeric 3-nitropyrid-4-thione: Stevens, Beutel, and Chamberlin (*J. Amer. Chem. Soc.*, 1942, **64**, 1093) have recorded an apparently analogous case in which a substituted 2-hydroxypyridine and its tautomeric pyridone can each be isolated, and differ markedly in solubility in organic solvents.

In a different type of experiment, a mixture of 3-nitropyridine-4-thiol (0·5 g.), 2-bromopyridine (1 c.c.), and copper powder (10 mg.) was boiled under reflux for 15 min., and the excess of 2-bromopyridine then removed in a vacuum. The residue, when twice sublimed at

130°/0·0005 mm., furnished solely the yellow crystalline sulphide (XIII) (95 mg.), m. p. and mixed m. p. 131°.

A solution of 4-chloro-3-nitropyridine (5 g.) and 4-hydroxypyridine (3 g., 1 mol.) in absolute ethanol (60 c.c.), when boiled under reflux, became deep red: after 1 hour's heating the colour began to fade and a yellow deposit to form, the process being apparently complete after 3 hr. The deposit, when collected and recrystallised from water, afforded 4-hydroxy-3-nitropyridine (I; R = NO_2) (2·7 g., 61%), m. p. and mixed m. p. 279°. No other product was isolated from the mother-liquor.

We are greatly indebted to Mr. O. D. Standen for the therapeutic tests, and to the Medical Research Council for a grant (S. K.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March* 11*th*, 1955.]