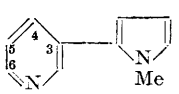
163. *A Contribution to the Study of Nicotine and the Synthesis of 7-Azaindole and Derivatives.*

By G. R. Clemo and G. A. Swan.

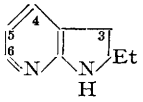
2- and 6-*Aminonicotyrines* have been obtained by the Tschitschibabin reaction on nicotyrine and by dehydrogenation of the known 2- and 6-aminonicotines. From these, 2- and 6-(p-*aminobenzenesulphonamido*)-*nicotyrines* have been prepared. From the product of dehydrogenation of 2-aminonicotine, a base $C_9H_{12}N_2$ has also been obtained; this is not 2-ethyl-2 : 3-dihydro-7-azaindole (II) and is therefore probably 2-methyl-1 : 2 : 3 : 4-tetrahydro-1 : 8-naphthyridine (III). 7-Azaindole (IV) has been synthesised; its 2-*methyl* and 2-*ethyl* derivatives and the corresponding 2 : 3-*dihydro*-compounds have also been prepared.

By the action of sodamide on nicotine in xylene solution, Tschitschibabin and Kirssanow (*Ber.*, 1924, **57**, 1163) obtained a mixture of 2- and 6-aminonicotines which were easily separated as the 6-compound was readily soluble and the 2-isomer was insoluble in water. The two amines were orientated by conversion to the corresponding chloronicotines, the oxidation of which led to 2- and 6-chloronicotinic acids respectively.

By carrying out a similar reaction on nicotyrine (I), 2- and 6-*aminonicotyrines* have now been obtained, and separated by fractional distillation; both these amines are nearly insoluble in water. Attempts to convert them to the corresponding chloronicotyrines failed, as the strongly acidic conditions required for diazotisation led to the formation of complex products.



(I.)



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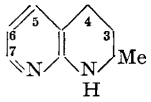

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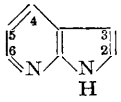

(IV.)

Preliminary experiments on the hydrogenation of the aminonicotyrines gave unpromising results. Finally, the aminonicotyrines were orientated by dehydrogenating the corresponding aminonicotines. By the

condensation of 2- and 6-aminonicotyrines with acetylsulphanilyl chloride, followed by hydrolysis, 2- and 6-(p-*aminobenzenesulphonamido*)-*nicotyrines* have been prepared and tested for antimalarial activity.

In the dehydrogenation of nicotine by palladised asbestos Frank, Holley, and Wikholm (*J. Amer. Chem. Soc.*, 1942, **64**, 2835) obtained, in addition to nicotyrine (about 35%), low- and high-boiling fractions which they proposed to investigate further. We have obtained a similar result in the dehydrogenation of 6-aminonicotine. In the case of 2-aminonicotine, however, the main product of the dehydrogenation consisted of a low-boiling fraction, from which a base $C_9H_{12}N_2$, m. p. 45—46°, has been isolated. A relatively small amount of the aminonicotyrine was obtained; and the high-boiling fraction was much smaller than in the case of the 6-aminocompound. During both these reactions, methylamine was evolved.

The base $C_9H_{12}N_2$ contains one secondary and one tertiary nitrogen atom in the molecule. Thus it gives a nitroso-derivative, and a *m*-nitrobenzenesulphonyl derivative which is insoluble in sodium hydroxide solution. (The corresponding derivative of 2-aminopyridine was prepared and found to be soluble.) It gives well-defined acetyl and benzoyl derivatives, a picrate and picrolonate and a mono-methiodide. On oxidation with alkaline permanganate, it gives 2-aminonicotinic acid. Attempts to hydrogenate the base with hydrogen at atmospheric temperature and pressure in the presence of Adams' catalyst failed; it was however attacked by sodium and boiling amyl alcohol. Attempts to dehydrogenate it further by selenium at 280—290° or at 320—330° were not promising. The base was recovered unchanged after fusion with potassium hydroxide for 3 hours at 280°. By oxidation of the methiodide with alkaline ferricyanide, a liquid base was obtained (picrate, m. p. 152°); the further oxidation by chromic acid of this did not result in the isolation of a definite product.

These results suggest that, during the dehydrogenation, the NMe group of the pyrrolidine nucleus has been eliminated as methylamine (noted above) and the resulting 4-carbon atom side chain has ring-closed on the amino-group to give either 2-ethyl-2 : 3-dihydro-7-azaindole (II) or 2-methyl-1 : 2 : 3 : 4-tetrahydro-1 : 8-naphthyridine (III).

Little work on 7-azaindole (IV) and its derivatives is recorded in the literature. Kruber (*Ber.*, 1943, **76**, 130) isolated from the lepidine fraction of coal-tar, by reaction with potassium hydroxide, a base which he believed to be 7-azaindole itself, although he did not confirm the structure by synthesis. Koenigs and Fulde (*Ber.*, 1927, **60**, 2106) prepared 2-methyl-6-azaindole by the action of sodium ethoxide on 3-acetamido-4-picoline; and we have adapted the method for the preparation of 7-azaindole and its derivatives. Preliminary experiments were directed to the preparation of the 2-methyl compound, as the intermediate 2-acetamido-3-picoline was already known (Seide, *Ber.*, 1924, **57**, 1802). Ring closure with sodium ethoxide led to the expected *2-methyl-7-azaindole*. The preparation of *2-formamido-3-picoline* gave rise to difficulty, as the action of anhydrous formic acid on 2-amino-3-picoline led only to the formation of the formate; the formyl derivative was finally obtained in good yield by the method of Gol'dfarb and Smorgonskii (*J. Gen. Chem. Russia*, 1942, **12**, 255). Ring closure with sodium or potassium ethoxide gave 7-azaindole in very low yield. Tyson (*J. Amer. Chem. Soc.*, 1941, **63**, 2024) has shown that in the ring closure of formo-*o*-toluidide, potassium ethoxide gives a much higher yield of indole than does sodium ethoxide. However, in the preparation of 7-azaindole, a similar result was not observed. The melting-points of the base, picrate, and acetyl derivative agreed with those of the material isolated by Kruber. By the action of propionic anhydride on 2-amino-3-picoline, followed by ring closure with sodium ethoxide, *2-ethyl-7-azaindole* was obtained.

These 7-azaindoles did not give the Ehrlich or the pine-shaving reaction. Koenigs and Fulde reported a failure to obtain the latter reaction from 2-methyl-6-azaindole.

Kruber (*loc. cit.*) has described the hydrogenation of 7-azaindole with a nickel catalyst at 200° and 118 atm. as giving 2 : 3-dihydro-7-azaindole. Our preliminary experiments under these conditions on 2-methyl-7-azaindole were not very promising for, whilst a little of the desired product was obtained, the main products were a gum of very high boiling-point and a mobile liquid, the boiling-point of the latter being lower than that of the desired dihydro-azaindole. The use of copper chromite catalyst with hydrogen at 180° and 160 atm., however, gave the desired product in much higher yield. The hydrogenation of 7-azaindole itself was not investigated, as it was obtained in such low yield. The hydrogenation of 2-ethyl-7-azaindole under the same conditions gave *2-ethyl-2 : 3-dihydro-7-azaindole*, m. p. 62—63° which was different from the base isolated by the dehydrogenation of 2-aminonicotine.

It is therefore suggested that the *base* $C_9H_{12}N_2$ obtained by dehydrogenating 2-aminonicotine is probably 2-methyl-1 : 2 : 3 : 4-tetrahydro-1 : 8-naphthyridine. Experiments are now in progress to confirm this conclusion by synthesis. Objection to this formulation might be raised on the grounds that such a compound should dehydrogenate further to give 2-methyl-1 : 8-naphthyridine. But the work of Koller and Kandler (*Sitzungsber. Akad. Wien*, 1931, **140**, IIb, 213) has shown that the dehydrogenation, in the presence of palladium at 220°, of decahydro-1 : 8-naphthyridine leads to the formation of tetrahydro-1 : 8-naphthyridine; and that further dehydrogenation does not occur under these conditions. The failure of the base $C_9H_{12}N_2$ to hydrogenate with Adams' catalyst is in accord with the work of Ochiai and Miyaki (*Ber.*, 1941, **74**, 1115) who showed that 2 : 4-dimethyltetrahydro-1 : 8-naphthyridine was not hydrogenated by platinum and hydrogen at 110 atm. and room temperature, although it was attacked by sodium and boiling alcohol.

Experimental.

All the picrates and picrolonates described in this paper were prepared in alcoholic solution.

The benzoyl derivatives were prepared by heating the base and benzoic anhydride in equi-molecular amounts for 3—5 hours on the water-bath, followed by stirring with dilute ammonia or sodium hydroxide solution.

2- and 6-*Aminonicotyrines*.—Finely powdered sodamide (12·5 g.), nicotyrine (25 g., Frank, Holley, and Wikholm, *loc. cit.*) and dry xylene (60 c.c.) were heated together in an oil-bath at 140—145° for 5 hours, the mixture cooled, ice and sodium hydroxide solution (40%) added, the xylene layer separated, and the aqueous layer extracted several times with benzene. The combined xylene–benzene extracts were dried (potassium carbonate), the solvents removed in a vacuum, and the residue fractionated at 1 mm. gave: (i) 3 g., b. p. 108—123°; this was dissolved in hot benzene–ligroin; on cooling, crystals (1·1 g., m. p. 73—77°) separated: (ii) 4·9 g., b. p. 123—129°; when treated as in (i) this gave crystals (1·75 g., m. p. 73—77°): (iii) 2·2 g., b. p. 129—145°; (iv) 7·7 g., b. p. 145—155°; when treated as in (i), this gave crystals (6·5 g., m. p. 92°).

The solvents were removed from the mother-liquors from the above crystallisations, and the remaining oils, as well as fraction (iii), were again subjected to fractional distillation, and the fractions of b. p. 110—130° and 140—155° crystallised as above. The residual oils were again subjected to the same process, when, finally, total yields of 5·35 g. (19%) of a base, *A*, having m. p. 73—75°, and 7·35 g. (26%) of a base, *B*, having m. p. 92—94°, together with oils of b. p. 100—110° and 123—150° were obtained.

The base, *A*, is 2-*aminonicotyrine* and crystallises from benzene–ligroin in colourless prisms, m. p. 77—78° (Found: C, 69·5; H, 6·2. $C_{10}H_{11}N_3$ requires C, 69·4; H, 6·4%). The picrate crystallised from acetone–alcohol in pale yellow needles, m. p. 189—190°. The *dipicrolonate* crystallised from alcohol in yellow needles, m. p. 173° (Found: C, 51·6; H, 4·2. $C_{10}H_{11}N_3,2C_{10}H_8O_5N_4$ requires C, 51·4; H, 3·9%).

The *diacetyl* derivative was prepared by refluxing the base (0·5 g.) with acetic anhydride (1·5 c.c.) for 1½ hours, pouring into water, adding dilute sodium hydroxide solution and collecting the resulting solid; it was recrystallised first from alcohol–water, then from benzene–ligroin, giving colourless prisms, m. p. 91—92° (Found: C, 65·1; H, 6·0. $C_{14}H_{15}O_2N_3$ requires C, 65·4; H, 5·85%). The *benzoyl* derivative, which separated as an oil, was stirred with a few drops of ether until it solidified; it was recrystallised first from alcohol–water, then from benzene–ligroin, giving colourless prisms, m. p. 141—142° (Found: C, 73·3; H, 5·5. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4%). The *monopicrate* of this benzoyl derivative crystallised from acetone–alcohol in orange-yellow prisms, m. p. 202°, softening at 190° (Found: C, 54·4; H, 3·4. $C_{17}H_{15}ON_3,C_6H_3O_7N_3$ requires C, 54·5; H, 3·55%).

The base, *B*, is 6-*aminonicotyrine* and crystallises from benzene–ligroin in colourless prisms, m. p. 97—98° (Found: C, 69·3; H, 6·8. $C_{10}H_{11}N_3$ requires C, 69·4; H, 6·4%). The *monopicrate* crystallised from acetone in orange-yellow crystals, m. p. 257° (decomp.) (Found: C, 47·9; H, 4·0. $C_{10}H_{11}N_3,C_6H_3O_7N_3$ requires C, 47·8; H, 3·5%). The *monoacetyl* derivative, prepared by warming the base (0·5 g.) with acetic anhydride (1 c.c.) for 10 minutes on the water-bath, pouring into water, and collecting the resulting solid, crystallised from alcohol–water in colourless leaflets, m. p. 174° (Found: C, 66·7; H, 6·15. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·05%). The *monopicrate* of this acetyl derivative crystallised from acetone–alcohol in orange-red needles, m. p. 189—190° (Found: C, 48·8; H, 4·2. $C_{12}H_{13}ON_3,C_6H_3O_7N_3$ requires C, 48·7; H, 3·6%). The *benzoyl* derivative was isolated by extracting with ether, drying the extract (potassium carbonate), removing the ether, dissolving the residual gum in hot benzene–ligroin, and allowing the solution to cool until crystallisation occurred; it was recrystallised first from benzene–ligroin, then from alcohol–water, giving colourless prisms, m. p. 122—123° (Found: C, 73·3; H, 5·4. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4%).

Dehydrogenation of 2-Aminonicotine.—The base (10 g.) and palladised asbestos catalyst-*d* (0·5 g.) (Linstead and Thomas, J., 1940, 1130) were heated together in a metal-bath at 220°, the temperature was raised to 280° during 10 minutes, and maintained thereat for a further 25 minutes. During the reaction, methylamine was evolved, and identified as its picrate. On cooling, the product was extracted with chloroform, the extract filtered, the chloroform removed, and the residue fractionated under 2 mm. to give: (i) 4·25 g. having b. p. 95—113°, (ii) 0·6 g. having b. p. 113—122°, (iii) 1·4 g. having b. p. 122—140°, (iv) a small amount having b. p. 140—175°. On cooling, fractions (ii) and (iii) deposited crystals of 2-aminonicotine, which were filtered off, and the remaining oils combined and redistilled under 2 mm. The fraction of b. p. 130—136° (0·5 g.), on seeding with aminonicotyrine, *A*, deposited crystals, which were separated, washed with ligroin, and recrystallised four times from benzene–ligroin giving *2-aminonicotyrine* in colourless prisms, m. p. 77° (unaffected on admixture with *A*). The picrate and dipicrolonate were identical with those obtained from *A*, and no depression of m. p. was observed on admixture, in either case.

Fraction (i) was redistilled under 2 mm., the fraction of b. p. 98—102° being collected. The *benzoyl* derivative (1·25 g.), prepared from the base (0·8 g.) and benzoic anhydride (1·44 g.), separated from alcohol–water in colourless prisms, m. p. 145° (Found: C, 76·3; H, 6·45. $C_{16}H_{16}ON_2$ requires C, 76·2; H, 6·35%). This benzoyl derivative (1·2 g.) was refluxed for 6 hours with concentrated hydrochloric acid (7 c.c.), the solution distilled in steam to remove the bulk of the hydrochloric and benzoic acids, the residue basified (40% sodium hydroxide solution) and extracted with ether. After the ether was removed from the dried (potassium carbonate) extract, the *base* (0·65 g.) remained as an oil which rapidly solidified, m. p. 45°. On recrystallisation from ligroin (b. p. 40—60°) it gave colourless prisms, m. p. 45—46° (Found: C, 72·7; H, 7·7; N, 18·5; *M*, 159. $C_9H_{12}N_2$ requires C, 72·95; H, 8·1; N, 18·95%; *M*, 148) which were optically inactive in alcoholic solution. The *monopicrate* separated from acetone in bright yellow needles, m. p. 189° (Found: C, 47·85; H, 4·2. $C_9H_{12}N_2,C_6H_3O_7N_3$ requires C, 47·75; H, 4·0%). The *picrolonate* separated from acetone–alcohol in yellow needles, m. p. 198°. The base (0·6 g.) was refluxed for 8½ hours with methyl iodide (1 c.c.) and dry acetone (10 c.c.), part of the acetone distilled off and the solution cooled. The resulting solid (0·85 g., m. p. 164—165°) on recrystallisation from methanol–acetone gave the *monomethiodide* in colourless prisms, m. p. 167° (Found: C, 41·5; H, 5·2. $C_{10}H_{15}N_2I$ requires C, 41·4; H, 5·2%). The m-*nitrobenzenesulphonyl* derivative, prepared by shaking the base with *m*-nitrobenzenesulphonyl chloride and dilute sodium hydroxide solution, separated from alcohol in colourless prisms, m. p. 169—170°, and was insoluble in dilute sodium hydroxide solution (Found: C, 54·0; H, 4·95. $C_{15}H_{15}O_4N_3S$ requires C, 54·05; H, 4·5%). The *nitroso*-derivative was obtained by adding a solution of sodium nitrite to a solution of the base in dilute sulphuric acid, extracting the resulting oil with ether, drying (potassium carbonate), removing the ether and recrystallising the product from ligroin (b. p. 60—80°). It crystallised in almost colourless prisms, m. p. 62° (Found: C, 61·6; H, 6·3. $C_9H_{11}ON_3$ requires C, 61·0; H, 6·2%). This gave the Liebermann nitroso-reaction. The *acetyl* derivative, obtained by heating the base with acetic anhydride on the water-bath, adding dilute sodium hydroxide solution and extracting with ether, separated from ligroin (b. p. 60—80°) in colourless prisms, m. p. 70° (Found: C, 69·4; H, 7·45. $C_{11}H_{14}ON_2$ requires C, 69·45; H, 7·4%). The benzoyl and *m*-nitrobenzenesulphonyl derivatives were recovered unchanged after refluxing for 4 hours with potassium permanganate in acetone solution.

2-(m-*Nitrobenzenesulphonamido*)-*pyridine*, prepared by the action of *m*-nitrobenzenesulphonyl chloride on 2-aminopyridine in acetone–pyridine solution, separated from alcohol as colourless needles, m. p. 223—225°; it is soluble in dilute sodium hydroxide solution (Found: C, 47·1; H, 3·45. $C_{11}H_9O_4N_3S$ requires C, 47·3; H, 3·25%).

Attempted hydrogenation of the base $C_9H_{12}N_2$. (*a*) No absorption of hydrogen was observed when a solution of the base in acetic acid–alcohol was shaken with previously reduced Adams' catalyst and hydrogen at 1 atmosphere and 11°. (*b*) To a solution of the base (0·8 g.) in boiling amyl alcohol (60 c.c.), sodium (2·4 g.) was added during 1½ hours. The product was distilled in steam, the acidified (hydrochloric acid) distillate evaporated in a vacuum on the water-bath, the residue dissolved in a small volume of water, the solution saturated with potassium carbonate, extracted with ether, the extract dried (potassium carbonate) and the solvent removed. The resulting oil (0·2 g.) gave a *picrate*, separating

from acetone in yellow crystals, m. p. 223—224° (Found: C, 41·8; H, 3·4. $C_9H_{18}N_2,C_6H_3O_7N_3$ requires C, 41·2; H, 3·9%).

Attempted oxidation of the methiodide of the base, $C_9H_{12}N_2$. A solution of potassium ferricyanide (1·5 g.) in water (7 c.c.) was added to one of potassium hydroxide (0·65 g.) in water (1 c.c.) and the mixture cooled in ice. This was added gradually, with shaking, to a solution of the methiodide (0·97 g.) in water (7·5 c.c.) also cooled in ice. The mixture was allowed to stand for 1 hour in ice and then for 1 hour at room temperature; it was saturated with potassium carbonate, extracted with benzene, the extract dried (potassium carbonate) and the benzene removed; the residue, distilled at 2 mm., gave an oil (0·25 g.) which did not crystallise. This gave a picrate, separating from alcohol in yellow needles, m. p. 152° (Found: C, 48·85, 48·95; H, 4·25, 4·45%). No definite product was isolated after oxidising this base with chromic acid.

Oxidation of the Base, $C_9H_{12}N_2$.—The base (0·5 g.) was heated with a solution of potassium permanganate (5 g.) in water (250 c.c.) for 1½ hours on the water-bath. The hot solution was filtered, the filtrate evaporated to small bulk in a vacuum, and the resulting solution acidified with glacial acetic acid (1 c.c.); on cooling, 2-aminonicotinic acid (70 mg.) having m. p. 298° (decomp.) separated; it was identified by decomposition at 300° to 2-aminopyridine and by conversion to its methyl ester (m. p. 85°).

Dehydrogenation of 6-aminonicotine. The base (4 g.) and palladised asbestos catalyst-*d* (0·2 g.) were heated together in a metal bath at 220°, the temperature raised to 280° during 10 minutes, and maintained thereat for a further 10 minutes. Methylamine was evolved during this reaction. The product was fractionated at 2 mm. to give: (i) 0·4 g., having b. p. 105° approx. and yielding a picrate, which separated from acetone–methanol in yellow needles, m. p. 213° (Found: C, 47·65; H, 4·35%); (ii) 0·7 g., b. p. 140—180°; and a large high-boiling residue was left. On seeding fraction (ii) with aminonicotyrine, *B*, crystals separated. The resulting pasty solid was heated with acetic anhydride (1 c.c.) for 10 minutes in the water-bath, the product poured into water, stirred and the resulting solid collected; it was recrystallised from alcohol–water, giving needles, m. p. 173—174°. On crystallising again from alcohol–water and seeding with the acetyl derivative of *B*, colourless leaflets, m. p. 173—175°, were obtained (mixed with acetyl derivative of *B*, m. p. 174—176°). The picrate of the free base and that of the acetyl derivative were identical with those obtained from *B*, and no depression of m. p. was observed on admixture, in either case.

2-(p-*Aminobenzenesulphonamido*)-*nicotyrine*.—2-Aminonicotyrine (1·75 g.), acetylsulphanilyl chloride (2·3 g.) and dry pyridine (10 c.c.) were heated together for 20 minutes on the water-bath and the mixture poured into water. The resulting gum was washed with water, refluxed with 2N sodium hydroxide (20 c.c.) for 1 hour, cooled and the solution acidified with dilute acetic acid; the crude product (1·05 g., m. p. 172—175°) which separated crystallised from alcohol–water (charcoal) in pale yellow prisms, m. p. 190—191° (Found: C, 58·15; H, 4·8. $C_{16}H_{16}O_2N_4S$ requires C, 58·5; H, 4·9%).

6-(p-*Aminobenzenesulphonamido*)-*nicotyrine*.—6-Aminonicotyrine (1·75 g.), acetylsulphanilyl chloride (2·3 g.) and dry pyridine (10 c.c.) were heated together for 1 hour on the water-bath, the mixture cooled and water (100 c.c.) added. The crude 6-(p-*acetamidobenzenesulphonamido*)-*nicotyrine* (2·2 g., m. p. 220—221°) which separated crystallised from methanol in pale yellow prisms, m. p. 227° (Found: C, 58·2; H, 5·1. $C_{18}H_{18}O_3N_4S$ requires C, 58·4; H, 4·5%). The crude solid (2·2 g.) was refluxed with 2N sodium hydroxide (22 c.c.) for 1 hour, cooled, the solution acidified with dilute acetic acid and the solid (1·75 g., m. p. 201—204°) collected. On recrystallisation from alcohol–water (charcoal) this gave 6-(p-*aminobenzenesulphonamido*)-*nicotyrine* (1·6 g.) as pale yellow needles, m. p. 208° (depressed on admixture with the above acetyl derivative) (Found: C, 58·75; H, 5·2. $C_{16}H_{16}O_2N_4S$ requires C, 58·5; H, 4·9%).

2-*Methyl*-7-*azaindole*.—2-Acetamido-3-picoline (7·5 g.) (Seide, *loc. cit.*) was added to a cooled solution of sodium (2·5 g.) in absolute alcohol (40 c.c.) contained in a flask fitted with a delivery tube for dry hydrogen and a fractionating column. Excess alcohol was rapidly distilled off by heating the flask in a metal-bath the temperature of which was subsequently raised to 350° for 20 minutes. After cooling, the residue in the flask was extracted with hot water and the cooled aqueous liquid extracted several times with ether. The extract was dried (potassium carbonate), the ether removed and the residue distilled at *ca.* 2 mm. to give: (i) 0·85 g., b. p. below 100°, (ii) 2·1 g., b. p. above 100°. The latter crystallised on cooling; it was stirred with an equal volume of warm benzene and, after cooling, the solid (1·3 g., m. p. 128—136°) was separated and recrystallised from benzene–ligroin, giving the *base* (1·1 g.) as colourless prisms, m. p. 136° (Found: C, 73·05; H, 6·1; N, 20·9. $C_8H_8N_2$ requires C, 72·75; H, 6·05; N, 21·2%). The *picrate* separated from acetone in pale yellow needles, m. p. 229°. The *benzoyl* derivative crystallised from benzene–ligroin in colourless needles, m. p. 94—95° (Found: C, 76·65; H, 5·4. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%).

2-*Acetamido*-3-*picoline picrate* separated from alcohol in bright yellow prisms, m. p. 157—159° (Found: C, 44·65; H, 3·35. $C_8H_{10}ON_2,C_6H_3O_7N_3$ requires C, 44·35; H, 3·45%).

2-*Methyl*-2 : 3-*dihydro*-7-*azaindole*.—2-Methyl-7-azaindole (2·23 g.), in absolute alcohol (100 c.c.), was hydrogenated while being stirred in an autoclave in the presence of copper chromite catalyst (1 g.) (*Org. Synth.*, **19**, 33). The initial hydrogen pressure was 106 atm. and the temperature was raised from 15° to 180° (160 atm.) during 4 hours, and maintained there for a further 4 hours. After cooling, the catalyst was filtered off through charcoal, the alcohol was distilled off from the filtrate (water bath) and the resulting oil distilled at *ca.* 2 mm.; 2 fractions, (i) 1·4 g., b. p. 90—105°, and (ii) 0·8 g., b. p. above 105°, were obtained. On cooling, both fractions crystallised, (ii) giving unchanged 2-methyl-7-azaindole. The solid from (i) was washed with and recrystallised from ligroin (b. p. 40—60°) giving a white solid (0·95 g., m. p. 50—54°). By crystallising this again twice, 2 : 3-*dihydro*-2-*methyl*-7-*azaindole* was obtained in colourless prisms, m. p. 57—59° (Found: C, 71·5; H, 7·45. $C_8H_{10}N_2$ requires C, 71·65; H, 7·45%). The *picrate* separated from acetone in bright yellow needles, m. p. 188—189° (Found: C, 46·4; H, 3·6. $C_8H_{10}N_2,C_6H_3O_7N_3$ requires C, 46·3; H, 3·6%). The *benzoyl* derivative crystallised from ligroin (b. p. 60—80°) in colourless prisms, m. p. 97° (Found: C, 75·6; H, 5·9. $C_{15}H_{14}ON_2$ requires C, 75·65; H, 5·9%). The *nitroso*-derivative was obtained by adding an aqueous solution of sodium nitrite (0·2 g.) to a solution of the base (70 mg.) in dilute sulphuric acid, basifying with ammonia and crystallising the separated solid (60 mg.) from benzene–ligroin; the product crystallised in cream-coloured leaflets, m. p. 128° (Found: C, 59·6; H, 5·7. $C_8H_9ON_3$ requires C, 58·9; H, 5·5%). This gave the Liebermann nitroso-reaction.

From an attempt to carry out the above hydrogenation under similar conditions but using Raney nickel instead of copper chromite catalyst, followed by benzoylation, the above benzoyl derivative was isolated in low yield.

2-*Formamido*-3-*picoline*.—Anhydrous formic acid (3·4 c.c.) and acetic anhydride (8·2 c.c.) were heated together for 2 hours at 50°. The cooled liquid was added gradually, with shaking, to a cold solution of 2-amino-3-picoline (8·6 g.) in dry ether (40 c.c.). After standing for 2 days at room temperature, the ether was removed and the residue distilled at 15 mm., giving 10·6 g. of distillate (b. p. *ca.* 165°) which rapidly crystallised. When recrystallised from benzene, this afforded 2-*formamido*-3-*picoline* (8·9 g.) in colourless needles, m. p. 138—139° (Found: C, 62·35; H, 5·6. $C_7H_8ON_2$ requires C, 61·8; H, 5·6%). The *picrate* separated from acetone–alcohol in bright yellow prisms, m. p. 167—168° (Found: C, 42·95; H, 3·35. $C_7H_8ON_2,C_6H_3O_7N_3$ requires C, 42·75; H, 3·0%).

When 2-amino-3-picoline (2 g.) was refluxed with anhydrous formic acid (5 c.c.) and the product distilled, the distillate (2·9 g., b. p. 110°/20 mm. approx.) solidified, and crystallised from benzene in colourless needles, m. p. 110°, apparently of 2-*amino*-3-*picoline formate* (Found: C, 53·85; H, 6·4. $C_7H_{10}O_2N_2$ requires C, 54·55; H, 6·5%). When treated in

alcoholic solution with picric acid, this gave 2-amino-3-picoline picrate (yellow prisms from acetone, m. p. 230°) identified by mixed m. p.

7-Azaindole.—2-Formamido-3-picoline was subjected to the same ring-closure process as in the preparation of 2-methyl-7-azaindole. The solid product crystallised from benzene–ligroin in colourless prisms of 7-azaindole, m. p. 106—107° (Kruber, *loc. cit.*, gave m. p. 107°), the yield being *ca.* 3% (Found: C, 71·6; H, 5·3. Calc. for $C_7H_6N_2$: C, 71·2; H, 5·1%). The picrate separated from acetone in bright yellow prisms, m. p. 232—233° (Kruber: m. p. 233°). The acetyl derivative separated from ligroin (b. p. 40—60°) in colourless crystals, m. p. 64° (Kruber: m. p. 67°). The use of potassium ethoxide instead of sodium ethoxide did not appreciably affect the yield of the azaindole.

2-Ethyl-7-azaindole.—2-Amino-3-picoline (13·5 g.) was refluxed for 20 minutes with propionic anhydride (27 c.c.) and the product distilled as a colourless gum of *2-propamido-3-picoline* (19·5 g., b. p. 158—160°/12 mm.), which gave a *picrate* crystallising from alcohol in bright yellow prisms, m. p. 157° (Found: C, 46·15; H, 3·9. $C_9H_{12}ON_2,C_6H_3O_7N_3$ requires C, 45·8; H, 3·8%). The gum (10·5 g.) was subjected to ring closure, as in the preparation of 2-methyl-7-azaindole, and the product distilled at *ca.* 2 mm. to give (i) 0·9 g., b. p. 80—100° and (ii) 2·5 g., b. p. 125—150°. On standing for several days at room temperature, the latter crystallised, and the resulting solid was filtered off, washed with light petroleum and pressed on porous porcelain, giving 1·1 g., m. p. 79—83°. By crystallising several times from ligroin (b. p. 60—80°) *2-ethyl-7-azaindole* was obtained in colourless prisms, m. p. 88° (Found: C, 73·9; H, 6·85. $C_9H_{10}N_2$ requires C, 73·95; H, 6·85%). The picrate separated from acetone in bright yellow needles, m. p. 232—233°.

2-Ethyl-2 : 3-dihydro-7-azaindole.—The above base was hydrogenated in the way described for the corresponding 2-methyl compound, and the product was crystallised several times from ligroin (b. p. 40—60°) giving colourless needles, m. p. 62—63° (Found: C, 73·4; H, 8·1. $C_9H_{12}N_2$ requires C, 73·0; H, 8·1%). The *picrate* separated from acetone solution in pale yellow needles, m. p. 162° (softening at 151°) (Found: C, 47·65; H, 4·0. $C_9H_{12}N_2,C_6H_3O_7N_3$ requires C, 47·75; H, 4·0%). The benzoyl derivative separated from benzene–ligroin in colourless needles, m. p. 77—78°.

Attempted Preparation of 3-Chloro-2-methyl-1 : 8-naphthyridine.—A solution of 2-methyl-7-azaindole (2 g.) in a mixture of alcohol (20 c.c.), water (4 c.c.) and chloroform (7·5 c.c.) was refluxed on the water-bath, while a solution of potassium hydroxide (5 g.) in water (5 c.c.) and alcohol (40 c.c.) was added during 1 hour and the mixture refluxed for a further 2 hours. The bulk of the alcohol was distilled off from the water-bath, and the residue extracted with ether, the extract dried (potassium carbonate), the ether removed and the residue distilled at 2 mm. The greater part of the azaindole was recovered unchanged; but from the higher-boiling fraction of the distillate a small amount of a different substance was obtained; this separated from benzene solution in yellow crystals, m. p. 206° (Found: C, 67·65; H, 5·05. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%). This is probably *2-methyl-3-aldo-7-azaindole.*

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UNIVERSITY OF DURHAM, KING'S COLLEGE, NEWCASTLE-UPON-TYNE. [*Received, June 19th,* 1945.]