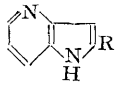
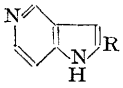
49. *The Synthesis of Derivatives of* 4- *and* 5-*Azaindole.*

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

4-Azaindole (I, R = H), *2-methyl-4-azaindole* (I, R = Me) and *2-methyl-5-azaindole* (II, R = Me) have been synthesised.

The preparation of derivatives of 6- and 7-azaindole by cyclisation of the appropriate acylamidopicolines has been described by Koenigs and Fulde (*Ber.*, 1927, **60**, 2106) and Clemo and Swan (*J.*, 1945, 603), respectively. The present communication records the synthesis of *4-azaindole* (I, R = H), *2-methyl-4-azaindole* (I, R = Me), and *2-methyl-5-azaindole* (II, R = Me) by the same general method.

(I.)   (II.)

For the preparation of the last, the hitherto unknown *4-amino-3-picoline* was required. Koenigs and Greiner (*Ber.*, 1931, **64**, 1049) prepared 4-aminopyridine by the action of ammonia on 4-pyridylpyridinium dichloride (obtained by the action of thionyl chloride on pyridine). Application of this method to β-picoline gave a product which appears to be the required 4-amino-3-picoline, for it gave an azaindole derivative, from which it follows that the amino-group must be in a position *o*- to the methyl group, *i.e.*, in position 2 or 4; further, since the product differed from 2-amino-3-picoline (Seide, *Ber.*, 1924, **57**, 1802), it must be 4-amino-3-picoline. The intermediate pyridinium salt was not isolated, and the yield of the amino-picoline was low, the

reaction also leading to the formation of a sulphur-containing *product*, the structure of which has not been definitely ascertained : it may be a dipicolyl sulphide (cf. Crum and Robinson, *J.*, 1943, 561), although attempts to oxidise this to the corresponding sulphone failed. Treatment of the intermediate pyridinium salt with water yielded 4-*hydroxy*-3-*picoline*, which was also obtained by the action of nitrous acid on 4-amino-3-picoline. By the action of ammonia, the hydroxy- could be converted into the amino-compound.

By cyclisation of 4-*acetamido*-3-*picoline* with sodium ethoxide, 2-methyl-5-azaindole was obtained in *ca.* 1% yield, but cyclisation of the corresponding 4-*formamido*-compound to give 5-azaindole itself was not successful, even when potassium ethoxide was used as condensing agent. The action of acetic anhydride on 3-amino-2-picoline gave a product which appeared to be a *diacetyl* derivative; and this was cyclised to give 2-methyl-4-azaindole in good yield. The cyclisation of the corresponding *formyl* derivative was not achieved by the use of sodium ethoxide, although with potassium ethoxide the required 4-azaindole was obtained in a 20% yield. Attempts to improve the yields obtained by cyclisation of the above formyl derivatives and also of 2-formamido-3-picoline by the use of potassium *tert.*-butoxide (cf. Clemo and Swan, *loc. cit.*) have not met with success (cf. Tyson, *J. Amer. Chem. Soc.*, 1941, **63**, 2024; Marion and Ashford, *Candian J. Res.*, 1945, **23** B, 26).

None of the above-described azaindoles gave the Ehrlich or the pine-shaving reaction.

Experimental.

The picrates and benzoyl derivatives were prepared as described by Clemo and Swan (*loc. cit.*) unless otherwise stated.

4-*Amino*-3-*picoline*.—Thionyl chloride (8·8 c.c.) was cooled in ice, and dry β-picoline (5 c.c.) gradually added with shaking. After standing at room temperature for 6 days, the flask containing the dark red liquid was attached to a water-pump, and its temperature then gradually raised to 100°, and kept there for 1 hour. The residue was warmed with absolute alcohol (5 c.c.), which was then distilled off under reduced pressure (water-bath). The residue (a brown, sticky, deliquescent solid) was heated in a sealed tube with ammonium hydroxide (15 c.c., *d* 0·88) for 10 hours at 180—190°, the liquid evaporated to dryness on the water-bath, the residue dissolved in a little water, sodium hydroxide solution (40%) added, and the mixture distilled with superheated steam. The distillate was acidified (hydrochloric acid) and evaporated to dryness from the water-bath. The residue was dissolved in a small volume of water, basified (40% sodium hydroxide solution), and extracted with chloroform, the extract dried (K_2CO_3), the chloroform removed, and the residue recrystallised from benzene–light petroleum, giving the *base* (0·83 g.) as colourless needles, m. p. 108—109° (Found : C, 66·7; H, 7·6. $C_6H_8N_2$ requires C, 66·6; H, 7·5%). The *picrate* separated from methanol in bright yellow needles, m. p. 224—225°, after sintering at 217° (Found : C, 43·0; H, 3·25. $C_6H_8N_2,C_6H_3O_7N_3$ requires C, 42·75; H, 3·25%). The *benzoyl* derivative, prepared by the Schotten–Baumann method, separated from benzene–light petroleum as colourless plates, m. p. 122—123° (Found : C, 74·25; H, 5·65. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·65%). The *m-nitrobenzenesulphonyl* derivative, prepared by warming the base in acetone–pyridine with *m*-nitrobenzenesulphonyl chloride, distilling off the acetone, and adding water, separated from methanol (charcoal) as colourless plates, m. p. 198—199°, soluble in dilute sodium hydroxide solution, reprecipitated by dilute acetic acid (Found : C, 47·1; H, 4·2. $C_{12}H_{11}O_4N_3S,CH_3{\cdot}OH$ requires C, 48·0; H, 4·6%).

From some preparations, a *product* containing sulphur was isolated in yields up to 0·2 g.; this was more readily soluble in benzene than was 4-amino-3-picoline, and separated from light petroleum (b. p. 60—80°) as colourless prisms, m. p. 88—89° (Found : C, 67·1; H, 5·7; N, 13·4. $C_{12}H_{12}N_2S$ requires C, 66·65; H, 5·6; N, 13·0%). This could also be separated by fractional distillation at 15 mm., the fraction distilling below 160° consisting mainly of 4-amino-3-picoline, and that above 160° being mainly this by-product. This gave a *picrate*, which separated from acetone (in which it is very sparingly soluble) as bright yellow prisms, m. p. 233—235° (decomp.) (Found : C, 43·9; H, 2·85. $C_{12}H_{12}N_2S,C_6H_3O_7N_3$ requires C, 42·75; H, 2·7%). Attempts to prepare a benzoyl derivative (by the Schotten–Baumann method) and a *m*-nitrobenzenesulphonyl derivative failed. When a solution of the base in acetic acid was treated with one of potassium dichromate in dilute sulphuric acid for 1½ hours in the water-bath, no sign of reduction of the chromic acid was observed.

4-*Hydroxy*-3-*picoline*.—*Method* (1). β-Picoline (10 c.c.) was treated with thionyl chloride as described above, and the residue left after alcohol treatment was stirred with water (10 c.c.), filtered from insoluble matter, the filtrate heated in the water-bath for 1 hour with charcoal, filtered again, and heated in a sealed tube for 18 hours at 155°. Excess of sodium carbonate was added to the cooled liquid, which was then evaporated to a paste on the water-bath. The residue was extracted several times with 95% alcohol, the extract evaporated to dryness on the water-bath, the residue dissolved in absolute alcohol, evaporated to dryness under reduced pressure (water-bath), and the residue heated for 1 hour at 150°. The dark, viscous mass which remained on cooling was dissolved in chloroform, the solution boiled with charcoal, filtered, the filtrate concentrated, and to it, light petroleum was added, an oil then separating. The solvent layer was decanted, and the oil rubbed first with light petroleum, then with benzene, whereupon it solidified. The resulting solid was recrystallised from acetone (charcoal), giving 4-*hydroxy*-3-*picoline* (0·72 g., m. p. 95—98°), which after two further recrystallisations from acetone formed colourless prisms, m. p. 97—98°, after sintering at 92° (Found : C, 61·3; H, 7·1. $C_6H_7ON,\frac{1}{2}H_2O$ requires C, 61·0; H, 6·8%).

Method (2). To a solution of 4-amino-3-picoline (50 mg.) in 10% sulphuric acid (2 c.c.) at room

temperature, one of sodium nitrite (0·1 g.) in water (1·5 c.c.) was added, the mixture warmed for 15 minutes (water-bath), basified (sodium carbonate), the solution evaporated to dryness from the water-bath, the residue extracted with chloroform, the solvent removed from the extract, the residue rubbed with benzene, and the resulting solid filtered off and washed with benzene; 37 mg., m. p. 94—96°. When recrystallised from acetone, this gave colourless needles or prisms, m. p. 96—97°, after sintering at 92° (Found: C, 61·25; H, 6·7%). The m. p. was not depressed by admixture with the product obtained by method (1). The picrate separated from alcohol as yellow prisms, m. p. 206—207°. When the base (0·2 g.) was heated with ammonium hydroxide (2 c.c., *d* 0·88) and a trace of copper powder and copper sulphate in a sealed tube for 19 hours at 200°, 4-amino-3-picoline was re-formed.

4-Acetamido-3-picoline.—4-Amino-3-picoline (2·26 g.) was refluxed for 15 minutes with acetic anhydride (5 c.c.), and the mixture distilled under 15 mm., the product which distilled above 180° being a very viscous gum (2·78 g.) which rapidly crystallised. This was stirred with benzene, and the solid collected and washed with benzene, giving 1·73 g., m. p. 140—152°. This was sufficiently pure for the subsequent preparation, but for analysis a portion was recrystallised from benzene, giving colourless plates, m. p. 152—154° (Found: C, 64·25; H, 7·35. $C_8H_{10}ON_2$ requires C, 64·0; H, 6·7%).

2-Methyl-5-azaindole.—The above *acetyl* derivative (1·7 g.) was cyclised as described for the preparation of 2-methyl-7-azaindole (Clemo and Swan, *loc. cit.*). On distillation of the product, a considerable amount of 4-amino-3-picoline passed over first, and this was followed by a small amount of a high-boiling fraction, which solidified rapidly. The latter was recrystallised from benzene, giving *2-methyl-5-azaindole* (20 mg.) as almost colourless prisms, m. p. 208—209°, after sintering at 203° (Found: C, 72·6; H, 6·1. $C_8H_8N_2$ requires C, 72·75; H, 6·05%). The picrate was recrystallised first from alcohol, then from acetone, affording bright yellow needles, m. p. 213—214°, after sintering at 210°.

Improved Preparation of 2-Methylnicotinamide.—The following method gives a better yield than that described by Dornow (*Ber.*, 1940, **73**, 79). Ammonium hydroxide (86 c.c., *d* 0·88) was added to ethyl 2-methylnicotinate (8·6 g.), contained in a thick-walled bottle, and the mixture cooled in ice and saturated with ammonia. The bottle was then stoppered tightly and kept for 2 days at room temperature. On each of the next 5 successive days, the liquid was again saturated with ammonia at 0°, the ester layer gradually disappearing. The homogeneous liquid was then evaporated to dryness under reduced pressure (water-bath), and the residue recrystallised from a small volume of methanol (yield 5·92 g., *ca.* 84%).

Diacetyl Derivative of 3-Amino-2-picoline.—3-Amino-2-picoline (Dornow, *loc. cit.*) (1 g.) was refluxed for 15 minutes with acetic anhydride (2 c.c.), and the mixture distilled at 2 mm., the fraction of b. p. 125—140° (1·3 g.) being collected. This gum of the *diacetyl* derivative was used without further purification in the subsequent preparation, but for analysis, it was redistilled, the fraction of b. p. 125—127°/2 mm. being collected (Found: C, 62·7; H, 6·2. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·2%). The *picrate* separated from alcohol as bright yellow needles, m. p. 155—156° after sintering at 146° (Found: C, 45·5; H, 3·7. $C_{10}H_{12}O_2N_2,C_6H_3O_7N_3$ requires C, 45·6; H, 3·6%).

2-Methyl-4-azaindole.—The above diacetyl derivative (0·9 g.) was subjected to the same cyclisation process as described previously, except that the duration of the reaction was only 10 minutes at 350°. After cooling, and addition of water, the product separated as a solid (0·6 g., m. p. 184—192°) which was filtered off, washed with water, dried, and recrystallised from benzene (in which it is very sparingly soluble), giving almost colourless prisms, m. p. 193—194° (Found: C, 73·3; H, 6·35. $C_8H_8N_2$ requires C, 72·75; H, 6·05%). The picrate separated from acetone as dark yellow prisms, m. p. 262° (decomp.).

4-Azaindole.—A mixture of anhydrous formic acid (0·45 c.c.) and acetic anhydride (1·1 c.c.) was heated at 50° for 2 hours, and the cooled solution added to a suspension of finely powdered 3-amino-2-picoline (1·05 g.) in dry ether (20 c.c.). An oil separated, but this gradually passed into solution. After standing for 4 days at room temperature the ether was removed, and the residue distilled, the formyl derivative being obtained as a gum (1·1 g., b. p. 145°/2 mm.). This gave a *picrate*, which separated from acetone–alcohol as bright yellow needles, m. p. 187—188° (Found: C, 43·35; H, 3·6. $C_7H_8ON_2,C_6H_3O_7N_3,\frac{1}{2}C_2H_6O$ requires C, 43·3; H, 3·6%). The above gum was treated with potassium ethoxide (prepared from potassium, 0·55 g.) for 30 minutes at 350°. After cooling, water was added and the product extracted with chloroform, the extract dried (K_2CO_3), the chloroform removed, and the residue recrystallised twice from benzene–light petroleum, and finally from benzene (charcoal), giving *4-azaindole* as colourless prisms, m. p. 127—128° (0·2 g.) (Found: C, 71·1; H, 5·6. $C_7H_6N_2$ requires C, 71·2; H, 5·1%). The *picrate* separated from acetone as bright yellow plates, m. p. 242—244° (decomp.) (Found: C, 46·0; H, 2·95. $C_7H_6N_2,C_6H_3O_7N_3,\frac{1}{2}C_3H_6O$ requires C, 46·25; H, 3·2%). The *benzoyl* derivative separated from benzene–light petroleum as colourless needles, m. p. 92—96° (Found: C, 75·1; H, 4·9. $C_{14}H_{10}ON_2$ requires C, 75·65; H, 4·5%).

4-Formamido-3-picoline.—4-Amino-3-picoline (0·65 g.) was formylated as described above for 3-amino-2-picoline. The resulting gum (0·69 g., b. p. 150°/2 mm.) set to a white solid. The *picrate* separated from alcohol as yellow needles, m. p. 199—200° (Found: C, 43·3; H, 3·75. $C_7H_8ON_2,C_6H_3O_7N_3,\frac{1}{2}C_2H_6O$ requires C, 43·3; H, 3·6%).

3-Acetomercuri-4-methylpyridine.—A mixture of 4-picoline (3·8 c.c.), mercuric acetate (1·6 g.), and water (0·7 c.c.) was heated in a sealed tube for 6 hours at 110°, the solution evaporated to dryness under reduced pressure (water-bath), and the residue extracted with hot benzene. On cooling, the extract deposited a solid, which was recrystallised from benzene, giving colourless plates, m. p. 148—150° (0·4 g.) (Found: N, 4·2. $C_8H_9O_2NHg$ requires N, 3·8%). Attempts to convert this into 3-bromo-4-methylpyridine were unsuccessful.

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UNIVERSITY OF DURHAM, KING'S COLLEGE,
NEWCASTLE-UPON-TYNE 1.

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