An Attempt to Simulate the Biogenesis of Strychnine. Part I. Experiments with 4-2′-Aminoethylpyridine.

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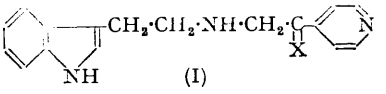
The preparation of 4-2′-aminoethylpyridine has been carefully investigated. A variety of derivatives of 3-indolylacetic acid and its 1-methyl analogue is described, but all attempts to condense the above-mentioned amine with these acids have failed.

ROBINSON AND SAXTON (*J.*, 1953, 2598) pointed out that a synthesis of strychnine, closely following the biogenesis, might be realised in a very simple manner from the pyridine derivative (I; X = :CH·CH_2·OH). Possible routes to this compound and to its simpler analogue (I; X = H_2) have been under investigation. This paper deals with the preparation of 4-2′-aminoethylpyridine and its attempted conversion into the latter compound.



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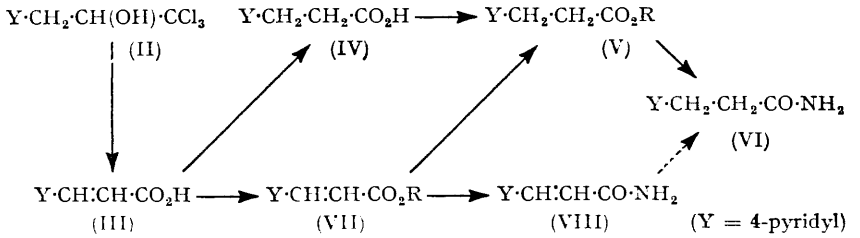
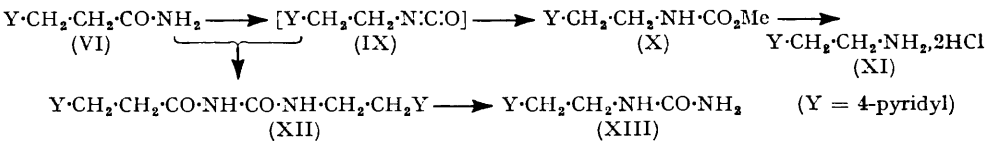


An improved version of Kleiman and Weinhouse's directions (*J. Org. Chem.*, 1945, **10**, 562) for conversion of 4-(3 : 3 : 3-trichloro-2-hydroxypropyl)pyridine (II) into β-4-pyridylacrylic acid (III) is given in the Experimental section. Walter, Hunt, and Fosbinder (*J. Amer. Chem. Soc.*, 1941, **63**, 2771) have briefly described the conversion of this compound into β-4-pyridylpropionamide (VI) by way of the saturated acid (IV) and ester (V). These intermediates have now been characterised and alternative routes to the amide investigated. Direct esterification of β-4-pyridylacrylic acid afforded the methyl and the ethyl ester (VII), but these reacted only slowly with aqueous ammonia to give the amide (VIII). Reduction of ethyl β-4-pyridylacrylate (VII) gave the saturated ester (V), but the overall yield was lower than that obtained by reduction at the acrylic stage.



The amide (VI) was reported (Walter *et al.*, *loc. cit.*) to be converted by a Hofmann reaction in methanol, *via* the oily urethane (X), into 4-2′-aminoethylpyridine dihydrochloride (XI). When a suspension of the amide (VI) was treated slowly with bromine at 0° according to the published directions, in place of the expected urethane (X), a new crystalline compound was obtained in 92% yield. It is known that attempted Hofmann reactions sometimes lead to the formation of ureas (*Organic Reactions*, 1946, **3**, 269) and this compound was proved .to be *N*-(2-4′-pyridylethyl)-*N*′-(β-4-pyridylpropionyl)urea (XII) [formed by reaction of the intermediate *iso*cyanate (IX) with unchanged amide] by hydrolysis to 4-2′-ureidoethylpyridine (XIII).

In the aliphatic series, formation of a urea in Hofmann reactions may be avoided by

working in methanol and adding the bromine rapidly (*ibid.*, p. 282). With β-4-pyridylpropionamide results were erratic; three experiments gave the oily urethane whence 4-2′-aminoethylpyridine dihydrochloride was obtained in good yield, but another under apparently the same conditions gave the urea (XII), possibly owing to variation in pH caused by not using sodium methoxide and bromine in exactly equivalent quantities.

Treating the hydrochloride with aqueous sodium hydroxide and ether gave three liquid layers, and so 4-2′-aminoethylpyridine could not be obtained quite pure. The free base would be expected to lose ammonia easily, for the amino-group is activated in much the same way as in a β-amino-ketone. It was characterised as a mono- and a di-picrate and underwent normal acylation with benzoyl chloride and toluene-*p*-sulphonyl chloride.

Goldschmit and Lautenschlager's method (*Annalen*, 1953, **580**, 74) of preparing amides from amines and acids seemed particularly suitable for the preparation of acylated derivatives of 4-2′-aminoethylpyridine because the amine (and/or acid) may be used as hydrochloride. In an assessment of the utility of the phosphoroazo-reaction, *N*-benzoylbenzylamine, *N*-phenylacetylbenzylamine, and *N*-benzoyl-2-phenylethylamine were obtained in excellent yield. 4-2′-Benzamidoethylpyridine and 4-2′-phenylacetamidoethylpyridine were prepared from 4-2′-aminoethylpyridine dihyrochloride but in lower yield.

The direct alkylation of 4-2′-aminoethylpyridine with, *e.g.*, 3-2′-bromoethylindole, would be difficult because of quaternisation of the pyridine nitrogen. 3-Indolylacetaldehyde is difficult to prepare (Brown, Henbest, and Jones, *J.*, 1952, 3172) and the Schiff base formed by condensation with 4-2′-aminoethylpyridine could tautomerise to another which could undergo facile ring closure. The possibility of acylating the amine with an indole derivative was therefore investigated. Baker and Happold (*Biochem. J.*, 1940, **34**, 657) were unable to isolate or to use as an intermediate the acid chloride from 3-indolylacetic acid. It was, however, hoped that 1-methyl-3-indolylacetic acid would form an acid chloride. On reaction with aqueous cyanide, 1-methylgramine methiodide has been shown to give a mixture of 3-cyanomethyl-1-methylindole and 2-cyano-1 : 3-dimethylindole (Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703, 1856), separable by distillation, but this method was found to be tedious and wasteful. As 2-cyano-1 : 3-dimethylindole is very resistant to alkaline hydrolysis (*idem*, *loc. cit.*), the mixed nitriles were hydrolysed directly and 1-methyl-3-indolylacetic acid was isolated in 50% yield.

1 : 3-Dimethylindole-2-carboxylic acid has been converted into its amide by treatment with phosphorus pentachloride and acetyl chloride followed by removal of volatile compounds *in vacuo* and addition of aqueous ammonia (*idem*, *loc. cit.*). An attempt to prepare 1-methyl-3-indolylacetamide by the same procedure gave a mixture. Analytical figures indicated that partial acetylation at the 2-position of the indole nucleus might have been responsible. Experiments with aniline and methylamine gave similar results, but when 4-2′-aminoethylpyridine was used, no solid product was obtained. Magnanini (*Ber.*, 1888, **21**, 1936) has shown that skatole with acetyl chloride and zinc chloride at room temperature gives 2-acetyl-3-methylindole; although 1-methyl-3-indolylacetic acid was not acetylated under these conditions, the corresponding methyl ester gave 2-acetyl-1-methyl-3-indolylacetate. The latter was readily hydrolysed by aqueous sodium hydroxide to the corresponding carboxylic acid.

It was found that methyl 1-methyl-3-indolylacetate reacted with aqueous ammonia and, on heating, with benzylamine to give the expected products, but the use of 4-2′-aminoethylpyridine gave no solid product in three attempts under different conditions.

Acid azides may often be used as acylating agents where sensitive groups in the molecule prevent the formation or use of an acid chloride. Methyl 1-methyl-3-indolylacetate with hydrazine hydrate gave the hydrazide; attempts to form the azide in dilute hydrochloric acid failed, but in aqueous acetic acid the azide was formed, although only as an oil, which soon decomposed. Small amounts of crystalline material of high m. p. were also produced, which were shown to be *NN′*-di-(1-methyl-3-indolylacetyl)hydrazine by treating the hydrazide with half an equivalent of nitrite; the azide then acylated unchanged hydrazide to give this compound in quantity. Benzylamine was smoothly acylated by the azide, but nothing crystalline could be isolated by using 4-2′-aminoethylpyridine.

By the phosphoroazo-method (see above) 1-methyl-3-indolylacetic acid was readily

converted into its anilide, but no crystalline amide could be isolated when 4-2′-aminoethylpyridine dihydrochloride was used.

A methyl group in the 1-position usually lowers the melting point of indole derivatives; as the experiments recorded above appeared to have failed as much from the lack of success in obtaining crystalline intermediates as for any other reason, a similar research starting with 3-indolylacetic acid was carried out. Results were very similar: simpler amines were readily acylated, but attempts with 4-2′-aminoethylpyridine failed. In one run in which the phosphoroazo-method was used, a small quantity of 3-indolylacetamide was isolated; as the mixture was worked up so as to isolate the basic fraction, it appears that this must have been formed by decomposition of the desired 4-(2-3′-indolylacetamidoethyl)pyridine, which is feasible in view of the formal resemblance of 4-2′-aminoethylpyridine to a β-amino-ketone.

While it was still hoped to prepare 4-(2-3′-indolylacetamidoethyl)pyridine by the methods indicated above, the reduction of 3-indolylacetanilide was undertaken as a model. 3-2′-Anilinoethylindole was readily obtained.

Experimental

β-4-*Pyridylpropionamide*.—Potassium hydroxide (96 g.) in ethanol (commercial absolute, 700 c.c), at room temperature, was added to 4-(3 : 3 : 3-trichloro-2-hydroxypropyl)pyridine (96 g.) in ethanol (700 c.c), and the whole warmed cautiously on the water-bath under a single wide reflux condenser, with periodic cooling as necessary. After the first reaction, the mixture was heated for 2 hr., filtered, and distilled under slightly reduced pressure until solid began to separate. Water (400 c.c.) was then added and the distillation continued until most of the ethanol had been removed. Acetic acid (50 c.c) then precipitated β-4-pyridylacrylic acid (average yield in 5 runs 78%), m. p. 289—291° (decomp.). Kleiman and Weinhouse (*loc. cit.*) give m. p. 296° (decomp.). Purification was carried out as described by them.

The above acid (66 g.) in aqueous sodium hydroxide (19 g. in 190 c.c.) was hydrogenated over Raney nickel at 100°/50 atm. (absorption approx. theor.). Addition of acetic acid (29 c.c.) gave β-4-pyridylpropionic acid (55·6 g., 83%), m. p. 214—220°, raised by crystallisation from ethanol to 228—230° (Found: C, 63·5; H, 5·9. Calc. for $C_8H_9O_2N$: C, 63·6; H, 6·0%) (Doering and Weil, *J. Amer. Chem. Soc.*, 1947, **69**, 2465, give m. p. *ca.* 220°; Rubtsov, *J. Gen. Chem. U.S.S.R.*, 1946, **16**, 461, gives m. p. 232°). This acid (10 g.), methanol (30 c.c.), and sulphuric acid (12 c.c.) were heated for 4 hr. on the water-bath, then poured on ice and aqueous ammonia (*d* 0·88; 30 c.c.). The whole was extracted with ether. Distillation of the dried extracts gave the *methyl ester* (8·5 g., 78%), b. p. 128—129°/11 mm. (Found: C, 65·7; H, 6·7. $C_9H_{11}O_2N$ requires C, 65·5; H, 6·7%) (Walter *et al.*, *loc. cit.*, give b. p. 95°/2 mm., but no analysis). The ester with excess of aqueous ammonia at 0° gave the amide (98%), m. p. 165—166° (Walter *et al.* give m. p. 166—167).

β-4-Pyridylacrylic acid (14 g.) was esterified as described above for β-4-pyridylpropionic acid to give the ethyl ester (13·5 g., 81%), m. p. 64·5—66° (from light petroleum) (Found: C, 67·3; H, 6·2. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·2%) (Rubtsov, *loc. cit.*, gives m. p. 67—69°). The *methyl ester*, similarly prepared, separated from light petroleum (b. p. 60—80°) in prisms, m. p. 74—77° (Found: C, 66·6; H, 5·7. $C_9H_9O_2N$ requires C, 66·3; H, 5·5%). These esters with ammonia gave the *amide*, which crystallised from ethanol in plates, m. p. 185—187° (Found: C, 64·7; H, 5·5. $C_8H_8ON_2$ requires C, 64·9; H, 5·4%).

Ethyl β-4-pyridylacrylate (40 g.) in ethanol (25 c.c.) was hydrogenated over Raney nickel at 100°/50 atm. for 24 hr. The mixture was filtered and distilled, to yield *ethyl* β-4-*pyridylpropionate* (26 g., 62%), b. p. 133°/9 mm., n_D^{20} 1·4968 (Found: C, 67·0; H 7·6. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%).

4-2′-*Ureidoethylpyridine*.—β-4-Pyridylpropionamide (6 g.) was added to a cold solution of sodium (1·84 g.) in methanol (60 c.c.), the whole cooled to < 0°, and bromine (6·4 g.) dropped in during 10 min. with vigorous stirring. The whole was refluxed for 1 hr., methanol removed on the water-bath, and water (30 c.c.) added. N-2-4′-*Pyridylethyl*-N′-β-4-*pyridylpropionylurea* separated and more was obtained by extraction of the mother-liquor with chloroform (total yield 5·5 g., 92%). The compound was obtained from ethanol–water (1 : 1) as prisms, m. p. 144—146° [Found: C, 64·2, 64·4; H, 6·1, 6·2%; *M* (Rast), 312. $C_{16}H_{18}O_2N_4$ requires C, 64·4; H, 6·0%; *M*, 298]. The *dipicrate* (from ethanol–benzene) had m. p. 216—217° (Found: C, 44·7; H, 3·4. $C_{28}H_{24}O_{16}N_{10}$ requires C, 44·4; H, 3·2%). This urea (3 g.) was boiled with concentrated hydrochloric acid (12 c.c) for 1 hr., and the whole poured into aqueous sodium hydroxide,

to give 4-2′-*ureidoethylpyridine*, which crystallised from acetone–water (10 : 1) in needles, m. p. 204—205·5° (Found: C, 57·8; H, 6·7; N, 25·4. $C_8H_{11}ON_3$ requires C, 58·2; H, 6·7; N, 25·4%). The *picrate* separated from ethanol–benzene in yellow prisms, m. p. 199—200° (Found: C, 42·6; H, 3·5. $C_{14}H_{14}O_8N_6$ requires C, 42·6; H, 3·5%).

4-2′-*Aminoethylpyridine*.—β-4-Pyridylpropionamide (15 g.) was added to a solution of sodium (4·6 g.) in methanol (150 c.c.) at room temperature, and bromine (16 g.) added all in one lot with good stirring. The mixture became warm and the colour of the bromine soon disappeared; the whole was then refluxed for 30 min., the methanol distilled off, water (50 c.c.) added, and the whole extracted with chloroform (3 × 20 c.c.). Solvent was removed from the dried extracts, the residue refluxed with hydrochloric acid (35 c.c.) for 4 hr. and evaporated to dryness, and the product recrystallised from acetic acid to give the dihydrochloride (15 g., 77%). The m. p. depends on the rate of heating; on immersion at 215° and rapid heating it was 226—229° (Walter *et al.*, *loc. cit.*, give m. p. 222°) (Found: C, 42·9; H, 6·3. Calc. for $C_7H_{12}N_2Cl_2$: C, 43·1; H, 6·2%). The dihydrochloride (5 g.) was mixed with ether (10 c.c.) and aqueous sodium hydroxide (30%; 9 c.c.). Three liquid layers were formed; the upper two were separated, solvent was removed, and the residue distilled *in vacuo*. On redistillation the amine was obtained as a colourless liquid, b. p. 112°/13 mm. Completely satisfactory analytical figures were not obtained for this compound. In ethanol it gave a *monopicrate*, yellow needles, m. p. 153—155° (Found: C, 43·8; H, 3·7. $C_{13}H_{13}O_7N_5$ requires C, 44·4; H, 3·7%), and a *dipicrate*, yellow microcrystalline powder, m. p. 190—192° (Found: C, 39·7; H, 3·1. $C_{19}H_{16}O_{14}N_8$ requires C, 39·9; H, 2·8%). The amine (0·12 g.) in benzene (1·5 c.c.) and triethylamine (0·3 c.c.) was treated with benzoyl chloride (0·16 g.). The resulting solid was extracted with water and recrystallised from benzene to give the *benzoyl derivative* in prisms, m. p. 115—116° (Found: C, 73·9; H, 6·3. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%). The *toluene*-p-*sulphonyl* derivative, similarly prepared, separated from benzene in needles, m. p. 137—138° (Found: C, 60·7; H, 5·9. $C_{14}H_{16}O_2N_2S$ requires C, 60·9; H, 5·8%).

Trial of the Phosphoroazo-method of Amide Formation.—(The pyridine used in these and other examples of the reaction was distilled off solid potassium hydroxide, refluxed for 24 hr. over calcium oxide, and redistilled. The phosphorus trichloride was a redistilled commercial product.) Phosphorus trichloride (0·43 c.c.) was added to benzylamine (1·07 g.) in pyridine (10 c.c.) at 0°. Phenylacetic acid (1·36 g.) was added 30 min. later and the whole heated for 3 hr. at 100°. Pyridine was removed at 100°/12 mm. and the residue triturated with water to give *N*-phenylacetylbenzylamine (2·25 g., 100%), m. p. 109—114°, raised by recrystallisation from ethanol to 120—121° (Weiss, *Monatsh.*, 1919, **40**, 401, gives m. p. 122°). *N*-Benzoylbenzylamine, m. p. 105°, and *N*-benzoyl-2-phenylethylamine, m. p. 114·5—115·5°, were similarly prepared.

Phosphorus trichloride (0·43 c.c.) was added to 4-2′-aminoethylpyridine dihydrochloride (1·95 g.) in pyridine (35 c.c.) at 0°. After 30 min., benzoic acid (1·22 g.) was added, the whole heated 20 hr. at 100°, solvent removed, and aqueous sodium hydroxide and chloroform were added. 4-2′-Benzamidoethylpyridine (1 g., 44%), recovered from the organic layer, had m. p. 112·5—114·5° after recrystallisation from benzene, mixed m. p. (see above) 113·5—115°. 4-2′-*Phenylacetamidoethylpyridine*, similarly prepared (20% yield), separated in prisms (from ethyl acetate), m. p. 83—86° (Found: C, 74·9; H, 6·8. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7%).

1-*Methyl*-3-*indolylacetic Acid*.—1-Methylgramine methiodide (127 g.) was refluxed with potassium cyanide (104 g.) in water (720 c.c.) for 2½ hr. Extraction with ether and removal of solvent from the dried extracts gave the mixed nitriles (61 g., 94%). These (17 g.) were boiled with potassium hydroxide (40 g.) in ethanol (160 c.c.) and water (30 c.c.) for 17 hr. Water (300 c.c.) was added and the mixture distilled to half its volume. Hydrochloric acid was added to give a small permanent precipitate, and the whole boiled for 15 min. with charcoal, filtered and made strongly acid, the acid (9·4 g., 50%) then separating; after two recrystallisations from benzene, the m. p. was 127—128° (Snyder and Eliel, *loc. cit.*, give m. p. 127—128·5°). The picrate separated from benzene in red needles; the m. p. varied with the rate of heating; with immersion at 165° it was 172—172·5° (decomp.) (Piccini, *Atti R. Accad. Lincei*, 1889, **8**, I, 315, records dark red prisms, m. p. 173—174°; Snyder and Eliel, *loc. cit.*, report red needles, m. p. 160·5—161·5°).

Methyl 1-*Methyl*-3-*indolylacetate*.—When prepared by ethereal diazomethane, and isolated (93%) by distillation the *ester* had b. p. 192—193°/16 mm. (Found: C, 71·1; H, 6·6. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4%). After three weeks the oil solidified; the ester separated from ethyl acetate–light petroleum (1 : 5) (cooling in ethanol–solid carbon dioxide) in colourless prisms, m. p. 35—36·5°. A red Ehrlich test was given on warming; the colour faded on cooling. The

picrate separated from benzene in dark red prisms, m. p. 78—80° (Found: C, 50·1; H, 3·7. $C_{18}H_{16}O_9N_4$ requires C, 50·0; H, 3·7%).

2-Acetyl-1-methyl-3-indolylacetic Acid.—The above ester (2 g.) in acetyl chloride (20 c.c.) was stirred for 5 min. with zinc chloride (1 g.) at room temperature, and the whole poured into water to give *methyl 2-acetyl-1-methyl-3-indolylacetate* (2·15 g., 89%), which separated from ethanol in needles, m. p. 113·5—115° (Found: C, 68·8; H, 6·2. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1%). No colour was given with Ehrlich's reagent. This compound (1·75 g.) was boiled with sodium hydroxide (3 g.) in water (20 c.c.) for 15 min. Dilute hydrochloric acid then precipitated the *acid* (1·25 g., 76%) which after three crystallisations from ethanol–water (1 : 1) (charcoal) was obtained in pale yellow plates, m. p. 167—168° (Found: C, 67·4; H, 5·6. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%). No colour was given with Ehrlich's reagent. The *semicarbazone*, prepared in pyridine, separated from ethanol in solvated needles, m. p. 195—197° (decomp.) (Found: C, 57·3; H, 6·4. $C_{14}H_{16}O_3N_4,C_2H_6O$ requires C, 57·5; H, 6·6%).

Acylation with Methyl 1-Methyl-3-indolylacetate.—Keeping the ester in aqueous ammonia for 10 days gave the *amide* which separated from ethanol–water (1 : 1) in needles, m. p. 182—184° (Found: C, 69·7; H, 6·4. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4%). A red Ehrlich test was given on warming. Heating the ester (0·5 g.) with benzylamine (3 c.c.) at 140° for 4 hr., and pouring the whole into dilute hydrochloric acid gave *N-benzyl-1-methyl-3-indolylacetamide* (0·5 g., 72%) which separated from ethanol–water (2 : 1) in needles, m. p. 111—113° (Found: C, 77·4; H, 6·5. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5%). It gave a weak red Ehrlich test on warming.

Acylations with 1-Methyl-3-indolylacetazide.—Methyl 1-methyl-3-indolylacetate (8 g.), hydrazine hydrate (100%, 8 c.c.), and water (12 c.c.) were heated at 100° for 2 hr. to give the *hydrazide* (7·5 g., 94%) which crystallised from ethanol in needles, m. p. 134—136° (Found: C, 65·0; H, 6·7. $C_{11}H_{13}ON_3$ requires C, 65·0; H, 6·4%). An orange-red Ehrlich test was given on warming. This hydrazide with benzaldehyde in warm ethanol gave a *benzylidene derivative*, m. p. 150·5—152·5° (from pentyl alcohol) (Found: C, 74·1; H, 5·9. $C_{18}H_{17}ON_3$ requires C, 74·2; H, 5·8%). Treatment of the hydrazide (0·5 g.) in acetic acid (2 c.c.) and ice (10 g.) with sodium nitrite (0·09 g.), followed, after 5 min., by potassium carbonate solution (2 c.c. of 30%) gave *NN'-di-(1-methyl-3-indolylacetyl)hydrazine* (0·3 g., 65%) which crystallised from pentyl alcohol in needles, m. p. 248—249° (Found: C, 70·7; H, 6·0. $C_{22}H_{22}O_2N_4$ requires C, 70·6; H, 5·9%).

Ice (10 g.) followed by sodium nitrite (0·2 g.) in water (1 c.c.) was added to the hydrazide (0·5 g.) in acetic acid (2·5 c.c.). The azide separated as an oil, and was taken up in chloroform (10 c.c.), and the chloroform layer was quickly dried (Na_2SO_4) and mixed with benzylamine (2 c.c.). After 12 hr., the whole was filtered, solvent removed, and dilute hydrochloric acid added to give *N*-benzyl-1-methyl-3-indolylacetamide (0·52 g., 75%), needles [from ethanol–water (2 : 1)], m. p. 112—113° and mixed m. p. 111—113° with a specimen prepared from the ester.

Acylations with 1-Methyl-3-indolylacetic Acid.—By the standard phosphoroazo-procedure this acid was converted into the *anilide* (73% yield) which separated from ethanol–water (2 : 1) as needles, m. p. 116—117·5° (Found: C, 77·1; H, 6·1. $C_{17}H_{16}ON_2$ requires C, 77·3; H, 6·1%). A deep red Ehrlich test was given on warming.

Experiments with 3-Indolylacetic Acid.—The following derivatives of this acid (prepared by a modification of the method of Snyder and Pilgrim, *J. Amer. Chem. Soc.*, 1948, **70**, 3771) were obtained by methods similar to those described above for their 1-methyl analogues: *methyl 3-indolylacetate* (69%), b. p. 205—208°/10 mm., 216—218°/17 mm., prisms (from ethyl acetate–light petroleum), m. p. 49—50·5° (Found: C, 70·0; H, 5·6. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·8%), giving a cherry-red Ehrlich reaction (Jackson, *J. Biol. Chem.*, 1930, **88**, 659, gives no analysis and describes it as an oil of b. p. "about 180°/2 mm."; Koegl and Kostermanns, *Z. physiol. Chem.*, 1935, **235**, 201, describe it merely as an oil). The orange-red picrate of this ester, crystallised from benzene, had m. p. 125—126° (Koegl *et al.*, *loc. cit.*, give m. p. 125°). *N-Benzyl-3-indolylacetamide* (87% from ester; 73% from the hydrazide *via* the azide; 91% from the acid by the phosphoroazo-method), separated from ethanol–water (2 : 1) in plates, m. p. 152·5—153·5°, and gave a cherry-red Ehrlich reaction (Found: C, 77·3; H, 6·1. $C_{17}H_{16}ON_2$ requires C, 77·3; H, 6·1%). *3-Indolylacethydrazide* (97%) crystallised from ethanol–water (1 : 4) in needles, m. p. 127·5—129·5° and gave a red Ehrlich test (Found: C, 63·3; H, 6·0. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8%). The *benzylidene derivative* of the latter separated from pentyl alcohol in prisms, m. p. 187—188° (Found: C, 73·6; H, 5·6. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4%). *3-Indolylacetanilide* (25% from the hydrazide *via* the azide; 80% from the acid by the phosphoroazo method) crystallised from ethanol–water (2 : 1) in prisms, m. p. 149·5—150°,

and gave a cherry-red Ehrlich test (Found : C, 76·6; H, 5·6. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%). NN'-*Di*-(3-*indolylacetyl*)*hydrazine* (55%) separated from acetic acid in needles, m. p. 229—230° (Found : C, 69·4; H, 5·2. $C_{20}H_{18}O_2N_4$ requires C, 69·4; H, 5·2%).

Attempted Preparation of 4-(2-3'-*Indolylacetamidoethyl*)*pyridine*.—The corresponding acid and amine dihydrochloride were subjected to the standard phosphoroazo-procedure; after 12 hours' heating at 100°, volatile matter was removed at 100°/14 mm. and dilute hydrochloric acid added to the residue to acidity to Congo-red. The whole was extracted 4 times with chloroform, made strongly alkaline, and extracted with ethyl acetate. From the latter extracts was obtained 3-indolylacetamide, m. p. and mixed m. p. 150·5—152° (Found : C, 68·8, 68·8; H, 5·8, 5·7. Calc. for $C_{10}H_{10}ON_2$: C, 69·0; H, 5·7%) (Majima and Hoshino, *Ber.*, 1925, **58**, 2046, give m. p. 150—151°).

3-2'-*Anilinoethylindole*.—3-Indolylacetanilide (2 g.) was refluxed for 24 hr. with lithium aluminium hydride solution (M in ether; 25 c.c.) and ether (80 c.c.). Ethyl acetate to decompose excess of hydride was added, followed by sodium hydroxide (15 g.) in water (40 c.c.). Removal of solvent from the dried ether layer gave the *amine* (0·9 g., 48%) which separated from ethanol–water (2 : 1) in prisms, m. p. 98—100° (Found : C, 81·2; H, 6·9. $C_{16}H_{16}N_2$ requires C, 81·3; H, 6·8%). Carbonyl bands were absent from the infrared spectrum. A cherry-red Ehrlich test was given. The *acetyl derivative* crystallised from ethanol–water (2 : 1) in needles, m. p. 120—121·5 (Found : C, 77·7; H, 6·7. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5%).

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