An Attempt to Simulate the Biogenesis of Strychnine. Part II. Preparation and Transformations of* 3-(2-4′-*Pyridylacetamidoethyl*)*indole.*

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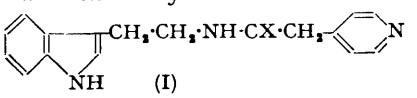
After some unsuccessful attempts, 3-(2-4′-pyridylacetamidoethyl)indole was prepared by condensing methyl 4-pyridylacetate with tryptamine. Pyrolysis of 4-(1-benzoyloxy-1-cyanoethyl)pyridine is shown to involve acyl–oxygen fission. The methiodide of the above indole with alkali gave the anhydro-base, and some transformations of this and analogous compounds are described. An example of the reduction of an αβ-unsaturated amide at the C:C double bond by lithium aluminium hydride is given. A mechanism is advanced for the reduction of pyridinium salts by borohydride to tetrahydropyridines in neutral or weakly acid solution.

THE preparation of the base (I; X = H_2) by reaction of an indole derivative with 4-2′-aminoethylpyridine having failed (Part I *), the preparation of this compound from tryptamine and a pyridine derivative was investigated. Preparation direct from tryptamine, formaldehyde, and, *e.g.*, γ-picoline appeared unpromising because of simultaneous formation of tetrahydrocarboline. It was hoped that 4-diazoacetylpyridine with silver powder and tryptamine would give 3-(2-4′-pyridylacetamidoethyl)indole (I; X = O); but Dornow's preparation of the diazo-ketone (*Ber.*, 1940, **73**, 185) could not be repeated; instead an ether-insoluble, water-soluble tar was obtained; *N*-methylation may have taken place.

Clemo, Morgan, and Raper (*J.*, 1937, 965) reported the preparation of 2-bromoacetylpyridine from 2-acetylpyridine, but when 4-acetylpyridine (prepared by a simplified modification of Kolloff and Hunter's method, *J. Amer. Chem. Soc.*, 1941, **63**, 490) was brominated under the same conditions an addition compound was produced. This changed above its melting point into 4-bromoacetylpyridine hydrobromide, but neither this nor the

* Part I, preceding paper.

free base could be obtained pure and nothing could be isolated after reactions with piperidine or tryptamine. These failures were probably due to quaternisation of the pyridine-nitrogen atom, and in an attempt to brominate a quaternary derivative of 4-acetylpyridine the methobromide was prepared *via* the methiodide, but it was not brominated smoothly in acetic acid.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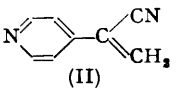
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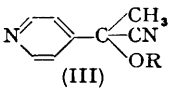
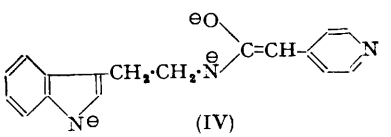

(III)

Addition of tryptamine to the doubly activated double bond of 4-1′-cyanovinylpyridine (II) would give a useful intermediate (cf. Doering and Weil, *J. Amer. Chem. Soc.*, 1947, **69**, 2461). 4-Acetylpyridine was converted quantitatively into the cyanohydrin (III; R = H) which when heated alone lost hydrogen cyanide, and was not dehydrated smoothly by thionyl chloride. The acetyl derivative (III; R = Ac) distilled at atmospheric pressure, for the most part unchanged, above 250°. The products of the pyrolysis of the benzoyl derivative (III; R = Bz) were shown to consist of benzoic acid, benzonitrile, and 4-acetylpyridine, in addition to a basic, non-ketonic fraction which was itself still a mixture. To explain this result it was postulated that, in addition to the normal alkyl–oxygen fission of esters, acyl–oxygen fission had taken place giving as primary products 4-acetylpyridine and benzoyl cyanide; the latter is known to undergo pyrolytic decomposition to benzonitrile and carbon monoxide. Ritchie (*Chem. and Ind.*, 1954, 37) independently also observed this reaction.

Alkaline hydrolysis of 4-pyridylthioacetomorpholide to 4-pyridylacetic acid hydrochloride has been described by Malan and Dean (*J. Amer. Chem. Soc.*, 1947, **69**, 1797) by a tedious procedure which in our hands failed. However, hydrolysis with hydrochloric acid gave a 70% yield. It was not possible to isolate free 4-pyridylacetic acid, even using an ion-exchange resin; this acid is formally similar to a β-keto-acid, so the zwitterion should be decarboxylated more readily than either of the ions which exist in alkaline and acid solution (cf. Doering and Pasternak, *ibid.*, 1950, **72**, 143). Although in the phosphoroazo-reaction (Goldschmit and Lautenschlager, *Annalen*, 1953, **580**, 74; cf. Part I) tryptamine and 4-pyridylacetic acid hydrochloride reacted separately in model experiments, attempts to cause them to react together failed.

In our hands ethyl 4-pyridylacetate was obtained as a stable crystalline hydrate (contrast Malan and Dean, *loc. cit.*; Lukes and Earnest, *Coll. Czech. Chem. Comm.*, 1949, **14**, 679). The methyl ester gave amides with ammonia, benzylamine, and 2-aminoethylindole. Concurrently, ethyl β-hydroxy-α-4-pyridylacrylate was prepared but did not condense smoothly with tryptamine under conditions useful for phenylformylacetic ester and other amines (Decombe, *Ann. Chim.*, 1932, **18**, 81).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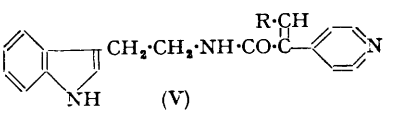

(V)

Attempts to reduce 3-(2-4′-pyridylacetamidoethyl)indole (I; X = O) to the base (I; X = H_2) with lithium aluminium hydride failed, probably owing to formation of a salt of the enolic form of the amide which is stabilised by mesomerism (as in IV). If the amide reacted with an aldehyde at the methylene group the αβ-unsaturated amide (V) obtained would be unable to lose a proton to give a similar resonating anion, and might therefore undergo reduction to the corresponding saturated or allylic amine (cf. Uffer and Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1397). Moreover this procedure would lead to the introduction of a side chain into the correct position (cf. Part I). 4-Pyridylthioacetomorpholide and litharge (not mercuric oxide) in boiling aqueous propanol gave 4-pyridylacetomorpholide in fair yield (cf. Chabrier and Renard, *Bull. Soc. chim. France*, 1949, D 272; Hofmann, *Ber.*, 1869, **2**, 455), which with benzaldehyde in acetic anhydride (cf. Philips. *J. Amer. Chem.*

Soc., 1954, **76**, 3986) gave β-phenyl-α-4-pyridylacrylomorpholide, reduced by lithium aluminium hydride to the propionomorpholide with the amide grouping intact. The selective reduction of a carbon–carbon double band in certain azlactones by lithium aluminium hydride has been reported by Baltazzi and Robinson (*Chem. and Ind.*, 1953, 868) and while the present work was in progress Snyder and Putnam (*J. Amer. Chem. Soc.*, 1954, **76**, 1893) gave another example of a reduction of unsaturated to a saturated amide. In the present case, the attachment of H^- (or an equivalent) to the β-position of the amide gives a stable mesomeric anion. In the lithium aluminium hydride reductions described, the procedure recommended by Micovic and Mihailovic (*J. Org. Chem.*, 1953, **18**, 1190) for decomposing the complex and isolating the product gave excellent results.

Attempts were now made to convert the amide (I; X = O) into the glutardialdehyde (VI), which it was considered should cyclise as indicated to a strychnine derivative (cf. Robinson and Saxton, *J.*, 1953, 2598). Panouse (*Compt. rend.*, 1951, **233**, 260, 1200) has shown that pyridinium salts are reduced by borohydride in alkaline solution to 1 : 2-dihydropyridines. The product from the methiodide of the amide (I; X = O) after this

FIG. 1. FIG. 2.

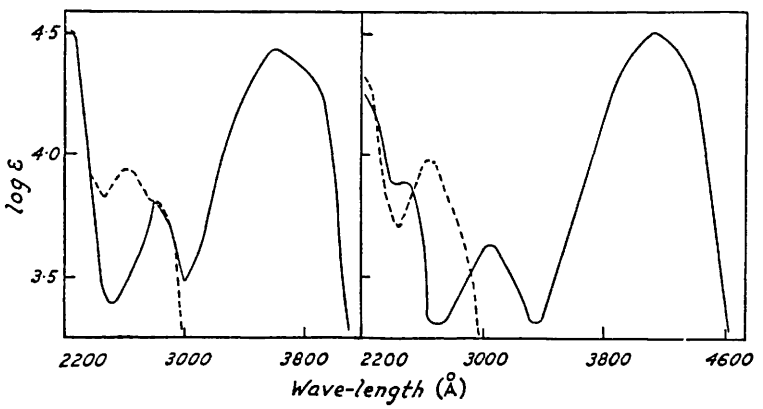
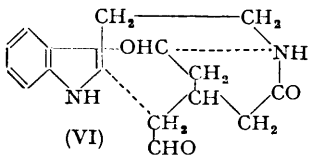


FIG. 1. *Absorption spectrum of* (– – –) *the methiodide of* (I; X = O), *in acid solution, and* (——) *the anhydro-base* (VII), *in alkaline solution.*

FIG. 2. *Absorption spectrum of the* S-*methyl derivative,* (– – –) *in acid solution* [cf. XI; R = C_4H_8O] *and* (——) *in alkaline solution* [cf. (X)].

treatment did not appear to be the dihydropyridine. Analytical figures for hydrogen were low, and whereas 1 : 2-dihydropyridines have an absorption maximum at 3400 Å (Panouse, *Bull. Soc. chim. France*, 1953, D 53), this compound had a broad band at 3600 Å (ε 27,000) in alkaline methanol, but in acid methanol only the bands expected for the indole and



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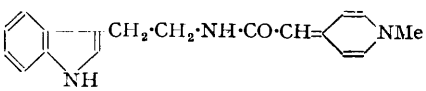
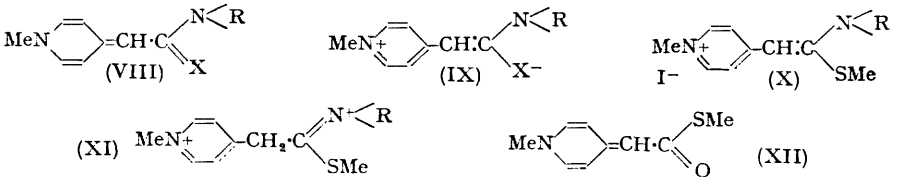


(VII)

pyridine chromophores (Fig. 1). These results were explained when the compound was shown to be reconverted by hydrogen iodide into the methiodide of (I; X = O), and to result from this methiodide by the action of alkali alone. The compound was thus the anhydro-base (VII).

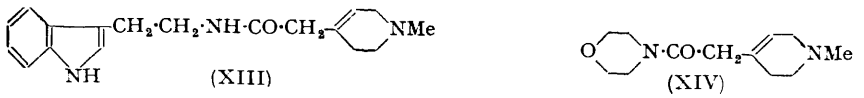
In a study of some analogous anhydro-bases, 4-pyridylthioacetopiperidide readily gave a monomethiodide, shown by a *N*-methyl determination to have the methyl group attached to the pyridine-nitrogen atom. This salt with alkali gave the anhydro-base (VIII; R = $>C_5H_{10}$, X = S), which in neutral methanol showed an intense absorption

band which disappeared on acidification. 4-Pyridylthioacetomorpholide and 4-pyridylacetomorpholide gave analogous anhydro-bases (VIII; R = C_4H_8O, X = S and O respectively). Hydrogen iodide caused reconversion into the pyridinium salts. These anhydro-bases are vinylogues of pyrid-4-one or pyrid-4-thione, and the structure (IX) must make a large contribution. No anhydro-base was isolated from the methiodide of γ-4-pyridylpropionamide where this stabilising influence would be absent.

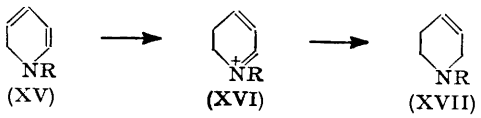


As hydrogen iodide reacted with the anhydro-bases to give a product with the hydrogen atom on the α-carbon atom, it appeared possible that the anhydro-bases would be alkylated at this point where a side chain was needed (cf. Part I). However, the morpholino-compound (XI; R = C_4H_8O, X = S) and methyl iodide gave the methylthio-iodide (X; R = C_4H_8O). This showed an intense band at 4100 Å (ε 32,000) which disappeared in acid solution. It was a cyanine dye, with large contributions also from the structures in which the charge was associated with the other nitrogen atom or with the sulphur atom, but in acid a proton must have added to give the cation (XI; R = C_4H_8O) which showed only the absorption expected from a pyridinium ion (Fig. 2). The structure was proved by the continued action of acid which gave the expected thiol-ester (XII) (cf. Chabrier and Renard, *loc. cit.*). The thioanhydro-base (VIII; R = C_5H_{10}, X = S) also gave a cyanine dye with methyl iodide, but no crystalline product could be isolated from the two *O*-anhydro-bases.

Reduction of these two *O*-anhydro-bases failed but they were smoothly hydrogenated over palladium–strontium carbonate to the piperidyl derivatives. The indole nucleus was shown to be intact in the former product by the ultra-violet spectrum and by a positive Ehrlich test; the latter product showed no high-intensity absorption above 2200 Å. The uptake of hydrogen was steady and it did not seem promising to stop the reduction at the dihydro-stage. Panouse (*loc. cit.*) has reported that reduction of pyridinium salts in neutral or weakly acid solution with borohydride favours the formation of tetrahydro-



pyridines, and both the amides (XIII) and (XIV) were readily prepared in this way. It has recently been shown that in acid solution an αβ-unsaturated amine $R_2C{:}CR{\cdot}NR_2$ is converted into the ion $R_2CH{\cdot}CR{:}NR_2^+$ (Leonard and Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781) and it is suggested that the reduction of a pyridine to the tetrahydro-stage in solutions of low pH is due to equilibrium between the intermediate dihydropyridine (XV) and (XVI), the latter undergoing reduction to (XVII). At high pH, the cation is not formed and no reduction can take place. In an attempt to reduce the methiodide of the



amide (I; X = O) in a solution of pH just not high enough to cause precipitation of anhydro-base, the tetrahydropyridine was again obtained; even when the correct quantity of borohydride was used part of the base was reduced to the tetrahydro-stage and part left unchanged.

Experimental

In the ultraviolet spectral data, alkaline methanol was *ca.* 0·1N in potassium hydroxide; acid methanol was *ca.* 0·1N in sulphuric acid; concentration of the compound was $8 \pm 3 \times 10^{-5}$M.

4-Acetylpyridine.—Dry ethanol (69 c.c.) was dropped on to powdered sodium (27 g.) under anhydrous ether (420 c.c.), with good stirring. After 4 hours' refluxing the ether was distilled off and ethyl *iso*nicotinate (113 g.) and ethyl acetate (150 c.c.) were added. The mixture was stirred for 1 hr., refluxed for 16 hr., and cooled. Water (500 c.c.) and hydrochloric acid (300 c.c.) were added, and the whole was refluxed for 2½ hr. Excess of potassium carbonate was added, and the mixture extracted with ether (9 × 150 c.c.). Distillation of the dried extracts gave 4-acetylpyridine (74—80·5 g., 82—89%), b. p. 90°/8 mm. (Kolloff and Hunter, *J. Amer. Chem. Soc.*, 1941, **63**, 490, give b. p. 211—212°). The phenylhydrazone had m. p. 146·5—147·5° (Pinner, *Ber.*, 1901, **34**, 4250, gives m. p. 150°). The *dibromide*, prepared in benzene–acetic acid, crystallised from acetone in pale brown needles, m. p. 98—99°, resolidifying, and remelting at 205° (decomp.) (varies with the rate of heating); it liberated iodine from aqueous potassium iodide, and the active bromine content was thus estimated (Found : C, 29·9; H, 2·6; active Br, 56·8. $C_7H_7ONBr_2$ requires C, 29·9; H, 2·5; Br, 56·9%). The *methiodide* crystallised from ethanol in orange-red needles, m. p. 171—172·5° (Found : C, 36·8; H, 3·8. $C_8H_{10}ONI$ requires C, 36·5; H, 3·8%), and with silver bromide in water gave the *methobromide* which crystallised from *n*-butanol in orange prisms, m. p. 183—184° (Found : C, 43·9; H, 4·6. $C_8H_{10}ONBr$ requires C, 44·4; H, 4·6%).

4-(1-Cyano-1-hydroxyethyl)pyridine.—4-Acetylpyridine (74 g.) and anhydrous hydrogen cyanide (100 c.c.) were left at room temperature for 2 days. Much *cyanohydrin* separated, and more was obtained by evaporation (total : 91 g., 100%) : it separated from benzene in prisms, the m. p. depending on the rate of heating; immersion at 85° gave m. p. 90—95° (decomp.) (Found : C, 65·0; H, 5·5. $C_8H_8ON_2$ requires C, 64·9; H, 5·4%). The *picrate* had m. p. 133—137° (decomp.) (from benzene) (Found : C, 44·9; H, 2·9. $C_{14}H_{11}O_8N_5$ requires C, 44·6; H, 2·9%). The cyanohydrin (10 g.), acetic anhydride (10 c.c.), and pyridine (20 c.c.) were kept at room temperature for 24 hr. and then distilled, to give *4-(1-acetoxy-1-cyanoethyl)pyridine*, b. p. 165—167°/14 mm., prisms, m. p. 76—78° (from benzene–light petroleum) (Found : C, 63·4; H, 5·3. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3%). The *picrate* separated from benzene in prisms, m. p. 171—174° (Found : C, 45·9; H, 3·2. $C_{16}H_{13}O_9N_5$ requires C, 45·8; H, 3·1%).

Prepared from the cyanohydrin (10 g.) and benzoyl chloride (12 c.c.) in pyridine (20 c.c.) and isolated by addition of water, *4-(1-benzoyloxy-1-cyanoethyl)pyridine* (17 g., 100%) crystallised from ethanol in needles, m. p. 112—113·5° (Found : C, 71·6; H, 4·8. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8%).

Pyrolysis of 4-(1-*Benzoyloxy*-1-*cyanoethyl*)*pyridine.*—This compound (40 g.) was heated in nitrogen to 350°. The semisolid condensate was shaken with ether and aqueous sodium hydroxide. Acidification of the aqueous layer gave benzoic acid (6·3 g.), m. p. and mixed m. p. 121—122°. Distillation of the dried ether layer gave a liquid, b. p. 58—120°/8 mm., which was treated with aqueous hydrochloric acid and ether; distillation of the ether layer gave benzonitrile (3·5 g.), b. p. 187—189° (Found : C, 81·4; H, 4·8. Calc. for C_7H_5N : C, 81·6; H, 4·8%), giving with hydrogen peroxide and aqueous sodium hydroxide benzamide (76%), m. p. and mixed m. p. 126·5—127·5° (Radziszewski, *Ber.*, 1885, **18**, 355). The acid layer was made strongly basic with sodium hydroxide; ether then removed a basic fraction (3·5 g.), b. p. 54—135°/9 mm., which with excess of semicarbazide hydrochloride and aqueous sodium acetate gave 4-acetylpyridine semicarbazone (0·53 g.), m. p. and mixed m. p. 216—219° (decomp.) [Emmert and Wolpert (*Ber.*, 1941, **74**, 1015) give m. p. 218—219° (decomp.)]. The mother-liquors were extracted with ether and the extracts dried (KOH, to remove acetic acid); distillation then gave a non-ketonic fraction (1 g.), b. p. 66—130°/19 mm.

4-Pyridylacetic Acid Hydrochloride.—4-Pyridylthioacetomorpholide, prepared in 85% yield by Malan and Dean's method (*loc. cit.*), gave a *hydrochloride* which separated from ethanol in prisms, m. p. 195—196·5° (Found : C, 51·2; H, 6·1. $C_{11}H_{15}ON_2ClS$ requires C, 51·1; H, 5·8%). The thiomorpholide (26·8 g.) was refluxed with hydrochloric acid (27 c.c.) for 2·5 hr., then kept at 0°. 4-Pyridylacetic acid hydrochloride (15·7 g., 70%) separated; its m. p. varied with the rate of heating; immersion at 120° gave m. p. 145—146°, unaffected by recrystallisation from ethanol (Found : C, 48·7; H, 4·7; N, 8·1. Calc. for $C_7H_8O_2NCl$: C, 48·4; H, 4·6; N, 8·1%). Malan and Dean (*loc. cit.*) give m. p. 130—131°.

Phosphoroazo-experiments.—From tryptamine and benzoic and phenylacetic acid were

prepared by the standard procedure 3-2′-benzamido- (38%), m. p. 137—138° (from benzene) (Ewins, *J.*, 1911, **99**, 273, gives m. p. 137—138°), and 3-2′-phenylacetamido-ethylindole (43%), m. p. 142—143·5°, prisms (from benzene) (Found: C, 77·3; H, 6·3. Calc. for $C_{18}H_{18}ON_2$: C, 77·7; H, 6·5%). Hahn and Ludwig (*Ber.*, 1934, **67**, 2031) give m. p. 144° for the latter.

4-Pyridylacetic acid hydrochloride was converted into the anilide (45%), m. p. 141·5—142·5° (from ethanol–water; 2 : 1) (Found: C, 73·4; H, 5·7. Calc. for $C_{13}H_{12}ON_2$: C, 73·6; H, 5·7%). Lukes and Earnest (*Coll. Czech. Chem. Comm.*, 1949, **14**, 685) give m. p. 139·5—140·5°.

Esters of 4-Pyridylacetic Acid.—The acid hydrochloride (10·7 g.) and a cold mixture of sulphuric acid (12 c.c.) and ethanol (30 c.c.) were left until dissolution was complete (2 days), then heated at 100° for 1 hr., cooled, and poured on ice and aqueous ammonia; the *ethyl ester monohydrate* separated, m. p. 41—43·5°. In a vacuum-desiccator the hydrate liquefied; on exposure to air or more quickly on addition of water, the anhydrous ester re-formed the hydrate. A sample obtained by equilibrating the anhydrous ester, after distillation, with air was analysed (Found: C, 58·9; H, 7·0. $C_9H_{11}O_2N,H_2O$ requires C, 59·0; H, 7·1%). The anhydrous ester, b. p. 122·5°/11 mm., was isolated by distillation after treatment of the hydrate with ether and magnesium sulphate. The ethyl ester picrate, separated from ethanol, had m. p. 120—121° (Malan and Dean, *loc. cit.*, give b. p. 107—108°/3 mm. for the ester, m. p. 121—123° for picrate; Lukes and Earnest, *loc. cit.*, give b. p. 119—120°/11 mm. and m. p. 121°).

The *methyl ester* (71%) was similarly prepared as an oil, b. p. 114·5°/10 mm., n^{20} 1·5084 (Found: C, 63·2; H, 6·0. $C_8H_9O_2N$ requires C, 63·6; H, 6·0%). With ammonia it gave the *amide* (70%), plates, m. p. 142—144·5° (from ethanol) (Found: C, 61·5; H, 5·8. $C_7H_8ON_2$ requires C, 61·8; H, 5·9%). Heating the methyl ester (0·5 g.) with benzylamine (3 c.c.) at 140° for 4 hr., under nitrogen, followed by removal of volatile material at 180°/11 mm. and recrystallisation from ethanol, gave needles of *4-pyridylacetylbenzylamine* (37%), m. p. 106—108° (Found: C, 74·5; H, 6·0. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%).

3-(2-4′-Pyridylacetamidoethyl)indole.—Methyl 4-pyridylacetate (0·5 g.) was heated at 150° with tryptamine (2 g.) for 4 hr. under nitrogen, then refluxed with acetic acid (4 c.c.) and acetic anhydride (4 c.c.) for 30 min., and volatile compounds were removed at 180°/11 mm. The residue was taken up in hydrochloric acid (6N; 5 c.c.), extracted four times with chloroform, made strongly alkaline with sodium hydroxide, and twice extracted with ethyl acetate. Material removed in the latter solidified; the *indole* then separated from benzene in prisms, m. p. 102—104° (Found: C, 72·9; H, 6·0; N, 15·4. $C_{17}H_{17}ON_3$ requires C, 73·1; H, 6·1; N, 15·0%). After 3 weeks the specimen had m. p. 155—157°, and separated from ethanol in needles, m. p. 160—160·5°. Subsequent preparations always gave this *polymorph* (Found: C, 73·3; H, 6·2; N, 14·9%).

Once seeds were available the following was convenient: ester (4·6 g.) and amine (5 g.) were heated at 140° for 4 hr. under nitrogen, then dissolved in ethanol, benzene was added, and the solution seeded to give the amide (5·95 g., 70%).

The amide was unaffected when refluxed with a large excess of lithium aluminium hydride in ether for 96 hr., in tetrahydrofuran for 45 hr., or in dioxan for 24 hr.

Ethyl β-Hydroxy-α-4-pyridylacrylate.—Powdered sodium (3 g.) was refluxed with ethanol (7·7 c.c.) in ether (50 c.c.) for 4 hr. Ether was then removed, and the residue refluxed with ethyl 4-pyridylacetate (10 g.) and ethyl formate (25 c.c.) for 24 hr. and poured on ice. After two ether-extractions to remove starting material, carbon dioxide precipitated the *ester* (2·25 g., 19%) which crystallised from ethyl acetate in needles; the m. p. varied with the rate of heating; immersion at 120° gave m. p. 130° (decomp.) (Found: C, 61·9; H, 5·8; N, 7·1. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·2%).

4-Pyridylacetomorpholide.—4-Pyridylthioacetomorpholide (44 g.) was refluxed with lead monoxide (150 g.) in *n*-propyl alcohol (500 c.c.) and water (140 c.c.) for 3 days. Lead compounds were removed at a centrifuge and washed with methanol. Evaporation of filtrate and washings gave the *morpholide* (24·4 g., 61%) which was obtained from benzene–light petroleum in deliquescent needles, m. p. 94—95° (Found: C, 63·7; H, 6·7. $C_{11}H_{14}O_2N_2$ requires C, 64·1; H, 6·8%). Light absorption max. at 2550 Å (ε 3500) in MeOH.

The *methiodide*, prepared in hot benzene, formed needles, m. p. 205—207° (decomp.), from ethanol (Found: C, 41·5; H, 5·0. $C_{12}H_{17}O_2N_2I$ requires C, 41·4; H, 4·9%). Light absorption max. at 2600 Å (ε 2600) in neutral MeOH, 2250, 3800 Å (ε 7800, 18,100) in alkaline MeOH. The *methotoluene-p-sulphonate* (92%) crystallised from ethanol–benzene in plates, m. p. 199—201° (decomp.) (Found: N, 7·4. $C_{19}H_{24}O_5N_2S$ requires N, 7·1%).

β-Phenyl-α-4-pyridylacrylomorpholide.—4-Pyridylacetomorpholide (4·1 g.), benzaldehyde (2·3 g.), and acetic anhydride (3·6 c.c.) were refluxed for 3½ hr., then poured into excess of aqueous

sodium hydroxide and extracted with benzene. The dried extracts were chromatographed on a short alumina column; evaporation of the eluate and recrystallisation of the residue from benzene–light petroleum gave the *acrylomorpholide* (2·62 g., 45%) which after further recrystallisation formed colourless needles, m. p. 133·5—135° (Found: C, 73·5; H, 6·3. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·1%). Light absorption max. at 2850 and 3000 Å (ε 20,000, 21,000) in neutral MeOH, 2300 and 3350 Å (ε 13,000 and 23,000) in acid MeOH. The *methiodide* separated from ethanol in pale yellow needles, m. p. 244·5—246·5° (decomp.) (Found: C, 52·4; H, 5·2. $C_{19}H_{21}O_2N_2I$ requires C, 52·3; H, 4·8%). Light absorption max. at 3400 Å (ε 10,200) in MeOH.

β-*Phenyl*-α-4-*pyridylpropionomorpholide*.—The foregoing morpholide (1 g.) was extracted (Soxhlet) into lithium aluminium hydride (0·3 g.) under ether (80 c.c.) in 1½ hr.; the whole was then refluxed for 30 min. more and cooled, and water (0·3 c.c.), aqueous 10% sodium hydroxide (0·45 c.c.), and water (0·3 c.c.) were added successively. After filtration, evaporation gave the *propionomorpholide* (0·75 g., 74%) which after two recrystallisations from ethanol formed prisms, m. p. 135·5—137° (Found: C, 72·9; H, 6·7. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·7%). Light absorption max. at 2600 Å (ε 3100) in MeOH.

1 : 4-*Dihydro*-4-(2-3′-*indolylethylaminocarbonylmethylidene*)-1-*methylpyridine*.—3-(2-4′-Pyridylacetamidoethyl)indole gave a *methiodide* (97%) (prepared in tetrahydrofuran) which crystallised in stout needles, m. p. 178—179°, from ethanol (Found: C, 51·4; H, 4·9. $C_{18}H_{20}ON_3I$ requires C, 51·3; H, 4·8%). Light absorption max. at 2600 Å, infl. at 2800 Å (ε 8400, 6300) in neutral MeOH, 2800, 3600 Å (ε 6300, 27,000) in alkaline MeOH. It was converted by aqueous-methanolic sodium hydroxide into the *anhydro-base* (100%), which separated from anisole in pale brown needles, m. p. 191—196° (decomp.) (Found: C, 73·7; H, 6·6; N, 14·0; *N*-Me, 4·7. $C_{18}H_{19}ON_3$ requires C, 73·7; H, 6·5; N, 14·3; *N*-Me, 5·1%). {The anhydro-base was readily soluble in dilute sulphuric acid; on addition of potassium iodide, the original methiodide crystallised [m. p. and mixed m. p. 208—210° (decomp.)]}. In later work the methiodide was always obtained as a *polymorph*, fine needles, m. p. 209—210° (Found: C, 51·1; H, 4·6%).

1 : 4-*Dihydro*-1-*methyl*-4-*piperidinothiocarbonylmethylidenepyridine*.—4-Acetylpyridine (4·5 g.), piperidine (3·6 c.c.), and sulphur (1·4 g.) were refluxed for 12 hr., then poured into water, and the product was chromatographed (alumina–benzene), to give 4-*pyridylthioacetopiperidide* (2·2 g., 27%), needles (from ethanol), m. p. 94—97° (Found: C, 65·4; H, 7·5. $C_{12}H_{16}N_2S$ requires C, 65·5; H, 7·3%). Light absorption max. at 2800 Å (ε 9600) in MeOH. The *methiodide* separated from ethanol in needles, m. p. 191—194° (decomp.) (Found: C, 43·4; H, 5·4; S, 9·0; *N*-Me, 4·4. $C_{13}H_{19}N_2SI$ requires C, 43·1; H, 5·2; S, 8·8; *N*-Me, 4·2%). Light absorption max. at 2250, 2750 Å (ε 29,000, 18,000) in neutral MeOH, 2250, 3300, 4250 Å (ε 27,000, 9500, 32,000) in alkaline MeOH.

Treatment of a solution of the methiodide with alkali precipitated the *anhydro-base*, yellow needles (from ethanol), m. p. 133—136° (Found: C, 66·3; H, 7·6; S, 13·5. $C_{13}H_{18}N_2S$ requires C, 66·6; H, 7·7; S, 13·7%), reconverted by hydrogen iodide into the methiodide, m. p. and mixed m. p. 191—194° (decomp.).

Similarly 4-pyridylthioacetomorpholide gave a *methiodide*, needles, m. p. 227—230° (decomp.), from methanol (Found: C, 40·0; H, 4·8. $C_{12}H_{17}ON_2IS$ requires C, 39·6; H, 4·7%), a *methotoluene*-p-*sulphonate*, prisms, m. p. 149—153·5° (decomp.), from ethanol (Found: C, 55·6; H, 5·8. $C_{19}H_{24}O_4N_2S_2$ requires C, 55·9; H, 5·9%), and an *anhydro-base*, yellow needles (from ethanol), m. p. 197—198° (decomp.) (Found: C, 61·0; H, 6·6; S, 13·6. $C_{12}H_{16}ON_2S$ requires C, 61·0; H, 6·8; S, 13·7%), reconverted by hydrogen iodide into the methiodide, m. p. and mixed m. p. 228—231° (decomp.).

1 : 4-*Dihydro*-1-*methyl*-4-*morpholinocarbonylmethylidenepyridine*.—4-Pyridylacetomorpholide methotoluene-*p*-sulphonate (19·1 g.) was shaken with chloroform (100 c.c.) and aqueous sodium hydroxide (10%; 25 c.c.), and the aqueous layer further extracted with chloroform (3 × 50 c.c.). Solvent was removed from the dried ($MgSO_4$) extracts, and the residue taken up in benzene and filtered. Addition of light petroleum ether gave the *anhydro-base* (7·47 g., 69%) which crystallised from the mixed solvent in brown needles, changing to prisms, m. p. 123—125° (Found: C, 65·4; H, 7·2. $C_{12}H_{16}O_2N_2$ requires C, 65·5; H, 7·3%). The compound formed dichroic solutions in chloroform, green in thin layers, brown in thick. It was freely soluble in water. On storage it soon decomposed to a black tar.

β-4-Pyridylpropionamide gave a *methiodide* which separated from ethanol in prisms; the m. p. on rapid heating was 150—160°, on slow heating 163—169° probably because of polymorphism (Found: C, 36·9; H, 4·5. $C_9H_{13}ON_2I$ requires C, 37·0; H, 4·5%).

Methiodides of the Thio-anhydro-bases.—Treatment of the thiomorpholide anhydro-base with

methyl iodide in tetrahydrofuran gave **1-*methyl*-4-(2-*methylthio*-2-*morpholinovinyl*)*pyridinium iodide***, which separated from ethanol–tetrahydrofuran (1 : 1) in yellow needles, m. p. 195—198° (decomp.) (Found : C, 41·6; H, 5·1; *N*-Me, 3·4; *C*-Me, 0·0. $C_{13}H_{19}ON_2SI$ requires C, 41·3; H, 5·0; 1*N*-Me, 4·0%). Light absorption max. at 2500, 3050, and 4100 Å (ε 7700, 4200, and 32,000) in neutral MeOH, 2650 Å (ε 9500) in acid MeOH.

This iodide (1 g.) was heated at 100° for 8 min. with 2N-sulphuric acid (10 c.c.), then cooled and treated with 2·5N-sodium hydroxide (15 c.c.), affording **1 : 4-*dihydro*-1-*methyl*-4-(S-*methylthiocarbonylmethylene*)*pyridine*** (0·35 g., 73%) which separated from ethanol in pale yellow prisms, m. p. 134·5—136·5° (Found : C, 59·9; 59·4; H, 6·1, 6·0; N, 7·9. $C_9H_{11}ONS$ requires C, 59·7; H, 6·1; N, 7·7%). Light absorption max. at 2300, 2600, 4100 (ε 5500, 2000, 21,600) in neutral MeOH, 2300, 2600 Å (ε 7000, 5000) in acid MeOH.

The thiopiperidide anhydro-base similarly gave **1-*methyl*-4-(2-*methylthio*-2-*piperidinovinyl*)-*pyridinium iodide***, which separated from methanol in yellow needles, m. p. 177—180° (Found : C, 44·5; H, 5·3. $C_{14}H_{21}N_2SI$ requires C, 44·7; H, 5·6%).

1-*Methyl*-4-*piperidylacetomorpholide*.—1 : 4-Dihydro-1-methyl-4-morpholinocarbonylmethylidenepyridine (1·5 g.) in ethanol (40 c.c.) was shaken with 1% palladium–strontium carbonate (7 g.) under hydrogen at normal pressure. Approx. 3 mols. of hydrogen were absorbed. The mixture was filtered, solvent removed from the filtrate, and the residue crystallised from light petroleum to give the ***morpholide*** (1·08 g., 70%) in deliquescent fronds, m. p. 65—67·5° (Found : C, 63·4; H, 9·8. $C_{12}H_{22}O_2N_2$ requires C, 63·7; H, 9·7%), which showed only end absorption above 2200 Å. The ***methotoluene*-p-*suphonate***, prepared in benzene, separated from ethanol in stout plates, m. p. 242—243° (Found : N, 7·0. $C_{20}H_{22}O_5N_2S$ requires N, 7·0%).

3-[2′-(1″-*Methyl*-4″-*piperidylacetamido*)*ethyl*]*indole*.—A suspension of **1** : 4-dihydro-4-(2-3′-indolylethylaminocarbonylmethylidene)-1-methylpyridine (2 g.) in ethanol (60 c.c.) was shaken with 1% palladium–strontium carbonate (4 g.) under hydrogen. After 24 hr., filtration and evaporation gave the ***piperidine*** derivative (1·83 g., 81%) which separated from ethanol in prisms, m. p. 181—182° (Found : C, 71·9; H, 8·4. $C_{18}H_{25}ON_3$ requires C, 72·2; H, 8·4%). Light absorption max. at 2800 Å (ε 7300) in MeOH. With warm Ehrlich's reagent a bright magneta colour appeared.

1 : 2 : 3 : 6-*Tetrahydro*-1-*methyl*-4-*pyridylacetomorpholide Methiodide*.—Potassium borohydride (0·3 g.) was added, all at once, to 4-pyridylacetomorpholide methotoluene-*p*-sulphonate (1 g.) in water (2 c.c.). The mixture became hot and effervesced vigorously. After 1 hr., the whole was extracted with chloroform (2 × 6 c.c.). The dried extracts were evaporated to an oil, which was taken up in benzene. When methyl iodide was added the ***methiodide*** (0·5 g., 54%) separated; recrystallised twice from ethanol, it formed prisms, m. p. 179—180° (Found : C, 42·2; H, 6·3; N, 7·6. $C_{13}H_{23}O_2N_2I$ requires C, 42·6; H, 6·3; N, 7·6%).

3-[2′-(1″ : 2″ : 3″ : 6″-*Tetrahydro*-1″-*methyl*-4″-*pyridylacetamido*)*ethyl*]*indole*.—1 : 4-Dihydro-4-(2-3′-indolylethylaminocarbonylmethylidene)-1-methylindole (1 g.) was dissolved in 2N-acetic acid (3 c.c.), and 2N-sodium carbonate (10 c.c.) added, followed by potassium borohydride (0·2 g.). There was a slight gas evolution, and solid began to separate. After 5 min., the ***product*** (0·82 g., 81%) was filtered off and twice recrystallised from ethanol, to give plates or needles, m. p. 216—217° (Found : C, 72·5; H, 7·8. $C_{18}H_{23}ON_3$ requires C, 72·7; H, 7·7%). Light absorption max. at 2800 Å (ε 4800) in MeOH.

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