Research and Development Division, Wyeth Laboratories, Inc.

New Reactions of Pyrroles. I. Pyridylethylpyrroles.

John L. Archibald

Pyrroles with unsubstituted 2- and/or 5-positions are found to react with 4-vinylpyridine, giving hitherto unreported 2- and 2,5-di- pyridylethylpyrroles. Pyrrole-2-carboxylic acids can also react to give the same products by displacement of the carboxyl group. Pyridylethylation at an available 3- and/or 4-position was not observed. Catalytic reductions and alkylations of the resulting piperidylethylpyrroles are also reported.

Pyrroles and indoles resemble one another in their susceptibility to electrophilic substitution, pyrroles being normally most prone to attack at the 2- and 5-positions and indoles at the 3-position. The aim of this work has been to exploit such resemblance by investigating reactions which have been reported to occur with indoles but not with pyrroles.

The first reaction to be considered with this in mind was the acid-catalyzed pyridylethylation of indoles reported by Gray and Archer (1). These workers found that by using acetic acid as a solvent-catalyst in the reaction between indoles and vinylpyridines, 3-[2-(pyridyl)ethyl]indoles could be obtained. Many of these compounds displayed interesting central depressant properties (2,3). Moreover, in a subsequent paper Gray and Kraus (4) described the catalytic reduction of pyridylethylindoles, and certain of the derived products were found to possess analgesic activity equivalent to morphine when tested in mice and rabbits.

In a paper on the reaction of 2-vinylpyridine with secondary amines, Reich and Levine (5) described the sodium metal-catalyzed *N*-pyridylethylation of pyrrole and 2,5-dimethylpyrrole. They reported, however, that these pyrroles could not be pyridylethylated under acidic conditions. It appears that they were anticipating *N*- rather than *C*-pyridylethylation, but the lack of reactivity of pyrrole was nonetheless surprising. We have been unable to find any reports in the literature of successful *C*-pyridylethylation of pyrroles.

In the present study, a number of pyrroles have been pyridylethylated, using acetic acid as the condensing agent. The product from the reaction between pyrrole and 4-vinylpyridine in refluxing acetic acid was 2,5-bis-[2-(4-pyridyl)ethyl]pyrrole (I). This was the only product isolated whether the molecular ratio of vinylpyridine to pyrrole was 2:1 or 1:1. I was clearly distinguished from the possible mono product (II) by n.m.r. (6). A sharp singlet at 2.28 p.p.m. integrated for 8 protons, and two multiplets centered at 7.1 and 8.45 p.p.m. integrated for 4 protons each (two pyridylethyl groups). The pyrrole-1,3 and 4-hydrogens gave rise to a broad absorption at 9.15 p.p.m. and a doublet at 5.85 p.p.m. (J = 3 c.p.s.), integrating for 1 and 2 protons, respectively. A corresponding product, 1-methyl-2,5-bis-[2-(4-pyridyl)ethyl]pyrrole (III), was obtained from the reaction between 4-vinylpyridine and 1-methylpyrrole. Again a 1:1 molar ratio resulted in the bis compound only. No pyridylethylation products were obtained from the reactions between 4-vinylpyridine and 1-phenylpyrrole or 2,5-dimethylpyrrole.

In order to obtain monopyridylethylpyrroles it was necessary to start with pyrroles having one α-position blocked. As examples of alkylpyrroles fulfilling this criterion, 2,4-dimethyl-3-ethylpyrrole and 2,4-dimethylpyrrole were refluxed with 4-vinylpyridine in acetic acid under nitrogen to give, respectively, 2,4-dimethyl-3-ethyl-5[2-(4-pyridyl)-ethyl]pyrrole (IV) and 2,4-dimethyl-5-[2-(4-pyridyl)-ethyl]pyrrole (V). N.m.r. confirmed that V was in fact the mono product. Singlets at 1.90 p.p.m. (4-methyl), 2.18 p.p.m. (2-methyl) and 2.82 p.p.m. (5-ethylene) integrated for 3,3, and 4 protons, respectively. One-proton absorptions were observed at 5.85 p.p.m. (3- H) and *ca.* 8.9 p.p.m. (N-H). Quartets centered at 7.03 and 8.78 p.p.m. integrated for 2 protons each. A further example of this type was prepared via the Johnson group's ingenious synthesis (7) of the diethyl ester of 5-carboxy-2,4-dimethylpyrrole-3-propionic acid (VI). Hydrolysis to the diacid (VII) and decarboxylation followed by pyridylethylation would have provided the requisite pyridylethylpyrrole (VIII). However, the possibility of obtaining VIII directly from the diacid through displacement of the 5-COOH by 4-vinylpyridine was considered. Pyrrole ring carboxyl groups are, for instance, readily displaced by bromine (8). On refluxing VII with 4-vinylpyridine in acetic acid, VIII was obtained.

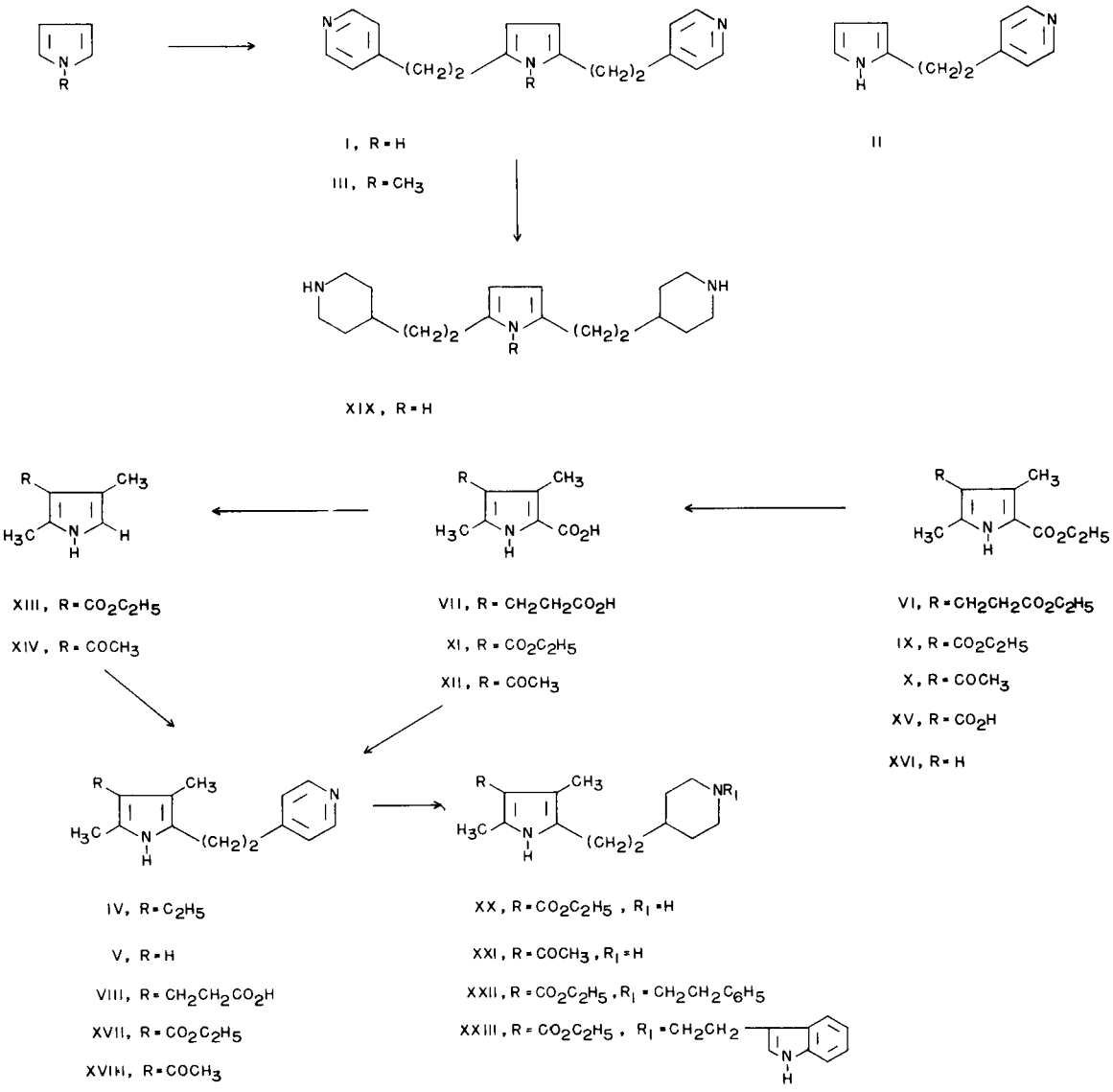
These monopyridylethylation products were all quite unstable, and in view of this, pyridylethylation of pyrroles with stabilizing electronegative substituents was next investigated. Diethyl 2,4-dimethylpyrrole-3,5-dicarboxylate (IX) and ethyl

3-acetyl-2,4-dimethylpyrrole-5-carboxylate (X) were prepared by published procedures and selectively hydrolyzed to the 5-carboxylic acids (XI and XII), which were then decarboxylated to the α-H pyrroles (XIII and XIV) (9,10,11). The diester (IX) was also selectively hydrolyzed to the 3-carboxylic acid (XV), which was decarboxylated to give XVI. 3-Carbethoxy-2,4-dimethyl-5-[2-(4-pyridyl)ethyl]pyrrole (XVII) was obtained by pyridylethylation of the acid (XI) or α-free pyrrole (XIII). Similarly, 3-acetyl-2,4-dimethyl-5-[2-(4-pyridyl)ethyl]pyrrole (XVIII) was obtained by pyridylethylation of XII or XIV. The 3-carboxy and 3-H pyrroles (XV and XVI) would not react with 4-vinylpyridine. In both cases, starting material was recovered.

Since in the pyridylethylindole series, reduction to piperidylethylindoles followed by alkylation had led to compounds with significant biological activity, similar transformations of pyridylethylpyrroles were studied.

Platinum-catalyzed hydrogenation of 2,5-bis-[2-(4-pyridyl)ethyl]pyrrole in aqueous alcohol containing hydrochloric acid provided the piperidine derivative (XIX). Similar reductions of the monopyridylethylpyrroles XVII and XVIII provided 3-acetyl- and 3-carbethoxy-2,4-dimethyl-5[2-(4-piperidyl)ethyl]-pyrrole (XX and XXI). Alkylation of XX with phenethyl bromide afforded XXII, and alkylation with 3-(2-bromoethyl)indole afforded 2,4-dimethyl-3-carbethoxy-5-[2-(1-[2-(3-indolyl)ethyl]-4-piperidyl)ethyl]-pyrrole (XXIII), which was also obtained by quaternization of the corresponding pyridylethylpyrrole (XVII) with 3-(2-bromoethyl)indole, followed by catalytic reduction.

The compounds prepared in this study were submitted for general pharmacological screening. Two of them (XIX and XXIII) were found to cause significant lowering of blood pressure when tested in rats and dogs (12).



EXPERIMENTAL (13)

Intermediates.

Diethyl 2,4-dimethylpyrrole-3,5-dicarboxylate (IX), ethyl 3-acetyl-2,4-dimethylpyrrole-5-carboxylate (X) and the diethyl ester of 5-carboxy-2,4-dimethylpyrrole-3-propionic acid (VI) were prepared by ring closure reactions (7,10,11). 3-Carbethoxy-2,4-dimethylpyrrole-5-carboxylic acid (XI) and 5-carbethoxy-2,4-dimethylpyrrole-3-carboxylic acid (XV) were prepared by selective hydrolyses (9,10). 3-Acetyl-2,4-dimethyl-pyrrole-5-carboxylic acid (XII) and 5-carboxy-2,4-dimethyl-pyrrole-3-propionic acid (VII) were prepared similarly (11,14). Ethyl 2,4-dimethylpyrrole-3-carboxylate (XIII), ethyl 2,4-dimethylpyrrole-5-carboxylate (XVI) and 3-acetyl-2,4-dimethyl-pyrrole (XIV) were prepared by a modified decarboxylation procedure involving heating an intimate mixture of the acid (1 part), sodium acetate (1 part) and potassium acetate (1 part) at 200-250° under nitrogen until carbon dioxide evolution ceased. 2,4-Dimethylpyrrole was prepared from diethyl-2,4-dimethylpyrrole-3,5-dicarboxylate (15).

2,5-Bis-[2-(4-pyridyl)ethyl]pyrrole (I).

Pyrrole (6.7 g., 0.1 mole), 4-vinylpyridine (10.5 g., 0.1 mole) and acetic acid (25 ml.) were mixed under nitrogen and refluxed for 30 minutes. The cooled mixture was added slowly, dropwise, to a vigorously stirred solution of sodium carbonate (50 g.) in ice-water. The colourless precipitate (8.3 g.) was collected, washed well, dried and recrystallized from ethanol-water. A further recrystallization from aqueous ethanol gave the product as a hydrate (5.3 g., 38%), m.p. 102-106° (123-124° after drying at 56°/0.01 mm.).

Anal. Calcd. for $C_{18}H_{19}N_3 \cdot H_2O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.01; H, 7.47; N, 14.33.

1-Methyl-2,5-bis[2-(4-pyridyl)ethyl]pyrrole (III).

1-Methylpyrrole (40.5 g., 0.5 mole) and 4-vinylpyridine (105 g., 1 mole) in acetic acid (100 ml.) were refluxed under nitrogen for 16 hours. Excess acetic acid was distilled out under reduced pressure. The residue was dissolved in ether and extracted with 2 *N* hydrochloric acid. The acid extracts were combined, basified with 50% aqueous sodium hydroxide and kept at 0° for 24 hours. A gummy solid resulted, which was filtered and washed with a little 50% aqueous ethanol. Two recrystallizations from ethanol provided the product as colourless needles (23.0 g., 16%), m.p. 125-126°.

Anal. Calcd. for $C_{19}H_{21}N_3$: C, 78.31; H, 7.26; N, 14.42. Found: C, 78.37; H, 7.29; N, 14.25.

2,4-Dimethyl-5-[2-(4-pyridyl)ethyl]pyrrole (V).

2,4-Dimethylpyrrole (5.0 g., 0.0526 mole), 4-vinylpyridine (5.6 g., 0.0534 mole) and acetic acid (20 ml.) were mixed under nitrogen and refluxed for 2 hours. Acetic acid was distilled under reduced pressure, and the residue was stirred with ice-water and basified with aqueous sodium hydroxide. The resulting precipitate was collected, washed, dried and recrystallized from *n*-hexane (decanting from some dark tar) to give the unstable product as pale yellow prisms (8.3 g., 79%), m.p. 79-80°.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 78.07; H, 8.01; N, 13.97.

2,4-Dimethyl-3-ethyl-5-[2-(4-pyridyl)ethyl]pyrrole (IV).

2,4-Dimethyl-3-ethylpyrrole (12.3 g., 0.1 mole), 4-vinylpyridine (10.5 g., 0.1 mole) and acetic acid (40 ml.) were refluxed under nitrogen for 3 hours and the product was isolated in essentially the same way as in the previous example. Two recrystallizations from *n*-hexane afforded 15.0 g. (66%) of unstable product, m.p. 97-98°.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 79.08; H, 9.04; N, 12.02.

2,4-Dimethyl-5-[2-(4-pyridyl)ethyl]pyrrole-3-propionic acid (VIII).

The diethyl ester of 5-carboxy-2,4-dimethylpyrrole-3-propionic acid (10.0 g., 0.038 mole) was hydrolyzed by heating on a steam-bath with water (50 ml.), ethanol (15 ml.) and sodium hydroxide (10.0 g.) for 3 hours. After ethanol was distilled out, the solution was acidified with sulfur dioxide and extracted with ether. The washed and dried ether extracts were evaporated under reduced pressure and the resulting diacid (VII) was used directly as follows. The diacid and 4-vinylpyridine (4.0 g., 0.038 mole) were dissolved in acetic acid (25 ml.) under nitrogen and heated on a steam-bath for 1 hour. Acetic acid was distilled out under reduced pressure, and the residual dark, light-sensitive oil was triturated with water, solidifying after several hours. The solid was recrystallized from aqueous ethanol to give orange needles (3.2 g., 23%), m.p. 164-167°. Two further recrystallizations were required to obtain analytically pure product, m.p. 167-168°, very sensitive to air and light.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.73; H, 7.55; N, 10.05.

3-Carbethoxy-2,4-dimethyl-5-[2-(4-pyridyl)ethyl]pyrrole (XVII).
Method A.

3-Carbethoxy-2,4-dimethylpyrrole (1.67 g., 0.1 mole), 4-vinylpyridine (1.07 g., 0.102 mole) and acetic acid (10 ml.) were mixed under nitrogen and refluxed for 5 hours. Acetic acid was distilled out (100°/0.01 mm.) and the residue was crystallized from ether (decanting from some insoluble tar). Recrystallization from aqueous ethanol afforded the product as colourless needles (0.95 g., 35%), m.p. 151-152°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.42; H, 7.44; N, 10.58.

Method B.

3-Carbethoxy-2,4-dimethylpyrrole-5-carboxylic acid (48.0 g., 0.228 mole), 4-vinylpyridine (25.0 g., 0.238 mole) and acetic acid (200 ml.) were mixed under nitrogen and heated under reflux for 3 hours. Removal of the acetic acid (100°/0.1 mm.) and crystallization of the residue from aqueous ethanol gave a product (34.5 g., 46%), m.p. 152-153°, whose I.R. spectrum was the same as that of the product from method A.

3-Acetyl-2,4-dimethyl-5[2-(4-pyridyl)ethyl]pyrrole (XVIII).
Method A.

3-Acetyl-2,4-dimethylpyrrole was pyridylethylated in the same manner as was the corresponding 3-carbethoxypyrrole. The yield of once-recrystallized product, m.p. 130-132°, was 68%.

Method B.

3-Acetyl-2,4-dimethylpyrrole-5-carboxylic acid (9.05 g., 0.05 mole) was pyridylethylated as in method B of the preceding example, and 5.8 g. (37%) of once-recrystallized material, m.p. 130-132°, was obtained. Recrystallization from ethyl acetate raised the melting point of the hemi-hydrate to 132-134°.

Anal. Calcd. for $C_{15}H_{18}N_2O \cdot {}^1/_2H_2O$: C, 71.68; H, 7.62; N, 11.15. Found: C, 71.35; H, 7.62; N, 11.10. % H_2O Calcd: 3.58. Found (Karl Fischer determination): 3.44.

2,5-Bis-[2-(4-piperidyl)ethyl]pyrrole (XIX).

A suspension of 2,5-bis-[2-(4-pyridyl)ethyl]pyrrole (3.2 g., 0.0127 mole) in water (10 ml.) and ethanol (8 ml.) was made just acid with hydrochloric acid. Platinum oxide (0.5 g.) was added and the mixture was hydrogenated for 5 hours at 47 p.s.i. initial pressure. The catalyst was filtered off and ethanol was distilled from the filtrate under reduced pressure. The residue was diluted with water, cooled and made strongly basic with sodium hydroxide. Two recrystallizations of the resulting solid from aqueous ethanol afforded the product as colourless needles (1.7 g., 51%), m.p. 108-112°.

Anal. Calcd. for $C_{18}H_{31}N_3$: C, 74.69; H, 10.80; N, 14.52. Found: C, 74.45; H, 10.71; N, 14.72.

3-Carbethoxy-2,4-dimethyl-5-[2-(4-piperidyl)ethyl]pyrrole (XX).

3-Carbethoxy-2,4-dimethyl-5-[2-(4-pyridyl)ethyl]pyrrole was hydrogenated as in the preceding example. The crude product was recrystallized from ethyl acetate-*n*-hexane to give a 60% yield of XX, m.p. 122-123°.

Anal. Calcd. for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.37; H, 9.46; N, 9.83.

3-Acetyl-2,4-dimethyl-5-[2-(4-piperidyl)ethyl]pyrrole (XXI).

This compound was prepared from the corresponding pyridylethylpyrrole (XVIII) exactly as in the preceding two examples. The product, after recrystallization from aqueous ethanol, melted at 158-159°.

Anal. Calcd. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.79; H, 9.78; N, 11.11.

3-Carbethoxy-2,4-dimethyl-5-[2-(1-phenethyl-4-piperidyl)ethyl]pyrrole (XXIII).

A stirred mixture of 3-carbethoxy-2,4-dimethyl-5-[2-(4-piperidyl)-ethyl]pyrrole (2.78 g., 0.01 mole), sodium carbonate monohydrate (2.75 g.) and 2-propanol (5 ml.) was heated under reflux, and a solution of 2-phenethyl bromide (1.85 g., 0.01 mole) in 2-propanol (5 ml.) was added dropwise. Stirring and heating were continued for 16 hours. The hot mixture was filtered and the filtrate was evaporated. The residue was dissolved in ether (a small amount of insoluble material was filtered) and made just acid with ethereal hydrogen chloride. Recrystallization from water afforded the product as the

hydrochloride (2.5 g., 65%), m.p. 189-191°.

Anal. Calcd. for $C_{24}H_{35}ClN_2O_2$: C, 68.79; H, 8.42; N, 6.69; Cl, 8.46. Found: C, 68.79; H, 8.53; N, 6.73; Cl, 8.7.

3-Carbethoxy-2,4-dimethyl-5-[2-(1-[-(3-indolyl)ethyl]-4-piperidyl)-ethyl]pyrrole (XXIII). Method A.

Alkylation of XX as in the previous example, but with 3-(2-bromoethyl)indole (16) in place of phenethyl bromide, afforded XXIII. The crude product was separated from a considerable amount of quaternary salt, which was insoluble in ether. The hydrochloride (22%), m.p. 199-202° (dec.), was crystallized from acetone.

Anal. Calcd. for $C_{26}H_{35}N_3O_2 \cdot HCl$: C, 68.19; H, 7.92; N, 9.15; Cl, 7.74. Found: C, 67.99; H, 8.23; N, 8.83; Cl, 7.85.

Method B.

A solution of 3-carbethoxy-2,4-dimethyl-5-[2-(4-pyridyl)ethyl]pyrrole (27.2 g., 0.1 mole) and 3-(2-bromoethyl)indole (23.5 g., 0.105 mole) in ethanol (500 ml.) was refluxed under nitrogen for 16 hours. Platinum oxide was added to the cooled solution, which was then hydrogenated at 400 p.s.i. for 5 hours. The filtered solution was evaporated *in vacuo* and the residue was dissolved in ethyl acetate, washed with 10% aqueous sodium carbonate, dried and chromatographed on basic alumina (Woelm grade 1). A fraction, eluted with ethyl acetate -25% *n*-hexane, was evaporated *in vacuo*, dissolved in acetone and made just acid with anhydrous hydrogen chloride, giving the hydrochloride (11.65 g., 26%), m.p. 201-203° (dec.). A second crop (3.2 g.) melted at 197-202° (dec.).

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