Addition Products of 2-(*N*-Arylformimidoyl)pyridines and Carbanions, and their Reduction to Octahydroindolizine Derivatives

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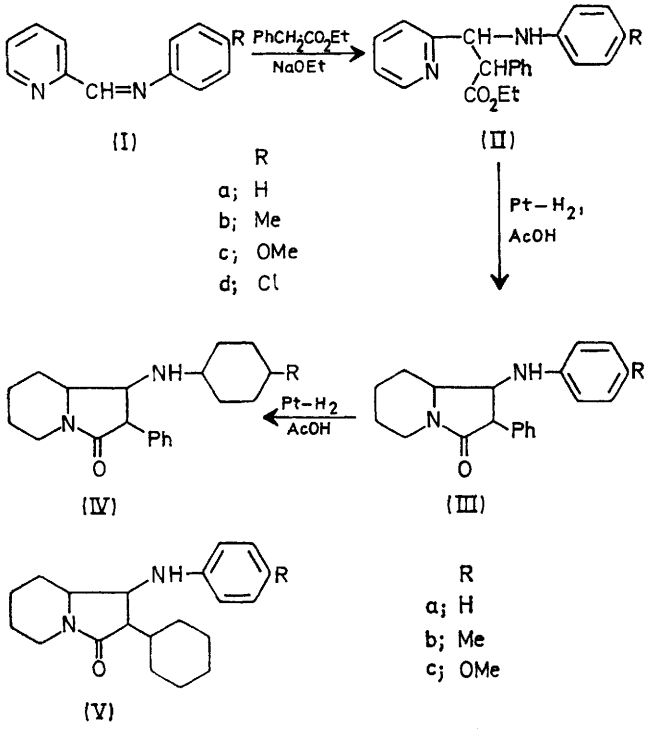
The reactions of 2-(*N*-arylformimidoyl)pyridines with a number of active methylene compounds have been investigated. Reduction of the products gave octahydroindolizine derivatives, some of which were also prepared by other routes. The interaction of 2-(*N*-phenylformimidoyl)pyridine and diethyl succinate gave an octahydropyrrolo[3,4-*c*]pyrrole.

THE addition of carbanions to azomethines is in general well documented. This paper describes the extension of these reactions to anils of pyridine-2-carbaldehyde, and the preparation of some novel biologically active octahydroindolizine derivatives by reduction of the addition products.

2-(*N*-Phenylformimidoyl)pyridine (Ia) [1] and its derivatives (Ib—d) [1,2] reacted with ethyl phenylacetate and sodium ethoxide to give the addition products (IIa—d). On catalytic hydrogenation, the esters (IIa and d) both gave 1-anilinohexahydro-2-phenylindolizin-3-one (IIIa) or the 1-cyclohexylamino-analogue (IVa). Reduction

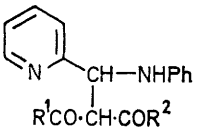


(I) (II) (IV) (III) (V)

R
a; H
b; Me
c; OMe
d; Cl

of the addition products (IIb and c) similarly gave the hexahydroindolizinones (IIIb and c) and (IVb and c). The more fully reduced compounds were assigned the structures (IVa—c), rather than (Va—c) since their u.v. spectra resembled that of toluene rather than those of substituted anilines.[3]

2-(*N*-Phenylformimidoyl)pyridine (Ia) reacted with diethyl malonate, ethyl acetoacetate, ethyl benzoylacetate, and acetylacetone, in the presence of piperidine, to give the addition products (VIa—d), but with ethyl



(VI)

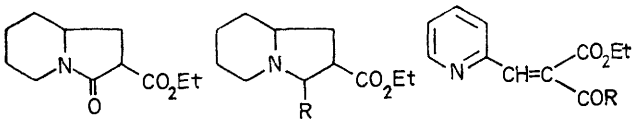
	R^1	R^2
a;	OEt	OEt
b;	Me	OEt
c;	Ph	OEt
d;	Me	Me

cyanoacetate no pure product was isolated. When the substituted ethyl acetoacetate (VIb) was treated with benzoyl chloride, a molecule of aniline was eliminated, and ethyl 3-oxo-2-(2-pyridylmethylene)butyrate [4] and benzanilide were obtained. The other addition products (VIa, c, and d) also gave benzanilide when treated with benzoyl chloride, and with methyl iodide compounds (VIa—d) gave *NNN*-trimethylanilinium iodide.

In contrast to the ethyl phenylacetate derivatives (IIa—d), the substituted diethyl malonate (VIa) lost a molecule of aniline on catalytic hydrogenation, yielding ethyl octahydro-3-oxoindolizine-2-carboxylate (VII).[5] When the substituted ethyl benzoylacetate (VIc) was reduced, the octahydroindolizine (VIIIa) and aniline were obtained; an alternative synthesis of the compound (VIIIa) was effected by reduction of ethyl α-benzoyl-β-(2-pyridyl)acrylate (IXa).[6] Reduction of the substituted ethyl acetoacetate (VIb) gave ethyl octahydro-3-methylindolizine-2-carboxylate (VIIIb), together with aniline and a compound of molecular formula $C_{24}H_{32}N_2O_4$. The sample of octahydroindolizine (VIIIb) was later found to contain a small amount of dicyclohexylamine,[7] the origin of which is not apparent. It is suggested, on the basis of spectroscopic evidence, that the compound of molecular formula $C_{24}H_{32}N_2O_4$ is a derivative (X) of the previously unknown 6a,12a-diazachrysene system, formed by partial reduction and combination of two molecules of the starting material, with elimination of two molecules of aniline. The

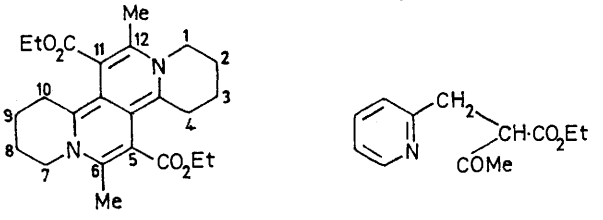
[1] B. P. Lugovkin, ' Khim Geterotsikl. Soedin., Sb. 1: Azotsoderzhashchie Geterotsikly,' ed. S. Hillers, Izd. Zinatne, Riga, 1967, p. 224.
[2] S. Miyano, N. Abe, and A. Abe, *Chem. and Pharm. Bull. (Japan)*, 1970, **18(3)**, 511.
[3] E. Schumacher and R. Taubenest, *Helv. Chim. Acta*, 1966, **49(5)**, 1455.
[4] C. S. Marvel and J. K. Stilte, *J. Org. Chem.*, 1957, **22**, 1451.
[5] K. Winterfeld and K. Kullmar, *Arch. Pharm.*, 1958, **291**, 485.
[6] T. Kutsuma, *Yakagaku Zasshi*, 1968, **88(8)**, 1016.
[7] J. M. Sprake and K. D. Watson, unpublished results.

catalytic reduction of ethyl 3-oxo-2-(2-pyridylmethyl)-butyrate (XI) [8] and of ethyl 3-oxo-2-(2-pyridylmethylene)butyrate (IXb) [4] also gave the octahydroindolizine (VIIIb), this being accompanied in the latter case by a

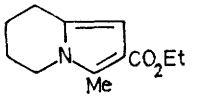


(VII) (VIII) (IX)

R
a; Ph
b; Me



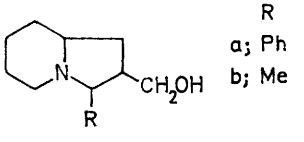
(X) (XI)



(XII)

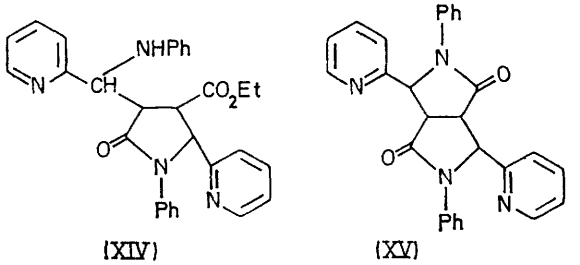
compound of molecular formula $C_{12}H_{17}NO_2$ to which is assigned the structure of a partially reduced indolizine (XII). This compound (XII) gave the octahydroindolizine (VIIIb) on further reduction.

Reduction of the octahydroindolizine esters (VIIIa and b) with lithium aluminium hydride gave the corresponding primary alcohols (XIIIa and b).



R
a; Ph
b; Me

(XIII)



(XIV) (XV)

The interaction of 2-(*N*-phenylformimidoyl)pyridine (Ia) and diethyl succinate unexpectedly gave a mixture of the pyrrolidone (XIV) and the octahydropyrrolopyrrole (XV). The pyrrolidone cyclised to the pyrrolopyrrole when heated.

In biological tests, the octahydroindolizine derivatives (IVa—c) exhibited CNS depressant activity, and compound (XIIIb) showed analgesic, antipyretic, and tranquillising activity.

Stereochemical studies on ethyl octahydro-3-methylindolizine-2-carboxylate (VIIIb) will be reported elsewhere.

EXPERIMENTAL

U.v. data for compounds (IIIa—c), i.r. data for compounds (IIa—d), (IIIa—c), (IVa—c), (VIa—d), (VIIIa and b), and (XIIIa and b), and n.m.r. data for compounds (IIa), (IIIa), and (IVa) are available as Supplementary Publication No. SUP 21562 (4 pp.).*

Ethyl 3-Anilino-2-phenyl-3-(2-pyridyl)propionate (IIa).—Sodium (3.5 g, 0.15 g atom) was dissolved in absolute ethanol (120 ml) and ethyl phenylacetate (24.6 g, 0.15 mol) was added, followed by a solution of 2-(*N*-phenylformimidoyl)pyridine (18.2 g, 0.10 mol) in ethanol (40 ml). The mixture was heated under reflux for 15 min, cooled, and kept at 0 °C for 1 h. The crystals which separated were collected and recrystallised from benzene to give the *addition product* (27.0 g, 78%) as prisms, m.p. 167° (Found: C, 76.5; H, 6.3; N, 8.2. $C_{22}H_{22}N_2O_2$ requires C, 76.3; H, 6.4; N, 8.1%).

The following compounds were prepared analogously from the azomethines (Ib—d): *ethyl 2-phenyl-3-(2-pyridyl)-3-p-toluidinopropionate* (IIb) (64%), prisms (from methanol), m.p. 82° (Found: C, 76.4; H, 6.7; N, 7.7. $C_{23}H_{24}N_2O_2$ requires C, 76.7; H, 6.7; N, 7.8%); *ethyl 3-p-anisidino-2-phenyl-3-(2-pyridyl)propionate* (IIc) (67%), prisms (from cyclohexane), m.p. 127° (Found: C, 73.3; H, 6.4; N, 7.5. $C_{23}H_{24}N_2O_3$ requires C, 73.4; H, 6.4; N, 7.4%); *ethyl 3-p-chloroanilino-2-phenyl-3-(2-pyridyl)propionate* (IId) (64%), prisms (from methanol), m.p. 112° (Found: C, 69.2; H, 5.45; N, 7.5. $C_{22}H_{21}ClN_2O_2$ requires C, 69.4; H, 5.6; N, 7.4%).

1-Anilinohexahydro-2-phenylindolizin-3-one (IIIa).—(*a*) A solution of ethyl 3-anilino-2-phenyl-3-(2-pyridyl)propionate (34.6 g) in ethanol (100 ml) was shaken with concentrated hydrochloric acid (11.0 g) and platinum dioxide (1.0 g) in the presence of hydrogen at 3 atm. The reaction was stopped after the theoretical amount of hydrogen had been absorbed. The mixture was filtered and evaporated to dryness, and the residue was basified with 10% sodium hydroxide solution. The mixture was extracted with chloroform (2 × 80 ml), the combined extracts were dried (K_2CO_3), and the solvent was removed. Crystallisation of the residue from ethanol gave the *indolizine* (12.9 g, 42%) as prisms, m.p. 175° (Found: C, 78.2; H, 7.05; N, 9.0%; M^+, 306.1725. $C_{20}H_{22}N_2O$ requires C, 78.4; H, 7.24; N, 9.15%; *M*, 306.1732).

(*b*) When the *p*-chloroanilino-compound (IId) was hydrogenated as described above, 1-anilinohexahydro-2-phenylindolizin-3-one (38%) was obtained; m.p. and mixed m.p. 175°.

The following compounds were prepared analogously from the esters (IIb and c): *hexahydro-2-phenyl-1-p-toluidinoindolizin-3-one* (IIIb) (38%), prisms [from ethyl

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

[8] J. Hurst, T. Melton, and D. G. Wibberley, *J. Chem. Soc.*, 1965, 2948.

acetate–ethanol (95 : 5)], m.p. 176° (Found: C, 78.7; H, 7.4; N, 8.6%. $C_{21}H_{24}N_2O$ requires C, 78.7; H, 7.55; N, 8.75%); 1-p-*anisidinohexahydro*-2-*phenylindolizin*-3-*one* (IIIc) (32%), prisms (from ethyl acetate), m.p. 158° (Found: C, 75.0; H, 7.0; N, 8.3. $C_{21}H_{24}N_2O_2$ requires C, 75.1; H, 7.2; N, 8.3%).

1-*Cyclohexylaminohexahydro*-2-*phenylindolizin*-3-*one* (IVa).—(*a*) Ethyl 3-anilino-2-phenyl-3-(2-pyridyl)propionate was hydrogenated as described above, but the reaction was allowed to proceed until the uptake of hydrogen ceased. Crystallisation of the oily residue from cyclohexane gave the *indolizine* (IVa) (48%) as needles, m.p. 89° (Found: C, 77.3; H, 9.2; N, 8.8%; M^+, 312.2199. $C_{20}H_{28}N_2O$ requires C, 76.9; H, 9.0; N, 9.0%; *M*, 312.2202).

(*b*) When the *p*-chloroanilino-compound (IId) was hydrogenated until the uptake of hydrogen ceased, 1-cyclohexylaminohexahydro-2-phenylindolizin-3-one (34%) was obtained; m.p. and mixed m.p. 89°.

The following compounds were prepared analogously from the esters (IIb and c): *hexahydro*-1-(4-*methylcyclohexylamino*)-2-*phenylindolizin*-3-*one* (IVb) (62%), needles (from cyclohexane), m.p. 134° (Found: C, 77.5; H, 9.3; N, 8.55%. $C_{21}H_{30}N_2O$ requires C, 77.25; H, 9.3; N, 8.6%); *hexahydro*-1-(4-*methoxycyclohexylamino*)-2-*phenylindolizin*-3-*one* (IVc) (54%), needles [from light petroleum (b.p. 40—60°)], m.p. 78° (Found: C, 73.8; H, 8.6; N, 8.3%. $C_{21}H_{30}N_2O_2$ requires C, 73.65; H, 8.8; N, 8.2%).

Compounds (IVa—c) had (respectively) $\lambda_{max.}$ 262, 264, and 264 nm (log ε 2.52, 2.41, and 2.39) both in ethanol and in ethanolic 0.1N-hydrochloric acid.

Addition of Active Methylene Compounds to 2-(N-*Phenylformimidoyl*)*pyridine*.— 2-(*N*-Phenylformimidoyl)pyridine (36.4 g, 0.2 mol), the active methylene compound (0.3 mol), and piperidine (4.0 ml) were heated under reflux in ethanol (150 ml) for 1 h. The solvent was removed under reduced pressure, the oily residue was triturated with light petroleum, and the resulting solid was crystallised from a suitable solvent. The products were: *diethyl* [*anilino*-(2-*pyridyl*)-*methyl*]*malonate* (VIa) (65%), prisms [from light petroleum (b.p. 60—80°)], m.p. 74° (Found: C, 67.0; H, 6.6; N, 8.4. $C_{19}H_{22}N_2O_4$ requires C, 66.65; H, 6.5; N, 8.2%); *ethyl* 2-[*anilino*-(2-*pyridyl*)*methyl*]-3-*oxobutyrate* (VIb) (70%), prisms (from ethanol), m.p. 127° (Found: C, 69.4; H, 6.3; N, 9.0. $C_{18}H_{20}N_2O_3$ requires C, 69.2; H, 6.45; N, 9.0%); *ethyl* 2-[*anilino*-(2-*pyridyl*)*methyl*]-3-*oxo*-3-*phenylpropionate* (VIc) (64%), prisms (from methanol), m.p. 107° (Found: C, 73.5; H, 5.8; N, 7.4. $C_{23}H_{22}N_2O_3$ requires C, 73.8; H, 5.9; N, 7.5%); 3-[*anilino*-(2-*pyridyl*)*methyl*]*pentane*-2,4-*dione* (VId) (55%), prisms (from methanol), m.p. 88° (Found: C, 72.3; H, 6.4; N, 10.0. $C_{17}H_{18}N_2O_2$ requires C, 72.3; H, 6.4; N, 10.0%). The reaction of 2-(*N*-phenylformimidoyl)pyridine with ethyl cyanoacetate gave no identified product.

Reactions of the Addition Products (VIa—d) *with Benzoyl Chloride and with Methyl Iodide*.—(*a*) When compound (VIb) was heated under reflux with benzoyl chloride in dry chloroform containing potassium carbonate, benzanilide (96%) and ethyl 3-oxo-2-(2-pyridylmethylene)butyrate [4] (57%) were obtained. When treated with benzoyl chloride, compounds (VIa, c, and d) gave benzanilide as the only isolable product.

When treated with methyl iodide, compounds (VIa—d) similarly gave *NNN*-trimethylanilinium iodide.

Ethyl Octahydro-3-*oxoindolizine*-2-*carboxylate* (VII).— Compound (VIa) (34.2 g, 0.1 mol) was reduced with hydrogen over platinum dioxide (1.0 g) in glacial acetic acid (200 ml) at 3 atm until uptake ceased (8—12 h). The mixture was filtered and evaporated to dryness, and the oily residue was basified with 10% sodium hydroxide solution. The mixture was extracted with chloroform (2 × 100 ml), and the combined extracts were dried (K_2CO_3) and evaporated to dryness. Distillation of the residue under reduced pressure gave an initial fraction of aniline, followed by the octahydroindolizine (13.5 g, 64%), b.p. 168—172° at 1.5 mmHg (lit.,[5] 136—138° at 0.3 mmHg).

Ethyl Octahydro-3-*phenylindolizine*-2-*carboxylate* (VIIIa).—(*a*) Compound (VIc) was hydrogenated as described above. Distillation of the product under reduced pressure gave an initial fraction of aniline, followed by the *octahydroindolizine* (61%), b.p. 188—194° at 8.0 mmHg (Found: C, 74.7; H, 8.5; N, 5.1. $C_{17}H_{23}NO_2$ requires C, 74.6; H, 8.6; N, 5.3%).

(*b*) Catalytic reduction of ethyl 3-oxo-3-phenyl-2-(2-pyridylmethylene)propionate [6] and distillation of the product at 188—194° and 8.0 mmHg gave the octahydroindolizine (71%).

The *hydrochloride*, prepared by passing dry hydrogen chloride through an ethereal solution, crystallised from methanol–ether as prisms, m.p. 204° (Found: C, 65.4; H, 7.6; N, 4.3. $C_{17}H_{24}ClNO_2$ requires C, 65.9; H, 7.8; N, 4.5%).

Ethyl Octahydro-3-*methylindolizine*-2-*carboxylate* (VIIIb).—(*a*) Ethyl 3-oxo-2-(2-pyridylmethyl)butyrate [8] was hydrogenated as described above. Distillation of the residue at 96—102° and 1.5 mmHg gave the *octahydroindolizine* (83%) (Found: C, 68.2; H, 10.1; N, 6.9. $C_{12}H_{21}NO_2$ requires C, 68.2; H, 10.0; N, 6.65%)

(*b*) Ethyl 3-oxo-2-(2-pyridylmethylene)butyrate [4] was reduced similarly. Distillation of the product gave an initial fraction of the octahydroindolizine (62%), b.p. 120—126° at 4.0 mmHg, and a second fraction of *ethyl* 5,6,7,8-*tetrahydro*-3-*methylindolizine*-2-*carboxylate* (XII), b.p. 176—180° at 4.0 mmHg, which solidified on cooling and crystallised from light petroleum (b.p. 60—80°) as needles (12%), m.p. 69° (Found: C, 69.85; H, 8.2; N, 6.9. $C_{12}H_{17}NO_2$ requires C, 69.5; H, 8.3; N, 6.8%), $\nu_{max.}$ 1 680 cm^{-1} (C=O), τ 3.82 (1 H, s, CH), 5.75 (2 H, q, $CO{\cdot}CH_2$), 6.27 (2 H, t, CH_2), 7.28 (2 H, t, CH_2), 7.57 (3 H, s, CH_3), 7.78—8.50 (4 H, m, 2 × CH_2), and 8.70 (3 H, t, $CH_2{\cdot}CH_3$).

Further hydrogenation gave the octahydroindolizine (VIIIb) (95%).

(*c*) Compound (VIb) (31.2 g, 0.1 mol) was reduced with hydrogen over platinum dioxide (1.5 g) in a mixture of ethanol (75 ml) and 10N-hydrochloric acid (11.0 g) at 3 atm until uptake ceased (10 h). The mixture was filtered and evaporated to dryness, and water (50 ml) was added to the residue. The oil which separated was extracted with chloroform (2 × 25 ml), and the combined extracts were dried (K_2CO_3) and evaporated. Trituration of the oily residue with light petroleum (b.p. 60—80°) gave a solid which, on crystallisation from ethyl acetate, gave *diethyl* 1,2,3,4,7,8,9,10-*octahydro*-6,12-*dimethyl*-6a,12a-*diazachrysene*-5,11-*dicarboxylate* (X) as prisms (2.8 g, 14%), m.p. 141° (Found: C, 69.9; H, 7.8; N, 7.0%; M^+, 412.2354. $C_{24}H_{32}N_2O_4$ requires C, 69.9; H, 7.8; N, 6.8%; *M*, 412.2362), $\nu_{max.}$ 1 700 cm^{-1} (C=O), τ 6.05 (4 H, q, 2 × $CO{\cdot}CH_2$), 6.15—6.60 (4 H, m, aliphatic), 7.60 (6 H, s, 2 × CH_3), 7.45—7.80 (4 H, m, aliphatic), 7.80—8.50 (8 H, m, aliphatic), and 8.97 (6 H, t, 2 × $CH_2{\cdot}CH_3$).

The aqueous layer from the above extraction was basified

and worked up in the usual way. Distillation of the residue under reduced pressure gave an initial fraction of aniline, and a second fraction of ethyl octahydro-3-methylindolizine-2-carboxylate (32—54%), b.p. 96—102° at 1.5 mmHg. In the course of some later g.l.c. studies,[7] the octahydroindolizine was found to contain a small amount of dicyclohexylamine.

The *octahydroindolizine hydrochloride*, prepared as described for the analogue (VIIIa), crystallised from methanol–ether as prisms, m.p. 218° (decomp.) (Found: C, 58.4; H, 9.15; N, 5.9. $C_{12}H_{22}ClNO_2$ requires C, 58.2; H, 8.95; N, 5.65%).

Octahydro-3-phenylindolizin-2-ylmethanol (XIIIa).—A suspension of lithium aluminium hydride (11.0 g, 0.3 mol) in tetrahydrofuran (100 ml) was slowly added to a stirred solution of ethyl octahydro-3-phenylindolizine-2-carboxylate (27.3 g, 0.1 mol) in tetrahydrofuran (300 ml). The mixture was heated under reflux for 1 h, then, with cooling, water (11 ml), sodium hydroxide solution (10%; 11 ml), and water (33 ml) were added. The mixture was filtered, and the organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Distillation of the residue at 138—142° and 3.0 mmHg gave the *alcohol* (12.0 g, 52%) (Found: C, 77.6; H, 9.1; N, 6.0. $C_{15}H_{21}NO$ requires C, 77.9; H, 9.15; N, 6.1%).

The *hydrochloride*, prepared as described for the octahydroindolizine (VIIIa), crystallised from methanol–acetone (80 : 20) as prisms, m.p. 184° (Found: C, 67.1; H, 8.1; N, 5.0. $C_{15}H_{22}ClNO$ requires C, 67.3; H, 8.3; N, 5.2%).

Octahydro-3-methylindolizin-2-ylmethanol (XIIIb) (53%) was prepared similarly from ethyl octahydro-3-methylindolizine-2-carboxylate, and was distilled at 102—105° and 3.5 mmHg (Found: C, 71.2; H, 11.2; N, 8.1. $C_{10}H_{19}NO$ requires C, 70.9; H, 11.3; N, 8.3%). The *hydrochloride* crystallised from methanol–acetone (80 : 20) as prisms, m.p. 197° (Found: C, 58.2; H, 9.6; N, 6.4. $C_{10}H_{20}ClNO$ requires C, 58.4; H, 9.8; N, 6.8%).

Ethyl 4-[Anilino-(2-pyridyl)methyl]-5-oxo-1-phenyl-2-(2-pyridyl)pyrrolidine-3-carboxylate (XIV).—Sodium (2.3 g, 0.1 g atom) was dissolved in dry ethanol (120 ml) and diethyl succinate (52.2 g, 0.3 mol) was added. A solution of 2-(*N*-phenylformimidoyl)pyridine (18.2 g, 0.1 mol) in ethanol (40 ml) was added dropwise, and the mixture was heated under reflux for 1 h, cooled, and kept at 0 °C overnight. The solid which separated was collected and recrystallised from butan-1-ol to give the *pyrrolidone* (3.0 g, 12%) as prisms, m.p. 234° (Found: C, 73.4; H, 5.8; N, 11.5. $C_{30}H_{28}N_4O_3$ requires C, 73.1; H, 5.7; N, 11.4%), $\nu_{max.}$ 3 300 (NH), 1 740 (ester C=O), and 1 690 cm^{-1} (amide C=O).

Hexahydro-2,5-diphenyl-3,6-bis-(2-pyridyl)pyrrolo[3,4-c]-pyrrole-1,4-dione (XV).—(*a*) The filtrate from the above reaction was evaporated to dryness under reduced pressure, and the residue was stirred with water. The resulting solid was dried, washed with light petroleum, and crystallised from butan-1-ol to give the *pyrrolopyrrole* (8.0 g, 36%) as needles, m.p. 275° (decomp.) (Found: C, 75.0; H, 5.0; N, 12.3%; M^+, 446.1755. $C_{28}H_{22}N_4O_2$ requires C, 75.3; H, 5.0; N, 12.6%; M^+, 446.1743), $\nu_{max.}$ 1 690 cm^{-1} (C=O), τ 1.45 (2 H, d, 2 × pyridine α-proton), 2.20—3.00 (16 H, m, aromatic), 4.27 (2 H, s, 2 × CH), and 6.27 (2 H, s, 2 × CH).

(*b*) The pyrrolidone (XIV) (4.9 g) was heated under reflux in toluene (30 ml) for 1 h. Removal of the solvent and crystallisation of the residue from butan-1-ol gave the pyrrolopyrrole (4.2 g, 93%), m.p. and mixed m.p. 275° (decomp.).

We thank the S.R.C. for a research studentship (for K. D. W.), and Dr. N. J. Harper, Sterling-Winthrop R and D, for his interest in the work.

[5/358 *Received*, 19*th February*, 1975