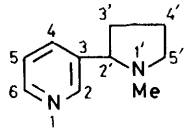
Transformations involving the Pyrrolidine Ring of Nicotine

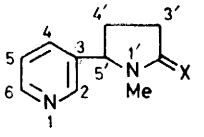
By R. Morrin Acheson,* Michael J. Ferris, and Neil M. Sinclair, Department of Biochemistry, South Parks Rd, Oxford, OX1 3QU

Nicotine was oxidised to cotinine and this successively alkylated and reduced to a series of 4'-mono- and 4',4'-di-alkylnicotines, the mass spectra of which are discussed. The pyrrolidine ring has been opened with ethyl chloroformate and the product both recyclised to *S*-nicotine without loss of optical activity and converted to metanicotine. The dihydrochloride of the last, on successive treatment with bromine and sodium hydrogencarbonate, yielded 3'-bromonicotine. Cotinine has been converted into various derivatives, and the demethylation of nicotine has been investigated.

NICOTINE, originally in the form of a *Nicotiana tabacum* extract, has been employed as an insecticide since 1763,[1] but its use has greatly diminished in recent years because of the many more effective synthetic insecticides which are available. Nicotine is readily metabolised to cotinine in man and animals,[2] and by liver microsomes,[3,4] and also to 4-(3-pyridyl)-4-oxobutyric acid, 3-pyridylacetic acid, and is methylated at the aromatic nitrogen atom. Nicotine 1'-oxide [5-8] and cotinine 1-oxide [9] are also metabolites. In recent years there have been three systematic attempts to assess the structural features of the nicotine molecule necessary for high toxicity to insects. Barlow and Hamilton [10] synthesised a series of pyridylalkylamines and attempted to relate insecticidal activity to pK_a and to stereochemistry, and Haglid *et al.*[11-13] examined nicotine analogues derived from pyrrolidines or 3-pyridylalkylamines. Yamamoto and



(1) Nicotine



(2) Cotinine, X = O

(3) X = S

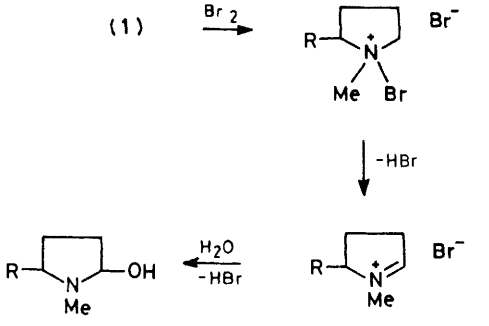
(4) X = NR

his co-workers in a series of papers described the synthesis of many analogues containing the pyridine ring, and summarised [14] the structural requirements necessary for high toxicity to *Musca domestica*. These include the presence of a pyridine ring unsubstituted at position 2, unquaternised nitrogen atoms, a nitrogen–nitrogen distance of *ca.* 4.2 Å, and the more basic nitrogen having a pK_a of 8—9. Unfortunately, owing to the different bioassays employed by the different research groups, an accurate overall structure–activity picture cannot be obtained, but none of the compounds examined had significantly more activity than nicotine itself. The object of the present work was to use nicotine itself as a starting material and to convert it into derivatives which might possess useful insecticidal (or other biological or medicinal) properties.

RESULTS AND DISCUSSION

A small number of nicotine derivatives alkylated at the 2'- and 5'-positions [15-18] and at the 2'- and 3'-positions [19,20] have been synthesised, but bioassays have not been reported. The synthesis of 4'-alkyl derivatives, in the hope of inhibiting sterically metabolism at position 5, but leaving insecticidal properties intact, was therefore contemplated. Cotinine (2), obtainable from nicotine by bromination to 3',3'-dibromocotinine hydrobromide perbromide which was isolated, followed by zinc–acetic acid reduction, proceeded as described [21] but increasing the scale of the preparation caused a drastic diminution in yield. Simplification of the procedure and reducing the dibromocotinine without isolation has now been found to give a satisfactory large-scale preparation of crystalline cotinine, which is highly deliquescent and has not hitherto been obtained solid. It was subsequently discovered that the oxidation of nicotine by mercuric acid gave a higher yield of cotinine (see below).

The structure of 3',3'-dibromocotinine has been established from its ^1H n.m.r. spectrum,[22] but its mode of formation has not been considered. It seems likely that the nicotine is attacked by bromine at the pyrrolidine nitrogen, and subsequent nucleophilic attack and loss of bromine anion gives an immonium salt (Scheme 1).



R = 3-Pyridyl

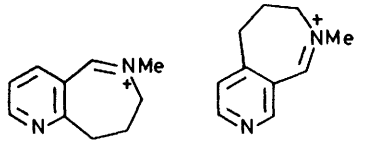
SCHEME 1

Addition of water and repetition of the procedure would give cotinine, where further bromination would be expected to occur adjacent to the carbonyl group. The 2'-position of the original nicotine is perhaps less susceptible to attack than the 5'-position because of the bulk of the pyridine ring. However, subsequent attack of the same type at the 2'-position could be a part of the sequence leading to the formation of dibromoticonine from nicotine, aqueous hydrogen bromide, and bromine.[23]

Alkylation of cotinine with 1 equiv. or an excess of methyl or ethyl iodide and sodium amide in liquid

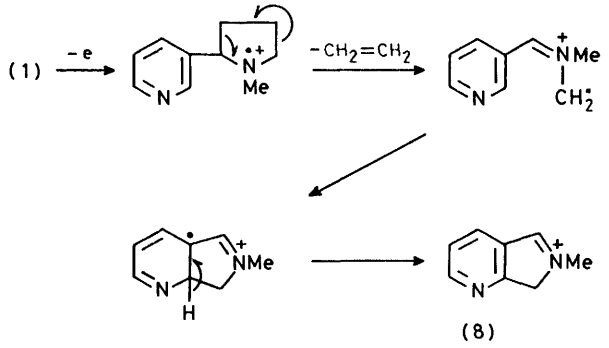
ammonia gave the 3′-mono- and 3′,3′-di-alkyl derivatives respectively, but allyl bromide only gave satisfactory yields of 3′-allylcotinine if ether was employed as solvent, and the 3′,3′-diallyl compound was not obtained. 3-Chloropropyldimethylamine hydrochloride, with 2 mol of sodium amide suspended in xylene, gave satisfactory 3′-monoalkylation, but 2-chloroethyl-diethyl- and -dimethylamine hydrochlorides did not, and propargyl bromide gave tars with cotinine under all conditions employed. Reduction of these cotinines with lithium aluminium hydride gave the corresponding nicotines [*cf.* (1)] and although promising insecticidal activity was found for the 4′,4′-diethyl derivative the other nicotines and the cotinines showed no interesting properties in our biological screens.

The mass spectrum of nicotine was originally studied using deuterium-labelling techniques,[24] but as scrambling occurs with both the hydrogen and carbon atoms of toluene [25] the original conclusions are less certain and the proposed formation of (5) or an isomer (6) through deuterium, or hydrogen, loss in the formation of the heaviest fragment (*m/e* 161) is impossible to establish.



(5) (6)

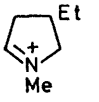
The mass spectra of the simple 3′-alkylcotinines (2) are similar to that of cotinine itself [24] except that the 3′,3′-diethyl derivative loses the elements of ethylene, accountably by a McLafferty rearrangement involving the carbonyl group, to give the base peak. Re-examination of the fragmentation using decoupling techniques [26] and direct analysis of daughter ions [27] suggest that the major fragment at *m/e* 133 (60%) is formed by the initial ejection of an ethylene molecule from nicotine followed by the loss of a hydrogen atom at position 2 to give (8) as shown in Scheme 2. The fragmentation patterns for all our 4′-alkylnicotines lend support to this scheme (Table 7 of SUP 22675). For example 4′-Et-(1) shows the molecular ion (18%), $[M - 1]^+$ (16%), and a base peak corresponding to (7). There is also a prominent peak at *m/e* 133 attributable to the initial loss of but-1-ene and a hydrogen atom which could lead to (8). The



(8)

SCHEME 2

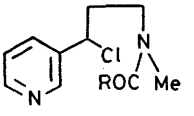
mass spectra of the 3′-alkylnicotines reported [19] (but not discussed) are in agreement with these conclusions, in particular the 3′,3′-dimethylnicotine having its base peak at *m/e* 133 and the corresponding 2′-deuteriated compound at *m/e* 134. Surprisingly, the base peak for 3′-methylnicotine is reported [20] at *m/e* 134 which is perhaps an error as no fragment at *m/e* 133 is noted.



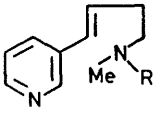
(7)

The n.m.r. spectra of the 4′-alkylnicotines, and in particular that of the 4′,4′-dimethyl derivative which is relatively simple, confirm the proton assignments originally reported [28] for nicotine itself. Decoupling experiments have enabled a complete assignment of resonances for the saturated ring and have shown that long-range coupling (0.5 Hz) occurs between the 2′- and 4-protons (Table 1). These results are in agreement with a recent [29] very detailed analysis of the n.m.r. spectrum of nicotine itself.

Opening of the pyrrolidine ring of nicotine followed successively by transformations and recyclisation appeared to be an attractive route to substituted nicotines. Nicotine with benzoyl chloride yields the chloroamide (9) [30] which loses hydrogen chloride to give *N*-benzoylmetanicotine (13) and thence metanicotine (12) itself on alkaline hydrolysis. However we obtained only low yields of (13) from nicotine, and reaction with acetyl chloride to give (14) proved very violent and difficult to control on a large scale. Ring-opening to (10)



(9) R = Ph
(10) R = OPh
(11) R = OEt



(12) R = H
(13) R = COPh
(14) R = COMe
(15) R = CO_2Ph
(16) R = CO_2Et

followed by a ready loss of hydrogen chloride yielding (15) occurred with phenyl chloroformate, a reagent which often causes demethylation.[31,32] Benzyl chloroformate with nicotine gave a complex mixture under all conditions employed, while the ethyl ester proved the best reagent for ring scission. The first product was (11), isolable by chromatography; treatment with very dilute alkali, or acid followed by alkali, re-formed *S*-nicotine with overall retention of configuration; this was independently observed by Hootelé and Lenders.[33] Heating of the chloro-compound (11) to 200 °C eliminated hydrogen chloride yielding (16), but better results were obtained using alcoholic potassium hydroxide. The hydrolysis of (16) to metanicotine (12) was effected best by concentrated aqueous hydrochloric acid; the anhy-

drous hydrogen bromide–acetic acid procedure [34] for decomposing carbamates giving only tar with this and the phenyl or methyl esters, along with unhydrolysed

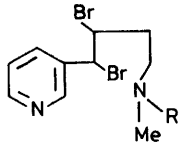
TABLE 1

^{1}H N.m.r. spectra (τ, J [a]/Hz, from internal tetramethylsilane)

Compound	Spectrometer frequency/MHz	Solvent	Assignments
4′-Me-(1)	60	CCl_4	2-H, 1.63 (br); 4-H, 2.45; 5-H, 2.93; 6-H, 1.77; $J_{2,4}$ 2.6; 1′-Me, 7.93 (s); 2′-H, 6.18 (q); 4′-Me, 8.99 (d, J 6.0); 5′-H, 6.80 (d, J 8); 3′-H_2, 4′-,5′-H_2, 7.5—8.5 (m)
4′,4′-Me_2-(1)	60, 100 [b]	CCl_4	2-H, 1.58 (br); 4-H, 2.40; 5-H, 2.91; 6-H, 1.62; $J_{2,4}$ 2.6; $J_{4,2'}$ 0.5; 1′-Me, 7.91 (s); 2′-H, 6.84 (t, $J \simeq J$ = 8.8); 3′-H, 8.1 (m); 3′-H, 8.55 (m); 4′-Me, 8.81 (s); 4′-Me, 8.93 (s); 5′-H, 7.13 (d); 5′-H, 7.87 (d); $J_{5',5'}$ 11.5
3′-Me-(2)	60	CCl_4	2-H, 1.58 (d); 4-H, 2.49 (dt); 5-H, 2.77 (dq); 6-H, 1.50 (q); $J_{2,4}$ 2.1; 1′-Me, 7.37; 3′-Me, 8.85 (d, J 6.6); 3′,4′,4′-H_3, 7.4—8.1; 5′-H, 5.46 (t, $J_{4',5'}$ 6)
3′,3′-Me_2-(2)	60	CCl_4	2,6-H_2, 1.58 (m); 4-H, 2.46 (dt); 5-H, 1.77 (dq); $J_{2,4}$ 2.1; 1′-Me, 7.45; 3′-Me_2, 8.83 and 8.87; 4′-H, 7.69 (q); 4′-H, 8.32 (q); 5′-H, 5.56 (t); $J_{4',4'}$ 13; $J_{4',5'}$ 7
(4)	60	$CDCl_3$	All virtually identical to that of (2) added to that of the substituent
(11)	60	$CDCl_3$	2,6-H_2, 1.47 (m); 4-H, 2.27 (m); 5-H, 2.73 (m); C*H*Cl, 5.04 (t, J 7.2); CHCl(CH_2)$_2$, 8.14 (m); CH_2N, 6.73 (t, J 6.6); NMe, 7.18; OCH_2CH$_3$, 5.94 (q); OCH$_2$CH_3, 8.79 (t, J 6.8)
(12)	60	$CDCl_3$	2-H, 1.58 (d); 4-H, 2.48 (m); 5-H, 2.97 (m); 6-H, 1.71 (m); C*H*=C*H*, 3.77 (m); $(CH_2)_2$, 7.2—8.2 (m); N*Me*, 7.67
(18)	60	D_2O	2-H, 0.99 (m); 4-H, 1.14 (m); 5-H, 1.77 (m); 6-H, 1.02 (m); PyC*H*Br, 4.27 (d, J 10.5); C*H*BrCH$_2$, 4.97 (m); CHBrCH_2, 7.41 (m); CH_2N, 6.60 (m); N*Me*, 7.16 (m)
(19)	60	$CDCl_3$	2,6-H_2 1.43 (m); 4-H, 2.30 (m); 5-H, 2.76 (m); 1′-Me, 7.78; 2′,5′-H_2, 6.60 (m); 3′-H, 5.58 (m); 4′,4′,5′-H_3, 7.48 (m)
(24) [c]	60	$CDCl_3$	2,6-H_2, 1.43 (m); 4-H, 2.28 (m); 5-H, 2.73 (m); N–Me, 7.65; 3′-H, 3.67 (t, J 7.3); 4′-H_2, 7.85 (m); 5′-H_2 7.42 (m)

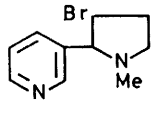
[a] $J_{2,4}$ *ca.* 1—2, $J_{2,5} \simeq 1$, $J_{4,5} \simeq 8$, $J_{4,6}$ *ca.* 1—2, $J_{5,6} \simeq 4.5$ for the pyridine ring unless stated. [b] Irradiation at τ 6.84 collapsed multiplets due to 3′-protons to two doublets and removed long-range coupling of 4-H. [c] Side-chain numbered as for (1).

starting materials; dilute alkali and acid were also unsatisfactory. Addition of bromine to the olefinic double bond of the carbamate (16) proceeded reasonably to give (17), but removal of the carbamate group leaving the bromine atoms intact could not be achieved as olefin formation always took place. Metanicotine (12) with bromine in ether precipitated a perbromide salt, no attack having taken place at the olefinic linkage. However, metanicotine dihydrochloride with bromine gave the corresponding salt of (18) and subsequent neutralisation with sodium hydrogencarbonate presumably liberated the free base which cyclised *in situ* to 3′-bromonicotine (19). This compound was extremely unstable, and an acceptable analysis was only obtained for the dipicrate. The structure proposed is in agreement with the observed differences between its n.m.r. spectrum and that of nicotine. Attempts to prepare this bromo-compound at low temperatures and react it *in situ* with sodium diethyl malonate caused elimination to (24) containing a small proportion of (22). There has been much confusion in the early literature concerning identities of dihydronicotyrines, and this has been clearly resolved in the case of the 2′,5′-compound (22)



(17) R = CO_2Et

(18) R = H, 2HCl



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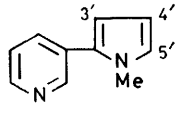

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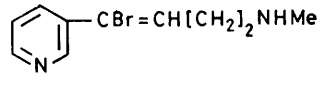
(21) 4′,5′-H_2

(22) 2′,5′-H_2

(23) 2′,3′-H_2



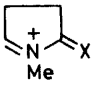
(24)

by ultraviolet [35] and n.m.r.[36] studies; the olefinic protons were clearly resolved and the data presented agrees with that of our synthetic material. Our compound (24) shows one olefinic proton at τ 3.67, assigned to the 3′-position, which is in the right range [37] for this structure. It appeared as a triplet, (J 7.3 Hz) which collapsed to a singlet on irradiating the multiplet at τ 7.42. The coupling constant is far too high for the compound to have a bicyclic structure. *N*-Methylmyosmine (21), identified by its conjugated u.v. spectrum,[38] has recently [39] been prepared again by the cyclisation of 3-methylaminopropyl 3-pyridyl ketone (earlier investigated by Haines and Eisner [40] and by Pinner [41]) and *N*-mesylmyosmine [42] have $J_{3',4'}$ 3.0 and 2.8 Hz, respectively. Open-chain compounds, structurally analogous to (24) have couplings of 6.4—7.4 Hz for comparable

protons.[37] The i.r. spectrum of (24) showed a strong absorption at 1 625 cm^{-1}, also characteristic of enamines (*ca.* 1 630 cm^{-1}).[43,44]

In view of the synthetic potential of enamines a simpler synthesis of (21) was sought, and the value of mercuric acetate as a dehydrogenating agent for nicotine examined. Murphy[45] has reported that mercuric acetate with nicotine and cyanide ion in the presence of ethylenediaminetetra-acetic acid form 5′-cyanonicotine but gave no yield nor did he mention other products; from a later footnote[46] it appears he obtained cotinine in 50% yield. Sanders *et al.*,[46] omitting the EDTA, obtained cotinine (50%) and 2′-cyanonicotine (5%). We have attempted to oxidise nicotine, similarly, but with EDTA, in the hope of isolating (21) or the 2′,3′-dihydro-isomer (23) from the anticipated intermediate iminium salt, but cotinine was obtained as the sole product in high yield. This is a good, simple, synthetic procedure. The oxidation proceeds in a mode contrary to the generalisation[47] that mercuric acetate in such situations gives the most highly substituted iminium cation.

Cotinine was readily converted by phosphorus pentasulphide into thiocotinine (3), which is very much more stable than cotinine to electron impact. The molecular ion is the base peak in the thio-compound, loss of the pyridine ring yielding a fragment (8%) corresponding to (25), while for cotinine the fragment shown as (26) accounts for the base peak while the molecular ion is



(25) X=S

(26) X=O

small (18%). Allyl bromide reacted with thiocotinine at the pyridinium nitrogen atom only. Cotinine (2) with phosphorus trichloride and a series of amines[48] gave the corresponding amidines (4) (Table 4).

Nornicotine [de-Me-(1)] has twice the insecticidal activity of nicotine towards *Aphis rumicus*,[49] and an easy *N*-demethylation procedure was sought. Earlier attempts using silver oxide,[50] potassium permanganate,[50] and treating nicotine 1′-oxide with an iron(III)–tartaric acid system[51] gave very poor conversions. Selenium dioxide at 150 °C in dioxan is reported[52] to give a 50% conversion, but at 100 °C and atmospheric pressure, or 150 °C in diphenyl ether, we obtained no demethylation. Attempted demethylation by treatment with oxygen in the presence of palladium on charcoal[53] or platinum,[54] or with lead tetra-acetate,[55] alkaline hexacyanoferrate(III),[56] activated manganese dioxide,[57] cyanogen bromide,[58] phosphorus pentachloride,[59] and diethyl azodiformate[60] failed. However demethylation was effected by silver nitrite[61] to *N*′-nitrosonornicotine, identified from its mass spectrum and comparison of its i.r. spectrum with that reported for authentic material.[62] It constituted over 70% of the reaction product, minor constituents being cotinine (2) and probably *N*′-nitrosodemethylcotinine. However owing to the carcinogenic nature[63] of *N*′-nitrosonornicotine, which can be present in tobacco, this approach was discontinued.

EXPERIMENTAL

The instruments and chromatographic procedures employed have been described previously.[64] ^1H N.m.r. spectra, except those in Table 1, i.r. spectra, mass spectra, and analytical data for new compounds are available in Supplementary Publication No. SUP 22675 (10 pp.).* U.v. spectra are given for nm (10^{-4} ε).

1-Methyl-5-(3-pyridyl)pyrrolidin-2-one (2).—(*cf.* H. McKennis *et al.*).[21] Bromine (565 ml) in acetic acid (800 ml) and water (200 ml) was added over 4 h to a stirred solution of 1-methyl-2-(3-pyridyl)pyrrolidine (1) (250 g) in acetic acid (800 ml) and water (200 ml) under nitrogen. The resulting dark red solution was diluted with water (1 500 ml) and heated at 100 °C until homogeneous (*ca.* 2 h). After cooling, hydrochloric acid (375 ml) was added followed by portions of zinc dust (total *ca.* 625 g) until a permanent green colouration was obtained. The solution was filtered, evaporated to about one-third its original volume, and brought to pH 9 with ammonia (density 0.880). Extraction with chloroform (4 × 500 ml) and distillation of the washed (aqueous saturated $NaHCO_3$, 2 × 500 ml, then water, 500 ml), dried extracts under nitrogen gave 1-methyl-5-(3-pyridyl)pyrrolidin-2-one (185.4 g, 68%), b.p. 142—144 °C at 0.4 Torr, which crystallised on standing to an exceedingly hygroscopic solid, m.p. 40—43 °C; $\lambda_{max.}$ (MeOH) 212 (ε 0.59 × 10^{-4}) and 263 nm (0.40); $\nu_{max.}$ (liquid film) 3 040w, 2 960, 1 690s, 1 594w, 1 579, 1 395s, 1 117, 1 028, and 718s cm^{-1}.

TABLE 2

Preparation of 3-alkylated-1-methyl-5-(3-pyridyl)-pyrrolidin-2-one

Alkyl substituent(s)	Reagent	Percentage yield	B.p. (°C)	Pressure/ Torr
Me [a]	MeI	59	123—130	0.1
Me_2 [b]	MeI (excess)	80	90—100	20
Et [c]	EtI	55	130—132	0.25
Et_2	EtBr	77.5	130—134	1.0
Allyl [d]	C_3H_7Br (excess)	42	144—146	0.25

[a] Contamination with the dimethyl compound prevented a satisfactory analysis. [b] Sublimes, fine needles (from light petroleum) m.p. 95—97 °C. [c] Extremely hygroscopic, not analysed. [d] After evaporation of NH_3, t.l.c. indicated only 9% reaction so dry ether (200 ml) was added and refluxed for 2 h, The product was chromatographed over deactivated alumina. and eluted with toluene, before distillation.

3-Alkyl-1-methyl-5-(3-pyridyl)pyrrolidin-2-ones [cf. (2)].—Sodium amide (1.95 g, 0.05 mol) was prepared by dissolving sodium (1.15 g, 0.05 mol) in liquid ammonia (250 ml) containing a catalytic amount of hydrated iron(III) chloride. 1-Methyl-5-(3-pyridyl)pyrrolidin-2-one (8.8 g, 0.05 mol) in dry ether (50 ml) was rapidly added and the mixture cooled to *ca.* −50 °C. The alkyl halide, *e.g.* ethyl iodide (9.35 g, 0.06 mol) was added as quickly as possible and the reaction mixture allowed to attain room temperature overnight. Water (100 ml) was added and the aqueous layer separated and extracted with chloroform (2 × 200 ml). The combined organic extracts were dried and distilled

* For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1978, Index issue.

under nitrogen to give the 3-*alkyl*-1-*methyl*-5-(3-*pyridyl*)-*pyrrolidin*-2-*one* (Table 2). The 3,3-dialkyl analogues were made similarly except that 0.2 mol of both alkyl halide and sodium were employed.

4-*Alkyl*-1-*methyl*-2-(3-*pyridyl*)*pyrrolidines* [cf. (1)].—The alkylpyrrolidone [*e.g.* 3'-Et-(2)] (5.5 g) in dry ether (100 ml) was slowly added to a stirred suspension of lithium aluminium hydride (2—3 mol equiv.) in ether (80 ml) to maintain refluxing, and after refluxing for a further 3 h unreacted hydride was destroyed with ethyl acetate. After addition of water the ether layer was collected and combined with chloroform extracts (3 × 50 ml) of the aqueous phase. Distillation of the dried extracts gave the pyrrolidines as colourless oils (Table 3).

3-[3-(*Dimethylamino*)*propyl*]-1-*methyl*-5-(3-*pyridyl*)-*pyrrolidin*-2-*one* [cf. (2)].—Sodium amide (7.8 g, 0.2 mol) was added to a well stirred mixture of 1-methyl-5-(3-pyridyl)-pyrrolidin-2-one (17.6 g) and 3-(dimethylamino)propyl chloride hydrochloride (16.1 g) in dry toluene (200 ml). The mixture was refluxed until reaction was complete (t.l.c.) (45 h). Aqueous hydrochloric acid (100 ml of 10%) was cautiously added, and the aqueous layer separated and basified with 10M sodium hydroxide. The product was extracted with chloroform (3 × 100 ml) and the extracts washed with a pH 5.5 aqueous buffer [3 × 200 ml, made from 0.1M citric acid (84 ml) and 0.2M disodium hydrogenphosphate (116 ml)]. The washings were basified (10M aqueous NaOH) and extracted with chloroform (2 × 200 ml). Distillation of the dried extracts under nitrogen gave 3-[3-(*dimethylamino*)*propyl*]-1-*methyl*-5-(3-*pyridyl*)*pyrrolidin*-2-*one* (9.6 g), b.p. 176—178° C at 0.1 Torr, which on trituration with light petroleum (b.p. 60—80 °C) gave colourless crystals, m.p. 86—88 °C.

TABLE 3

4-Alkyl-1-methyl-5-(3-pyridyl)pyrrolidines

Alkyl substituent	Percentage yield	B.p. (°C)	Pressure/ Torr
Me [a]	64	115—119	13
Me_2 [b]	79	128—130	13
Et	47	133—137	13
Et_2	60	168—170	13
CH_2=$CHCH_2$	59	140—142	0.3
$Me_2N[CH_2]_3$	55	128—132	0.3

[a] Analysed as derivative with 2.5 mol picric acid (from MeOH) m.p. 205—207 °C (decomp.). [b] Analysed as dipicrate (from MeOH), m.p. 195—198 °C (decomp.).

3-(2-*Dimethylaminoethyl*)-1-*methyl*-5-(3-*pyridyl*)*pyrrolidin*-2-*one*.—This was obtained (15% yield) similarly to the propyl analogue above, but using 2-(*NN*-dimethylamino)-ethyl chloride hydrochloride, and was a colourless oil, b.p. 164—166 °C at 0.1 Torr, which gave an extremely hygroscopic solid on standing. The 3-(2-*diethylaminoethyl*) analogue was obtained similarly (4% yield), b.p. 178—184 °C at 0.1 Torr.

N-*Methyl*-N-[4-(3-*pyridyl*)*but*-3-*enyl*]*acetamide* (14).—1-Methyl-2-(3-pyridyl)pyrrolidine (1) (20.0 g) in acetonitrile (50 ml) was cautiously added to a well stirred solution of freshly distilled acetyl chloride (23.6 g) in acetonitrile (150 ml) under nitrogen, when an extremely vigorous reaction ensued. The mixture was refluxed for 4 h, ethanol (50 ml) was added and the solvent evaporated. The residue was dissolved in 20% aqueous sulphuric acid (100 ml), the solution washed with ether (2 × 100 ml), brought to pH 7 with ammonia and extracted with chloroform (3 × 100 ml). The dried extracts were chromatographed on silica gel (1 400 g, made up in chloroform). Chloroform eluted starting material, and chloroform–methanol (9 : 1 v/v) gave an oil which distilled under nitrogen to give N-*methyl*-N-[4-(3-*pyridyl*)*but*-3-*enyl*]*acetamide* (14) (6.5 g, 26%) b.p. 150—155 °C at 0.4 Torr.

Phenyl N-*Methyl*-N-[4-(3-*pyridyl*)*but*-3-*enyl*]*carbamate* (15).—Phenyl chloroformate (15.6 g) in dichloromethane (30 ml) was added dropwise to a stirred solution of 1-methyl-2-(3-pyridyl)pyrrolidine (1) (16.0 g) in dichloromethane (80 ml) under nitrogen. The mixture was refluxed for 3 h, and distilled under nitrogen to give the *carbamate* (15) as a colourless, extremely viscous oil (11—18 g), b.p. 186—189 °C at 0.3 Torr.

Ethyl N-*Methyl*-N-[4-*chloro*-4-(3-*pyridyl*)*butyl*]*carbamate* (11).—1-Methyl-2-(3-pyridyl)pyrrolidine (30.0 g) in dichloromethane (150 ml) was added dropwise to a stirred solution of ethyl chloroformate (18.6 g) in dichloromethane (100 ml) under nitrogen. The mixture was refluxed for 3 h, the solvent evaporated, and the residue chromatographed on silica gel (800 g, made up in chloroform). Chloroform eluted starting material, and then chloroform–methanol (3 : 1 v/v) gave *ethyl* N-*methyl*-N-[4-*chloro*-4-(3-*pyridyl*)-*butyl*]*carbamate* (11) (32.9 g, 65%) as a colourless oil, which was analysed directly. Distillation caused decomposition to *ethyl* N-*methyl*-N-[4-(3-*pyridyl*)*but*-3-*enyl*]*carbamate* (16), b.p. 149—152 °C at 0.4 Torr, an extremely deliquescent viscous oil which crystallised from acetone (no m.p. possible); (16) was also obtained by refluxing (11) with potassium hydroxide in ethanol under nitrogen.

N-*Methyl*-N-4-(3-*pyridyl*)*but*-3-*enylamine* (12).—Ethyl *N*-methyl-*N*-[4-(3-pyridyl)but-3-enyl]carbamate (20.7 g) in hydrochloric acid (10M) (100 ml) was refluxed for 16 h and then evaporated to dryness. Ethanol (50 ml) was added, followed by a solution of sodium (5.0 g) in ethanol (150 ml) with stirring. The solvent was evaporated, water (100 ml) was added and the solution extracted with chloroform (3 × 100 ml). The dried extracts were distilled under nitrogen to give the amine (12) (9.5 g, 67%), b.p. 98—100 °C at 0.4 Torr.

Conversion of Ethyl N-*Methyl*-N-[4-*chloro*-4-(3-*pyridyl*)-*butyl*]*carbamate* (11) *to Nicotine* (1).—A solution of the carbamate (11) (5.0 g) in 10% sulphuric acid (100 ml) was refluxed under nitrogen for 5 h. The solution was cautiously made alkaline with 10M aqueous sodium hydroxide. The mixture was extracted with chloroform (3 × 100 ml) and distillation of the dried extracts under nitrogen gave 1-methyl-2-(3-pyridyl)pyrrolidine (1) (2.7 g, 90%), b.p. 114—116 °C at 16 Torr, identified from its i.r. and ^{1}H n.m.r. spectra, and with $[\alpha]_D^{20}$ −164.1° (lit.,[65] $[\alpha]_D^{20}$ −166.4 to −168.5°). Treatment of (11) with 2.5% aqueous sodium hydroxide similarly gave 1-methyl-2-(3-pyridyl)pyrrolidine (1) of similar optical activity.

Ethyl N-[3,4-*Dibromobutyl*-4-(3-*pyridyl*)]-N-*methylcarbamate* (17).—Bromine (8.8 g) in carbon tetrachloride (80 ml) was added to a stirred solution of ethyl *N*-methyl-*N*-[4-(3-pyridyl)but-3-enyl]carbamate (16) (12.9 g). A small amount of solid, probably a perbromide, was deposited. The mixture was evaporated to a semi-solid mass which was treated with saturated sodium hydrogencarbonate solution until all the solid had dissolved (*ca.* 500 ml). The solution was extracted with chloroform (3 × 200 ml) and the dried extracts were evaporated to a dark orange oil (13.8 g, 63%) identified as ethyl *N*-[3,4-dibromo-4-(3-pyridyl)-*N*-methyl]carbamate (17) from its n.m.r. spectrum (Table 5

of SUP 22675). It was used without further purification. Compound (17) (7.4 g) was dissolved in 10% aqueous sulphuric acid (50 ml), and the solution refluxed for 1 h, cooled, and basified (ammonia). The product was extracted with chloroform (3 × 50 ml), dried, and distilled to give (16) (2.6 g, 62%), b.p. 102—105 °C at 0.45 Torr, and quantities of other elimination products (n.m.r.) which were not characterised.

N-[3,4-*Dibromo*-4(3-*pyridyl*)*butyl*]*methylamine Dihydrochloride* (18).—*N*-Methyl-4-(3-pyridyl)but-3-enylamine (12.9 g) in ether (150 ml) was saturated with dry hydrogen chloride gas for 0.5 h. The precipitate was collected, washed with ether, and dissolved in chloroform (100 ml). Bromine (12.8 g) in chloroform (50 ml) was added with stirring, the solvent was evaporated, and the residue was recrystallised from ethanol–ether to give the *dihydrochloride* (18) (25.5 g, 81%).

3-*Bromo*-1-*methyl*-2-(3-*pyridyl*)*pyrrolidine* (19).—An ice-cold saturated solution of sodium hydrogencarbonate was added to a stirred solution of *N*-[3,4-dibromo-4-(3-pyridyl)-butyl])methylamine dihydrochloride (18) (8.6 g) in water (100 ml) at 0 °C until the pH reached 8. Chloroform (100 ml) was added and the mixture stirred for 12 h. The organic phase was separated and was combined with the chloroform extracts (3 × 100 ml) of the aqueous phase. The dried extracts were evaporated to give 3-bromo-1-methyl-2-(3-pyridyl)pyrrolidine (19) (3.6 g, 68.5%) as a dark red oil which tarred on standing or warming. It was identified from its n.m.r. spectrum (Table 1) and the formation in methanol of a *dipicrate*, yellow needles from water, m.p. 185—187 °C (decomp.).

1-*Bromo*-4-*methylamino*-1-(3-*pyridyl*)*but*-1-*ene* (24).—*N*-[3,4-Dibromo-4-(3-pyridyl)butyl]methylamine dihydrochloride (18) (8.9 g) and sodium (1.55 g) dissolved in ethanol (100 ml) were stirred at 0 °C until no solid remained. After addition of sodium diethyl malonate (from 3.6 g of the ester) in ethanol (100 ml) and stirring for 0.5 h at 0 °C the solvent was removed and the residue dissolved in water (150 ml). Extraction with chloroform (3 × 100 ml) and distillation of the dried extracts gave 1-methyl-2-(3-pyridyl)-3-pyrroline (22) (0.3 g), b.p. 120—135 °C at 16 Torr, identified by comparison of its i.r. and n.m.r. spectra with an authentic specimen prepared as described;[39] and the olefin (24) (2.6 g), b.p. 135—141 °C at 16 Torr; $\lambda_{max.}$ (EtOH) 212 (ε 0.37 × 10^{-4}) and 243 nm (0.39); $\nu_{max.}$ (liquid film) 1 625s cm^{-1}, which gave a *picrate*, yellow needles from water, m.p. 204—205 °C (decomp.).

1-*Methyl*-2-(3-*pyridyl*)*pyrrolidine* (1) *with Mercury*(II) *Acetate*.—Mercury(II) acetate (78.8 g) and ethylenediaminetetra-acetic acid (91.85 g) were dissolved in 2% aqueous acetic acid (1 000 ml). 1-Methyl-2-(3-pyridyl)pyrrolidine (1) (10.0 g) was added and the mixture heated on a steam-bath for 2 h. After cooling, the mixture was basified (2M aqueous NaOH), filtered, extracted with chloroform (3 × 200 ml), and the dried extracts distilled under nitrogen to give 1-methyl-5-(3-pyridyl)pyrrolidin-2-one (2) (7.7 g, 70%), b.p. 142—144 °C at 0.1 Torr.

1-*Methyl*-5-(3-*pyridyl*)*pyrrolidine*-2-*thione* (3).—A mixture of 1-methyl-5-(3-pyridyl)pyrrolidin-2-one (2) (18.3 g) and phosphorus pentasulphide (20.0 g) was heated at 130 °C for 16 h. When cool, saturated aqueous sodium hydrogencarbonate was added until effervescence ceased (*ca.* 200 ml). Extraction with chloroform (3 × 100 ml), drying, and evaporation gave a dark red oil which slowly crystallised. Recrystallisation from ethanol gave 1-*methyl*-5-(3-*pyridyl*)-*pyrrolidine*-2-*thione* (3) (15.3 g, 77%) as yellow crystals, m.p. 90 °C; $\lambda_{max.}$ (MeOH) 206 (ε 0.37 × 10^{-4}) and 269 nm (1.01). The thione (3) (7.8 g), allyl bromide (5.0 g), and acetonitrile (150 ml) were refluxed for 16 h. A white precipitate (0.5 g) of 1-*methyl*-5-(3-*pyridyl*)*pyrrolidine*-2-*thione hydrobromide*, m.p. 250 °C (decomp.) formed. An excess of anhydrous sodium carbonate was added to the filtrate, and the mixture was stirred for 16 h and filtered. The filtrate was evaporated to dryness and the ^1H n.m.r. spectrum of the crude product showed the presence of an allyl group and pyridinium protons, in the correct ratio for an *N*-allylpyridinium salt.

1-*Methyl*-5-*imino*-2-(3-*pyridyl*)*pyrrolidines* (4).—*General procedure*. Phosphorus oxychloride (8.3 g, 0.054 mol) was added dropwise below 25 °C to a stirred solution of 1-methyl-5-(3-pyridyl)pyrrolidin-2-one (2) (9.5 g, 0.054 mol) in dry benzene or dichloromethane (50 ml). The solution was stirred for 16 h. A solution of the amine (0.054 mol) in benzene or dichloromethane (10 ml) was added dropwise and the mixture heated at 80 °C for 16 h. The solvent was decanted, the residue dissolved in ice–water (100 ml), and the solution made alkaline with aqueous 2M sodium hydroxide. Extraction with chloroform (3 × 100 ml) and distillation of the dried extracts under nitrogen gave the pyrrolidines (4) (Table 4), some of which were hygroscopic and crystallised on exposure to air.

TABLE 4

Preparation of the 5-iminopyrrolidines (4)

R	Yield (%)	B.p. (°C)	Pressure/ Torr	M.p. (°C)
Ph	48	172—174	0.35	60—65
4-$NO_2C_6H_4$	48 [a]			
4-ClC_6H_4	75	188—190	0.3	82.5—83.5
Ph_2N [a,b]	18			130—131 [c]
Me_2N [a,b]	11			239—242 [c]

[a] Isolated by chloroform elution from a deactivated alumina column. [b] The $POCl_3$–(4) reaction was allowed 15 min, the amine added and the mixture refluxed for 20 min. [c] From toluene.

1-*Nitroso*-2-(3-*pyridyl*)*pyrrolidine*.—A suspension of silver nitrite (21.9 g) and 1-methyl-2-(3-pyridyl)pyrrolidine (1) (5.8 g) in dimethylformamide (250 ml) was stirred under nitrogen at 70 °C until no starting material could be detected by t.l.c. (*ca.* 4 h). The solvent was evaporated, and the residue treated with sodium carbonate solution (100 ml) and extracted into chloroform (3 × 50 ml). The dried extracts were evaporated to an oil (1.5 g) which was analysed by g.l.c.–m.s. and found to contain five major constituents: (*i*) *m/e* 142 (M^+) and 113 (base peak), unidentified (8%); (*ii*) 1-methyl-5-(3-pyridyl)pyrrolidin-2-one (2) (5%); (*iii*) 1-nitroso-2-(3-pyridyl)pyrrolidine (71%); (*iv*) *m/e* 190 (M^+?) and 131 (base peak), possibly 1-nitroso-5-(3-pyridyl)pyrrolidin-2-one (7%); (*v*) unidentified (9%).

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