UNUSUAL FORMATION OF STERICALLY HINDERED PRIMARY AMINES IN A SERIES OF PYRROLO- AND PYRIDO[1,2-*a*]INDOLES

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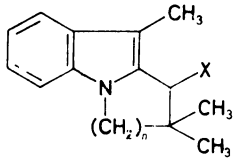
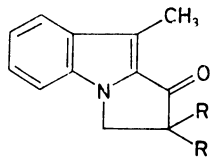
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

2,3-Dihydro-2,2,9-trimethyl-1*H*-pyrrolo[1,2-*a*]indol-1-amine and its 1-(1-pyrrolidinyl) analog have been synthesized from the corresponding 1-ol via mesylation in pyridine followed by treatment with pyrrolidine. Mechanisms of the former, unexpected amination are briefly discussed. Evidence is presented that the pyridine ring serves as a masked amino group. The phenomenon is partly attributed to steric congestion. Similar preparation of 2-bromo-6,7,8,9-tetrahydro-8,8,10-trimethylpyrido[1,2-*a*]indol-9-amine supports this notion.

In recent years, we have successfully utilized a pentacyclic eburnan skeleton as a template in the design of both cardiovascular[1] and psychotropic agents[2]. The minimum structure concept led to the discovery of a series of 6,7,8,9-tetrahydro--8,8,10-trimethylpyrido[1,2-*a*]indol-9-amines[2] represented by the pyrrolidine derivative *I* which was shown to be an antihypoxic agent superior to vincamine, vinconate, vinpocetine, eburnamine, and hexahydrocanthinone in several animal models. Importantly, the antihypoxic activity was not associated with the ability to cause hypothermia[3]. The corresponding primary amine *II* was not only an useful intermediate but it effectively protected mice in the hypoxia survival test (ED_{50} 6·9 mg/kg



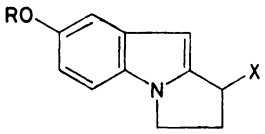
I, $n = 2$; X = 1-pyrrolidinyl
II, $n = 2$; $X = NH_2$
III, $n = 1$; X = 1-pyrrolidinyl
IV, $n = 1$; $X = NH_2$



V, R = H
VI, $R = CH_3$

i.p.) and exhibited an excellent 1·1 ratio of i.p./p.o. antihypoxic activities. Unfortunately, higher doses of *II* produced untoward side-effects which were not observed with *I* (ED_{50} 11·2 mg/kg i.p. in the hypoxia survival). These findings prompted our efforts to prepare and evaluate analogs *III*–*IV* in a series of 2,3-dihydro-2,2,9-trimethyl-1*H*-pyrrolo[1,2-*a*]indol-1-amines[4].

The requisite pyrroloindolone *V* was previously synthesized[5] by a three-step process. Acrylonitrile was added to 3-methylindole, the product was hydrolyzed to give 3-(3-methylindol-1-yl)propanoic acid, and subsequent cyclization with phosphorus pentoxide in boiling xylene afforded *V* in a poor yield (14·3%). We have improved this cyclization step upon using polyphosphoric acid at 90°C to obtain analytically pure ketone *V* in 54·5% yield. Treatment of *V* with sodium hydride in DMF, followed by addition of methyl iodide, furnished *VI*. Synthetic studies[6–9] aiming at mitosenes and mitomycin antibiotics employed unsubstituted 2,3-dihydropyrrolo[1,2-*a*]indol-1-ones in a straightforward manner, for example, catalytic hydrogenation of the corresponding oxime provided amine *VII*, and reduction of an enamino intermediate yielded *VIII* (ref.[7]). Unfortunately, we were unable to follow

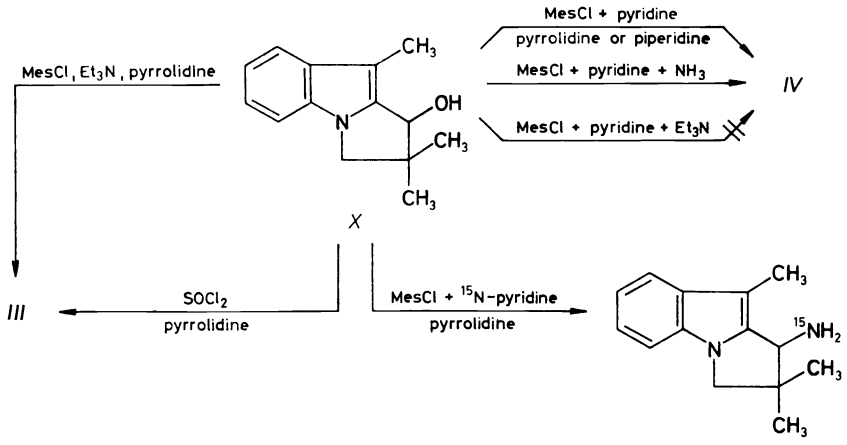


VII, R = H ; X = NH_2
VIII, R = CH_2–Ph ; X = 1-pyrrolidinyl
IX, R = CH_2–Ph ; X = OH

similar routes. Attempts to prepare and purify an oxime of *VI* in sufficient quantities were unsuccessful. The lethargic, low yield oximation of *VI* can be attributed to the steric hindrance afforded by the flanking methyl groups, and it contrasts with a facile oximation of *V* (ref.[5]). An obvious, alternative approach to amines *III*–*IV* involves N-alkylation procedures. Remers et al. reported[7] that alcohol *IX* failed to react with mesyl or tosyl chloride in pyridine, however, our experience[2] indicated that these workers did not use the necessary excess of reagents, and a routine workup either hydrolyzed the desired product back to the starting material, or, it triggered elimination. Sodium borohydride reduction of *VI* proceeded smoothly to yield an alcohol *X*. Treatment of *X* with two moles of mesyl chloride in pyridine at 0°C gave a colored solution which was then diluted, dropwise, with an excess (32 moles) of pyrrolidine. On workup, we have isolated a totally unexpected product (Scheme 1), the primary amine *IV* in 37% yield.

The fact that the pyrrolidinyl compound *III* was not at first even detectable left us somewhat perplexed. The seemingly irrational formation of the primary amine was

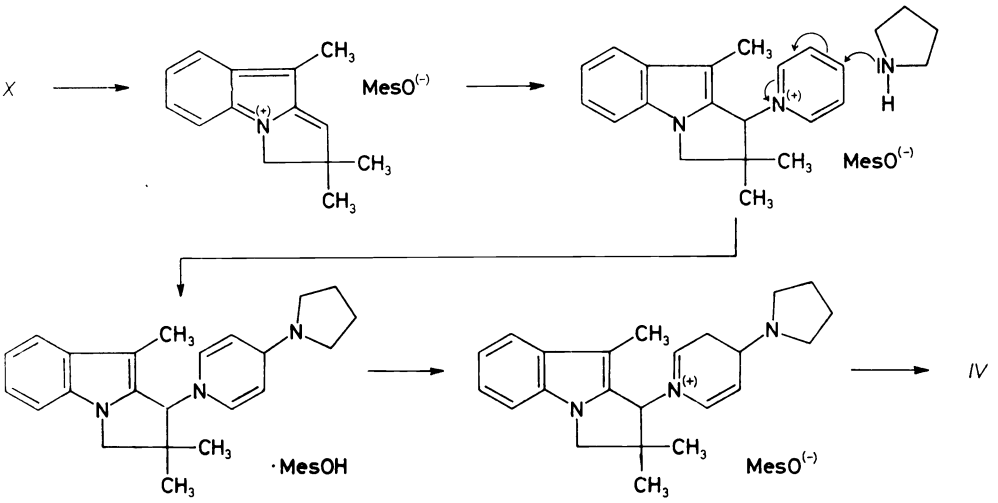
reliably reproducible with unoptimized yields fluctuating in a 35–65% range, according to the purification procedure. Replacement of pyrrolidine by piperidine did not affect the course of the reaction, and *IV* was obtained in comparable yields.



SCHEME 1

These results per se strongly suggest that the newly introduced atom of nitrogen comes from pyridine. A plausible mechanism that may explain the above described formation of *IV* is shown in Scheme 2. Although we had surmised a bona fide intermediacy of an O-mesyl derivative of *X*, a series of experiments with *X* and analogous 6,7,8,9-tetrahydro-10-methyl-pyrido[1,2-*a*]indol-9-ols, using mesyl or tosyl chloride in pyridine or triethylamine, did not support this assumption. We were unable to isolate the intermediate O-sulfonates, and direct TLC analyses of the reaction mixtures indicated only the presence of very polar material. Apparently, a rapid heterolysis of the C—O bond produces an intimate ion pair[10], and this ionization is anchimerically assisted by the indole nucleus which annihilates the carbocation (Scheme 2). The existence of an indoliminium ion would not be surprising since such a species has been repeatedly invoked in numerous biosynthetic and synthetic pathways. While the mesylation of *X* clearly follows an ion pair mechanism[11–12], we have to consider that other reactive species[10] can be also generated in the presence of pyridine. Whether dealing with a tight ion pair, a solvent separated ion pair, or a pair of dissociated ions, they can be collapsed[10–11] by an intervening pyridine molecule to form a pyridinium derivative. A number of chemists have asserted the intermediacy of pyridinium salts[13] in nucleophilic substitutions, however, an alternative view[14] favors the term "nucleophilically pyridine-solvated ion pair". The following attack by pyrrolidine (or piperidine) gives rise to a dihydropyridine intermediate which is protonated to set the stage for hydration of an iminium salt. One

can readily visualize the resulting carbinolamine–enamine as an unstable species whose hydrolysis leads to the primary amine *IV*.

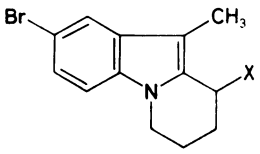


SCHEME 2

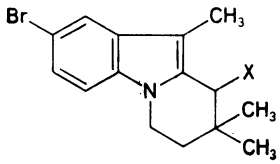
The unusual conversion of *X* into *IV*, or formation of *III*, did not occur when pyridine was replaced by 4-methylpyridine, hence, we must assume that in this particular case, position 2 of the pyridinium intermediate is not an alternative site for the pyrrolidine attack. It is highly likely that the present observations are partly due to steric congestion around C-1. Normally, pyridinium salts are known to undergo the addition of soft nucleophiles at C-4 whereas hard nucleophiles attack at C-2 (ref.[15]). To further validate the mechanisms proposed in Scheme 2, mesylation of *X* in pyridine was run in tandem with the addition of triethylamine (Scheme 1). Virtually quantitative recovery of the alcohol *X* ensued upon work up, since the postulated pyridinium species could not act as an acceptor of tertiary amine. Compound *IV* was also prepared by introducing dry, gaseous ammonia into the solution of mesylated *X*. This was a low yield (8%) transformation which provided no information as to the origin of the nitrogen atom. Convincing evidence that the proposed mechanisms may be operative came from a ^{15}N-incorporation experiment. Using the same set of conditions (mesylation followed by pyrrolidine) in ^{15}N-pyridine, *X* was converted into exclusively labelled primary amine *XI* (Scheme 1).

The next phase of our study involved reactions aiming at the pyrrolidinyl derivative *III*. Treatment of *X* with thionyl chloride gave an unstable product which was stirred with pyrrolidine to afford *III* in 32% yield. Importantly, no primary amine *IV* was formed in the absence of pyridine. Mesylation of *X* in triethylamine followed

by pyrrolidine also furnished *III* as the sole product (Scheme 1). Curiously, *III* could be obtained from *X* in the presence of pyridine as long as the amounts of mesyl chloride and pyridine were equimolar, and the reaction was conducted in methylene chloride. This means that an excess of free pyridine is essential for the formation of an intermediate pyridinium salt (Scheme 2). Careful reinvestigation of some earlier experiments in the series of 6,7,8,9-tetrahydro-10-methylpyrido[1,2-*a*]indol-9-amines[2] showed that insignificant amounts of primary amine (1–2% by HPLC) were formed in every instance of preparing tertiary amines by the herein described displacement reaction upon using pyridine. In several cases, comparing mesylation and tosylation of the starting alcohols, we have noticed that the mesylation process slightly favors the pathway to primary amines. Introduction of a geminal dialkyl group also contributed to an increased product ratio of primary/tertiary amine. A 2-bromo substituted subseries turned out to be an extreme case worthwhile mentioning. The primary amine *XII* was preparatively isolated (8% yield) after treatment of *XIII* with tosyl chloride in pyridine followed by dimethylamine. The principal product, representing a 71% yield, was the tertiary amine *XIV*. An analogous amine *XV* (yield 36%) was obtained by mesylation of *XVI* in pyridine followed by pyrrolidine, along with the tertiary amine *XVII* (yield 49%).



XII, X = NH_2
XIII, X = OH
XIV, X = $N(CH_3)_2$



XV, X = NH_2
XVI, X = OH
XVII, X = 1-pyrrolidinyl

In 1903, Zincke[16,17] discovered that the pyridine ring might serve as a masked amino group. Apart from relatively few examples[15–19], this classical reaction has had little preparative importance, and its extensions have been mainly elaborated to utilize intermediate derivatives of glutaconic dialdehyde in nucleophilic recyclizations[15]. It has been concluded[19] that the ring cleavage of quaternized pyridines effectively generates primary amines only in molecules with a pyridinium moiety conjugated to a π-deficient system. The present paper is an indicative that the Zincke reaction may have a broader scope of applications.

The target 2,3-dihydro-2,2,9-trimethyl-1*H*-pyrrolo[1,2-*a*]indol-1-amines *III–IV* were clearly less potent antihypoxic agents than their homologs *I–II*. In the hypoxia-induced lethality in mice, *III* and *IV* (50 mg/kg i.p.) offered 75% and 100% protection, respectively, but produced some undesirable side effects at the same time.

EXPERIMENTAL

Melting points (uncorrected) were determined in open capillaries on a Thomas–Hoover apparatus. Proton NMR spectra were recorded on a Varian XL-200 instrument at 200 MHz; chemical shifts are reported in δ ppm relative to TMS. Mass spectra were obtained using either Hewlett Packard 5995 or Finnigan 8230 instruments. IR and UV spectra were measured on Perkin–Elmer 781 and Beckman DU7 spectrophotometers, respectively. HPLC analyses were carried out on a 3μ Sotaphase C18E reverse phase column using 70% acetonitrile/30% 0·1M $(NH_4)_2HPO_4$, pH 7·6 as mobile phase, or the same system with the addition of 0·05% $HClO_4$ on a C6 column; flow rate 3 ml/min. Flash chromatography was performed with silica gel 60 (E. Merck, mesh 230–400), unless otherwise stated. Organic extracts were dried over magnesium sulfate, filtered, and evaporated under reduced pressure with a rotavapor.

2,3-Dihydro-9-methyl-1*H*-pyrrolo[1,2-*a*]indol-1-one (*V*)

A mixture of 3-(3-methylindol-1-yl)propanoic acid[5] (8·48 g) and polyphosphoric acid (90 g, 83% as P_2O_5) was heated in a beaker under mechanical stirring at 90°C for 1 h, cooled to 60°C, and poured into ice-water (200 ml). The products were extracted with ether (3 × 80 ml), the combined extracts were washed with a saturated solution of sodium carbonate, separated, and prepared for chromatographic purification. Elution with 30% hexane in chloroform afforded 4·21 g (yield 54·5%) of *V*, m.p. 173·5–175°C (benzene–hexane). Ref.[5], m.p. 170–171°C. ^{1}H NMR spectrum ($CDCl_3$): 2·65 s, 3 H (CH_3); 3·25 t, 2 H (CH_2CO, $J = 6·4$); 4·45 t, 2 H (CH_2N, $J = 6·4$); 7·1–7·5 m, 3 H (H-5, 6, 7); 7·8 d, 1 H (H-8, $J = 8$). Mass spectrum, *m/e* (% rel. intensity, fragment): 185 (100, M^+), 184 (50, M – H), 157 (52, M – C_2H_4). For $C_{12}H_{11}NO$ (185·2) calculated: 77·81% C, 5·99% H, 7·56% N; found: 78·00% C, 6·01% H, 7·44% N.

2,3-Dihydro-2,2,9-trimethyl-1*H*-pyrrolo[1,2-*a*]indol-1-one (*VI*)

Under exclusion of moisture, sodium hydride (440 mg, 10 mmol, 60% in mineral oil) was added portionwise to a solution of *V* (926 mg, 5 mmol) in distilled dimethylformamide (20 ml) at room temperature. The mixture was stirred for 1 h, and methyl iodide (1·56 g, 11 mmol) was added dropwise upon mild cooling. The reaction mixture was stirred for 2 h at ambient temperature, evaporated in vacuo, and the residue was partitioned between water (70 ml) and chloroform (2 × 75 ml). The combined organic extracts were washed with brine, and prepared for chromatographic purification. Elution with hexane–chloroform 1 : 1 gave 713 mg (yield 67%) of *VI*, m.p. 65·5–67·5°C (ether). ^{1}H NMR spectrum ($CDCl_3$): 1·38 s, 6 H (gem. CH_3); 2·58 s, 3 H (CH_3); 4·14 s, 2 H (CH_2); 7·20–7·35 m, 3 H (H-5, 6, 7); 7·72 d, 1 H (H-8, $J = 8$). Mass spectrum, *m/e* (% rel. intensity, fragment): 213 (56, M^+), 198 (38, loss of methyl), 157 (100, loss of isobutylene). For $C_{14}H_{15}NO$ (213·3) calculated: 78·84% C, 7·09% H, 6·57% N; found: 78·60% C, 7·13% H, 6·39% N.

2,3-Dihydro-2,2,9-trimethyl-1*H*-pyrrolo[1,2-*a*]indol-1-ol (*X*)

Sodium borohydride (1·93 g), was added by small portions to a cooled solution of *VI* (3·62 g, 16·9 mmol) in methanol (80 ml). The reaction mixture was stirred at room temperature overnight, the solvent was removed with a rotavapor, and the residue was suspended in water (80 ml). The product was extracted with chloroform (3 × 50 ml) and the combined extracts were processed to yield 3·49 g (yield 96%) of *X*, m.p. 82–85°C (benzene–hexane). ^{1}H NMR spectrum ($CDCl_3$): 1·14 s and 1·30 s, 6 H (gem. CH_3); 1·56 d, 1 H (OH, $J = 6$); 2·38 s, 3 H (CH_3); 3·75 d

and 3·92 d, 2 H (CH_2, $J = 10$); 4·74 d, 1 H (H-1, $J = 6$); 7·08—7·30 m, 3 H (H-5, 6, 7); 7·60 d, 1 H (H-8, $J = 8$). For $C_{14}H_{17}NO$ (215·3) calculated: 78·10% C, 7·96% H, 6·51% N; found: 77·89% C, 8·02% H, 6·49% N.

2,3-Dihydro-2,2,9-trimethyl-1*H*-pyrrolo[1,2-*a*]indol-1-amine (*IV*)

A solution of methanesulfonyl chloride (458 mg, 4 mmol) in dry pyridine (2 ml) was added dropwise to a solution of *X* (430 mg, 2 mmol) in the same solvent (10 ml) at 0°C. The mixture was stirred for 30 min at 0°C, and 30 min at 25°C. A solution of pyrrolidine (2·3 g, 32 mmol) in pyridine (5 ml) was added slowly at 0°C, and the resultant mixture was stirred at ambient temperature overnight. Volatiles were removed in vacuo, the residue was dissolved in methylene chloride (50 ml), and washed with 5% sodium carbonate and brine. The organic layer was prepared for chromatography which afforded 168 mg (yield 37%, yellowish oil, homogeneous by TLC) of *IV* upon elution with chloroform. ^{1}H NMR spectrum ($CDCl_3$): 1·08 s and 1·13 s, 6 H (gem. CH_3); 1·46 br, 2 H (NH_2); 2·29 s, 3 H (CH_3); 3·61 d and 3·78 d, 2 H (CH_2, $J = 10$); 4·01 s, 1 H (H-1); 6·94—7·12 m, 3 H (H-5, 6, 7); 7·43 d, 1 H (H-8, $J = 8$). In a repeated experiment, purifying the product rapidly by flash chromatography, and crystallizing the corresponding hydrochloride, *IV* (325 mg) was obtained in a 65% yield. The hydrochloride salt was prepared in acetonitrile with ethanolic HCl, m.p. 242·5—245°C (acetonitrile–ether). IR (KBr): 3 440 (broad), 2 970, 2 880, 2 620, 1 610 cm^{-1}. UV (MeOH), $\lambda_{max}(\varepsilon)$: 277·5 (6 600), 226 (18 275). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1·14 s and 1·32 s, 6 H (gem. CH_3); 2·35 s, 3 H (CH_3); 3·86 d and 4·13 d, 2 H (CH_2, $J = 10$); 4·43 br s, 1 H (H-1); 7·07 t, 1 H (H-7, $J = 8$); 7·18 t, 1 H (H-6, $J = 8$); 7·36 d, 1 H (H-5, $J = 8$); 7·57 d, 1 H (H-8, $J = 8$); 8·67 br, 3 H (NH_3^+). Mass spectrum, *m/e* (% rel. intensity, fragment): 214 (19, M^+), 197 (2·5, M — NH_3), 158 (100, loss of isobutylene). For $C_{14}H_{19}ClN_2$ (250·8) calculated: 67·05% C, 7·64% H, 11·17% N; found: 66·74% C, 8·05% H, 11·20% N.

Using the same conditions for the mesylation of *X*, and replacing pyrrolidine with piperidine, *IV* (150 mg) was obtained in a 35% yield.

The same conditions were used for the mesylation of *X*, but the addition of pyrrolidine was replaced by the introduction of dry, gaseous ammonia. The reaction mixture was actually saturated with ammonia at 0—5°C, and then stirred at ambient temperature for 48 h. The above described workup procedure afforded 34 mg (yield 8% of *IV*, identical with the standard sample in every respect.

2,3-Dihydro-2,2,9-trimethyl-1*H*-pyrrolo[1,2-*a*]indol-1-(^{15}N)amine (*XI*)

Methanesulfonyl chloride (114·5 mg, 1 mmol) was added to a solution of *X* (107·5 mg, 0·5 mmol) in ^{15}N-labelled pyridine (Cambridge Isotope Labs., 500 mg, 6·25 mmol) at 5°C. The reaction mixture was allowed to warm to room temperature, pyrrolidine (426 mg, 6 mmol) was added, and stirring was continued for 3 h. The solvent was evaporated in vacuo, and the residue was partitioned between saturated sodium bicarbonate (2 ml) and methylene chloride (2 × 2 ml). The combined organic extracts were subjected to flash chromatography, eluting with 1% methanol in chloroform. There was obtained 38 mg (yield 35%) of *XI*. High-resolution mass spectrum was obtained on Finnigan 8230 in EI mode at 70 eV; calculated for $C_{14}H_{18}N^{15}N$ 215·1450; found 215·1449. Mass spectrum, *m/e* (% rel. intensity, fragment): 215 (27, M^+), 159 (100, loss of isobutylene).

2,3-Dihydro-2,2,9-trimethyl-1-(1-pyrrolidinyl)-1*H*-pyrrolo[1,2-*a*]indole (*III*)

Thionyl chloride (1·57 g, 13·2 mmol) was added to a solution of *X* (2·58 g, 12 mmol) in benzene

(150 ml). The mixture was refluxed for 15 min, and evaporated under reduced pressure. The residue was stripped with benzene (3 × 60 ml), dissolved in THF (150 ml), and a solution of pyrrolidine (1·87 g, 26·4 mmol) in THF (30 ml) was added dropwise at 0°C. The reaction mixture was stirred at ambient temperature for 48 h. Volatiles were removed with a rotavapor, and the residue was partitioned between water (200 ml) and ether (300 ml). The separated organic layer was extracted with 2% hydrochloric acid (2 × 150 ml), the aqueous portion was rendered basic (pH 9) with sodium carbonate, and extracted with toluene (3 × 100 ml). The combined extracts were dried over $MgSO_4$, filtered, and evaporated to give 1·49 g (yield 46%) of *III* (yellow oil, homogeneous by TLC). The hydrochloride salt was prepared in acetonitrile, and recrystallized from ethanol–ether, m.p. 205—206°C. IR (KBr): 3 420 (broad), 2 950, 2 520, 2 440 cm^{-1}. ^1H NMR spectrum ($(CD_3)_2SO$): 0·91 s and 1·51 s, 6 H (gem. CH_3); 1·75—2·05 m, 4 H (pyrrolidine C-3 and C-4 protons); 2·33 s, 3 H (CH_3); 2·80 m, 1 H (pyrrolidine C-2 proton); 3·25 to 3·50 m, 2 H (pyrrolidine C-2 and C-5 protons); 3·75 m, 1 H (pyrrolidine C-5 proton); 3·79 d and 4·22 d, 2 H (CH_2N, J = 11·8); 4·68 d, 1 H (H-1, J = 4); 7·05 t, 1 H (H-7, J = 8); 7·18 t, 1 H (H-6, J = 8); 7·32 d, 1 H (H-5, J = 8); 7·56 d, 1 H (H-8, J = 8). Mass spectrum, *m/e* (% rel. intensity, fragment): 268 (38, M^+), 212 (100, loss of isobutylene), 198 (28, loss of pyrrolidine). For $C_{18}H_{25}ClN_2$ (304·9) calculated: 70·92% C, 8·26% H, 9·19% N; found: 70·46% C, 7·90% H, 9·09% N.

Alternatively, alcohol *X* (430 mg, 2 mmol) in triethylamine (15 ml) was treated with methanesulfonyl chloride (458 mg, 4 mmol) at 0—5°C. The resulting slurry was allowed to stand for 1 h, the supernatant was decanted off, the solids were redissolved in methylene chloride (15 ml), and pyrrolidine (2·3 g, 32 mmol) was added at 5°C. The reaction mixture was stirred overnight at room temperature, evaporated, and partitioned between methylene chloride (20 ml) and saturated sodium bicarbonate (3 × 10 ml). The organic extracts were processed for flash chromatography, and elution with chloroform afforded 223 mg (yield 41%) of *III*, identical in all respects with a sample obtained previously.

Finally, to a solution of *X* (430 mg, 2 mmol) in methylene chloride (15 ml) was added methanesulfonyl chloride (916 mg, 8 mmol) and pyridine (632 mg, 8 mmol), and the mixture was stirred at ambient temperature for 26 h. Then, pyrrolidine (2·3 g, 32 mmol) was added at 5°C and stirring was continued for 15 h. Volatiles were removed with a rotavapor. The residue was partitioned between methylene chloride (20 ml) and 5% sodium bicarbonate (3 × 10 ml). The combined organic extracts were processed for flash chromatography, and elution with chloroform gave 158 mg (yield 29·5%) of pure *III*.

2-Bromo-6,7,8,9-tetrahydro-N,N,10-trimethylpyrido[1,2-*a*]indol-9-amine (*XIV*) and 2-Bromo-6,7,8,9-tetrahydro-10-methylpyridol[1,2-*a*]indol-9-amine (*XII*)

To a solution of the starting alcohol *XIII* (ref.[2], 2·8 g, 10 mmol) in dry pyridine (150 ml) was added a solution of *p*-toluenesulfonyl chloride (7·6 g, 40 mmol) in the same solvent (50 ml) at 0°C. Maintaining this temperature, stirring was continued for 1 h, and an excess of dimethylamine gas was introduced from a lecture bottle. The mixture was allowed to warm to ambient temperature, and after 3 h, it was poured into water (200 ml) and extracted with methylene chloride (3 × 70 ml). The combined extracts were prepared for chromatographic separation on a gravity column with an automatic fraction collector. Elution with 5% methanol in methylene chloride afforded 2·2 g (yield 71%) of *XIV* which was converted into the hydrochloride salt, m.p. 202 to 203°C (ethanol). ^1H NMR spectrum ($(CD_3)_2SO$): 2·30 s, 3 H (CH_3); 2·64 d and 2·86 d, 6 H ($N(CH_3)_2$, J = 3·5); 4·78 m, 1 H (H-9); 7·2—7·5 m, 2 H (H-3, 4); 7·74 d, (H-1, J = 2). Mass spectrum, *m/e* (% rel. intensity, fragment): 308 (10, M + 2), 306 (10, M^+), 264 (100), 263 (55),

262 (100), 261 (55), 183 (33). For $C_{15}H_{20}BrClN_2$ (343·7) calculated: 52·15% C, 5·86% H, 8·15% N; found: 51·97% C, 5·75% H, 8·02% N. More polar fractions were collected to give 223 mg (yield 8%) of *XII* as a semi-solid homogeneous by TLC. ^{1}H NMR spectrum ($CDCl_3$): 2·25 s, 3 H (CH_3); 4·7 t, 1 H (H-9, $J = 5$); 6·95–7·25 m, 2 H (H-3, 4); 7·58 d, 1 H (H-1, $J = 2$). Mass spectrum, *m/e* (% rel. intensity, fragment): 280 (90, M + 2), 278 (90, M^+), 263 (98), 261 (100, M − NH_3), 182 (15, further loss of Br).

2-Bromo-6,7,8,9-tetrahydro-8,8,10-trimethyl-9-(1-pyrrolidinyl)-pyrido[1,2-*a*]indole (*XVII*) and 2-Bromo-6,7,8,9-tetrahydro-8,8,10-trimethylpyrido[1,2-*a*]indol-9-amine (*XV*)

Methanesulfonyl chloride (2·82 g, 24·7 mmol) was added to a solution of the starting alcohol *XVI* (ref.[2], 3·8 g, 12·3 mmol) in dry pyridine (60 ml) at 5°C. The reaction mixture was stirred at room temperature for 2 h, it was cooled to 0°C, pyrrolidine (10·5 g, 148 mmol) was added, and stirring was continued at ambient temperature for 14 h. Volatiles were removed in vacuo, and the residue was partitioned between 5% sodium bicarbonate (100 ml), and ether (3 × 50 ml). The combined organic extracts were washed with 1·5% hydrochloric acid (3 × 40 ml) and the separated, combined aqueous portion was rendered basic (pH 8) with sodium bicarbonate. The products were extracted with ether (3 × 50 ml) to be separated by chromatography on neutral alumina (activity III). Slow elution with chloroform–hexane 1 : 1 afforded 2·18 g (yield 49%) of *XVII* which was characterized in the form of hydrochloride salt, m.p. 183·5–184·5°C (ethanol–ether). IR (KBr): 3 450 (broad), 2 960, 2 860, 2 530, 2 440 cm^{-1}. UV (MeOH), $\lambda_{max}(\varepsilon)$: 285 (7 440). ^{1}H NMR spectrum ($(CD_3)_2SO$): 0·80 s and 1·49 s, 6 H (gem. CH_3); 2·32 s 3 H; (CH_3); 4·80 d, 1 H (H-9, $J = 5$); 7·42 m, 2 H (H-3, 4); 7·78 d, 1 H (H-1, $J = 2$); 10·1 br, 1 H (NH^+). Mass spectrum, *m/e* (% rel. intensity, fragment): 362 (15, M + 2), 360 (15, M^+), 290 (100, loss of pyrrolidine). For $C_{19}H_{26}BrClN_2$ (397·8) calculated: 57·33% C, 6·59% H, 7·04% N; found: 57·33% C, 6·54% H, 6·93% N.

Evaporation of the remaining fractions furnished 1·37 g (yield 36%) of *XV* which was converted into the hydrochloride salt, m.p. 233–236°C (acetonitrile–ether). IR (KBr): 3 420 (broad), 2 880 (broad), 1 590 cm^{-1}. UV (MeOH), $\lambda_{max}(\varepsilon)$: 286 (7 000). ^{1}H NMR spectrum ($(CD_3)_2SO$): 0·90 s and 1·27 s, 6 H (gem. CH_3); 2·28 s, 3 H (CH_3); 4·32 br s, 1 H (H-9); 7·32 m, 2 H (H-3, 4); 7·7 d, 1 H (H-1, $J = 2$); 8·5 br, 3 H (NH_3^+). Mass spectrum, *m/e* (% rel. intensity, fragment): 308 (50, M + 2), 306 (53, M^+), 291 (100 M − CH_3), 289 (31, M − NH_3). For $C_{15}H_{20}BrClN_2$ (343·7) calculated: 52·41% C, 5·87% H, 8·15% N; found: 52·20% C, 5·74% H, 8·08% N.

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