THE PREPARATION OF "ELONGATED" NICOTINE ANALOGUES

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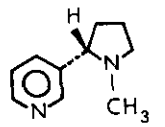
Abstract - The preparation of four nicotine analogues having one or two additional methylene units between the N-methylpyrrolidinyl moiety and the aromatic ring are reported. Also prepared are the corresponding nornicotine and myosmine analogues. The course of the Späth condensation used in these syntheses is examined, especially with regard to possible proton transfer reactions.

The search for the structural relationships between nicotine (1) and acetylcholine (2) has usually centered on the possible correspondence between the N---N' intramolecular distance in 1 compared with the N---O intramolecular distances in 2.[1] As part of our structure-reactivity studies, we have prepared numerous analogues in which the basic nicotine ring skeleton remains constant while various substituents have been added to affect molecular properties by steric and/or electronic perturbations (c.f. 3).[2-4] We herein report the preparation of a series of nicotine analogues in which the two basic structural units of nicotine again remain fixed and unmodified, namely the 3-monosubstituted pyridyl ring and the 2-monosubstituted pyrrolidinyl moiety. However, methylene units have been inserted between these molecular fragments [e.g. (4)] in such a fashion as to modify N---N' distance.



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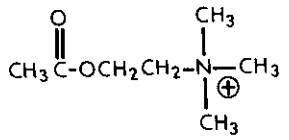

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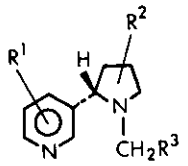

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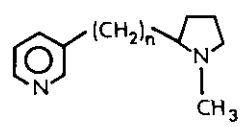

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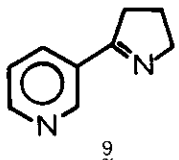
R_i = H, alkyl, halogen, cyano, etc.

The preparation of the nicotine analogues was achieved in a direct fashion, as illustrated in Scheme I and summarized in Table I. In all cases, the corresponding myosmine (9) and nor-



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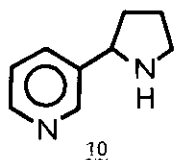

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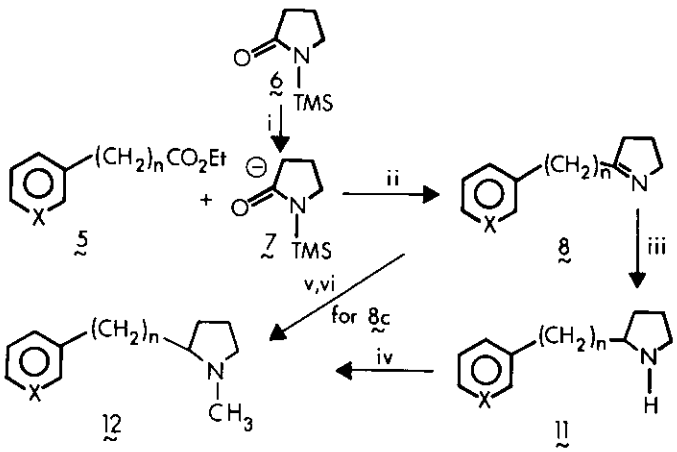
nicotine (10) analogues were also prepared. These syntheses are similar to the earliest modern preparation of nicotine in 1928 by Späth[5] who condensed the anion of N-methylpyrrolidinone with ethyl nicotinate. To extend the scope of our syntheses, we performed the Späth condensation[5,6] in both the 3-pyridyl series (12a-12b) and the phenyl series (12c-12d), in each case starting with either one or two methylene units between the aromatic ring and the ester moiety.

Scheme I



a, X = N, n = 1
b, X = N, n = 2
c, X = CH, n = 1
d, X = CH, n = 2

i, LDA, Et_2O; ii, -78°C to RT; H^+, heat; $OH^\ominus$; iii, $NaCNBH_3$;
iv, H_2CO, $NaCNBH_3$, CH_3CN; v, CH_3I, CH_3CN; vi, $NaBH_4$, MeOH.

Initially, we prepared the lithium amide enolate 7 by treating N-trimethylsilylpyrrolidinone (6)[6] with lithium diisopropylamide (LDA). The appropriate aromatic ester 5 was then added to the reaction mixture. The intermediate condensation product was then isolated, directly hydrolyzed, and decarboxylated in refluxing HCl to yield, after basification, the myosmine analogues 8a and 8b. In the 3-pyridyl series, 8a-8b were each cleanly reduced with sodium cyanoborohydride[7] to give the corresponding nornicotine analogues 11a and 11b respectively. These were methylated using the Borch procedure[8] (formaldehyde, sodium cyanoborohydride) to give the respective nicotines 12a-12b.

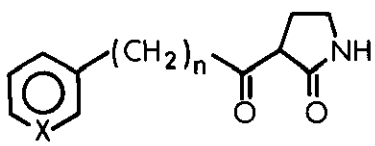
TABLE I. Summary of Isolated Yields of Purified Reaction Products.

Series	Substitution Pattern		Reactions/Yields (%)			
			5 + 7 ⟶ 8	5 + 7 ⟶ 13	8 ⟶ 11	11 ⟶ 12
	X	n				
a	N	1	84.1	88.0	89.4	83.2
b	N	2	61.9	---[a]	66.0	84.4
c	CH	1	51.2	82.3	83.9	56.3[b]
d	CH	2	59.1	60.5	90.1	80.0

[a] Not isolated. [b] By reduction of the N-methylpyrrolinium salt 8c.

A similar sequence was followed for the phenyl series, starting from 5c-5d. In the n = 1 case, the pyrroline 8c was treated with iodomethane to form the N-methylpyrrolinium iodide which was reduced with sodium borohydride directly to the nicotine analogue 12c; the nornicotine analogue 11c was prepared by reduction of 8c.

An interesting consideration of the Späth condensation between the esters 5 and anion 7 is the possibility, illustrated in Scheme II, of forming two different initial condensation products, 13 or 14. Upon hydrolysis and decarboxylation, both 13 and 14 could lead to the same myosmine

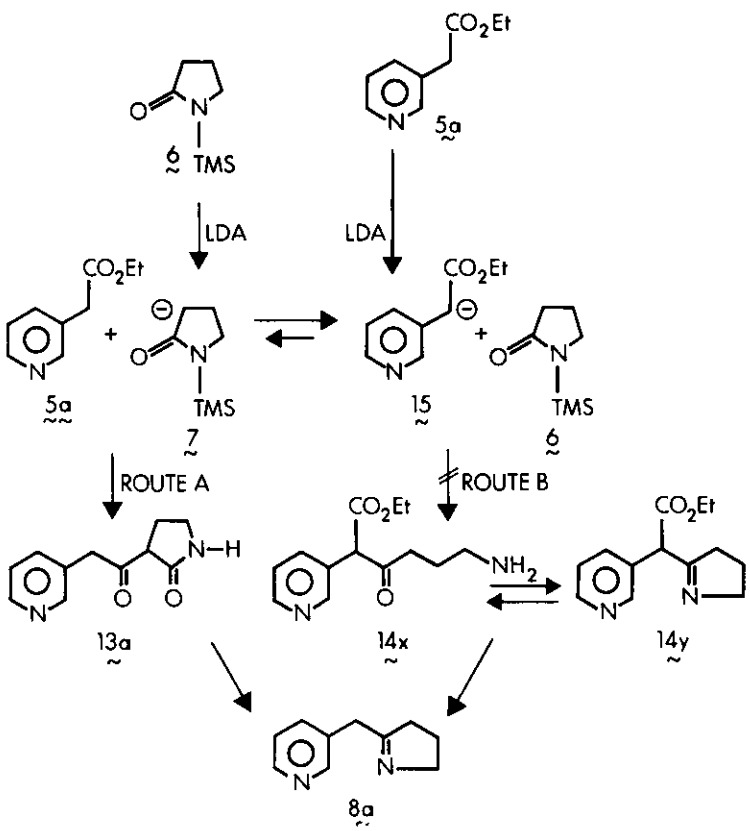


13a, X = N, n = 1
13b, X = N, n = 2
13c, X = CH, n = 1
13d, X = CH, n = 2

analogue 8 As the reactions were performed by treating 6 with preformed LDA, the condensation could occur directly (Route A), or following proton exchange (Route B), to result in 13 or 14 respectively. Acid hydrolysis of either 13 or 14 followed by decarboxylation and cyclization would result in the formation of the same myosmine analogue 8. To explore and resolve this ambiguity, we performed a number of additional reactions and carefully examined the initial adducts formed in the Späth condensations.

The Späth reactions of 7 with 5a-5d were rerun with the goal of isolating, in the highest yields, the pure initial condensation products. Without exception, the condensation products were the β-ketolactams 13 formed via Route A in Scheme II. These structural assignments were based on elemental analyses and NMR (^{1}H and ^{13}C) spectroscopic properties. We note at this stage that

Scheme II



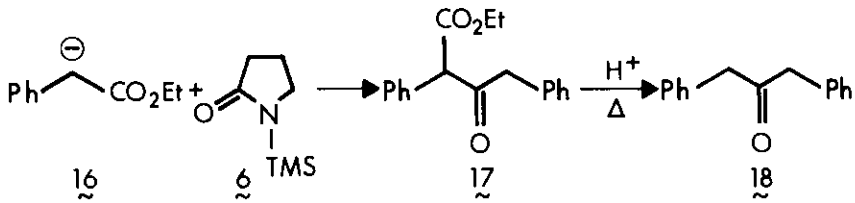
the Späth condensations of 5a, 5c and 5d all lead to isolable products in high yields. We thus exclude the possibility that the second pathway B in Scheme II proceeds simultaneously with pathway A, with the product 14 being lost in the workup and purification procedures.

In order to evaluate the involvement of proton transfer in Scheme II chemistry, we examined the reaction of preformed ester enolate 15 with N-trimethylsilylpyrrolidinone. Enolate 15 (Scheme II), prepared by reacting ethyl 3-pyridylacetate with LDA, was allowed to react with N-trimethylsilylpyrrolidinone (6). A high yield (88%) of β-ketolactam 13a was obtained after correcting for recovered ester.

It is interesting that Route A operates, even when the reaction flows from the right hand side of the Scheme II equilibrium (i.e., 5a + 7 $\rightleftarrows$ 15 + 6). While the acidities of the active methylene compounds ethyl 3-pyridylacetate (5a) and N-trimethylsilylpyrrolidine (6) have not been reported, we can estimate[9] them to be ca. pK_a(6) ≃ 28-30 and pK_a(5a) ≃ 19-20. Thus, 15 is far less basic than is 7 and the equilibrium shown in Scheme II is shifted considerably toward 15. For Route A to operate exclusively (>95%), then the lower concentration of 5a + 7 (relative to 15 + 6)

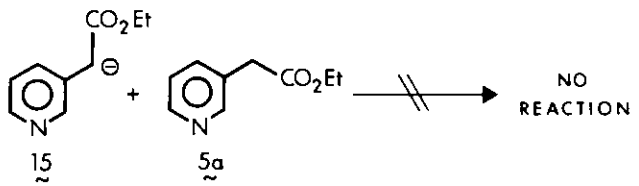
must be made up by a much greater reaction rate between 5a + 7 (than between 15 + 6). This argument is related to a Curtin-Hammett kinetic analysis[10] in which the minor component(s) react at a much greater rate to give product. In the case herein, 7 must be significantly more nucleophilic than 15 to over come ca. 8 orders of magnitude difference in basicity. We note that 5a is likely to be more electrophilic than 6.

The analogous reaction (eq 1) of the lithium enolate 16 of ethyl phenylacetate (17) with 6 led only to the β-ketoester self-condensation product 17 in 92% yield. The structure of 17 was confirmed by its hydrolysis and decarboxylation to dibenzylketone (18).[11] It is interesting to compare the different reactivity patterns of 15 and 16; the former reacts with N-trimethylsilylpyrrolidinone to yield 13a (Scheme II) while the latter forms the self-condensation product 17 (eq 1).

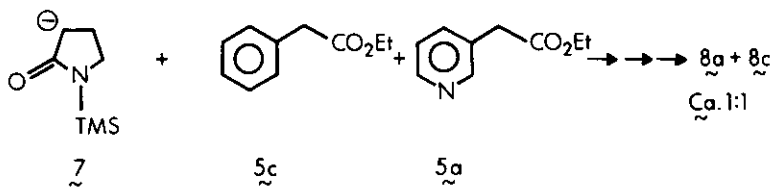


16 6 17 18 (1)

Two experimental results help explain this anomaly. First, the lithium enolate 15 of ethyl 3-pyridylacetate was allowed to react with 5a under the same reaction conditions as the condensation reactions were performed (eq 2). No β-ketoester was formed. Second, the lithium enolate 7 of N-trimethylsilylpyrrolidinone was allowed to react with a one-fold excess of a 1:1 mixture of the esters 5a and 5c (eq 3). Following hydrolysis, decarboxylation and cyclization of the entire reaction mixture, the two myosmines 8a and 8c were formed in ca. 1:1 ratio. Thus, the two esters are equally reactive to condensation with the lithium enolate 7 (eq 3), but the lithium enolate 15 of ethyl 3-pyridylacetate (5a) is not sufficiently reactive as a nucleophile under these conditions to condense with its precursor 5a. Alternatively, anion 15 is stabilized, relative to anion 16, by the pyridine ring and does not decompose as readily to a highly electrophilic ketene.[12]



15 5a (2)



7 5c 5a (3)

We thus conclude that the Späth condensations between N-trimethylsilylpyrrolidinone and the aromatic esters 5 occur by way of the anion of the former, as illustrated in Scheme I (and Scheme II, Route A). These procedures result in the facile, high yield preparations of a series of myosmine, nornicotine, and nicotine analogues shown in Table I and Scheme I and should be applicable to a wide range of related compounds.

EXPERIMENTAL

Methods and Materials.

^1H and ^{13}C NMR spectra were obtained on either a Varian XL-100 NMR spectrometer equipped with a Digilab NMR-3 FT accessory, a Bruker WP-80 spectrometer operated in the FT mode, or a Varian XL-400 NMR spectrometer. The coupling constants and chemical shifts reported herein are taken from the digital output from the spectrometer and are uncorrected. We estimate an error of ± 0.1 Hz for the coupling constants. Mass spectra were obtained on a Finnigan 3300 GC/MS/DS-6000. Infrared spectra were obtained on a 283B Perkin Elmer spectrophotometer. Elemental analyses were obained from Galbraith Laboratories, Inc.

(R,S)-3-(3-Pyridylacetyl)-2-pyrrolidinone (13a) and 2-(3-Pyridylmethyl)-1-pyrroline (8a).

A stirred solution of diisopropylamine (12.14 g, 0.12 mol) in ether (200 ml) under nitrogen was cooled to -75°C and treated with 2.5 M n-butyllithium (36.0 ml, 0.09 mol) in hexanes followed by N-trimethylsilyl-2-pyrrolidinone (15.28 g, 0.097 mol) and stirred for 15 min at -70°C. Ethyl 3-pyridylacetate (10.0 g, 0.0605 mol) was added and the reaction allowed to warm to and stir at room temperature for 20 h. The resulting precipitate was collected, washed with ether and air dried to give 20.3 g of a colorless solid. A sample (10.3 g) of this material was added at 0°C to 10% HOAc (50 ml) and the resulting solution extracted with methylene chloride. The resulting extract was dried (Na_2SO_4) and concentrated, finally at 95°C (0.01 mm), and gave on cooling, reddish-brown crystals (5.52 g; 88%). Recrystallization from ethyl acetate gave an analytical sample of 13a: mp 98-99°C; IR (nujol) 3174, 3090, 1716, 1691, 1598, 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07-2.18 (m, 1H), 2.59-2.70 (m, 1H), 3.29-3.45 (m, 2H), 3.62 (dd, 1H, J = 9.2, 6.6 Hz), 3.94 (d, 1H, J = 17.0 Hz), 4.28 (d, 1H, J = 17.0 Hz), 6.75 (br s, 1H, NH), 7.25 (dd, 1H, J = 7.8, 4.9 Hz), 7.55 (dt, 1H, J = 7.8, 2.0 Hz), 8.45 (d, 1H, J = 2.0 Hz), 8.48 (dd, 1H, J = 4.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 22.2, 40.4, 46.1, 53.6, 123.4, 129.6, 137.5, 148.3, 150.7, 173.2, 202.0. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.86; H, 5.95; N, 13.53.

The remaining crude product (10.0 g) was mixed with 6N HCl (150 ml) , heated at reflux for 20 h, concentrated at reduced pressure to a syrup and then basified with 10% KOH. The resulting two phase mixture was extracted with ether and the extract dried (Na_2SO_4) and concentrated.

Bulb-to-bulb distillation [oven temperature 80°C (0.005 torr)] gave 8a (4.07 g; 84.1%) as a colorless oil: IR (film) 1643, 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (m, 2H), 2.43 (t, 2H, J = 7.3 Hz), 3.67 (s, 2H), 3.8-3.88 (m, 2H), 7.23 (dd, 1H, J = 7.8, 4.8 Hz), 7.58 (br d, 1H, J = 7.8 Hz), 8.49 (dd, 1H, J = 4.8, 1.6 Hz), 8.50 (d, 1H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 22.65, 36.82, 37.66, 61.07, 123.47, 132.55, 136.54, 148.16, 150.25, 175.54. Analysis was obtained on the dipicrate salt, mp 199-200°C. Anal. Calcd for $C_{22}H_{18}N_8O_{14}$: C, 42.73; H, 2.93; N, 18.12. Found: C, 42.81; H, 2.96; N, 18.08.

(R,S)-2-(3-Pyridylmethyl)pyrrolidine (11a).

A stirred solution of 8a (6.0 g, 37.45 mmol) in MeOH (200 ml) was treated with a trace of bromcresol green indicator, $NaCNBH_3$ (2.56 g, 40.7 mmol). 2N HCl in MeOH (prepared from conc hydrochloric acid and MeOH) was added to maintain a yellow color. The reaction was quenched after 10 h with conc HCl (30 ml), heated briefly under reflux, then concentrated under reduced pressure. The residue was taken up in water, washed with ether and basified (50% KOH), extracted with ether and the ethereal extract dried (Na_2SO_4). The filtered solution was concentrated and distilled bulb-to-bulb [oven temperature 85°C (0.005 torr)] to give 11a (5.43 g; 89.4%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.3-1.4 (m, 1H), 1.67-1.9 (m, 4H), 2.74 (d, 2H, J = 15.8 Hz), 2.80-2.90 (m, 1H), 2.98-3.08 (m, 1H), 3.18-3.30 (m, 1H), 7.54 (dt, 1H, J = 7.9, 1.6 Hz), 8.45 (dd, 1H, J = 3.2, 1.6 Hz), 8.47 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 25.00, 31.35, 39.73, 46.33, 60.11, 123.27, 135.57, 136.40, 147.62, 150.34. Analysis was obtained on the dipicrate salt, mp 154-155°C. Anal. Calcd for $C_{22}H_{20}N_8O_{14}$: C, 42.59; H, 3.25; N, 18.06. Found: C, 42.72; H, 3.30; N, 18.09.

(R,S)-1-Methyl-2-(3-pyridylmethyl)pyrrolidine (12a).

A stirred, cooled (0°C) solution of CH_3CN (60 mL) containing 11a (3.0 g, 18.5 mmol) and 37% aqueous formaldehyde (7.0 ml) was treated with $NaCNBH_3$ (1.75 g, 27.8 mmol) in one portion. After being allowed to stir for 1 h at 0°C, the reaction was warmed to room temperature and stired overnight, concentrated on a rotary evaporator, and the residue treated with 10% KOH and ether. The aqueous phase was further extracted with ether and the combined ethereal extracts were in turn extracted with 20% HOAc (3x15 ml) . The combined HOAc extracts were washed with ether, basified (50% KOH), extracted with ether, and dried (Na_2SO_4). The filtered solution was concentrated and bulb-to-bulb distilled [oven temperature 85-90°C (0.005 torr)] to give 12a (2.71 g; 83.2%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.4-1.6 (m, 1H), 1.6-1.76 (m, 3H), 2.2 (m, 1H), 2.2-2.24 (m, 1H), 2.39 (s, 3H), 2.47 (dd, 1H, J = 13.2, 9.1 Hz), 2.99 (dd, 1H, J = 13.4, 4.2 Hz), 3.09 (dt, 1H, J = 7.4, 1.9 Hz), 7.2 (ddd, 1H, J = 7.8, 4.8, 0.8 Hz), 7.52 (dt, 1H, J = 7.9, 1.8 Hz), 8.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.74, 30.60, 37.58, 40.63,

57.23, 67.15, 123.12, 135.18, 136.54, 147.50, 150.48. Analysis was obtained on the dipicrate salt, mp 196-197°C. Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.61; H, 3.54; N, 17.53.

2-(2-(3-Pyridyl)ethyl)-1-pyrroline (8b).

The same procedure was employed as used in the preparation of 8a using 5b (5.0 g, 30.3 mmol). Bulb to bulb distillation [oven temperature 105°C (0.05 torr)] gave 8b (3.27 g; 61.9%) as a light tan colored oil: IR (film) 1646, 1591, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8-1.9 (m, 2H), 2.46 t, 2H, J = 8 Hz), 2.63 (t, 2H, J = 6.5 Hz), 2.99 (t, 2H, J = 8.5 Hz), 3.78-3.86 (m, 2H), 7.2 (ddd, 1H, J = 7.8, 4.8, 0.8 Hz), 7.53 (dt, 1H, J = 7.4, 1.6 Hz), 8.40 (dd, 1H, J = 4.8, 1.6 Hz), 8.48 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 22.56, 29.52, 34.78, 37.69, 60.86, 123.30, 135.70, 136.83, 147.54, 149.81, 176.68. Analysis was obtained on the dipicrate salt, mp 165.5-167.5°C. Anal. Calcd for $C_{23}H_{20}N_8O_{14}$: C, 43.68; H, 3.19; N, 17.72. Found: C, 43.46; H, 3.21; N, 17.56.

(R,S)-2-(2-(3-Pyridyl)ethyl)pyrrolidine (11b).

The same procedure was employed as used in the preparation of 11a using 8b (1.12 g, 6.44 mmol). Bulb to bulb distillation [oven temperature 110°C (0.05 torr)] gave 11b (0.75 g, 66%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.23-1.35 (m, 1H), 1.66-1.82 (m, 5H), 1.85-1.96 (m, 1H), 2.6-2.76 (m, 2H), 2.78-2.89 (m, 1H), 2.94-3.05 (m, 2H), 7.19 (dd, 1H, J = 7.8, 4.8 Hz), 7.51 (d, 1H, J = 7.8 Hz), 8.43 (dd, 1H, J = 4.8, 1.6 Hz), 8.46 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 25.49, 30.97, 31.86, 37.96, 46.65, 58.53, 123.26, 135.69, 137.51, 147.32, 149.90. Analysis was obtained on the dipicrate salt, mp 154-155°C. Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.55; H, 3.60; N, 17.68.

(R,S)-1-Methyl-2-(2-(3-pyridyl)ethyl)pyrrolidine (12b).

The same procedure was employed as used in the preparation of 12a using 11b (2.80 g, 15.9 mmol). Bulb to bulb distillation [100°C oven temperature (0.05 torr)] gave 12b (2.55 g; 84.4%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.75-1.9 (m, 2H), 1.9-2.1 (m, 2H), 2.2-2.38 (m, 3H), 2.38-2.47 (m, 1H), 2.58 (s, 3H), 2.8-3.0 (m, 2H), 3.35 (td, 1H, J = 9.5, 2.4 Hz), 7.48 (dd, 1H, J = 7.8, 4.8 Hz), 7.98 (br d, 1H, J = 8 Hz), 8.71 (dd, 1H, J = 4.8, 1.6 Hz), 8.75 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.92, 29.89, 30.65, 35.07, 40.46, 57.29, 65.67, 123.28, 135.61, 137.59, 147.34, 149.84. Analysis was obtained on the dipicrate salt, mp 151-152°C. Anal. Calcd for $C_{24}H_{24}N_8O_{14}$: C, 44.45; H, 3.73; N, 17.28. Found: C, 44.56; H, 3.65; N, 17.19.

(R,S)-3-Phenylacetyl-2-pyrrolidinone (13c) and 2-Benzyl-1-pyrroline (8c).

A stirred solution of diisopropylamine (6.07 g, 60 mmol) in ether (100 ml) under nitrogen was cooled to -75°C and treated with 2.5 M n-butyllithium (18.2 ml, 45.4 mmol) in hexanes followed by N-trimethylsilyl-2-pyrrolidinone (7.64 g, 48.6 mmol) and stirred for 15 min. at -70°C. One portion of methyl phenylacetate (4.55 g, 30.3 mmol) was added and the reaction allowed to warm to and stir at room temperature for 20 h. The resulting colorless precipitate was collected by filtration, washed with ether and dried in vacuo to give a crystalline product (9.1 g). A 1.0 g sample of this material was taken up in methylene chloride and washed with dilute HCl and $NaHCO_3$ solution. The dried (Na_2SO_4) solution was concentrated to give a reddish colored oil (680 mg; 100%) which solidified on trituration with hexane. Two recrystallizations from a mixture of ethyl acetate and cyclohexane gave the analytical sample of colorless 13c: mp 84-85°C; IR (nujol) 3250, 1728, 1690, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03-2.15 (m, 1H), 2.57-2.69 (m, 1H), 3.28-3.46 (m, 2H), 3.63 (dd, 1H, J = 9.1, 6.3 Hz), 4.03 (d, 1H, J = 15.4 Hz), 4.10 (d, 1H, J = 15.4 Hz), 6.29 (br s, 1H, NH), 7.22-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.53, 40.52, 49.39, 52.95, 127.04, 128.65, 129.77, 133.78, 173.77, 203.17. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.82; H, 6.50; N, 6.70.

The remaining crude product (8.10 g) was mixed with 6N HCl (85 ml), heated under reflux for 12 h (gives slow steady gas evolution), concentrated, basified (50% KOH) and thoroughly extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated and bulb-to-bulb distilled [oven temperature 80°C (0.025 torr)] to give 8c (4.28 g; 51.8%) as a colorless oil: IR (film) 1646, 1606, 1588 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77-1.87 (m, 2H), 2.39 (br t, 2H, J = 10 Hz), 3.67 (s, 2H) 3.79-3.85 (m, 2H), 7.21-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.63, 36.52, 40.71, 60.23, 126.58, 128.52, 129.02, 136.99, 176.78. Analysis was obtained on the picrate salt which was formed in EtOH and recrystallized from EtOH, mp 97-98°C (lit.[13] 114-115°C). Anal. Calcd for $C_{17}H_{16}N_4O_7$: C, 52.58; H, 4.15; N, 14.43. Found: C, 52.46; H, 4.20, N, 14.28.

(R,S)-2-Benzylpyrrolidine (11c).

The same procedure was employed as used in the preparation of 11a using 8c (0.5 g, 3.14 mmol) in MeOH (10 mL) and $NaCNBH_3$ (0.22 g, 3.50 mmol) . The product was bulb-to-bulb distilled [oven temperature 65° (0.025 torr)] to give 11c (0.425 g; 83.9%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.34-1.44 (m, 1H), 1.67-1.88 (m, 3H) 1.94 (br s, 1H, NH), 2.74 (d, 2H, J = 6.7 Hz), 2.76-2.84 (m, 1H), 2.98-3.06 (m, 1H), 3.16-3.26 (m, 1H), 7.15-7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.73, 31.13, 42.29, 46.06, 60.38, 125.93, 128.25, 128.87, 140.07. The picrate salt was formed in EtOH and recrystallized from water, mp 135-136°C (lit.[13] 139-140°C). Anal. Calcd for $C_{17}H_{18}N_4O_7$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.24; H, 4.65; N, 14.31.

(R,S)-1-Methyl-2-benzylpyrrolidine (12c).

A stirred solution of CH_3CN (15 ml) containing 8c (1.0 g, 6.28 mmol) was treated with CH_3I (1.0 ml) and let stand for 5 days at room temperature. The solution was concentrated on a rotary evaporator and the residue triturated with hot ethyl acetate. The slightly off-colored hygroscopic quaternary salt was collected and directly dissolved in MeOH (25 mL) . The solution was cooled (0-10°C), treated with $NaBH_4$ (0.75 g, 19.8 mmol), stirred for 2 h in the cold and then allowed to sit overnight at room temperature. The solution was concentrated and the residue solubilized with dilute HCl. The aqueous phase was basified (50% KOH) and extracted with ether. The dried (Na_2SO_4) ethereal phase was filtered, concentrated and bulb-to-bulb distilled [oven temperature 68°C (0.025 torr)] to give 12c (0.62 g; 56.3%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.5-1.8 (m, 4H), 2.17 (m, 1H), 2.25-2.37 (m, 1H), 2.38 (s, 3H), 2.4-2.47 (m, 1H), 3.04 (dd, 1H, J = 12.5, 3.2 Hz), 3.09 (td, 1H, J = 7.8, 1.8 Hz), 7.15-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.71, 30.88, 40.68, 57.34, 67.76, 125.91, 128.22, 129.09, 140.03. The picrate salt was prepared in EtOH, mp 143-144°C (lit.[13] 144-145°C). Anal. Calcd for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.85. Found: C, 53.29; H, 5.00; N, 13.80.

(R,S)-3-(3-Phenylpropionyl)-2-pyrrolidinone (13d).

The same procedure as used in the preparation of 8a was employed using diisopropylamine (12.1 g, 0.12 mol), ether (200 ml), n-butyllithium (0.09 mol), N-trimethylsilyl-2-pyrrolidinone (15.2 g, 0.10 mol) and ethyl hydrocinnamate (10.7 g, 0.06 mol). The heterogeneous reaction mixture was allowed to stir for 20 h and was then quenched with 3N HCl (70 ml) to give a clear solution from which a precipitate appeared. The solid was collected, triturated with CH_2Cl_2 and dried (Na_2SO_4). The filtered CH_2Cl_2 solution was concentrated, triturated with ether and the resulting solid collected to give colorless 13d (7.89 g; 60.5%): mp 105-106°C; IR (nujol) 3410, 3340, 3215, 1715, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05-2.17 (m, 1H), 2.5-2.64 (m, 1H), 2.8-2.95 (m, 3H), 3.26-3.4 (m, 4H), 6.94 (br s, 1H, NH), 7.14-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.56, 29.37, 40.63, 44.07, 54.26, 126.03, 128.36, 128.42, 140.90, 173.91, 204.79. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.88; H, 7.16; N, 6.34.

2-Phenethyl-1-pyrroline (8d).

A stirred mixture of 13d (6.72 g, 30.9 mmol) and 6N HCl (70 ml) was heated under reflux until gas evolution ceased (ca. 5 h). The reaction was worked up exactly as described for 8a. Bulb-to-bulb distillation [oven temperature 95°C (0.005 torr)] gave 8d (5.24 g; 97.8%) as a colorless oil: IR (film) 1644, 1604, 1587 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.82 (m, 2H), 2.4 (t, 2H, J = 8 Hz), 2.6 (t, 2H, J = 8 Hz), 2.9 (t, 2H, J = 8 Hz), 3.79 (tt, 2H, J = 7.3, 1.8 Hz), 7.13-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.56, 32.59, 33.36, 37.57, 60.74, 126.02, 128.27, 128.44,

141.54, 177.84. Analysis was obtained on the picrate salt, mp 139-140°C. Anal. Calcd for $C_{18}H_{18}N_4O_7$: C, 53.73; H, 4.51; N, 13.93. Found: C, 53.57; H, 4.72; N, 13.70.

(R,S)-2-Phenethylpyrrolidine (11d).

The same procedure was employed as used in the preparation of 11a using 8d (3.86 g, 22.3 mmol), MeOH (75 ml) and $NaCNBH_3$ (0.70g, 11.1 mmol). Bulb-to-bulb distillation [oven temperature 90°C (0.005 torr)] gave 11d (3.52 g; 90.1%) as a clear colorless oil: ^1H NMR $CDCl_3$ δ 1.2-1.3 (m, 1H), 1.68 (s, 1H, NH), 1.65-1.9 (m, 5H), 2.6-2.9 (m, 3H), 2.91-3.03 (m, 2H), 7.13-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.43, 31.82, 33.85, 38.25, 46.58, 58.68, 125.65, 128.28 (C2+C3), 142.30. Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.11; H, 9.69; N, 7.97.

(R,S)-1-Methyl-2-phenethylpyrrolidine (12d).

The same procedure was employed as used in the preparation of 12a using 11d (2.21 g, 12.6 mmol), CH_3CN (45 ml), 37% aqueous formaldehyde (4.7 ml) and $NaCNBH_3$ (0.79 g, 12.6 mmol). Bulb-to-bulb distillation [oven temperature 85°C (0.005 torr)] gave 12d (1.91 g; 80.0%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.5-1.9 (m, 2H), 1.9-2.0 (m, 3H), 2.12 (q, 1H, J = 8.2 Hz), 2.29 (s, 3H), 2.54-2.69 (m, 2H), 3.05 (br t, 1H, J = 7.3 Hz), 7.15-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.89, 30.68, 32.78, 35.41, 40.39, 57.31, 65.84, 125.65, 128.19, 128.25, 142.41. Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.18; H, 10.13; N, 7.48.

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REFERENCES

1. C. Chothia and P. Pauling, Proc. Natl. Acad. Sci. USA, 1970, 65, 477; U. S. von Euler, Ed., 'Tobacco Alkaloids and Related Compounds', Macmillan, New York, 1965; R. W. Ryall, 'Neuropoisons, Their Pathophysiological Actions', ed. by L. L. Simpson and D. R. Curtis, Plenum Press, New York, 1974, Vol II.; A. M. P. Koskinen and H. Rapoport, J. Med. Chem., 1985, 28, 1301 and references cited therein.

2. C. G. Chavdarian, E. B. Sanders and R. L. Bassfield, J. Org. Chem., 1982, 47, 1069; J. I. Seeman, H. V. Secor, C. G. Chavdarian, E. B. Sanders, R. L. Bassfield and J. F. Whidby, J. Org. Chem., 1981, 46, 3040; E. B. Sanders, H. V. Secor and J. I. Seeman, J. Org. Chem., 1978, 43, 324; J. I. Seeman, Synthesis, 1977, 498; C. G. Chavdarian, J.

I. Seeman and J. B. Wooten, J. Org. Chem., 1983, 48, 492; C. G. Chavdarian and J. I. Seeman, Tetrahedron Lett., 1982, 2519; J. I. Seeman, L. E. Clawson, and H. V. Secor, Synthesis, 1985, 953.

3. For a recent general review on nicotine chemistry, see: J. I. Seeman, Heterocycles, 1984, 22, 165.

4. H. V. Secor, C. G. Chavdarian and J. I. Seeman, Tetrahedron Lett., 1981, 3151; J. I. Seeman, H. V. Secor, C. G. Chavdarian, C. R. Howe and L. W. Morgan, J. Org. Chem., 1983, 48, 4899.

5. E. Späth and H. Bretschneider, Chem. Ber., 1928, 61B, 327.

6. M. W. Hu, W. E. Bondinell and D. Hoffmann, J. Labelled Compd., 1974, 10, 79.

7. R. F. Borch, M. D. Bernstein and H. D. Durst, J. Am. Chem. Soc., 1971, 93, 2897.

8. R. F. Borch and A. I. Hassid, J. Org. Chem., 1972, 37, 1673.

9. R. R. Fraser, M. Bresse, and T. S. Mansour, J. Chem. Soc., Chem. Commun., 1983, 620; R. A. Cox, L. M. Druet, A. E. Klausner, T. A. Modro, P. Wan, and K. Yates, Can. J. Chem., 1981, 59, 1568; H. O. House, 'Modern Synthetic Reactions', W. A. Benjamin, Inc., 2nd Edition, Menlow Park, CA, 1972, Chapter 9.

10. J. I. Seeman, Chem. Rev., 1983, 83, 83; J. I. Seeman, J. Chem. Ed., 1986, 63, 42. In this discussion, we do not intend to imply that an equilibrium is reached between 5a + 7 $\rightleftarrows$ 15 + 6 in Scheme II chemistry or for the related analogues. Experimental data is not available at this time to compare the rate constants of proton transfer with the rate constants for the condensation reactions.

11. For previous syntheses of 17, see: G. Büchi, U. Hochstrasser, and W. Pawlak, J. Org. Chem., 1973, 38, 4348. For a structure proof of 18 via its oxime, see: K. Kotera and K. Kitahonoki, Org. Syn., Coll. Vol. 5, 1973, 83.

12. R. Häner, T. Laube, and D. Seebach, J. Am. Chem. Soc., 1985, 107, 5396.

13. J. H. Burckhalter and J. H. Short, J. Org. Chem., 1958, 23, 1281.

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