Preparation of Hydroxyalkyl-Substituted Nicotinoids

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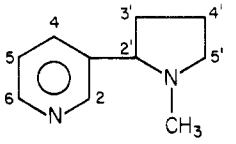
Received November 19, 1985

The synthesis of a series of hydroxyalkyl-substituted nicotine analogues is reported. Included in this series are four pyridine-substituted analogues [4- and 6-(hydroxymethyl)nicotine, 6-(2-hydroxyethyl)nicotine, and 6-(3-hydroxypropyl)nicotine] and three pyrrolidine-substituted analogues [1′-(2-hydroxyethyl)nornicotine, *trans*-4′-(2-hydroxyethyl)nicotine, and *cis*-5′-(3-hydroxypropyl)nicotine]. These compounds were designed for use as haptens in the radioimmunoassay of tobacco alkaloids.

The synthesis of nicotine (**1**) analogues is important not only in the assessment of structure–reactivity relationships[1] but also in the development of radioimmunoassays (RIA) for tobacco alkaloids.[2] In the development of ligands for RIA, one cannot predict a priori which, if any, candidates will eventually lead to the required specificities. With this in mind, we have prepared a group of seven hydroxy-substituted nicotines, **2**–**8**. Taken together with the previously synthesized *trans*-3′-(hydroxymethyl)nicotine[3] and 4′-hydroxy- and 4′-(hydroxymethyl)nicotines[4] the accumulated set of hydroxynicotines now represents a wide assortment of pyridine- and pyrrolidine-substituted compounds.



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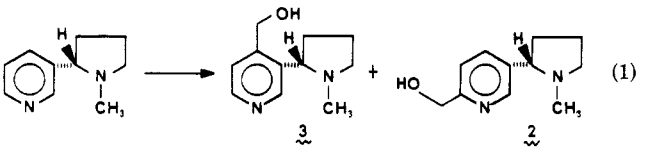
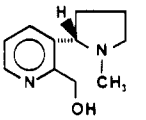
In 1978, Itokawa et al.[5] reported that radical hydroxymethylation of nicotine led to 6-(hydroxymethyl)nicotine (**2**). We have reexamined this reaction and have obtained **2**, as reported, as well as a low yield of the isomeric 4-(hydroxymethyl)nicotine (**3**) (eq 1). We saw no evidence for 2-(hydroxymethyl)nicotine (**9**) as a product in the reaction.[6]

The homologous (hydroxyalkyl)nicotinoid, 6-(2-hydroxyethyl)nicotine (**4**), was readily prepared in one step from 6-methylnicotine (**10**) in 42% yield (Scheme I). Nicotinoid **10** is available as a racemate via the condensation of ethyl 6-methylnicotinate and the lithium anion of *N*-(trimethylsilyl)pyrrolidinone[8] or in high optical purity



(1)

3 **2**



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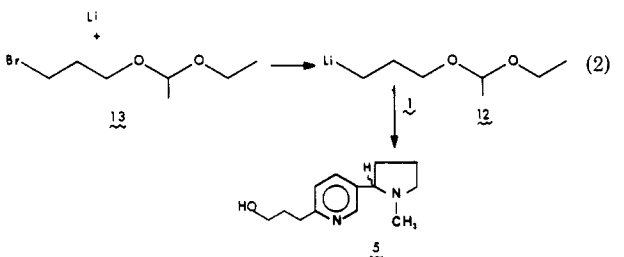
via free radical alkylation of optically pure (*S*)-(−)-nicotine with methyl radicals.[5,7] Thus, treatment of racemic **10** with 0.95 equiv of *n*-butyllithium in THF at −20 °C formed the desired picolyl anion[9] **11** which was directly allowed to react with gaseous formaldehyde (Scheme I).

The hydroxypropyl homologue **5** was prepared by using Eaton's organolithium reagent **12**,[10] obtained from bromo acetal **13** (eq 2). Addition of (*S*)-(−)-nicotine to a pre-



(2)

13 **1** **12**

5

formed mixture of **12** in ether in the presence of tetramethylethylenediamine at −70 °C led, after air oxidation, to (*S*)-(−)-6-(hydroxypropyl)nicotine (**5**). Although the specific rotation of **5** was moderately high ($[\alpha]_D$ −120°) compared to that of nicotine ($[\alpha]_D$ −169°), we suspect that **5** is partially racemized, based on our previous results on the alkyllithium reactions with optically pure nicotine.[7,11]

Nicotinoids substituted in their pyrrolidine ring were synthesized as shown in Scheme II from one of two readily available natural products: nornicotine (**14**), both enan-

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(2) (a) Shibagaki, M.; Matsushita, H.; Shibata, S.; Saito, A.; Tsujino, Y.; Kaneko, H. *Heterocycles* **1982**, *19*, 1641–1645. (b) Langhals, E.; Langhals, H.; Rüchardt, C. *Liebigs Ann. Chem.* **1983**, 330–333. (c) Langone, J. J.; Van Vanakis, H.; Levine, L. *Acc. Chem. Res.* **1975**, *8*, 335–342. (d) Castro, A.; Monji, N.; Ali, H.; Yi, M.; Bowman, E. R.; McKennis, H., Jr. *Eur. J. Biochem.* **1980**, *104*, 331–340.

(3) Cushman, M.; Castagnoli, N., Jr. *J. Org. Chem.* **1972**, *37*, 1268–1271.

(4) Edwards, W. B., III. U.S. Pat. 4 332 945, 1982.

(5) Itokawa, H.; Inaba, T.; Haruta, R.; Kameyama, S. *Chem. Pharm. Bull. Jpn.* **1978**, *26*, 1295–1297.

(6) It is interesting to note that Itokawa et al.[5] have reported that the methyl radical alkylation of nicotine led to a mixture of 4- and 6-methylnicotine, while on reexamination of this reaction we observed 2-methylnicotine as an additional major product.[7]

(7) (a) Secor, H. V.; Chavdarian, C. G.; Seeman, J. I. *Tetrahedron Lett.* **1981**, *22*, 3151–3154. (b) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G., Howe, C. R.; Morgan, L. W. *J. Org. Chem.* **1983**, *48*, 4898–4904. (c) Seeman, J. I.; Clawson, L. E.; Secor, H. V. *Synthesis* **1985**, 953–955.

(8) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L; Whidby, J. F. *J. Org. Chem.* **1981**, *46*, 3040–3048.

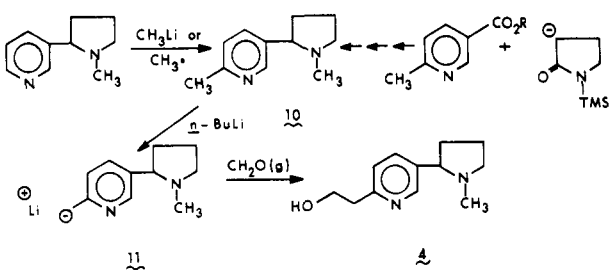
(9) Micetich, R. G. In *Pyridine and Its Derivatives*; Abramovitch, R. A., Ed.; Wiley: New York, 1974; Vol. 14, Part 2, pp 315–317.

(10) Eaton, P. E.; Cooper, G. F.; Johnson, R. C.; Mueller, R. H. *J. Org. Chem.* **1972**, *37*, 1947–1950.

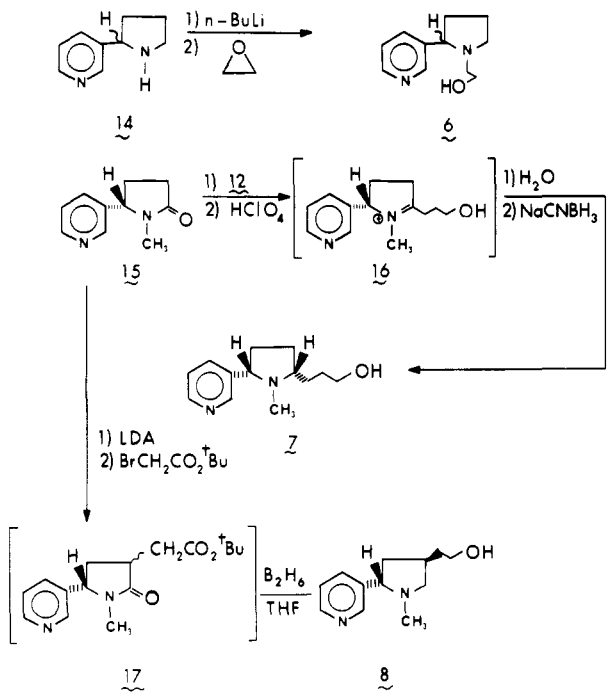
(11) Seeman, J. I.; Chavdarian, C. G.; Kornfeld, R. A.; Naworal, J. D. *Tetrahedron* **1985**, *41*, 595–602.

0022-3263/86/1951-1548$01.50/0

Scheme I



Scheme II



tiomers of which can be prepared in optically pure form;[12] or (*S*)-(−)-cotinine (**15**), synthesized from (*S*)-(−)-nicotine as a pure enantiomer in two simple steps.[13] As shown in Scheme II, the (hydroxyethyl)nornicotine analogue **6** was readily prepared by reacting nornicotine with *n*-butyllithium followed by treatment with ethylene oxide. Bulb-to-bulb distillation led to **6** in 52% yield. Furthermore, cotinine readily reacts[14] with Eaton's organolithium reagent **12**. The resultant iminium salt **16** was directly reduced with sodium cyanoborohydride to give the 5′-(3-hydroxypropyl)nicotines in 22% yield as a mixture of diastereomers. The reaction proceeded with high stereoselectivity (>9:1) as adjudged by ^{1}H and ^{13}C NMR spectroscopy. The major diastereomer obtained was assigned the stereochemistry shown as **7** by examining the ^{1}H NMR spectrum of the diacid salt obtained by careful deuteration with trifluoroacetic acid-*d* (TFA-*d*).[15] We had previously found[16,17] that treatment of *cis*- and *trans*-5′-methylnicotines (**18** and **19**) with TFA-*d* led to a single dideuterated salt **20** from **18** and two dideuterated salts **21** and **22** from **19** (Scheme III). In the case of **7**, only a single

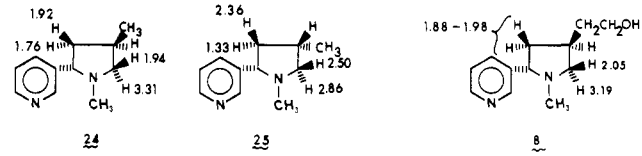
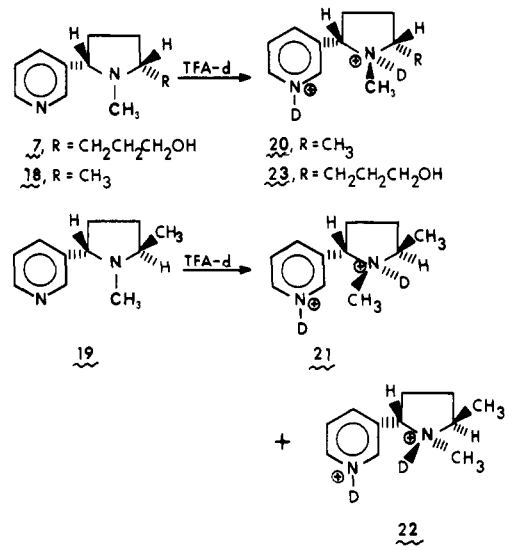


Figure 1. Relevant ^{1}H NMR resonances (in ppm) are indicated alongside the appropriate protons.

Scheme III



product was observed, assigned as **23**.

Cotinine could also be alkylated with *tert*-butyl bromoacetate to form the corresponding lactam ester **17** which was directly reduced with diborane in THF to give the diastereomeric 4-(hydroxyethyl)nicotines in 48% overall yield. Again, the reaction occured with high stereoselectivity (>9:1), as determined by ^{1}H NMR analysis. The predominant diastereomer was assigned to be **8** by comparison of its ^{1}H NMR spectrum with those of *trans*- and *cis*-4′-methylnicotines **24** and **25**.[16,17] The crucial proton NMR resonances for **8**, **24**, and **25** are shown in Figure 1.

The assignments for **24** and **25** were made previously[17] by careful evaluation of the chemical shifts and coupling constants for all the protons in the three pairs of *cis*- and *trans*-monomethylnicotinoids (3′-, 4′-, and 5′-methylnicotines).[16] The proton assignments for **8** were made by heteronuclear carbon–proton correlation experiments, proton decoupling experiments, and by comparison with **24** and **25**. The most important observation is that for **8**, the two 3′-protons have nearly identical chemical shifts while the two 5′-protons have different (>1.3 ppm) chemical shifts. The assignment for **8** is consistent with only the *R* configuration at C-4′.

In conclusion, a variety of hydroxy-substituted nicotine analogues have now been prepared.[18] We anticipate that many of these compounds will find use for a wide variety of analytical procedures in the expanding chemistry of the tobacco alkaloids.[1d,e]

Experimental Section

Methods and Materials. ^{1}H 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. Mass spectra were obtained on a Finnigan 3300 GC/MS/DS-6000. TLC were performed on Analtech/Silica/Gel

(12) (a) Seeman, J. I.; Chavdarian, C. G.; Secor, H. V. *J. Org. Chem.* **1985**, *50*, 5419–5421. (b) See also: Jacob, P., III. *J. Org. Chem.* **1982**, *47*, 4165–4167.

(13) Bowman, E. R.; McKennis, H., Jr. *Biochem. Prep.* **1963**, *10*, 36–39.

(14) For previous nucleophilic additions to the carbonyl group of cotinine, see: (a) Leete, E. *J. Org. Chem.* **1976**, *41*, 3438–3441. (b) Sanders, E. B.; Osdene, T. S.; DeBardeleben, W. F. *J. Org. Chem.* **1975**, *40*, 2848–2849.

(15) Seeman, J. I.; Whidby, J. F. *J. Org. Chem.* **1976**, *41*, 1585–1590.

(16) Seeman, J. I.; Secor, H. V., unpublished results.

(17) Cox, R. H., unpublished results.

(18) For a recent report on the first preparation of 4-aminonicotinoids, see: Shibagaki, M.; Matsushita, H.; Kaneko, H. *Heterocycles* **1985**, *23*, 1681–1684.

GF plates, 250 μm. Chromatotron plates were made with Kieselgel 60 PF_{254} gipshaltig (EM Reagents). Optical rotations were determined on a Perkin-Elmer Model 241 MC polarimeter at 20 °C. Elemental analyses were obtained from Galbraith Laboratories, Knoxville, TN.

(*S*)-(−)-6-(Hydroxymethyl)nicotine (2) and (*S*)-(−)-4-(Hydroxymethyl)nicotine (3). A solution of 20.0 g (0.123 mol) of (*S*)-(−)-nicotine and 5.61 g (0.0246 mol) of ammonium peroxydisulfate in 60 mL of water, 120 mL of methanol, and 6.6 mL of concentrated sulfuric acid was heated under reflux for 26 h. The reaction mixture was cooled to 5 °C and treated with 30 mL of 50% KOH to give a pH of ca. 10. The resulting insolubles were removed by filtration and the filter cake was washed with water and $CHCl_3$. The aqueous phase of the filtrate was further basified (50% KOH) and extracted with $CHCl_3$. The combined chloroform extracts were dried (Na_2SO_4) and the solvent removed. The oil obtained was distilled Kugelrohr) to give a forerun (80 °C, 0.025 mm) consisting of starting material; the crude product mixture (3.32 g) was then collected (80–115 °C, 0.025 mm). Removal of residual nicotine was carried out on a 1.1-g portion of the oil using a Harrison Chromatotron with a 4-mm thickness silica gel plate and petroleum ether–acetone–triethylamine eluate (80:20:8). Further chromatography using the Chromatotron was then carried out using chloroform–ethanol–ammonium hydroxide (92.5:7:0.5). The first band eluted from three independent runs were combined and concentrated, dried (Na_2SO_4), and distilled (Kugelrohr) to give 220 mg (0.9%) of pure (*S*)-(−)-4-(hydroxymethyl)nicotine (**3**) as a colorless oil which spontaneously crystallized: bp 120 °C (0.025 mm); mp 90–91 °C; R_f 0.18 (80:20:8 petroleum ether/acetone/Et_3N); R_f 0.65 (85:14:1 $CHCl_3$–EtOH–NH_4OH); $[\alpha]_D$ −59.8° (*c* 0.739, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.9–2.4 (m, 5), 2.17 (s, 3), 3.1–3.8 (m, 2), 4.3 (d, *J* = 14 Hz, 1), 5.0 (d, *J* = 14 Hz, 1), 7.2 (d, *J* = 6 Hz, 1), 8.5 (d, *J* = 5 Hz, 1), 8.55 (s, 1); dipicrate, mp 160–161 °C.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.81; H, 8.63; N, 14.48.

The second bands eluted from the three runs were combined, concentrated, dried (Na_2SO_4), and distilled (Kugelrohor; 120 °C at 0.05 mm) to give 1.69 g (7.1%) of colorless (*S*)-(−)-6-(hydroxymethyl)nicotine (**2**): bp 120 °C (0.05 mm); R_f 0.48 (85:14:1 $CHCl_3$–EtOH–NH_4OH); $[\alpha]_D$ −160.4° (*c* 0.7, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.75–2.65 (m, 5), 2.13 (s, 3), 3.10–3.50 (m, 2), 7.42 (d, *J* = 8 Hz, 1), 7.78 (dd, *J* = 8, 2 Hz, 1), 8.48 (d, *J* = 2 Hz, 1); ^{13}C NMR ($CDCl_3$) δ 22.47, 35.01, 40.30, 56.94, 64.47, 68.69, 120.83, 135.92, 137.16, 148.31, 159.45.

Precise mass determined for M^+: calcd $C_{11}H_{16}N_2O$ 192.1263, found, 192.1262.

The dipicrate was formed in EtOH, mp 157–158 °C.

Anal. (dipicrate) Calcd for $C_{23}H_{22}N_8O_{15}$: C, 42.46; H, 3.41; N, 17.23. Found: C, 42.39; H, 3.44; N, 17.22.

(*R,S*)-6-(2-Hydroxyethyl)nicotine (4). To a stirred solution of 1.606 g (15.90 mmol) of diisopropylamine in 50 mL of tetrahydrofuran (THF) under nitrogen at −25 °C was added 5.91 mL (14.77 mmol) of 2.5 M *n*-butyllithium in hexane. The solution was stirred at −25 °C for 15 min and then cooled to −70 °C. A solution of 2.0 g (11.36 mmol) of *R,S*)-6-methylnicotine[8] (**13**) in 10 mL of THF was then added over 10 min and the resulting clear, reddish-colored solution was stirred at −70 °C for 20 min. The solution was allowed to warm to −25 °C and gaseous formaldehyde (generated from 5.11 g of paraformaldehyde heated to 180–190 °C) was swept with the aid of a dry nitrogen stream into the anion solution with the temperature being allowed to rise to 0 °C during the addition. Scrupulous care was taken to avoid any trace of oxygen which could also react with the anion. The solution, which quickly decolorized to pale yellow, was stirred for 30 min at 0 °C and 30 min at 20–25 °C, and then quenched with 25 mL of 10% HCl. The resultant solution was washed with ether and the aqueous phase was basified (NaOH) and in turn extracted with ether and methylene chloride. The combined extracts were dried ($MgSO_4$) and evaporated to give 1.86 g of crude **4** as an orange-colored viscous oil. Kugelrohr distillation [100 °C (0.25 mm)] removed the bulk of unreacted 6-methylnicotine. The residue was then distilled bulb-to-bulb at 105–125 °C (0.25 mm) to give 1.184 g of a nearly colorless viscous oil contaminated with small amounts of starting material and possibly 6-(hydroxymethyl)-nicotine as a byproduct. An 800-mg portion was purified by use of a Harrison Chromatotron utilizing a rotor with 2-mm-thick silica gel and a solvent system of $CHCl_3$–EtOH–NH_4OH (85:14:1). The fraction containing the product was evaporated, dried ($MgSO_4$) and distilled bulb-to-bulb to give 662 mg (42%) of (*R,S*)-6-(2-hydroxyethyl)nicotine (**4**) as a clear, colorless, viscous oil: bp 100–110 °C (0.1 mm); R_f 0.45 (85:14:1, $CHCl_3$–EtOH–NH_4OH); ^1H NMR ($CDCl_3$) δ 1.4–2.4 (m, 5), 1.95 (s, 3), 2.75–3.3 (m, 2), 2.90 (t, *J* = 6 Hz, 2), 4.08 (t, *J* = 6 Hz, 2), 4.38 (br s, 1, OH), 7.0 (d, *J* = 8 Hz, 1), 7.5 (dd, *J* = 8, 2 Hz, 1), 8.3 (d, *J* = 2 Hz, 1); ^{13}C NMR ($CDCl_3$) δ 22.75, 35.32, 39.14, 40.51, 57.18, 61.98, 68.84, 123.62, 135.86, 136.71, 148.76, 159.63. The dipicrate derivative was prepared in EtOH, mp 150–152 °C.

Anal. (dipicrate) Calcd for $C_{24}H_{24}N_8O_{15}$: C, 43.37; H, 3.61; N, 16.87. Found: C, 43.26; H, 3.69; N, 16.60.

(*S*)-6-(3-Hydroxypropyl)nicotine (5). A suspension of 440 mg (63.4 mmol) of lithium wire in 22 mL of ether was reacted with 5.36 g (25.4 mmol) of **13** according to Eaton et al.[10] to give the organolithium reagent **12**. The stirred reaction mixture was cooled to −70 °C and 15 mL of *N,N,N′,N′*-tetramethylethylenediamine was added followed by 2.02 g (12.47 mmol) of (*S*)-nicotine. Stirring was continued at −70 °C for 1 h and then at room temperature for 15 h. The reaction mixture was diluted with ether and filtered to remove unreacted lithium. The residue remaining after concentration of the filtrate was taken up in 20 mL of 3 N HCl, stirred first in an ice bath for 1 h and then overnight at room temperature. The solution was washed with ether, basified (50% KOH), and extracted with ether. The ether extract was dried (Na_2SO_4), filtered, and concentrated to give 1.76 g of a tan oil which was distilled (Kugelrohr). The forerun (bp up to 80 °C (0.025 mm)) was discarded and a 525-mg fraction (bp 80–150 °C (0.025 mm)) was collected. This material was chromatographed on a Harrison Chromatotron using a 4-mm-thick silica gel plate and $CHCl_3$–EtOH–NH_0H (85:14:1) eluate to give 326 mg (12.0%) of distilled (Kugelrohr) (*S*)-6-(3-hydroxypropyl)nicotine (**5**): bp 135 °C (0.025 mm); R_f 0.36 (85:14:1 $CHCl_3$–EtOH–NH_4OH); *c* 0.59, $[\alpha]_D$ −120° (*c* 0.59, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.25–2.4 (m, 9), 2.13 (s, 3), 2.90 (t, *J* = 7.0 Hz, 2), 3.3–3.7 (m, 3), 7.13 (d, *J* = 8 Hz, 1), 7.68 (dd, *J* = 8, 2 Hz, 1), 8.36 (d, *J* = 2 Hz, 1).

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.67; H, 9.22; N, 12.92.

(*R,S*)-1′-(2-Hydroxyethyl)nornicotine (6). To a solution of 4.0 g (0.027 mmol) of (*R,S*)-nornicotine in 50 mL of methanol at 0 °C under nitrogen was added 1.49 mL (0.0297 mol) of ethylene oxide. The solution was stirred at 0 °C for 30 min and at room temperature for 5 h. The solution was again cooled to 0 °C, and an additional 1.49 mL of ethylene oxide was added. The solution was then stirred at 0 °C for 10 min and at room temperature for 16 h. The solution was evaporated to a viscous dark oil. Two bulb-to-bulb distillations of the oil [oven temperature 100–115 °C (0.1 mm)] afforded 2.70 g (52%) of (*R,S*)-1′-(2-hydroxyethyl)nornicotine (**6**): ^1H NMR ($CDCl_3$) δ 1.50–3.13 (m, 8), 3.2–3.9 (m, 4), 7.25 (ddd, *J* = 8, 5, 2 Hz, 1), 7.73 (dt, *J* = 8, 2 Hz, 1), 8.49 (dd, *J* = 5, 2 Hz, 1), 8.51 (d, *J* = 2 Hz, 1); ^{13}C NMR ($CDCl_3$) δ 22.44, 34.63, 53.27, 55.50, 59.78, 67.24, 123.84, 135.08, 139.38, 148.96, 149.75.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.60; H, 8.46; N, 14.47.

(2′*S*,5′*R*)-5′-(3-Hydroxypropyl)nicotine (7). To a magnetically stirred solution of 2.0 g (11.36 mmol) of (*S*)-cotinine[13] in 30 mL of tetrahydrofuran under an argon atmosphere and which was cooled to −55 °C to −65 °C was added 23 mL of a 1 M solution of the organolithium reagent **12**.[10] After being stirred for 30 min at −55 °C to −65 °C the solution was treated dropwise with 3 mL of EtOH, warmed to 0 °C, and treated with 15 mL of brine and 50 mL of ether keeping the temperature of 0–5 °C. During the following workup, the materials were kept cold and the procedures were performed swiftly. The ether phase was separated and the aqueous phase extracted with ether. The combined etherereal extracts, maintained at 0–5 °C, were dried ($MgSO_4$), filtered, and treated with 3.4 mL of a 1:1 solution of 70% perchloric acid and EtOH. The resulting gummy precipitate was separated from the supernatant, triturated with ether, and taken up in 30 mL of methanol. The methanolic solution was treated with 2.0 g (31.8 mmol) of sodium cyanoborohydride and stirred overnight. A trace of bromcresol green was added to the clear colorless solution along with sufficient 2 N HCl in MeOH

to impart a yellow color. Stirring was continued for 1 h and the resulting solution, showing no change in appearance, was then concentrated on a rotary evaporator. The residue was taken up in 30 mL of 3 N HCl and stirred for 1 h at room temperature, basified (50% KOH), and thoroughly extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to give 1.33 g of a colorless oil. Purification was carried out with a Harrison Chromatotron using a 4-mm silica gel rotor and petroleum ether, acetone, and triethylamine (80:50:8) eluate. The solvent was removed under vacuum to afford 550 mg (22%) of (2′*S*,5′*R*)-5-(3-hydroxypropyl)nicotine (**7**) as a clear, colorless viscous oil which could not be distilled without decomposition: R_f 0.56 (80:50:8 petroleum ether–acetone–Et_3N); $[\alpha]_D$ −80.2° (*c* 0.32, CH_2Cl_2); ^{1}H NMR[19] ($CDCl_3$) δ 1.40–1.95 (br m, 8), 2.13 (s, 3), 2.43 (m, 1), 3.18 (m, 1), 3.6 (m, 2), 4.9 (br s, 1, OH), 7.2 (dd, *J* = 8, 2 Hz, 1), 7.6 (dt, *J* = 8, 2 Hz, 1), 8.45 (m, 2); ^{13}C NMR[19] ($CDCl_3$) δ 27.23, 27.68, 29.57, 32.56, 38.09, 62.61, 65.76, 69.65, 123.90, 135.08, 138.66, 148.96, 149.77; dipicrate, mp 128–130 °C.

Anal. (dipicrate) Calcd for $C_{25}H_{26}N_8O_{15}$: C, 44.25; H, 3.86; N, 16.51. Found: C, 44.43; H, 4.02; N, 16.32.

(2′*S*,4′*R*)-4′-(2-Hydroxyethyl)nicotine (8). To a solution of 10.4 mL (0.0741 mol) of diisopropylamine in 200 mL of THF under nitrogen at −20 °C was added 27.5 mL (0.0684 mol) of 2.5 M *n*-butyllithium in hexane such that the temperature did not rise above −20 °C. The solution was stirred keeping the temperature below −20 °C for 10 min; it was then cooled to −70 °C. To the solution was added a solution of 10.0 g (0.057 mol) of (*S*)-cotinine[13] in 50 mL of THF over 15 min. The resultant yellow solution was stirred at −70 °C for 30 min and then added over 20 min via a double-tipped needle to a solution of 10.1 mL (0.0625 mol) of *tert*-butyl bromoacetate in 50 mL of THF at −70 °C. The cloudy mixture was stirred at −70 °C for 15 min and then at room temperature for 16 h. The mixture was quenched with 100 mL of 10% aqueous HCl and washed with 2 × 100 mL of ether. The aqueous layer was basified with concentrated aqueous NaOH and extracted with 3 × 100 mL of ether. The ehtereal layers were combined, dried with $MgSO_4$, and filtered, and the resultant solution was evaporated to yield 7.55 g of a viscous red oil. Purification by the Harrison Chromatotron (silica gel GF plate with 1:1 petroleum ether/acetone eluent) provided 5.88 g (35%) of **17** as a viscous oil which was utilized directly in the next step.

To a solution of 1.183 g (4.08 mmol) of **17** in 45 mL of THF under nitrogen was added 23.1 mL (24.48 mmol) of 1.06 M borane in THF at room temperature. The mixture was heated at reflux for 24 h. After being allowed to cool, the mixture was carefully quenched with 30 mL of 6 N aqueous HCl and then refluxed for 3 h. The mixture was then concentrated to a volume of approximately 25 mL and washed with 4 × 25 mL of ether. The aqueous layer was basified and extracted with 3 × 25 mL of methlene chloride. The organic layers were combined and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to a viscous oil. Bulb-to-bulb distillation [oven temperature 110–120 °C (0.1 mm)] afforded 0.40 g (48%) of (2′*S*,4′*R*)-4′-(2-hydroxyethyl)nicotine (**8**) as a clear, colorless, viscous oil: $[\alpha]^{20}_D$ −136° (*c* 0.434, CH_2Cl_2); ^{1}H NMR[19] ($CDCl_3$) δ 1.66–1.73 (m, 2, CH_2CH_2OH), 1.90–1.97 (m, 2, H-3′), 2.08 (dt, *J* = 9.4, 1 Hz, 1, H-5′a), 2.16 (s, 3, N-CH_3), 2.44–2.51 (m, 1, H-4′), 3.20 (t, *J* = 8.3 Hz, 1, H-2′), 3.37 (dd, *J* = 9.4, 3.4 Hz, 1, H-5′b), 3.67 (t, *J* = 6.9 Hz, 2, CH_2OH), 7.26 (dd, *J* = 7.8, 4.9 Hz, 1), 7.70 (dt, *J* = 7.8, 2.0 Hz, 1), 8.48 (dd, *J* = 4.9, 1), 8.51 (d, *J* = 2.0 Hz, 1); ^{13}C NMR ($CDCl_3$) δ 33.34, 37.90, 40.40, 47.74, 61.37, 63.94, 67.96, 123.61, 134.97, 138.92, 148.43, 149.25; IR (film) 3300 cm^{-1}.

Precise mass determined for M^+: Calcd for $C_{12}H_{18}H_2O$ 206.1419, found 206.1470.

(19) A number of additional weak resonances were observed, assigned to the minor diastereoisomer formed in the reduction step.

Acknowledgment. We thank Drs. R. H. Cox and J. Wooten and R. Bassfield for assistance with the NMR experiments and interpretations; Dr. E. B. Sanders for helpful discussions; A. Donathan for typing the manuscript; C. Nilles for preparing the art work; and one referee for particularly helpful comments.

Synthesis of [3.3]Heterophanes Containing the Pyridine, Furan, and Thiophene Rings by the TosMIC Method[1]

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Received October 4, 1985

[3.3](2,5)- and [3.3](2,6)pyridinophanes as well as [3]metacyclo[3](2,5)furanophane (**20**) and [3]metacyclo[3](2,5)thiophenophane (**23**) have been synthesized by the conventional or modified TosMIC coupling reaction, followed by acid treatment and reduction. ^{1}H NMR data suggest that the stable conformation of the [3.3]metacyclophane-2,11-dione system (**3**, **6**, **19**, and **22**) is anti, whereas that of the [3.3]metacyclophane system (**4**, **7**, **20**, and **23**) is syn. In [3.3](2,5)pyridinophanes (**17a–d**) the average deshielding effects for protons located pseudogeminal and pseudoortho to a nitrogen atom are found to be 0.28 and 0.15 ppm, respectively, as compared to those pseudopara to the nitrogen.

In a previous paper,[2] we reported a new general method for the synthesis of [3.3]cyclophanes. This method takes advantage of the coupling reaction between (*p*-tolylsulfonyl)methyl isocyanide (TosMIC[3]) and an appropriate bis(halomethyl) compound, followed by acid hydrolysis and reduction of the carbonyl groups.[4] We now report an application of this method to the synthesis of [3.3]heterophanes.

Various synthetic methods have been developed to prepare [2.2]heterophanes, and their chemistry has been

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