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(24) **Noted Added in Proof.** We have prepared nicotine-*3',3',4',4',5',5'-d*$_6$. NMR analysis of this substance in TFA-*d* substantiates our assignments for **3** and **4** (see Figures 4–6).

Novel Synthesis of Imidazole Derivatives from 1-Phenyl-1,2-propanedione and Methylguanidine

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Received December 2, 1975

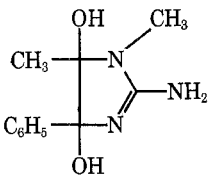
The reaction of 1-phenyl-1,2-propanedione (I) with methylguanidine (II) at −10 °C yielded 2-amino-4,5-dihydroxy-1,5-dimethyl-4-phenylimidazoline (IIIa) in methanol and 2-amino-4,5-dihydroxy-1,4-dimethyl-5-phenylimidazoline (IIIb) in ethanol. Catalytic hydrogenation of the reaction mixture of I and II in methanol produced 2-methylamino-4(5)-methyl-5(4)-phenylimidazole (VIc). IIIa and IIIb were converted to 2-amino-5-chloromethyl-1-methyl-4-phenyl- and 2-amino-4-chloromethyl-1-methyl-5-phenylimidazoles (Va and Vb) by concentrated hydrochloric acid treatment. Va and Vb produced 2-amino-1,5-dimethyl-4-phenyl- and 2-amino-1,4-dimethyl-5-phenylimidazoles (VIa and VIb) by catalytic hydrogenation and 2-amino-5-ethoxymethyl-4-phenyl- and 2-amino-4-ethoxymethyl-5-phenylimidazoles (VIIa and VIIb) by ethanolysis. 2-Amino-5-hydroxymethyl-1-methyl-4-phenylimidazole (VIIIa) was obtained by hydrolysis of Va in dilute hydrochloric acid.

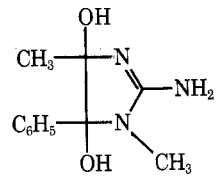
We have previously reported that 2-(disubstituted amino)-4-methyl-5-phenyl-4*H*-imidazoles, produced in good yields by the reaction of 1-phenyl-1,2-propanedione with 1,1-disubstituted guanidines in methanol at −10 °C, are useful as intermediates for synthesizing various 2-(disubstituted amino)imidazoles.[1] We have now explored the synthesis of 2-amino-1-methyl- and 2-methylaminoimidazoles by the application of this method to methylguanidine.

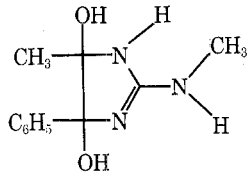
The reaction of 1-phenyl-1,2-propanedione (I) and methylguanidine (II) in methanol at −10 °C yielded a white powder, mp 54.5–55 °C dec (A-1), with molecular formula $C_{11}H_{15}N_3O_2{\cdot}CH_3OH$. This material showed absorption bands at 1650 and 1570 cm^{-1}, which may be assigned to a 4*H*-imidazole ring.[1] When the reaction mixture was hydrogenated in the presence of Pt catalyst without isolation of A-1, 2-methylamino-4(5)-methyl-5(4)-phenylimidazole (VIc) was obtained. The NMR spectrum of VIc exhibited a doublet for the *N*-methyl protons due to coupling with the proton on the same nitrogen atom. Ir and mass spectral and elemental analyses were consistent with this structure. Accordingly, one of the possible structures for A-1 was 2-methylamino-4*H*-imidazole (IV) but this structure was inconsistent with the observed mass spectral fragmentation pattern. The mass spectrum of A-1 lacked the $M^+ - C_6H_5CN$ fragment ion characteristic for 2-(disubstituted amino)-4*H*-imidazoles.[1] The abundant ions in the mass spectrum of A-1 were those of *m/e* 105 (22%, $C_6H_5C{\equiv}O^+$) and 104 (59%, $C_6H_5C{\equiv}N^+H$). Neither ion is conspicuous in 2-(disubstituted amino)-4*H*-imidazoles[1] but the former ion is abundant in 2-alkyl-4,5-dihydroxyimidazolines.[2] The mass spectral behavior of the latter compound is consistent with the fact that they are liable to decompose to starting materials.[3,4] The above spectral evidence strongly suggests 4,5-dihydroxyimidazoline (IIIc) as the structure of A-1; however, additional evidence did not support this structure, but rather the structure IIIa. Measuring NMR and uv spectra of A-1 was impossible because of quick decomposition of A-1 in the usual solvents, although they are obvious methods of establishing the structure of A-1.

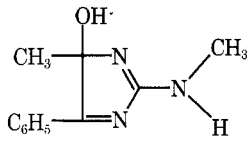
Reaction of I and II in ethanol rather than methanol unexpectedly gave a different unstable compound, mp 45–47 °C dec (B-1). The abundance (86%) of the *m/e* 105 ion in the mass spectrum of B-1 together with elemental and ir analysis suggests either IIIa or IIIb as its structure. The structures of A-1 and B-1 were unraveled from the following series experiments. Treatment of B-1 hydrochloride (prepared by treating B-1 with a small amount of concentrated hydrochloric acid at −10 °C) with concentrated hydrochloric acid at room temperature gave a new compound B-2 as colorless prisms, mp 251 °C dec. The ir, NMR, and mass spectral and elemental analyses of B-2 were consistent with 1-methylimidazole Va or Vb. Treatment of A-1 with concentrated hydrochloric acid at −10 °C and then at room temperature precipitated colorless needles, mp 238–240 °C dec (A-2). On the basis of elemental and spectral data, A-2 was determined to be Va or Vb but isomeric to B-2. The NMR spectrum of A-2 showed an NCH_3 absorption at δ 3.73, which is consistent with that reported for the 1-methyl protons in 1-methylimidazoles (δ 3.42–4.05).[5] The chemical shift of *N*-methyl protons on the 2-amino nitrogen in 2-(disubstituted amino)imidazoles is reported to be δ 2.96–3.30.[1] Moreover, the ir spectrum of A-2 showed a medium peak at 1540 cm^{-1} (δ NH_2).

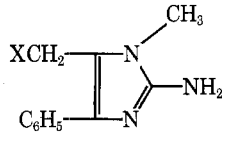
Hydrogenation of A-1 in the presence of Pt catalyst yielded pale yellow prisms, mp 225 °C dec (A-3). Similar treatment of B-2 afforded yellow plates, mp 226–227 °C dec (B-3). The NMR NCH_3 proton signals for these substances were consistent with the 1-methylimidazole structure. However, in their mass spectra, the relative intensity of the *m/e* 118 ($C_6H_5C{\equiv}N^+CH_3$) fragment ion was 8.3% in B-3 but only 1.2% in A-1. On the other hand, the *m/e* 56 ($CH_3C{\equiv}N^+CH_3$) ion was observed (13%) in A-3 but not in B-3. On the basis of these observations, it was established that A-3 is 2-amino-1,5-dimethyl-4-phenylimidazole (VIa) and B-3 is 2-amino-1,4-

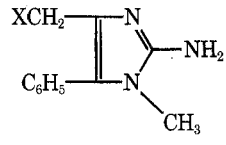

IIIa

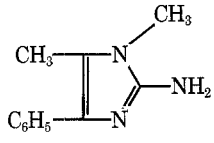

IIIb

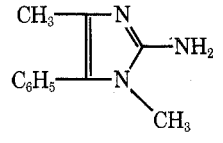

IIIc

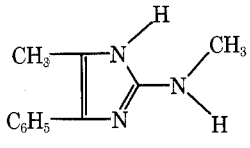

IV


Va, X = Cl
VIIa, X = OC_2H_5
VIIIa, X = OH


Vb, X = Cl
VIIb, X = OC_2H_5

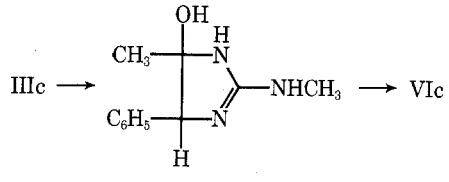

VIa


VIb


VIc

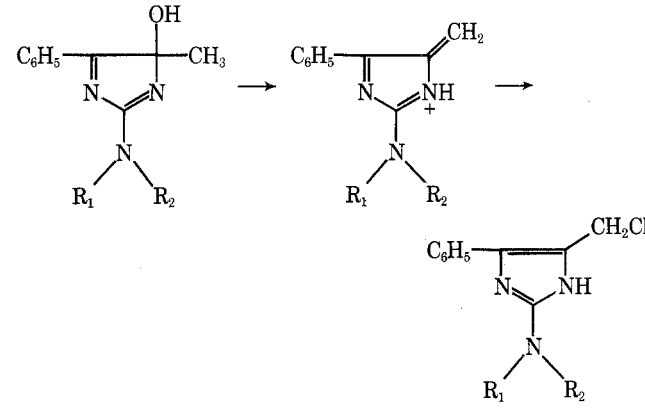
dimethyl-5-phenylimidazole (VIb). This is the first synthesis of two isomeric 1-substituted 2-aminoimidazoles having two different substituents at the 4 and 5 positions. From the foregoing discussions it is concluded that A-2 is 2-amino-5-chloromethyl-1-methyl-4-phenylimidazole (Va) and B-2 is 2-amino-4-chloromethyl-1-methyl-5-phenylimidazole (Vb). Accordingly A-1 is 2-amino-1,5-dimethyl-4,5-dihydroxy-4-phenylimidazoline (IIIa) rather than IIIc and B-1 is 2-amino-1,4-dimethyl-4,5-dihydroxy-5-phenylimidazoline (IIIb).

IIIa is stable at room temperature for 1 month, but IIIb easily decomposes to a brown oil within 2–3 h. This might be ascribed to the strain of the ring due to the steric interaction between the 1-CH_3 and 5-phenyl groups. Though 4*H*-imidazole (IV) was not isolated in these experiments, the existence of IV in the reaction mixture is beyond doubt, since hydrogenation of said mixture gave the corresponding reduced compound VIc. It could arise via a benzylic alcohol hydrogenolysis and dehydration of IIIc. However, the formation of VIc

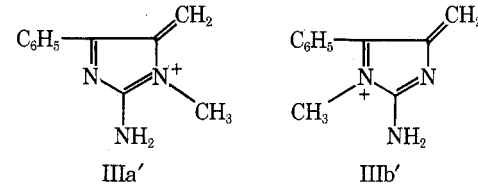


via this route is not probable on the basis of the fact that 2-methoxy-, 2-alkyl-, and 2-aryl-4,5-dihydroxy-4(5)-methyl-5(4)-phenylimidazolines are not amenable to hydrogenation.[6] Interestingly, IIIa was converted to IIIb when suspended in ethanol at −10 °C and similarly IIIb suspended in methanol yielded IIIa. The experimental results described above indicate that the reaction products IIIa, IIIb, IIIc, and IV exist in equilibrium in the reaction mixture of I with II. IIIa and IIIb may be the primary products because of low solubility in their respective reaction solvents.

We have previously reported that a plausible mechanism for the formation of 4(5)-chloromethylimidazoles by the reaction of 2-(disubstituted amino)-4-hydroxy-4*H*-imidazoles with concentrated hydrochloric acid is the formation of protonated diazafulvene followed by nucleophilic attack of chloride ion at the 6 position of the diazafulvene.[1]



The mechanism of formation of Va and Vb from IIIa and IIIb is analogous to the one mentioned above, since protonation and dehydration of IIIa and IIIb may produce cations IIIa′ and IIIb′


IIIa′ IIIb′

It is known[7,8] that 4(5)-chloromethylimidazoles are highly reactive and their hydrolysis proceeds through an intermediate carbonium cation (protonated diazafulvene) rather than a neutral diazafulvene. Va and Vb were also highly reactive and heating in ethanol at 60 °C in a short time easily gave the corresponding 5(4)-ethoxymethylimidazoles (VIIa and VIIb). Hydrolysis of Va with dilute hydrochloric acid afforded 5(4)-hydroxymethylimidazole (VIIIa) in good yield but VIIIb was not obtained in the case of Vb. Hydroxymethyl compound VIIIa changed to Vb by treatment with concentrated hydrochloric acid.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were obtained on a Hitachi spectrophotometer EPI-G_2 as KBr tablets and the following abbreviation were used: s = strong; m = medium; v = very; sh = shoulder. NMR spectra were obtained on a Varian T-60 (60 MHz) spectrometer or Hitachi R-24 (60 MHz) spectrometer in the solvent indicated. Chemical shifts are reported relative to Me_4Si. The mass spectra were determined on a Japan Electron Optics JMS-OIS high-resolution mass spectrometer operating with an ionizing energy of 70 eV by the direct inlet procedure.

1-Methylguanidine (II). 1-Methylguanidine hydrosulfate ($\frac{1}{2}H_2SO_4$)[9] (0.265 g, 3 mmol) was dissolved in a solution of 0.112 g (2.8 mmol) of sodium hydroxide in 10 ml of methanol, the precipitated sodium sulfate was filtered off, and the filtrate was concentrated to dryness under reduced pressure. The residue was extracted with 6 ml of 2-propanol and the extract was concentrated to dryness under reduced pressure to give 0.187 g (92%) of II, hygroscopic needles, mp 123–125 °C.

2-Amino-4,5-dihydroxy-1,5-dimethyl-4-phenylimidazoline (IIIa). A. A solution of 0.365 g (5 mmol) of II in 7 ml of methanol

and a solution of 0.740 g (5 mmol) of 1-phenyl-1,2-propanedione (I) in 3 ml of methanol were cooled at about −10 °C (bath temperature) and mixed. The mixture was stirred at this temperature for 10 min. The resulting precipitates were collected, washed twice with 1 ml each of cold methanol, and dried over phosphorus pentoxide under reduced pressure for 1 day to give a white powder, 0.920 g (72%): mp 54.5–55 °C dec; ir 3650 (w, OH), 3250 (vs, NH), 1650 and 1573 (vs and s, imidazoline ring or NH_2), 1115 (s, C–O), 763 and 698 cm^{-1} (s and s, C_6H_5); mass spectrum *m/e* (rel intensity) 203 (37, $M^+ - H_2O$), 188 (100, $M^+ - H_2O - CH_3$), 148 (9, $C_6H_5COCOCH_3^+$), 105 (22, $C_6H_5C{\equiv}O^+$), 104 (59, $C_6H_5C{\equiv}N^+H$), 57 (84, $CH_3NHC{\equiv}N^+H$), 43 (25, $CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{11}H_{15}N_3O_2{\cdot}CH_3OH$: C, 56.90; H, 7.56; N, 16.59. Found: C, 57.16; H, 7.56; N, 16.98.

B. A solution of 0.22 g (0.7 mmol) of IIIb in 2 ml of cooled methanol was allowed to stand for 30 min at about −10 °C. The resulting precipitates were collected and dried under reduced pressure for 3 h to give 0.05 g (28%) of IIIa. Its ir spectrum was identical with that of IIIa.

2-Amino-4,5-dihydroxy-1,4-dimethyl-5-phenylimidazoline (IIIb). A. A solution of 0.365 g (5 mmol) of II in 6 ml of ethanol and a solution of 0.740 g (5 mmol) of I in 2 ml of ethanol were cooled at about −10 °C (bath temperature) and mixed. The mixture was maintained at this temperature for 30 min. The resulting precipitates were collected, washed with 10 ml of cold ethanol and then with 10 ml of cold ether, and dried over phosphorus pentoxide under reduced pressure for 1 h below 25 °C to give colorless needles, 0.925 g (64%): mp 45–47 °C dec; ir 3220 (s, NH), 1680, 1640, and 1595 (s, s, and vs, imidazoline ring), 1585 (vs, ring or NH_2), 1130 (s, C–O), 760 and 700 cm^{-1} (s and s, C_6H_5); mass spectrum *m/e* (rel intensity) 203 (46, $M^+ - H_2O$), 188 (100, $M^+ - H_2O - CH_3$), 148 (7, $C_6H_5COCOCH_3^+$), 105 (86, $C_6H_5C{\equiv}O^+$), 104 (66, $C_6H_5C{\equiv}N^+H$), 103 (25, $C_6H_5C{\equiv}N^+$), 57 (75, $CH_3NHC{\equiv}N^+H$), 43 (29, $CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{11}H_{15}N_3O_2{\cdot}\frac{3}{2}C_2H_5OH$: C, 57.91; H, 8.43; N, 14.47. Found: C, 57.30; H, 8.05; N, 14.34.

B. A suspension of 0.20 g (0.8 mmol) of IIIa in 7.3 ml of cooled ethanol was allowed to stand for 4 h at about −10 °C. The resulting precipitates were collected and dried over silica gel for 3 h in an evacuated glass tube kept in a refrigerator to give 0.06 g (21%) of IIIb. Its ir spectrum was identical with that of IIIb.

IIIb HCl. To 1.01 g (3.5 mmol) of IIIb cooled at about −10 °C was added 1.8 ml of cooled concentrated hydrochloric acid and the reaction mixture maintained at this temperature for 30 min. The resulting precipitates were filtered, washed with 0.5 ml of cold concentrated hydrochloric acid, and dried over phosphorus pentoxide under reduced pressure for 1 day at room temperature to give 0.36 g (40%) of a white powder: mp 111 °C sinter, 126 °C dec; ir 3300 and 3200 (vs sh and vs, NH and OH), 1685 and 1620 (vs and m, imidazolinium ring), 1590 (s, NH_2 or imidazolinium ring), 1140, 1120, and 1100 (m, m, and s, C-O), 750 and 695 cm^{-1} (s and s, C_6H_5); mass spectrum *m/e* (rel intensity) 148 (30, $C_6H_5COCOCH_3^+$), 105 (100, $C_6H_5C{\equiv}O^+$), 77 (74, $C_6H_5^+$), 73 (10, $HN{=}C(NH_2)NHCH_3^+$), 43 (25, $CH_3C{\equiv}O^+$); NMR (CD_3OD) δ 1.00 (s, 3, CH_3), 2.83 (s, 3, NCH_3), 7.38 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{15}N_3O_2{\cdot}HCl$: C, 51.26; H, 6.25; N, 16.30. Found: C, 51.02; H, 5.97; N, 16.29.

2-Amino-5-chloromethyl-1-methyl-4-phenylimidazole (Va) Hydrochloride. A. To IIIa (1.26 g, 5 mmol) cooled at about −10 °C was added 5.3 ml of cooled, concentrated hydrochloric acid and the mixture stirred for 2–3 min at this temperature. Then the reaction mixture was allowed to stand for 1 h at room temperature. The resulting precipitates were collected on a glass filter, washed three times with 0.7 ml each of concentrated hydrochloric acid, and dried over phosphorus pentoxide to yield 1.14 g (82%) of Va $HCl{\cdot}H_2O$, colorless needles: mp 238–239 °C dec; ir 3370, 3300, and 3150 (s, s, and vs, NH_2), 1680 (vs, imidazolium ring), 1540 (m, NH_2), 1280 (m, CH_2Cl), 650 cm^{-1} (m, C–Cl); NMR (CF_3COOD) δ 3.73 (s, 3, CH_3N), 4.66 (s, 2, CH_2Cl), 7.60 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}N_3Cl{\cdot}HCl{\cdot}H_2O$: C, 47.83; H, 5.47; N, 15.21. Found: C, 47.80; H, 5.83; N, 15.30.

B. A solution of 25 mg (0.1 mmol) of VIIIa HCl in 0.1 ml of concentrated hydrochloric acid was kept for 10 min at room temperature. The resulting precipitates were collected and dried over phosphorus pentoxide under reduced pressure for 1 day to give 18 mg (66%) of Va $HCl{\cdot}H_2O$, colorless needles, mp 240 °C dec.

2-Amino-4-chloromethyl-1-methyl-5-phenylimidazole (Vb) Hydrochloride. A solution of 0.358 g (1.3 mmol) of IIIb HCl in 0.7 ml of concentrated hydrochloric acid was kept for 20 min at room temperature. The resulting precipitates were collected on a glass filter, washed twice with 0.1 ml each of concentrated hydrochloric acid, and dried over phosphorus pentoxide under reduced pressure for 1 day to give 0.24 g (67%) of Vb HCl, colorless plates: mp 249–250 °C dec; ir 3280 and 3100 (s and vs, NH_2), 1680 (vs, imidazolium ring), 1540 (m, NH_2), 1270 (s, CH_2Cl), 770 and 700 (s and s, C_6H_5), 670 cm^{-1} (s, CCl); NMR (CF_3COOD) δ 3.45 (s, 3, NCH_3) 4.47 (s, 2, CH_2Cl), 7.20–7.78 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}N_3Cl{\cdot}HCl$: C, 51.18; H, 5.08; N, 16.28. Found: C, 51.18; 5.28; N, 16.29.

2-Amino-1,5-dimethyl-4-phenylimidazole (VIa) Hydrochloride. Phenylimidazole Va hydrochloride ($\frac{1}{2}H_2O$) (5.34 g, 20 mmol) obtained by drying Va $HCl{\cdot}H_2O$ at 100 °C in vacuo for 2 h was hydrogenated in 80 ml of dry DMF in the presence of 0.53 g of PtO_2 at room temperature. After completion of the hydrogenation, the catalyst was filtered off, and the solvent was removed by vacuum distillation. The resulting residue was dissolved in 80 ml of water, and a small amount of insoluble substance was filtered off. The filtrate was concentrated to dryness under reduced pressure and dried over phosphorus pentoxide in vacuo for 2 days to give a hygroscopic, yellowish powder. The powder was dissolved in a small amount of 15% methanol in chloroform, and the solution was charged onto a column (made of 175 g of 200 mesh Wako-gel 55 mm diameter) and then eluted with the same solvent mixture. After the fastest yellowish band (110 ml) had been removed, a faintly yellow main band (about 500 ml) was collected, the solvent was removed, and the residue was dried over phosphorus pentoxide under reduced pressure for 1 day to yield 2.64 g (58%) of crude VIa HCl, a hygroscopic, yellowish powder. The powder was dissolved in 21 ml of ethanol and after 40 ml of ether was added the solution was allowed to stand for 5 h at room temperature to give 1.79 g (40%) of VIa HCl, yellowish prisms, mp 223–225 °C dec. One recrystallization from etaanol and ether gave an analytical sample, yellowish prisms: mp 225 °C dec; ir 3100 (vs, NH_2), 1680 (vs, imidazolium ring), 1560 (m, NH_2), 775 and 700 cm^{-1} (s and m, C_6H_5); NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.28 (s, 3, C–CH_3), 3.52 (s, 3, NCH_3), 7.20–7.70 (m, 7, C_6H_5 and NH_2); mass spectrum *m/e* (rel intensity) 187 (100, M^+), 172 (15, $M^+ - CH_3$), 144 (11, $M^+ - NCNH_2 - H$), 131 (12, $M^+ - HN{=}C{=}NCH_3$), 130 (12, $M^+ - HN{=}C{=}NCH_3 - H$), 103 (14, $C_6H_5CN^+$), 56 (13, $CH_3C{\equiv}NCH_3^+$).

Anal. Calcd for $C_{11}H_{13}N_3{\cdot}HCl$: C, 59.06; H, 6.31; N, 18.78. Found: C, 58.87; H, 6.03; N, 18.60. Use of Va $HCl{\cdot}H_2O$ instead of Va $HCl{\cdot}\frac{1}{2}H_2O$ decreased the yield to 30% (crude), because of the formation of VIIIa. Attempted complete dehydration of Va $HCl{\cdot}H_2O$ resulted in decomposition of Va.

2-Amino-1,4-dimethyl-5-phenylimidazole (VIb) Hydrochloride. Phenylimidazole Vb hydrochloride (0.426 g, 1.6 mmol) in 20 ml of THF was hydrogenated in the presence of 0.04 g of PtO_2 at room temperature. After completion of the hydrogenation, 10 ml of methanol was added and the catalyst filtered off. The filtrate was evaporated to dryness and allowed to stand for 1 day at room temperature. To the crystalline residue was added 8 ml of THF and the resulting crystals were collected, washed twice with 1 ml each of THF, and dried over phosphorus pentoxide under reduced pressure for 1 day to give 0.292 g (81%) of VIb HCl, yellowish plates, mp 227–231 °C. One recrystallization from ethanol and ether gave an analytical sample, yellowish plates: mp 228–230 °C dec; ir 3100 (vs, NH_2), 1675 (vs, imidazolium ring), 1560 (m, NH_2), 775 and 715 cm^{-1} (m and s, C_6H_5); NMR ($CDCl_3$) δ 2.15 (s, 3, C–CH_3), 3.47 (s, 3, NCH_3), 7.10–7.45 (m, 5, C_6H_5), 7.53 (s, 2, NH_2); mass spectrum *m/e* (rel intensity) 187 (100, M^+), 172 (25, $M^+ - CH_3$), 144 (13, $M^+ - NCNH_2 - H$), 131 (20, $M^+ - HN{=}C{=}NCH_3$), 130 (13, $M^+ - HN{=}C{=}NCH_3 - H$), 103 (8, $C_6H_5CN^+$).

Anal. Calcd for $C_{11}H_{13}N_3{\cdot}HCl$: C, 59.06; H, 6.31; N, 18.78. Found: C, 58.93; H, 6.15; N, 18.59.

2-Methylamino-4(5)-methyl-5(4)-phenylimidazole (VIc) Hydrochloride. A solution of II (0.14 g, 2 mmol) in 10 ml of methanol and a solution of I (0.29 g, 2 mmol) in 10 ml of methanol were cooled to about −10 °C (bath temperature) and then mixed. The solution was hydrogenated in the presence of 100 mg of PtO_2 while cooling with ice–water. Immediately after completion of the hydrogenation, 0.1 ml of concentrated hydrochloric acid was added to the reaction mixture, the catalyst filtered off, and the filtrate evaporated to dryness under reduced pressure at about 30 °C. The residue was dissolved in 2 ml of ethanol and about 50 ml of ether added until white opacity was observed in the solution. The mixture was kept for 2 weeks in a refrigerator to give 0.19 g (37%) of VIa HCl, colorless needles, mp 185–186 °C. One recrystallization from ethanol and ether in the same manner as above yielded pure VIa HCl: mp 188.5–189 °C; ir 2950 (vs, NH), 1675, 1655, 1625, and 920 cm^{-1} (vs, s sh, m sh, and m, imidazolium ring); NMR ($CDCl_3$) δ 2.40 (s, 3, CH_3), 3.16 (d, J = 5 Hz, 3, CH_3NH), 6.93 (broad q, J = 5 Hz, 1, CH_3NH).

Anal. Calcd for $C_{11}H_{13}N_3{\cdot}HCl$: C, 59.05; H, 6.30; N, 18.78. Found: C, 58.77; H, 6.04; N, 18.86.

2-Amino-5-ethoxymethyl-1-methyl-4-phenylimidazole (VIIa)

Hydrochloride. A solution of 55 mg (0.2 mmol) of Va HCl·H_2O in 10 ml of ethanol was warmed at 60 °C for 5 min and the mixture was concentrated to about 2 ml under reduced pressure. To the concentrate was added 3 ml of ether and the solution was allowed to stand for 1 day. The resulting precipitates were collected by filtration, washed with 5 ml of ether, and dried over phosphorus pentoxide under reduced pressure to give 45 mg (80%) of VIIa HCl·H_2O, colorless needles: mp 119 °C dec; ir 3350 and 3150 (vs and vs, NH_2), 1680 (vs, imidazolium ring), 1540 (m, NH_2), 1095 (vs, C–O–C), 770 and 700 cm^{-1} (m and s, C_6H_5); NMR (CF_3COOD) δ 1.36 (t, J = 7 Hz, 3, OCH_2CH_3), 3.75 (s, 3, NCH_3), 4.70 (s, 2, $CH_2OC_2H_5$), 4.85 (q, J = 7 Hz, 2, OCH_2CH_3), 7.60 (s, 5, C_6H_5); mass spectrum *m/e* (rel intensity) 231 (16, M^+), 186 (100, $M^+ - OC_2H_5$).

Anal. Calcd for $C_{13}H_{17}N_3O$·HCl·H_2O: C, 54.63; H, 7.05; N, 14.70. Found: C, 54.58; H, 7.24; N, 14.48.

2-Amino-4-ethoxymethyl-1-methyl-5-phenylimidazole (VIIb) Hydrochloride. In the same manner as VIIa 0.258 g (1 mmol) of Vb HCl gave 0.150 g (57%) of VIIb, pale yellow needles, mp 164 °C effervescence, 246–250 °C dec. Two recrystallization from ethanol and ether afforded colorless plates: mp 171 °C effervescence, 249 °C dec; ir 3260 and 3100 (s and vs, NH_2), 1675 (vs, imidazolium ring), 1540 (m, NH_2), 1100 (s, C–O–C), 775 and 700 cm^{-1} (m and s, C_6H_5); NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3, OCH_2CH_3), 3.50 (q, J = 7 Hz, 2, OCH_2CH_3), 3.55 (s, 3, NCH_3), 4.28 (s, 2, $CH_2OC_2H_5$), 7.10–7.70 (broad s, 5, C_6H_5); mass spectrum *m/e* (rel intensity) 231 (44, M^+), 186 (100, $M^+ - C_2H_5O$), 103 (23, $C_6H_5C{\equiv}N^+$), 45 (76, $CH_3CH{=}O^+H$).

Anal. Calcd for $C_{13}H_{17}N_3O$·HCl·½H_2O: C, 56.43; H, 6.91; N, 15.14. Found: C, 56.88; H, 6.53; N, 15.23.

2-Amino-5-hydroxymethyl-1-methyl-4-phenylimidazole (VIIIa) Hydrochloride. Compound Va HCl·H_2O (0.552 g, 2 mmol) was dissolved in 6.0 ml of 2% hydrochloric acid at 60 °C. After standing for 1 day in a refrigerator, the precipitates were collected and washed twice with 0.3 ml each of 2% hydrochloric acid to give 0.373 g (72%) of VIIIa HCl, pale pink needles, mp 70 °C sinter, 96 °C. One recrystallization from 2% hydrochloric acid gave colorless needles: mp 70 °C sinter, 102 °C; ir 3300 and 3120 (vs and vs, NH_2), 1675 (vs, imidazolium ring), 1555 (m, NH_2), 1025 or 1000 (s and s, C–O), 785 and 710 cm^{-1} (s and s, C_6H_5); NMR (Me_2SO-d_6) δ 3.60 (s, 3, NCH_3), 4.46 (s, 2, CH_2OH), 5.50 (broad, about 1, CH_2OH), 7.50 (s, 5, C_6H_5), 7.80 (s, 2, NH_2).

Anal. Calcd for $C_{11}H_{13}N_3O$·HCl·2H_2O: C, 47.91; H, 6.57; N, 15.24. Found: C, 47.02; H, 6.20; N, 15.52.

Registry No.—I, 579-07-7; II, 471-29-4; II ½H_2SO_4, 598-12-9; IIIa, 58325-27-2; IIIb, 58325-28-3; IIIb HCl, 58325-29-4; Va HCl, 58325-30-7; Vb HCl, 58325-31-8; VIa HCl, 58325-32-9; VIb HCl, 58325-33-0; VIc HCl, 58325-34-1; VIIa HCl, 58325-35-2; VIIb HCl, 58325-36-3; VIIIa HCl, 58325-37-4.

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Analogues of Sparteine. II. Synthesis of *N*-Monoalkylbispidines and *N,N'*-Dialkylbispidines

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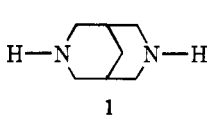
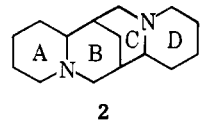
Received August 26, 1975

The structural and physiochemical similarity of the bicyclic diamine bispidine (1) to the antiarrhythmic–oxytocic agent sparteine (2) prompted the development of synthetic routes to bispidines containing substituents on one or both nitrogens, for studies directed toward elucidation of optimum molecular characteristics required for sparteine-like bioactivity. Condensation of N-substituted 4-piperidones with benzylamine and formaldehyde, followed by modified Wolff–Kishner reduction of the resulting diamino ketones (8) furnished hydrogenolytically labile intermediates (11) which were converted to *N*-alkylbispidines (12). Alkylation of these last compounds by formation and reduction of amides (15) or by selective alkylation of the secondary amine functions afforded several *N,N'*-dialkylbispidines (3).

Investigations concerning the synthesis and reactivity of the bicyclic amine bispidine (1) have been reported by a number of groups.[1] Although bispidine itself is not naturally occurring, the bispidine moiety constitutes the B and C rings of the C-15 lupine alkaloid sparteine (2).[2] As a result, both compounds have similar physical properties: they are strong bases[3] and form complexes with certain divalent metal cations.[1b,4]

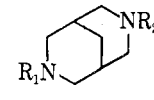


1



2

Sparteine has been shown to affect muscular activity, especially the myocardium (heart) and myometrium (uterus).[5] Its chemical and physical similarity to bispidine prompted our efforts to develop facile synthetic routes to *N*-alkylbispidines (3, R_2 = H) and *N,N'*-dialkylbispidines (3) for pharmacologic studies.



3

Bispidine was originally prepared in six steps from pyridine-3,5-dicarboxylic acid ester.[1a] Difficulties encountered in attempted conversion of 1 to 3 (R_1 = R_2 = CH_3)[1e] and the number of steps required prompted us to investigate alternate routes for preparation of 3.

The syntheses of various 1,5-dicarboalkoxybispidinones[6] and 1,5-diarylbispidinones[7] (4) and 2,4,6,8-tetraarylbispidinones[8] (5) via Mannich condensations have been reported (Scheme I). Reductive removal of the carbonyl group in the N-substituted condensation products (e.g., 4, R_1 = H, or 5, R_3 = R_4 = H) would constitute a two-step synthesis of 3. Alternatively, formation of 4 (R_1 = $COOC_2H_5$) followed by hy-

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