A Novel Synthesis of 2-(Disubstituted amino)-5(4)phenylimidazoles

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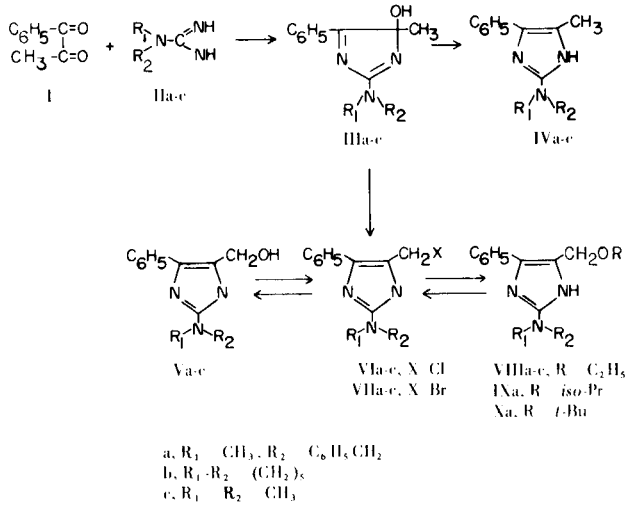
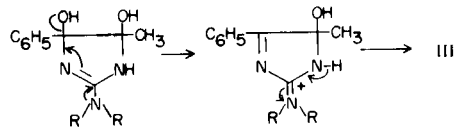
The reaction of 1-phenyl-1,2-propanedione with 1,1-disubstituted guanidines in methanol yielded 2-(disubstituted amino)-4-hydroxy-4-methyl-4*H*-imidazoles (III). Compound III produced 5(4)methylimidazoles by catalytic hydrogenation and 5(4)chloromethylimidazoles (IV) by concentrated hydrochloric acid treatment. Solvolysis of IV in water and alcohols gave 5(4)hydroxymethyl- and 5(4)alkoxymethylimidazoles, respectively.

2-Aminoimidazoles have been synthesized by the reduction of *p*-substituted benzeneazoimidazoles (1,2,3, 4,5) and 2,2-azoimidazole (6), and the reaction of cyanamide with α-aminoacetals (7) or aminoketones (8). 2-(Monosubstituted amino)imidazoles have been obtained by acidic cyclization of 1-substituted-3-(β,β-dialkoxyalkyl)-guanidines prepared by the reaction of α-aminoacetals or ketals with substituted cyanamide or *S*-methylisothiuronium iodide (9). However, 2-(disubstituted amino)-imidazoles have never been reported to our knowledge. In connection with an investigation on the mechanism of the Voges-Proskauer reaction (10), we found that 2-(*N*-benzyl-*N*-methylamino)-4-hydroxy-4-methyl-4*H*-imidazole (IIIa) was easily produced by the reaction of 1-phenyl-1,2-propanedione (I) and 1-benzyl-1-methylguanidine (IIa) in water under nitrogen. As such a type of compound is very useful as an intermediate for synthesizing various 2-(disubstituted amino)imidazoles, we attempted the extension of this method to the other 1,1-disubstituted guanidines.

The reaction of 1,1-pentamethylene- (IIb) or 1,1-dimethyl-guanidines (IIc) with I in water did not give the corresponding 4*H*-imidazoles in a pure state. However, when the reaction of I and IIc was performed in methanol at about -10°, IIIc was obtained as yellow prisms in excellent yield. This product was, however, rapidly changed to blue violet *via* red on contact with air. Fairly stable IIIc was obtained by immediate dissolution of the crude product in chloroform followed by concentration of the solution and addition of ether to the concentrate. On dissolution of the crude product in chloroform, a small amount of undissolved colorless needles, m.p. 228-229° was obtained, which was identified as 1,1-dimethylguanidinium benzoate by comparison of its ir spectrum with that of the authentic sample. Other 4*H*-imidazoles, IIIa and IIIb were similarly obtained and a small amount of 1-benzyl-1-methyl- and 1,1-pentamethyl-eneguanidinium benzoates were also isolated from the respective crude products. It is probable that these guanidinium salts are formed by a side reaction (11). The structure of III was consistent with uv, ir, mass spectra and elemental analysis. Strong ir bands at 1625-1650 cm^{-1} and 1567-1575 cm^{-1} can be assigned to 4*H*-imidazole ring stretching vibrations (12,13).



It has been known that the reaction of I with amidines gives 4,5-dihydroxyimidazolines (14). Thus, the formation of 4*H*-imidazole (III) in our case can be ascribed to the strong electron-donating ability of 2-disubstituted amino group as shown below.



We furthermore found that III can be easily hydrogen-

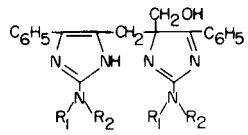
ated in the presence of platinum catalyst to give 2-(disubstituted amino)-5(4)methyl-4(5)phenylimidazoles (IV). Thus, the solutions obtained by reacting I and II were subjected to hydrogenation without isolating III. Acidification with hydrochloric acid and evaporation of the reaction mixture gave excellent yield of IV·HCl. The ir and nmr spectra and the elemental analysis were consistent with the structure.

Dissolution of III in concentrated hydrochloric acid at room temperature yielded 5(4)chloromethylimidazoles (VI). The ir, nmr, and mass spectra can be explained by the previously proposed structure, 2-(*N*-benzyl-*N*-methylamino)-4-phenyl-1,3,-diazafulvene dihydrochloride (10). This structure, however, seems unreasonalbe because of the strong electrophilic nature of the 6-carbon of heterofulvenes (15,16,17,18). This point was confirmed by comparing the ir spectra of VI hydrochlorides with those of the corresponding 5(4)bromomethyl compounds (VII). The observation that the ir absorption bands at 1295-1300 cm^{-1} (δ CH_2) and 630-670 cm^{-1} (ν C-Cl) observed in the spectra of VI·HCl disappeared or decreased and 1210 cm^{-1} (δ CH_2) and 580-560 cm^{-1} (ν C-Br) bands increased or newly appeared in the hydrobromides supports the halomethylimidazole structure. Direct conversion of III into VI is valuable from a synthetic point of view, since such chloromethyl compounds have been synthesized by treating difficultly accessible hydroxymethyl compounds with thionyl chloride (14,19,20,21).

In the preliminary report (10), 2-(*N*-benzyl-*N*-methylamino)-5(4)hydroxymethyl compound (Va) was prepared by dissolution of IIIa in dilute hydrochloric acid and evaporation to dryness of the solution. However, such treatment of IIIa was found by ir to give mainly 5(4)-chloromethylimidazole (VIa) hydrochloride. The ir spectra of the products from IIIb suggested to be IIIb·HCl with 2% HCl, a mixture of HCl salts of IIIb, Vb, and VIb with 5% HCl, VIb·HCl with 10% HCl. Thus, hydrolysis of VI was attempted to obtain V.

Treatment of 5(4)chloromethyl compound VIc·HCl with a small amount of water gave a yellow powder, m.p. 248-249° dec. When the powder was extracted with hot chloroform, pure 5(4)hydroxymethylimidazole Vc·HCl, m.p. 247-248° dec., was obtained as an insoluble residue in 88% yield.

Evaporation of the chloroform extract afforded yellow needles, m.p. 271-272° dec. The ir spectrum suggests the presence of the imidazolium ring (1695 cm^{-1}) and the 4*H*-imidazolium ring (1720, 1560 cm^{-1}). In conjunction with the presence of four methylene protons (δ 2.84) and the m/e 478 (M^+-H_2O) ion revealed by nmr and mass spectroscopy, respectively, the structure of this yellow substance was deduced to be XIc. Similar treatment of VIb·HCl gave XIb·2HCl in 60% yield with only a small amount of the desired Vb·HCl. However, treatment of VIb·HCl with 2% HCl and recrystallization from the same solvent afforded pure Vb·HCl in 44% yield. Crude Va·HCl obtained by hydrolysis of VIa·HCl could not be purified by the two procedures described above.



XIb,c

Extraordinary high reactivity of 5(4)chloromethylimidazoles has been known (22,23). Compound VIa,b,c are also highly reactive and easily gave the corresponding 5(4)alkoxymethylimidazoles (VIIIa,b,c IXa, Xa) by heating in alkanols at 60° for 5 minutes. Methanol failed to afford the desired product. The hydroxymethyl (Vc) and ethoxymethyl (VIIIa) compounds changed to VIc and VIa by treatment with concentrated hydrochloric acid.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were obtained on a Hitach recording spectrophotometer EPI-G_2 as potassium bromide tablets and the following abbreviations were used: s = strong; m = medium; v = very; sh = shoulder. Uv spectra were recorded with a Hitachi spectrophotometer 101 or Toshiba Beckman recording spectrophotometer DB 1402. 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 as relative to TMS, using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. 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-Benzyl-1-methylguanidine (IIa).

Compound IIa·HCl, m.p. 66° sintered at 90-95° [lit. (24) 123-124°] and IIa, m.p. 120-124° [lit. (24) 141-143°] were prepared according to the literature (24).

Compound IIa, benzoate, colorless needles (from methanol and ether) had m.p. 255-256°; ir: 1695 (m, ν C=O), 1620, 1600, 1570 and 1400 (s, s, vs and vs, ν as CO_2^-, ν s CO_2^- and δ $\overset{+}{N}H_3$), 730 and 700 (m and s, phenyl δ CH out-of-plane) cm^{-1}.

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.34; H, 6.71; N, 14.73. Found: C, 67.13; H, 6.66; N, 14.81.

1,1-Pentamethyleneguanidine (IIb).

Compound IIb·1/2H_2SO_4, m.p. 296° dec. [lit (24) 286° dec.] was prepared according to the literature (24). Compound IIb·1/2H_2SO_4 (2.46 g., 0.014 mole) was dissolved in a solution of 0.64 g. (0.016 mole) of sodium hydroxide in 30 ml. of methanol and the solution was concentrated to dryness under reduced pressure. The residue was extracted with 30 ml. of 2-propanol and the extract concentrated to dryness under reduced pressure to give 1.47 g. (79%) of IIb, colorless plate, m.p. 134.5-135.5°.

Compound IIb, benzoate, colorless needles (from methanol and ether) had m.p. 280°; ir: 1690 (m, ν C=O), 1600, 1575 and

1395 (vs, vs and s, ν as CO_2^-, ν s CO_2^- and δ $\overset{+}{N}H_3$), 725 (m, phenyl δ CH out-of-plane) cm^{-1}.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 62.37; H, 7.50; N, 16.70.

1,1-Dimethylguanidine (IIc).

Compound IIc·$1/2H_2SO_4$, m.p. 288-289° [lit. (24) 291°] was obtained according to the literature (24). In the same manner as in IIb, 2.04 g. (0.015 mole) of IIc·$1/2H_2SO_4$ yielded 1.14 g. (87%) of IIc, colorless plates, m.p. 105° effervescence.

Compound II benzoate, colorless prisms (from methanol and ether) had m.p. 235°; ir: 1690 (m, ν C=O), 1625, 1600, 1565 and 1390 (s, s, vs and vs, ν as CO_2^-, ν s CO_2^- and δ $\overset{+}{N}H_3$), 720 (m, phenyl δ CH out-of-plane) cm^{-1}.

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.15; H, 7.14; N, 19.99.

2-(*N*-Benzyl-*N*-methylamino)-4-hydroxyl-5-phenyl-4*H*-imidazole (IIIa).

A solution of 1.63 g. (10 mmoles) of 1-benzyl-1-methylguanidine (IIa) in 10 ml. of methanol and a solution of 1.48 g. (10 mmoles) of 1-phenyl-1,2-propanedione (I) in 10 ml. of methanol were cooled at about -10° (bath temperature) and mixed. The mixture was maintained at this temperature for 10 minutes, and then evaporated to dryness under reduced pressure at 10°. The resulting crystalline residue was dissolved in 30 ml. of chloroform, and a small amount of insoluble 1-benzyl-1-methylguanidinium benzoate (Xa), m.p. 218-219° was filtered off. The filtrate was concentrated under reduced pressure at 20°, and 25 ml. of ether was added to the bluish green viscous concentrate. After standing overnight, 2.30 g. (78%) of IIIa, yellow prisms m.p. 139-140° was obtained. Recrystallization by the same procedure furnished pure IIIa, 141-142°; uv λ max (methanol) (ϵ max): 274 mμ (7,100); ir: 1630 and 1569 (vs and m, 4*H*-imidazole skeletal vibration), 1150 (s, ν C-O), 745 and 700 (s and s, phenyl δ CH out-of-plane) cm^{-1}; mass spectrum m/e (rel. intensity): 293 (53, M^+-CH_3), 190 (21, M^+-C_6H_5CN), 99 (56, M^+-C_6H_5CN-$C_6H_5CH_2$), 91 (62, $C_6H_5CH_2^+$), 43 (21, CH_2=C=O$^+$H).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.43. H, 6.50; N, 14.24.

4-Hydroxy-4-methyl-2-pentamethyleneamino-5-phenyl-4*H*-imidazole (IIIb).

A solution of 1.27 g. (10 mmoles) of 1,1-pentamethyleneguanidine (IIb) in 10 ml. of methanol and a solution of 1.48 g. (10 mmoles) of I in 10 ml. of methanol were reacted in the same manner as in IIIa. The reaction mixture was concentrated to dryness under reduced pressure while cooling in ice-water. The resulting reddish yellow crystalline residue was dissolved in 30 ml. of chloroform and insoluble 1,1-pentamethyleneguanidinium benzoate (Xb), m.p. $>$ 280°, 0.06 g. was removed. The filtrate was concentrated to about 3 ml. under reduced pressure at 20° and then 10 ml. of petroleum ether was added to the concentrate. The mixture was kept in a refrigerator for 3 hours to yield 1.51 g. (59%) of IIb, yellowish green prisms, m.p. 142°. An analytical sample, yellow prisms, m.p. 146° was obtained by dissolving the crude product in chloroform, concentrating the solution, and allowing it to stand overnigh; uv λ max (methanol) (ϵ max): 278 mμ (5,100); ir: 1625 and 1576 (vs and m, 4*H*-imidazole skeletal vibration), 1180 (s, ν C-O), 724 and 700 (s and s, phenyl δ CH out-of-plane) cm^{-1}; nmr (deuteriochloroform): 1.46 (3H, s, CH_3), 1.63 (6H, m, $(CH_2)_3$), 3.66 (4H, broad s, $N(CH_2)_2$), 6.08 (1H, s, OH), 7.92-7.62 (3H, m, phenyl 3,4-H), 8.16-8.46 (2H, m, phenyl 2-H); mass spectrum m/e (rel. intensity): 257 (17, M^+), 242 (16, M^+-CH_3) 154 (100, M^+-C_6H_5CN), 139 (93, M^+CH_3-C_6H_5CN), 111 (82, $(CH_2)_5NC{\equiv}NH^+$), 84 (25, $(CH_2)_5N^+$), 43 (31, CH_2=C=O$^+$H).

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 69.99; H, 7.45; N, 16.34. Found: C, 69.78; H, 7.45; N, 16.45.

Compound IIIb·HCl

A suspension of 2.57 g. (10 mmoles) of IIIb in 2 ml. of water was acidified with 1.2 ml. of concentrated hydrochloric acid. The resulting clear solution was allowed to stand for 2 hours to precipitate 2.20 g. (86%) of crystals, m.p. 106-107° dec. Recrystallization from 2% hydrochloric acid gave an analytical sample, colorless needles, m.p. 123° dec.; ir: 3400 and 3120 (vs and vs, ν N-H), 1670 and 1520 (vs and s, 4*H*-imidazolium skeletal vibration), 1040 (s, ν C-O), 780 and 700 (m and s, phenyl δ CH out-of-plane).

Anal. Calcd. for $C_{15}H_{19}N_3O{\cdot}H_2O{\cdot}HCl$: C, 57.78; H, 7.11; N, 13.48. Found: C, 57.43; H, 6.60; N, 13.87.

2-Dimethylamino-4-hydroxy-4-methyl-5-phenyl-4*H*-imidazole (IIIc).

1,1-Dimethylguanidine (0.87 g., 10 mmoles) and I (1,48 g., 10 mmoles) were treated in the same manner as IIIa to obtain a reddish yellow solid residue. It was dissolved in 30 ml. of chloroform, and insoluble 1,1-dimethylguanidinium benzoate (Xc), m.p. 228-229°, 0.16 g. was filtered off. The filtrate was concentrated under reduced pressure at 20° to about 4 ml. and 3 ml. of ether was added to the bluish green concentrate. After standing for 1 hour, the crystals which separated were filtered to give 1.48 g. (68%) of IIIc, yellow prisms, m.p. 131-132°. Concentration of the filtrate gave an additional crop of the desired product (0.16 g.). Further recrystallization from chloroform and ether did not change the melting point; uv λ max (methanol) (ϵ max): 273 mμ (3900); ir: 1635 and 1567 (vs and m, 4*H*-imidazole skeletal vibration), 1170 (s, ν C-O), 742 and 698 (s and s, phenyl δ CH out-of-plane) cm^{-1}; nmr (deuteriochloroform): 1.46 (3H, s, CH_3), 3.15 (6H, s, N-CH_3), 5.43 (1H, broad s, OH), 7.30-7.63 (3H, m, phenyl 3,4-H), 8.16-8.46 (2H, m, phenyl 2-H); mass spectrum m/e (rel. intensity): 217 (30, M^+), 202 (16, M^+-CH_3), 104 (100, M^+-C_6H_5CN), 99 (93, M^+-CH_3-C_6H_5CN), 71 (31, $(CH_3)_2$-N-C$\equiv$N$^+$H).

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.35. Found: C, 66.08; H, 6.94; N, 19.29.

2-(*N*-Benzyl-*N*-methylamino)-5(4)methyl-4(5)phenylimidazole (IVa·HCl).

A methanolic solution, obtained from 0.81 g. (5 mmoles) of IIa and 0.74 g. (5 mmoles) of I in the same manner as for IIIa, was hydrogenated in the presence of 100 mg. of platinum oxide while cooling with ice-water. Immediately after completion of the hydrogenation, 0.4 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 40°. The residue was dissolved in 20 ml. of ethanol, the solution concentrated to about 3 ml., and ether added until white opacity was observed in the solution. The mixture was kept overnight in a refrigerator to give 1.08 g. (68%) of IVa·HCl, colorless plates, m.p. 210°. One recrystallization from ethanol and ether in the same manner as above yielded pure IVa·HCl, m.p. 213-214°; uv λ max (methanol) (ϵ max): 246 (9500), 270 (11,000) mμ; ir: 1670, 1650 and 922 (vs, vs and m, imidazolium skeletal vibration); nmr (deuteriochloroform): 2.20 (3H, s, CH_3), 2.96 (3H, s, NCH_3), 4.76 (2H, s, NCH_2), 7.20 (5H, s, $NCH_2C_6H_5$), 6.95-7.66 (5H, m, C_6H_5), 12.16 (1H, broad s, NH), 12.50 (1H, broad s, NH).

Anal. Calcd. for $C_{18}H_{18}N_3$·HCl: C, 68.88; H, 6.42; N, 13.39.

Found: C, 68.61; H, 6.69; N, 13.14.

5(4)Methyl-2-pentamethyleneamino-4(5)phenylimidazole (IVb•HCl).

The procedure described for the preparation of IVa•HCl was employed. Compound IIb (0.25 g., 2 mmoles) and I (0.29 g., 2 mmoles) gave 0.36 g. (64%) of IVb•HCl, colorless rocks, m.p. 257-258°. Recrystallization from ethanol afforded pure IVb•HCl, 262° dec.; uv λ max (methanol) (ε max); 264 (9,000), 272 (9,900) mμ; ir: 1665, 1635 and 930 (vs, vs and s, imidazolium skeletal vibration) cm^{-1}; nmr (deuteriochloroform): 1.58 (6H, broad s, $(CH_2)_3$), 2.28 (3H, s, CH_3), 3.65 (4H, broad s, $N(CH_2)_2$), 7.00-7.69 (5H, m, C_6H_5), 12.13 (1H, broad s, NH), 12.43 (1H, broad s, NH).

Anal. Calcd. for $C_{15}H_{19}N_3$•HCl: C, 64.85; H, 7.26; N, 15.13. Found: C, 64.72; H, 7.45; N, 14.85.

2-Dimethylamino-5(4)methyl-4(5)phenylimidazole (IVc•HCl).

In the same manner as in IVa•HCl, 0.29 g. (2 mmoles) of IIc and 0.17 g. (2 mmoles) of I yielded 0.29 g. (61%) of IVc•HCl, colorless needles, mp. 210-218° dec. Recrystallization from ethanol and ether in the same manner as in IVa•HCl gave pure IVc•HCl, m.p. 243-244° dec.; uv λ max (methanol) (ε max): 222 (11,700), 271 (11,500) mμ; ir: 1670, 1650 and 905 (vs, s and s, imidazolium skeletal vibration) cm^{-1}; nmr (deuteriotrifluoroacetic acid): 2.38 (3H, s, CH_3), 3.30 (6H, s, $N(CH_3)_2$), 7.50 (5H, s, C_6H_5).

Anal. Calcd. for $C_{12}H_{15}N_3$•HCl: C, 60.60; H, 6.78; N, 17.68. Found: C, 60.64; H, 7.00; N, 17.63.

2-(*N*-Benzyl-*N*-methylamino)-5(4)hydroxymethyl-4(5)phenylimidazole (Va•HCl).

Compound VIa•HCl (1.04 g. 3 mmoles) was triturated with 2.6 ml. of water. The resulting gummy product was washed twice with 0.6 ml. of water each time and dried over phosphorus pentoxide for 3 days under reduced pressure to give 0.40 g. (40%) of crude Va•HCl, yellow powder, m.p. 105° sinters, 128-130° dec.; ir: 1660 and 930 (broad vs and m, imidazolium skeletal vibration), 1030 (m, ν C-O), 700 (s, phenyl δ CH out-of-plane) cm^{-1}; nmr (deuteriochloroform): 2.92 (3H, s, NCH_3), 3.85 (1H, s, OH), 4.32-4.93 (4H, broad m, NCH_2 and CH_2OH), 6.83-7.71 (10H, m, $NCH_2C_6H_5$ and C_6H_5); mass spectrum m/e (rel. intensity): 275 (9, M^+-CH_2O), 263 (76, M^+-CH_2O), 248 (34, M^+-CH_2O-CH_3), 172 (100, M^+-H_2O-C_6H_5CN).

5(4)-Hydroxymethyl-2-pentamethylenamion-4(5)phenylimidazole (Va•HCl).

Compound VIb•HCl 100 mg. (0.3 mmoles) was triturated with 1 ml. of 2% hydrochloric acid. After standing for one hour, the precipitate was collected and washed with 0.4 ml. of 2% hydrochloric acid and air-dried on a clay plate, yellowish powder, m.p. 245-246°, 80 mg. (91%). One recrystallization from 2% hydrochloric acid yielded pure Vb•HCl, m.p. 272-273°; ir: 1663, 1629 and 898 (vs, vs and m, imidazolium skeletal vibration) 1025 (s, ν C-O), 700 (s, phenyl δ CH out-of-plane) cm^{-1}; nmr (deuteriotrifluoroacetic acid): 1.85 (6H, broad s, $(CH_2)_3$), 3.63 (4H, broad s, $N(CH_2)_2$), 4.65 (2H, s, CH_2OH), 7.56 (5H, s, C_6H_5); mass spectrum m/e (rel. intensity): 257 (5, M^+), 239 (100, M^+-H_2O), 227 (19, M^+-CH_2O), 210 (58, M^+-H_2O-C_2H_4-H), 198 (51, M^+-CH_2O-C_2H_4).

Anal. Calcd. for $C_{15}H_{19}N_3O$•HCl: C, 61.30; H, 6.87; N, 14.31. Found: C, 60.67; H, 6.94; N, 14.25.

2-Dimethylamino-5(4)hydroxymethyl-4(5)phenylimidazole (Vc•HCl).

A suspension of 0.27 g. (3 mmoles) of VIc•HCl in 0.7 ml. of water was stirred for 30 minutes. The precipitate was filtered and air-dried to yield 0.24 g. of yellow powder, m.p. 248-249° dec. A suspension of the powder in 5 ml. of chloroform was refluxed for 5 minutes, the undissolved Vc•HCl was collected and washed with 0.6 ml. of chloroform to give 0.22 g. (88%) of white powder, m.p. 247-248° dec. Recrystallization from 2% hydrochloric acid gave pure Vc•HCl, m.p. 247-248° dec.; ir: 1690 and 930 (vs and m, imidazolium skeletal vibration), 1030 (s, ν C-O), 780 and 700 (s and s, phenyl δ CH out-of-plane) cm^{-1}; nmr (deuteriotrifluoroacetic acid): 3.30 (6H, s, $N(CH_3)_2$), 4.46 (2H, s, CH_2OH), 7.58 (5H, s, C_6H_5): mass spectrum m/e (rel. intensity): 217 (12, M^+), 199 (100, M^+-H_2O), 184 (26, M^+-H_2O-CH_3), 170 (31, M^+-CH_3-H-CH_2OH), 81 (27, M^+-H_2O-CH_3-C_6H_5CN).

Anal. Calcd. for $C_{12}H_{15}N_3O$•HCl: C, 56.80; H, 6.35; N, 16.56. Found: C, 56.83; H, 6.38; N, 16.94.

2-(*N*-Benzyl-*N*-methylamino)-5(4)chloromethyl-4(5)phenylimidazole (VIa•HCl).

(a)

To a suspension of 0.62 g. (1.8 mmoles) of IIIa in 1.8 ml. of water was added 0.3 ml. of concentrated hydrochloric acid to dissolve IIIa. An additional 50 ml. of concentrated hydrochloric acid was added to the solution and the mixture was allowed to stand overnight in a refrigerator. The resulting precipitate was collected on a glass filter and dried over phosphorus pentoxide under reduced pressure for seven days and over potassium hydroxide for three days, colorless needles, 0.61 g. (98%) of VIa•HCl, m.p. 63° sinter 118-119° dec., was obtained; ir: 1660 and 930 (vs and m, imidazolium skeletal vibration), 1300 (m, CH_2Cl δ CH), 670 (m, ν C-Cl) cm^{-1}; nmr (deuteriochloroform): 2.98 (3H, s, NCH_3), 4.63 (2H, s, CH_2Cl), 4.76 (2H, broad s, NCH_2), 7.20 5H, s, $NCH_2C_6H_5$), 7.20-7.46 (5H, C_6H_5), 12.85 (1H, broad s, NH), 12.96 (1H, broad s, NH).

Anal. Calcd. for $C_{18}H_{18}N_3Cl$•HCl: C, 62.07; H, 5.50; N, 12.07. Found: C, 62.32, H, 5.19; N, 12.08.

(b)

A suspension of 0.357 g. (1 mmole) of VIIIa•HCl in 5 ml. of concentrated hydrochloric acid was kept for one day at room temperature. The resulting precipitate was collected on a glass filter and dried over phosphorus pentoxide under reduced pressure for five days to give 0.34 g. (96%) of Va•HCl, colorless needles, m.p. 70° sinters 107-108° dec.

5(4)-Chloromethyl-2-(*N*,*N*-pentamethyleneamino)-4(5)phenylimidazole (VIb•HCl).

A solution of 1.28 g. (5 mmoles) of IIIb in 30 ml. of concentrated hydrochloric acid was kept in a refrigerator for one day. The resulting precipitate was collected on a glass filter and dried over potassium hydroxide under reduced pressure for three days to give 0.70 g. (45%) of VIb•HCl, colorless needles, m.p. 245-248° dec.; ir: 1680, 1650 and 910 (vs, vs and m, imidazolium skeletal vibration), 1420 and 1295 (m and s, CH_2Cl δ CH), 635 (w, ν C-Cl) cm^{-1}; nmr (deuteriochloroform): 1.68 (6H, broad s, $(CH_2)_3$), 3.17 (4H, broad s, $N(CH_2)_2$), 4.70 (2H, s, CH_2Cl), 7.14-7.85 (6H, m, C_6H_5), 12.55 (1H, broad s, NH), 12.91 (1H, broad s, NH).

Anal. Calcd. for $C_{15}H_{18}N_3Cl$•HCl: C, 57.70; H, 6.13; N, 13.46. Found: C, 57.82; H, 6.11; N, 13.20.

5(4)-Chloromethyl-2-dimethylamino-4(5)phenylimidazole (VIc•HCl).

(a)

In the same procedure as in VIb•HCl, 1.08 g. (5 mmoles) of IIIc afforded 1.06 g. (78%) of VIc•HCl, colorless needles, m.p. 260° dec.; ir: 1695, 1680, 1650 and 920 (vs, vs, s and s, imidazolium skeletal vibration), 1418 and 1295 (msh and s, CH_2Cl δ CH), 630 (m, ν C-Cl) cm^{-1}; nmr (deuteriotrifluoroacetic acid): 3.31 (6H, s, $N(CH_3)_2$), 4.61 (2H, s, CH_2Cl), 7.53 (5H, s, C_6H_5).

Anal. Calcd. for $C_{12}H_{14}N_3Cl$•HCl•1/2H_2O: C, 51.26; H, 5.38; N, 14.94. Found: C, 51.40; H, 5.29; N, 15.01.

(b)

Compound Vc•HCl (0.05 g., 0.2 mmole) was dissolved in 2 ml. of concentrated hydrochloric acid, and the solution kept in a refrigerator for one day. The resulting precipitate was collected on a glass filter and dried over phosphorus pentoxide for two days to yield 0.05 g. (89%) of VIc•1/2H_2O•HCl, colorless needles, m.p. 252-253° dec.

2-(*N*-Benzyl-*N*-methylamino)-5(4)bromomethyl-4(5)phenylimidazole (VIIa•HBr).

To a suspension of 100 mg. (0.34 mmole) of IIIa in 0.6 ml. of water was added 0.5 ml. of 47% hydrobromic acid to dissolve IIIa. An additional 16 ml. of concentrated hydrobromic acid was added to the solution and the mixture was kept in a refrigerator for one day. The resulting precipitate was collected on a glass filter and dried over potassium hydroxide for three days under reduced pressure to give 113 mg. (76%) of VIIa•HBr, pale yellow powder, m.p. 96° sinters, 130° dec.; ir: 1660 and 922 (vs and m, imidazolium skeletal vibration), 1220 (m, CH_2Br δ CH), 570 (m, ν C-Br) cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_3Br$•HBr: C, 49.44; H, 4.58; N, 9.61. Found: C, 49.06; H, 4.35; N, 9.74.

5(4)Bromomethyl-2-pentamethyleneamino-4(5)phenylimidazole (VIIb•HBr).

A solution of 139 mg. (0.54 mmole) of IIIb in 20 ml. of 47% hydrobromic acid was kept in a refrigerator for one day. The resulting precipitates were collected on a glass filter and dried over potassium hydroxide under reduced pressure for three days to yield 180 mg., (83%) of VIIb•HBr, pale pink prisms, m.p. 253-254° dec.; 1655, 1635 and 900 (vs, vs and m, imidazolium skeletal vibration), 1412 and 1218 (m and s, CH_2Br δ CH), 578 or 562 (w and w, ν C-Br) cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}N_3Br$•HBr: C, 44.90; H, 4.77; N, 10.47. Found: C, 45.16; H, 4.87; N, 10.50.

5(4)Bromomethyl-2-dimethylamino-4(5)phenylimidazole (VIIc•HBr).

In a manner similar to the preparation of VIIa•HBr, 125 mg. (0.56 mmole) of III produced 192 mg. (78%) of VII•HBr, pale yellow prisms, m.p. 235° dec.; ir: 1688, 1675, 1640 and 920 (vssh, vs, ssh and s, imidazolium skeletal vibration), 1420 (m, δ CH), 1202 (s, CH_2Br δ CH), 578 or 568 (w and m, C-Br) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_3Br$•HBr: C, 39.91; H, 4.18. Found: C, 40.19; H, 4.18.

2-(*N*-Benzyl-*N*-methylamino)-5(4)ethoxymethyl-5(4)phenylimidazole (VIIIa•HCl).

A solution of 0.35 g. (1 mmole) of Vla•HCl in 10 ml. of ethanol was warmed at 60° for 5 minutes, and the mixture was concentrated to about 1 ml. under reduced pressure at 40°. To the concentrate was added 3.6 ml. of ether and the solution was kept in a refrigerator for one day. The resulting precipitate was collected by filtration and washed with 3 ml. of ether and air-dried, yellowish needles, 0.33 g. (94%), m.p. 145° sinters, 206° dec.; ir: 1660 and 920 (vs and m, imidazolium skeletal vibration), 1095 (s, ν C-O-C), 775 and 700 (s and s, phenyl δ CH out-of-plane); nmr (deuteriotrifluoroacetic acid); 1.41 (3H, t, J = 7 Hz, OCH_2CH_3), 3.28 (3H, s, NCH_3), 4.51 (2H, q, J = 7 Hz, OCH_2CH_3), 4.61 (2H, s, $CH_2OC_2H_5$), 4.78 (2H, s, $NCH_2C_6H_5$), 7.50 (5H, s, $NCH_2C_6H_5$), 7.53 (5H, s, C_6H_5); mass spectrum m/e (rel. intensity): 321 (8, M^+), 276 (46, M^+-OCH_2CH_3), 275 (100, M^+-OC_2H_5-H), 260 (87, M^+-OC_2H_5-H-CH_3), 59 (43, $C_2H_5OCH_2^+$), 45 (100, $C_2H_5O^+$).

Anal. Calcd. for $C_{20}H_{23}N_3O$•HCl: C, 76.12; H, 6.76; N, 11.74. Found: C, 66.82; H, 6.89; N, 11.52.

5(4)-Ethoxymethyl-2-pentamethyleneamino-4(5)phenylimidazole (VIIIb•HCl).

By the same procedure employed in the preparation of VIIIa•HCl, 0.31 g. (1 mmole) of VIb•HCl yielded 0.22 g. (67%) of VIIIb•HCl, colorless needles, m.p. 130-131° dec.; ir: 1665, 1640 and 930 (vs, vs and m, imidazolium skeletal vibration), 1090 (s, ν C-O-C), 770 and 700 (s and s, phenyl δ CH out-of-plane); nmr (deuteriochloroform): 1.21 (3H, t, J = 8 Hz, OCH_2CH_3) 1.63 (6H, broad s, $(CH_2)_3$), 3.36 (2H, q, J = 8 Hz, OCH_2CH_3), 3.66 (4H, broad s, $N(CH_2)_2$), 4.45 (2H, s, $CH_2OC_2H_5$), 7.09-7.49 (3H, m, phenyl 3,4-H), 7.49-7.89 (2H, m, phenyl 2-H), 12.46 (1H, broad s, NH), 12.70 (1H, broad s, NH); mass spectrum m/e (rel. intensity): 285 (17, M^+), 240 (37, M^+-OC_2H_5), 239 (77, M^+-OC_2H_5-H), 45 (100, $C_2H_5O^+$), 31 (100, $CH_2{=}OH^+$).

Anal. Calcd. for $C_{17}H_{23}N_3O$•HCl: C, 63.43; H, 7.46; N, 13.05. Found: C, 63.34; H, 7.60; N, 13.02.

2-Dimethylamino-5(4)ethyoxymethyl-4(5)phenylimidazole (VIIIc•HCl).

In the same manner as in VIIIa•HCl, 0.27 g. (1 mmole) of VIc•HCl produced 0.21 g. (75%) of VIIIc•HCl, colorless needles, m.p. 102° dec.; ir: 1680, 1650 and 900 (vs, s and m, imidazolium skeletal vibration), 1090 (vs, γ C-O-C), 700 and 697 (s and vs, phenyl δ CH out-of-plane) cm^{-1}; nmr (deuteriochloroform); 1.16 (3H, t, J = 7 Hz, OCH_2CH_3), 1.66 (4H, broad s, $N(CH_2)_2$), 3.21 (6H, s, $N(CH_2)_3$), 3.43 (2H, q, J = 7 Hz, OCH_2CH_3), 4.45 (2H, s, $CH_2OC_2H_5$), 7.13-7.43 (3H, m, phenyl 3,4-H), 7.46-7.82 (2H, m, phenyl 3,4-H), 7.46-7.82 (2H, m, phenyl 2-H), 12.58 (1H, broad s, NH), 12.65 (1H, broad s, NH); mass spectrum m/e (rel. intensity): 245 (2, M^+), 199 (17, M^+-OCH_2CH_3-H) 45 (100 $C_2H_5O^+$), 31 (100, $CH_2{=}\overset{+}{O}H$).

Anal. Calcd. for $C_{14}H_{19}N_3O$•HCl•H_2O: C, 56.08; H, 7.39; N, 14.01. Found: C, 56.07; H, 7.45; N, 13.77.

2-(*N*-Benzyl-*N*-methylamino)-5(4)isopropoxymethyl-4(5)phenylimidazole (IXa•HCl).

A solution of 0.35 g. (1 mmole) of Vla•HCl in 30 ml. of 2-propanol was stirred at room temperature for 30 minutes, and the reaction mixture concentrated to about 5 ml. under reduced pressure at 25°. To the concentrate was added 12 ml. of ether and the solution was kept in a refrigerator for one day to give 0.32 g. (88%) of IXa•HCl, colorless needles, m.p. 127-129° dec. Recrystallization from 2-propanol afforded an analytical sample of 128-129° dec.; ir: 1665 and 920 (vs and m, imidazolium skeletal vibration) 1060 (vs, ν C-O-C), 770 and 698 (s and vs, phenyl δ CH out-of-plane); nmr (deuteriochloroform): 1.14 (6H, d, J = 6 Hz, $OCH(CH_3)_2$), 2.93 (3H, s, NCH_3), 3.67 (1H, q, J = 6 Hz, $OCH(CH_3)_2$), 4.38 (2H, $CH_2OCH(CH_3)_2$), 4.74 (2H, s, NCH_2), 7.20 (5H, s, $NCH_2C_6H_5$), 7.23-7.70 (5H, m, C_6H_5), 12.51 (1H,

broad s, NH), 12.58 (1H, broad s, NH); mass spectrum m/e (rel. intensity): 335 (18, M^+), 276 (30, M^+-OCH$(CH_3)_2$), 275 (56, M^+-OCH$(CH_3)_2$-H), 260 (51, M^+-OCH$(CH_3)_2$-H-CH_3).

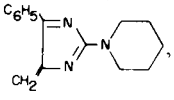
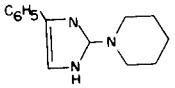
Anal. Calcd. for $C_{12}H_{25}N_3O$·HCl: C, 67.81; H, 7.05; N, 11.30. Found: C, 67.40; H, 7.07; N, 11.01.

2-(*N*-Benzyl-*N*-methylamino)-5(4)-*t*-butoxylmethyl-4(5)phenylimidazole (Xa·HCl).

In a manner similar to the preparations of IXa·HCl, VIa·HCl, 0.35 g. (1 mmole) gave 0.18 g. (48%) of Xa·HCl, pale yellow prisms, m.p. 129° sinters, 208-219° dec.; ir: 1665, 1650 and 925 (vs, vs and m, imidazolium skeletal vibration) 1060 (vs, ν C-O-C). 760 and 700 (s and vs, phenyl δ CH out-of-plane); nmr (deuteriochloroform): 1.27 (9H, s, OC$(CH_3)_3$), 2.93 (3H, s, NCH_3), 4.33 (2H, s, CH_2O), 4.40 (2H, s, NCH_2), 7.20 (5H, s, $NCH_2C_6H_5$), 7.23-7.70 (5H, m, C_6H_5), 12.48 (1H, broad s, NH), 12.70 (1H, broad s, NH); mass spectrum m/e (rel. intensity): 349 (77, M^+), 276 (66, M^+-OC$(CH_3)_3$), 275 (100, M^+-OC(CH_3)-H), 260 (66, M^+-OC$(CH_3)_3$-H-CH_3), 45 (100, $C_2H_5O^+$).

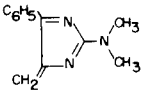
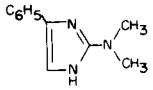
Anal. Calcd. for $C_{22}H_{27}N_3O$·HCl: C, 68.64; H, 7.37; H, 10.80. Found. C, 68.60; H, 7.15; N, 10.97.

4-Hydroxymethyl-4(2-pentamethyleneamino-4(5)phenyl-5(4)-imidazolylmethyl)-2-pentamethylenoamino-5-phenyl-4*H*-imidazole (XIb·2HCl).

Compound VIb·HCl, 0.40 g. (1.2 mmoles) was triturated with 0.4 ml. of water, and the supernatant removed by decantation. The same procedure was repeated twice with 2 ml. of water each time. The resulting yellow powder, m.p. 88° sinters, 130° dec., 0.29 g., was suspended in 8 ml. of chloroform, the suspension refluxed for 5 minutes, and a small amount of undissolved Vb·HCl filtered off. The filtrate was evaporated to dryness to yield 0.20 g. of yellow powder, m.p. 85-90° dec. Recrystallization from 2% hydrochloric acid gave 0.12 g. of the desired product, m.p. 271-272° dec.; ir: 1695 and 1560 (s and m, 4H-imidazolium skeletal vibration), 1670, 1645 and 910 (vs, s and m, imidazolium skeletal vibration), 1030 (m, ν C-O), 780 and 700 (m and m, phenyl δ CH out-of-plane); nmr (deuteriotrifluoroacetic acid): 1.84 (12H, broad s, $(CH_2)_3$), 2.85 (4H, broad s, CH_2OH and $-CH_2-$), 3.25-4.08 (8H, broad s, $N(CH_2)2$ 7.10-7.95 (8H, m, phenyl attached to imidazole ring and 3,4-H of phenyl attached to 4*H*-imidazole ring), 8.15-8.65 (2H, m, 2-H of phenyl attached to 4H-imidazole ring); mass spectrum m/e (rel. intensity); 478 (12, M^+-H_2O), 464 (32, M^+-CH_3OH), 239 (97, ), 227 (100, ).

Anal. Calcd. for $C_{30}H_{36}N_6O$·2HCl·2H_2O: C, 59.49; H, 6.99; N, 13.87. Found: C, 59.36; H, 6.75; N, 13.91.

4-Hydroxymethyl-4-(2-dimethylamino-4(5)phenyl-5(4)imidazolylmethyl)-2-dimethylamino-5-phenyl-4*H*-imidazole (XIc·2HCl).

The filtrate obtained in the case of Vc was allowed to stand for 2 days at room temperature to afford 0.02 g. of yellow prisms, m.p. 295° dec. One recrystallization from 2% hydrochloric acid gave an analytical sample, yellow needles, m.p. 295° dec.; ir: 1720 and 1560 (s and s, 4H-imidazolium skeletal vibration), 1090 (m, ν C-O), 775 and 700 (m and s, phenyl δ CH out-of-plane); nmr (deuteriotrifluoroacetic acid): 2.84 (4H, broad s, CH_2OH and CH_2), 3.06, 3.25 and 3.37 (6H, 3H and 3H, s, $N(CH_3)_2$), 7.10-7.90 (8H, m, phenyl attached to imidazole ring and 3,4-H of phenyl attached to 4*H*-imidazole ring), 8.15-8.45 (2H, m, 2-H of phenyl attached to 4*H*-imidazole ring); mass spectrum m/e (rel. intensity): 398 (54, M^+-H_2O), 384 (13, M^+-CH_3OH), 199 (100, ). 187 (91, ).

Anal. Calcd. for $C_{24}H_{28}N_6O$·2HCl·3H_2O: C, 53.03; H, 6.67; N, 15.46. Found: C, 52.93; H, 6.64; N, 15.76.

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