prepared **1-3** by simple acylation of cyclohexylamine, methyl L-valinate, and methyl L-isoleucinate, respectively, while Z-Ile-Val (the precursor of **4**) and **5** were purchased from Sigma.

Nitrosation of 1-5 with NO_2BF_4. Typical Procedure. To a stirred, ice-cooled solution of 183 mg (1.0 mmol) of **1**, 124 mg (2.0 mmol) of Me_2S, and ca. 160 mg (2.0 mmol) of anhydrous pyridine in 5 mL of anhydrous CH_3CN was added 264 mg (2.0 mmol) of NO_2BF_4, under N_2. After 2 h, the solution was added to CH_2Cl_2 and cold H_2O. The organic layer was isolated, washed again, and dried. Elimination of the solvent in vacuo, without heating, and separation of the residue by filtration through a short column of silica gel, with cold CH_2Cl_2 as eluent, afforded 75 mg (35%) of **1a**; then, 110 mg (60%) of **1** was recovered. (See Table I for experiments carried out at different reaction times or with an excess of reagent.)

N-Nitroso derivatives **2a** and **3a** were similarly prepared. For the nitrosation of **4** and **5**, double amounts of Me_2S, pyridine, and NO_2BF_4 were used (see Table I).

1a: yellow oil; dec[19] at 40-42 °C; ^1H NMR δ 1.15 (s, 9 H), 1.0-2.0 (m, 10 H), 4.40 (m, 1 H); IR 1715, 1510. It affords, in refluxing CH_2Cl_2, cyclohexyl pivalate [bp 97-99 °C at 16 Torr (lit.[20] bp 87 °C at 12 Torr)] in 78% yield.

2a: yellow oil; bp 40 °C (furnace temperature) at 0.10 Torr; ^1H NMR δ 0.55 (d, J = 6.8, 3 H), 1.10 (d, J = 6.6, 3 H), 2.40 (m, 1 H), 2.81 (s, 3 H), 3.62 (s, 3 H), 4.89 (d, J = 9.0, 1 H); IR 1755, 1740. Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.36; H, 7.20; N, 13.52. Treatment of **2a** with pyrrolidine[3a] in CH_2Cl_2 affords readily methyl 2-diazo-3-methylbutanoate (identical by TLC, ^1H NMR, and IR with an authentic sample[3a,21]).

3a: yellow oil; bp 45 °C (furnace temperature) at 0.10 Torr; ^1H NMR 0.70 (m, 1 H), 0.76 (m, 3 H), 0.98 (m, 2 H), 1.07 (d, J = 6.6, 3 H), 2.20 (m, 1 H), 2.81 (s, 3 H), 3.61 (s, 3 H), 4.95 (d, J = 9.2, 1 H); IR 1760, 1740. Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.50; H, 7.70; N, 12.95. Treatment of **3a** with pyrrolidine[3a] in CH_2Cl_2 affords readily methyl 2-diazo-3-methylpentanoate [yellow oil; R_f = 0.45 (Merck aluminum sheets of silica gel 60 F_{254}; CH_2Cl_2); ^1H NMR δ 0.96 (t, J = 6.8, 3 H), 1.15 (d, J = 6.8, 3 H), 1.45 (m, 2 H), 2.4 (m, 1 H), 3.77 (s, 3 H); IR 2090, 1690].[21]

***N*-Benzyloxycarbonyl-*N*-nitroso-L-isoleucyl-*N*-nitroso-L-valine methyl ester (4a)**: yellow oil (nondistillable);[19] ^1H NMR δ 0.40 (d, J = 7.0, 3 H), 0.83 (m, 4 H), 1.05 (d, J = 6.6, 6 H), 1.10 (m, 1 H), 2.44 (m, 1 H), 2.55 (m, 1 H), 3.57 (s, 3 H), 4.81 (d, J = 8.8, 1 H), 5.48 (s, 2 H), 5.79 (d, J = 9.6, 1 H), 7.40 (m, 5 H); ^{13}C NMR δ 11.1 (CH_3CH_2), 17.0 (CH_3CHCH_2), 18.7 (CH_3CHCH_3), 21.5 (CH_3CHCH_3), 24.3 (CH_2CH_3), 27.2 (CH), 33.0 (CH), 52.3 (CH_3O), 57.7 (CHCO), 58.2 (CHCO), 70.2 (CH_2O), 128.4 (CH), 128.8 (CH), 128.9 (CH), 134.3 (C), 153.3 (OCON), 167.2 (CON), 169.7 (COO); IR 1760, 1730 (br).

***N*-Benzyloxycarbonyl-*N*-nitroso-L-valyl-*N*-nitroso-L-leucine methyl ester (5a)**: yellow oil (nondistillable);[19] ^1H NMR δ 0.73 (d, J = 7.0, 3 H), 0.80 (d, J = 7.0, 3 H), 0.84 (d, J = 7.0, 3 H), 1.15 (m, 1 H), 1.10 (d, J = 6.6, 3 H), 1.42 (ddd, J = 14.4, 8.9, 5.6, 1H), 1.88 (ddd, J = 14.4, 8.8, 5.2, 1 H), 2.81 (d of heptuplets, J = 9.2, 6.8, 1 H), 5.17 (dd, J = 8.8, 5.6, 1 H), 5.48 (s, 2 H), 5.66 (d, J = 9.2, 1 H), 7.40 (m, 5 H); ^{13}C NMR δ 18.1 (CH_3CH), 20.8 (CH_3CH), 21.7 (CH_3CH), 22.7 (CH_3CH), 25.0 (CH_3CHCH_3), 27.0 (CH_3CHCH_3), 36.7 ($CHCH_2CH$), 51.4 (CHCO), 52.6 (CH_3O), 58.9 (CHCO), 70.2 (CH_2O), 128.2 (CH), 128.8 (CH), 128.9 (CH), 134.2 (C), 153.4 (OCON), 167.8 (CON), 169.5 (COO); IR 1760-1740.

Nitrosation of 1-5 with $NOBF_4$. Typical Procedure. To a stirred solution of 183 mg (1.0 mmol) of **1** and 160 mg (2 mmol) of anhydrous pyridine in 5 mL of CH_3CN, cooled at -20 °C, was added 232 mg (2.0 mmol) of $NOBF_4$. The solution was maintained at 0 °C under N_2 for 2 h and then added to CH_2Cl_2 and ice. The organic layer was further extracted with cold H_2O and dried and the solvent eliminated in vacuo without heating, to yield a yellow residue containing only **1a** and **1** (TLC and ^1H NMR), which were separated by filtration through a small column of silica gel with cold CH_2Cl_2 as eluent, to afford 131 mg (62%) of chromatographically and spectroscopically pure **1a**.

Compounds **2a**, **3a**, **4a**, and **5a**, were similarly prepared, although 4 mmol of $NOBF_4$ and pyridine were employed in the case of **4a** and **5a**. Other related experiments, performed in the same way but with a change in the base or the solvent, are summarized in Table II.

Acknowledgment. This work has been supported by the Comisión Asesora de Investigación Científica y Técnica (CAICYT, Grant No. 2608/83). Thanks are also due to the Spanish Ministerio de Educación y Ciencia for a fellowship to one of us (P.R.) and to Dr. Jean Martinez (CNRS, Montpellier) for the gift of compound **6**.

(18) (a) Tisue, G. T.; Linke, S.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 6303. (b) Reihlen, H.; Knöpfle, *Justus Liebigs Ann. Chem.* **1936**, *523*, 199. (c) Applewhite, T. H.; Waite, H.; Niemann, C. *J. Am. Chem. Soc.* **1958**, *80*, 1465. (d) Lloyd, K.; Young, G. T. *J. Chem. Soc. C* **1971**, 2890. (e) Okada, Y.; Iguchi, S.; Hirai, T.; Goto, Y.; Yagyu, M.; Yajima, H. *Chem. Pharm. Bull.* **1984**, *32*, 4608 and ref 3a. (f) Martinez, J.; Laur, J.; Castro, B. *Tetrahedron* **1985**, *41*, 739.

(19) These nitroso derivatives are oils that are very sensitive to heat, which precludes purification by distillation (even at 0.10-0.01 Torr), so that elemental analysis cannot be used as the standard of purity. Attempts to determine their exact molecular mass were unsuccessful due to the extensive decomposition of the samples at the temperature required (40-50 °C) to detect any signal. Thus, we had to rely upon the lack of other spots on TLC—nitroso derivatives afford intense yellow spots, whereas unnitrosated CONH groups are clearly revealed by the chlorine-tolidine method (see: Reindel, F.; Hoppe, W. *Chem. Ber.* **1954**, *87*, 1103)—and the absence of unexpected peaks in the ^1H NMR spectra (200 MHz, below 18 °C) as purity criteria.

(20) Tinkelenberg, A.; Kooyman, E. C.; Louw, R. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 3.

(21) Also see: Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* **1975**, *31*, 227.

Convenient Synthesis of 4-Methylhistamine and Racemic α,4-Dimethylhistamine and α,4-Dimethylhistidine

D. D. Davey* and W. C. Lumma, Jr.

Department of Medicinal Chemistry, Berlex Laboratories, Inc., 110 E. Hanover Avenue, Cedar Knolls, New Jersey 07927

Received November 22, 1988

The search for selective histamine agonists and antagonists remains one of the most active fields in medicinal chemistry. An important compound in this area, 4-methylhistamine (**1**), a selective H_2 agonist, is valuable as both a pharmacological standard and chemical intermediate. Recently, α,4-dimethylhistamine (**2**) has been found to be more selective than **1** as an H_2 agonist, with the *S* isomer having the greater specificity.[1,2] In support of a program in this area, it became necessary to prepare both **1** and **2**, as well as the unreported histidine analogue **3**. The reported preparations for **1**[3,4] and **2**[2,5,6] require tedious isolation procedures, provide low overall yields, and are inconvenient for large-scale synthesis. We now report a convenient method for the synthesis of compounds **1-3** which provides good overall yields and is well suited toward large-scale preparation.

(1) Schwartz, S.; Schunack, W. *Arch. Pharm. (Weinheim, Ger.)* **1982**, *315*(8), 674-80.

(2) Schunack, W.; Schwartz, S.; Gerhard, G.; Bueyuektimkin, S.; Elz, S. *Adv. Biosci.* **1985**, *51*(Front. of Histamine Res.), 39-46.

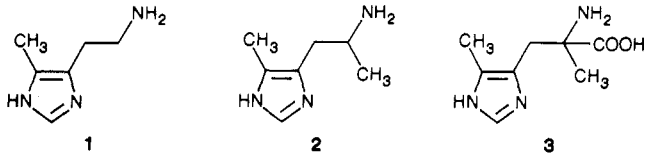
(3) Fox, S. W.; Sargent, H.; Buchman, E. R. *J. Am. Chem. Soc.* **1945**, *67*, 496.

(4) Pfister, J. R.; Kurz, W.; Harrison, I. T. *J. Heterocycl. Chem.* **1981**, *18*, 831.

(5) Plazzi, P. V.; Bordi, F.; Vitto, M.; Impicciatore, M. *Farmaco, Ed. Sci.* **1981**, *36*, 921-31.

(6) Alles, G. A.; Wisegraver, B. B.; Chapmann, N. B.; Tompsett, A. J. *J. Org. Chem.* **1957**, *22*, 221.

0022-3263/89/1954-3211$01.50/0



1 2 3

We have previously described the preparation of **4** from commercially available 5-methyl-1*H*-imidazole-4-carboxylic acid ethyl ester in 71% isolated yield.[7] A published procedure for the reduction of **4** to the alcohol **5** with lithium aluminum hydride[8] (LAH) resulted in unacceptable yields of 20–30%. The low yields obtained for this reaction appear to result from hydride addition to the 4,5-double bond, followed by further reduction of the imidazole ring. However, we observed *no* ring reduction when diisobutylaluminum hydride was employed as the reducing agent, which afforded **5** in 95% yield. Oxidation of the alcohol with activated MnO_2[9] proceeded smoothly at room temperature to provide the aldehyde **6** in 91% (Scheme I).

For the preparation of 4-methylhistamine (**1**), the aldehyde **6** was treated with 1 equiv of ammonium acetate in excess nitromethane to provide the nitroalkene **7** in 82% yield. Attempts to reduce **7** with lithium aluminum hydride to the benzyl-protected 4-methylhistamine **9** resulted in ring reduction, similar to that observed in the LAH reduction of **4**. To circumvent this problem, we converted **7** to the aldoxime **8** in 74% yield under transfer-hydrogenation conditions with palladium on carbon in tetrahydrofuran using sodium hypophosphite as the hydrogen donor.[10] Lithium aluminum hydride reduction of **8** gave **9** as an oil, which could not be easily purified. Hydrogenolysis of the crude oil with palladium on carbon in 95% ethanol containing 3 equiv of HCl afforded **1** as the dihydrochloride in 85% overall yield (Scheme II).

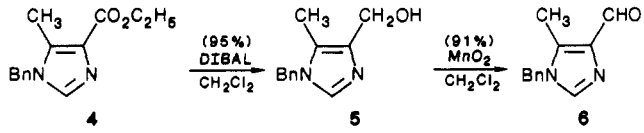
α,4-Dimethylhistamine (**2**) was prepared in similar fashion to **1**. Condensation of the aldehyde **6** with nitroethane and ammonium acetate at 70–80 °C provided nitroalkene **10** in 93% yield. Reduction of **10** with palladium on carbon and sodium hypophosphite afforded the ketoxime **11** as a mixture of *E* and *Z* isomers in 83% yield. Hydrogenation of **11** with palladium on carbon in HCl/ethanol at 50 °C and 50 psi gave α,4-dimethylhistamine as the dihydrochloride in 70% yield (Scheme III).

For the synthesis of the histidine analogue **3**, the ketoxime **11** was hydrolyzed to the corresponding ketone **12** in quantitative yield with sodium nitrite in dilute sulfuric acid at 0 °C.[11] Treatment of **12** with ammonium chloride and potassium cyanide under standard Strecker conditions gave the amino nitrile, which was hydrolyzed without purification in 6 N hydrochloric acid to the amino acid **13** in 51% overall yield. Hydrogenolysis of **13** with palladium on carbon in dilute HCl afforded **3** in 77% yield as the dihydrochloride (Scheme IV).

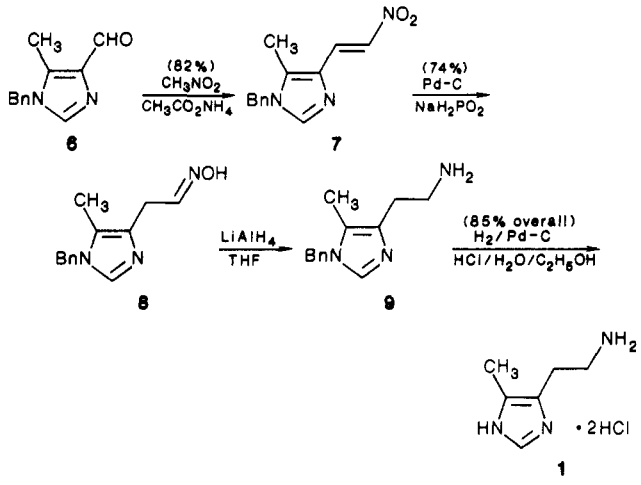
Summary

In conclusion, the methods presented here offer a convenient synthesis of 4-methylhistamine and related analogues which avoids the tedious workups and low yields of previously reported preparations. These compounds are valuable as pharmacological standards and, in particular compounds **9** and **12**, as chemical intermediates for the preparation of novel histamine H_2 agonists and antagonists.

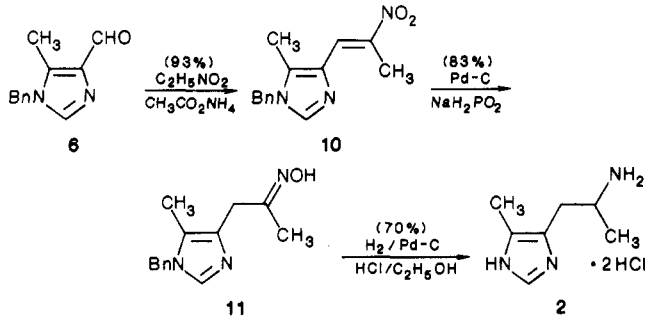
Scheme I



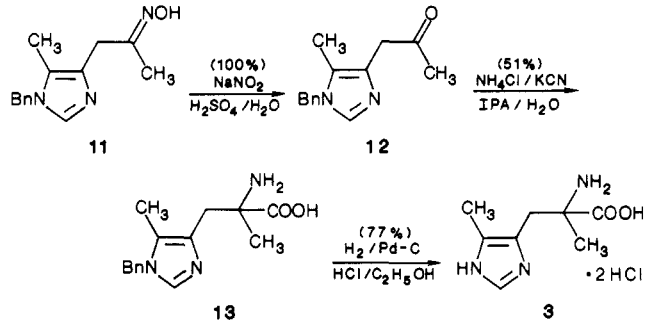
Scheme II



Scheme III



Scheme IV



Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Sargent/Welch 3-300 spectrophotometer. ^1H NMR spectra were recorded on a Varian XL-300 spectrometer. Elemental analyses were performed by the Berlex Analytical Department.

5-Methyl-1-(phenylmethyl)-1*H*-imidazole-4-methanol (5). To a solution of 250 g (1.02 mol) of **4** in 2.5 L of CH_2Cl_2 at 0 °C under nitrogen was added 450 mL (2.52 mol) of diisobutylaluminum hydride over 1 h. After the mixture was stirred for 1 h at 0 °C, 1.5 L of 20% NaOH was added with cooling, and the CH_2Cl_2 was removed under vacuum. The resulting precipitate

(7) Davey, D. *J. Org. Chem.* **1987**, *52*, 4379–81.
(8) Bolhofer, W. A.; Cragoe, E. J.; Hoffman, J. M. U.S. Patent 4,220,654, 1980.
(9) Aldrich Chemical Co., catalog no. 22,432-4.
(10) Varma, R. S.; Varma, M.; Kabalka, G. W. *Synth. Commun.* **1986**, *16*(1), 91–6.
(11) Olah, G. A.; Ho, T. *Synthesis* **1976**, 610.

was filtered and washed with 1 L of 20% NaOH, 2 L of water, and 1 L of ether to afford 196 g (95%) of a white solid: mp 173–4 °C (lit.[8] mp 176–80 °C).

5-Methyl-1-(phenylmethyl)-1*H*-imidazole-4-carboxaldehyde (6). To a solution of 70 g (0.35 mol) of **5** in 1 L of CH_2Cl_2 was added 210 g (2.42 mol) of activated manganese dioxide, and the mixture was stirred at room temperture for 18 h. The reaction mixture was filtered over Celite and the filter cake washed with 2 L of CH_2Cl_2. The filtrate was concentrated under vacuum, and the residue was crystallized from hexanes to provide 63 g (91%) of a white solid: mp 110–1 °C (lit.[8] mp 107–10 °C).

2-[5-Methyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]-1-nitroethene (7). A mixture of 70 g (0.35 mol) of **6** and 30 g (0.39 mol) of ammonium acetate in 400 mL of nitromethane was heated at 40–5 °C under nitrogen for 5 h. The reaction mixture was concentrated under vacuum, slurried in 500 mL of CH_2Cl_2, and filtered over 300 g of silica gel. The filtrate was concentrated under vacuum, and the residue was crystallized from ether to provide 70 g (82%) of a yellow solid (light sensitive): mp 129–30 °C; IR (CH_2Cl_2) 1630, 1500, 1325 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3), 5.11 (s, 2), 7.07 (d, 2), 7.34 (m, 3), 7.57 (s, 1), 7.75 (d, 1), 7.89 (d, 1). Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.94; H, 5.37; N, 17.23.

2-[5-Methyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]ethanone Oxime (8). To a mixture of 50 g (0.21 mol) of **7** and 5 g of 10% palladium on carbon in 1 L of THF under nitrogen was added a solution of 200 g (2.27 mol) of sodium hypophosphite hydrate in 500 mL of water over 1.5 h. Occasional cooling was required to maintain temperature at 20–5 °C. After the mixture was stirred for 1 h at room temperature, the catalyst was removed, and 500 mL of ethyl acetate was added. The reaction mixture was washed with 1 L of saturated K_2CO_3, dried over $MgSO_4$, and concentrated under vacuum. The residue was crystallized from CH_3CN to afford 35 g (74%) of a white solid: mp 145–6 °C; IR (CH_2Cl_2) 1690, 1500, 1445, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, 3), 3.46 (d, 1), 3.67 (d, 1), 5.02 (s, 2), and 6.94–7.53 (m, 7). Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.81; H, 6.40; N, 18.39.

2-[5-Methyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]ethanamine (9). To a slurry of 10 g (0.26 mol) of LAH in 350 mL of THF under nitrogen was added in portions 30 g (0.13 mol) of **8**, and the mixture was stirred for 3 h at room temperature. Following standard workup, the solvent was removed under vacuum to provide 28 g of a crude oil, which was used without further purification.

2-(5-Methyl-1*H*-imidazol-4-yl)ethanamine Dihydrochloride (1). A mixture of 28 g of crude **9** and 3 g of 10% palladium on carbon in 500 mL of ethanol was hydrogenated at 50 °C and 50 psi for 20 h. After removal of the catalyst, 25 mL of 12 N HCl was added, and the mixture was concentrated under vacuum. Crystallization of the residue from 1-propanol afforded 22 g (85% overall) of an off-white solid: mp 233–5 °C (lit.[4] mp 236–8 °C).

1-[5-Methyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]-2-nitropropene (10). A mixture of 40 g (0.20 mol) of **6** and 17 g (0.22 mol) of ammonium acetate in 250 mL of nitroethane was heated at 70–80 °C for 4 h. The excess nitroethane was removed under vacuum, and the residue was slurried in 700 mL of CH_2Cl_2, dried over $MgSO_4$, charcoal treated, and concentrated under vacuum. Crystallization of the residue from ether gave 48 g (93%) of a yellow solid: mp 158–9 °C; IR (CH_2Cl_2) 1655, 1500, 1305 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3), 2.79 (s, 3), 5.12 (s, 2), 7.05 (d, 2), 7.35 (m, 3), 7.61 (s, 1), and 7.94 (s, 1). Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 64.98; H, 5.80; N, 16.18.

1-[5-Methyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]propan-2-one Oxime (11). To a mixture of 60 g (0.23 mol) of **10** and 5 g of 10% palladium on carbon in 1.5 L of THF under nitrogen was added a solution of 200 g (2.27 mol) of sodium hypophosphite hydrate in 500 mL of water over 1 h. After the mixture was stirred for 0.5 h, the catalyst was removed, and the reaction mixture was washed with 1 L of saturated K_2CO_3. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was crystallized from ether to provide 47 g (83%) of a white solid: mp 137–8 °C; IR (CH_2Cl_2) 1690, 1500, 1445, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (s, 0.4), 1.86 (s, 2.6), 2.03 (s, 3), 3.44 (s, 1.8), 3.70 (s, 0.2), 5.01 (s, 2), 7.02 (m, 2), 7.30 (m, 3), and 7.45 (s, 1). Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 68.97; H, 6.89; N, 17.11.

1-(5-Methyl-1*H*-imidazol-4-yl)propan-2-amine Dihydrochloride (2). A mixture of 10 g (41 mmol) of **11** and 5 g of 10% palladium on carbon in 300 mL of 1 M HCl(g)/EtOH was hydrogenated at 50 °C and 50 psi for 20 h. After the mixture was cooled to room temperature, 100 mL of water was added, and the catalyst was removed by filtration. The filtrate was concentrated under vacuum, and the residue was crystallized from THF/AcOH (1:1) to provide 6.2 g (70%) of a tan solid: mp 228–30 °C (lit.[1] mp 223–4 °C).

1-[5-Methyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]propan-2-one Hydrochloride (12). To a solution of 30 g (0.12 mol) of **11** in 300 mL of 20% (v/v) sulfuric acid at 0 °C was added a solution of 18 g (0.26 mol) of sodium nitrite in 50 mL of water, the temperature being maintained at <5 °C. After stirring for 0.5 h at 0 °C, the reaction mixture was made basic with 20% K_2CO_3 and extracted with two 700-mL portions of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and charcoal treated, and the solvent was removed under vacuum to give 28 g (99%) of the free base as an oil. Conversion to the hydrochloride with HCl(g) in acetone afforded 27 g (83% recovery) of a white solid: mp 159–61 °C; IR (CH_2Cl_2) 1870, 1730, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3), 2.31 (s, 3), 3.98 (s, 2), 5.43 (s, 2), 7.22–7.38 (m, 5), and 9.32 (s, 1). Anal. Calcd for $C_{14}H_{16}N_2O$·HCl: C, 63.51; H, 6.47; N, 10.58. Found: C, 63.49; H, 6.34; N, 10.46.

α-Amino-α,5-dimethyl-1-(phenylmethyl)-1*H*-imidazole-4-propanoic Acid (13). A mixture of 20 g (76 mmol) of **12**, 15 g of NH_4Cl, 20 g of KCN, 10 mL of 2-propanol, and 200 mL of concentrated NH_4OH was stirred for 5 h at room temperature. The reaction mixture was poured into 400 mL of 10% K_2CO_3 and extracted with two 400-mL portions of CH_2Cl_2. The combined extracts were charcoal treated and concentrated under vacuum. The residue was dissolved in 500 mL of 6 N HCl and heated at reflux for 6 h. The mixture was concentrated to 100 mL and the pH adjusted to 7 with NaOH. The resulting precipitate was filtered and washed with water and ether to provide 10.5 g (51%) of a white, hygroscopic solid: mp 218–22 °C; IR (Nujol) 3180, 1600, 1490 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.45 (s, 3), 2.06 (s, 3), 2.80 (d, 1), 3.04 (d, 1), 5.15 (s, 2), 7.09 (d, 2), 7.30 (m, 3), 7.63 (s, 1). Anal. Calcd for $C_{15}H_{19}N_3O_2$·0.1H_2O: C, 65.48; H, 7.03; N, 15.27. Found: C, 65.42; H, 6.90; N, 15.26.

α-Amino-α,5-dimethyl-1*H*-imidazole-4-propanoic Acid Dihydrochloride (3). A mixture of 11.8 g (43 mmol) of **13** and 5 g of 10% palladium on carbon in 300 mL of 1 M HCl was hydrogenated at 50 °C and 50 psi for 24 h. The catalyst was removed by filtration, and the filtrate was concentrated to dryness under vacuum. Crystallization of the residue from AcOH afforded 8.5 g (77%) of a white solid: mp 236–8 °C; IR (Nujol) 3150, 1730, 1625, 1585 cm^{-1}; ^1H NMR (D_2O) δ 1.64 (s, 3), 2.32 (s, 3), 3.35 (s, 2), 8.60 (s, 1). Anal. Calcd for $C_9H_{13}N_3O_2$·2HCl: C, 37.52; H, 5.90; N, 16.41. Found: C, 37.69; H, 6.03; N, 16.22.

Registry No. **1**·2HCl, 36376-47-3; **2**·2HCl, 120231-05-2; **3**·2HCl, 120262-58-0; **4**, 75815-53-1; **5**, 75815-55-3; **6**, 75815-57-5; **7**, 120231-06-3; **8**, 120231-07-4; **9**, 120231-08-5; **10**, 120231-09-6; (*E*)-**11**, 120231-12-1; (*Z*)-**11**, 120262-59-1; **12**·HCl, 120231-10-9; **12** (free base), 120231-11-0; **13**, 120231-13-2.

A Convenient Route to Adenine N^1-Oxide Mono- and Polynucleotides by Oxidation with Potassium Monopersulfate

Anass Ech-Cherif Kettani, Jean Bernadou,* and Bernard Meunier*

Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, 31077 Toulouse Cedex, France

Received December 30, 1988

Direct oxidation to *N*-oxides of purines and related derivatives has been previously described, but syntheses are not straightforward: the oxidizing reagent is not always readily and easily available (case of monopermaleic acid[1]),

0022-3263/89/1954-3213$01.50/0