An Improved Synthesis of 5,6-Diacetoxy-*N*-methylindole and of Epinine

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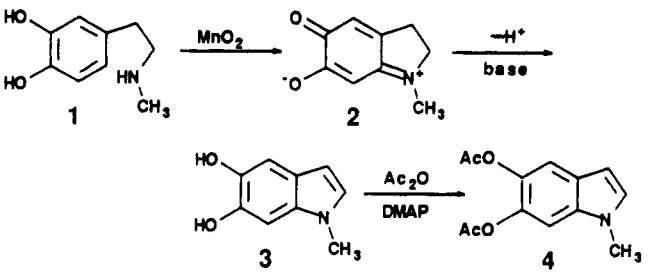
5,6-Diacetoxy-*N*-methylindole (4) is a stable, protected form of 5,6-dihydroxyindole (3), which itself is a precursor to melanin-like polymers.[1] As such precursors have potential applications in hair-coloring formulations[2] and as antioxidants,[3] an efficient synthesis of 4 is needed. Here we describe a new route to 4 based on the oxidative cyclization of epinine (1) using manganese dioxide, followed by a base-catalyzed isomerization and then acetylation. Epinine, a biologically active[4] derivative of the hormone epinephrine (7), was synthesized by a new, highly-practical process in which the key step was a hydrogenolysis in aqueous HCl.

In general, 5,6-dihydroxyindoles are unstable in oxidizing, basic, and strongly acidic environments. Consequently, synthetic strategies must avoid these conditions once the indolic system is formed. Reductive cyclization of 2,β-dinitrostyrenes[1b,5] or 2-(2-nitroaryl)acetaldehydes[1a] meet these conditions, but these approaches involve inefficient protecting group manipulations. Oxidative cyclizations of epinine[6,7] or epinephrine[8,9] to first form aminochromes (indole precursors) have also been developed. These approaches typically use expensive oxidants and reductants, and they often afford low yields. A subsequent N-alkylation would be required to obtain the desired product 4. Successful commercialization requires a better process.

Synthesis of 5,6-Diacetoxy-*N*-methylindole

Epinine (1) is an amino catechol which can be oxidized to an *o*-quinone and cyclized in a Michael-like fashion. The indoline product is further oxidized to the relatively stable epinochrome (2), which is deep red and water soluble (Scheme I). Isomerization, driven here by the thermodynamic stability of aromaticity, gives a colorless, organic-soluble dihydroxyindole (3). This indole is extremely sensitive to further oxidation, which would afford melanin-like polymers. In the overall process to 4, the key to good yields is to oxidatively cyclize the catechol carefully without concomitant isomerization, to completely remove all of the oxidant, and then to effect the isomerization.

Scheme I



Using manganese dioxide[10] in an aqueous buffered system was an excellent method to effect the oxidative cyclization. The hydrochloride salt of 1 was first dissolved in a pH 6 phosphate buffer. This solution was then stirred with manganese dioxide for 1–2 min[11] and filtered. Alternatively this solution was eluted through a column of MnO_2 dispersed on diatomaceous earth. In either case, the oxidant was separated, and then the aminochrome 2 was isomerized using a weakly-basic solid or supported catalyst. Both alumina and Amberlyst A-21 worked well, and these catalysts were easily recovered by filtration. By effecting this isomerization in a triphasic system (organic, aqueous, and solid catalyst), the produce indole 3 was extracted as it was formed. Acetylation (acetic anhydride and DMAP) afforded the targeted diacetate 4 in a 61% overall yield. If acetic anhydride was directly added to the organic phase of the isomerization step, the overall yield jumped to 80%. Presumably, the indole 3 was protected from oxidative polymerization as it was formed.

Manganese dioxide is inexpensive, and any excess of it and the reduced manganese coproduct are easily removed by filtration. Other oxidizing agents (H_2O_2, $H_2O_2/FeSO_4$, O_2, NaOCl, $NaClO_3/V_2O_5$) gave little or no indole product. Earlier workers effected this oxidative cyclization using potassium ferricyanide[6] and silver oxide,[7] the former of which required an inefficient quench, the latter of which was prohibitively expensive.

The buffer–solvent system appeared to be critical. An aqueous, pH 6, potassium monobasic phosphate solution had sufficient acidity to ensure solubility of epinine in the aqueous phase. Moreover, it had adequate basicity so that the intermediate *o*-quinone could cyclize. In addition, both aminochrome 2 and the subsequent rearrangement product dihydroxyindole 3 were relatively stable in this buffer. Other aqueous and organic solvent mixtures (H_2O/HCl, H_2O/NaOAc, toluene/Huenig's base, HOAc/NaOAc) were less satisfactory.

In our studies of an analogous system—the oxidation of epinephrine (7) to its corresponding aminochrome—we found that initially acidifying the reaction medium to pH 6 with a small amount of phosphoric acid and *not* employing the phosphate buffer gave unacceptable recoveries. Moreover, we learned that the concentration of the substrate in the aqueous medium was also critical.[11]

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(2) Semuller, J. R.; Charle, R.; Pigerol, C. U.S. Patent 3,194,734, 1965. Charle, R.; Pigerol, C. U.S. Patent 2,934,396, 1960. Schultz, T.; Brown, K.; Murphy, B. P.; Mayer, A.; Lim, M. I. Eur. Pat. Application 335477, 1989. Brown, K.; Mayer, A.; Murphy, B.; Schultz, T.; Wolfram, L. *J. Chem. Soc. Cosmet. Chem.* **1989**, *40*, 65.

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(5) Murphy, B. P. *Synth. Commun.* **1985**, *15*, 321. Murphy, B. P.; Schultz, T. M. *J. Org. Chem.* **1985**, *50*, 2790. Beer, R. J. S.; Clarke, K.; Davenport, H. F.; Robertson, A. *J. Chem. Soc.* **1951**, 2029. Beer, R. J. S.; Clarke, K.; Khorana, H. G.; Robertson, A. *J. Chem. Soc.* **1948**, 2223. Benigni, J. D.; Minnis, R. L. *J. Heterocycl. Chem.* **1965**, *2*, 387. Batcho, A. D.; Leimgruber, W. U.S. Patent 3,976,639, 1976.

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(8) Mattock, G. L.; Heacock, R. A. *Can. J. Chem.* **1964**, *42*, 484. Harley-Mason, J. *J. Chem. Soc.* **1950**, 1276. Lim, M. I.; Patil, D. G. *Tetrahedron Lett.* **1987**, *28*, 3775.

(9) The standard epinephrine-based route to 4 requires a second reduction step after the oxidation/isomerization.

(10) (a) Lund, A. *Acta Pharmacol.* **1950**, *6*, 137. (b) Lund, A. *Acta Pharmacol.* **1949**, *5*, 231. (c) Cohen, G.; Goldberg, M. *J. Neurochem.* **1957**, *2*, 58.

(11) Wyler, v. H.; Chiovini, J. *Helv. Chem. Acta* **1968**, *51*, 1476.

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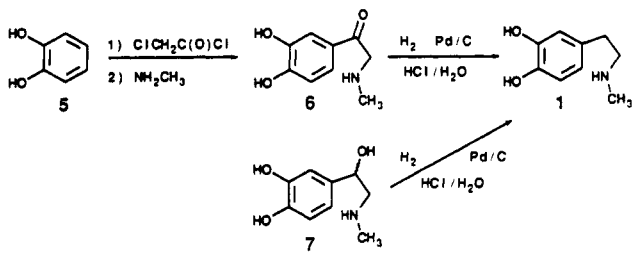
Scheme II



Increasing the concentration from 1% to 10% caused a 14-fold decrease in the isolated yields of the acetylated product 4. The epinine-based chemistry is anticipated to have similar limitations.

The conversion of aminochrome 2 to 5,6-dihydroxy-*N*-methylindole (3) involves a proton shift. This isomerization was readily effected with the weakly-basic catalysts alumina and also Amberlyst A-21. Here, the yields were as good or better than earlier approaches. Moreover, the catalyst and the aqueous buffer were readily isolated, recovered, and recycled. The advantages are implicit: waste-disposal and material costs are minimized, and thus the economic returns are maximized. Other catalytic isomerization systems, namely palladium on carbon,[12] Lewis acids[13] (particularly zinc acetate[6]), and acetic anhydride/pyridine[6,12b] were less attractive from these perspectives. Clearly, solid and solid-supported, weakly-basic catalysts present a novel and practical approach for effecting this isomerization.[14]

Synthesis of Epinine

The usefulness of this epinine-based chemistry to synthesize 4 is only assured if a practical route to epinine (1) itself is available. Unfortunately, the published approaches involve highly inefficient chemistries, often with tedious functional and protecting group manipulations.[15] Thus we developed a more direct route (Scheme II).

As in the commercial process[16] to epinephrine (7), catechol (5) was chloroacetylated[17] and then methaminated to give adrenalone (6).[18] The key, unprecedented step to epinine was the hydrogenolysis of 6.[19] This was efficiently effected at approximately 70 °C with H_2 in the presence of 10% Pd on carbon in aqueous hydrochloric solutions (5% or 38%). A 91% yield (^{1}H NMR spectroscopy, internal standard) of clean 1 was obtained, with a weight recovery in excess of 100%; this recovery suggests that a hydrate of the hydrochloride salt was isolated.

Quantitative conversions to epinine were also obtained by hydrogenating epinephrine (7), using the same conditions as above. This phenomenon is consistent with epinephrine's being an intermediate in the hydrogenolysis of adrenalone.

Interestingly, adrenalone (6) dissolved in an *alcoholic* hydrogen chloride solution gave *epinephrine* (7) when hydrogenated in the presence of Pd/C.[20] Moreover, a literature procedure[21] tailored specifically for the hydrogenolysis of α-aminoacetophenones (hydrogenation with Pd/C in acetic acid–perchloric acid) failed to give 1 at all but gave, instead, trace quantities of 7 plus polymers.

Experimental Section

^{1}H NMR and ^{13}C NMR (300 and 75.5 MHz, respectively) spectra were obtained on a General Electric QE-300 spectrometer. The chemical shifts are reported in parts per million (ppm) downfield relative to the internal standard either tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)propionate-*2,2,3,3-d*$_4$ (TSP). Along with the standard carbon experiment, an attached proton test (APT) was run. Here the methylene/quaternary centers are indicated with a positive (+) absorption, and the methyl/methine centers are indicated with a negative (−) absorption. All reagents were used as obtained from commercial sources without purification, unless otherwise noted. The palladium on carbon catalyst was obtained from Aldrich, and the aluminum oxide catalyst was obtained from Fisher. Both epinine and epinephrine are highly toxic and should be handled accordingly.

5,6-Diacetoxy-*N*-methylindole (4) by Oxidative Cyclization of Epinine (1) with Manganese Dioxide Followed by Isomerization with Alumina. To 51 mg (0.20 mmol) of 79% epinine hydrochloride (1·HCl) dissolved in 3.7 g of pH 6 phosphate buffer (100 mL of 0.10 M KH_2PO_4 plus 11.2 mL of 0.10 N NaOH) was added 0.27 g (3.10 mmol) of manganese dioxide. After 2 min, this red mixture was filtered under N_2 into a mixture of 2.0 g of aluminum oxide (Alumina Adsorption previously washed with water) plus 10 mL of ethyl acetate. After 1 h of rapid stirring, nearly all of the pink coloring had faded. This was filtered again under N_2, and the bilayer was separated. The aqueous fraction was extracted with four 15-mL portions of ethyl acetate. The organic fractions were combined, dried over sodium sulfate, and concentrated to approximately 2 mL. This solution was treated with 2.0 g (19.6 mmol) of acetic anhydride plus 2 mg (0.016 mmol) of 4-(*N,N*-dimethylamino)pyridine. This mixture was heated at 60 °C with stirring for 1.5 h and then allowed to stand overnight. The reaction mixture was diluted with 50 mL of ethyl acetate and then washed with two 25-mL portions of brine and with one portion each of 5% aqueous HCl, 3% aqueous sodium bicarbonate, and brine again. The mixture was dried over sodium sulfate and then concentrated. Recrystallization from ethanol afforded 30 mg (61% yield) of yellow crystals which were >95% pure as shown by proton NMR spectroscopy: mp 109–110 °C (lit.[22] mp 109–110 °C); ^{13}C NMR ($CDCl_3$, TMS)[1b] 170.1 (ester carbonyl, +), 169.9 (ester carbonyl, +), 138.5 (C8, +), 136.8 (C6, +), 134.8 (C5, +), 131.2 (C2, −), 126.8 (C9, +), 114.9 (C4, −), 104.3 (C7, −), 102.1 (C3, −), 33.9 (C10, −), 21.5 (CH_3 of acetate, −); ^{1}H NMR ($CDCl_3$, TMS)[23] 7.37 (s, 1 H), 7.14 (s, 1 H), 7.06 (d, J = 3 Hz, 1 H), 6.44 (d, J = 3 Hz, 1 H), 3.74 (s, 3 H), 2.31 (s, 3 H), 2.31 (s, 3 H).

5,6-Diacetoxy-*N*-methylindole (4) by Oxidative Cyclization with Manganese Dioxide Followed by Isomerization with Amberlyst A-21 in the Presence of Acetic Anhydride. To 56 mg (0.22 mmol) of 79% epinine hydrochloride in 5.0 g of buffer (see above) was added 0.26 g (3.0 mmol) of manganese

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(13) Katritzky, A. R. *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1965; Vol. 5, p 205.

(14) Aqueous alkali has been used to catalyze the isomerization of adrenochrome to adrenolutine,[10b,c] but it was found that the product polymerizes under these conditions. This can be minimized by adding ascorbic acid or other reducing agents.

(15) From isoquinolines: Pyman, F. L. *J. Chem. Soc.* **1910**, *97*, 264. By deprotection of methyl[(3,4-dimethoxyphenyl)ethyl]amine: Buch, J. S. *J. Am. Chem. Soc.* **1930**, *52*, 4119. By dechlorination of 3,4-diacetoxy-1-[1-chloro-2-(methylamino)ethyl]benzene: Bretschneider, H. *Monatsh.* **1948**, *78*, 82. From methylhomoveratrylamine: Bretschneider, H. *Monatsh.* **1947**, *76*, 355.

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(17) Ott, E. *Chem. Ber.* **1926**, *59*, 1068.

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(20) For reductions of phenones with similar structures, please refer to Norlander, J. E.; Payne, M. J.; Njoroge, F. G.; Balk, M. A.; Laikos, G. D.; Vishwanath, V. M. *J. Org. Chem.* **1984**, *49*, 4107.

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(23) Heacock, R. A.; Hutzinger, O.; Scott, B. D.; Daly, J. W.; Witkop, B. *J. Am. Chem. Soc.* **1963**, *85*, 1825.

dioxide. After 1.5 min, this mixture was filtered through diatomaceous earth under a blanket of N_2. The red effluent was rapidly stirred with 15 mL of ethyl acetate and 2.0 g of acetic anhydride for 60 min. Then 2.0 g of water-washed Amberlyst A-21 was added, and the mixture was stirred for a second hour while the red hue slowly faded. The reaction mixture was again filtered under N_2. The phases were separated, and the aqueous layer was extracted with three 30-mL portions of ethyl acetate. The organic fractions were combined, dried over sodium sulfate, and then evaporated. The residue was acetylated as above, affording 43 mg of brown crystals. This corresponded to an 80% yield of 4 which was clean by proton NMR spectroscopy.

Epinine (1) Hydrochloride by Hydrogenolysis of Adrenalone (6). A Parr hydrogenation apparatus was charged with 110 mg (0.49 mmol) of 6·HCl, 5.0 g of 5% aqueous HCl, and 27 mg of 10% Pd/C catalyst. This was shaken for 20 h at 67 °C under 50 psi of H_2. After cooling, the mixture was vacuum filtered and concentrated. A 91% yield of clean 1 was detected[24] (by proton NMR spectroscopy using the internal standard *N,N*-dimethylbenzylamine); 102 mg of a yellow oil was obtained: ^{13}C NMR (D_2O, TSP) 145.0 (C2, +), 143.8 (C1, +), 129.8 (C4, +), 122.0 (C5, -), 117.3 (C3&6, -), 51.0 (C8, +), 33.6 (C9, -), 31.7 (C7, +); ^1H NMR (D_2O, TSP) 6.90 (d, J = 8 Hz, 1 H), 6.84 (d, J = 3 Hz, 1 H), 6.74 (dd, J = 8, 3 Hz, 1 H), 3.24 (t, J = 8 Hz, 2 H), 2.88 (t, J = 8 Hz, 2 H), 2.72 (s, 3 H), 1.71 (bs, 2 H).[24]

Epinine (1) by Hydrogenolysis of Epinephrine (7). A Parr hydrogenation apparatus was charged with 2.0 g (11 mmol) of 7, 20 g of 5% aqueous HCl, and 0.40 g of 10% Pd/C catalyst. This was shaken for 24 h at 60 °C under 50 psi of H_2. After cooling, the mixture was vacuum filtered and concentrated to afford 2.25 g of a yellow oil which crystallized upon standing over a several-day period. By proton NMR spectroscopy, this was identified as a hydrate of the hydrochloride salt of epinine, with no traces of the starting material 7.

(24) An authentic sample of epinine hydrochloride was obtained commercially from Sigma.

Registry numbers provided by author: 1, 501-15-5; 2, 3736-29-6; 3, 99855-01-3; 4, 13988-19-7; 5, 120-80-9; 6, 99-45-6; 7, 329-65-7.