Anal. Calcd for $C_{52}H_{56}O_4$: C, 83.83; H, 7.58. Found: C, 83.79; H, 7.63.

Reduction of 2 with DN=ND. Reaction conditions were first worked out with unlabeled diimide and were shown to give **3**, after which the following procedure was used. To a stirred solution of **2** (0.30 g, 0.41 mmol) in 50 mL of ethanol-d_1 and 50 mL of tetrahydrofuran containing 2 g of suspended potassium azodicarboxylate under nitrogen was added 2 mL of acetic acid-d_1 dropwise over 30 min. The mixture was stirred for an additional 19 h and then concentrated under reduced pressure, and the resulting solid was recrystallized from chloroform–acetone or from methylene chloride to give **3**-d_8 (0.30 g, 97%): ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 24 H), 2.93 (s, 8 H), 6.90–7.13 (m, 8 H), 7.20–7.47 (m, 8 H).

Reduction of 6. Catalytic hydrogenation of **6**[12] (3.0 g, 17.4 mmol) in 100 mL of methanol over 0.5 g of Pd/C at 50 psi for 19 h gave a nearly quantitative yield of **5** as a liquid: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.500 (d, 2 H, J = 7 Hz), 1.813 (s, 6 H, CH_3), 1.921 (d, 2 H, J = 7 Hz), 7.136 (m, 2 H, arom), 7.144 (m, 2 H, arom). Reduction of **6** with DN=ND by a procedure analogous to that described for **2** gave, from 0.52 g (3.0 mmol) of **6**, 0.51 g (2.87 mmol, 96%) of **5**-d_2: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.45 (s, 2 H), 1.78 (s, 6 H), 6.98 (br s, 4 H).

Benzyne Addition to 7.[6] A solution of **7** (2.01 g, 4.3 mmol) and benzenediazonium carboxylate hydrochloride (2.0 g, 10.8 mmol) in 100 mL of 1,2-dichloroethane containing 10 mL of propylene oxide was heated at reflux with stirring for 3 h. The reaction mixture was concentrated under reduced pressure, filtered, washed, and recrystallized from acetone–ethanol or methylene chloride–hexane to give 2.60 g (4.19 mmol, 97%) of **8**[13] as colorless needles: mp 260–262 °C; IR (Nujol), 1710 (s), 1410 (m), 1305 (s), 1050 (s), 1025 (s), 950 (s), 770 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 24 H, CH_3), 2.60 (s, 8 H, CH_2), 6.67 (s, 4 H, =CH), 6.63–6.83 (m, 4 H, arom), 7.00–7.20 (m, 4 H, arom); ^{13}C NMR ($CDCl_3$) δ 211.57, 150.12, 143.36, 124.45, 121.40, 95.61, 48.75, 35.27, 21.98, 21.06; mass spectrum, m/e 620 (M^+), 185 (base).

Anal. Calcd for $C_{40}H_{44}O_6$: C, 77.39; H, 7.14. Found: C, 77.46; H, 7.13.

Hydrogenation of 8. Hydrogenation of **8** (1.85 g, 3 mmol) in 100 mL of tetrahydrofuran and 30 mL of ethanol over 0.5 g of 10% Pd/C at 50 psi overnight gave 1.75 g (2.8 mmol, 93%) of **9**, recrystallized from benzene as colorless prisms: mp 306–308 °C; IR (Nujol) 1700 (s), 1410 (w), 1030 (s), 760 cm^{-1} (s); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.284 (d, 4 H, J = 7 Hz), 1.485 (s, 12 H, CH_3), 1.500 (s, 12 H, CH_3), 2.050 (d, 4 H, J = 7 Hz), 2.579 (s, 8 H, O=CCH_2), 7.098 (m, 4 H, arom), 7.102 (m, 4 H, arom); ^{13}C NMR ($CDCl_3$) δ 211.94, 145.59, 126.38, 120.11, 90.67, 49.60, 33.60, 29.22, 21.66, 21.36; mass spectrum, m/e (relative intensity) 596 (17), 568 (3), 540 (17), 242 (42), 200 (53), 185 (100), 171 (33), 159 (47).

Anal. Calcd for $C_{40}H_{48}O_6$: C, 76.89; H, 7.74. Found: C, 76.77; H, 7.69.

Dehydration of 9. A solution of **9** (1.0 g, 1.60 mmol) and *p*-toluenesulfonic acid hydrate (1 g) in 100 mL of benzene was heated at reflux for 8 h. The reaction mixture was washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4), and concentrated under vacuum to give **10**, which recrystallized from methylene chloride as colorless prisms (0.88 g, 99%): mp 332–333 °C; IR (Nujol) 1140 (s), 1020 (s), 1010 (s), 960 (s), 830 (s), 780 (vs), 760 cm^{-1} (vs); ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 12 H, CH_3), 1.73 (s, 12 H, CH_3), 6.10 (s, 4 H, furan), 6.60–6.80 (m, 4 H, arom), 7.10 (s, 4 H, arom), 7.33–7.58 (m, 4 H, arom); ^{13}C NMR ($CDCl_3$) δ 162.04, 140.38, 131.58, 125.91, 124.01, 122.16, 101.70, 40.00, 32.23, 26.95; mass spectrum, m/e (relative intensity) 552 (78), 537 (100), 522 (2), 507 (4), 492 (7), 276 (5), 261 (39).

Anal. Calcd for $C_{40}H_{40}O_2$: C, 86.92; H, 7.29. Found: C, 86.87; H, 7.34. The ^{1}H NMR spectrum of **10** was measured in dimethyl-d_6 sulfoxide from room temperature to 113 °C. Only the signals at δ 1.63 and 1.73 for the methyl groups changed; they coalesced to a broad singlet at 83 °C and became sharp at 113 °C; on cooling, the original spectrum reappeared, and **10** was recovered unchanged.

Compound **10** was recovered quantitatively from attempted reactions with benzyne and *N*-phenyltriazolinedione.

Acknowledgment. We are indebted to the National Science Foundation (Grant CHE 8017746) for financial support of this research.

Registry No. **1**, 22900-44-3; **2**, 83077-43-4; **3**, 83077-44-5; **3**-d_8, 83077-45-6; **5**, 61200-08-6; **5**-d_2, 83077-46-7; **6**, 7405-93-5; **7**, 78804-50-9; **8**, 83095-77-6; **9**, 83095-78-7; **10**, 83095-79-8; benzyne, 462-80-6.

(12) Prepared from benzyne and 2,5-dimethylfuran in the usual way.

(13) Compound **8** was also obtained by (a) addition of benzyne to the bis(enedione) precursor of **7** (compound **3** in ref 6) to give an adduct in 68% yield, followed by (b) reduction of the adduct with zinc and acetic acid to give **8** (99%), identical (mp, NMR) with the product obtained from **7**.

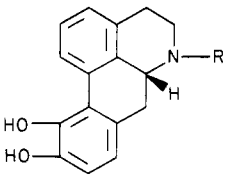
Aporphines. 42.[1] Synthesis of (*R*)-(-)-11-Hydroxyaporphines from Morphine

Vishnu J. Ram and John L. Neumeyer*

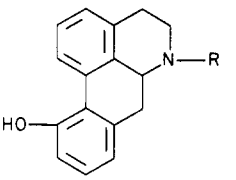
Section of Medicinal Chemistry, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115

Received January 29, 1982

Apomorphine (**1a**) and its *N*-alkyl congener **1b** are potent dopamine (DA) receptor agonists and have found clinical application in a variety of neurological disorders.[2] In earlier studies we evaluated 8-, 10-, or 11-hydroxyaporphines and concluded that (±)-11-hydroxy-*N*-*n*-propylnoraporphine((±)-**2b**) yields apparent DA-receptor



1a, R = CH_3; apomorphine
b, R = $CH_2CH_2CH_3$; *N*-*n*-propylnorapomorphine



2a, R = CH_3
b, R = n-C_3H_7

agonist activity when administered to rats in vivo.[3,4] Recent studies[5] with (±)-**2b** confirmed the earlier in vivo DA agonist activity of this hydroxyaporphine by in vitro evaluation against the high-affinity binding of [^{3}H]apomorphine and [^{3}H]spiroperidol with a subcellular fraction of caudate nucleus from bovine brain and DA-sensitive adenylate cyclase activity in homogenates of rat brain striatal tissue. These results led us to the preparation of (-)-**2a,b** for further biological studies. We report the details of the preparation of the 6a*R* (levorotatory) isomer of **2a,b** since it has been well established that DA agonist activity in apomorphine and related aporphines resides principally in the 6a*R* (levorotatory) isomer[6,7]

Our earlier synthesis[3] of (±)-**2a,b** involved a Reisert alkylation–Pschorr cyclization route which was used successfully for the synthesis of a variety of mono- and dihydroxyaporphines. It is possible to obtain levorotatory

(1) For part 41, see: Campbell, A.; Baldessarini, R. J.; Ram, V. J.; Neumeyer, J. L. *Neuropharmacology*, in press.

(2) Neumeyer, J. L.; Lal, S.; Baldessarini, R. J. In "Apomorphine and Other Dopaminomimetics"; Gessa, G. L., Corsini, G. U., Eds.; Raven Press: New York, 1981; Vol. 1, p 1.

(3) Neumeyer, J. L.; Granchelli, F. E.; Fuxe, K.; Ungerstedt, U.; Corrodi, H. *J. Med. Chem.* **1974**, *17*, 1090.

(4) Schoenfeld, R. I.; Neumeyer, J. L.; Dafeldecker, W.; Roffler-Tarlov, S. *Eur. J. Pharmacol.* **1975**, *30*, 63.

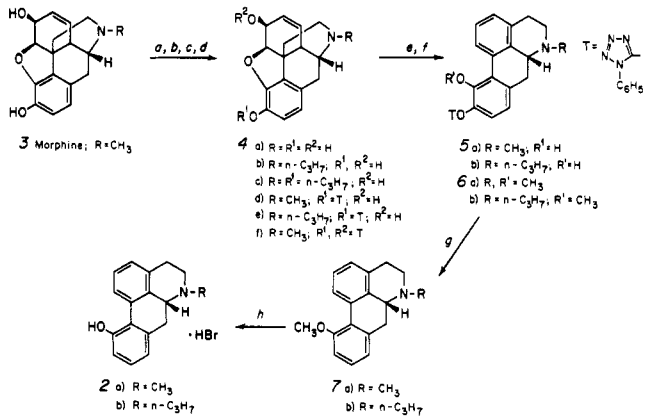
(5) Neumeyer, J. L.; Arana, G. W.; Law, S. J.; Lamont, J. S.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1981**, *24*, 1440.

(6) Saari, W.; King, S. W.; Lotti, V. J. *J. Med. Chem.* **1973**, *16*, 171.

(7) Neumeyer, J. L.; Law, S. J.; Lamont, J. S., ref 2., pp 209–218.

0022-3263/82/1947-4372$01.25/0

Scheme I. Synthesis of (−)-(*R*)-11-Hydroxyaporphines from Morphine[a]



[a] (a) CH_3OCOCl, $NaHCO_3$; (b) N_2H_4; (c) n-C_3H_7I, $NaHCO_3$; (d) TCl; (e) CH_3SO_3H; (f) CH_2N_2; (g) H_2, 5% Pd/C, AcOH; (h) HBr.

2a,b by the resolution of the (±)-11-methoxyaporphines (±)-**7a,b**,[3] followed by ether cleavage as carried out for the enantiomers of APO.[6] We chose, however, to develop a more direct stereoselective synthesis of **2a,b** from morphine. The strategy for this synthesis involved the removal of the phenolic hydroxyl group on morphine, which could be obtained by the procedure of Brossi et al.[8] in several steps, followed by rearrangement to the aporphine. Alternatively, the selective removal of one of the phenolic hydroxyl groups via the phenyltetrazolyl ether could be effected on the aporphine ring by a procedure which we have recently applied to the conversion of morphothebaine to apomorphine.[9] The former method proved to be unsatisfactory since the hydrogenolysis of the phenyltetrazole ether **4d** with Pd/C (5%) in AcOH gave 3-*O*-(1-phenyltetrazolyl)-7,8-dihydromorphine which could not be rearranged in CH_3SO_3H[10] to the desired aporphine **5a**. The latter procedure involving the rearrangement of the phenyltetrazolyl ether of morphine **4d** to the 10-*O*-(1-phenyltetrazolyl) ether of apomorphine **5a** proved to be more advantageous. We had previously observed that the rearrangement of the 6-*O*-(1-phenyltetrazolyl) ether of codeine led to a high yield of apocodeine.[10] The 3-*O*-(1-phenyltetrazolyl) derivatives of morphine **4d** or *N*-*n*-propylnormorphine **4e** were prepared by generating the phenolic alkoxide with K_2CO_3 which reacts with equimolar quantities of 5-chloro-1-phenyl-1*H*-tetrazole (TCl) in acetone (Scheme I). The bis(phenyltetrazolyl) ether **4f** was obtained by generating both the allylic and the phenolic alkoxides with NaH in THF and 2 molar equiv of TCl. Rearrangement of **4d**, **4f**, or **4e** in CH_3SO_3H led to the aporphines **5a,b** in 70–75% yield. Hydrogenolysis of **5a** with Pd/C (5%) in acetic acid for 2 days at room temperature and at elevated pressure led to recovery of starting materials. We also attempted the conversion of **5a** to **2a** by a recently reported catalytic hydrogen-transfer procedure[11] but failed to isolate the desired monophenol **2a**. Etherification of the 11-hydroxy group in **5a,b** with CH_2N_2 led to **6a,b** which could be successfully hydrogenolyzed to **7a,b** in 50–57% yield. The reaction was carried out at room temperature and required 11–19 days for completion. These conditions were required to avoid racemization at the chiral 6a-position. *O*-Demethylation of **7a,b** with 48% HBr led to the desired products (−)-**2a,b** as the hydrobromide in 73–74% yields. The mass, UV, and IR spectra as well as the TLC properties of (−)-**2a** were identical with those of an authentic sample of (±)-**2a** prepared previously via an alternate procedure.[3]

The enantiomeric purity of (*R*)-(−)-11-hydroxy-*N*-*n*-propylnoraporphine [(−)-**2b**] was established to be >99% by using a procedure[12] for the chiral derivatization and chromatographic resolution of the resulting diastereomers. Thus both (±)-**2a** (available in our laboratory from previous studies[3]) and (−)-**2b** were treated with (−)-α-methylbenzyl isocyanate and converted to the diastereomeric carbamates which could be resolved chromatographically. The chromatogram of the carbamate derived from (±)-**2b** shows two peaks of equal intensity with retention times of 8.15 and 8.7 min, whereas the carbamate derived from (−)-**2b** has a retention time of 8.7 min (peak height 116.5 mm) with only a trace of the (+) enantiomer at 8.15 min (peak height 0.5 mm). The stereoselective synthesis of (−)-**2a,b** from morphine has thus been demonstrated.

Experimental Section

General Methods. Evaporations were carried out in a Büchi rotary evaporator in vacuo at a bath temperature below 50 °C. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Analysis were performed by Galbraith Laboratories, Knoxville, TN. Samples for analyses were dried at 10^{-2} mm over silica gel at 55 °C. Preparative TLC was carried out on silica gel (Analteck, 20 × 20 cm, 2000 μm). Column chromatography was performed on silica gel (Baker, 5–3405, 60–200 mesh). Detection was done in UV light (Minerallight) or with iodine vapor. The IR spectra were measured in $CHCl_3$ or KBr with a Perkin-Elmer Model 700 spectrometer. NMR spectra were obtained with a Varian T-60 spectrometer in $CDCl_3$ or CD_3SOCD_3; $(CH_3)_4Si$ was used as an internal standard. UV spectra were carried out in EtOH with a Beckman DB-G grating spectrophotometer. Mass spectra were determined on a Nuclide 12-90-G mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter, Model 142. Chromatographic separations were carried out on a high-pressure LDC double-pump gradient system equipped with a Valco injector, a Supelcosil C-8 column (15 cm × 4.5 mm i.d., particle size 5 μm), and a 214-nm LDC UV detector.

Normorphine (4a) was prepared by the procedure of Brine et al.[13] with methyl chloroformate: 78% yield; mp 270–272 °C (lit.[13] mp 272–274 °C).

***N*-*n*-Propylnormorphine (4b).** A mixture of **4a** (3.0 g, 11 mmol), n-C_3H_7I (1.9 g, 11.2 mmol), and $NaHCO_3$ (1.5 g, 17.8 mmol) in 300 mL of EtOH was allowed to reflux for 18 h, cooled, and filtered. The filtrate was evaporated, and the crude product was applied to a silica column and eluted with $MeOH/CHCl_3$ (10.1) mixture to yield **4b**: 2.5 g (72.3%); mp 214–220 °C; (lit.[14] mp 233–235 °C); mass spectrum, m/e 313 (M^+), 312 ($M^+ - 1$), 298 ($M^+ - CH_3$), 284 ($M^+ - Et$). In a second run of this reaction, the reactants were allowed to reflux for 48 h in 75 mL of EtOH, which led to **4b** and a second fraction with a higher R_f value (12% yield), was converted into ***N*-*n*-propyl-3-*O*-*n*-propylnormorphine hydrochloride (4c)** with etheral HCl: mp 120–135 °C; $[\alpha]^{22.5}_{578}$ −95.4° (*c* 0.151, MeOH); mass spectrum, m/e 355 (M^+), 354 ($M^+ - 1$), 326 ($M^+ - C_2H_5$). Anal. Calcd for $C_{22}H_{29}NO_3 \cdot HCl \cdot H_2O$: C, 64.47; H, 7.81; N, 3.42. Found: C, 64.71; H, 7.86; N, 3.59.

3-*O*-(1-Phenyltetrazol-5-yl)morphine (4d). A suspension of **3** (10 g, 35.1 mmol) in 500 mL of acetone was allowed to reflux

(8) Reden, J.; Reich, M. F.; Rice, K. C.; Jacobson, A. E.; Brossi, A.; Streaty, R. A.; Klee, W. A. *J. Med. Chem.* **1979**, *22*, 256.
(9) Ram, V. J.; Neumeyer, J. L. *J. Org. Chem.* **1981**, *46*, 2830.
(10) Granchelli, F. E.; Filer, C. N.; Soloway, A. H.; Neumeyer, J. L. *J. Org. Chem.* **1980**, *45*, 2275.
(11) Entwistle, I. D.; Hussey, B. J.; Johnstone, R. A. W. *Tetrahedron Lett.* **1980**, *21*, 4747.
(12) Thompson, J. A.; Holtzman, J. L.; Tsuru, M.; Lerman, C. L.; Holtzman, J. L. *J. Chromatogr.* **1982**, *238*, 470.
(13) Brine, G. A.; Boldt, K. G.; Hart, C. K.; Carroll, F. I. *Org. Prep. Proced. Int.* **1976**, *8*, 103.
(14) Atkinson, E. R.; Bullock, F. J.; Granchelli, F. E.; Archer, S.; Rosenberg, F. J.; Teiger, D. G.; Nachod, F. C. *J. Med. Chem.* **1975**, *18*, 1000.

with 5-chloro-1-phenyl-1*H*-tetrazole (6.33 g, 35.1 mmol) and K_2CO_3 (10.53 g, 76.3 mmol) for 24 h. The reaction mixture was cooled, diluted with H_2O (500 mL), and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and filtered. The filtrate, on evaporation to dryness and trituration with ether, gave a white solid: 14.0 g (92.6%); mp 108 °C (lit.[15] mp 121–123 °C); mass spectrum, *m/e* 431 (M^+). Similarly prepared from **4b** was **3-*O*-(1-phenyltetrazol-5-yl)-*N*-*n*-propylnormorphine hydrochloride (4e)**: 79.4% yield; mp 144–146 °C. Anal. Calcd for $C_{26}H_{27}N_5O_3$·HCl·0.5H_2O: C, 62.09; H, 5.77; N, 13.97. Found: C, 62.13; H, 5.83; N, 13.88.

3,6-Bis-*O*-(1-phenyltetrazol-5-yl)morphine Hydrochloride (4f). To a suspension of sodium hydride (0.68 g, 28.3 mmol) in THF (5 mL) was added a solution of **3** (1.0 g, 3.5 mmol) in 50 mL of acetone, and the mixture was stirred for 1 h. A solution of 5-chloro-1-phenyl-1*H*-tetrazole (1.5 g, 8.3 mmol) in 45 mL of THF was gradually added to the above suspension, and stirring was continued for 0.5 h. The reaction was terminated by carefully adding a few drops of H_2O, and then the mixture was diluted further with 50 mL of H_2O. The aqueous phase was extracted from $CHCl_3$, washed with H_2O, dried over $MgSO_4$, and filtered. The filtrate was evaporated, and the crude material was purified on a column by using silica gel and $CHCl_3$/MeOH (20:1) as the eluant to yield 1.4 g (70%) of **4f**. The base was converted into the hydrochloride salt by using Et_2O–HCl: mp 180–181 °C; $[\alpha]^{22.5}_{578}$ −54.1° (*c* 0.1452, MeOH); mass spectrum, *m/e* 573 (M^+), 530 ($M^+ - CH_2N-CH_3$). Anal. Calcd for $C_{31}H_{27}N_9O_3$: C, 64.92; H, 4.71; N, 21.99. Found: C, 65.03; H, 4.81; N, 21.98.

(*R*)-(+)-10-*O*-(1-Phenyltetrazol-5-yl)apomorphine Hydrochloride (5a). A solution of **4d** (1.4 g, 3.25 mmol) in CH_3SO_3H (5 mL) was heated at 90–95 °C for 1 h. The solution was cooled and added dropwise to a saturated solution of $NaHCO_3$. After neutralization, the suspension was extracted from $CHCl_3$, dried over $MgSO_4$, treated with charcoal, filtered, and evaporated to dryness to yield 0.9 g (67.4%) of **5a**. The free base was converted into the HCl salt by adding Et_2O–HCl: mp 182–188 °C; $[\alpha]^{23.5}_{578}$ +43.2° (*c* 0.132, MeOH); mass spectrum, *m/e* 411 (M^+), 368 ($M^+ - CH_2N-CH_3$), 325 (368 − HN_3), 266 (M^+ − phenyltetrazoly), 206 (325 − C_6H_5NCO). Anal. Calcd for $C_{24}H_{21}N_5O_2$·HCl·H_2O: C, 61.87; H, 5.16; N, 15.05. Found: C, 62.30; H, 5.31; N, 15.05.

The similar rearrangement of **4f** in CH_3SO_3H led to **5a** in comparable yields. Similarly prepared from **4e** (2.0 g, 4.05 mmol) was (*R*)-(+)-10-*O*-(1-phenyltetrazol-5-yl)-*N*-*n*-propylnorapomorphine hydrochloride (**5b**): yield 1.6 g (89.9%); mp 175–178 °C; $[\alpha]^{23.5}_{578}$ +30.8° (c 0.175, MeOH). Anal. Calcd for $C_{36}H_{25}N_5O_2$·HCl·H_2O: C, 63.22; H, 5.67; N, 14.18. Found: C, 62.73; H, 5.76; N, 14.01.

(*R*)-(−)10-*O*-(1-Phenyltetrazol-5-yl)-11-methoxyaporphine Hydrochloride (6a). To an etheral solution of CH_2N_2 (3.0 g in 300 mL of ether) was added **5a** (1.1 g, 268 mmol), and the resulting suspension was stirred overnight and filtered. Evaporation of the filtrate gave chromatographically pure product, 1.1 g (96.7%). The free base was converted into the hydrochloride by adding Et_2O–HCl: mp 146–155 °C; $[\alpha]^{23.5}_{578}$ −62.4 (*c* 0.0834, MeOH); mass spectrum, *m/e* 425 (M^+), 280 (M^+ − phenyltetrazolyl), 249 (280 − OCH_3), 237 (280 $-CH_2N-CH_3$). Anal. Calcd for $C_{25}H_{23}N_5O_2$·HCl·H_2O: C, 62.56; H, 5.42; N, 14.60. Found: C, 62.87; H, 5.53; N, 14.73.

Similarly prepared from **5b** (1.4 g, 3.2 mmol) and CH_2N_2 was **(*R*)-(−)-10-*O*-(1-phenyltetrazol-5-yl)-11-methoxy-*N*-*n*-propylnoraporphine hydrochloride (6b)**: 1.1 g (76.4%); mp 152–155 °C; $[\alpha]^{23.5}_{578}$ −68.1 (*c* 0.163, MeOH); mass spectrum, *m/e* 453 (M^+). Anal. Calcd for $C_{27}H_{27}N_5O_2$·HCl·H_2O: C, 63.84; H, 5.91; N, 13.79. Found: C, 63.94; H, 5.97; N, 14.35.

(*R*)-(−)-11-Methoxyaporphine Hydrochloride (7a). A solution of **6a** (1.0 g, 2.35 mmol) in 90 mL of acetic acid with 5% Pd/C (1.1 g) was hydrogenolyzed in a Parr apparatus at room temperature and 45 psi of H_2 for 11 days. The catalyst was removed by filtration, and the solvent was evaporated to dryness. The semisolid product was dissolved in $CHCl_3$ and treated with 10% of KOH. The organic layer was separated, washed with brine and H_2O, dried over $CaSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography with silica gel and Et_2O–hexane (1:1) as the eluant to yield 0.35 g (56.2%) of product. The free base was converted to the hydrochloride salt with Et_2O–HCl and gave a white precipitate of **7a**: mp 235–242 °C; $[\alpha]^{22}_{578}$ −74.9°, $[\alpha]^{22}_{548}$ −101.2° (*c* 0.0494, MeOH); mass spectrum, *m/e* 265 (M^+), 264 (M^+ − 1), 222 ($M^+ - CH_2N - CH_3$), 206 (222 − CH_3). The compound showed identical R_f values on TLC when compared with (±)-**7a** prepared previously.[3] Anal. Calcd for $C_{18}H_{19}NO$·HCl: C, 71.64; H, 6.30; N, 4.64. Found: C, 71.63; H, 6.46; N, 4.66.

(*R*)-(−)-11-Methoxy-*n*-propylnoraporphine Hydrochloride (7b). This compound was similarly prepared from **6b** (0.9 g, 1.99 mmol) to give **7b**: 0.32 g (50%); mp 227–229 °C; $[\alpha]^{26}_{578}$ −69.9°, $[\alpha]^{26}_{546}$ −89.32° (*c* 0.0515, MeOH); mass spectrum, *m/e* 293 (M^+), 292 (M^+ − 1), 264 (M^+ − Et), 262 ($M^+ - OCH_3$), 251 ($M^+ - C_3H_6$), 235 ($M^+ - NHC_3H_7$). Anal. Calcd for $C_{20}H_{23}NO$·HCl·0.25H_2O: C, 71.86; H, 7.34; N, 4.19. Found: C, 71.47; H, 7.54; N, 4.36.

(*R*)-(−)-11-Hydroxyaporphine Hydrobromide (2a). A suspension of **7a** (0.2 g, 0.66 mmol) in 4 mL 48% HBr was heated at 115–120 °C for 4 h. In 1 h a clear solution was obtained which on further heating gave a brown precipitate. The mixture was allowed to cool, filtered, washed with ether, and dried. The powder was dissolved in a minimum quantity of MeOH, treated with charcoal, and filtered. The filtrate was added dropwise to Et_2O with stirring. The resulting white precipitate was filtered and dried to yield **2a**: 0.16 g (73%); mp 280–281 °C; $[\alpha]^{22}_{578}$ −51.76°, $[\alpha]^{22}_{546}$ −75.29° (*c* 0.0425, MeOH). Anal. Calcd for $C_{17}H_{17}NO$·HBr: C, 61.45; H, 5.4; N, 4.22. Found: C, 61.24; H, 5.58, N, 4.05.

Similarly prepared from **7b** was **(*R*)-(−)-11-hydroxy-*N*-*n*-propylnoraporphine hydrobromide (2b)**: mp 270 °C $[\alpha]^{26}_{546}$ −52.63° (*c* 0.0228, MeOH). Anal. Calcd for $C_{19}H_{21}NO$·HBr: C, 63.33; H, 6.11; N, 3.89. Found: C, 63.03; H, 6.22; N, 3.73.

Enantiomeric Purity Determinations. A 10-mg sample of each of (±)-2b and (−)-2b was treated with 4 μL of triethylamine and extracted from 3 mL of petroleum ether. The 500 μL of each extract were evaporated to dryness with N_2 and allowed to react with triethylamine (1 μL) and (−)-α-methylbenzyl isocyanate (5 μL, Aldrich) for 3 h at room temperature. A 10-μL sample of the reaction mixture was evaporated under a stream of N_2 and redissolved in 100 μL of mobile phase [45% CH_3CN/phosphate buffer (pH 2.1), 10 mM]. Chromatographic separations were carried out by using 54% CH_3CN/phosphate buffer (pH 2.1, 10 mM), and 0.2 μg of each carbamate derivative was injected.

Acknowledgment. This research was supported in part by NIH Grant NA-15439 and a Northeastern University Distinguished Professor Award to J.L.N. We thank Dr. Paul Vouros and Mr. Hamdy Maksoud for the mass spectral data and interpretations, Dr. Markus Joppich for the enantiomeric purity determinations, Mallinckrodt Inc. for generous samples of morphine, and Ms. Stephanie Legatos for typing the manuscript.

(15) Bognar, R.; Gaal, G. Y.; Kerekes, P.; Horvath, G.; Kovacs, M. T. *Org. Prep. Proced. Int.* **1974**, *6*, 305.

High-Yield Benzyne Synthesis of Diaryl Ethers

Robert B. Bates* and Kim D. Janda

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received April 27, 1982

For a synthesis of the antitumor agent deoxybouvardin,[1] we needed to prepare a diaryl ether linkage from protected tyrosine derivatives without racemization. The cuprous oxide catalyzed reaction of iodobenzenes with phenoxides

(1) Jolad, S. D.; Hoffman, J. J.; Torrance, J. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040.

0022-3263/82/1947-4374$01.25/0