applied to a DEAE-cellulose (0.9 × 46 cm) column, washed with 300 mL of water, and then eluted with a gradient of water (2 L) and 0.1 M NH_4HCO_3 (2 L), collecting 10-mL fractions. The water eluant contained 1580 AU and was discarded. The gradient eluant (200 mL) contained 5310 AU and weighed 135 mg after lyophilization. This material was rechromatographed on DEAE-cellulose with a H_2O (2 L)–0.02 M NH_4HCO_3 (2 L) gradient, and 20-mL fractions were collected. Fractions 65–73 (center cut of fractions containing UV-absorbing material) were combined and lyophilized to yield 61 mg (14%) of product as a white solid. Anal. Calcd for $C_{11}H_{14}N_5O_7P\cdot0.5NH_3\cdot H_2O$: C, 31.32; H, 5.13; N, 18.26; P, 7.34. Found: C, 30.96; H, 4.48; N, 18.42; P, 7.39. UV λ_{max} at pH 1, 258 nm (ϵ 14 700); at pH 7, 260 (15 400); at pH 11, 260 (15 400); mass spectrum (Me_3Si derivative), m/e 647 [M^+ of $(Me_3Si)_4$ derivative], 632 ($M^+ - CH_3$), 544 [$M^+ - CH_2O(Me_3Si)$], 440 (k + H), 338 (a + H), 270, 208 (M^+ – sugar moiety + 2 H); HPLC on 4.6 × 250 mm Partisil 10 SAX, 15% MeOH in 0.04 M KH_2PO_4 at 2 mL/min: 2.14 (99%) and 2.71 min (1%); ^{13}C NMR, see Table I; ^1H NMR (D_2O) δ 4.0–4.46 (m, 6 H, nonexchangable sugar protons other than 3′-CH), 5.03 (br s, 1 H, 3′-CH), 8.19 (very br s, 2 H, aromatic). Another 22 mg of impure material was obtained in fractions from DEAE-cellulose chromatography before and after the above-collected material. The free acid isolated from passage through Dowex 50 (H^+) slowly suffered glycosidic cleavage. The sodium salt isolated by chromatography on Dowex 50 (Na^+) gave ^1H NMR (Me_2SO-d_6–D_2O) δ 3.78–4.40 (m, 6 H, nonexchangable sugar protons other than 3′-CH), 5.0 (asym d, 1 H, 3′-CH), 7.18 (remnant of br s, NH_2), 8.02 (aromatic s, 1 H), 8.16 (aromatic s, 1 H); ^{13}C NMR, see Table I. Anal. Calcd for $C_{11}H_{13}N_5O_7PNa\cdot1.5H_2O$: C, 32.36; H, 3.95; N, 17.16. Found: C, 32.64; H, 3.73; N, 16.69.

Acknowledgment. We gratefully acknowledge the support of this research by the United States Public Health Service (Grant GM 25697). We thank Dr. David Thomas for the determination of mass spectral data and assistance with their interpretation.

Registry No. 1, 23267-28-9; 2, 16638-76-9; 3, 83005-53-2; 3 NH_3, 83005-52-1; 3 Na, 83005-54-3.

Adducts Derived from Furan Macrocycles and Benzyne

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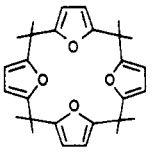
The macrocycle 1 is readily synthesized from furan and



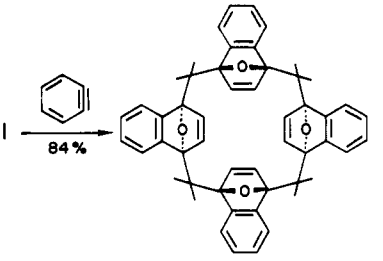
1

acetone.[1-5] Although 1 and related macrocycles are fairly accessible, attention has focused so far on their synthesis and not on their chemistry. Aside from catalytic hydrogenation,[2] the only exception is the recent elegant work of Williams and LeGoff,[6] who used 1 and related compounds as precursors for novel macrocyclic polyketones.

We have been exploring the use of bisaryne equivalents in the synthesis of novel compounds,[7] particularly through cycloadditions with dienes. It occurred to us that a bisaryne equivalent might react with two "opposite" furan moieties in 1 to give unique structures. Preliminary to such investigations, we examined and report here on the reaction of benzyne itself with 1.

Results and Discussion

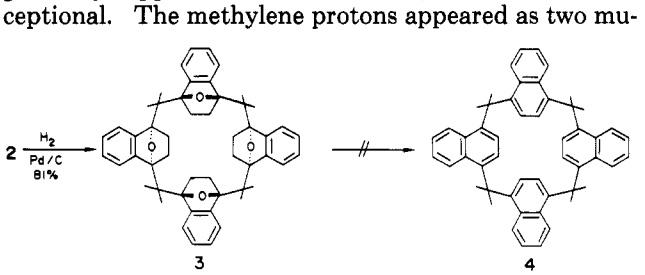
Treatment of 1 with 4 equiv of benzyne (generated from benzenediazonium carboxylate hydrochloride) gave a singlet adduct, 2, in 84% yield. The D_{2d} symmetry is assigned



2

to 2 on the basis of its NMR spectrum, which showed all methyl groups equivalent (singlet, δ 1.78). The ^{13}C NMR spectrum was consistent with the structure, showing only seven peaks for this C_{52} compound (see Experimental Section).

Attempts to directly deoxygenate 2 to produce the novel [1.1.1.1]paranaphthalenophane 4 were unsuccessful.[8] Accordingly, 2 was hydrogenated with the hope that the hydrogenation product could be dehydrated with acid. Catalytic hydrogenation of 2 over Pd/C gave a good yield of a single product, 3, whose NMR spectrum, though generally supportive of the structure, was somewhat exceptional. The methylene protons appeared as two mu-



3 4

tually coupled doublets at δ 3.00 and 1.23 (J = 7.0 Hz). It seemed unusual that one set of these methylene protons should appear at such an extrordinarily low field (δ 3.00). For comparison, model compound 5 was prepared and showed H_x at δ 1.92 and H_n at δ 1.50. Molecular models of 3 suggest that it has a geometry similar to what is shown in 3′. All of the aryl rings are oriented to the outside of

(1) Ackman, R. G.; Brown, W. H.; Wright, G. F. *J. Org. Chem.* **1955**, *20*, 1147.
(2) Chastrette, M.; Chastrette, F. *J. Chem. Soc., Chem. Commun.* **1973**, 534. Chastrette, M.; Chastrette, F.; Sabadie, J. *Org. Synth.* **1977**, *57*, 74.
(3) Rest, A. J.; Smith, S. A.; Tyler, I. D. *Inorg. Chim. Acta* **1976**, *16*, 11.
(4) Healy, M. deS.; Rest, A. J. *J. Chem. Soc., Chem. Commun.* **1981**, 149.
(5) For a review of synthetic macrocycles possessing subheterocyclic rings, see Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513.
(6) Williams, P. D.; LeGoff, E. *J. Org. Chem.* **1981**, *46*, 4143.
(7) Hart, H.; Lai, C-y.; Nwokogu, G.; Shamouilian, S.; Teuerstein, A.; Zlotogorski, C. *J. Am. Chem. Soc.* **1980**, *102*, 6649. Hart, H.; Nwokogu, G. *J. Org. Chem.* **1981**, *46*, 1251. Hart, H.; Shamouilian, S.; Takehira, Y. *Ibid.* **1981**, *46*, 4427; Hart, H.; Shamoulian, S. *Ibid.* **1981**, *46*, 4874.
(8) $LiAlH_4$–$TiCl_4$, BuLi–$TiCl_3$, and Zn–HOAc gave only recovered starting material. Lithium naphthalenide or thermolysis gave only oily decomposition products.

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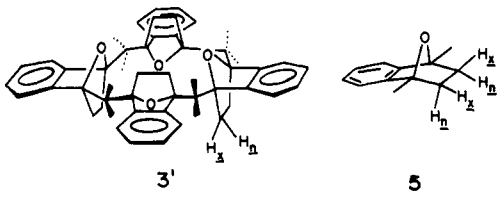
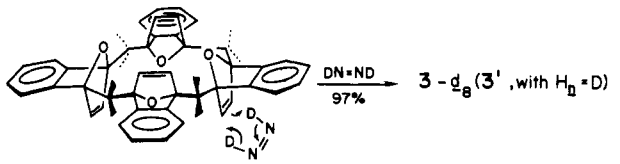


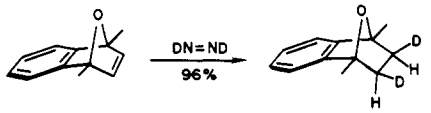
3' 5

the structure and lie roughly in the mean molecular plane. Consequently, the *exo*-methylene protons H_x experience a substantial deshielding effect from the oxygen atoms of both adjacent dihydronaphthalene 1,4-endoxide moieties.

To verify the assignments of the methylene protons in **3**, **2** was reduced with dideuterio diimide to give **3**-d_8. The



methylene protons appeared as a singlet at δ 2.93; the peak at δ 1.23 was absent. It is well known that diimide reductions occur in a cis manner.[9] The geometry of **2** permits reduction by diimide only from "outside" the ring, so that with DN=ND the product has H_n replaced by deuterium. This result is different from diimide reduction of model compound **6** in which diimide again attacks from the sterically less hindered side, but to give the exo-d_2 product **5**-d_2.

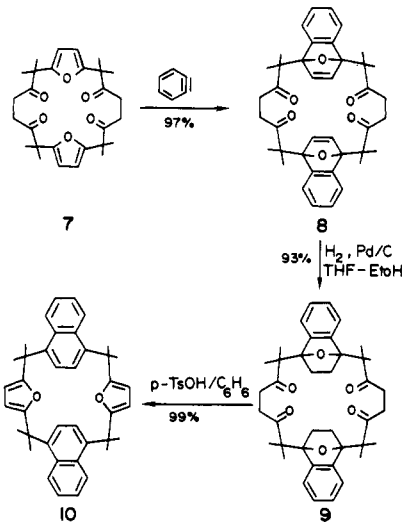


6 5-d2

Attempts to remove the oxygen bridges from **3** with *p*-toluenesulfonic acid, concentrated suulfuric acid, triphenylphosphine–bromine and trifluoroacetic acid all failed, either giving recovered starting material or intractable products.[10]

With the idea that **2** and **3** were too rigid or hindered for manipulation to remove the oxygen bridges, the reaction of **1** with less than 4 equiv of benzyne was tried, with the hope that **4** could be approached in a stepwise manner. However no benzyne adduct of **1** with fewer than four benzyne moieties could be obtained pure. Therefore, the more flexible difuran macrocycle **7** was used as a starting point. Treatment of **7** with excess benzyne gave a nearly quantitative yield of **8**. Hydrogenation of **8** gave **9**, which on treatment with *p*-toluenesulfonic acid lost the endoxide bridges and also reconverted the 1,4-diketone moieties to furans to give a nearly quantitative yield of **10**.

The structure of **10** is based on spectral properties. The proton NMR spectrum showed two multiplets of four protons each for the aromatic protons on the "outer" ring of the naphthalene moieties and two sharp four-proton singlets for the remaining naphthalene and furan sets of protons. The methyl protons appeared as two singlets (δ 1.63, 1.73), instead of the one singlet expected if **10** were planar or if the rings were freely rotating. Also, if **10** were planar the ^{13}C NMR spectrum should show nine signals,



7 8 10 9

whereas, in fact, ten were seen, there being two aliphatic methyl signals (δ 26.95, 32.23). Proton NMR spectra of **10** at elevated temperatures caused coalescence at 83 °C of the aliphatic methyl signals to a broad signal, which sharpened above 110 °C. Consequently, we attribute the appearance of two methyl singlets in the room-temperature spectrum to a conformational restriction.

All attempts to proceed to **4** from **10** were frustrated by its complete lack of reactivity toward benzyne and other dienophiles. Nevertheless, synthetic macrocycles posessing subheterocyclic rings[5] warrant further study as precursors of carbocyclic macrocycles.

Experimental Section

General Methods. ^1H NMR spectra were measured either at 60 MHz (Varian T-60) or at 250 MHz (Bruker WM-250). ^{13}C NMR spectra were determined on a Varian CFT-20 spectrometer. All NMR spectra were measured against tetramethylsilane as an internal reference. IR spectra were measured with a Perkin-Elmer Model 167 Grating spectrometer. Mass spectra were measured at 70 eV with a Finnigan 4000 spectrometer equipped with the INCOS data system and were determined by Ernest Oliver. Melting points were measured in capillary tubes and are uncorrected.

Benzyne Adduct 2. A solution of furan–acetone "tetramer" **1**[1] (0.70 g, 1.62 mmol) and benzenediazonium carboxylate hydrochloride (1.31 g, 7.1 mmol) in 70 mL of 1,2-dichloroethane containing 3 mL of propylene oxide was heated under reflux with stirring for 2 h. The mixture was concentrated under reduced pressure, and the resulting crystals were filtered, washed with methanol, and recrystallized from methylene chloride–hexane or acetone to give colorless prisms (1.00 g, 84%) of **2**. The product decomposes gradually above 280 °C and does not show a melting point: IR (Nujol) 1110 (s), 1055 (s), 983 (s), 960 (s), 760 (s), 750 cm^{-1} (s); ^1H NMR ($CHCl_3$) δ 1.78 (s, 24 H, CH_3), 6.53 (s, 8 H, =CH), 6.77–6.93 (m, 8 H, arom), 7.30–7.47 (m, 8 H, arom); ^{13}C NMR ($CDCl_3$)[11] δ 154.33 (s, C4a), 141.76 (d, C2), 123.21 (d, C5 or C6), 121.54 (d, C6 or C5), 97.46 (s, C1), 37.59 (s, C9), 21.47 (q, CH_3); mass spectrum, *m/e* 736 (M^+), 135 (base).

Anal. Calcd for $C_{52}H_{48}O_4$: C, 84.75; H, 6.56. Found: C, 84.65; H, 6.53.

Hydrogenation of 2. A solution of **2** (0.80 g, 1.08 mmol) in 20 mL of ethanol and 20 mL of ethyl acetate containing 0.5 g of 10% Pd/C was hydrogenated at 60 psi for 2 days. Filtration, evaporation, and recrystallization of the residue from chloroform or methylene chloride gave 0.65 g (0.87 mmol, 81%) of **3**, which did not show a melting point but decomposed gradually above 295 °C: IR (Nujol) 1160 (s), 1120 (s), 1060 (s), 1035 (vs), 1005 (s), 750 (vs), 620 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.23 (d, 8 H, J = 7 Hz), 1.75 (s, 24 H, CH_3), 3.00 (d, 8 H, J = 7 Hz), 6.97–7.15 (m, 8 H, arom), 7.33–7.50 (m, 8 H, arom); ^{13}C NMR ($CDCl_3$) δ 148.57, 125.13, 121.11, 95.35, 38.37, 30.51, 22.98; mass spectrum, *m/e* 744 (M^+), 135 (base).

(9) Corey, E. J.; Pasto, D. J.; Mock, W. L. *J. Am. Chem. Soc.* **1961**, *83*, 2957.

(10) A similar difficulty was previously encountered in attempts to dehydrate the reduction product of the 2:1 cycloadduct of benzyne and [2.2](2.5)-furanophane: Kapicak, L. A.; Battiste, M. A. *J. Chem. Soc., Chem. Commun.* **1973**, 930.

(11) Numbering corresponds to the dihydronaphthalene moiety; the quaternary carbon between these moieties is C9.

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

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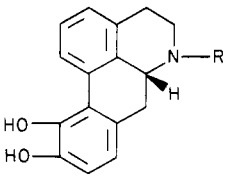
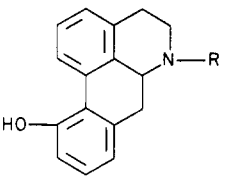
Apomorphine (**1a**) and its *N*-alkyl congener **1b** are potent dopamine (DA) receptor agonists and have found clinical application in a variety of neurological disorders.[2] In earlier studies we evaluated 8-, 10-, or 11-hydroxyaporphines and concluded that (±)-11-hydroxy-*N*-*n*-propylnoraporphine((±)-**2b**)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