Synthesis of B/C-*cis*- and -*trans*-6-Hydroxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene

Shunsaku Shiotani[1]

Section on Medicinal Chemistry, Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Disease, National Institutes of Health, Bethesda, Maryland 20014

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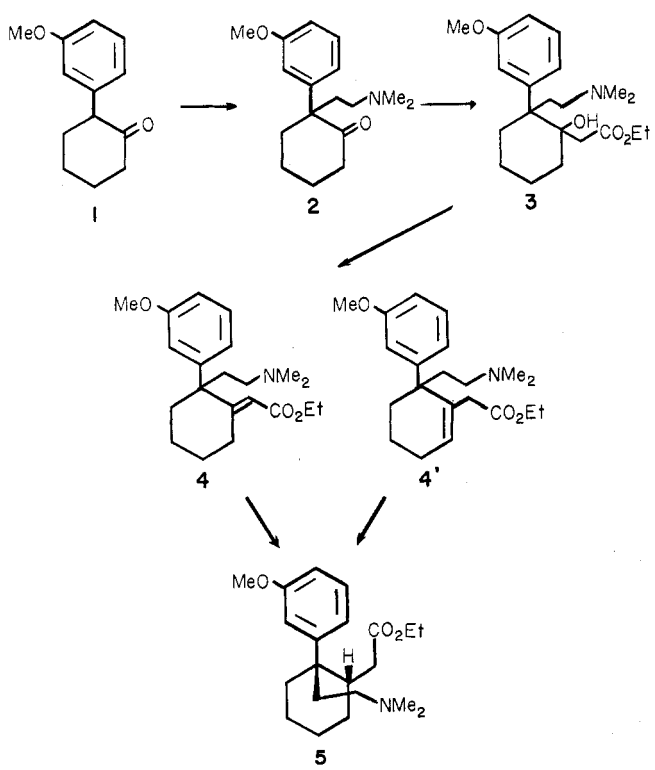
Ring-D-enlarged morphinans and isomorphinans (**13** and **21**) have been synthesized. A five-step sequence [from 2-(*m*-methoxyphenyl)cyclohexanone (**1**)] gave B/C-*cis*-4a(2-dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone (**6**); the B/C-trans isomer (**17**) resulted in six steps from the α-tetralone, **14**. Compounds **6** and **17** were converted to their *N*-methyl analogs, followed by the Mannich reaction to afford the B/C-*cis*- and -*trans*-9-keto D-ring homomorphinans, **10** and **19**, from which **13** and **21**, respectively, were obtained.

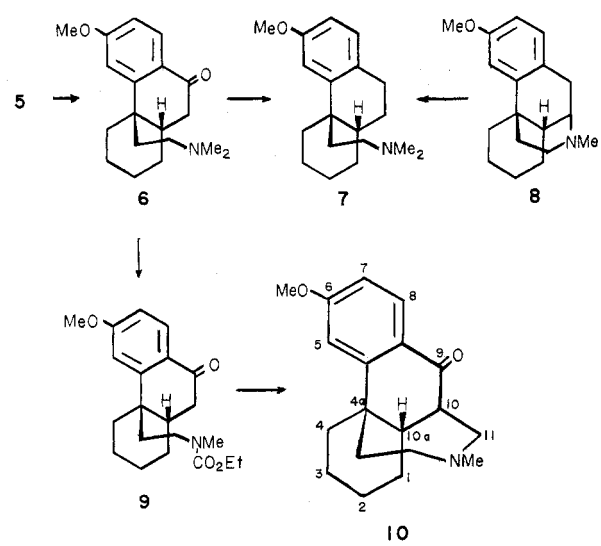
Recently, intramolecular Mannich reaction of 4-(2-methylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one derivatives was shown to give seven-membered, nitrogen heterocycles,[2a] some of which exhibit considerable analgesic activity.[2b] This reaction has now been used to prepare the heterocyclic compounds **13b** and **21b**, ring-D-enlarged morphinans having an extra methylene group between the nitrogen and the bridgehead carbon.

2-(2-Dimethylaminoethyl)-2-(*m*-methoxyphenyl)cyclohexanone (**2**)[3] prepared by the condensation of 2-(*m*-methoxyphenyl)cyclohexanone (**1**) and *N*,*N*-dimethylaminoethyl chloride was alkylated with $LiCH_2CO_2Et$ to give compound **3**. Dehydration of **3** afforded a mixture of two olefinic compounds, **4** and **4'** (4.5:1), which were separated by fractional recrystallization of their hydrochlorides.

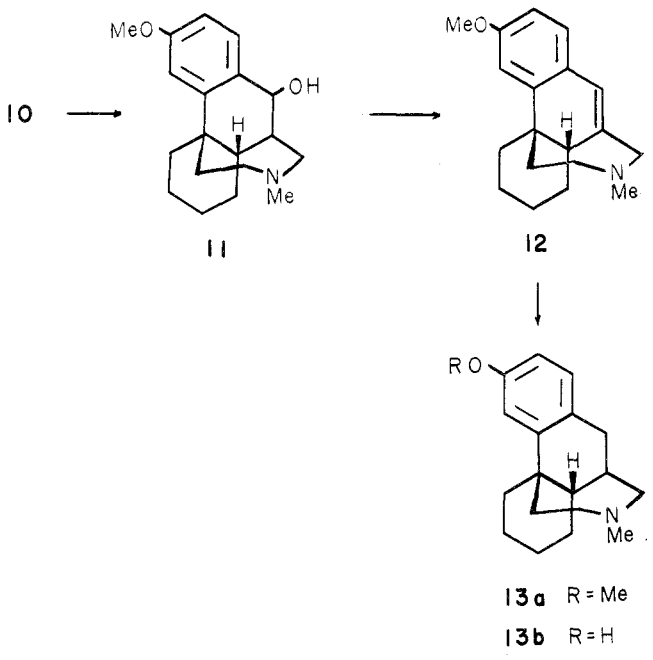


Hydrogenation of **4** over Pt in methanol and in ethanol–HCl and **4'** over Pt in methanol gave the same product, **5**. The configuration of **5** was established by its cyclization to **6** and as follows. If the conformation of the aminoethyl group of **4** and **4'** in methanol is axial, and the aromatic group is equatorially oriented, then the catalytic hydrogenation of **4** and **4'** should be influenced by an anchoring effect of the amino group, giving the cis isomer. Under strongly acidic conditions, the aminoethyl group would exist equatorially, preferentially, owing to solvation around the ammonium cation. Consequently, hydrogen should attack from the less hindered side to again give the cis isomer. Indeed, subsequent reactions indicated the validity of these rationalizations.

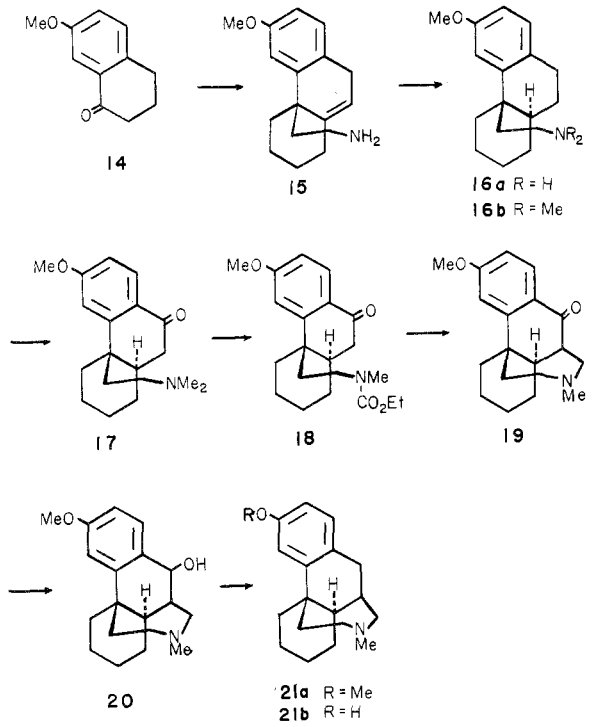
Compound **5** was hydrolyzed with $Ba(OH)_2$, followed by cyclization with PPA to give a phenanthrenone derivative, **6**. The B/C-cis ring junction of **6** was confirmed by the fact that the Wolff–Kishner reduction product **7**, from **6**, was identical with the B/C-cis product obtained from (±)-3-methoxy-*N*-methylmorphinan (**8**) by Hofmann elimination and hydrogenation.[4]



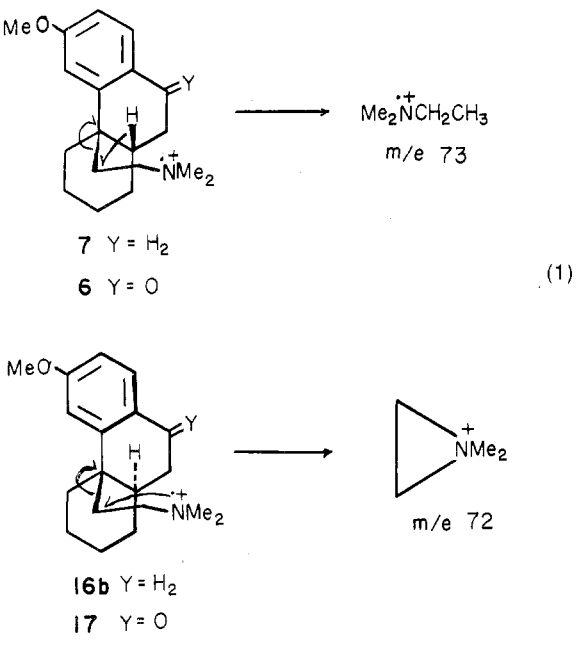
Reaction of **6** with $ClCO_2Et$ in refluxing benzene afforded carbamate **9**. Subsequent hydrolysis and a Mannich reaction with formaldehyde gave the desired B/C-cis homomorphinan, **10**. Reduction of **10** with $LiAlH_4$ gave the hydroxy compound **11**. On treating with HCl in methanol, compound **11** was easily converted to olefinic compound **12**. Structural assignment of **12** was made by spectral measurements. It showed no OH absorption band in the ir. The uv spectrum gave λ_{max} (EtOH) 216 nm (log ε 4.71) and 287 (4.24). The NMR spectrum indicated an olefinic proton singlet at 6.13 ppm. The mass spectrum showed the molecular ion at *m/e* 283. Although structure **12** is obviously in violation of Bredt's rule, these data, examination of Dreiding models, and conversion of **12** (hydrogenation over Pd/C, followed by hydrolysis with refluxing 48% HBr) to the desired B/C-cis homomorphinan, **13b**, leave little doubt about its correctness.



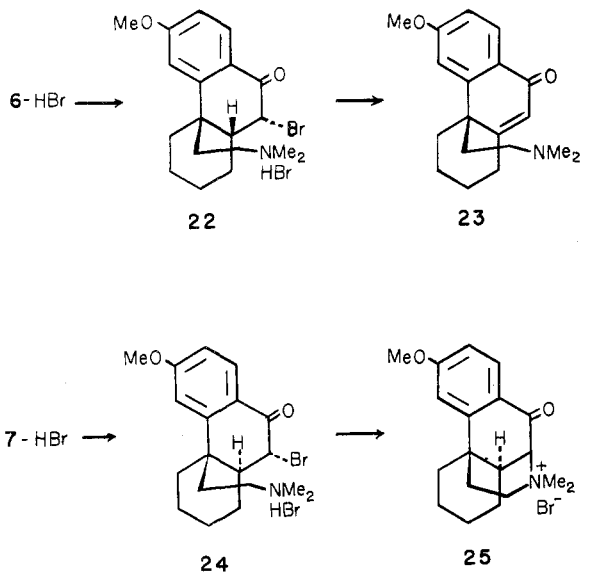
The B/C-trans isomers, **19**, **20**, **21a**, and **21b**, were synthesized by the following route. Compound **15** was prepared from 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**14**).[5] It was hydrogenated (Pt) in AcOH–$HClO_4$, followed by N-methylation with HCO_2H–CH_2O to give compound **16b**. Oxidation of **16b** with $Na_2Cr_2O_7$ in aqueous H_2SO_4 afforded oxo compound **17**. The carbonyl absorption band at 1675 cm^{-1}, a doublet at 7.98 ppm (J = 9.0 Hz, aromatic proton at the peri position to the carbonyl group), and an m/e 301 for the molecular ion provided the principal basis for the structural assignment of **17**.



The trans geometry for **16b** and **17** was suggested by the following facts. The intensity of the peak m/e 72 in **16b** and **17** is greater than that of m/e 73, while the m/e peak at 73 in **7** and **6** is more intense than that of m/e 72. These differences are similar to the observations made in the *trans*- and *cis*-morphinan series,[6] and are due to the fact that the hydrogen at C-10a in **16b** and **17** is unable to participate in the formation of an m/e 73 fragment (eq 1). Since the



NMR spectrum of **17** suggested, but did not prove, its trans configuration, owing to overlap of the C-10 methylene proton signals with other proton signals, compound **17** was transformed to the α-bromo keto derivative **24**. The NMR spectrum of **24** exhibited a doublet for C-10 proton at 5.28 ppm (J = 12.0 Hz) [the corresponding B/C-cis isomer **22** showed a doublet for the C-10 proton at 6.07 ppm (J = 4.5 Hz)]. The large coupling constant in compound **24** indicates a trans-diaxial arrangement of the C-10 and C-10a protons in **24**. Treatment of the bromo compound **24** with $NaHCO_3$ produced the B/C-trans morphinan derivatives **25**, while the cis α-bromo isomer **22** gave an olefinic compound **23**. These results are similar to those in the *cis*- and



trans-4-(2-dimethylaminoethyl)-3-methyl-3,4-dihydronaphthalen-1(2*H*)-one series,[7] and support a cis arrangement of C-10 bromine and C-10a proton in **24** and a trans arrangement of C-10 bromine and C-10a proton in **22**.

Reaction of **17** with $ClCO_2Et$ in refluxing benzene gave carbamate **18**. Hydrolysis, and the subsequent Mannich reaction of **18**, afforded the B/C-trans homomorphinan derivative **19**. The carbonyl group in **19** was reduced with $LiAlH_4$ to give an alcoholic compound, **20**. Treatment of **20** with HCl gave a mixture of several compounds, unlike the cis isomer, which could not be separated by chromatogra-

phy. Hydrogenolysis of the hydroxyl group in **20** over Pd/C gave compound **21a**, which was transformed to the desired **21b** by refluxing with hydrobromic acid.

Compound **13b** appears to be as active as morphine in preliminary animal tests.

Experimental Section

Melting points (Hershberg) are corrected. Infrared data were obtained on a Perkin-Elmer 257, ultraviolet spectra from a Beckman DBG spectrometer, mass spectra from an Hitachi RMU-6E double-focusing spectrometer at 70 eV, and CI mass spectra from a Finnigan 1015D spectrometer. NMR spectra, at 100 MHz, were obtained on a Varian HA-100 or 60 MHz on a Varian A-60 (Me_4Si at δ 0.00 ppm as internal standard).

1-Carbethoxymethylene-2-(*m*-methoxyphenyl)-2-(2-dimethyaminoethyl)cyclohexane (4) and Ethyl 6-(*m*-Methoxyphenyl)-6-(2-dimethylaminoethyl)-1-cyclohexaneacetate (4'). BuLi (1 *M*) in hexane (65 ml) was added to a stirred solution of $(Me_3Si)_2NH$ (9.9 g) in ether (50 ml) over 15 min under N_2 and with ice cooling. After gentle refluxing (30 min) and stirring at room temperature (1.5 hr), the solution was evaporated in vacuo. The resultant mass was dissolved in dry THF (100 ml) and cooled in a Dry Ice–acetone bath (−80°). To this cooled solution was added a solution of AcOEt (5.0 g) in dry ether (20 ml) during 25 min. After stirring at this temperature for 30 min, a solution of **2**[3] (14.0 g) in ether (100 ml) was added during 40 min (under N_2) with stirring; stirring was continued for 3 hr. After addition of H_2O (20 ml), the cold bath was removed. The mixture (at room temperature) was poured into H_2O (100 ml). The dried ($MgSO_4$) organic layer gave 18.0 g of **3** as a yellow oil, which was used without purification: ir (neat) 3500 (OH), 2770, 2820 (NMe_2), 1715 cm^{-1} (CO_2Et); NMR ($CDCl_3$) δ 1.19 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.16 (s, 6, NMe_2), 3.83 (s, 3, OMe), 4.06 (q, J = 7.0 Hz, 2, OCH_2CH_3), 3.93 (broad s, 1, OH, removed by D_2O), 6.70–7.35 (m, 4, aromatic).

Ester **3** (17.5 g), *p*-TsOH·H_2O (28 g), C_6H_6 (300 ml), and PhMe (700 ml) were refluxed (H_2O separator) for 1 week, made alkaline with 20% NaOH, washed with H_2O, dried ($MgSO_4$), and evaporated to give 12.7 g of a yellow oil, which was converted to the HCl salt and fractionally recrystallized from EtOH–Me_2CO to give 4.5 g of **4** HCl, mp 196–199°, 1.05 g of **4'** HCl, mp 167–168.5°, and 2.9 g of a mixture of **4**-HCl and **4'**-HCl.

4 HCl: Anal. Calcd for $C_{21}H_{31}NO_3$·HCl: C, 66.04; H, 8.45; N, 3.67. Found: C, 65.80; H, 8.72; N, 3.55.

The free base showed ν_{max} (film) 2770, 2820 (NMe_2), 1717 (CO_2Et), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.13 (s, 6, NMe_2), 3.81 (s, 3, OMe), 4.24 (q, J = 7.0 Hz, 2, OCH_2CH_3), 5.99 (s, 1, $C=CHCO_2Et$), 6.65–7.35 (m, 4, aromatic).

4' HCl: Anal. Calcd for $C_{21}H_{31}NO_3$·HCl: C, 66.04; H, 8.45; N, 3.67, Found: C, 65.63; H, 8.52; N, 3.42.

The free base showed ν_{max} (film) 2760, 2810 (NMe_2), 1735 cm^{-1} (CO_2Et); NMR ($CDCl_3$) δ 1.22 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.30 (s, 6, NMe_2), 3.83 (s, 3, OMe), 2.85 (broad, one peak, $=C-CH_2CO_2Et$), 4.11 (q, J = 7.0 Hz, 2, OCH_2CH_3), 6.01 (broad, one peak, 1, $-CH=C<$), 6.67–7.33 (m, 4, aromatic).

Ethyl 2-(2-Dimethylaminoethyl)-2-(*m*-methoxyphenyl)cyclohexane-1-acetate (5). A. Hydrogenation of **4** (0.9 g) over PtO_2 (0.1 g) in MeOH (25 ml) for 19 hr gave 0.9 g of **5** as a colorless oil: ir (neat) 2760, 2810 (NMe_2), 1730 cm^{-1} (CO_2Et); NMR ($CDCl_3$) δ 1.15 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.12 (s, 6, NMe_2), 3.82 (s, 3, OMe), 4.02 (q, J = 7.0 Hz, 2, OCH_2CH_3), 6.60–7.30 (m, 4, aromatic).

B. Hydrogenation of **4'** (0.6 g) over PtO_2 (1.0 g) in MeOH (30 ml) for 4.5 days gave 0.6 g of a colorless oil identical with **5** obtained from **4** (ir, GLC).

C. Hydrogenation of **4** (1.5 g) (in 12 *M* HCl, 10 ml) over PtO_2 (0.3 g) in EtOH (25 ml) followed by removal of solvent gave a product which was dissolved in H_2O, basified with 20% NaOH, extracted with ether, and dried ($MgSO_4$). Removal of solvent gave 1.0 of colorless oil which was identical with the product obtained in A and B (ir, GLC).

B/C-*cis*-4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone (6) Hydrochloride. Ester **5** (0.87 g), $Ba(OH)_2$·$8H_2O$ (8.0 g), and H_2O (50 ml) were refluxed for 18 hr, cooled, neutralized with dilute H_2SO_4, and filtered (Celite). The filtrate was evaporated to dryness. The residue (0.8 g) and PPA (25 g) were heated at 110–130° for 0.5 hr and at 150–160° for 0.5 hr, cooled, treated with ice–H_2O, basified with KOH, and extracted with $CHCl_3$. Drying (K_2CO_3) and evaporation of solvent gave 0.66 g of a yellow oil. It was converted to HCl salt which, recrystallized from Me_2CO, gave 0.5 g of **6** HCl, mp 229.5–232°.

Anal. Calcd for $C_{19}H_{27}NO_2$·HCl: C, 67.54; H, 8.35; N, 4.15. Found: C, 67.33; H, 8.11; N, 4.07.

The free base was molecularly distilled (bath temperature 180–200°, 0.2 mm): ir (neat) 2760, 2810 (NMe_2), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.12 (s, 6, NMe_2), 3.82 (s, 3, OMe), 6.74 (d, $J_{5,7}$ = 3.0 Hz, 1, C-5 H), 6.78 (q, $J_{5,7}$ = 3.0, $J_{7,8}$ = 9.0 Hz, 1, C-7 H), 8.01 (d, $J_{7,8}$ = 9.0 Hz, 1, C-8 H); mass spectrum *m/e* 301 (M^+), 230 ($M^+ - Me_2NCH{=}CH_2$), 229 ($M^+ - Me_2NCH_2CH_2\cdot$), 228 ($M^+ - Me_2NEt$), 73 ($EtN^{\cdot+}Me_2$), 72 ($c\text{-}C_2H_4N^+Me_2$), 58 ($CH_2{=}C\text{-}NMe_2\cdot^+$); *m/e* 73 > *m/e* 72.

B/C-*cis*-4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (7). The hydrochloride of **6** (54 mg), KOH (0.1 g), 95% NH_2NH_2 (0.1 ml), and triethylene glycol (1 ml) were kept at 160–170° for 18 hr, then at 200° for 1 hr. The cooled mixture was treated with H_2O and ether. Evaporation of the dried (K_2CO_3) ethereal layer gave 44.2 mg of crude **7**, which was distilled in vacuo to give a pure sample of **7**, colorless oil of bp 160–180° (0.05 mm) (bath temperature). The distillate was identical with the sample prepared from (±)-3-methoxy-*N*-methylmorphinan (**8**) by Hofmann elimination and hydrogenation[4] [ir, GLC, TLC (silica gel, 8:2 $CHCl_3$–MeOH)]: NMR ($CDCl_3$) δ 2.15 (s, 6, NMe_2), 2.72 (br t, 2, C-9 H,), 3.74 (s, 3, OMe), 6.64 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.77 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.96 (d, $J_{7,8}$ = 8.0 Hz, 1, C-8 H); mass spectrum *m/e* 287 (M^+), 216 ($M^+ - Me_2NCH{=}CH_2$), 73 ($Me_2N^{\cdot+}Et$), 72 ($c\text{-}C_2H_4N^+Me_2$), 58 ($Me_2N^+{=}CH_2$), 45 ($Me_2N^{\cdot+}H$); *m/e* 73 > *m/e* 72.

Picrate: mp 158–160° (from MeOH) (lit.[4] mp 158–159°).

Anal. Calcd for $C_{25}H_{32}N_4O_8$: C, 58.13; H, 6.25; N, 10.85. Found: C, 58.37; H, 6.18; N, 10.61.

B/C-*cis*-6-Methoxy-12-methyl-1,3,4,10a-tetrahydro-2*H*-10,4a-methanoiminoethano-10*H*-9-phenanthrone (10). $ClCO_2Et$ (360 mg) was rapidly added to a refluxing solution of **6** (664 mg) in benzene (25 ml). The mixture was refluxed for 2.5 hr. The cooled mixture was washed with 10% HCl and H_2O and dried ($MgSO_4$). Evaporation of the benzene gave 752 mg of carbamate **9**: ir (neat) 1675 (C=O), 1695 cm^{-1} (>NCO_2Et); NMR ($CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.77 (s, 3, NMe), 3.88 (s, 3, OMe), 4.07 (q, J = 7.0 Hz, 2, OCH_2CH_3), 6.81 (d, $J_{5,7}$ = 2.2 Hz, 1, C-5 H), 6.84 (q, $J_{7,5}$ = 2.2, $J_{7,8}$ = 9.6 Hz, 1, C-7 H), 8.10 (d, $J_{8,7}$ = 9.5 Hz, 1, C-8 H).

Carbamate **9** (730 mg), 12 *M* HCl (50 ml), and AcOH (25 ml) were refluxed for 24 hr. After evaporation of AcOH and HCl, the light-brown syrup was dissolved in MeOH (10 ml) and Formalin (35–40%, 1.5 ml). The mixture was kept at 55–60° for 44 hr. After evaporation to dryness, the residue was dissolved in H_2O, basified with 20% NaOH, extracted with ether, and dried ($MgSO_4$). The residue from the ethereal solution was chromatographed on a silica gel column (20 g). Elution with $CHCl_3$–MeOH (99:1) gave 319 mg of pure **10**: mp 92–95.5°; ir (Nujol) 2750, 2800 (NMe), 1665 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.30 (s, 3, NMe), 3.88 (s, 3, OMe), 2.80–3.38 (AB part of ABX, J_{AB} = 12.0, J_{AX} = 7.0, J_{BX} = 3.0 Hz, 2, C-11 H), 6.76 (d, $J_{5,7}$ = 3.0 Hz, 1, C-5 H), 6.81 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 3.0 Hz, 1, C-7 H), 8.04 (d, $J_{8,7}$ = 9.0 Hz, 1, C-8 H); mass spectrum *m/e* 299 (M^+), 284 (M^+ – Me), 230 ($M^+ - C_4H_7N$), 71 [$MeN^{\cdot+}{=}CH_2)CH_2CH_2\cdot$], 70 [$MeN^+(=CH_2)CH{=}CH_2$]. Picrate: mp 221–223° (from Me_2CO).

Anal. Calcd for $C_{25}H_{28}N_4O_9$: C, 56.80; H, 5.34; N, 10.60. Found: C, 56.90; H, 5.15; N, 10.39.

B/C-*cis*-6-Methoxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethano-9-phenanthrol (11). A mixture of $LiAlH_4$ (0.5 g) and **10** (0.9 g) in Et_2O (70 ml) was refluxed for 2 hr. When cooled, the mixture was treated with H_2O and sodium tartrate solution. The aqueous layer was extracted with $CHCl_3$. The ethereal layer and the $CHCl_3$ extract were combined, washed with H_2O, dried (K_2CO_3), and evaporated to give 0.85 g of compound **11** as a colorless syrup: ir (neat) 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.14 (s, 3, NMe), 2.74–3.06 (AB part of ABX, J_{AB} = 14.0, J_{AX} = 5.5, J_{BX} = 3.0 Hz, 2, C-11 H_2), 3.74 (s, 3, OMe), 4.42 (broad s, removed by D_2O, 1, OH), 4.48 (d, J = 8.0 Hz, C-9 H), 6.67 (d, $J_{5,7}$ = 3.0 Hz, 1, C-5 H), 6.77 (q, $J_{7,5}$ = 3.0, $J_{7,8}$ = 8.0 Hz, 1, C-7 H), 7.73 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); CI mass spectrum *m/e* 302 (M^+ for 301).

B/C-*cis*-6-Methoxy-12-methyl-1,3,4,10a-tetrahydro-2*H*-10,4a-methanoiminoethanophenanthrene (12). A solution of **11** (426 mg) in ether was treated with dry HCl gas to give a colorless, crystalline precipitate, which was recrystallized from MeOH–Me_2CO to give 350 mg of **12** HCl, mp 142.5–144.5°.

Anal. Calcd for $C_{19}H_{25}NO\cdot HCl\cdot MeOH$: C, 68.26; H, 8.59; N, 3.98. Found: C, 68.03; H, 8.62; N, 3.98.

Free base: uv λ_{max} (EtOH) 216 nm (log ϵ 4.71), 287 (4.24); NMR ($CDCl_3$) δ 2.32 (s, 3, NMe), 2.86–3.57 (AB quartet, J = 10.0 Hz, 2, C-11 H_2), 3.78 (s, 3, OMe), 6.13 (s, 1, C-9 H), 6.67 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 3.0 Hz, 1, C-7 H), 6.80 (d, $J_{5,7}$ = 3.0 Hz, 1, C-5 H), 7.10 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); mass spectrum m/e 283 (M^+).

B/C-*cis*-6-Methoxy- (13a) and B/C-*cis*-6-Hydroxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (13b). Hydrogenation of **12** (400 mg) over 10% Pd/C (0.3 g) in MeOH (20 ml) and 10% HCl (10 ml) for 6 hr gave a colorless residue which was dissolved in H_2O, made alkaline with 20% NaOH, and extracted with ether. The residue (375 mg) of the dried (K_2CO_3) ethereal solution was distilled (bath temperature 170–180°, 0.05 mm) to give 370 mg of **13a** as a colorless oil: NMR ($CDCl_3$) δ 2.22 (s, 3, NMe), 2.32–2.98 (AB part of ABX, J_{AB} = 13.0, J_{AX} = 5.0, J_{BX} = 5.0 Hz, 2, C-11 H_2), 2.47–3.13 (AB part of ABX, J_{AB} = 16.0, J_{AX} = 8.0, J_{BX} = 2.5 Hz, 2, C-9 H_2), 3.76 (s, 3, OMe), 6.67 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.79 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.99 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); mass spectrum m/e 285 (M^+), 214 ($M^+ - C_4H_9N$), 213 ($M^+ - C_4H_{10}N$), 212 ($M^+ - C_4H_{11}N$), 73 ($Me_2N\cdot^+Et$), 72 [$MeN^+(=CH_2)Et$], 71 ($Me_2N\cdot^+CH{=}CH_2$), 70 [$MeN^+(=CH_2)CH{=}CH_2$].

Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.54; N, 4.91. Found: C, 80.01; H, 9.62; N, 4.86.

Methoxy compound **13a** (106 mg) and 48% HBr (3 ml) were refluxed for 30 min. Evaporation and recrystallization from MeOH–Me_2CO gave 102 mg of **13b** HBr, mp 240–242°.

Anal. Calcd for $C_{18}H_{25}NO\cdot HBr\cdot \frac{1}{3}H_2O$: C, 60.33; H, 7.50; N, 3.91. Found: C, 60.40; H, 7.13; N, 3.97.

Ir (Nujol) 3200 (OH), 2640 cm^{-1} ($^+$NH); NMR (CD_3OD) δ 2.86 (s, 3, $^+$NMe), 6.66 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.74 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.02 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); CI mass spectrum m/e 272 (M^+ for 271).

B/C-*trans*-4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (16b). Hydrogenation of **15**[5] (2.0 g) over PtO_2 (0.3 g) in 60% $HClO_4$ (1.0 ml) and AcOH (50 ml) for 6 hr gave a residual solid which was dissolved in H_2O, made alkaline with 20% NaOH, extracted with ether, and dried (K_2CO_3). Evaporation of the ether gave 1.9 g of **16a**. Primary amine **16a** (1.9 g), HCO_2H (10 ml), and Formalin (35–40%, 10 ml) were heated on a steam bath for 1.5 hr. After evaporation to dryness, the residue was dissolved in H_2O, basified with 20% NaOH, extracted with $CHCl_3$, and dried (K_2CO_3). Evaporation of the $CHCl_3$ gave 2.0 g of crude **16b**, which was distilled in vacuo to give 1.8 g of pure **16b**: bp 175–185° (0.05 mm) (bath temperature); ir (neat) 2760, 2810 cm^{-1} (NMe_2); NMR ($CDCl_3$) δ 2.08 (s, 6, NMe_2), 2.80 (br t, 2, C-9 H), 3.73 (s, 3, OMe), 6.64 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.0 Hz, 1, C-7 H), 6.71 (d, $J_{5,7}$ = 2.0 Hz, 1, C-5 H), 6.96 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); mass spectrum m/e 287 (M^+), 216 ($M^+ - Me_2N{-}CH{=}CH_2$), 73 ($Me_2N\cdot^+Et$), 72 (Me_2N^+-c-C_2H_4), 58 ($Me_2N\cdot^+{=}CH_2$); m/e 73 ≪ m/e 72 (see eq 1).

Oxalate: mp 205–208° (from MeOH–Me_2CO).

Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.55; H, 8.36; N, 3.63.

B/C-*trans*-4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone (17). To a stirred mixture of **16b** (750 mg) and $Na_2Cr_2O_7$ (1.0 g) in 1 *N* H_2SO_4 (30 ml) was added 10 *N* H_2SO_4 (60 ml) at room temperature during 2 hr. After stirring for 17 hr, the mixture was cooled (ice bath), basified with 12 *M* NH_4OH, extracted with ether, and dried (K_2CO_3). Evaporation of the ether gave 600 mg of crude **17**, which was purified by recrystallization of its hydrochloride from MeOH–Me_2CO, mp 233–235°.

Anal. Calcd for $C_{19}H_{27}NO_2\cdot HCl\cdot MeOH$: C, 64.94; H, 8.72; N, 3.79. Found: C, 64.67; H, 8.61; N, 3.71.

The free base: ir (neat) 2760, 2810 (NMe_2), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.05 (s, 6, NMe_2), 3.82 (s, 3, OMe), 6.77 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.74 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.98 (d, $J_{8,7}$ = 9.0 Hz, 1, C-8 H); mass spectrum m/e 301 (M^+), 230 ($M^+ - Me_2NCH{=}CH_2$), 73 ($Me_2N\cdot^+Et$), 72 (c-$C_2H_4N^+Me_2$), 58 ($Me_2N^+{=}CH_2$), 45 ($Me_2N\cdot^+H$) (m/e 73 < m/e 72).

B/C-*trans*-6-Methoxy-12-methyl-1,3,4,10a-tetrahydro-2*H*-10,4a-methanoiminoethano-10*H*-9-phenanthrone (19). To a refluxing solution of **17** (720 mg) in C_6H_6 (50 ml) was added a solution of $ClCO_2Et$ (400 mg) in C_6H_6 (10 ml) during 7 min. After refluxing for 2 hr, the mixture was cooled, washed with 10% HCl, dried ($MeSO_4$), and evaporated to give 827 mg of **18**: ir (neat) 1680 (C=O), 1700 cm^{-1} (NCO_2Et); NMR ($CDCl_3$) δ 1.76 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.65 (s, 3, NMe), 3.86 (s, 3, OMe) 4.04 (q, J = 7.0 Hz, 2, OCH_2CH_3), 6.77 (d, $J_{5=7}$ = 2.5 Hz, 1, C-5 H), 6.82 (q, $J_{7,8}$ = 8.5, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 8.04 (d, $J_{8,7}$ = 8.5 Hz, 1, C-8 H).

Carbamate **18** (1.47 g), 12 *M* HCl (70 ml), and AcOH (30 ml) were refluxed for 24 hr. The mixture was evaporated, dissolved in MeOH (20 ml) and Formalin (2.0 ml), and kept at 60–70° for 3.5 days. After evaporation to dryness, the residue was dissolved in H_2O, basified with 20% NaOH, extracted with ether, and dried ($MgSO_4$). The residue (1.08 g) of the ethereal solution was chromatographed on a silica gel (20 g) column. Elution with $CHCl_3$–MeOH (99:1) gave 0.9 g of **19** as an almost colorless oil: ir (neat) 2760, 2805 (NMe), 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.22 (s, 3, NMe), 2.83–3.29 (AB part of ABX, J_{AB} = 12.5, J_{AX} = 6.0, J_{BX} = 2.5 Hz, 2, C-11 H), 3.84 (s, 3, OMe), 6.81 (q, $J_{7,8}$ = 9.5, $J_{7,5}$ = 2.0 Hz, 1, C-7 H), 6.83 (d, $J_{5,7}$ = 2.0 Hz, 1, C-5 H), 8.03 (d, $J_{8,7}$ = 9.5 Hz, 1, C-8 H).

Picrate: mp 228–230° (from MeOH).

Anal. Calcd for $C_{25}H_{28}N_4O_9$: C, 56.80; H, 5.34; N, 10.60. Found: C, 56.92; H, 5.45; N, 10.66.

B/C-*trans*-6-Methoxy- (21a) and B/C-*trans*-6-Hydroxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (21b). A mixture of **19** (592 mg) and $LiAlH_4$ (0.3 g) in ether (50 ml) was refluxed for 2 hr. After cooling, the mixture was treated with H_2O and sodium tartrate solution. The aqueous layer was extracted with $CHCl_3$. The ethereal layer and the extract were combined, washed with H_2O, and dried (K_2CO_3). Evaporation of the solvent gave 608 mg of **20** as a slightly yellow syrup: ir (neat) 3430 (OH), 2770, 2810 cm^{-1} (NMe); NMR ($CDCl_3$) δ 2.14 (s, 3, NMe), 2.59–3.02 (six lines, AB part of ABX, J_{AB} = 14.0, J_{AX} = 6.5, J_{BX} = 0 Hz, 2, C-11 H_2), 3.78 (s, 3, OMe), 4.89 (d, J = 7.5 Hz, 1, C-9 H), 6.75 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.78 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 7.53 (d, $J_{8,7}$ = 9.0 Hz, C-8 H).

Hydrogenation of **20** (500 mg) in 10% HCl (6 ml) and MeOH (20 ml) over 10% Pd/C (0.3 g) for 5.5 hr gave, after removal of the catalyst and solvent, a residue which was dissolved in H_2O, made alkaline with 20% NaOH, extracted with ether, and dried (K_2CO_3). Evaporation of the solvent gave 421 mg of **21a** as a colorless oil, distilled at 155–170° (bath temperature, 0.01 mm): NMR ($CDCl_3$) δ 2.38 (s, 3, NMe), 3.76 (s, 3, OMe), 6.70 (q, $J_{7,8}$ = 8.5, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.78 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.00 (d, $J_{8,7}$ = 8.5 Hz, 1, C-8 H).

Picrate: mp 186–189° (from MeOH).

Anal. Calcd for $C_{25}H_{30}N_4O_9$: C, 58.36; H, 5.88; N, 10.89. Found: C, 58.04; H, 6.02; N, 10.99.

A mixture of **21a** (157 mg) and 48% HBr (3.5 ml) was refluxed for 30 min. Evaporation and recrystallization from MeOH gave 161 mg of **21b** HBr as colorless crystals: mp 287–289°; ir (Nujol) 3390 (OH), 2650 cm^{-1} ($^+$NH); NMR (CD_3OD) δ 2.81 (s, 3, $^+$NMe), 6.65 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.72 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.99 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); CI mass spectrum m/e 272 (M^+ for 271).

Anal. Calcd for $C_{18}H_{25}NO\cdot HBr$: C, 61.36; H, 7.44; N, 3.98. Found: C, 61.08; H, 7.69; N, 3.90.

B/C-*cis*-10-Bromo-4a-(2-dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone Hydrobromide (22). Ketone **6** was converted to the hydrobromide (mp 227–230° from MeOH–Me_2CO). This hydrobromide (191 mg) in refluxing AcOH (1 ml) was treated with Br_2 (108 mg) in AcOH (1.2 ml) during 5 min. The solution was refluxed for 10 min and ether was added to precipitate a crystalline mass. After refrigeration, the bromo derivative separated and was recrystallized from MeOH–Me_2CO to give 175 mg of pure **22**, colorless plates: mp 192–194°; ir (Nujol) 2350–2710 ($^+$NH), 1690 cm^{-1} (C=O); NMR (DMSO-d_6) δ 3.33 (s, 6, $>N^+Me_2$), 3.86 (s, 3, OMe), 6.07 (d, J = 4.5 Hz, 1, C-10 H), 6.89 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.03 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 7.98 (d, $J_{8,7}$ = 9.0 Hz, 1, C-8 H).

Anal. Calcd for $C_{19}H_{26}BrNO_2\cdot HBr$: C, 49.49; H, 5.90; N, 3.04. Found: C, 49.24; H, 6.13; N, 2.95.

4a-(2-Dimethylaminoethyl)-6-methoxy-2,3,4,4a-tetrahydro-1*H*-9-phenanthrone (23). To **22** (64.3 mg) in H_2O (25 ml) was added $NaHCO_3$ (100 mg). Extraction with ether, drying ($MgSO_4$), and evaporation of the ether gave 49.3 mg of an oil which soon solidified. The solid product was recrystallized from Me_2CO to give **23** HBr as colorless, fine needles: mp 230–233°; ir (Nujol) 2390 (broad, $^+$NH), 1660 cm^{-1} (C=O); NMR (CD_3OD) δ 2.70 (s, 6, $>^+NMe_2$), 3.90 (s, 3, OMe), 6.38 (s, 1, C-10 H), 7.05 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 7.23 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 8.09 (d, $J_{8,7}$ = 9.0 Hz, 1, C-8 H).

Anal. Calcd for $C_{19}H_{25}NO_2\cdot HBr$: C, 60.00; H, 6.89; N, 3.68. Found: C, 59.91; H, 6.80; N, 3.72.

B/C-*trans*-10-Bromo-4a-(2-dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone Hydrobromide (24). Ketone **17** was converted to the hydrobromide (mp 236–238° from MeOH–Me_2CO). As described in the bromination of **6** HBr, the hydrobromide (152 mg) and Br_2 (77 mg) yielded, after addition of ether to the reaction mixture and cooling, 145 mg of **24**: mp 188–190°; ir (Nujol) 2400–2700 (N^+H), 1680 cm^{-1} (C=O); NMR (DMSO-d_6) δ 3.33 (s, 6, $>N^+Me_2$), 3.88 (s, 3, OMe), 5.28 (d, J = 12.0 Hz, 1, C-10 H), 6.87 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.03 (q, $J_{7,5}$ = 2.5, $J_{7,8}$ = 8.5 Hz, 1, C-7 H), 7.92 (d, $J_{8,7}$ = 8.5 Hz, 1, C-8 H).

Anal. Calcd for $C_{19}H_{26}BrNO_2$·HBr: C, 49.48; H, 5.90; N, 3.04. Found: C, 49.77; H, 5.80; N, 2.95.

3-Methoxy-10-oxo-*N*-methylisomorphinan Methobromide (25). The bromo ketone hydrobromide **24** (58 mg) was converted to the free base (40 mg). It solidified on standing. Recrystallization from MeOH–Me_2CO gave **25** as colorless prisms: mp 234–235°; ir (Nujol) 1675 cm^{-1} (C=O); NMR (CD_3OD) δ 3.04 (s, 3, N^+Me), 3.48 (s, 3, N^+Me), 3.90 (s, 3, OMe), 3.95 (d, J = 6.0 Hz, 1, C-9 H), 6.98–7.10 (m, 2, C-2 and C-4 H), 8.02 (d, J = 9.0 Hz, 1, C-1 H).

Anal. Calcd for $C_{19}H_{26}BrNO_2$: C, 60.00; H, 6.81; N, 3.68. Found: C, 60.01; H, 6.99; N, 3.61.

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Registry No.—**2,** 53661-21-5; **3,** 55156-34-8; **4,** 55156-35-9; **4** HCl, 55156-36-0; **4′,** 55156-37-1; **4′** HCl, 55156-38-2; **5,** 55156-39-3; **6,** 55156-40-6; **6** HCl, 55156-41-7; **6** HBr, 55156-42-8; **7,** 55156-43-9; **7** picrate, 55156-44-0; **9,** 55156-45-1; **10,** 55156-46-2; **10** picrate, 55177-18-9; **11,** 55156-47-3; **12,** 55156-48-4; **12** HCl, 55177-19-0; **13a,** 55156-49-5; **13b** HBr, 55156-50-8; **15,** 50282-12-7; **16b,** 55156-51-9; **16b** oxalate, 55156-52-0; **17,** 55156-53-1; **17** HCl, 55156-54-2; **17** HBr, 55156-55-3; **18,** 55156-56-4; **19,** 55177-20-3; **19** picrate, 55220-80-9; **20,** 55156-47-3; **21a,** 55177-21-4; **21a** picrate, 55220-81-0; **21b** HBr, 55177-22-5; **22,** 55156-57-5; **23** HBr, 55156-58-6; **24,** 55156-59-7; **24** HBr, 55156-60-0; **25,** 55177-47-4.

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Aromatic Nucleophilic Substitution Reactions of Ambident Nucleophiles. II.[1a] Reactions of Nitrite Ion with Nitrohalobenzenes

T. J. Broxton, D. M. Muir, and A. J. Parker* [1b]

Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia 6009, and the Research School of Chemistry, Australian National University, Canberra, A.C.T. 2600

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Nitrophenols are the eventual products of the aromatic nucleophilic substitution reactions of the ambident nitrite ion with suitably substituted nitrobenzenes. This is the case no matter whether the nitrogen or the oxygen of the nitrite ion is the original site for bonding to aromatic carbon. However, the intermediacy of di- or trinitroaromatics, i.e., the first products of N-attack, has been demonstrated by labeling the substituted nitrobenzenes with deuterium, or with a methyl group, or by using $^{15}NO_2^-$ as the nucleophile. N-Attack is faster than O-attack when Cl, Br, or I is displaced from the nitrohalobenzenes by nitrite ion but O-attack is faster when fluorine is displaced. Reactions are about 10^5 faster in dipolar aprotic solvents than in methanol and the rate of O-attack is enhanced more than N-attack on transfer from methanol to dipolar aprotic solvents. The principles discussed here enable one to optimize the conditions for a maximum yield of the initial product of N-attack and for a minimum yield of nitrophenols. If the substrate has a substituent ortho to the site of nucleophilic attack, the proportion of nitrophenol to dinitrobenzene is very high throughout the reaction.

Aromatic nucleophilic substitution (SNAr) reactions of aryl halides (ArX) with nitrite ion have the potential for preparing nitroaromatic compounds in which the nitro group is in a specifically predetermined position. This position might be inaccessible by electrophilic nitration procedures.[1c] However, SNAr reactions of nitrite ion with many aryl halides give phenols rather than nitroaromatics as the major or only product. This paper investigates such reactions in an attempt to optimize conditions for a maximum yield of nitroaromatics.

The SNAr reactions of nitrite ion have been studied in methanol, DMF, DMSO, and HMPT. This choice of solvents allows a wide range of substrate (ArX) reactivity to be covered, including ArX as the weakly activated ortho and para nitrohalobenzenes, as well as the 2,4-dinitrohalobenzenes.

Nucleophilic substitution by nitrite ion at a *saturated* carbon atom gives both nitro compounds (RNO_2) and nitrite esters RONO.[2,3] Kornblum has noted that bonding by oxygen to saturated carbon (O-attack) is pronounced when the transition state has a well-developed positive charge on the carbon atom (loose SN2 or SN1 reactions) and bonding by nitrogen to carbon (N-attack) is pronounced in tight SN2 transition states where the carbon is softer and carries little if any positive charge.[2] Pearson's hard and soft acids and bases principle is relevant;[4] the harder oxygen atom of NO_2^- prefers to bond to hard positively charged carbon in the loose transition state, the softer nitrogen of NO_2^- prefers to bond to softer carbon in the tighter transition state.

The situation for nucleophilic substitution of ArX by nitrite ion at an *aromatic* (sp^2) carbon atom requires different considerations. Aromatic nitrite esters ArONO are very unstable under SNAr conditions. The nitro group in $ArNO_2$ is an extremely labile leaving group in the presence of nucleophiles. Thus SNAr reactions of nitrite ion are often complicated by reactions in which the entering nitrite ion is displaced from the initial product by the leaving group, by other nucleophiles, or by another nitrite ion. The pathways for the reactions of nitrite ion with aromatics are set out in Scheme I. They are similar to those proposed by Rosen-