Studies in the Synthesis of C Ring Bridged Morphinans. 2.[1] The Synthesis and Structural Verification of a Novel 3,11c-Ethano-10-hydroxy-6-methyl-1,2,3,3a,11b,11c-hexahydroaporphine

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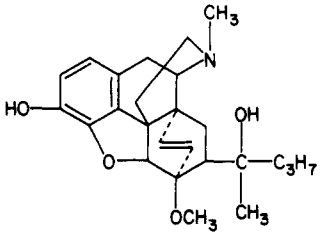
The title compound and its 10-methoxy congener were prepared from bicyclo[2.2.2]oct-2-ene in approximately 2% overall yield. In the course of the synthesis of the final product, 14 novel bicyclo[2.2.2]- and -[3.2.1]octane derivatives were isolated and characterized. Entry into the aporphine ring system was accomplished by cyclizing the appropriate *N*-formylisoquinoline precursor with liquified hydrofluoric acid which gave the bridged 6-formyl-10-methoxyhexahydroaporphine molecule in essentially quantitative yield. Structural verification of the final product was through ^{13}C and ^{1}H NMR and X-ray crystallography.

The presence of C ring alkyl bridging units in narcotic analgetic molecules has, until recently,[3] been restricted to oripavaine derivatives such as etorphine, **1**. Etorphine is



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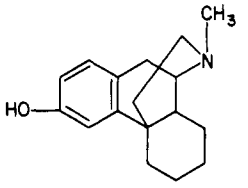

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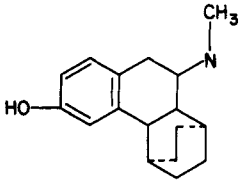

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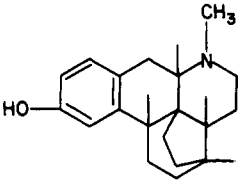

4

one of the most potent of all synthetic narcotics,[4] being 200 times more potent than morphine in man.[5] While much of the superior analgetic potency of **1** is due to its high lipophilicity[6,7] and the enhanced distribution properties which accompany it, efficacious drug–receptor interactions also contribute significantly to the strong antinociceptive properties of this molecule.[5,6]

An interest in bridged opiates is found in the medicinal chemistry literature,[1,3] and it was believed that interesting comparative drug–receptor interaction data would be provided by 5,8-endo alkyl derivatives. The morphinans exemplified by the clinically useful analgesic levorphanol, **2**, have the conformational freedom necessary to make the 5,8-bridged derivative **3** feasible.

It was the initial purpose of this study to synthesize (±)-5,8-*endo*-ethano-3-hydroxy-*N*-methylmorphinan, **3**; however, acid-catalyzed (HF) cyclization of the racemic *N*-formylisoquinoline precursor **18** (Scheme I) proceeded with total rearrangement to give a nearly quantitative yield of (±)-3,11c-ethano-6-formyl-10-methoxy-1,2,3,3a,5,6,6a,7,11b,11c-decahydro-4*H*-dibenzo[*de*,*g*]-quinoline (**4**), also known as 3,11c-ethano-6-formyl-10-methoxy-1,2,3,3a,11b,11c-hexahydroaporphine. Hereafter, compounds in this class will be referred to by the hexahydroaporphine nomenclature.

Results and Discussion

The proposed synthesis of **3** was based on a modification of the classic Grewe synthesis of morphinan[9] which was modified by Schnider et al.[10] for the production of **2**.

Scheme I outlines the synthetic procedure designed to produce **3** starting with bicyclo[2,2,2]oct-2-ene, **5**. Hydroboration[11] of **5** with borane–methyl sulfide (BMS) gave the bicyclo alcohol **6** in 70% yield. Chromic acid oxidation[12] of **6** followed by cyanomethylation[13] and lithium aluminum hydride reduction[14] produced the amino alcohol, **9**, in moderate yield. When free radical formation was inhibited, reaction of **9** with triphenylphosphine and bromine[15] gave an equal mixture of two olefinic isomers **10** and **11**. When free radical formation was not inhibited, a third product, **12**, which resulted from anti-Markovnikov addition of hydrogen bromide across the endocyclic double bond of **10**, was also present in the crude reaction mixture.[1] Acylation[16] of the mixture of **10** and **11** with *p*-methoxy-

(1) Part 1 of this series: Roche, V. F.; Roche, E. B.; Nagel, D. L. *J. Org. Chem.* **1982**, *7*, 1368.
(2) American Foundation for Pharmaceutical Education W. Paul Briggs Memorial Fellow, 1980–1981.
(3) Ghosh, A. C.; Portlock, D. E.; Dalzell, H. C.; Malmberg, C.; Herlihy, P.; Razdan, R. K.; Duax, W. L.; Smith, D. G. *J. Org. Chem.* **1983**, *48*, 4137–4139.
(4) Dole, V. P.; Cuatrecasas, P.; Goldstein, A. "Neuroscience Research Program Bulletin"; Snyder, S. H., Matthysee, S., Eds.; MIT Press: Cambridge, 1975; Vol. 13, p 24.
(5) Hite, G. T. "Principles of Medicinal Chemistry", 2nd ed.; Foye, W. O., Ed.; Lea and Febiger: Philadelphia, 1981; p 261.
(6) Hollt, V.; Wuster, H. "Developments in Opiate Research"; Herz, A., Ed.; Dekker Inc: New York, 1978; p 1.
(7) Herz, A.; Teschemacher, H. *Adv. Drug Res.* **1971**, *6*, 79.
(8) Crabbendam, P. R.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays*-Bas **1981**, *100*, 293.
(9) Grewe, R.; Mondon, A. *Chem. Ber.* **1948**, *81*, 279.
(10) Schnider, O.; Hellerbach, J. *Helv. Chim. Acta* **1950**, *33*, 1437.
(11) Lane, C. F. *J. Org. Chem.* **1974**, *39*, 1437.
(12) Eisenbraun, E. J. "Organic Syntheses"; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect Vol. V, p 310.
(13) Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 3402.
(14) Monkovic, I.; Wong, H.; Belleau, B.; Pachter, I. J.; Perron, V. G. *Can. J. Chem.* **1975**, *53*, 2515.
(15) Schafer, J. P.; Weinberg, D. S. *J. Org. Chem.* **1965**, *30*, 2635.
(16) White, E. "Organic Syntheses"; Baumgarten, H. E., Ed; Wiley: New York, 1973; Collect. Vol. V, p 336.

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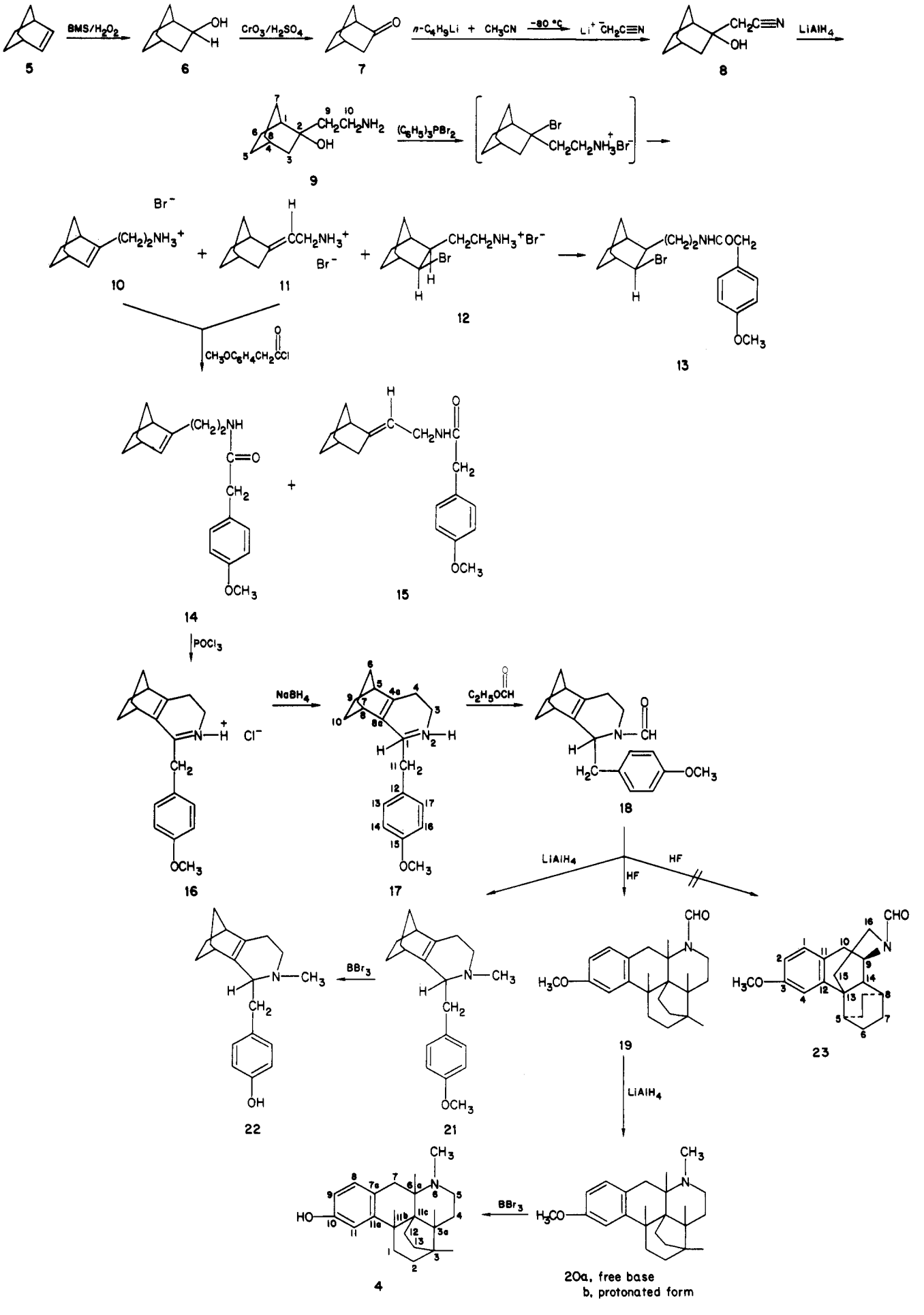
Scheme I


BMS/H2O2
CrO3/H2SO4
n-C4H9Li + CH3CN
-80 °C
Li+ -CH2C≡N
CH2C≡N
OH
LiAlH4
5
6
7
8
9
10
(C6H5)3PBr2
Br-
(CH2)2NH3+
CCH2NH3+
CH2CH2NH3+Br-
(CH2)2NHC OCH2
OCH3
10
11
12
13
CH3OC6H4CH2COCl
(CH2)2NH
C=O
CH2
CH2NHC
14
15
POCl3
NaBH4
C2H5OCH
Cl-
16
17
18
LiAlH4
HF
BBr3
CHO
N-CH3
OH
19
20a, free base
b, protonated form
21
22
23
4

phenylacetyl chloride afforded the amides **14** and **15**. An identical acylation reaction utilizing **12** afforded the haloamide **13**.

A Bischler–Napieralski cyclization reaction[17] with the mixture of amides **14** and **15** allowed isomer separation, and after sodium borohydride reduction, the desired secondary amine **17** was obtained in 42% yield from the isomeric primary amines. Intermediate **17** was formylated[18] and either cyclized in liquified hydrofluoric acid or reduced with lithium aluminum hydride[18] to give 6-formyl-10-methoxyhexahydroaporphine **19** or the 2-methyloctahydroisoquinoline derivative **21**, respectively. The formylated hexahydroaporphine was reduced with lithium aluminum hydride[18] and O-dealkylated with boron tribromide[19] to give the final product, **4**, which was characterized as the hydrochloride salt. The methoxyisoquinoline derivative **21** was also O-dealkylated with boron tribromide and gave the 1-*p*-hydroxybenzyl derivative **22**.

The assigned structures of key intermediates were corroborated with ^{13}C NMR and ^1H NMR spectroscopy. X-ray crystallographic analyses have verified the structures of **18** and **20**.

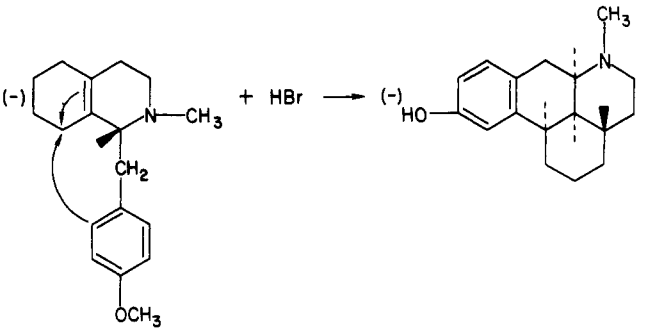
The production of **8** in good yield was dependent on reaction time and temperature parameters. The nucleophilic lithioacetonitrile anion which formed at −80 °C reacted successfully with ketone **7** only when the −80 °C temperature was maintained and condensation time was limited to 10 min prior to acidic hydrolysis. Infrared spectroscopy verified that varying either the condensation time (up to 3 h) or the reaction temperature (up to room temperature) prevented the formation of the desired β-hydroxynitrile (C≡N, 2240 cm^{-1}) and promoted the formation of ketonic products (C=O, 1716 cm^{-1}).

The conversion of the amino alcohol **9**, synthesized from **8** through lithium aluminum hydride reduction, to olefins **10** and **11** has been previously discussed.[1] A heat-catalyzed dehydrohalogenation reaction on the bromo intermediate in a nonpolar solvent (*p*-xylene), and in the presence of a catalytic quantity of the free radical inhibitor hydroquinone, led to a 1:1 mixture of olefinic isomers, one of which was the desired bicyclo[2.2.2]octene derivative **10**.

After acylation of the above mixture of olefinic amines to form the (*p*-methoxybenzyl)amido derivatives **14** and **15**, the Bischler–Napieralski reaction permitted chemical separation of these isomers. The single product isolated was not analyzed, but spectroscopic and elemental analysis of the sodium borohydride reduced derivative **17** indicate that its structure corresponded to the imine hydrochloride **16**. Amide **15** apparently did not cyclize since no basic products of corresponding structure were found in the reaction workup.

Although the cyanoborohydride anion is a more selective imine reducing agent and has an acid stability greater than sodium borohydride,[20,21] the use of the former reagent at the pH of 4.0 in the conversion of **16** to amine **17** resulted in nonselective reduction of the molecule. This was evidenced by the examination of the ^1H NMR and ^{13}C NMR spectra of the cyanoborohydride-reduced product, which indicated the presence of two phenyl rings. In addition, both peaks representing the protons adjacent to the olefinic linkage and the olefinic carbons were greatly reduced in intensity when compared to a sodium borohydride reduced sample. Selective reduction of the imine with sodium borohydride successfully produced enantiomeric **17**.

Scheme II



The structure of **17** was verified, in part, by ^1H NMR spectroscopy. The C_1 methine proton was distinct at approximately 3.5 ppm and appeared as a complex multiplet.

The formylation of **17** with ethyl formate was undertaken for two reasons. The first involved the use of the formylated derivative **18** as an intermediate in the possible synthesis of the desired morphinan derivative, **23**. Leimgruber et al.[22] have shown that 2-formyl derivatives of octahydroisoquinoline cyclize in concentrated phosphoric acid to classical morphinans almost 400 times faster than the corresponding 2-methyl derivatives. They have further demonstrated that the electron-withdrawing 2-formyl substituent minimized the formation of undesired hexahydroaporphine byproducts upon cyclization of nonbridged isoquinolines, giving the nonbridged *N*-formylmorphinan derivatives in 90% yield or better.[23] Secondly, the formylation of **17** provided a clean and convenient route to the 2-methylisoquinoline derivatives **21** and **22**, which were of interest to us.

The ^1H NMR spectrum of **18** indicated the presence of a formamide group through a sharp singlet at 7.3 ppm. The C_1 methine proton was observed at approximately 4.3 ppm, which was almost 1 ppm downfield from its observed position in the ^1H NMR spectrum of **17**. Examination of molecular models indicated the possibility that the downfield shift was due to an interaction between the carbonyl group of the formamide moiety and the aromatic ring, which could cause deshielding of the C_1 methine proton of **18** through the aromatic ring current.

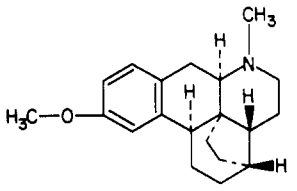
The loss of the aromatic AA′BB′ splitting pattern that is common in freely rotating *p*-methoxy-substituted benzenes and was evident in the ^1H NMR spectrum of **17** was a further indication of the restricted rotation of the aromatic ring in **18**. In the ^1H NMR spectrum of the *N*-methyl derivative of **17** (**21**), the C_1 methine proton appeared at approximately 3.0 ppm which is close to where it was observed in the spectrum of the nor derivative **17**, indicating that deshielding of the C_1 proton by the aromatic ring current did not occur. The freely rotating nature of the aromatic ring of **21** was evidenced by the return of the AA′BB′ splitting pattern for the aromatic protons of this molecule.

Until the aforementioned discovery of Leimgruber et al.,[22] the formation of hexahydroaporphine byproducts through olefinic isomerization was a common problem in Grewe and related procedures for the synthesis of traditional morphinan molecules from *N*-methyloctahydroiso-

(17) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Sotah, F.; Sugi, H.; Uryu, T. *J. Heterocycl. Chem.* **1975**, *9*, 1065.
(18) Schnider, O.; Hellerback, J. *Helv. Chim. Acta* **1951**, *34*, 2218.
(19) Hutchins, C. W.; Cooper, G. K.; Purro, S.; Rappoport, H. *J. Med. Chem.* **1981**, *24*, 773.
(20) Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 3996.
(21) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(22) Leimgruber, W.; Mohacsi, E.; Baruth, H.; Randall, L. O. "Advancers in Biochemical Psychopharmacology"; Braude, M. C., Harris, L. S., May, E. O., Smith, J. P., Villareal, J. E., Eds.; Raven Press: New York, 1974; Vol. 8, p 45.
(23) Leimgruber, W.; Mohacsi, E. U.S. Patent 3 634 429, 1972.

quinoline precursors[24-26] (e.g., Scheme II). While this isomerization is forbidden in the bridged octahydroisoquinoline **18**, quantitative hexahydroaporphine ring formation presumably occurs in the presence of HF through a Wagner–Meerwein type rearrangement,[27-30] and a quantitative yield of **19** results. TLC analysis indicates that the same single product is formed when either anhydrous or polyphosphoric acids are used as catalysts, however, the yields only approach 60%.

Whether the carbonium ion at C_{8a} forms directly as a result of H^+ addition or is the result of more extensive skeletal rearrangement or hydride shift in the bicyclo system is uncertain. The negative inductive effect of the formamide group should make C_{8a} the most attractive for electrophilic attack by H^+. The fact that very high yields of traditional morphinans have been generated from nonbridged *N*-formylisoquinolines[23] (which requires nucleophilic attack of the aromatic ring at C_{4a}) is also indicative of initial carbonium ion formation at the desired C_{4a} with subsequent rearrangement to give a final C_8 cation. Three enantiomeric pairs of **19** are possible with product structure dependent on stereochemistry at C_1 and C_{4a}, and on which carbon migrates in the Wagner–Meerwein process. A small sample of **20b** was slowly crystallized from acetone/methanol and the resulting crystal was subjected to crystallographic analysis. X-ray crystallographic analysis indicated a single enantiomeric pair, one isomer of which is represented as **20c**.



20c

O-dealkylation of the bridged 10-methoxyhexahydroaporphine **20** and the 1-(*p*-methoxybenzyl)isoquinoline **21** derivatives to the desired phenolic derivatives **4** and **22**, respectively, was accomplished by heating with boron tribromide. Reactions conducted at −78 °C for 3 h or at −78 °C for 1 h followed by stirring outside of the cold bath for 5 h were unsuccessful. The O-dealkylation of both **21** and **20** could be conveniently and successfully accomplished by refluxing the reaction for 1 h after having let the reagents warm from −78 to 0 °C over 12 h.

The hydrolysis of the alkoxy boron intermediate of **4** was accomplished with the slow addition of ice water. However, since there was a chance of hydrogen halide addition across the isolated double bond of **22**, the alkoxyborane intermediate of this phenol was decomposed by utilizing a 6% excess over the stoichiometric quantity of 10% ammonium hydroxide needed to neutralize the acid.

The final racemic bridged *N*-methyloctahydroisoquinoline derivatives **21** and **22** and *N*-methylhexahydro-

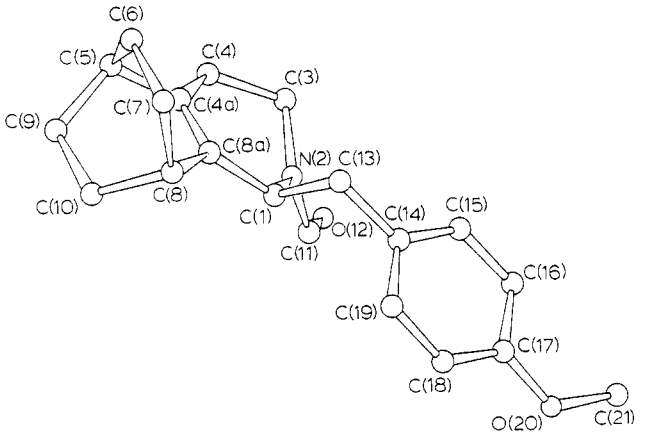


Figure 1. Structure and solid-state conformation of one enantiomer of **18**; hydrogen atoms have been omitted for clarity.

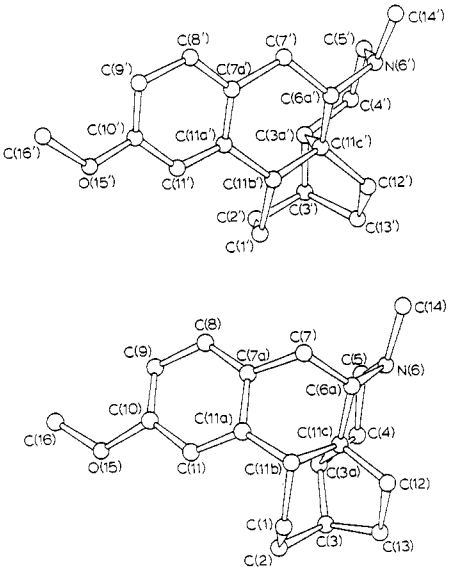


Figure 2. Structure and solid-state conformation of the two cations in the asymmetric unit of **20b**; hydrogen atoms have been omitted for clarity.

aporphine derivatives **20** and **4** displaced [^{3}H]naloxone from the opiate receptors of rat brain in a stereospecific fashion.[31] The phenolic hexahydroaporphine derivative exhibited the lowest ID_{50} indicating an affinity for these receptors approximately 100-fold lower than optically pure levorphanol.[32] These data will be discussed in a subsequent publication.

The crystal structures of **18** and the monohydrate of **20b** were solved by direct methods. Least-squares adjustment of atomic positional and thermal parameters converged to R[33] values of 0.043 and 0.084, respectively, over 1523 reflections for **18** and 1603 reflections for **20b**. Final atomic parameters, interatomic distances and angles are in Tables I–VII.[34] Views of the solid-state conformations are in Figures 1 and 2.

Bond lengths and angles in **18** reveal no unusual features. Endocyclic torsion angles characterizing the azacyclohexene ring conformation are related by an approximate C_2 symmetry axis bisecting the C_2–C_3 and C_4–C_{8a} bonds; thus, this ring adopts a half-chair conformation with the bulky benzyl substituent in a pseudoaxial orientation. The molecular geometry of **20b** is much less well defined

(24) Sawa, T. K.; Kawasaki, K.; Mayeda, S. *Chem. Pharm. Bull. (Tokyo)* **1960**, *8*, 960.
(25) Kametani, T.; Uryu, T.; Fukumoto, K. L. *J. Chem. Soc., Perkin Trans. 1* **1977**, 383.
(26) Hellerback, J.; Schnider, O.; Besendorf, H.; Pellmont, B. "Synthetic Analgesics"; Janssen, P. A. J., Ed.; Pergamon Press: Oxford, 1966; Part IIA, p 3.
(27) Goering, H. L.; Sloan, M. F. *J. Am. Chem. Soc.* **1961**, *83*, 1397.
(28) Olah, G. A.; Bollinger, J. M.; Kelly, D. P. *J. Am. Chem. Soc.* **1970**, *92*, 1432.
(29) Monti, S. A.; Chen, S. C.; Yang, Y. L.; Yuan, S. S.; Bourgeois, O. P. *J. Org. Chem.* **1978**, *43*, 4062.
(30) Saunders, M.; Schleyer, P. v R.; Olah, G. A. *J. Am. Chem. Soc.* **1964**, *86*, 5679.
(31) Pert, C. B.; Snyder, S. H. *Mol. Pharmacol.* **1974**, *10*, 868.
(32) Unpublished results.
(33) $R = \sum||F_o| - |F_c||/\sum|F_o|$.
(34) Supplementary material; see paragraph at the end of the paper.

than that of 18 due to disordering of a chloride ion and water molecules of crystallization (see Experimental Section) and the associated paucity of data obtainable from the poorly diffracting sample. Despite these shortcomings, the primary objective of the analysis, viz., unequivocal proof of structure for **20b**, was attained. Moreover, the results reveal that whereas the quite rigid bicyclo[3.2.1]ring system and the piperidine ring fused thereto are very similar in both of the crystallographically independent cations, the conformations of their cyclohexene rings differ significantly. Endocyclic torsion angles[35] defining the cyclohexene ring conformation in the primed cation are related by an approximate C_2 symmetry axis passing through the midpoints of the C_{7a}–C_{11a} and C_{6a}–C_{11c} bonds, indicating that this ring has a half-chair form. In contrast, in the unprimed cation two nonadjacent torsion angles have small values and here an approximate C_2 symmetry axis passes through the midpoints of the C_7–C_{7a} and C_{11b}–C_{11c} bonds, showing that this ring has a 1,3-diplanar form. Inspection of molecular models reveals that these alternative forms apparently serve equally well to minimize unfavorable nonbonded interactions between syn related hydrogen atoms at C_5 and C_7 in addition to those between one of the hydrogen atoms at C_1 and that at C_{11}.

Experimental Section

Synthetic Data. The details of the synthesis of derivatives **6–12** have been previously reported.[1]

Melting points were determined on either a Mel-Temp or a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-18A infrared spectrophotometer and are referenced to polystyrene. Proton NMR spectra were obtained with a Varian EM-360 60 MHz spectrometer and are referenced to tetramethylsilane (Me_4Si) or hexamethyldisiloxane. Mass spectra were recorded on an AEI MS9 mass spectrometer. Elemental analyses were conducted by Galbraith Laboratories, Inc., Knoxville, TN. Experimental values within ±0.4% of the calculated values for **14**, **17**, **18**, **21**, **20**, **22**, and **4** were submitted for review.

***p*-Methoxyphenylacetyl Chloride.** In a 500-mL three-necked flask, equipped with a power stirrer, condenser, and addition funnel was placed 6.036 g (0.036 mol) of 99% *p*-methoxyphenylacetic acid. To the acid, 2.64 mL (0.036 mol) of thionyl chloride (previously triple distilled over triphenyl phosphite) was added and the mixture was stirred 3 h at room temperature. The reaction was heated to 35–40 °C for 25 h, benzene was added, and the excess thionyl chloride was removed by distillation. Distillation of the product under vacuum (79–80 °C (0.125 mmHg)) afforded the chloride in 85–90% yield as a colorless to very pale yellow liquid with a characteristic odor: ^{1}H NMR ($CDCl_3$) δ 7.07 (AA′BB′, 4 H, aromatic), 4.08 (s, 2 H, CH_2), 3.83 (s, 3 H, OCH_3); IR (neat) 1800 (C=O stretch), 1260 (C—O—C stretch, asymmetric), 1030 (C—O—C stretch, symmetric), 1510 (aromatic C=C stretch) cm^{-1}.

[[[(*p*-Methoxybenzyl)carbonyl]amino]ethyl]bicyclo[2.2.2]oct-2-ene (14) and 2-[[[(*p*-Methoxybenzyl)carbonyl]amino]ethylidene]bicyclo[2.2.2]octane (15). To a 250-mL single-necked flask, equipped with a magnetic stirrer, was added 4.27 g (0.018 mol) of an approximately equal mixture of the olefinic amine hydrobromides **10** and **11** in 150 mL of dry benzene. After the addition of 4.4 mL of dry pyridine, the mixture was stirred for 15 min, a solution of 3.89 g (0.018 mol) of *p*-methoxyphenylacetyl chloride in 25 mL of dry benzene was added, and the reaction was stirred for 4 h at room temperature. The precipitated pyridine salts were filtered and washed with benzene, and the combined organic phases were washed consecutively with 50 mL of dilute hydrochloric acid, 50 mL of water, 50 mL of dilute ammonium hydroxide, and three 50-mL portions of water. After drying ($MgSO_4$) and concentrating, a quantitative yield of a pale yellow oil was isolated. The ^{1}H NMR spectrum of this oil indicated the presence of both the endocyclic (**14**), and the exocyclic (**15**) olefinic amides in approximately a 1:1 ratio based on the integration ratio of the isomeric olefinic protons. The oil was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 5.65 (d, 1 H, 3-H), 5.00 (m, 1 H, 2-CH); IR (neat) 3300 (NH stretch), 1660 (C=O stretch), 1260 (C—O—C stretch, asymmetric), 1050 (C—O—C stretch symmetric) cm^{-1}.

A sample of pure **14** as a yellow oil was synthesized for spectroscopic purposes by the above procedure, utilizing 50 mg of purified **10**: ^{1}H NMR ($CDCl_3$) δ 7.03 (AA′BB′, 4 H, aromatic), 5.73 (d, 1 H, 3-H), 5.43 (m, 1 H, NH), 3.82 (s, 3 H OCH_3), 3.50 (s, 2 H, OC–CH_2), 3.25 (t, 2 H, CH_2N), 1.87–2.64 (m, 4 H, 1-H, 2-CH_2, 4-H), 0.67–1.67 (m, 8 H, remaining protons).

5,8-Ethano-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (17). A 250-mL single-necked flask, equipped with a reflux condenser and a magnetic stirrer was charged with 5.38 g (0.018 mol) of the mixture of amides **14** and **15** in 150 mL of dry benzene. In one lot, 2.74 mL (9.030 mol) of phosphorus oxychloride was added and the mixture heated to reflux for 2 h. The reaction mixture was reduced in vacuo to a thick red syrup which was shaken vigorously with 50 mL of water and twice the volume of ethyl ether. The ether phase was extracted several times with 25–50-mL portions of water. The water was evaporated in vacuo, leaving 5.36 g of a honey colored tacky oil, corresponding to 0.0169 mol of imine hydrochloride **16**. The oil was dissolved in 60 mL of water and the pH was adjusted to 5.0 with a dilute sodium hydroxide solution. After transferring to a 250-mL one-necked flask and adding 100 mL of 95% ethanol, the flask was cooled in an ice bath and 1.54 g (0.0406 mol) of sodium borohydride was added as a solid in very small increments and with vigorous stirring. The reaction mixture was refluxed 1 h, and after ethanol evaporation, the aqueous solution was extracted four times with ether. All organic phases were combined, dried (Na_2SO_4), and concentrated to give a dark yellow oil which was distilled under vacuum with an air-cooled condenser (160–170 °C (0.2–0.1 mmHg)). A thick, pale yellow oil (**17**) distilled in 41.6% overall yield from the isomeric amides: ^{1}H NMR ($CDCl_3$) δ 7.02 (AA′BB′, 4 H, aromatic), 3.77 (s, 3 H, OCH_3), 3.30–3.96 (m, 1 H, 1-H), 2.34–3.20 (m, 5 H, NH, 3-H_2, 1-CH_2), 1.90–2.30 (m, 4 H, 4-H_2, 5-H, 8-H), 0.90–1.83 (m, 8 H, remaining protons); IR (neat) 3300 (NH stretch), 1245 (C–O–C stretch, asymmetric), 1040 (C–O–C stretch, symmetric) cm^{-1}; mass spectrum, m/z 283 (M^+), 162 (M^+ – *p*-methoxybenzyl, base), 91 (tropylium ion).

The amine (**17**) could also be purified via the formation of the oxalate or the methanesulfonate salts. The oxalate was recrystallized from acetone and melted at 142.5–143 °C. The methanesulfonate was purified from methanol:benzene (1:1) with ethyl ether added to induce crystallization: mp 132–132.5 °C.

5,8-Ethano-2-formyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (18). The ethyl formate used in this reaction was purified immediately before use by storing 20 mL of purchased reagent over 3.0 g of sodium carbonate for 1 h with occasional swirling, followed by distillation from 1.0 g of phosphorus pentoxide.[36] A 100-mL three-necked flask was equipped with a stirring bar, gas inlet adapter, condenser with attached drying tube, and a thermometer adapter. After the system was flushed with dry nitrogen for 15 min, 1.12 g (0.0040 mol) of **17** in 50 mL of dry benzene was introduced, 12 mL (0.148 mol) of ethyl formate was rapidly added, the nitrogen flow was discontinued, and the reaction was heated to 50 °C for 18–24 h. Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel 60, precoated glass plates (E. Merck) (5 × 20 cm), which were developed in acetone/dichloromethane (70:30) R_f (**17**) 0.20, R_f (**18**) 0.80. After removal of solvent in vacuo, the product was dissolved in ethyl ether and washed consecutively with water, 10% hydrochloric acid, and twice again with water. After drying ($MgSO_4$) and concentrating the remaining clear oily formamide **18**, in 84% crude yield, was crystallized as colorless plates from a minimum amount of ethyl ether in 66% overall yield: mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 1 H, CHO), 6.57–7.03 (m, 4 H, aromatic), 4.20–4.63 (m, 1 H, 1-H), 3.73 (s, 3 H, OCH_3),

(35) Endocyclic torsion angles (ω_{ij}, $\sigma \pm 1°$) about the bond between atom *i* and *j* in the unprimed cation of **20b**, with corresponding values for the primed cation in parentheses, follow: $\omega_{6a,7}$ −7 (41), $\omega_{7,7a}$ 32 (−16), $\omega_{7a,11a}$ −5 (7), $\omega_{11a,11b}$ −42 (−23), $\omega_{11b,11c}$ 63 (45), $\omega_{11c,6a}$ −38 (−55).

(36) Fieser, L. F.; Fieser, M. "Reagents for Organic Syntheses"; Wiley: New York, 1967; Vol. I, p 380.

2.53–3.15 (m, 4 H, 1-CH_2, 3-H_2), 1.92–2.53 (m, 4 H, 4-H_2, 5-H, 8-H), 1.00–1.92 (m, 8 H, remaining protons); IR (KBr) 2860 (aldehydic stretch, asymmetric), 1045 (C–O–C stretch, symmetric) cm^{-1}; mass spectrum, m/z 311 (M+), 190 (M+ – *p*-methoxybenzyl, base), 121 (*p*-methoxybenzyl$^+$).

5,8-Ethano-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (21). A three-necked 100-mL flask was dried by heating in a high temperature oven at 210 °C for 18 h and allowed to cool under a stream of dry nitrogen. When totally cooled, 102 mg (2.67 mmol) of lithium aluminum hydride in 20 mL of anhydrous tetrahydrofuran (freshly distilled from lithium aluminum hydride) was introduced. With ice cooling and magnetic stirring, a solution of 300 mg (0.96 mmol) of **18** in 20 mL of tetrahydrofuran was added dropwise to the hydride. The mixture was then refluxed for 4–6 h or until TLC analysis in acetone/dichloromethane (70:30) indicated a completed reaction (silica gel 60, glass plates (5 × 20 cm): R_f(**21**) 0.19. The cooling bath was replaced and the excess hydride was cautiously decomposed by the slow addition of 100 μL of water, 100 μL of 15% sodium hydroxide, and 300 μL of water.[37] A granular precipitate resulted which was filtered and triturated three times with ethyl ether. The organic filtrate was removed in vacuo, the residue was dissolved in ether, and all organic phases were combined and dried (Na_2SO_4). Concentration left 301 mg of **21** as an off-white oil (100% crude yield).

The hydrochloride monohydrate salt of **21** was prepared in 79% crude yield from the base and recrystallized from acetone: mp (sealed tube) 178–180 °C dec, 209–211 °C; ^{1}H NMR (base in $CDCl_3$) δ 6.97 (AA′BB′, 4 H, aromatic), 3.78 (s, 3 H, OCH_3), 2.87–3.27 (m, 1 H, 1-H), 2.40–2.87 (m, 4 H, 1-CH_2, 3-H_2), 2.33 (s, 3 H, NCH_3), 1.83–2.27 (m, 4 H, 4-H_2, 5-H, 8-H), 1.03–1.77 (m, 8 H, remaining protons); IR (KBr) 3460 (OH stretch), 2600–2460 (NH^+ stretch), 1245 (C–O–C stretch asymmetric), 1035 (C–O–C stretch, symmetric) cm^{-1}; mass spectrum, m/z 297 (M$^+$), 176 (M$^+$ – *p*-methoxybenzyl, base), 148 (retro-Diels–Alder), 121 (*p*-methoxybenzyl$^+$), 42 (CH_2=N=CH_2^+).

5,8-Ethano-1-(*p*-hydroxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (22). A 100-mL three-necked flask was dried for 24 h at 210 °C. While cooling under a stream of dry nitrogen, the flask was immersed in an ethanol/dry ice bath and cooled to −75 °C. Boron tribromide (300 μL, 3.16 mmol) was introduced, followed by 10 mL of dry dichloromethane. Purified **21** (224 mg, 0.754 mmol), as the base, in 30 mL of dry dichloromethane was added in a dropwise fashion. Thirty minutes after the addition of **21**, the stirring was stopped, the nitrogen was replaced by a calcium sulfate drying tube, and the mixture was left in the cold for 12 h. After refluxing for 1 h, the reaction mixture was recooled in an ice bath and 3.5 mL of 10% ammonium hydroxide was slowly added and a flocculent precipitate formed. After stirring for 15 min, the cold bath was removed and 50 mL of water was added. The subsequent isolation of the product was conducted in the dark to minimize photooxidation. The phases were separated, the dichloromethane was removed in vacuo and the residue was dissolved in ethyl ether. The aqueous phase (pH 8.4) was adjusted to pH 9.1 with 10% ammonium hydroxide and extracted eight times with 20-mL portions of ether. All ether phases were combined, dried (Na_2SO_4), and concentrated to give a yellow oil. An attempt was made to purify this base by methansulfonate salt formation, but this salt form resisted crystallization. The hydrochloride salt was made and recrystallized from acetone/ethanol/ethyl ether in 29% yield. There was evidence of additional product in the mother liquor but it resisted crystallization: mp (sealed tube) 218–220 °C sublime; ^{1}H NMR (base in $CDCl_3$) δ 6.67 (AA′BB′, 4 H, aromatic), 4.58 (s, 1 H, OH), 2.87–3.30 (m, 1 H, 1-H), 2.43–2.87 (m, 4 H, 1-CH_2, 3-H_2), 2.33 (s, 3 H, NCH_3), 1.90–2.27 (m, 4 H, 4-H_2, 5-H, 8-H), 0.93–1.72 (m, 8 H, remaining protons); IR (base, neat) 3300 (OH stretch) cm^{-1}; mass spectrum, m/z 283 (M$^+$), 176 (M$^+$ – *p*-hydroxybenzyl, base), 148 (retro-Diels–Alder), 107 (*p*-hydroxybenzyl$^+$), 106 (*p*-hydroxybenzyl – 1$^+$), 42 (CH_2=N=CH_2^+).

3,11c-Ethano-6-formyl-10-methoxy-1,2,3,3a,11b,11c-hexahydroaporphine (19). To 402 mg (1.29 mmol) of thoroughly dried formamide **18** in a nitrogen-flushed 125-mL teflon bottle was cautiously added 90–95 mL of liquified hydrogen fluoride. The bottle was quickly capped and the solution was stirred overnight. After 15 h, nitrogen was again swept through the system to aid in removing the gaseous hydrogen fluoride. The red oily product was dissolved in 50 mL of chloroform and shaken with an equal volume of 10% ammonium hydroxide. The aqueous phase was extracted four times with 25-mL portions of chloroform and all organic extracts were combined and dried ($MgSO_4$). Removal of the chloroform in vacuo left derivative **19** as a pale yellow oil in 98–100% crude yield: ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1 H, CHO), 6.57–7.20 (m, 3 H, aromatic), 4.53–4.90 (m, 1 H, 6a-H), 3.80 (s, 3 H, OCH_3), 1.00–3.70 (m, 17 H, remaining protons); TLC acetone/dichloromethane (70:30), silica gel 60 glass plates (5 × 20 cm) R_f(**18**) 0.79, R_f(**19**) 0.71. The product (**19**) was not characterized further in this form, but rather was directly converted to the *N*-methyl derivative (**20**) for structural verification.

3,11c-Ethano-10-methoxy-6-methyl-1,2,3,3a,11b,11c-hexahydroaporphine (20). When 393 mg (1.26 mmol) of the formamide **19** and 144 mg (3.78 mmol) of lithium aluminum hydride were utilized, a reduction reaction identical to that described for the synthesis of the 2-methyloctahydroisoquinoline derivative (**21**) was performed. After drying and concentrating, **20** was isolated in 94% crude yield as a thick yellow oil. The hydrochloride monohydrate salt was prepared and recrystallized from acetone in 50% yield from the crude base: mp (sealed tube) 138–139 °C dec; TLC acetone/dichloromethane (70:30), silica gel 60 glass plates (5 × 20 cm) R_f (**20**) 0.19; mass spectrum, m/z 297 (M$^+$), 282 (M$^+$ – CH_3), 148 (M$^+$ – $C_{10}H_{13}O$, base), 121 (*p*-methoxybenzyl$^+$), 91 (tropylium ion); IR (KBr) 3396 (OH stretch), 2506 (NH^+ stretch), 1240 (C–O–C stretch, asymmetric), 1060 (C–O–C stretch, symmetric) cm^{-1}.

The free base was regenerated from the purified hydrochloride salt and was further characterized: mp (sealed tube) 72–74 °C; ^{1}H NMR ($CDCl_3$) δ 6.55–7.20 (m, 3 H, aromatic) 3.75 (s, 3 H, OCH_3), 2.55–3.15 (m, 3 H, 6a-H, 5-H_2), 2.32 (s, 3 H, NCH_3), 1.00–2.55 (m, 15 H, remaining protons).

3,11c-Ethano-10-hydroxy-6-methyl-1,2,3,3a,11b,11c-hexahydroaporphine (4). Utilizing 389 mg (1.31 mmol) of the hexahydroaporphine **20** and 350 μL (3.69 mmol) of boron tribromide, a dealkylation reaction identical with the one described for the synthesis of the isoquinoline derivative (**22**) was conducted. After reflux the flask was cooled to 0–5 °C at which time 20 mL of ice water was cautiously added, and the mixture was stirred for 30 min. In the dark, the phases were separated, and the extraction procedure continued as described for the synthesis of **22**. After concentrating, a yellow oil was isolated which was immediately converted to the hydrochloride salt. The salt was recrystallized from methanol/ethyl ether and gave a 42% yield of a white crystalline solid: mp (sealed tube) 273–275 °C dec; ^{1}H NMR (base in $CDCl_3$) δ 6.27–6.93 (m, 3 H, aromatic), 6.03 (br s, 1 H, 2 OH), 2.63–3.17 (m, 3 H, 6a-H, 5-H_2), 2.30 (s, 3 H, NCH_3), 1.03–2.57 (m, 15 H, remaining protons).

Crystal Data. **18**: $C_{20}H_{25}NO_2$, M_r 311.43, monoclinic, a = 10.933 (4) Å, b = 7.855 (3) Å, c = 10.185 (4) Å, β = 102.74 (1)°, U = 853.1 Å^3, Z = 2, D_{calcd} = 1.212 g cm^{-3}. Absorption coefficient for Cu Kα radiation (λ 1.5418 Å) μ = 6.2 cm^{-1}. Space group $P2_1(C_2^2)$ or $P2_1/m(C_{2h}^2)$ from systematic absences: 0*k*0 when $k \neq 2n$; required to be the former since **18** lacks either a center or mirror plane of symmetry.

20b: $C_{20}H_{28}ClNO{\cdot}H_2O$, M_r 351.93, monoclinic, a = 37.622 (19) Å, b = 10.166 (5) Å, c = 22.416 (11) Å, β = 112.88 (1)°, U = 7899 Å^3, Z = 16, D_{calcd} = 1.184 g cm^{-3}. Absorption coefficient for Cu Kα radiation, μ = 18 cm^{-1}. Space group $Cc(C_s^4)$ or $C2/c(C_{2h}^6)$ from systematic absences: *hkl* when $h + k \neq 2n$, *h*0*l* when $l \neq 2n$; shown to be the latter by structure solution and refinement.

Crystallographic Measurements. A crystal of **18** with dimensions ca. 0.24 × 0.30 × 0.70 mm was mounted on the end of a thin glass fiber and a platelike crystal of hydrochloride **20b**, dimensions ca. 0.04 × 0.42 × 0.60 mm, was sealed inside a thin-walled glass capillary for *X*-ray investigations. Oscillation and Weissenberg photographs (Cu Kα radiation) and precision photographs (Mo Kα radiation, λ 0.7107 Å) yielded preliminary unit cell dimensions and space group information. Subsequently, these crystals were transferred to an Enraf–Nonius CAD-3 automated diffractometer (Ni filtered Cu Kα radiation) where intensity data (forms *hkl*, Θ_{max} = 67° for **18**, and *hk*±*l*, Θ_{max} = 57° for **20b**) were

(37) Fieser, L. F.; Fieser, M. "Reagents for Organic Syntheses"; Wiley: New York, 1967; Vol. I., p 584.

recorded by means of the $\theta - 2\theta$ scanning procedure as described previously.[38] From totals of 1650 and 5297 independent measurements for 18 and **20b**, respectively, 1523 reflections for the former were judged to be observed ($I > 2.0\sigma(I)$) whereas only 1603 satisfied this criterion for the latter. The observed data were retained for use in the structure analyses and were corrected for the usual Lorentz and polarization effects but not for absorption. Refined unit cell parameters were derived by least-squares treatment of the diffractometer setting angles for 40 high order reflections from each sample.

Structure Analysis. The crystal structures of 18 and **20b** were solved by use of direct methods and subsequent Fourier syntheses. With regard to 18 the analysis proceeded quite smoothly. The largest $250|E|$ values were input to the MULTAN76[39] suite of programs, and an E map, computed by use of that set of phase angles which yielded the highest combined figure of merit, gave approximate positions for all non-hydrogen atoms. Subsequent full-matrix least-squares adjustment of atomic positional and thermal parameters, with hydrogen atoms included in the later cycles at their calculated positions, converged to $R = 0.043$.

Solution of the crystal structure of the poorly diffracting hydrochloride (**20b**) progressed in a less straightforward manner due to partial site occupation by one of the chloride ions in the asymmetric crystal unit as well as some of the water molecules of crystallization. In this case, an E map, evaluated by use of phase angles which gave rise to the highest combined figure of merit for the 398 highest $|E|$ values, contained one large peak corresponding to a chloride ion, two other peaks of approximately equal magnitude indicating fractional site occupation by a chloride ion and water molecule, and a number of smaller peaks from which it was possible to derive a structure model containing 42 of the 44 non-hydrogen atoms comprising the two cations in the asymmetric crystal unit. An F_0 Fourier synthesis phased by this partial structure ($R = 0.33$) gave positions for the remaining 2 atoms. Several rounds of least-squares adjustment of atomic positional and isotropic thermal parameters decreased R to 0.168. Subsequent F_0 and difference Fourier syntheses revealed four additional significant maxima three of which were ascribed to relatively well ordered water molecules. The fourth peak, somewhat broader and much smaller in magnitude, lay with its maximum on a crystallographic 2-fold axis and was interpreted as representing a further very disordered water molecule. With cation hydrogen atoms included at their calculated positions, continuation of the least-squares iterations, during which the chlorine and ordered water oxygen atoms were allowed to assume anisotropic thermal parameters, led to convergence at $R = 0.084$.

Final atomic positional and thermal parameters for 18 and **20b** are in Tables I–III and Tables V and VI.[34]

Atomic scattering factors for chlorine, carbon, nitrogen, and oxygen were taken from ref 40, and for hydrogen from ref 41, with that for chlorine corrected for anomalous dispersion effects[42]; for the disordered chlorine/oxygen situations, a modified scattering factor $(2f_{Cl} + f_0)/3$ was employed. In the least-squares iterations, $\sum w\Delta^2$ ($\Delta = ||F_0| - |Fc||$) was minimized with weights, w, assigned according to the scheme: $(w)^{1/2} = 1$ for $|F_0| \leq K$, $(w)^{1/2} = K/|F_0|$ for $|F_0| > K$ ($K = 7.0$ for (**18**), $K = 100.0$ for **20b**), which revealed no systematic dependence of $\langle w\Delta^2 \rangle$ values when analyzed in ranges of $|F_0|$ and $\sin\theta$.

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Registry No. (±)-**4**, 91817-15-1; (±)-**4**·HCl, 92007-79-9; **5**, 931-64-6; (±)-**6**, 91877-78-0; **7**, 2716-23-6; (±)-**8**, 91817-16-2; (±)-**9**, 91817-17-3; **10**, 80641-35-6; **11**, 91817-18-4; (±)-**12**, 91817-19-5; (±)-**13**, 91817-20-8; **14**, 91817-21-9; **15**, 91817-22-0; **16**, 91817-23-1; (±)-**17**, 91817-24-2; (±)-**18**, 91817-25-3; (±)-**19**, 91817-26-4; (±)-**20**, 91877-79-1; (±)-**20**·HCl, 91926-14-6; (±)-**21**, 91817-27-5; (±)-**21**·HCl, 91817-14-0; (±)-**22**, 91817-28-6; (±)-**22**·HCl, 91817-29-7; *p*-methoxyphenylacetic acid, 104-01-8; *p*-methoxyphenylacetyl chloride, 4693-91-8.

Supplementary Material Available: Tables of atomic postional and thermal parameters (Tables I–III, V, VI) and interatomic distance and angles (Tables IV and VII) for 18 and **20b** (19 pages). Ordering information is given on any current masthead page.

(38) Miller, R. W.; McPhail, A. T. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 1527.
(39) Main, P.; Lessinger, L.; Woolfson, M. M; Germain, G.; Declerq, J. P. "MULTAN76, A system of computer programmes for the Automatic Solution of Crystal Structures"; Universities of York and Louvain, 1976.
(40) Cromer, D. T.; Waber, J. T. *Acta Crystallogr.* **1965**, *18*, 104.
(41) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *18*, 104.
(42) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, England, 1968; Vol. III, p 214.

Tricarbonylcyclohexadienyliron Complexes as Aryl Cation Equivalents: A Formal Synthesis of (±)-*O*-Methyljoubertiamine[1]

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The use of tricarbonyl(4-methoxycyclohexadienyl)iron hexafluorophosphate **1b** as a synthetic equivalent of the *p*-anisyl cation for a formal synthesis of (±)-*O*-methyljoubertiamine is described.

There is already appreciable documentation in the literature[3] showing that cyclohexadienyl–$Fe(CO)_3$ cationic complexes of type 1 may be used as aryl cation equivalents. Thus, 1 reacts with a range of carbon nucleophiles to give diene complexes type 2, and these can be demetalated and oxidized to aromatic compounds in a number of ways. Of

(1) Organoiron Complexes in Organic Synthesis. Part 33. Preliminary communication, see: Pearson, A. J.; Gardner, D. V.; Richards, I. C. *J. Chem. Soc., Chem. Commun.* **1982**, 807. For Part 32, see: Pearson, A. J.; Perrior, T. R. *J. Organomet. Chem.*, in press.
(2) (a) Case Western Reserve University. (b) Beecham Pharmaceuticals, Ltd.
(3) Birch, A. J.; Cross, P. E.; Lewis, J.; White, D. A.; Wild, S. B. *J. Chem. Soc. A* **1968**, 332. Kelly, L. F.; Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1980**, *21*, 2455.

0022-3263/84/1949-3887$01.50/0