Skeletal Rearrangement of 3-Methoxy-*N*-chloromorphinan

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3-Methoxymorphinan (**1**) was converted to the corresponding *N*-chloro derivative **2** by treatment with aqueous sodium hypochlorite. Upon exposure to methanolic silver nitrate, **2** was rearranged to the carbinolamine ether **3**. In addition, considerable amounts of the dechlorinated morphinan **1** were formed. The structure of **3** was secured by spectral analysis and its degradation to the hexahydroindoline derivative **4**. The observed skeletal rearrangement of **2** which requires the migration of an alkyl group is discussed in terms of a nitrenium ion.

Dedicated to the Memory of Dr. Willy Leimgruber, Deceased July 8, 1981

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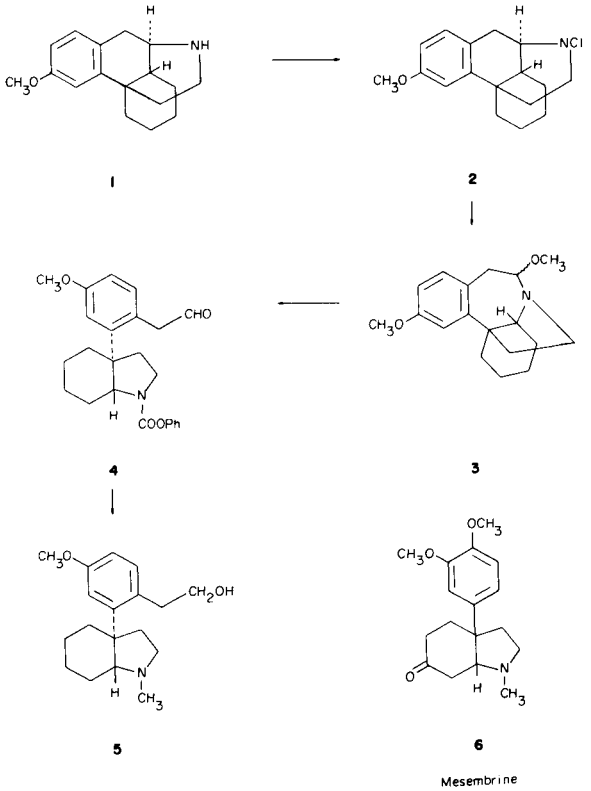
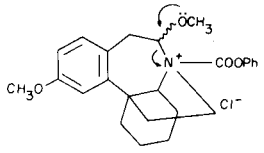
The silver ion catalyzed migration of alkyl groups to electron-deficient nitrogen has recently been elaborated by Gassman (1). We have now successfully applied this method to rearrange the carbon skeleton of morphinans. Thus, the known (2) 3-methoxymorphinan (**1**) gave, on treatment with aqueous sodium hypochlorite, crystalline 3-methoxy-*N*-chloromorphinan (**2**) in 78% yield (Scheme 1). Exposure of **2** to a methanolic solution of silver nitrate at room temperature gave a 13% yield of rearranged product as a colorless viscous liquid, bp 140-145° (0.5 mm), to which structure **3** was assigned. In addition, a 60% yield of the dechlorinated morphinan **1** was also isolated.

Scheme I



Evidence supporting the structure of the carbinolamine ether **3** was provided by spectral data. Thus, the mass spectrum of **3** shows the molecular ion peak as anticipated at m/e 287. The nmr spectrum (deuteriochloroform) features a characteristic ABX pattern for the three aromatic protons, namely two doublets centered at δ 7.00 (J = 8 Hz) and 6.91 (J = 2 Hz), and a quartet at 6.58 (J = 8 Hz). A three proton singlet for the aromatic methoxy protons appears at δ 3.75, a three proton singlet for the methoxyl protons of the carbinolamine ether at 3.34, and a one proton quartet at 4.09 (J = 3 and 11 Hz) assignable to the hydrogen on the methoxyl-bonded carbon. The nmr spectrum of the crystalline hydrochloride of **3** was of particular interest for analysis of the carbinolamine ether region. Thus, the spectrum (deuteriochloroform) revealed an A_2X system for the two proton doublet centered at δ 3.19 (J = 8 Hz) that could be assigned to the benzylic protons and the one proton triplet at 4.63 (J = 8 Hz) belonging to the hydrogen on the methoxyl-bonded carbon. On the basis of the observed coupling constants, however, it was not possible to assign the stereochemistry of the methoxyl group of the carbinolamine ether function. It should be mentioned in this connection that the nmr spectrum of the crude rearrangement product indicates the presence of a minor amount of an isomeric carbinolamine ether. No attempt was made to isolate this isomer.

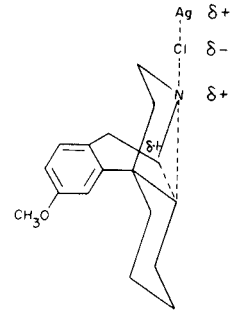
Unequivocal evidence for the correctness of our structural assignment for **3** was provided by degradation experiments. Since this compound could not be reduced with lithium aluminum hydride and also since it was resistant to acid hydrolysis, in conformity with the behavior of structurally related carbinolamine ethers which contain a bridgehead nitrogen (1), other methods of transformation were sought. When a methylene chloride solution of the carbinolamine ether **3** was treated with phenyl chloroformate (3), the aldehyde **4** was obtained as the sole product. This reaction undoubtedly proceeds via the following intermediate:



The aldehyde **4** was isolated as a colorless liquid, homogeneous by thin layer chromatography, which could not be distilled without decomposition. Its mass spectrum exhibits the molecular ion peak as required at m/e 393 and the infrared spectrum reveals the carbonyl groups at 1720 cm^{-1}. The nmr spectrum of **4** is consistent with the structure indicated, showing in particular an aldehyde proton triplet at δ 9.8 (J = 2 Hz). This compound was characterized as its corresponding crystalline phenylhydrazone whose nmr spectrum (deuteriochloroform) showed a one proton triplet at δ 7.52 (J = 6 Hz), attributable to the Schiff base proton. The aldehyde **4** was finally converted to 4-methoxy-2-(1-methylhexahydroindolin-3a-yl)phenethyl alcohol (**5**) by reduction with lithium aluminum hydride. The nmr spectrum (deuteriochloroform) of this compound shows, amoung other signals, a three proton singlet at δ 3.71 for the aromatic methoxyl protons, a three proton singlet at 2.28 for the *N*-methyl protons, and a hydroxylic proton as a broad singlet centered at 1.99 which is exchangeable by deuterium oxide. This amino alcohol was further characterized as its crystalline oxalate.

It is of interest to note that the degradation products **4** and **5** possess the same skeleton as the alkaloid mesembrine (**6**) (4).

We suggest that the silver ion catalyzed skeletal rearrangement of the *N*-chloroamine **2** proceeds via a nitrenium ion species, which is involved in a transition state that may be pictured as follows:



EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were measured in 95% ethanol with a Cary Model 14 spectrophotometer. Infrared spectra were determined with a Beckman Model IR 9 spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian A-60 or HA-100 spectrometer and recorded in δ values with deuteriochloroform as the solvent and tetramethylsilane as an internal reference. The proton signals are designated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (70 eV, direct inlet system) were determined with a CEC type 21-110 spectrometer.

3-Methoxy-*N*-chloromorphinan (**2**).

A solution of 140.0 g (0.54 mole) of 3-methoxymorphinan (**1**) (2) in 3 l of methanol was flushed with nitrogen and cooled to -10° in an acetone–dry ice bath while 135 ml of a 16.4% aqueous sodium hypochlorite solution was added slowly with stirring over a period of 30 minutes. After the addition was completed, the reaction mixture was stirred at room temperature for 1 hour, cooled to -10°, and then treated with an additional 135 ml of the sodium hypochlorite solution as before. Stirring was continued at room temperature for 3 hours and then methanol was removed under reduced pressure. The residue was partitioned between 2.5 l of water and 3 l of ether. The ethereal extract was dried (magnesium sulfate) and filtered. The solvent was removed *in vacuo*, and the product was allowed to crystallize from 500 ml of hexane at -20° overnight. Recrystallization from the same solvent afforded 123.8 g (78%) of **2**, mp 86-88°; ir (chloroform): 3000, 2940, 2850 and 1610 cm^{-1}; uv (95% ethanol): max 219 mμ (ϵ 8150), 224 (7900), 279 (2950) and 287 (2700); ms: (70 eV) m/e (relative intensity), 293 (11), 291 (17), 257 (72), 256 (47), 213 (72), 212 (100), 198 (6), 184 (11), 171 (34), 136 (26), 128 (14), 121 (36).

Anal. Calcd. for $C_{17}H_{22}ClNO$: C, 69.96; H, 7.60; N, 4.80; Cl, 12.15. Found: C, 70.10; H, 7.36; N, 4.73; Cl, 12.36.

2,3,4,4a,6,7-Hexahydro-6,10-dimethoxy-1*H*,5,11b-ethanodibenz[*b*,*d*]-azepine (**3**, epimeric mixture).

To a solution of 100.0 g (0.34 mole) of **2** in 4 l of absolute methanol was added 76.0 g (0.44 mole) of silver nitrate. The reaction was stirred under nitrogen at room temperature for 180 hours and then the silver chloride was filtered and thoroughly washed with methanol. The filtrate and washings were combined and the solvent was removed under pressure. The residue was partitioned between 1.5 l of ether and 200 ml of dilute ammonium hydroxide. The ethereal solution was dried over magnesium sulfate, filtered, and the solvent removed *in vacuo* to afford 65.8 g of an oily residue. This residue was chromatographed on a 30-fold amount of neutral aluminum oxide (Woelm, activity I) which had been initially packed in hexane. Fractions containing the desired product were eluted with methylene chloride and combined according to tlc (silica gel, chloroform-ether, 1:1, r_f of **3** ~ 0.18) to afford 12.6 g (13%) of **3**, homogeneous by tlc. A sample of this compound was distilled, bp 140-150° (0.5 mm), and subjected to nmr-analysis which indicated the presence of two epimers of structure **3**. In order to characterize the major epimer, it was purified *via* the corresponding hydrochloride (*vide infra*).

In addition to the rearranged product **3**, 48.1 g (60%) of **1** was also isolated by chromatography. Crude **1** thus obtained was dissolved in ether and treated with a slight excess of ethereal hydrogen chloride. The resulting salt was filtered and recrystallized from ethanol-ether to give 49.1 g of hydrochloride, mp 227-228°, identical with authentic material as shown by mixture mp and spectral properties.

2,3,4,4a,6,7-Hexahydro-6,10-dimethoxy-1*H*,5,11b-ethanodibenz[*b*,*d*]-azepine Hydrochloride (**3**•HCl, pure epimer).

Ethereal hydrogen chloride was added to a solution of 3.1 g (11 mmoles) of **3** (mixture of epimers) in 10 ml of ether. The resulting solid was collected by filtration and recrystallized from ethyl acetate to give 3.2 g (90%) of **3**•HCl (pure epimer), mp 175-176°; ir (chloroform): 2975, 2450, 1620 and 1589 cm^{-1}; uv max (95% ethanol): 228 mμ (ϵ 9900), 280 (1760), and 286 (1520); nmr (deuteriochloroform): δ 7.05 (d, 1, J = 8 Hz, ArH), 6.88 (d, 1, J = 2 Hz, ArH), 6.66 (q, 1, J = 8 Hz, ArH), 4.63 (tr, 1, O-CH-N<, J = 8 Hz), 3.76 (s, 3, $ArOCH_3$), 3.69 (s, 3, OCH_3), 3.19 (d, 2, J = 8 Hz, >CH_2-; ms: (70 eV) m/e (relative intensity), 287 (48), 272 (100), 256 (29), 244 (11), 226 (7), 215 (12), 200 (16), 185 (8), 159 (20), 128 (17), 72 (29).

Anal. Calcd. for $C_{18}H_{26}NO_2$•HCl: C, 66.79; H, 8.08; N, 4.33. Found: C, 66.99; H, 8.32; N, 4.45.

2,3,4,4a,6,7-Hexahydro-6,10-dimethoxy-1*H*,5,11b-ethanodibenz[*b*,*d*]-azepine (**3**, pure epimer).

An aqueous solution of 326 mg (1 mmole) of 3•HCl (pure epimer) was basified with concentrated ammonium hydroxide and extracted with ether. The combined ethereal extracts were washed with water, dried (magnesium sulfate), and evaporated. The residue was distilled to give 240 mg (83%) of **3** (pure epimer), bp 140-150° (0.5 mm); ir (chloroform): 3000, 2940, 2870, 2830, 1610 and 1090 cm^{-1}; uv (95% ethanol): max infl 230 mμ (ε 6800), 278 (1840), and 286 (1740); nmr (deuteriochloroform): (δ 7.00 (d, 1, J = 8 Hz, ArH), 6.91 (d, 1, J = 2 Hz, ArH), 6.58 (q, 1, J = 8 Hz, ArH), 4.09 (q, 1, >N-CH-O-, J = 3 and 11 Hz), 3.75 (s, 3, $ArOCH_3$), 3.34 (s, 3, OCH_3); ms: (70 eV) m/e (relative intensity), 287 (M^+, 75), 272 (100), 256 (60), 244 (12), 226 (15), 215 (35), 200 (30), 72 (50).

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 74.93; H, 8.51; N, 5.14.

3a[(5-Methoxy-2-formylmethyl)phenyl]hexahydro-1-indolinecarboxylic Acid Phenyl Ester (**4**).

A solution of 1.77 g (6.1 mmoles) of **3** (epimeric mixture) in 150 ml of dry methylene chloride was cooled to 5° and treated with 1.1 g (7.0 mmoles) freshly distilled phenyl chloroformate in 100 ml of dry methylene chloride. The solution was stirred at room temperature for 48 hours and then it was washed successively with 2 × 100 ml of 2*N* sodium hydroxide, 100 ml of water, 2 × 100 ml of 2*N* hydrochloric acid and 100 ml of water. Evaporation of the dried solvent at reduced pressure gave 2.21 g (94%) of **4** as a colorless liquid which was homogeneous by tlc, but could not be distilled without decomposition; ir (chloroform): 3000, 2940, 2860, 1720, 1610 and 1580 cm^{-1}; uv (95% ethanol): max infl 230 mμ (ε 7150), 276 (1850), and infl 283 (1655); nmr (deuteriochloroform): δ 9.89 (t, 1, -CHO, J = 2 Hz), 7.8 (m, 8, ArH), 3.81 (s, 3, $ArOCH_3$); ms: (70 eV) m/e (relative intensity), 393 (M^+, 100), 365 (5), 300 (65), 282 (87), 239 (73).

Anal. Calcd. for $C_{24}H_{27}NO_4$: C, 73.25; H, 6.92; N, 3.56. Found: C, 73.42; H, 6.70; N, 3.38.

3a-[5-Methoxy-2-(2,4-dinitrophenylhydrazonoethyl)phenyl]hexahydro-1-indolinecarboxylic Acid Phenyl Ester.

In the usual manner (5) 500 mg (1.2 mmoles) of **4** in ethanol was treated with 2,4-dinitrophenylhydrazine in the presence of sulfuric acid. The reaction was maintained under nitrogen and at room temperature for 16 hours. The resulting crystals were collected by filtration and were washed with cold ethanol. Recrystallization from the same solvent yielded 420 mg (61%) of yellow 2,4-dinitrophenylhydrazone, decomposition point 116°; ir (chloroform): 3300, 3040, 2950, 1720, 1630, 1600 and 1340 cm^{-1}; uv (95% ethanol): max infl 260 mμ (ε 11,900), 357 (23,350), and infl 420 (5800); nmr (deuteriochloroform): δ 9.02 (d, 1, J = 2 Hz, ArH), 8.24 (q, 1, J = 8 Hz, ArH), 7.86 (d, 1, J = 8 Hz, ArH), 7.20 (m, 7, ArH), 6.72 (q, 1, J = 8 Hz, ArH), 7.52 (tr, 1, J = 6 Hz, -N=CH-), 3.75 (s, 3, $ArOCH_3$).

Anal. Calcd. for $C_{30}H_{31}N_5O_7$: C, 62.82; H, 5.45; N, 12.21. Found: C, 63.08; H, 5.52; N, 11.96.

4-Methoxy-2-(1-methylhexahydroindolin-3a-yl)phenethyl alcohol (**5**).

To a magnetically stirred slurry of 270 mg of lithium aluminum hydride in 20 ml of dried, distilled tetrahydrofuran was added slowly a solution of 847 mg (2.1 mmoles) of **4** in 5 ml of dry tetrahydrofuran. The solution was stirred at room temperature for 1.5 hours, then refluxed for an additional hour and cooled to room temperature. The excess lithium aluminum hydride was decomposed by careful addition of a few drops of water and the resulting slurry was filtered through a sintered glass funnel. The solvent was removed *in vacuo* to afford 602 mg (98%) of crude **5** as a colorless glassy residue; nmr (deuteriochloroform): δ 7.66 (d, 1, J = 2 Hz, ArH), 7.0 (d, 1, J = 8 Hz, ArH), 6.54 (q, 1, J = 8 Hz, ArH), 3.78 (tr, 2, $-OCH_2-$), 3.71 (s, 3, $ArOCH_3$), 2.28 (s, 3, NCH_3), 1.99 (broad s, 1, OH).

The oxalate salt of **5** was prepared in acetone and crystallized from ethanol. The colorless crystals had mp 225-226° (decomposition): ir (potassium bromide): 3400, 2950, 2750, 1740, 1660 and 1620 cm^{-1}; uv (95% ethanol): max 228 mμ (ε 9900), 279 (2100), and 287 (1900); ms: (70 eV) m/e (relative intensity), 289 (55), 288 (85), 274 (24), 261 (18) 244 (100), 232 (9), 214 (28), 202 (10), 84 (14), 70 (22).

Anal. Calcd. for $C_{20}H_{29}NO_6$: C, 63.30; H, 7.70; N, 3.68. Found: C, 63.22; H, 8.03; N. 3.56.

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