The Demethylation of 1,2,3,4,5,6,7,8-Octahydro-1-(2-methoxybenzyl)-2-methylisoquinoline. The Synthesis of 1-Hydroxy-*N*-methylmorphinan and 1,2,3,4,4a,5,6,7,7a,8-Decahydro-7-methyl[1]benzopyrano[2,3-*j*]isoquinoline.

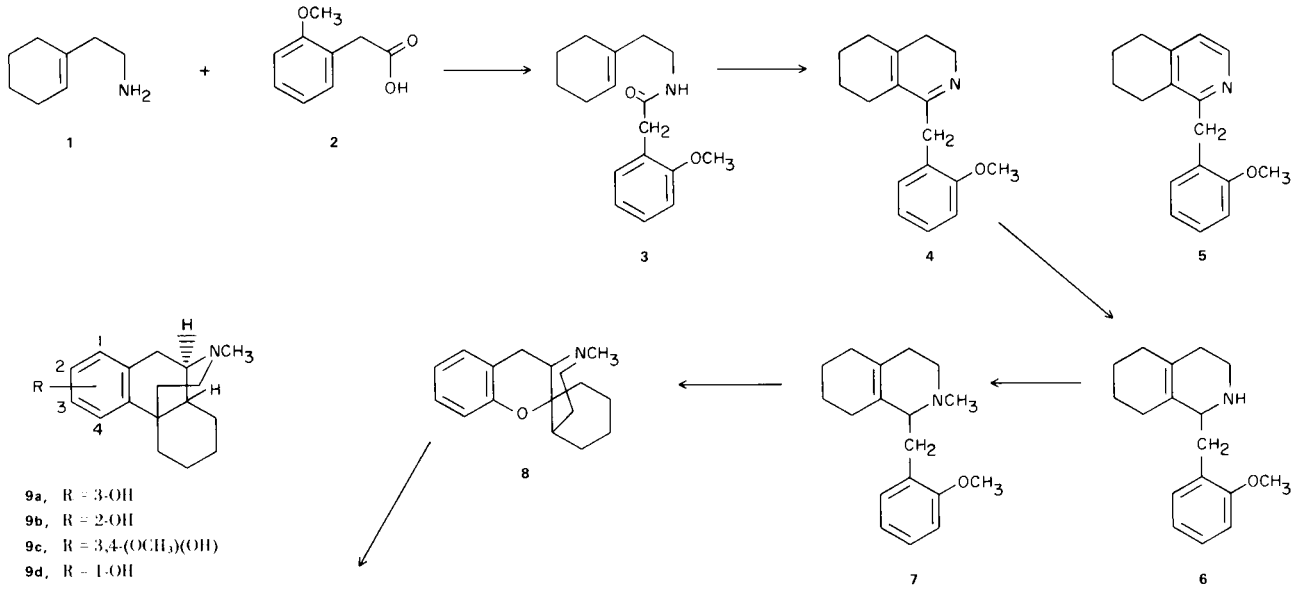
Raymond R. Wittekind, Thomas Capiris and Sam Lazarus (1)

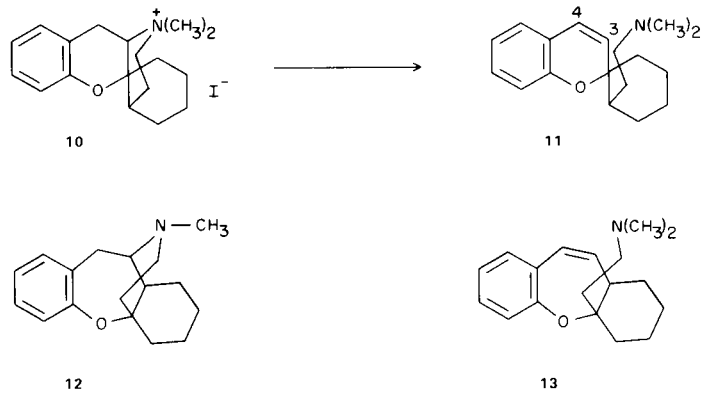
Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey 07950

Received September 1, 1972

More than 20 years have elapsed since the synthesis of the analgesic/antitussive (2) 3-hydroxy-*N*-methylmorphinan (**9a**) (3), the 2-hydroxy isomer **9b** (3,4) and the 4-hydroxy-3-methoxy derivative **9c** (5) were reported. Surprisingly, elaboration of the 1-hydroxy compound **9d** and derivatives thereof have not been disclosed (6). This Note describes the preparation of **9d** by the Grewe reaction (**7**→**9d**) (7), which in this case proceeds *via* the intermediate benzopyran **8**.

The requisite octahydroisoquinoline **7** was prepared by the previously described process (8) for the synthesis of the corresponding *para*-methoxy isomer. Treatment of 2-(1-cyclohexen-1-yl)ethylamine (**1**) (5) with 2-methoxyphenylacetic acid (**2**) gave amide **3** which was subjected





to the conditions of the Bischler-Napieralski reaction (9). The hexahydroisoquinoline **4** was catalytically hydrogenated to amine **6** which was reductively alkylated to **7**. The anticipated by-product of this process (10), the 5,6,7,8-tetrahydroisoquinoline **5**, was isolated as the hydrobromide in low (1%) yield. The proton magnetic spectrum of **5** (after deuterium oxide exchange), which showed an AB pattern at δ 7.60 and 8.41 ppm (J = 6 cps) characteristic of the C_3-, C_4- protons (11), confirmed the structural assignment.

The octahydroisoquinoline hydrobromide **7**-hydrobromide was treated with boiling 48% hydrobromic acid. The reaction mixture was quenched with 5% sodium bicarbonate solution-ice at various time intervals, extracted with methylene chloride and the product examined by gas-liquid partition chromatography (2% XE-60-on-Gas Chrom Z 80/100, column temperature 135°, flame detector). The starting material, the methyl ether **7**-hydrobromide, was consumed in about 30 minutes and the ratio of the areas of the two bands at 11 and 28 minutes, subsequently shown to be associated with the morphinan **9d** and the benzopyran **8**, respectively, increased until the band corresponding to **8** was virtually absent after about 24 hours. When the reaction was quenched after 1 hour, the pyran **8** was obtained in 34% yield as the hydrobromide; when it was allowed to proceed for 16 hours, the morphinan **9d** was isolated in 19% yield in addition to a comparable amount of **8**.

The structure of the dihydropyran **8** was established chemically. Alkylation of **8** with methyl iodide afforded methiodide **10** which was treated with boiling aqueous potassium hydroxide. The ultraviolet spectrum of **11**, which was similar to that (λ max 270 mμ (ε, *ca.* 6,000), 320 (*ca.* 6,000)) of 2,2-dimethyl-2*H*-1-benzopyran (12) and the proton magnetic resonance spectrum, which showed a 2-proton AB pattern at δ 5.61 and 6.39 ppm (J = 10 cps), were consistent with benzopyran structure **11**, derivable from **8**. The proton magnetic resonance spectrum of the olefin **13** derivable from the oxepin **12**, a reaonsable alternate cyclization product, would be expected to show a typical ABX pattern in the vinyl proton region.

The stereochemistry of **8** could not be assigned on the basis of the available evidence.

The morphinan structure **9d** was assigned to the phenolic product by analogy with the structure of the products, for example **9a**, of the Grewe synthesis (7). The spectral properties (see Experimental) were in accord with this formulation.

EXPERIMENTAL (13)

N-[2-(1-Cyclohexen-1-yl)ethyl]-2-(2-methoxyphenyl)acetamide (**3**).

A solution of 2-(1-cyclohexen-1-yl)ethylamine (**1**) (253 g., 2.02 moles), 2-methoxyphenylacetic acid (**2**) (335 g., 2.02 moles) moles) and xylene (2.5 l.) was heated under reflux with azeotropic water separation (Dean-Stark trap) for 24 hours. Methylene chloride (1 l.) and ether (1 l.) were added to the reaction mixture, cooled in an ice-bath, and the solution was washed with 1*N* hydrochloric acid, water and saturated potassium carbonate solution. The organic phase was separated, dried over anhydrous potassium carbonate and filtered. Recrystallization of the residue, obtained by evaporation of the filtrate, from cyclohexane gave 472 g. (85.7%) of the acetamide **3**, m.p. 90-92°.

A sample, recrystallized from cyclohexane for analysis, had m.p. 92-94°; ν max (dichloromethane) 3440 (NH), 1668 (C=O), 1600, 1590 (aromatic) cm^{-1}; λ max 272 mμ (ε, 2,250), 278 (2,050); δ (DMSO-d_6) 3.54 (singlet, 2H, -CH_2-), 3.84 (singlet, 3H, CH_3O-), 5.25 (multiplet, 1H, vinyl proton), 5.67 (deuterium oxide exchangeable broad signal, 1H, -NH-), 7.2 (multiplet, 4H, aromatic), ppm.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.98; H, 8.44; N, 5.30.

Preparation of 1,2,3,4,5,6,7,8-Octahydro-1-(2-methoxybenzyl)isoquinoline (**6**).

A solution of the acetamide **3** (450 g., 1.65 moles), phosphorus oxychloride (680 g., 4.45 moles), benzene (2.2 l.) and absolute ethanol (5 ml.) was heated under reflux for 2.5 hours and allowed to stand at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure. Water (3 l.) was added and the mixture was stirred for 16 hours. The solution was extracted with chloroform. The combined organic extracts were washed with 5% sodium carbonate solution until the washings were basic, water until the washings were neutral and evaporated; yield 387 g. (92%) of the hexahydroisoquinoline **4** as a highly colored viscous oil.

The picrate of **4**, obtained in 46% yield, had m.p. 146-147°; ν max (dichloromethane) 1675 (C=C), 1630 (C=N), 1613, 1590 (aromatic), 1668, 1360 (NO_2) cm^{-1}; λ max 300 mμ (ε, 8,900), 359 (16,400).

Anal. Calcd. for $C_{23}H_{24}N_4O_8$: C, 57.02; H, 4.99; N, 11.57. Found: C, 56.97; H, 5.12; N, 11.72.

A mixture of the crude hexahydroisoquinoline **4** (13.5 g., 0.0535 mole), Raney nickel (14) (2.5 g.) and ethanol (100 ml.) was hydrogenated on a Parr shaker at room temperature and an initial pressure of 40 psi. After 24 hours, the theoretical quantity of hydrogen was absorbed and there was no additional uptake. The catalyst was collected, washed with ethanol and the filtrate was evaporated under reduced pressure. The residual yellow oil (13.5 g.) was dissolved in ether (250 ml.) and was added to saturated ethereal hydrogen bromide. The resulting solid was collected, washed with ether and recrystallized from 2-propanol and then from acetonitrile; yield 4.10 g. (29.8%) of the octahydroisoquinoline **6** hydrobromide, m.p. 194-196°.

An analytical sample prepared by repeated recrystallization from acetonitrile had m.p. 197-198°; ν max (chloroform) 2300-3000 ($\overset{+}{N}H_2$), 1605, 1495 (aromatic) cm^{-1}; λ max 272 mμ (ε-2,560), 278 (2,400); δ (DMSO-d_6) 3.86 (singlet, 3H, CH_3O-), 7.1 (multiplet, 4H, aromatic), 8.2-8.9 (deuterium oxide-exchangeable broad signal, 2H, -$\overset{+}{N}H_2$-) ppm.

Anal. Calcd. for $C_{17}H_{24}BrNO$: C, 60.36; H, 7.15; Br, 23.66; N, 4.41. Found: C, 60.66; H, 7.06; Br, 23.61; N, 4.28.

In a subsequent experiment, the total crude product, obtained by hydrogenation (25°, 50 psi) of a solution of the hexahydroisoquinoline **4** (387 g.) and ethanol (3 l.) in the presence of Raney

nickel (14) (110 g.), was distilled through a 1 foot Vigreux column at 0.1-0.2 mm. The fraction (249 g.) boiling at 150-160° was collected, dissolved in anhydrous ether (2 l.) and added to a solution of oxalic acid (105 g.) and the minimum volume of ethanol. The precipitate was collected, washed with ethanol and ether and dried. The oxalate salt (265 g.), m.p. 165-167°, was dissolved in the minimum volume of water. The solution was cooled in an ice-bath, basified with 85% potassium hydroxide and extracted with methylene chloride. The combined organic extracts were dried over anhydrous potassium carbonate, filtered and the filtrate was concentrated under reduced pressure. The residual oil (192 g.) was dissolved in ether (500 ml.) and the solution was added to saturated etheral hydrogen bromide. The solid (234 g.) was repeatedly recrystallized from 2-propanol and from acetonitrile; yield 4.73 g. (1.25%) of the hydrobromide of the octahydroisoquinoline **6**, m.p. 197-198°.

A second crop, obtained from the second recrystallization from 2-propanol, was also recrystallized repeatedly from 2-propanol and from acetonitrile; yield 4.44 g. (1.19%) of 5,6,7,8-tetrahydro-1-(*o*-methoxybenzyl)isoquinoline (5) hydrobromide, m.p. 225-226°; ν max (dichloromethane) 2810 (OCH_3), 2300-2700 ($\overset{+}{N}H$), 1629 ($C{=}\overset{+}{N}$), 1603, 1514, 1497 (aromatic) cm^{-1}; λ max 268 mμ (ϵ, 7,510); δ (DMSO-d_6) 3.82 (singlet, 3H, CH_3O-), 4.51 (singlet, 2H, -CH_2-), 7.00 (multiplet, 4H, aromatic), 7.60 (doublet, J = 6 cps, 1H, C_4-H), 8.41 (doublet of doublets, J = 6 cps, 1H, C_3-H), 15.8 (deuterium oxide-exchangeable broad signal, 1H, =$\overset{+}{N}H$-) ppm.

Anal. Calcd. for $C_{17}H_{20}BrNO$: C, 61.08; H, 6.03; Br, 23.91; O, 4.78. Found: C, 61.36; H, 6.19; Br, 23.93; O, 4.92.

The gas-liquid chromatograms (2% XE-60-on-Gas Chrom Z 80/100, column temperature 150°, flame detector) of the polyhydroisoquinolines, **5** and **6**, obtained by basification of the corresponding hydrobromides, showed one symmetrical band.

1,2,3,4,5,6,7,8-Octahydro-1-(2-methoxybenzyl)-2-methylisoquinoline (**7**).

A solution of 1,2,3,4,5,6,7,8-octahydro-1-(2-methoxybenzyl)-isoquinoline (**6**) (160 g., 0.621 mole), obtained by basification of the oxalate followed by extraction with methylene chloride, 37% formaldehyde solution (60 ml., 0.74 mole) and ethanol (3 l.) was allowed to stand at room temperature for 45 minutes. Raney nickel (14) (20 g.) was added and the mixture was agitated on a Parr shaker at room temperature and an initial pressure of 40 psi. After 24 hours, the theoretical quantity of hydrogen was absorbed. The catalyst was collected and washed with ethanol. The filtrate was evaporated under reduced pressure. The residual oil was dissolved in ether and the solution was washed with water, dried over anhydrous potassium carbonate and filtered. The filtrate was added to a solution of oxalic acid (650 g., 0.720 mole) and ethanol (650 ml.). The solid was collected; yield 77.0 g. (34.3%) of the 2-methyloctahydroisoquinoline **7** oxalate, m.p. 166-167°; ν max (dichloromethane) 3200 (OH), 2400 ($\overset{+}{N}H$), 1777 (CO_2H), 1655 (CO_2^-), 1600, 1490 (aromatic) cm^{-1}; λ max 273 mμ (ϵ, 2,600), 278 (2,350).

Anal. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.38; H, 7.55; N, 4.15.

The above oxalate was dissolved in water, basified with 85% potassium hydroxide and extracted with ether. The ether extracts were dried over anhydrous potassium carbonate and filtered. The filtrate was added to saturated ethereal hydrogen bromide. The precipitate was collected. Recrystallization from ethanol gave 50.5 g. (63.8%) of 2-methyloctahydroisoquinoline **7** hydrobromide, m.p. 152-153°; ν max (dichloromethane) 2850 (CH_3O), 2500 ($\overset{+}{N}H$), 1605, 1590, 1495 (aromatic) cm^{-1}; λ max 273 mμ (ϵ, 2,790), 279 (2,600); δ (DMSO-d_6) 2.84 (doublet, J = 5 cps, 3H, $CH_3\overset{+}{N}H<$) 3.94 (singlet, 3H, CH_3O-), 6.8-7.6 (multiplet, 4H, aromatic), 10.6 (D_2O-exchangeable broad signal, 1H, -$\overset{+}{N}H$-) ppm.

Anal. Calcd. for $C_{18}H_{26}BrNO_2$: C, 61.36; H, 7.44; Br, 22.68; N, 3.98. Found: C, 61.65; H, 7.37; Br, 22.63; N, 4.19.

1,2,3,4,4a,5,6,7a,8-Decahydro-7-methyl[1]benzopyrano[2,3-*j*]isoquinoline (**8**).

A solution of the octahydroisoquinoline hydrobromide **7** (1.00 g., 2.84 millimoles) and 48% hydrobromic acid (15 ml.) was heated under reflux for 1 hour under a nitrogen atmosphere. The reaction mixture was cooled in an ice-bath, basified with 20% potassium hydroxide solution and extracted with methylene chloride. The combined organic extracts were washed with 1*N* potassium hydroxide solution, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in anhydrous ether and the solution was saturated with hydrogen bromide. The solution was evaporated *in vacuo*; ethanol (10 ml.) and anhydrous ether (10 ml.) were added to the residue and the resulting solid was collected. Recrystallization from ethanol-ether gave 0.32 g. (34%) of the benzopyran **8** as the hydrobromide, m.p. 277-278° dec.; ν max (Nujol) 2650 ($\overset{+}{N}H$), 1583, 1484 (aromatic) cm^{-1}; λ max 273 mμ (ϵ, 1,980), 280 (2,000); δ (deuterium oxide) 1.2-2.1 (multiplet, 11H, -CH_2-, -CH<), 2.93 (singlet, 3H, CH_3-), 3.2-3.8 (multiplet, 5H, ϕCH_2-, -CH_2NCH<) 6.8-7.5 (multiplet, 4H, aromatic) ppm.

Anal. Calcd. for $C_{17}H_{24}BrNO$: C, 60.36; H, 7.15; Br, 23.62; N, 4.14; O, 4.73. Found: C, 60.22; H, 7.29; Br, 23.71; N, 4.37; O, 5.00.

The base **8**, obtained from the hydrobromide by basification (potassium hydroxide), extraction (methylene chloride) and sublimation (bath temperature 85° (0.05 mm.)) had m.p. 83-84°; ν max (dichloromethane) 1585, 1485 (aromatic) cm^{-1}; λ max 273 mμ (ϵ, 1,460), 280 (1,500); δ (deuteriochloroform) 2.22 (singlet, 3H-CH_3-), 6.9 (multiplet, 4H, aromatic) ppm.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44; mol. wt. 257. Found: C, 79.55; H, 9.16; N, 5.24; mol. wt. (mass spectrometry) 257.

The gas-liquid chromatogram (2% XE-60-on-Gas Chrom Z 80/100, column temperature 140°, flame detector) showed one symmetrical band.

1,3,4,9,10,10a-Hexahydro-11-methyl-2*H*-10,4a-iminoethanophenanthren-8-ol (**9d**).

A solution of the octahydroisoquinoline hydrobromide **7** (1.00 g., 2.84 millimole) and 48% hydrobromic acid (15 ml.) was boiled under reflux for 16 hours under a nitrogen atmosphere. The reaction mixture was cooled in an ice-bath, basified with 20% potassium hydroxide solution and extracted with methylene chloride. The organic extracts were washed with 20% potassium hydroxide solution, dried over anhydrous sodium sulfate, filtered and concentrated. The residual oil (0.39 g.) was dissolved in saturated ethanolic hydrogen bromide (1 ml.). Ether was added. The solid was collected and washed with ether; yield 0.20 g. (21%) of the hydrobromide of the benzopyran **8**, m.p. 274-277°, alone or admixed with an authentic sample.

The aqueous phase was cooled in an ice-bath, acidified with concentrated hydrochloric acid and then neutralized (*p*H 8) with sodium bicarbonate. The solution was extracted with methylene chloride, dried over anhydrous sodium sulfate and filtered. Recrystallization of the residue, obtained by evaporation of the filtrate, from acetone-ether afforded 0.13 g. (19%) of the morphinan **9**, m.p. 234-235° dec.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44; O, 6.21. Found: C, 79.37; H, 8.78; N, 5.45; O, 6.04.

The hydrobromide had m.p. 308-314° dec.; ν max (Nujol) 3150 (OH), 2200-2700 ($\overset{+}{N}H$), 1595 (aromatic) cm^{-1}; λ max 274 mμ (ϵ, 2,010); δ (D_2O) 1.0-2.0 (multiplet, 11H, $-CH_2-$, $-CH<$), 2.98 (singlet, 3H, CH_3-), 3.3-3.7 (multiplet, 5H, ϕCH_2-, $-CH_2N<$), 6.9-7.4 (multiplet, 4H, aromatic) ppm.

Anal. Calcd. for $C_{17}H_{24}BrNO$: C, 60.36; H, 7.15; Br, 23.62; N, 4.14; mol. wt. 257 (free base). Found: C, 60.28; H, 7.13; Br, 23.93; N, 4.26; mol. wt. 257 (mass spectrometry).

The electrophoretogram showed one well-defined spot.

1,2,3,4,4a-5,6,7,7a,8-Decahydro-7,7-dimethyl[1]benzopyrano[2,3-*j*]isoquinolinium iodide (**10**).

The benzopyran hydrobromide **8** (1.00 g., 2.96 millimoles) was dissolved in saturated sodium bicarbonate solution (25 ml.) and extracted with methylene chloride. The organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The oily residue was dissolved in acetone (25 ml.) and methyl iodide (34 g., 0.23 mole) was added. The solution was allowed to stand at room temperature for three days and was concentrated to about one third of its original volume. The precipitate was collected and recrystallized from acetone-ethanol-ether (4:1:8); yield 0.93 g. (79%) of the methiodide **10**, m.p. 242-244° dec.

A sample recrystallized from ethanol-ether for analysis had m.p. 246-247° dec.; ν max (dichloromethane) 2850 ($\overset{+}{N}(CH_3)_2$), 1588, 1490 (aromatic) cm^{-1}; λ max 273 mμ (ϵ, 1,820), 279 (1,840); δ (DMSO-d_6) 3.66 (singlet, CH_3-), 6.7-7.5 (multiplet, 4H, aromatic) ppm.

Anal. Calcd. for $C_{18}H_{26}INO$: C, 54.14; H, 6.56; I, 31.78; N, 3.51; O, 4.01. Found: C, 54.29; H, 6.54; I, 31.87; N, 3.79; O, 4.28.

2′-[2-(Dimethylamino)ethyl]spiro[2*H*-1-benzopyran-2,1′-cyclohexane] (**11**).

A solution of the methiodide **10** (1.00 g., 2.51 millimoles), 85% potassium hydroxide (4 g.) and water (10 ml.) was heated under reflux under an atmosphere of nitrogen for 24 hours and allowed to cool to room temperature. The reaction mixture was extracted with methylene chloride. The organic extracts were dried over anhydrous sodium sulfate and evaporated. The residue was dissolved in ethanol, saturated with hydrogen chloride and concentrated. Recrystallization of the residual solid from methanol-ether gave 0.48 g. (62%) of the unsaturated tertiary amine **11** as the hydrochloride, m.p. 191-192°; ν max (dichloromethane) 1632 (C=C), 1604, 1490 (aromatic) cm^{-1}; λ max 266 mμ (ϵ, 4,080), 309 (3,280); δ (DMSO-d_6) 2.75, 2.79 (doublet of doublets, J = 5 cps, 6H, $(CH_3)_2\overset{+}{N}H-$), 5.61, 6.39 (AB, J = 10 cps, 2H, vinyl protons), 6.7-7.2 (multiplet, 4H, aromatic) ppm.

Anal. Calcd. for $C_{18}H_{26}ClNO$: C, 70.23; H, 8.51; Cl, 11.52; N, 4.55; O, 5.20. Found: C, 70.33; H, 8.39; Cl, 11.43; N, 4.62; O, 5.46.

Acknowledgment.

The authors are grateful to Mrs. U. Zeek for microanalyses and Mr. R. Puchalski for spectral determinations. We thank Dr. R. I. Meltzer for advice and interest in this project.

REFERENCES

(1) Present address: Photoproducts Department, E. I. DuPont De Nemours and Co., Inc., Parlin, New Jersey, 08859.

(2) J. Hellerbach, O. Schnider, H. Besendori and B. Pellmont, "Synthetic Analgesics," Part 2A, Pergamon Press, Inc., New York, N.Y., 1966, p. 71.

(3) O. Schnider and A. Grussner, *Helv. Chim. Acta*, **32**, 821 (1949).

(4) J. Hellerbach, O. Schnider, H. Besendorf and B. Pellmont, "Synthetic Analgesics," Part 2A, Pergamon Press, Inc., New York, N.Y., 1966, p. 17.

(5) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950).

(6) 1-Hydroxy-*N*-methylisomorphinan has been described; M. Gates and W. G. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958).

(7) R. Grewe, *Angew. Chem.*, **59**, 194 (1947).

(8) M. Walter, H. Besendorf and O. Schnider, *Helv. Chim. Acta*, **44**, 1546 (1961).

(9) W. M. Whaley and T. R. Govindachari, in "Organic Reactions," Vol. 6, R. Adams, Ed., John Wiley and Sons, Inc., New York, N.Y., 1951, p. 74.

(10) J. Hellerbach, O. Schnider, H. Besendorf and B. Pellmont, "Synthetic Analgesics," Part 2A, Pergamon Press, Inc., New York, N.Y., 1966, p. 21.

(11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Ed., Pergamon Press, Elmsford, New York, 1969, p. 211, 307.

(12) R. Livingston, D. Miller and S. Morris, *J. Chem. Soc.*, 602 (1960).

(13) Melting points were determined in open capillary tubes on a Thomas-Hoover Unimelt, previously calibrated against known standards. The infrared spectra were determined on a Barid Model 455 spectrophotometer. The ultraviolet spectra were measured in 95% ethanol with a Beckman DK-1 spectrophotometer. The nuclear magnetic resonance spectra were meausred on a Varian A-60 spectrometer with tetramethylsilane as the internal standard. The gas-liquid partition chromatograms were determined on a Research Specialties Model 60-10 instrument. Mass spectra were determined on a Consolidated Electronics Corp. Model 21-103C spectrometer.

(14) No. 28, W. R. Grace and Company, South Pittsburgh, Tennessee.