Experimental Section[23]

(+)-α-Isomethadol Benzoylformate Methiodide (5).—A mixture of (−)-α-isomethadol[7] (0.79 g, 0.0016 mol) and 0.7 g of benzoylformyl chloride in 20 ml of EtOAc was refluxed for 10 hr. The solvent was removed *in vacuo* to afford an oily residue which resisted attempts at crystallization. A cooled EtOAc solution (10 ml) containing 0.2 g of this oil was shaken with 0.2 g of Ag_2O for 15 min. Excess MeI was added to the filtrate and cooled overnight to yield 0.3 g (82%) of **5**, mp 198–200° dec, $[\alpha]D$ +22.5° (*c* 0.4, MeOH), after recrystallization (MeOH). *Anal.* ($C_{30}H_{36}INO_3$) C,H,N.

(+)-α-Isomethadol Benzoylformate Methiodide and Methylmagnesium Iodide.—A fivefold excess of MeMgI and 0.28 g (0.00048 mol) of finely powdered **5** was stirred under N_2 for 3 hr. The reaction mixture was decomposed with cold, saturated NH_4Cl solution and the solvent removed *in vacuo*. Inorganic salts were removed by dissolving the residue in MeCN and filtering. The MeCN was removed and the resultant brown oil refluxed with 5% MeOH-KOH for 6 hr. The MeOH was removed, the residue taken up in H_2O and then extracted with EtOAc. The alkaline extract was acidified (HCl), extracted several times with EtOAc, and the solvent removed *in vacuo*. The resultant oil was extracted several times with aq $NaHCO_3$, acidified (HCl), extracted (EtOAc), and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield 0.053 g (67%) of (−)-atrolactic acid. Recrystallization (cyclohexane) afforded atrolactic acid, mp 87–90°, $[\alpha]D$ −14.4° (*c* 1.29, 1 *N* NaOH), corresponding to 25.2% optical purity.[24]

Apparent Dissociation Constants.—Approximately 0.02 mol of the HCl salts was dissolved in analytical grade MeOH (5 ml) and titrated against aq 0.115 *N* NaOH. The titration curves were recorded using a Radiometer automatic titrator Model TTT-1, outfitted with an autoburette and recorded (Radiometer-Copenhagen, the London Co., Westlake, Ohio). The titrations were carried out at 23° under constant conditions and the average values of 3 determinations are recorded in Table II.

Acknowledgment.—We wish to thank Dr. E. L. May, National Institutes of Health, for quantities of isomethadol and 3-deoxymethadone, and Dr. R. D. Rands of Mallinckrodt Pharmaceuticals for the supply of (−)-isomethadone.

(23) All melting points were recorded using a Thomas-Hoover melting point apparatus and are corrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Routine ir spectra were recorded using a Perkin-Elmer 337B spectrophotometer, and high resolution ir spectra were obtained on a Perkin-Elmer 521 spectrophotometer. Optical rotations were obtained on a Perkin-Elmer 114 polarimeter with a 1-dm cell.

(24) A. McKenzie and C. Clough, *J. Chem. Soc.*, **97**, 1016 (1910).

Homologs of Benzomorphan Derivatives. I

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9-Hydroxy-3,7-dimethyl-1,2,4,5,6,7-hexahydro-2,7-methano-3*H*-3-benzazonine (XIX) and its 12-methyl derivatives (XV and XVI) were synthesized and tested for analgetic activity.

Seven-membered homologs of some piperidine derivatives are known to have analgetic activity.[1] Generally, they have weaker analgetic activity and fewer side effects than the corresponding piperidine derivatives. Since the benzomorphan derivatives have been extensively explored as analgetics, and no reports have appeared on their homologs, we undertook the study on 7-membered homologs of benzomorphan derivatives.

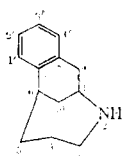
The synthesis of 9-methoxy-12-hydroxy-3,7,12-trimethyl-1,2,4,5,6,7-hexahydro-2,7-methano-3*H*-3-benzazonine (VII)[2] followed the procedure employed in the benzomorphan series[3] (Scheme I). Thus, 3,4-dihydro-1-(3-dimethylaminopropyl)-7-methoxy-1-methyl-2(1*H*)-naphthalenone (II), prepared from I and 3-dimethylaminopropyl chloride, was brominated to give the bromo ketone III hydrobromide. Cyclization of III·HBr with NH_4OH gave the keto methobromide IV in up to 40% yield. The elimination product V accompanied this reaction and gave II on catalytic hydrogenation. Reaction of IV with MeMgI afforded the methylcarbinol derivative VI. Upon pyrolysis, VI gave the tertiary base VII together with the phenolic derivative VIII, which was methylated (CH_2N_2) to give VII.

The OH group of VII was assigned the β configuration on the basis of its ir spectrum. A strong band due to an intramolecular OH---N bonding was observed at 3340 cm^{-1}. (0.03 and 0.003 mol cones in CCl_4). An unexpected difficulty arose, however, when dehydration of VII to the 10-methylene derivative IX was attempted following the procedure successfully used for the benzomorphan analog.[4] $SOCl_2$, $POCl_3$, and TsCl in the presence of pyridine failed to give IX. When treated with $SOCl_2$ in the absence of pyridine, VII gave a very small amount of IX. Pyrolysis of the acetoxy derivative X also gave IX in an unsatisfactory yield.

It was probable that the 10α-hydroxy isomer of VII would be more easily dehydrated than VII. However, the reaction of XI, obtained by pyrolysis of IV, with MeLi gave a product identical with VII,[5] and the 10α-hydroxy isomer was not available for dehydrat-

(1) For instance, refer to the article by R. A. Hardy, Jr., and M. G. Howell in "Analgetics," G. deStevens, Ed., Academic Press, New York and London, 1965, p 206.

(2) For convenience, the term "homobenzomorphan" will be given to this series of derivatives in general. Numbering is analogous to that used for benzomorphan.

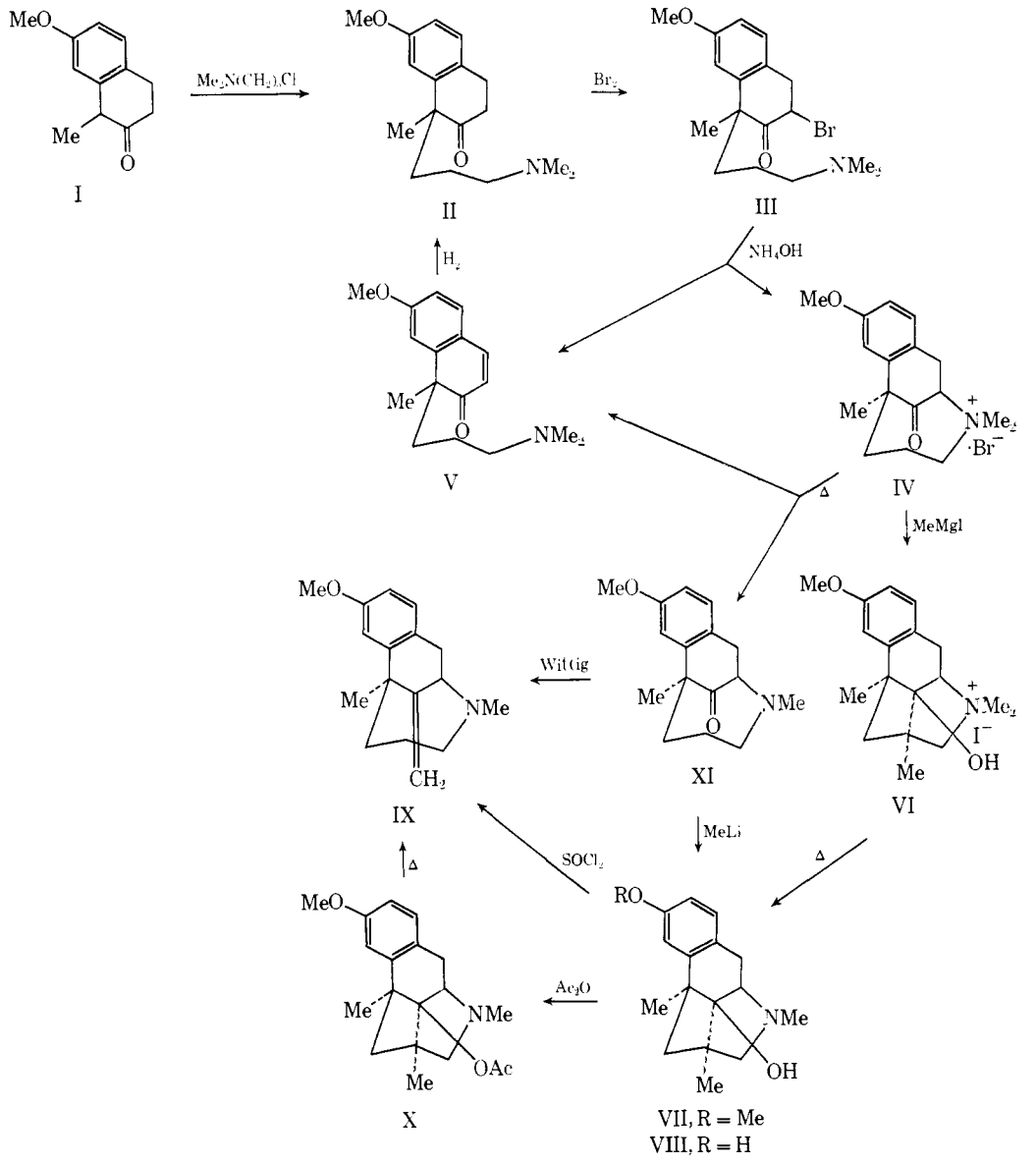


(3) (a) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960); (b) E. L. May and H. Kugita, *ibid.*, **26**, 188 (1961).

(4) (a) S. Saito and E. L. May, *ibid.*, **27**, 1087 (1962); (b) H. Kugita and M. Takeda, *Chem. Pharm. Bull. (Tokyo)*, **12**, 1163 (1964).

(5) This result constitutes a major deviation from the benzomorphan series. In the latter, the reaction gives stereospecifically the α-OH derivative. See ref 3b.

SCHEME I



tion. Finally, IX was obtained in good yield by the reaction of XI with methylenetriphenylphosphorane.

Hydrogenation of IX (free base) with PtO_2 gave the 10α-Me derivative XII and the 10β-Me derivative XIII in 7.4 and 24.6% yields[6] together with the secondary amine XIV (mixture of the diastereoisomers)[7] (Scheme II). On the other hand, hydrogenation in the presence of 15% HCl in EtOH[4a] gave two products, XIII (85%) and XII (12%), respectively. Nmr spectrum of XII showed the signal of the secondary Me at τ 9.1, while the β isomer XIII showed the signal at τ 8.7. This paralleled the reported observation in the benzomorphan series.[8] O-Demethylation of XII and XIII with 48% HBr gave the respective phenolic derivatives XV and XVI.

Wolff–Kishner reduction of XI gave a mixture of the deoxo derivative XVII and the dihydronaphthalene derivative XVIIIa[9] (Scheme III). Methylation of XVIIIa gave XVIIIb, identical with the product obtained by exhaustive methylation of XVII. Demethylation of XVII afforded the phenolic derivative XIX.

CrO_3 oxidation[10] of XVII gave the 9-oxo derivative XX. The methoperchlorate XXIb prepared from XX was also obtained from II by a series of reactions (Scheme IV), although the reaction of XXIV·HBr with NH_4OH[11] gave the cyclized product in a very low yield according to the concurrent production of an elimination product XXV. This confirms the structure of XX and hence that of XVII.

These compounds were tested for analgetic activity by the hot plate method.[12] Analgetic activity of the

(6) Stereospecific formation of the α-Me derivative has been reported for the benzomorphan derivative. See ref 4a.

(7) Hydrogenation of the IX·HCl in EtOH also gave these three products. See the Experimental Section.

(8) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

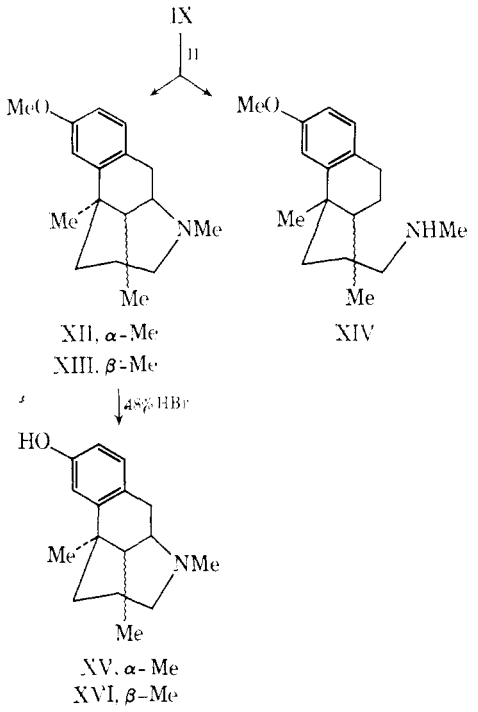
(9) Concurrent elimination of the α-amino group during the Wolff–Kishner reduction of a 7-membered α-aminoketone has been reported. See N. J. Leonard and S. Gelfand, *J. Amer. Chem. Soc.*, **77**, 3269 (1955).

(10) S. Ohshiro, *Tetrahedron*, **10**, 175 (1960).

(11) (a) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955); (b) H. Kugita, S. Saito, and E. L. May, *J. Med. Pharm. Chem.*, **5**, 357 (1962).

(12) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953). The tests were conducted by Dr. G. Hayashi and associates in the Clinical Pharmacology Department.

SCHEME II



10β-methyl derivative XVI surpassed that of the 10α-methyl derivative XV. Compound XIX was so toxic that the observed activity was equivocal (see Table I).

TABLE I

ANALGETIC ACTIVITY OF HOMOBENZOMORPHAN DERIVATIVES

Compd	ED_{50}, mg/kg sc	LD_{50}, mg/kg sc
VIII	33.8 (14.7–77.5)	225.3 (191.5–265.0)
XIX	4.1 (3.1–5.1)	15.2 (11.0–20.5)
XV	11.1 (7.4–16.6)	78.7 (59.4–104.6)
XVI	3.8 (2.9–4.9)	150.6 (128.0–177.1)
Morphine	4.5 (3.8–5.3)	407.0 (351.2–461.5)

Experimental Section

All melting points were determined in an open capillary tube and are uncorrected. Ir spectra were measured in Nujol and nmr spectra were taken in $CDCl_3$ (containing Me_4Si as internal standard) at 60 MHz, unless otherwise stated. When analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

3,4-Dihydro-1-(3-dimethylaminopropyl)-7-methoxy-1-methyl-2(1*H*)-naphthalenone (II)·HBr.—A mixture of $NaNH_2$ (3.4 g), I (15.7 g), and anhyd C_6H_6 (80 ml) was refluxed for 1 hr, a solution of 3-dimethylaminopropyl chloride (12.6 g) in anhyd C_6H_6 (35 ml) was added to the mixture, refluxed for 6 hr, and worked up in a usual manner[3a] to give an oil (11.3 g), bp 155–158° (0.5 mm), which gave the hydrobromide (13.8 g, 49%), mp 159–163°, recrystallized from Me_2CO–EtOH, mp 164–166°. *Anal.* ($C_{17}H_{26}BrNO_2$) C, H, N.

3-Bromo-3,4-dihydro-1-(3-dimethylaminopropyl)-7-methoxy-1-methyl-2(1*H*)-naphthalenone (III)·HBr.—To a solution of II·HBr (1 g) in AcOH (7 ml), Br_2 (0.47 g) in AcOH (7 ml) was added at 55–65° (8 min) and stirred at the same temperature for 20 min. Et_2O was added to the mixture, filtered, and washed with Et_2O–Me_2CO, 1.11 g (91%), mp 138–141° dec, recrystallized from Me_2CO–MeOH, mp 147–149 dec. *Anal.* ($C_{17}H_{25}Br_2NO_2$) C,H,N.

9-Methoxy-12-oxo-3,7-dimethyl-1,2,4,5,6,7-hexahydro-2,7-methano-3*H*-3-benzazonine Methobromide (2′-Methoxy-2,6-dimethyl-10-oxo-7,8-homobenzomorphan Methobromide[13] (IV).—A mixture of III·HBr (35.5 g), ice–H_2O (180 ml), Et_2O (200 ml), and 28% NH_4OH (12 ml) was shaken in a separatory funnel. The organic layer was evaporated *in vacuo*, the residue was warmed with Me_2CO (100 ml), cooled, and filtered to give IV (11.5 g, 40%), mp 190–194°, recrystallized from EtOH, mp 193–194°; ir, 1715, 3475 cm^{-1}. *Anal.* ($C_{17}H_{23}BrNO_2 \cdot 0.5H_2O$) C,H,N. The filtrate ($Me_2CO$) was evaporated, the residue was dissolved in H_2O, basified with NH_4OH, and extracted with Et_2O. The distilled free base (12 g), bp 160–166° (0.2 mm), gave **1-(3-dimethylaminopropyl)-7-methoxy-1-methyl-2(1*H*)-naphthalenone (V)·HBr** (13 g, 45%), mp 128–135°, recrystallized from Me_2CO: mp 137–140°; ir, 1645 cm^{-1}; uv (EtOH), 248 mμ (ε 18,300), 340 (11,240).[3a] *Anal.* ($C_{17}H_{24}BrNO_2$) C,H,N. Hydrogenation of V·HBr (13 g) in EtOH (150 ml) with 10% Pd–C gave II·HBr (12.5 g, 88%), mp 159–162°.

2′-Methoxy-10-hydroxy-2,6,10-trimethyl-7,8-homobenzomorphan Methiodide (VI).—Grignard reaction of IV with MeMgI[3b] gave VI (85%), mp 219–228°, recrystallized from EtOH, mp 237–239°. *Anal.* ($C_{18}H_{28}INO_2$) C,H,N.

2′-Methoxy-10-hydroxy-2,6,10-trimethyl-7,8-homobenzomorphan (VII)·HCl.—Pyrolysis of VI (1 g) in boiling 1-octanol (10 ml)[3b] gave VII·HCl (440 mg, 56%), mp 247–249° dec (from Me_2CO–EtOH–Et_2O). *Anal.* ($C_{17}H_{26}ClNO_2$) C,H,N. From the alkaline extract (NaOH) of the reaction mixture, **2′,10-dihydroxy-2,6,10-trimethyl-7,8-homobenzomorphan (VIII)** (22%) was obtained, mp 139–141° (from AcOEt–hexane); hydrochloride, mp 246–248° dec (from EtOH–Et_2O). *Anal.* ($C_{16}H_{24}ClNO_2$) C,H,N. O-Methylation of VIII with CH_2N_2 in Et_2O (4 days at room temperature) gave VII as the hydrochloride (85%), identical with VII·HCl (mp and ir).

VIII from VII.—A solution of VII·HCl (950 mg) in 48% HBr (7 ml) was refluxed for 20 min, evaporated *in vacuo*, basified with NH_4OH, and filtered to give VIII, mp 137–140°, which gave the hydrochloride (700 mg, 82%), mp 244–246°.

Dehydration of VII.—A mixture of VII·HCl (800 mg), $CHCl_3$ (15 ml), and $SOCl_2$ (608 mg) was allowed to stand at room temperature for 2 days, then warmed at 50° for 2 hr, evaporated, the residue was digested with Me_2CO, and filtered to give recovered VII·HCl (605 mg). Free base was recovered from the filtrate and converted into the picrate in EtOH to give **2′-methoxy-10-methylene-2,6-dimethyl-7,8-homobenzomorphan (IX) picrate** (93 mg, 6%), mp 152–154° (from EtOH). *Anal.* ($C_{29}H_{26}N_4O_8$) C,H,N. The free base had ir (liq), 900 cm^{-1}; **hydrochloride**, mp 176–177° (from Me_2CO–EtOH–Et_2O). *Anal.* ($C_{17}H_{25}ClNO \cdot 0.5H_2O$) C,H,N.

2′-Methoxy-10-acetoxy-2,6,10-trimethyl-7,8-homobenzomorphan (X)·HCl. Acetylation of VII (1.43 g) with Ac_2O (15 ml) (2-hr reflux) gave X (1.43 g, 94%): bp 200–230° (0.2 mm) (bath temp); ir (liq) 1730 cm^{-1}; hydrochloride, mp 132–135° (from Me_2CO–Et_2O), ir, 1718, 3400 cm^{-1}. *Anal.* ($C_{19}H_{28}ClNO_3 \cdot H_2O$) H,N; C: calcd, 61.36; found, 60.93.

Pyrolysis of X. X (2.59 g) was heated in a metal bath (310–330°, 6 min) under N_2, cooled, dissolved in Et_2O, extracted with 5% HCl, made alkaline (NH_4OH), and extracted with Et_2O. Free base from the extract was converted into the picrate in EtOH (795 mg, 20%), mp 152–154°.

Pyrolysis of IV. IV (1.5 g) was heated in octanol for 7 min and worked up as usual.[3a] The crude base was chromatographed on Al_2O_3 and eluted with C_6H_6 to give **2′-methoxy-10-oxo-2,6-dimethyl-7,8-homobenzomorphan (XI)** (280 mg, 24.3%): mp 82–84° (from hexane); ir, 1710 cm^{-1}. *Anal.* ($C_{16}H_{21}NO_2$) C,H,N. The **hydrochloride** had mp 118–121° (from Me_2CO–EtOH–Et_2O); ir, 3400, 1720 cm^{-1}. *Anal.* ($C_{16}H_{22}ClNO_2 \cdot H_2O$) H,N; C: calcd, 61.23; found, 60.82. V (350 mg, 30%) was obtained from the Et_2O eluate; hydrobromide, mp 136–138°.

Reaction of XI with MeLi. Reaction of XI (2.59 g) with ethereal MeLi[3b] gave VII·HCl (3.1 g, 93%), mp 246–248°.

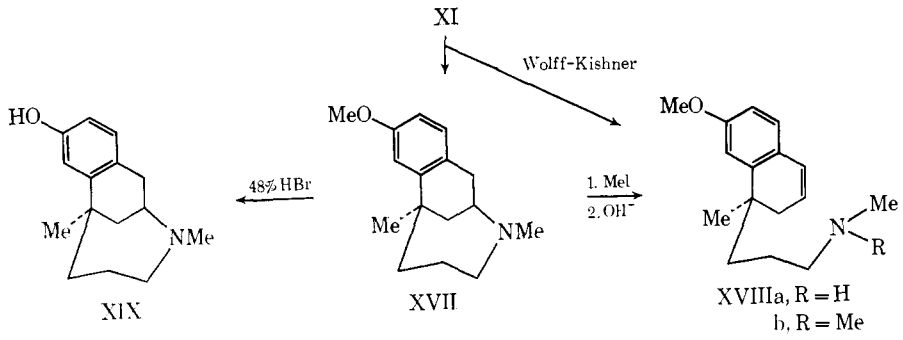
Wittig Reaction of XI. A solution of XI (2 g) in THF (18 ml) was added to a solution of methylenetriphenylphosphorane in THF prepared in the usual manner[14] (from 5.64 g of Ph_3PMeBr), at 5–8°, stirred at room temperature for 16 hr, then refluxed for 2 hr, filtered, and the solvent was removed *in vacuo*.

The residue in $CHCl_3$ was extracted with 2% H_3PO_4, made alkaline with NH_4OH, extracted with Et_2O, dried, and evap-

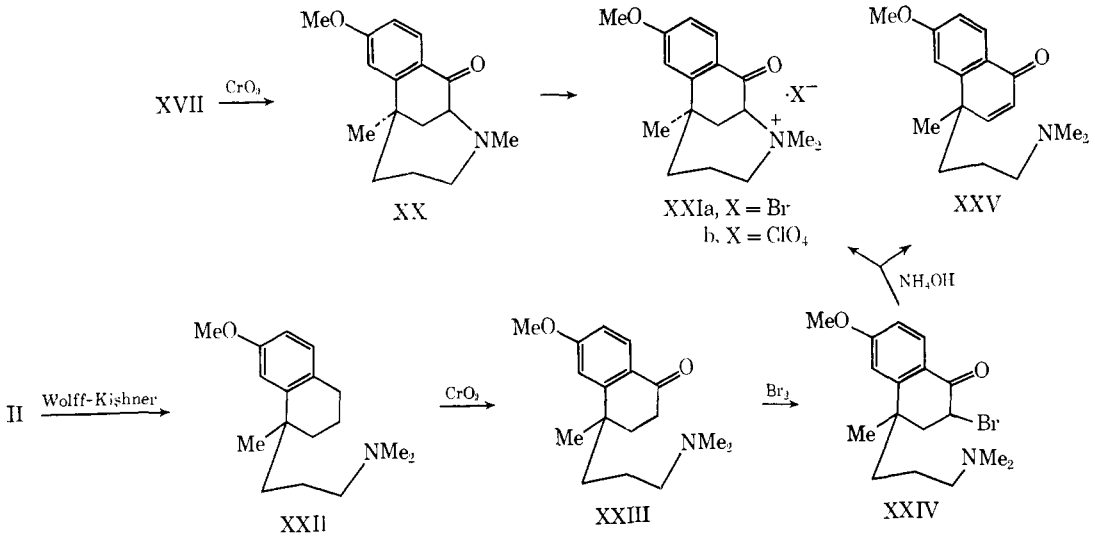
(13) Naming based on "homobenzomorphan" will substitute those based on "3*H*-3-benzazonine" hereafter. See ref 2.

(14) Two equivalents. Use of excess reagent gave a good result. We are indebted to Mr. M. Konda of this laboratory for this observation.

Scheme III



Scheme IV



orated. The residue was converted into a picrate in EtOH (3.7 g, 98%), mp 151–154°.

Hydrogenation of IX. a.—Free base IX (1.5 g) was hydrogenated with PtO_2 (200 mg) in EtOH (15 hr). The crude base in Et_2O was converted into its picrate and filtered to give 1.22 g, mp 131–140°. The base regenerated from the picrate was dissolved in Me_2CO and converted into the hydrochloride (520 mg), mp 112–116°, recrystallized from Me_2CO to give **2′-methoxy-2,6,10β-trimethyl-7,8-homobenzomorphan (XIII)·HCl** (425 mg, 24.6%) had mp 118–121°; nmr (free base), τ 8.7 (d, 3, J = 7Hz, 10β-CH_3). *Anal.* ($C_{17}H_{26}ClNO \cdot H_2O$) C,H,N. The free base was recovered from the combined Me_2CO and converted into the picrate in EtOH, filtered, recrystallized from EtOH to give **2′-methoxy-2,6,10α-trimethyl-7,8-homobenzomorphan (XII)·picrate** (210 mg, 7.4%): mp 148–152°; analytical sample, mp 153–155°; nmr (free base), τ 9.1 (d, 3, J = 7 Hz, 10α-CH_3). *Anal.* ($C_{23}H_{28}N_4O_8$) C,H,N. Free base was recovered from the mother liquor of the first picrate, converted into hydrochloride (0.65 g), recrystallized from AcOEt to give **XIV·HCl** (0.56 g, 32.4%): mp 127–130°; analytical sample, mp 130–132°.[15] *Anal.* ($C_{18}H_{28}ClNO$) C,H,N. Reaction of XIV with TsCl gave an oily N-tosylate in quantitative yield.

b.—IX·HCl was hydrogenated likewise and worked up in a similar way to give XIII·HCl (15%), XII·picrate (20%), and XIV·HCl (33%). In another run XIII·HCl, XII·picrate, and XIV·HCl were obtained in 62.3%, 11%, and 7.2% yields, respectively.

c.—IX·HCl (1.4 g) was hydrogenated in EtOH (15 ml) in the presence of 15% HCl (30 ml), EtOH was evaporated and the residue was recrystallized from Me_2CO to give XIII·HCl (1.19 g, 85%), mp 118–121°. The base was recovered from the filtrate (Me_2CO) and converted into XII·picrate (340 mg, 12%), mp 150–152°.

(15) Nmr (free base) showed two secondary CH_3 signals at τ 8.66 and 9.05 respectively. Furthermore, each signal of NCH_3, OCH_3, and tertiary CH_3 was split into two peaks. These suggest XIV is a mixture of diastereoisomers.

2′-Hydroxy-2,6,10α-trimethyl-7,8-homobenzomorphan (XV)·HBr.—O-Demethylation of XII with 48% HBr (20-min reflux) gave 56% of XV·HBr, mp 217–220° (from Me_2CO–EtOH–Et_2O). *Anal.* ($C_{16}H_{24}BrNO$) C,H,N.

2′-Hydroxy-2,6,10β-trimethyl-7,8-homobenzomorphan (XVI)·HBr, mp 209–212° (from Me_2CO–EtOH–Et_2O), was obtained in 86.5% yield. *Anal.* ($C_{16}H_{24}BrNO$) C,H,N.

2′-Methoxy-2,6-dimethyl-7,8-homobenzomorphan (XVII)·HCl.—A mixture of XI (4 g), KOH (4 g), $NH_2NH_2 \cdot H_2O$ (4 ml), and diethyleneglycol (35 ml) was refluxed for 2 hr, the condenser was taken off and the mixture was heated to 175°, stirred for 30 min at that temperature, and cooled. H_2O and Et_2O were added, the organic phase was separated, washed with H_2O, dried, and evaporated. The crude base in Me_2CO gave XVII·HCl (0.67 g), mp 160–163°. The base recovered from the mother liquor (Me_2CO) was chromatographed on Al_2O_3 and eluted with C_6H_6–Et_2O (7:3) to give additional XVII (0.85 g as the hydrochloride, total yield, 35%), mp 163–165° (from Me_2CO–EtOH–Et_2O), ir, 3400 cm^{-1}. *Anal.* ($C_{16}H_{24}ClNO \cdot H_2O$)C,H,N. The **methiodide** was prepared in Me_2CO, mp 229–231° (from EtOH). *Anal.* ($C_{17}H_{26}INO$) C,H,N. **1,2-Dihydro-7-methoxy-1-methyl-1-(3-methylaminopropyl)naphthalene (XVIIIa)** was obtained from the Et_2O eluate; **hydrochloride**, 1.1 g (25%), mp 105–108° (from Me_2CO), uv (MeOH), 272 mμ (ε 15,800). *Anal.* ($C_{16}H_{24}ClNO$) C,H,N.

1,2-Dihydro-1-(3-dimethylaminopropyl)-7-methoxy-1-methylnaphthalene (XVIIIb)·HCl. a.—XVIIIa was methylated with Me_2SO_4 in Et_2O (1-hr reflux): hydrochloride, mp 139–140° (from Me_2CO–Et_2O); uv (MeOH), 272 mμ (ε 15,500). *Anal.* ($C_{17}H_{26}ClNO$) C,H,N.

b.—The methiodide of XVII (250 mg) was refluxed with 10% NaOH (10 ml) for 20 min, extracted with Et_2O, dried, and evaporated. The free base (180 mg) gave XVIIIb·HCl (170 mg, 88%), mp 138–140° (from Me_2CO–Et_2O).

2′-Hydroxy-2,6-dimethyl-7,8-homobenzomorphan (XIX)·HBr.—O-Demethylation of XVII·HCl with 48% HBr was carried out in a usual manner: mp 245–247° (from EtOH); 87% yield. *Anal.* ($C_{15}H_{22}BrNO$) C,H,N.

2'-Methoxy-2,6-dimethyl-9-oxo-7,8-homobenzomorphan (XX).—To a solution of XVII (306 mg), CrO_3 (165 mg) in 1 *N* H_2SO_4 (62 ml), was added 10 *N* H_2SO_4 (9 ml) at room temperature during 3 hr, and the mixture was allowed to stand for 20 hr. It was basified with NH_4OH, extracted with Et_2O, dried, and evaporated. The residue was recrystallized from hexane to give XX (165 mg, 52%): mp 118–119°; ir, 1660 cm^{-1}; uv (EtOH): 227 mμ (ε 12,000), 278 (12,300).[10] *Anal.* ($C_{16}H_{21}NO_2$) C,H,N. **Methobromide XXIa** was prepared in Me_2CO in a usual manner, mp 211–213°. *Anal.* ($C_{17}H_{24}BrNO_2$) C,H,N. **Methoperchlorate XXIb** was prepared from XXIa by addition of aq $NaClO_4$, mp 217–219° (from MeOH). *Anal.* ($C_{17}H_{24}ClNO_6$) C,H,N.

1-(3-Dimethylaminopropyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (XXII)·HCl.—A mixture of II (10.35 g), KOH (10 g), $NH_2NH_2 \cdot H_2O$ (10 ml), and diethyleneglycol (90 ml) was heated at 175° for 3 hr and worked up in the usual manner to give XXII·HCl (5.4 g, 46%), mp 151–153° (from Me_2CO–EtOH–Et_2O). *Anal.* ($C_{17}H_{28}ClNO$) C,H,N.

3,4-Dihydro-4-(3-dimethylaminopropyl)-6-methoxy-4-methyl-1(2*H*)-naphthalenone (XXIII)·HBr.—XXII (from 5.38 g of the hydrochloride) was oxidized with CrO_3 in H_2SO_4 in the usual manner.[10] Crude base was converted into the hydrobromide to give 3.29 g (54%): mp 137–141°; analytical sample, mp 142–144° (Me_2CO–Et_2O); ir, 1652 cm^{-1}; uv (EtOH), 227 mμ (ε 14,100), 280 (15,700).[10] *Anal.* ($C_{17}H_{26}BrNO_2$) C,H,N.

2-Bromo-3,4-dihydro-4-(3-dimethylaminopropyl)-6-methoxy-4-methyl-1(2*H*)-naphthalenone (XXIV)·HBr.—XXIII·HBr (2.35 g) was brominated in AcOH (30 min, at 55–65°) to give XXIV·HBr (2.41 g, 87.5%) mp 113–116°; analytical sample, mp 115–117° (from Me_2CO). *Anal.* ($C_{17}H_{25}Br_2NO_2 \cdot 0.5H_2O$) C,H,N.

Cyclization of XXIV·HBr.—To a stirred suspension of XXIV·HBr (2.4 g) in H_2O (8 ml), 5.6% NH_4OH (4 ml) was added with cooling. The mixture was stirred at room temperature for 2 hr and evaporated *in vacuo* to dryness below 40°. The residue was extracted with hot Me_2CO (100 ml in two portions) and filtered from inorganic material. Evaporation of the combined Me_2CO gave a crystalline residue (1.72 g, mp 120–123°),[16] which was dissolved in H_2O, basified with NH_4OH, extracted with Et_2O, dried, and evaporated. Conversion of the residue into the salt gave **4-(3-dimethylaminopropyl)-6-methoxy-4-methyl-1(4*H*)-naphthalenone (XXV)·HBr** (1.67 g, 85%): mp 125–127° (from Me_2CO–Et_2O); ir, 1643 cm^{-1}; uv (EtOH), 237 mμ (ε 15,500), 303 (ε 11,300); nmr (D_2O), olefinic protons, τ 3.55 (d, 1, *J* = 10 Hz) and τ 2.88 (d, 1, *J* = 10 Hz). *Anal.* ($C_{17}H_{24}BrNO_2 \cdot 0.5H_2O$) C,H,N. The H_2O layer was evaporated *in vacuo* below 40°, the residue was dissolved in H_2O (1 ml), $NaClO_4$ (140 mg) was added, and the solution was cooled in a refrigerator overnight to give XXIb (10 mg, 0.5%), mp 216–218°. This was identical with the sample previously obtained from XX (mp, ir, and tlc).

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(16) This was found to be mostly XXV·HBr.

Preparation of Substituted Naphthylcyclohexane Derivatives and Related Compounds[1]

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The synthesis of various naphthylcyclohexenone derivatives is reported. Methylation of 3-(6-methoxy-2-naphthyl)-2-cyclohexen-1-one (**2**) by various procedures allowed us to prepare the monomethyl (**5c**), dimethyl (**5d**), trimethyl (**6a**), and tetramethyl (**6b**) derivatives, the structure of which derives from their physical properties. Reduction of the tetrahydrodimethoxyphenylnaphthalene **8c** afforded a mixture of the α,β- and β,γ-unsaturated ketones (**11a**, **11b**). The new substances were submitted for a variety of bioassays. Compounds **4b**, **6a**, **8a**, **9b**, and **11b** were inactive when tested for oral estrogenic and oral antifertility activity.

Interest in seco-steroids generated by the potent antifertility activity of 2-methyl-3-ethyl-4-phenylcyclohex-4-ene carboxylic acid[2] lead us to prepare a series of phenylated cyclohexenones. Condensation reactions between aryl β-dialkylamino ketones and acetoacetic ester or similar compounds possessing an active CH_2 constitutes a convenient route for the synthesis of arylcyclohexen-1-one derivatives.[3] This method has been employed to prepare new compounds in the phenylcyclohexenone,[3] naphthylcyclohexenone,[4] and phenylnaphthalenic[5] series. In this work we wish to report the synthesis of new related tricyclic keto derivatives as well as some of their methylated analogs.

Condensation between 2-(β-dimethylaminopropionyl)-6-methoxynaphthalene·HCl (**1b**), readily obtained[1] from 6-methoxy-2-acetyl-naphthalene (**1a**)[6,7] and acetoacetic ester in a basic medium, afforded 3-(6-methoxy-2-naphthyl)-2-cyclohexen-1-one (**2**)[4] as the major compound. Another substance formed during the reaction corresponded to $C_{31}H_{28}O_4$, as evidenced by the mass spectrum molecular ion (M^+ 462), and the elemental analysis. Structure **3** is proposed for this compound on the basis of its nmr spectrum which showed 12 aromatic protons and only one olefinic H, besides 2 aromatic methyl ether groupings (see Experimental Section).

Catalytic hydrogenation[4] of **2** provided the substituted cyclohexanone **4a**, along with some of the corresponding alcohol (**4b**). LAH reduction of **4a** yielded a

(1) Contribution No. 370 from Syntex Institute of Organic Chemistry; for Contribution No. 369, see: I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J. H. Fried, *J. Med. Chem.*, **13**, 203 (1970).

(2) J. McL. Morris and G. Van Wagenen, *Amer. J. Obstet. Gynecol.*, **96**, 804 (1966); see also: G. W. Duncan, *Excerpta Med. Found. Int. Congr. Ser.*, **No. 156**, 69 (1967).

(3) F. C. Novello, M. E. Christy, and J. M. Sprague, *J. Amer. Chem. Soc.*, **75**, 1330 (1953).

(4) F. C. Novello and M. E. Christy, *ibid.*, **75**, 5431 (1953).

(5) P. A. Robins and J. Walker, *J. Chem. Soc.*, 177 (1957).

(6) R. D. Haworth and G. Sheldrick, *ibid.*, 864 (1934).

(7) R. Robinson and H. N. Rydon, *ibid.*, 1394 (1939).