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Structures Related to Morphine. XVIII.[1] Stereochemical Control of Addition of Hydrogen and Methylmetallo Reagents to 5-Ethyl-2-methyl-9-oxo-6,7-benzomorphan

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3,4-Dihydro-7-methoxy-2[1*H*]-naphthalenone has been converted to 5-ethyl-2′-methoxy-9-oxo-6,7-benzomorphan methobromide (IV). The reaction of IV with catalytic hydrogen or methylmagnesium iodide was sluggish but gave (after pyrolysis of the alkohalides VIII) the carbinols XIIa and XIIb respectively with the hydroxyl groups oriented toward the nitrogen as deduced from infrared spectral analysis. Pyrolysis of IV in boiling 1-octanol resulted partly in elimination of methyl bromide to give VI and partly in rupture of the nitrogen ring by hydrogen bromide loss to yield VII. The base VI reacted smoothly with hydrogen (platinum oxide) or methyllithium producing the carbinols Va and Vb, diastereoisomers of XII. Ethylmagnesium bromide added readily to the carbonyl group of 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan (XIII), giving the β-ethylcarbinol (XIV) (hydroxyl oriented away from nitrogen), but ethylmagnesium iodide would not add to the methiodide of XIII. Compounds V, XII, XIII, and several derivatives of V and XII have been tested for analgesic activity in mice.

In previous papers[3] we reported that the addition of methylmagnesium iodide, methyllithium, or hydrogen to the carbonyl function of 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan (XIII) methobromide afforded the α-alcohols[4] (hydroxyl oriented toward nitrogen), while XIII (base) yielded principally diastereoisomers. The present report is concerned with such additions to the 5-ethyl homologs, IV and VI; with the reaction of XIII and its methiodide and ethylmagnesium halide; and with the analgesic potential of some of the products and their derivatives.

The sequence of reactions used in the preparation of IV and VI was the same as that described previously.[5] Ethylation of 3,4-dihydro-7-methoxy-2[1H]-naphthalenone (I) by the method of Stork[6] produced the 1-ethyl derivative (II) in 75% yield. Reaction of III with 2-chloro-*N*,*N*-dimethylethylamine and sodamide gave the amino ketone (III) which, upon bromination and cyclization of the resultant 3-bromide by quaternization, led to IV. On heating IV in boiling 1-octanol, a 3:2 mixture of the base VI and α,β-unsaturated ketone VII resulted in analogy to the 5-methyl series.[5]

The reaction of IV with platinum oxide-catalyzed hydrogen or methylmagnesium iodide was unexpectedly sluggish (based on experience with the 5-methyl homolog), but eventually the α-carbinols[4] VIIIa and b respectively were obtained in 70–80% yields, minimal amounts, if any, of the diastereoisomers being formed. Pyrolysis of VIII in boiling 1-nonanol yielded the bases XII. Similar reactions with the base VI yielded relatively rapidly the β-isomers[4] (V) in 80–85% yield.

Configurational assignments for V, XII, and thus VIII[7] rest on infrared data. In analogy with the 5-methyl series,[1,3a] XII showed strong OH—N bonding and V OH—π bonding. In XII and the corresponding 5-methyl compounds[3] (α-series) the hydroxyl band appears at approximately 3450 cm.$^{-1}$ when R is CH_3 and at 3493–3500 cm.$^{-1}$ when R is H. In the β-series there is only 4–5 cm.$^{-1}$ difference between Va and Vb, and this is also true for the corresponding 5-methyl relatives.[3] These peaks did not shift on tenfold dilution, ruling out intermolecular bonding.

The phenolic compounds IX and XI were obtained from V and XII respectively with boiling 48% hydrobromic acid. The diacetyl compound Xb was converted to the 9-acetyl derivative XV by boiling water but Xa was unaffected by this treatment.

Although the addition of methylmagnesium iodide or catalytic hydrogen to the carbonyl group of IV is unexpectedly slower than in the 5-methyl series,[3] the eventual stereochemistry of the additions (α-carbinol formation)[4] is not materially different. The free bases VI and XIII seem to differ little regarding carbonyl reactivity or stereochemistry of acceptance of hydrogen or Grignard reagents (β-carbinol formation).[4] Furthermore, as stated previously,[3b] ethyl- or propylmagnesium iodide would not react with the methobromide of XIII except to give a small yield of reduction product (α-

(1) Communication XVII, E. L. May, H. Kugita, and J. H. Ager, *J. Org. Chem.*, 26, 1621 (1961).

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(3)(a) E. L. May and H. Kugita, *J. Org. Chem.*, 26, 188 (1961), (b) H. Kugita and E. L. May, *J. Org. Chem.*, 26, 1954 (1961).

(4) The α-designation has been assigned to those carbinols in which hydroxyl is oriented toward nitrogen. The diastereoisomers have the prefix β.

(5) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, 25, 1386 (1960).

(6) G. Stork and J. Szmuszkovicz, *J. Am. Chem. Soc.*, 76, 2029 (1954).

(7) It has been shown[3a] that pyrolysis is achieved without inversion in the 5-methyl series.

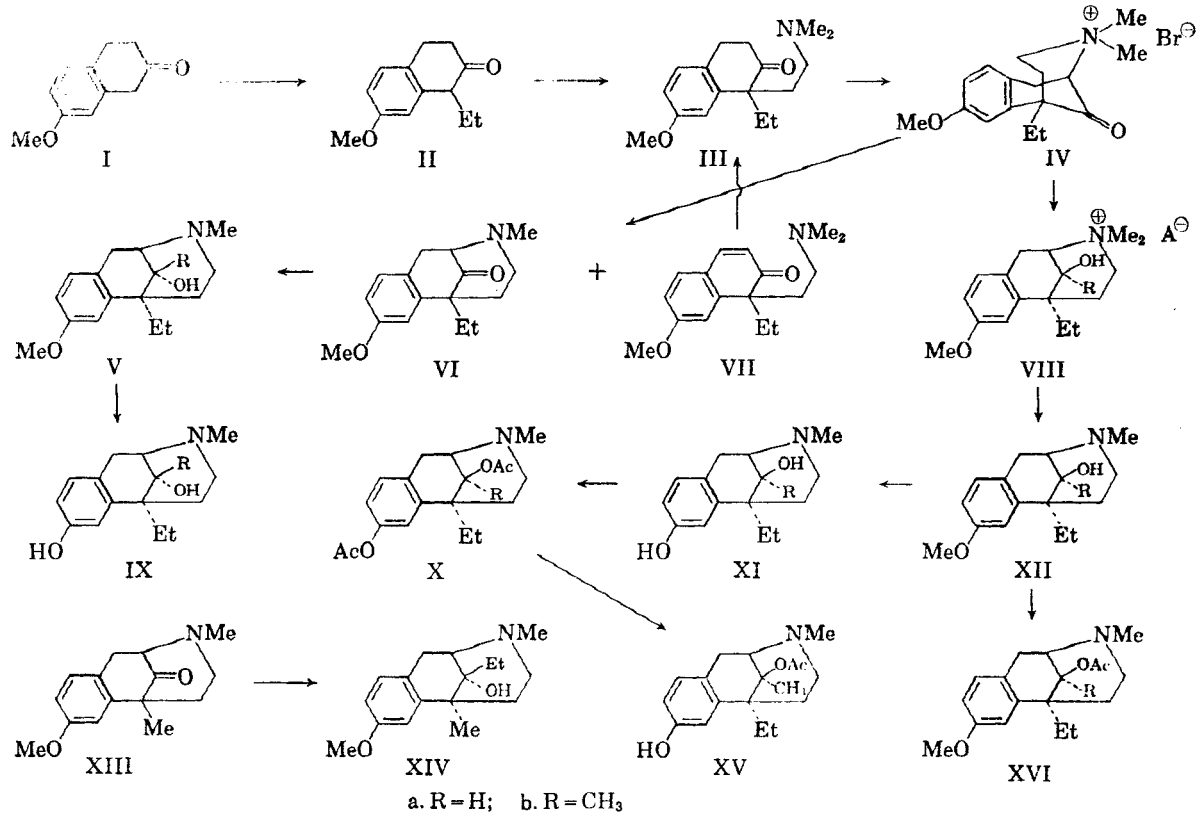

Figure 1

carbinol),[3b,4] whereas ethylmagnesium bromide and the free base XIII gave readily the β-9-ethylcarbinol (XIV), no α-isomer being detected. Thus it has been possible to control the stereochemistry of additions to the carbonyl function of 9-oxo-6,7-benzomorphans simply by controlling the valency state of the nitrogen. Within the narrow limits of our study, steric effects, as they have increased, have retarded or voided reaction but have not substantially altered stereochemistry. We feel that the change in geometry produced by conversion of the nitrogen from tertiary to methyl-quaternary cannot alone account for the almost complete reversal of the stereochemistry of these additions. Consequently, the electrical environment due to the nitrogen appears to have relevance. The imposition of greater steric restrictions, particularly at the nitrogen function, should shed more light on this matter.

In general the pattern of analgesic activity of these compounds (Table I) is similar to that of the 5-methyl analogs.[1] One marked deviation is the β-9-methylcarbinol (IXb) which, even as the racemate, is as potent as morphine in mice and is by far the most effective of any of unacetylated compounds of the 9-hydroxy series. As is true of the 5-methyl series acetylation of both hydroxyl groups of XI is advantageous, increasing activity fivefold or more. Thus compound Xa (ED_{50} 2.2) is equivalent to morphine and compound Xb (ED_{50} 1.1) is twice as potent. Little change in effectiveness was noted on removal of the phenolic *O*-acetyl group of Xb to XV. Finally it is curious that the phenolic α-9-carbinol XIa, as is the case in the 5-methyl series,[1] is of a very low order of activity ($ED_{50} > 50$), lower than the corresponding 2′-methoxy compound again an exception to the general rule for such compounds.

TABLE I

ANALGESIC ACTIVITY OF 9-HYDROXY-6,7-BENZOMORPHANS

α-9-Hydroxy-2-methyl-6,7-benzomorphan	ED_{50}, Mg./Kg.[a]
2′-Methoxy-5-ethyl (XIIa)	45.4
O-Acetyl derivative (XVIa)	22.6
2′-Methoxy-5-ethyl-9-methyl (XIIb)	13.8
O-Acetyl derivative (XVIb)	14.8
2′-Hydroxy-5-ethyl (XIa)	>50
Di-*O*-acetyl derivative (Xa)	2.2
2′-Hydroxy-5-ethyl-9-methyl (XIb)	6.7
9-Acetyl derivative (XV)	1.1
Di-*O*-acetyl derivative (Xb)	1.2
β-9-Hydroxy-2-methyl-6,7-benzomorphans	
2′-Hydroxy-5-ethyl (IXa)	12.2
2′-Hydroxy-5-ethyl-9-methyl (IXb)	1.7
2′-Methoxy-5-methyl-9-ethyl (XIV)	8.4

[a] The testing method and analysis of data are given in ref. 1.

EXPERIMENTAL

Melting points were determined by capillary, in a Hershberg apparatus with total-immersion thermometers. Micro-

analyses are by the Institute's service analytical unit, Harold McCann, director. Infrared determinations in which values are expressed in cm.$^{-1}$ were made in the Beckman IR.7 by Katherine Warren of the Heart Institute, all others by Ann Wright and H. K. Miller (Perkin-Elmer, Model 20) of this laboratory.

1-Ethyl-3,4-dihydro-7-methoxy-2[1H]-naphthalenone (II). To 52 g. of I[5] and 120 ml. of benzene was added during 5 min. 31 ml. of pyrrolidine. The mixture was refluxed for 1 hr. (azeotropic distillation of 7.5 ml. of water), cooled, and added to 80 ml. of ethyl iodide so as to cause gentle refluxing. After an additional reflux period of 3–4 hr., 400 ml. of water was added, and refluxing was continued for 3 hr. The benzene layer was separated, cooled, and shaken with a saturated solution of sodium bisulfite, then dried and evaporated at the water pump. Distillation of the residue gave 47 g. (75%) of II, b.p. 114–118°/0.3 mm., n_D^{20} 1.5482. A small sample was converted to the semicarbazone in nearly quantitative yield; prisms from methanol, m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.32; H, 7.36; N, 16.36.

1-Ethyl-3,4-dihydro-7-methoxy-1-(2-dimethylaminoethyl)-2-[1H]-naphthalenone (III) *hydrobromide.* To 2 g. of sodamide in 25 ml. of dry, refluxing benzene (stirring) was added as rapidly as possible 10 g. of II in 30 ml. of benzene. After 1 hr. of refluxing, 6 g. of 2-chloro-*N,N*-dimethylethylamine in 80 ml. of benzene was added during 1–2 hr. Refluxing and stirring were continued overnight. The benzene was washed twice with water and these washings were extracted with ether. The combined benzene and ether fractions were extracted with excess 10% hydrochloric acid. The extracts were made alkaline with concentrated ammonium hydroxide and shaken twice with ether. The dried extracts were evaporated at the water pump, leaving a residue which was distilled at 0.25 mm. (bath temperature 170–190°) to give 9.3 g. of crude III. This in 120 ml. of dry ether was acidified with about 10 ml. of 30% hydrogen bromide in acetic acid giving a rapidly crystallizing oil. The crystals were collected and washed with 25 ml. of acetone; yield of III hydrobromide 10.6 g. (61%), m.p. 178–181°. It crystallized from ethanol in plates, m.p. 187–188.5°, λ_{max}^{Nujol} 5.85 μ.

Anal. Calcd. for $C_{17}H_{26}BrNO_2$: C, 57.30; H, 7.35; N, 3.93. Found: C, 57.03; H, 7.54; N, 3.84.

3-Bromo-3,4-dihydro-1-ethyl-7-methoxy-1-(2-dimethylaminoethyl)-2[1H]-naphthalenone hydrobromide. To a stirred, refluxing solution of 10 g. of III hydrobromide in 40 ml. of acetic acid was added during 15–25 min., 4.5 g. of bromine in 25 ml. of acetic acid. The solution was cooled to 45° under a stream of nitrogen and treated carefully (stirring) with 200 ml. of ether; cubic crystals gradually separated. After cooling at −5° for 2 hr., the mixture was filtered and the crystals were washed with acetone to give 11.6 g. (95%) of hydrobromide, m.p. 165–177°; cubes from methanol, m.p. 175–177° dec., λ_{max}^{Nujol} 5.78 μ.

Anal. Calcd. for $C_{17}H_{25}Br_2NO_2$: C, 46.97; H, 5.80; N, 3.22. Found: C, 47.27; H, 5.88; N, 3.32.

5-Ethyl-2'-methoxy-2-methyl-9-oxo-6,7-benzomorphan methobromide (IV). Ten grams of finely divided bromo ketone hydrobromide above, 50 ml. of cold water, and 5.2 ml. of concd. ammonium hydroxide were shaken vigorously in a separatory funnel until all but a few small lumps had disappeared. The aqueous layer was extracted twice with ether. The combined ethereal fractions were evaporated to dryness at the water pump. The residue and 20 ml. of acetone (or 10 ml. of methanol) were warmed to complete crystallization and kept at −5° overnight to give 6 g. (74%) of IV, m.p. 194–196°. It was recrystallized from methanol; flakes, m.p. 201–202°, λ_{max}^{Nujol} 5.75 μ.

Anal. Calcd. for $C_{17}H_{24}BrNO_2$: C, 57.66; H, 6.75; N, 3.95. Found: C, 57.31; H, 6.84; N, 3.65.

α-5-Ethyl-9-hydroxy-2'-methoxy-2,9-dimethyl-6,7-benzomorphan methiodide (VIIIb. A = I.). Five grams of IV was covered with 50 ml. of dry ether, and 60 ml. of 1.7*M* ethereal methylmagnesium iodide was added (stirring). Stirring was continued for 45 hr. The mixture was poured into 17 ml. of concd. hydrochloric acid and 40 g. of ice, and 10 g. of potassium iodide in 15 ml. of water was added. After stirring for another 2.5 hr. at 0°, the precipitate was collected and washed with water then ethyl acetate to give 4 g. (69%) of VIIIb (A = I), m.p. 197–199°; plates from methanol-ether, m.p. 203–204.5°, λ_{max}^{Nujol} 3.0 μ.

Anal. Calcd. for $C_{18}H_{28}INO_2$: C, 51.80; H, 6.76; N, 3.36. Found: C, 51.86; H, 6.75; N, 3.21.

α-5-Ethyl-9-hydroxy-2'-methoxy-2,9-dimethyl-6,7-benzomorphan (XIIb) *hydrochloride.* 1-Nonanol (45 ml.) and 5.5 g. of VIIIb (A = I) were refluxed for 15 min. and cooled under nitrogen. When this solution was shaken with 30 ml. of 10% hydrochloric acid and ether, crystals separated. They were collected and washed with a little water then acetone giving 1.3 g. of XIIb hydrochloride, m.p. 120–122°. The filtrate was made alkaline with ammonium hydroxide and extracted with ether. The dried extracts were evaporated leaving an oil to which was added 2 ml. of concd. hydrochloric acid to give 2.5 g. more XIIb hydrochloride (total yield 88%). It crystallized from methanol-ether apparently as the monohydrate; plates, m.p. 123–125°.

Anal. Calcd. for $C_{17}H_{26}ClNO_2 \cdot H_2O$: C, 61.92; H, 8.56; N, 4.20. Found: C, 61.92; H, 8.85; H, 4.04.

The oily base (XIIb) gave $\nu_{max}^{CCl_4}$ 3445 (strong, OH—N bonding) and 3620 (weak, sharp, free OH) cm.$^{-1}$

The *acetate* (XVIb) was prepared (87% yield) by 2 hr. of refluxing of 0.6 g. of XIIb and 10 ml. of acetic anhydride. It was purified by distillation at 0.3 mm. (bath temperature 200–220°) and crystallized from ligroin (b.p. 30–60°) in needles; m.p. 87–89°, λ_{max}^{Nujol} 5.77 μ.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.69; H, 8.84; H, 4.46.

The *hydrochloride* of XVIb crystallized from ethanol-ether in needles, m.p. 204–206°, λ_{max}^{Nujol} 5.73 μ.

Anal. Calcd. for $C_{19}H_{28}ClNO_3$: C, 64.48; H, 8.16; N, 3.96. Found: C, 64.28; H, 7.98; N, 3.97.

α-5-Ethyl-2',9-dihydroxy-2,9-dimethyl-6,7-benzomorphan (XIb). Two grams of XIIb hydrochloride and 16 ml. of 48% hydrobromic acid were refluxed for 15 min., cooled, and made alkaline with concentrated ammonium hydroxide. Addition of sodium chloride, extraction with chloroform, and evaporation of the chloroform *in vacuo* left a brown oil which crystallized from a little acetone; yield of XIb, 1 g. (66%), m.p. 146–148°; plates from acetone-ether λ_{max}^{Nujol} 3.04 μ (broad).

Anal. Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.60; H, 8.98; N, 5.28.

The *di-O-acetyl derivative* (Xb) was prepared in 82% yield (acetic anhydride, 1 hr. of reflux). The *hydrochloride* (prepared from distilled material) crystallized from methanol-ether in needles, m.p. 242–244°, λ_{max}^{Nujol} 5.66, 5.74 μ.

Anal. Calcd. for $C_{20}H_{28}ClNO_4$: C, 62.90; H, 7.89; N, 3.67. Found: C, 62.46; H, 7.93; N, 3.46.

α-9-Acetoxy-5-ethyl-2'-hydroxy-2,9-dimethyl-6,7-benzomorphan (XV) *hydrochloride.* Water (5 ml.) and 0.3 g. of Xb hydrochloride were refluxed for 1 hr., made alkaline with concentrated ammonium hydroxide and extracted with ether. Evaporation of the dried (sodium sulfate) extracts left an oil which, in 4 ml. of acetone, was acidified with hydrogen chloride to a *p*H of 2. At −15° overnight 0.2 g. (70%) of XV hydrochloride separated and was recrystallized from methanol-ether; cubes, m.p. 250–252° dec., λ_{max}^{Nujol} 3.15, 5.72 μ.

Anal. Calcd. for $C_{18}H_{26}ClNO_3$: C, 63.67; H, 7.71; N, 4.12. Found: C, 63.37; H, 7.99; N, 4.00.

α-5-Ethyl-9-hydroxy-2'-methoxy-2-methyl-6,7-benzomorphan methobromide (VIIIa. A = Br). Platinum oxide (3 g.), 14 g. of IV, and 300 ml. of methanol absorbed one molar equivalent of hydrogen during 2–3 days. The filtered solution was evaporated to dryness at the water pump. The residue was dissolved in 20 ml. of hot ethanol[8] and the solution was

(8) This methobromide would not crystallize from acetone. The analytical data indicate one mole of solvate ethanol.

kept at −15° overnight to give 8.6 g. (61%) of crystals, m.p. 160–163°, which was recrystallized from ethanol; plates, m.p. 163–166° dec. λ_{max}^{Nujol} 2.9, 3.05, 3.11 μ.

Anal. Calcd. for $C_{17}H_{26}BrNO_2 \cdot C_2H_5OH$: C, 56.71; H, 8.00; N, 3.48. Found: C, 56.60; H, 7.57; N, 3.1.

The *methiodide* (VIIIa. A = I), obtained by addition of potassium iodide to an aqueous solution of the methobromide crystallized in needles, m.p. 198–199.5°, λ_{max}^{Nujol} 2.92, 3.0 μ (shoulder).

Anal. Calcd. for $C_{17}H_{26}INO_2$: C, 50.63; H, 6.35; N, 3.39. Found: C, 50.34; H, 6.79; N, 3.31.

The filtrate from the 8.6 g. of methobromide above was evaporated to dryness to give a viscous oil which would not crystallize but which gave 4 g. of methiodide (aqueous potassium iodide), m.p. 102–105°. Two recrystallizations from water gave 3 g. of methiodide, m.p. 197–198° identified as VIIIa (A = I); total yield of VIIIa,[9] 80%.

α-5-Ethyl-9-hydroxy-2'-methoxy-2-methyl-6,7-benzomorphan (XIIa). 1-Nonanol (35 ml.) and 4.8 g. of VIIa (A = Br) were refluxed for 1 hr., cooled under nitrogen, and diluted with ether. The mixture was extracted thrice with 10% hydrochloric acid. The extracts were made alkaline and extracted with chloroform. Evaporation of the dried extracts left an oil which was evaporatively distilled at 0.3 mm. (bath temperature 200–220°) giving 2.3 g. (74%) of XIIa which crystallized on trituration with ether. It crystallized from ethanol in pillars, m.p. 122–124°, λ_{max}^{Nujol} 3.17 μ, $\nu_{max}^{CCl_4}$ 3500 (strong, OH—N bonding), 3640 cm.$^{-1}$ (very weak, free OH).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.25; H, 8.73; N, 5.28.

The *hydrochloride* crystallized from ethanol-ether in plates, apparently the monohydrate; m.p. 123–126°, λ_{max}^{Nujol} 2.87, 2.94, 3.13, 3.20 μ.

Anal. Calcd. for $C_{16}H_{24}ClNO_2 \cdot H_2O$: C, 60.84; H, 8.30; N, 4.44. Found: C, 61.13; H, 8.49; N, 4.62.

The *O-acetyl derivative* (XVIa) prepared by refluxing XIIa and acetic anhydride for 2 hr., melted at 90–92°. The *hydrochloride* of XVIa crystallized from methanol-ether in flakes, m.p. 258–259°, λ_{max}^{Nujol} 5.75 μ.

Anal. Calcd. for $C_{18}H_{26}ClNO_3$: C, 63.61; H, 7.71; N, 4.12. Found: C, 63.76; H, 7.81; N, 4.15.

α-5-Ethyl-2',9-dihydroxy-2-methyl-6,7-benzomorphan (XIa). As described for XIb, 1.8 g. (85%) of XIa resulted from 2.7 g. of XIIa hydrochloride; cubes from methanol, m.p. 174–176°, λ_{max}^{Nujol} 2.88, 3.12 μ.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.58; H, 8.54; N, 5.49.

The *hydrochloride* crystallized from methanol-ether, apparently as the hemihydrate, in prisms, m.p. 178–180°, λ_{max}^{Nujol} 2.85, 2.90, 3.00, 3.10 μ.

Anal. Calcd. for $C_{15}H_{22}ClNO_2 \cdot 1/2\ H_2O$: C, 61.53; H, 7.92; N, 4.82. Found: C, 61.94; H, 8.17; N, 4.94.

The *di-O-acetyl derivative* (Xa) *hydrochloride*,[10] 80% yield, crystallized from ethanol-acetone in flakes, m.p. 275–277°; λ_{max}^{Nujol} 5.65, 5.75 μ.

Anal. Calcd. for $C_{19}H_{26}ClNO_4$: C, 62.03; H, 7.12; N, 3.81. Found: C, 62.22; H, 7.48; N, 3.61.

5-Ethyl-2'-methoxy-2-methyl-9-oxo-6,7-benzomorphan (VI). 1-Octanol (25 ml.) and 5.4 g. of IV were immersed in a bath preheated to 210°, stirred and refluxed for 13 min. After cooling under nitrogen, ether was added and the mixture extracted thrice with 10% hydrochloric acid. The extracts were made alkaline and extracted with ether. The dried extracts were distilled, the residue at 0.3 mm. (bath temperature 180–200°) giving 3 g. of oil. It was dissolved in 10 ml. of acetone and acidified to a *p*H of 5.5 with hydrogen chloride. Kept overnight at −15° the solution deposited 0.95 g. (20%) of VII hydrochloride, m.p. 217–219° (from methanol-ether), λ_{max}^{Nujol} 6.05 μ, $\lambda_{max}^{C_2H_5OH}$ 224, 246, 345 mμ (ε 10,200; 10,650; 10,600)[11] which, in methanol (5% palladium on charcoal), absorbed one molar equivalent of hydrogen to give an almost quantitative yield of III identified as the hydrobromide. The filtrate, from the 0.95 g. of VII hydrochloride, combined with the acetone-ether washings was treated with hydrogen chloride to *p*H 2 and kept at −15° overnight giving 1.5 g. (35%) of VI hydrochloride, m.p. 208–210°; cubes from methanol-ether, λ_{max}^{Nujol} 5.74 μ.

Anal. Calcd. for $C_{16}H_{22}ClNO_2$: C, 64.96; H, 7.50; N, 4.74. Found: C, 64.77; H, 7.45; N, 4.65.

Recrystallization of the VI hydrochloride from water or water-acetone gave needles, m.p. 116–118°. After drying over phosphorus pentoxide at 25° *in vacuo* it gave λ_{max}^{Nujol} 2.92, 3.09 μ and was transparent in the carbonyl region.[12]

Anal. Calcd. for $C_{16}H_{24}ClNO_2 \cdot H_2O$: C, 57.91; H, 7.90. Found: C, 57.20; H, 8.08.

β-5-Ethyl-9-hydroxy-2'-methoxy-2,9-dimethyl-6,7-benzomorphan (Vb) *hydrochloride.* To 0.85 g. of VI in 10 ml. of ether was added 10 ml. of 1.3*M* ethereal methyllithium during several minutes, and the mixture was refluxed for 0.5 hr. It was poured into ice water and the ethereal layer was dried and evaporated. The residue was distilled evaporatively at 0.3 mm. (bath temperature 200–220°) giving 0.75 g. (81%) of Vb, $\nu_{max}^{CCl_4}$ 3591 (OH—π), 3610 cm.$^{-1}$ (shoulder, free OH) whose hydrochloride crystallized from acetone-methanol-ether in cubes, m.p. 210–212°, λ_{max}^{Nujol} 3.04 μ.

Anal. Calcd. for $C_{17}H_{26}ClNO_2$: C, 65.47; H, 8.43; N, 4.49. Found: C, 65.07; H, 8.49; N, 4.27.

β-5-Ethyl-2',9-dihydroxy-2,9-dimethyl-6,7-benzomorphan (IXb). As described for the *O*-demethylation of XIIb, 0.5 g. of Vb hydrochloride gave 0.3 g. (72%) of IXb; cubes from methanol, m.p. 200–202°, λ_{max}^{Nujol} 2.8 μ.

Anal. Calcd. for $C_{16}H_{23}NO_2$: N, 5.36. Found: N, 5.67.

The *hydrobromide*, prisms from methanol-ether, melted at 202–204°, λ_{max}^{Nujol} 2.92, 3.00, 3.20 μ. Analytical data indicated methanol of solvation.

Anal. Calcd. for $C_{16}H_{24}BrNO_2 \cdot CH_3OH$: C, 54.70; H, 7.56; N, 3.75. Found: C, 54.57; H, 7.51; N, 3.66.

β-5-Ethyl-9-hydroxy-2'-methoxy-2-methyl-6,7-benzomorphan (Va). Platinum oxide (0.2 g.), 1.04 g. of VI and 20 ml. of ethanol absorbed one molar equivalent of hydrogen during 40 min. The filtered solution was evaporated to dryness. The residue crystallized from methanol-water as the monohydrate of Va in a yield of 0.9 g. (82%); prisms, m.p. 81–82°. For analysis it was dried over phosphorus pentoxide *in vacuo* at 25°; λ_{max}^{Nujol} 2.89; 3.10 μ.

Anal. Calcd. for $C_{16}H_{23}NO_2 \cdot H_2O$: C, 68.78; H, 9.02; N, 5.01. Found: C, 69.02; H, 9.07; H, 5.37.

Dried at 60° (25 mm.) the monohydrate became liquid and anhydrous; $\nu_{max}^{CCl_4}$ 3595 (OH—π), 3625 cm.$^{-1}$ (free OH).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.11; H, 8.98; N, 5.33.

The *hydrochloride* of Va crystallized from methanol-ether in needles, m.p. 215–217°, λ_{max}^{Nujol} 3.04 μ.

Anal. Calcd. for $C_{16}H_{24}ClNO_2$: C, 64.52; H, 8.12; N, 4.70. Found: C, 64.62; H, 8.44; N, 4.46.

β-5-Ethyl-2',9-dihydroxy-2-methyl-6,7-benzomorphan (IXa).[13] A mixture of 0.7 g. of Va hydrochloride and 7 ml. of 48% hydrobromic acid was refluxed for 15 min., cooled, and made alkaline with concentrated ammonium hydroxide. The

(9) No β-carbinol (Va) could be isolated.

(10) Boiling water left Xa unchanged unlike Xb which was thereby converted to XV.

(11) The hydrochloride of the 5-methyl analog of VII gave $\lambda_{max}^{C_2H_5OH}$ 222, 244, 339 mμ (ε 10,952; 11,676; 12,250); in reference 5 the ε at 340 mμ was erroneously given as 26,400. We are indebted to Dr. S. E. Fullerton, Visiting Fellow, from London, England, for rechecking our data.

(12) On drying at 60°, carbonyl absorption began to appear. Probably because of the greater bulk of the 5-ethyl substituent, the carbonyl group of VI does not become solvated as readily as that of XIII (*cf.* reference 5).

(13) As it was shown that rearrangements or inversion at carbon 9 did not occur in the 5-methyl series (*cf.* ref. 3), we assume that this is also true of *O*-demethylations of the 5-ethyl homologs.

crystals which separated overnight at −5° were washed with water and recrystallized from methanol-water in cubes; yield 0.4 g. (69%), m.p. 216–218°, λ_{max}^{Nujol} 2.90 μ.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.62; N, 5.66. Found: C, 72.86; H, 8.81; N, 5.92.

The *hydrochloride* crystallized from methanol-ether in cubes of m.p. 236–238°, λ_{max}^{Nujol} 2.91, 3.22 μ.

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.37; H, 8.26; N, 4.95.

β-9-Ethyl-9-hydroxy-2'-methoxy-2,5-dimethyl-6,7-benzomorphan (XIV). To 0.5 g. of XIII[5] in 20 ml. of dry ether was added rapidly (stirring) 15 ml. (*ca.* 3 molar equivalents) of 0.4*M* ethereal ethylmagnesium bromide. After refluxing for 2 hr. the solution was poured into ice cold ammonium chloride solution and a little concentrated ammonium hydroxide was added. The dried ethereal layer was evaporated and the 0.5 g. of oil distilled evaporatively at 0.15 mm. (bath temperature 150–160°). It gave $\lambda_{max}^{CHCl_3}$ 2.79 μ (sharp, medium, OH—π bonding).

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.73; H, 9.45.

The *picrate* was prepared in a yield of 0.45 g. (45% based on XIII) by heating together the distillate above, 0.5 g. of picric acid and 12 ml. of ethanol, then cooling gradually, finally to 5°; yellow prisms from alcohol-acetone, m.p. 214–215°.

Anal. Calcd. for $C_{23}H_{28}N_4O_9$: C, 54.75; H, 5.60. Found: C, 54.87; H, 5.41.

The *hydrochloride* apparently the monohydrate, crystallized from ethanol-acetone in prisms, m.p. 164–175°.

Anal. Calcd. for $C_{17}H_{26}ClNO_2 \cdot H_2O$: C, 61.90; H, 8.56. Found: C, 61.92; H, 8.43.

Neither ethyl- nor propylmagnesium iodide would add to the methobromide of XIII, giving instead a small yield of α-9-carbinol (reduction product).[3]

BETHESDA 14, MD.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

Syntheses Related to Etiojervane. I. The Synthesis of 1,8-Dimethyl-7-methoxy-1,2,3,4,4a,9a-hexahydrofluorenone-2-carboxylic Acid

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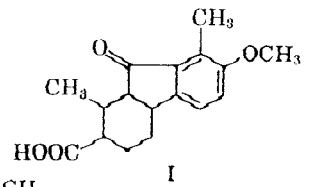
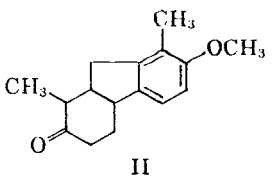
The Diels-Alder reaction of styrylacrylic acid and 4-methoxy-3-methylstyrylacrylic acid (IX) with crotonic acid has been investigated. The product from acid IX could be reduced and after bromination, cyclized to a hexahydrofluorene. This latter substance is potentially an intermediate in the synthesis of a jervine derivative.

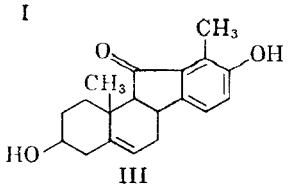
The veratrum alkaloid, jervine, has been found by Fried, Wintersteiner, and co-workers[2,3] to have an abnormal steroid skeleton. The work reported here was part of a program which had as its objective the synthesis of substances with the "etiojervane" ring system. The basic scheme was to prepare ketone II which should be readily transformable to III, a degradation product of jervine.[3]



I



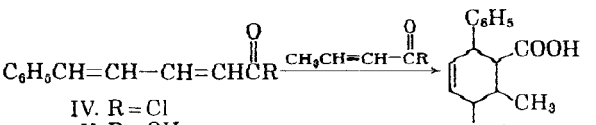
II



III

The Diels-Alder reaction has been used as the key synthetic step and the reaction sequence carried as far as acid I, a substance which can be converted to II.[4]

Alder and co-workers[5] have reported that styrylacrylyl chloride (IV) would react at several temperatures with acrylyl chloride. However, an attempt to replace acrylyl chloride by crotonyl chloride was not successful. Only decomposition of the acid chlorides took place as the reaction temperature was raised. The corresponding acids were more stable and did react in boiling tetralin at 190° to yield the desired adduct VI.



IV. R = Cl
V. R = OH

VI

The diene acid IX necessary for the synthesis of acid I was prepared from 3-methoxy-4-methylbenzaldehyde (VII). Aldehyde VII was conveniently prepared from *o*-methylanisole by reac-

(1) Abstracted from a portion of the thesis presented by N. N. Gerber to the Graduate School for the Ph.D. degree, May 1957.

(2) J. Fried, O. Wintersteiner, M. Moore, B. M. Islin, and A. Klingsberg, *J. Am. Chem. Soc.*, 73, 2790 (1951).

(3) J. Fried and A. Klingsberg, *J. Am. Chem. Soc.*, 75, 4929 (1953).

(4) To be described in a future communication. An extension of this synthetic plan to the preparation of a hexahydrofluorene related to gibberone has been previously reported; see N. N. Gerber, *J. Am. Chem. Soc.*, 82, 5216 (1960).

(5) K. Alder, M. Schumacher, and O. Wolff, *Ann.*, 570, 237 (1950).