in a minimum quantity of warm EtOH and converted into the hydrogen maleate salt,[27] $[\alpha]^{25}D$ −15° (*c* 2, H_2O), as described for the Me ether.

B.—A solution of 2.1 g (0.012 mole) of $PhCH_2Br$ in 10 ml of DMSO was added slowly to a stirred mixture of 2.0 g (0.012 mole) of (1*R*,2*S*)-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol (metaraminol) in 100 ml of DMSO and 6.0 ml of 2 *N* NaOH at 85°. After addition was complete, the reaction mixture was stirred at 85° for an additional 2 hr and then poured into 500 ml of ice H_2O. After saturating with NaCl, and extracting with four 200-ml portions EtOAc, the organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was converted into the hydrogen maleate salt and recrystallized (EtOH–Et_2O) to give 3.2 g (72%) of product, mp 150.0–154.0°. Repeated recrystallization did not improve the melting point. *Anal.* ($C_{16}H_{19}NO_2 \cdot C_4H_4O_4$)H; C: calcd, 64.32, found 65.16, 65.15.

(1*R*,2*S*)-α-(1-Aminoethyl)-*m*-(4-cyanobenzyloxy)benzyl Alcohol Methanesulfonate (IV, R = $CH_2C_6H_4CN$).—The intermediate (1*R*,2*S*)-α-(1-acetamidoethyl)-*m*-(4-cyanobenzyloxy)-benzyl alcohol was prepared by the general method using 9.2 g (0.0405 mole) of (1*R*,2*S*)-α-(1-acetamidoethyl)-*m*-hydroxybenzyl alcohol hydrate,[7] 7.6 g (0.050 mole) of *p*-cyanobenzyl chloride, and 30.4 g of K_2CO_3 in Me_2CO (500 ml). A solution of 6 g (0.0185 mole) of the amide in EtOH (50 ml) was converted into the corresponding amine by heating 4 hr at reflux with 1 *N* HCl (100 ml). After removing most of the EtOH under reduced pressure, the residue was neutralized with excess satd $NaHCO_3$ solution. The product was extracted into EtOAc, dried (Na_2SO_4), filtered, and concentrated to 4 g of a yellow oil. The crude product was converted into the methanesulfonate salt in the usual manner. When purification proved difficult, the salt was reconverted into the free base with dil NaOH and EtOAc extraction. The 1.7 g of recovered oil was chromatographed on 85 g of silica gel. Elution with $CHCl_3$ then 10–50% MeOH–$CHCl_3$ removed 0.7 g of side products. The desired ether (0.7 g) was eluted from the column with MeOH (900 ml). The methanesulfonate salt was prepared in the usual manner and recrystallized from *i*-PrOH–Et_2O to give an analytical sample.[27]

(1*R*,2*S*)-α-[1-(4-Cyanobenzylamino)ethyl]-*m*-(4-cyanobenzyloxy)benzyl Alcohol Methanesulfonate.—A solution of 3.0 g (0.020 mole) of *p*-cyanobenzyl chloride in 20 ml of DMSO was added slowly to a stirred solution of 3.4 g (0.020 mole) of (1*R*,2*S*)-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol (metaraminol) in 200 ml of DMSO and 8.0 ml of 2 *N* NaOH at 85°. After stirring 2.5 hr at 85°, the reaction mixture was poured into 1 l. of ice H_2O and extracted with EtOAc (4 × 200 ml). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was converted into the methanesulfonate and recrystallized from *i*-PrOH–Et_2O to give 0.8 g (16.2%) of product, mp 194.5–196.5°. *Anal.* ($C_{25}H_{23}N_3O_2 \cdot CH_4O_3S$) C, H, N.

Hydrogenolysis of (1*R*,2*S*)-α-(1-Aminoethyl)-*m*-benzyloxybenzyl Alcohol.—The free base (1.3 g, 5.06 mmoles), liberated from 2 g of the hydrogen maleate salt of the benzyl ether, was hydrogenated in 25 ml of EtOH with a 5% Pd–C catalyst at atmospheric pressure until 1 equiv of H_2 was taken up. After filtering and concentrating under reduced pressure, the crude product was converted into a fumarate salt (0.86 g), mp 192–195° dec. Further recrystallization (MeOH–EtOAc) gave 0.70 g (61.5%) of the pure fumarate salt of metaraminol, mp 199–200° dec, $[\alpha]^{25}D$ − 22.3° (*c* 2, H_2O). This product was identical by mmp and nmr with an authentic sample of metaraminol fumarate, mp 200–201° dec, prepared from metaraminol.

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Agonists–Antagonists Derived from Desomorphine and Metopon

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N-Phenethyl, -3-methyl-2-butenyl, and -cyclopropylmethyl derivatives (**3b, c**; **4c, d**; and **5a, b**) of normetopon, nordesomorphine, and 5-methyldihydronormorphine (**3a**, **4b**, and **5**, R = H) have been synthesized and evaluated for analgetic activity (mice) as well as for physical dependence capacity and properties of antagonism (monkeys). Marked separation of favorable and undesirable pharmacologic properties has been achieved in some instances.

It is well documented that the substitution of such radicals as allyl, 3-methyl-2-butenyl, and cyclopropylmethyl for Me on the N of morphine, levorphanol, and certain 6,7-benzomorphans confers a combination of agonist (analgetic) and antagonist properties that renders these molecules much less prone to abuse without markedly impairing their analgetic effectiveness.[1] Similar substitution of phenethyl is known to increase analgetic potency five- to tenfold with some decrease in abuse liability.[1,2] Consequently, we wish to report the preparation and some pharmacologic properties of *N*-3-methyl-2-butenyl- and -cyclopropylmethylnordesomorphine (**4c, d**); *N*-3-methyl-2-butenyl- and -phenethylnormetopon (**3c, b**); and *N*-cyclopropylmethyl and -phenethyl derivatives (**5a, b**) of the corresponding 6-carbinol. Desomorphine (**4a**)[3] was chosen as a base structure, because it is 10 times more potent than morphine with a rapid onset of action;[4] metopon (**1**)[5] is 3 times as active as morphine after parenteral administration and is very effective orally.[1,4,5]

Nordesomorphine (**4b**), the starting material for **4c, d,** was obtained in 20–30% yield by demethylation of the *O*-acetyl derivative of **4a** by either the von Braun method[6] or with diethyl azodicarboxylate.[7] Reaction of **4b** with cyclopropylcarbonyl chloride followed by reduction of the resultant amide with LAH gave **4d**.[8] Compound **4c** resulted from direct alkylation[9] of **4b** with 1-bromo-3-methyl-2-butene.

(1) E. L. May and L. J. Sargent in "Analgetics," G. deStevens, Ed., Academic, New York, N. Y., Chapter 4, 1965.

(2) N. B. Eddy and E. L. May, "Synthetic Analgesics," Part II B, Pergamon Press, Ltd., Oxford, 1966, p 155 ff.

(3) L. F. Small, K. C. Yuen, and L. K. Eilers, *J. Amer. Chem. Soc.*, **55**, 3863 (1933). This compound is also known as dihydrodesoxymorphine-D and was supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

(4) N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. W. H. O.*, **17**, 569 (1957).

(5) L. F. Small, H. M. Fitch, and W. E. Smith, *J. Amer. Chem. Soc.*, **58**, 1457 (1936); G. Stork and L. Bauer, *ibid.*, **75**, 4373 (1953).

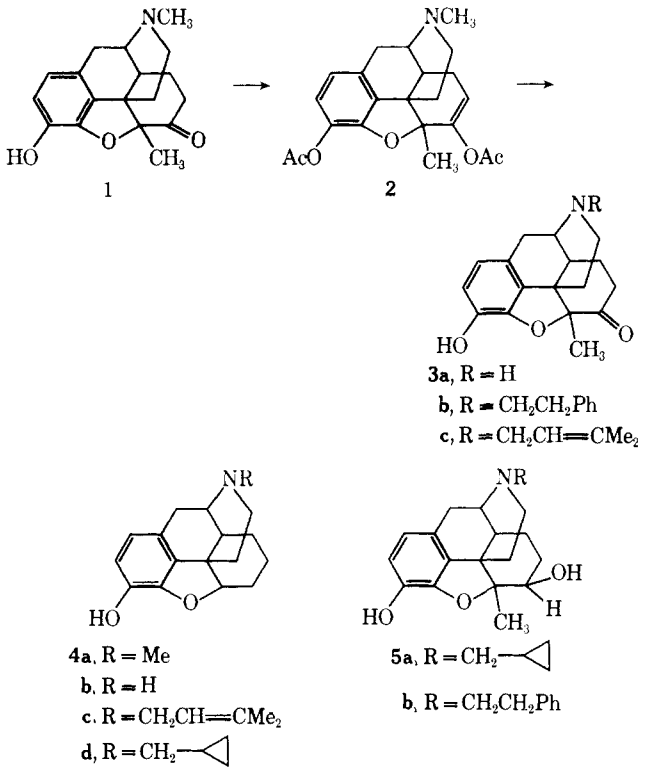
(6) J. Von Braun, *Ber.*, **47**, 2312 (1914).

(7) A. Pohland and H. R. Sullivan, U. S. Patent 3,342,824 (Sept 19, 1967).

(8) This is essentially the method of M. Gates and T. Montzka, *J. Med. Chem.*, **7**, 127 (1964).

(9) Procedure of S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *ibid.*, **7**, 123 (1964).

Chart I



Products **5a**, **5b**, and **3c** were prepared similarly from 5-methyldihydromorphinone (metopon, **1**) *via* diacetate, **2**, and nor compound, **3a**. Oxidation of the 6-carbinol function of **5b** to give carbonyl compound **3b** was achieved in modest yield through the use of dicyclohexylcarbodiimide (DCC) in DMSO.[10]

Pharmacology.—In Table I are given analgetic activities,[11] physical dependence capacities,[3,12] and antagonistic potencies[13] for **1**, **3**, **4**, and **5** along with morphine as the standard. Secondary amines, **3a** and **4b**, have surprisingly good analgetic activity compared with morphine, but **4b** also has high physical dependence capacity (PDC). The pentazocine-like[1,2,9] (*N*-dimethylallyl) structures **3c** and **4c** *do not* exhibit nalorphine-like (antagonistic) properties. In fact metopon derivative **3c**, will completely support a morphine dependence in monkeys at a relatively low dose; **4c** has no PDC to 4 mg/kg, but gives partial suppression of abstinence at 8 mg/kg. Both are strong analgetics. Surprising, too, is the lack of antagonistic activity of the structurally cyclazocine-like[1,2,8,9] dihydromorphine derivative, **5a**, which has marginal analgetic activity. On the other hand, *N*-cyclopropylmethylnordesomorphine, **4d**, is cyclazocine-like in antagonistic potency but is a much stronger analgetic than is cyclazocine in the hot-plate method.[2] Phenethyl derivatives, **3b** and **5b**, very strong analgetics, will completely suppress morphine abstinence only at a dose which is 15–30 times the mouse analgetic dose, reminiscent of phenazocine.[1,2] A final interesting point to emphasize is that **4c** and **4d**, comparable to morphine in analgetic potency, have little or *no* PDC, unusual for morphine-type structures.

Table I
Pharmacologic Properties of N-Substituted Derivatives of Nordesomorphine (**4b**) and Normetopon (**3a**)

Compd[a]	ED_{50} (mice)[b] mg/kg, sc	Physical dependence[c] capacity	Antagonistic act.[c]
4a	0.2[d]	High[e]	No
4b	2.2	High[f]	No
4c	1.1	Intermediate[g]	No
4d	4.5	No	Yes[h]
1	0.5[d]	Yes[i]	No
3b	0.06	High[j]	No
5b	1.0	High[k]	No
3a	2.7		
5a	27.0	No[l]	No
3c	2.0	High[m]	No
Morphine	1.2	High[n]	No

[a] Administered as HCl salts in water unless otherwise noted. [b] See ref 11. [c] See ref 12, 13. [d] See N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. W. H. O.*, **14**, 353 (1956), and ref 11b. [e] Determined only for man; ibid, **17**, 569 (1957). [f] Complete suppression of abstinence at 8 mg/kg. [g] To 4 mg/kg (free base dissolved in dil HCl), no suppression; partial suppression at 8 mg/kg. [h] Twice as potent as nalorphine. [i] About three times as potent as morphine. [j] As HBr salt. [k] Nearly complete suppression at 32 mg/kg as the HBr salt. [l] Moderate to severe signs of CNS stimulation from 0.1 to 1.6 mg/kg (as HBr salt). [m] Complete suppression plus sedation at 8 mg/kg. [n] Stabilization dose 3 mg/kg (as sulfate salt).

(10) *Cf.* A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **89**, 2697 (1967), for a leading reference.

Experimental Section

Melting points (capillary) are corrected. Analytical figures for the elements indicated were within ±0.4% of the theoretical values and were determined by the Section on Instrumentation and Analytical Services of this laboratory. Ir spectra were confirmatory of the structures shown.

Nordesomorphine (4b) Hydrochloride.—A mixture of 20 g of **4a**,[3] 60 ml of Ac_2O, and 1 ml of C_5H_5N was warmed to solution and poured onto ice. After 2.5 hr of stirring, NH_4OH was added (cooling) in excess. The liberated *O*-acetyl derivative (24 g) was dried in $CHCl_3$ and N-demethylated with 8 g of BrCN in the usual way[6,14] to give 4.5 g of **4b**·HCl mp >315° (from MeOH–Me_2CO, charcoal). *Anal.* ($C_{16}H_{19}NO_2$·HCl) C, H.

The yield of **4b** was not improved when diethyl azodicarboxylate[4] was used instead of BrCN.

***N*-Cyclopropylmethylnordesomorphine (4d) Hydrochloride.**—A mixture of 1.9 g of **4b** (from the HCl salt with dil NH_4OH), 14 ml of Et_3N, 80 ml of CH_2Cl_2, and 2.1 g of cyclopropylcarbonyl chloride[15] was refluxed for 15 hr,[8] shaken with dil HCl, then H_2O, and dried (K_2CO_3). Evaporation of the CH_2Cl_2 gave a residue which crystallized from Et_2O in a yield of 2.5 g, mp 130–134°. This (*O*,*N*-dicarbonyl compound) was stirred in 20–30 ml of dry Et_2O while adding dropwise, 23 ml of 1.3 *M* ethereal LAH. After 1–2 hr of stirring and refluxing 10 ml of EtOAc was added carefully followed by 30 ml of saturated ammonium tartrate and 75 ml of CH_2Cl_2. Filtration, drying, and evaporation left 2 g of oily base which was acidified (HCl gas) in Me_2CO containing a little MeOH; yield of **4d**·HCl, 1.3 g, mp 274–276°, after recrystallization from MeOH–Me_2CO. *Anal.* ($C_{20}H_{25}NO_2$·HCl) C, H, Cl.

***N*-3-Methyl-2-butenyldesomorphine (4c).**—One gram of **4b**·HCl, 1.5 g of $NaHCO_3$, 0.8 g of 1-bromo-3-methyl-2-butene,[16] and 14 ml of DMF were refluxed for 15 hr, cooled, and

(11) Determined by the hot-plate method: (a) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); (b) see also A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

(12) G. A. Deneau, J. E. Villarreal, and M. H. Seevers, Addendum 2, Minutes of the 28th and 30th Meetings of the Committee on Problems of Drug Dependence, 1966, 1968; and J. E. Villarreal, personal communication.

(13) J. E. Villarreal, private communication.

(14) H. Rapoport and M. Look, U. S. Patent 2,890,221 (June 9, 1959); *Chem. Abstr.*, **54**, 612 (1960).

(15) Purchased from K & K Laboratories, Inc.

(16) H. Staudinger, W. Kreis and W. Schilt, *Helv. Chim. Acta*, **5**, 750 (1922). We are grateful to Dr. Noel Albertson, Sterling-Winthrop Research Institute for helpful hints in preparing this material.

filtered and the filtrate evaporated to dryness *in vacuo*. Trituration of the residue in Et_2O, filtration, shaking the filtrate with 3 portions of dil HCl in excess, basification of the combined HCl extracts, and drying the liberated base in Et_2O gave 0.6 g of **4c** (needles), mp 166–166.5° (from Me_2CO). *Anal.* ($C_{21}H_{27}NO_2$) C, H.

3-Acetyl-5-methyldihydromorphinone Enol Acetate (2).—5-Methyldihydromorphinone (1, 16.1 g),[5] 225 ml of Ac_2O, and 15 g of fused NaOAc were heated under reflux for 6 hr. Concentration *in vacuo* left an oily residue which was treated with ice–NH_4OH and extracted with Et_2O. Drying (Na_2SO_4) and evaporation of the Et_2O left 9.6 g of pale yellow **2**, mp 161–163°. Sublimation (160–165°, 0.1 mm) and recrystallization (Et_2O) of the sublimate gave pure **2**, mp 171–173°. *Anal.* ($C_{22}H_{25}NO_5$) C, H. During 48 hr 3.9 g of 1 separated from the dark NH_4OH solution above.

5-Methyldihydronormorphinone (3a).—To 7.1 g of **2** in 45 ml of $CHCl_3$, 2.7 g of BrCN in 45 ml of $CHCl_3$ was added during 30 min. After refluxing for 3.5 hr, solvent was evaporated. The sirupy residue and 140 ml of 6% HCl were refluxed for 18 hr. Addition of a slight excess of 12 *M* NH_4OH to the ice-cooled solution yielded 4.4 g of crude **3**. Recrystallization from 95% EtOH afforded 3.4 g (64%) of minute, colorless prisms, mp >300°. *Anal.* ($C_{17}H_{19}NO_3$) C, H.

***N*-Phenethyl-5-methyldihydronormorphine (5b).**—To 2.6 g of **3a**, 120 ml of CH_2Cl_2, and 18.5 ml of Et_3N was added dropwise during 15 min (stirring), 4.2 g of phenylacetyl chloride. The system was refluxed overnight, cooled, washed with cold 1 *N* HCl then H_2O, dried (K_2CO_3), and concentrated *in vacuo* to 4.5 g of pale yellow foam. This bis-*O*,*N*-phenylacetyl derivative in 115 ml of Na-dried THF was added gradually to 24 ml of 1.3 *M* ethereal LAH. The mixture was stirred at room temperature for 24 hr. After careful addition of 14 ml of EtOAc and 200 ml of saturated ammonium tartrate, the mixture was stirred for 1.5 hr. The organic phase was separated and the aq phase extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation of the combined organic solutions to dryness gave 4.1 g of yellow sirup. This sirup in 150 ml of CH_2Cl_2 was extracted with several portions of 1.5 *N* HCl. The combined extracts were washed with Et_2O and basified (ice-cold) with 12 *M* NH_4OH to give, after drying (Na_2SO_4) in Et_2O, 1.8 g of **5b** which was twice evaporatively distilled at 180–190° (0.1 mm). *Anal.* ($C_{25}H_{29}NO_3$) C, H, For pharmacologic testing, **5b** was converted into the hydrobromide with ethereal HBr. The salt was purified by digesting in Me_2CO and recrystallizing from *i*-PrOH–Et_2O, mp 292–295° dec.

***N*-Phenethyl-5-methyldihydronormorphinone (3b).**—Crystalline orthophosphoric adid (0.7 g) was added to a solution of 1.7 g of **5b** and 2.7 g of DCC in 12 ml of DMSO. The mixture was shaken and left at room temperature for 20 hr. The resultant semisolid *brei* was treated with 50 ml of CH_2Cl_2, and the insoluble material was collected and again triturated in 25 ml of CH_2Cl_2. The combined filtrates were repeatedly extracted with 30-ml portions of 2 *N* HCl to a negative Mayer's test. The combined extracts were washed with Et_2O, cooled, basified with 12 *M* NH_4OH, and extracted. After drying and removal of solvent, 0.4 g of a colorless tacky solid (crop I) remained. A small sample was twice evaporatively distilled at 180–190° (0.1 mm) and the clear, colorless glass analyzed; $\lambda_{max}^{CHCl_3}$ 5.8 μ. *Anal.* ($C_{25}H_{27}NO_3$) C, H. The base crystallizes in small, colorless plates (solvated) from 60% EtOH, mp 120–125° (froth). An additional 0.4 g (Crop II) of **3b** was obtained by extracting the CH_2Cl_2-insoluble 1,3-dicyclohexylurea (filter cake above) with a hot AcOH–H_2O (1:2) mixture and basification of the ice-cold extracts. The ir spectrum of this material was identical with that of crop I.

The hydrobromide was prepared by adding ethereal HBr (to faint, permanent acidity) to a solution of **3b** prepared by dissolving **3b** in the minimum of hot *i*-PrOH, cooling, and diluting with 10 volumes of dry Et_2O. The supernate was decanted, and the precipitate was washed with dry Et_2O (by decantation) then collected. This solid was dissolved in a large vol of boiling Me_2CO. The solution was filtered and concentrated to a small vol when the **3b**·HBr separated; mp 309–312° dec. The analytical sample (from abs EtOH) melted at 313–315° dec. *Anal.* ($C_{25}H_{28}BrNO_3$) Br.

3,*N*-Dicyclopropylcarbonyl-5-methyldihydronormorphinone.—As described in the preparation of **4d**, 3.5 g of **3a**, 3.7 g of cyclopropylcarbonyl chloride, 24 ml of Et_3N, and 130 ml of CH_2Cl_2 gave 5.3 g of solid which, after sublimation at 195–200° (0.1 mm) and recrystallization from EtOAc-Et_2O, melted at 195–196°. *Anal.* ($C_{25}H_{27}NO_5$) C, H.

***N*-Cyclopropylmethyl-5-methyldihydronormorphine (5a).**—The above diacyl derivative (5.2 g) in 140 ml of dry THF was added gradually to 50 ml of 1.3 *M* ethereal LAH. As described in the preparation of **5b**, 3 g of crude **5a** was obtained. It was recrystallized by dissolving 0.2 g in 75 ml of boiling Et_2O, filtering, concentrating to a small vol and adding ligroin (bp 30–60°) to faint turbidity. After 48 hr the crystals of **5a**, mp 157–159°, were collected. *Anal.* ($C_{21}H_{27}NO_3$) C, H.

Hydrobromide of 5a.—Crude **5a** (2.1 g) in 50 ml of dry Et_2O was treated with a slight excess of ethereal HBr. The initial precipitate gave way to a gel which, after removal of the supernate, crystallized when rubbed with a few drops of H_2O. This solid was dissolved in 50 ml of hot 95% EtOH (Norit), filtered, and concentrated *in vacuo* to *ca.* 20 ml. Dilution with 1 vol of dry Et_2O and seeding initiated crystallization. Dropwise addition of Et_2O was continued to faint turbidity. After 15 hr, 2.1 g of cream-colored hydrobromide, mp 240–242°, dec, was obtained. For analysis it was recrystallized again (95% EtOH–Et_2O) and dried to constant weight (100°, 0.1 mm). *Anal.* ($C_{21}H_{28}BrNO_3$) C, H, Br.

***N*-3-Methyl-2-butenyl-5-methyldihydronormorphinone (3c).**—1-Bromo-3-methyl-2-butene (0.55 g), 1.05 g of **3a**, 0.63 g of $NaHCO_3$, and 20 ml of DMF were refluxed for 4.5 hr and filtered. The filter-cake was washed with warm EtOH and the combined filtrates concentrated *in vacuo* to a brown sirup which was triturated in four 60-ml portions of boiling Et_2O. The combined extracts were treated with Norite and concentrated to a thick yellow sirup which crystallized during 24 hr. This solid was triturated twice in small portions of dry, ice-cold Et_2O and dried—0.75 g, mp 215–217°. A sample was sublimed at 190–200° (0.1 mm). Recrystallization of the sublimate from MeOH gave minute prisms, mp 218–220°. *Anal.* ($C_{22}H_{27}NO_3$) C, H. For pharmacologic testing, the hydrochloride was prepared with ethereal HCl; microcrystalline powder, mp 205–208° (froth).