separated by chromatography on silica gel using hexane–ethyl acetate. Hydrolysis of **20a** afforded **21a** as a colorless solid which was recrystallized from acetone–hexane to give needles, mp 206–208°.

The ir spectrum shows absorption at 3600, 1734, and 1713 cm^{-1}. The NMR spectrum shows three-proton singlets at δ 0.90 and 1.25 and a broad one-proton signal at δ 3.70. Anal. ($C_{19}H_{28}O_3$) C, H.

4α,6-Cyclo-5β-androstane-3,17-dione (22). The tosylate **21b** was prepared in the usual manner as a white foam. To a solution of **21b** (1.40 g, 3.16 mmol) in 100 ml of *tert*-butyl alcohol was added 3.2 ml of a 1.0 *M* solution of potassium *tert*-butoxide. The solution was stirred for 30 min and worked up in the usual manner to give 0.90 g of a pale yellow solid. Two recrystallizations from ethanol afforded 0.65 g (72%) of colorless crystals, mp 195–197°.

The ir spectrum shows carbonyl absorption at 1730 and 1679 cm^{-1}. The NMR spectrum has three-proton singlets at δ 0.85 and 1.21. Anal. ($C_{19}H_{26}O_2$) C, H.

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Synthesis and Pharmacology of 2,9α-Dimethyl-2'-hydroxy-6,7-benzomorphan

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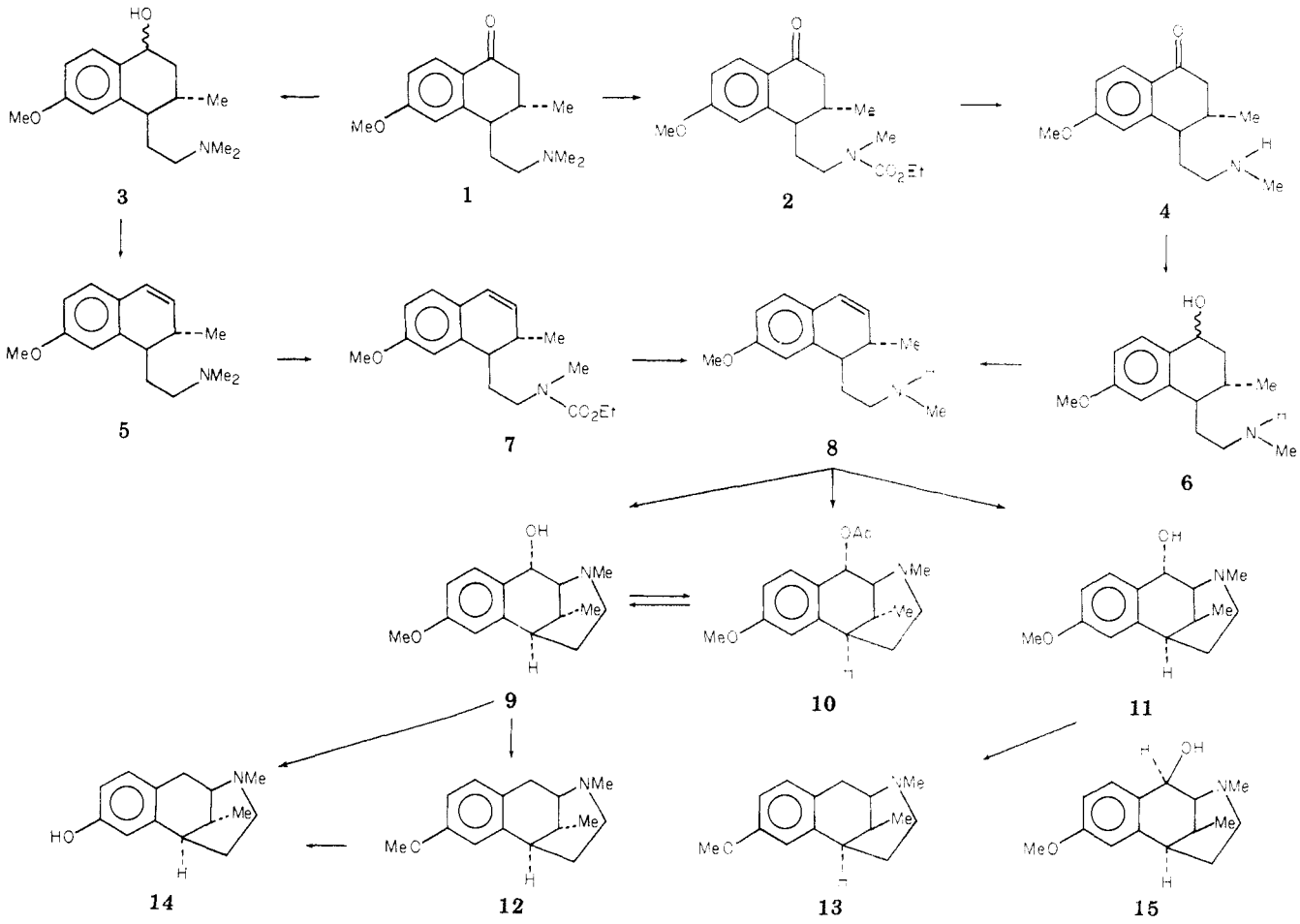
2,9α-Dimethyl-2'-hydroxy-6,7-benzomorphan (14) has been synthesized in six to seven steps from *trans*-3,4-dihydro-4-(2-dimethylaminoethyl)-6-methoxy-3-methyl-1(2*H*)-naphthalenone (1). The key reaction of the sequence was mercuric acetate cyclization of *trans*-1,2-dihydro-1-(2-methylaminoethyl)-7-methoxy-2-methylnaphthalene (8) which gave a mixture of 9α-methyl-8α-hydroxy-6,7-benzomorphan (9, 49%), the corresponding acetate (10, 13%), and the 9β-methyl-8α-hydroxy-6,7-benzomorphan (11, 5%). In the presence of Et_3N, the yields were 16, 37, and 0%, respectively. Structural assignments are based on ir, NMR, and mass spectral data and on chemical conversions.

Recently,[2] we reported that cyclization of 2,3-*trans*-3,4-*cis*-2-bromo-3,4-dihydro-4-(2-dimethylaminoethyl)-6-methoxy-3-methyl-1(2*H*)-naphthalenone gave 2,9β-dimethyl-2'-methoxy-8-oxo-6,7-benzomorphan methobromide from which 2,9β-dimethyl-2'-hydroxy-6,7-benzomorphan was obtained. The corresponding 2,3-cis-3,4-trans isomer gave, instead of the expected 9α-methylbenzomorphan methobromide, 4-(2-dimethyl-

Scheme I



aminoethyl)-6-methoxy-3-methyl-1-naphthol.[2] The synthesis of 2,9α-dimethyl-2'-hydroxy-6,7-benzomorphan (**14**)[3] by an alternate route starting from *trans*-3,4-dihydro-4-(2-dimethylaminoethyl)-6-methoxy-3-methyl-1(2*H*)-naphthalenone (**1**)[2] has now been achieved.

Chemistry. The key intermediate, *trans*-1,2-dihydro-1-(2-methylaminoethyl)-7-methoxy-2-methylnaphthalene (**8**), was best prepared (overall yield 41%) by treatment of **1** with $ClCO_2Et$, hydrolysis of the resultant urethane (**2**) to **4** with 12 *M* HCl, reduction of **4** to **6** ($LiAlH_4$), and dehydration of **6** with $ClCO_2Et$ in CH_2Cl_2. Compound **8** was obtained from **1** in 19% overall yield in a slightly altered sequence as shown at the left of Scheme I (**1** → **3** → **5** → **7** → **8**). The low-yield step in this case was in the hydrolysis (KOH-*n*-BuOH) of urethane **7**. When 12 *M* HCl was used instead of KOH, polymerization took place.

Treatment of **8** with $Hg(OAc)_2$ in THF-H_2O[4] gave the 9α-methyl-8α-hydroxy-6,7-benzomorphan **9** (49%), the corresponding acetate **10** (13%), and the 9β-methyl-8α-hydroxy isomer **11** (5%). When Et_3N was used in the cyclization medium, the yields of **9** and **10** were 16 and 39%, respectively, and no **11** was detected. Evidently, inversion (by allylic rearrangement)[5] at C-2 of **8** to give the 5% of **11** isolated in the first instance is inhibited by base. Compounds **9** and **10** were interconvertible.

$$9 \underset{\text{NaOMe–MeOH}}{\overset{Ac_2O}{\rightleftharpoons}} 10$$

Treatment of **9** with 50% HI-AcOH and red P (reflux) gave 36% of desired benzomorphan **14**, which was better prepared (70% overall yield) by reduction of **9** (H_2, Pd, $HClO_4$, AcOH) to **12** and subsequent hydrolysis (refluxing 48% HBr). Compound **11** was converted to the known 2,9β-dimethyl-2'-methoxy-6,7-benzomorphan **13** (Pd/C, $HClO_4$, AcOH).

The mass spectra of **9** and **11** were similar to the spectrum of 2,9β-dimethyl-8β-hydroxy-2'-methoxy-6,7-benzomorphan (**15**).[2] However, in **9**, **12**, and **14**, the ratios of the relative intensities of *m/e* 84 to 110 were higher than those for **11** and **15** and corresponding 9β isomers in accordance with the findings of Vaughan and Beckett.[6]

NMR spectra served to establish the 8-OH of **9** and **11** and 9-CH_3 of **9**, **10**, **12**, and **14** as α.[3] Thus **9** and **11** showed singlets[7] at 4.98 and 4.87, respectively, for the C-8 H as opposed to a doublet for **15**, δ 5.18 (J = 6 Hz).[2] Methyl signals for C-9 appeared at δ 1.09 (CD_3OD–D_2O), 0.96 ($CDCl_3$), 0.97 (CD_3OD), and 0.89 (CD_3OD) for **9**, **10**, **12**, and **14**, respectively, and at 1.33 ($CDCl_3$) and 1.45 (D_2O) for **11** and 2,9β-dimethyl-2'-hydroxy-6,7-benzomorphan,[2] respectively.[2,8,9] These mass and NMR spectral data leave little doubt about stereochemistry at C-8 and C-9.

Pharmacology. In the hot-plate test for analgesia,[10] the α-isomer **14** has an ED_{50} of 4.3 (3.1–5.9) mg/kg (white, male mice, sc administration) compared with 1.1 for the β isomer[2] (in general, β isomers are 10–30 times more potent than corresponding α compounds).[11] In the same test the ED_{50} for morphine is 1.2 and that of pethidine is 4.5.[10] Like the β compound,[2] **14** is not morphine-like in morphine-dependent monkeys. It precipitates an abstinence syndrome of long duration which is characterized almost entirely by abdominal cramps and irritability on handling without the signs of hyperexcitability or movement within the monkey cage which are normally seen in precipitated abstinence. The 9β analog[2] and the

9-demethyl homolog[12] also have antagonistic properties.

Thus it is apparent that when carbon 5 is unsubstituted (tertiary) analgesic activity is somewhat but not markedly lower than when it contains an alkyl substituent.[11,12] Also, in the three test cases to date, these C-5 nor compounds have mixed agonist–antagonist properties in contrast to *rac*-5-alkyl- and 5,9-dialkyl-6,7-benzomorphans.[11]

Finally, only when the 9-substituent is in β orientation is there a pronounced enhancement of analgesic potency whether C-5 is tertiary[12] or quaternary.[11] It is well known[8,9,13] that a 9β-alkyl substituent hinders reaction of the free electron pair of nitrogen with CH_3^+ but probably not with H^+. Therefore, it is presumed that the "receptor effect" of a 9-alkyl substituent is topological rather than steric (for nitrogen) or electronic.

Experimental Section

Melting points (Hershberg) are corrected. Ir, NMR, and mass spectra were obtained on a Perkin-Elmer 257, Varian Model A-60A (unless otherwise noted), and a Hitachi RMU-6E (70 eV), respectively. Analytical results are indicated only by symbols of the elements and are within 0.4% of theory.

trans-**3,4-Dihydro-6-methoxy-3-methyl-4-(2-methylaminoethyl)-1(2*H*)-naphthalenone (4) Oxalate.** $ClCO_2Et$ (3.6 g, 33.2 mmol) was added to 6.4 g (24.6 mmol) of 1 in 200 ml of C_6H_6 (reflux). After refluxing for 2 hr, the cooled solution was washed with dilute HCl and H_2O, then dried ($MgSO_4$), and evaporated to dryness to give 7.3 g (90%) of oily **2**; from the HCl layer, 360 mg of 1 was recovered.

The crude **2** (7.3 g, 22.9 mmol) and 300 ml of 12 *M* HCl were kept under reflux for 16.5 hr. After evaporation of the solution to dryness in vacuo, the residue was dissolved in H_2O, made basic with K_2CO_3, and extracted with Et_2O. The extracts were dried ($MgSO_4$) and evaporated to give 3.7 g (66%) of 4: ν (liquid) 1675 cm^{-1}. The oxalate (from EtOH) melted at 180–181°. Anal. ($C_{17}H_{23}NO_6$) C, H, N.

trans-**1,2-Dihydro-2-methyl-7-methoxy-1-(2-dimethylaminoethyl)naphthalene (5) Oxalate.** To 1.53 g (5.85 mmol) of 1 (base) in 40 ml of dry Et_2O was added 300 mg (7.9 mmol) of $LiAlH_4$. The mixture was stirred at room temperature for 2 hr, treated with 20 ml of H_2O (ice cooling), and filtered. The filtrate was washed with H_2O, dried, and evaporated to give 1.43 g (93%) of an oil (**3**): ν (liquid) 3450 cm^{-1}.

A mixture of 527 mg (2.0 mmol) of **3**, 20 ml of C_6H_6, and 440 mg (4.1 mmol) of $ClCO_2Et$ was stirred at room temperature for 18 hr and evaporated to dryness in vacuo. The residual oil (547 mg) in H_2O was made basic with 12 *M* NH_4OH and extracted with Et_2O to give, after drying and evaporation of the Et_2O, 450 mg (92%) of oily **5**: mass spectrum M^+ 245, 73 (base, $CH_3CH_2N^+HMe$). The oxalate (from Me_2CO–Et_2O) melted at 121–122°. Anal. ($C_{16}H_{23}NO{\cdot}C_2H_4O_2$) C, H, N.

trans-**1,2-Dihydro-7-methoxy-2-methyl-1-(2-methylaminoethyl)naphthalene (8) Oxalate. A. From 4.** To 3.7 g (15.0 mmol) of 4 (base) in 300 ml of dry Et_2O was added 1.5 g (0.0395 mol) of $LiAlH_4$ at room temperature. The mixture was refluxed for 30 min and treated (ice cooling) with H_2O. The mixture was filtered and the precipitate was washed with THF. Drying and evaporation of the Et_2O–THF filtrate gave 3.5 g (86%) of oily **6** which was converted to 3.7 g (13 mmol) of gummy hydrochloride. To this in 100 ml of CH_2Cl_2 was added 2.1 g (19.4 mmol) of $ClCO_2Et$. The mixture was stirred at room temperature for 2 days and evaporated to dryness in vacuo. The residue, in H_2O, was made alkaline with 12 *M* NH_4OH and extracted with Et_2O. The extracts, after drying and evaporation, gave 2.7 g of **8** which was converted to 3.3 g (80%) of oxalate: mp 168–170° (from EtOH); ir (liquid base) 3320, 1640 cm^{-1}; NMR (oxalate, CD_3OD) δ 0.92 (d, J = 7 Hz, 3, C-2 CH_3), 2.63 (s, 3, NCH_3), ca. 5.9 (m, 1, C-3, H), 6.4 (d, J = 10 Hz, 1, C-4 H); mass spectrum 231 (M^+), 44 (base, $CH_3N^+H{=}CH_2$). Anal. ($C_{15}H_{21}NO{\cdot}C_2H_2O_4$) C, H, N.

B. **From 5.** To 387 mg (1.58 mmol) of **5** in 20 ml of refluxing C_6H_6 was added 220 mg (2.03 mmol) of $ClCO_2Et$. Refluxing was continued for 4 hr. After cooling, H_2O and Et_2O were added. The organic layer was dried and evaporated to give 330 mg of oily **7**: ν 1700 cm^{-1}; mass spectrum 303 (M^+), 116 [base, $CH_2{=}N^+(CH_3)CO_2Et$]. The aqueous layer, after treatment with NH_4OH, gave 120 mg of **5**.

A mixture of 140 mg (0.461 mmol) of **7**, 120 mg (2.1 mmol) of KOH, and 3 ml of *n*-BuOH was refluxed for 40 hr (N_2 atmosphere), evaporated in vacuo, treated with 2 ml of H_2O, and extracted with Et_2O. The Et_2O was shaken with dilute HCl. The HCl extracts were basified with 12 *M* NH_4OH and extracted with Et_2O. Drying and evaporation of the extracts gave 55 mg of oily **8** which was converted to 50 mg of **8** oxalate (34%) (GLC pure), mp 167–168°.

Cyclization of 5. A. In THF–H_2O. To 1.6 g (6.93 mmol) of **8** (GLC pure), 75 ml of THF, and 38 ml of H_2O was added 2.6 g (8.2 mmol) of $Hg(OAc)_2$, and the mixture was stirred at room temperature for 27–45 hr. To this stirred mixture (ice cooling) was added 40 ml of 10% KOH and 1 g (26 mmol) of $NaBH_4$. After 1 hr and Et_2O extraction, 1.6 g of colorless oil was obtained from the dried Et_2O extracts. It was chromatographed on 80 g of SiO_2.

Elution with $CHCl_3$–MeOH (98:2) gave 350 mg (13%) of **8α-acetoxy-2,9α-dimethyl-2'-methoxy-6,7-benzomorphan (10)** which, recrystallized from ligroine (bp 30–60°), had mp 94–95°: ir ($CHCl_3$) 1730, 1650 cm^{-1}; mass spectrum 289 (M^+), 228 (base); NMR ($CDCl_3$, 100 MHz) δ 6.01 (s, 1, C-8 H). Anal. ($C_{17}H_{23}NO_3$) C, H, N.

Elution with $CHCl_3$–MeOH (96:4) gave 155 mg of **2,9β-dimethyl-8α-hydroxy-2'-methoxy-6,7-benzomorphan (11)** which was converted to the oxalate (110 mg, 4.8%), mp 179–180°, after a recrystallization from EtOH: ir (liquid, free base) 3400 (broad), 1620, 1580 cm^{-1}; mass spectrum 247 (M^+, base). Anal. ($C_{15}H_{21}NO_2{\cdot}C_2H_2O_4$) C, H, N.

Elution with $CHCl_3$–MeOH (9:1) gave 960 mg of **2,9α-dimethyl-8α-hydroxy-2'-methoxy-6,7-benzomorphan (9)** which was converted to 960 mg (49%) of the HCl salt: mp 227–228° dec (from EtOH–Et_2O); ir ($CHCl_3$, free base) 3300 (broad), 1615, 1585 cm^{-1}; mass spectrum 247 (M^+), 84 (base). Anal. ($C_{15}H_{21}NO_2{\cdot}HCl{\cdot}0.5H_2O$) C, H, N.

B. **In THF–H_2O–Et_3N.** Similar reaction of **8** (216 mg, 0.935 mmol) with 388 mg (1.22 mmol) of $Hg(OAc)_2$, 120 mg (1.19 mol) of Et_3N, and 10 ml of THF for 45 hr followed by reduction with 100 mg (2.64 mmol) of $NaBH_4$ and 5 ml of 10% KOH gave **10** (37%) and **9** (16%) but no 11. When $HgCl_2$ was used, two dimeric compounds of unknown structure were obtained.

2,9α-Dimethyl-2'-methoxy-6,7-benzomorphan (12) Hydrochloride. Hydrogenolysis of **9** (350 mg, 1.23 mmol) was effected with 160 mg of 10% Pd/C, 80 ml of AcOH, and 3 ml of 60% $HClO_4$ (H_2 55 psi, 40°) during 4 days. Filtration and evaporation of the AcOH in vacuo gave a residue which was dissolved in H_2O and treated with 12 *M* NH_4OH and Et_2O. Drying and evaporation of the Et_2O gave 295 mg of **12** which yielded 273 mg (83%) of the HCl salt, mp 254–256° dec, after a recrystallization from *i*-PrOH–Me_2CO: mass spectrum M^+ 231 (base). Anal. ($C_{15}H_{21}NO{\cdot}HCl$) C, H, N.

2,9α-Dimethyl-2'-hydroxy-6,7-benzomorphan (14) Hydrobromide. A. From 9. Red phosphorus (60 mg, 1.94 mmol), 120 mg (0.485 mmol) of **9**, 4 ml (23.5 mmol) of 50% HI, 8 ml of AcOH, and 2 ml of H_2O were refluxed for 6 hr, cooled, diluted with H_2O, and filtered. The filtrate was concentrated in vacuo, diluted with H_2O, made basic with NH_4OH, and extracted with $CHCl_3$–EtOH (3:1). Drying and evaporation of the extracts left 100 mg of a brown solid which was triturated in *i*-PrOH, filtered, and washed with Me_2CO to give 20 mg of **14**, mp 217–219° dec. The filtrate was evaporated to dryness, and the residue was purified over SiO_2. Elution with $CHCl_3$–EtOH (9:1–8:2) gave an additional 28 mg of 14. Recrystallization of the combined crops from *i*-Pr_2O gave 38 mg (36%) of prisms, mp 225–227°. The hydrobromide (from EtOH–Et_2O) melted at 245–246°: NMR (CD_3OD, free base, 60 MHz) 0.89 (d, J = 7 Hz, 3, C-9, CH_3);[2,8,9] mass spectrum M^+ 217 (base). Anal. ($C_{14}H_{19}NO{\cdot}HBr$) C, H, N.

B. **From 12.** Compound **12** (285 mg, 1.06 mmol) and 9 ml of 48% HBr were refluxed together for 1.5 hr and evaporated to dryness in vacuo. The gummy residue was treated with Me_2CO to give 273 mg (86.4%) of **14**·HBr, mp 243–245° (from EtOH–Et_2O), identical with that described under A.

2,9β-Dimethyl-2'-methoxy-6,7-benzomorphan (13) Oxalate. The oxalate (20 mg, 0.059 mmol) of 11 was hydrogenated (10 mg of 10% Pd/C, 5 ml of HOAc, and 4 drops of 60% $HClO_4$) for 4 days at 40° and 55 psi. After removal of catalyst and HOAc, the

residue, in H_2O, was made basic with 12 M NH_4OH and extracted with Et_2O. Drying and evaporation of the extracts gave 17 mg of oil which was converted to 11 mg (58%) of **13**·oxalate, mp 196–197°, identical with authentic material.[2]

Interconversion of 9 and 10. Compound **10** (10 mg, 0.034 mmol) and the MeOH–NaOMe prepared from 2 mg (0.087 mmol) of Na and 0.2 ml of MeOH were stirred overnight at room temperature. Removal of MeOH in vacuo, solution of the residue in $CHCl_3$, and evaporation of the H_2O-washed, dried $CHCl_3$ solution gave 8 mg of **9**, identical (TLC, ir) with that described above.

Ac_2O (10 drops), 8 mg (0.032 mmol) of **9**, and 1 drop of C_5H_5N were stirred at room temperature for 1 day, poured into ice–H_2O, basified with K_2CO_3, and extracted with $CHCl_3$. The dried, evaporated (in vacuo below 20°) extract gave 10 mg of solid which was recrystallized from ligroine (bp 30–60°) yielding 6 mg of **9**, mp 94–96°, identical with that described above.

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Interferon Inducing Activities of Derivatives of 1,3-Dimethyl-4-(3-dimethylaminopropylamino)-1*H*-pyrazolo[3,4-*b*]quinoline and Related Compounds

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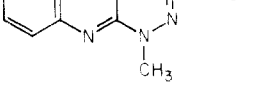
Syntheses and interferon inducing activities are reported for 137 relatives of 1,3-dimethyl-4-(3-dimethylaminopropylamino)-1*H*-pyrazolo[3,4-*b*]quinoline (1). Three different generalized synthetic schemes for the preparation of pyrazolo[3,4-*b*]quinolines are presented and limitations contrasted. Other heterocyclic nuclei containing the 3-dimethylaminopropylamino side chain include pyridine, quinoline, acridine, pyrazolo[3,4-*b*]pyridine, pyrazolo[3,4-*b*][1,8]naphthyridine, pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine, dipyrazolo[3,4-*b*:4',3'-*e*]pyridine, pyrrolo[2,3-*b*]quinoline, isothiazolo[5,4-*b*]quinoline, and pyrido[2,3-*h*]pyrazolo[3,4-*b*]quinoline. Structural requirements for interferon induction in this series are discussed and two of the more active compounds (**172** and **196**) are compared directly with tilorone.

The capacity of an organism to produce interferon in response to infection by viruses or certain protozoan parasites is thought to be an important nonspecific defense mechanism. The interferon system is the earliest component of the host defense to become operative following virus infection and may also play a role in the later stages of recovery.[1] It is now well established that, once evoked, interferon will inhibit the replication of a wide variety of both RNA- and DNA-containing cytopathic and oncogenic viruses.[2] An agent which stimulates release and/or in vivo synthesis of interferon thus has implications for the development of a clinically useful broad-spectrum antiviral drug. Since the discovery of the interferon system in 1957,[3] a number of polymeric substances have been reported which stimulate interferon production, but all of these have limitations in clinical utility.[4] Impetus for the search for a monomeric low-molecular-weight inducer of interferon was provided by reports that 2,7-bis[2-(diethylamino)-ethoxy]fluoren-9-one (tilorone) and congeners induce interferon activity in mice.[5,6] A preliminary report from our laboratories disclosed the interferon-eliciting activity of an entirely different structural type, viz. the pyrazolo[3,4-*b*]quinoline **1** (BL-20803).[7] We now report results



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of a research program designed to (i) define structural features of **1** responsible for the interferon-eliciting activity and (ii) increase potency relative to **1** with a concomitant improvement in therapeutic ratio.

Chemistry. Relatives of **1** which were prepared for biological evaluation are listed in Tables III and IV. Some of the simpler fragment moieties of **1** and related acridines were prepared by literature procedures as indicated in Table III. The amide **65**, which may be viewed as a hydrolytically cleaved form of **1**, was prepared from the corresponding acid chloride and 3-dimethylaminopropylamine. Treatment of **65** with diborane in THF gave the reduced derivative **66**.