(±)-3-(4-Amino-1*H*-pyrrolo[2,3-*d*]pyrimidin-1-yl)-5-(hydroxymethyl)-(1α,2α,3β,5β)-cyclopentanediol (9). Crude **8** from the above reaction was dissolved in 50 mL of ethanol saturated at 5 °C with anhydrous ammonia and heated in a glass-lined stainless-steel vessel at 140 °C for 3 days. After cooling, the reaction solution was evaporated to dryness, the residue was dissolved in water, and the pH was adjusted to 8 with ammonium hydroxide. Cooling to 0–5 °C caused the precipitation of a gray solid, which was collected and allowed to recrystallize from water after decolorization. The white solid was filtered, washed with cold water, and dried under reduced pressure at 100 °C: yield 1.14 g (overall yield from **7**, 28%); mp 243–245 °C dec; UV λ_{max} (pH 1) 275 nm (10.0); UV λ_{max} (pH 7) 273 nm (10.0); UV λ_{max} (pH 13) 272 nm (10.0); ^{1}H NMR (Me_2SO-d_6) δ 1.58 and 2.09 (2 m, 3, H-4′ and cyclopentane ring CH_2), 3.49 (m, 2, 2 H-5′), 3.84 (m, 1, H-3′), 4.18 (m, 1, H-2′), 4.45–5.05 (m, 4, H-1′, 3 OH), 6.55 (d, 1, $J_{5,6}$ = 3.5 Hz, H-5), 6.89 (s, 2, NH_2), 7.24 (d, 1, H-6), 8.04 (s, 1, H-2); after the addition of D_2O, δ 3.83 (dd, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 3 Hz, H-3′), 4.17 (dd, 1, $J_{1',2'}$ = 8.5 Hz, H-2′); ^{13}C NMR (Me_2SO-d_6) δ 29.81 (cyclopentane ring CH_2), 45.00 (C-4′), 58.67 (C-1′), 62.72 (C-5′), 71.75, 75.18 (C-2′, C-3′), 98.58 (C-5), 102.58 (C-4a), 121.91 (C-6), 149.86 (C-7a), 151.06 (C-2), 157.14 (C-4). Anal. ($C_{12}H_{16}N_4O_3$) C, H, N.

Acknowledgment. This investigation was supported by the National Cancer Institute, National Institutes of Health (Grant PO1 CA 34200). The authors thank Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section for analytical and spectral data, Dr. L. L. Bennett, Jr., for the enzyme and cytotoxicity data, and Dr. W. M. Shannon for the antiviral data.

Registry No. **5**, 14052-82-5; **6**, 62138-01-6; **7**, 88767-11-7; **8**, 88767-12-8; **9**, 88767-13-9.

Racemic and Optically Active 2,9-Dimethyl-5-(*m*-hydroxyphenyl)morphans and Pharmacological Comparison with the 9-Demethyl Homologues

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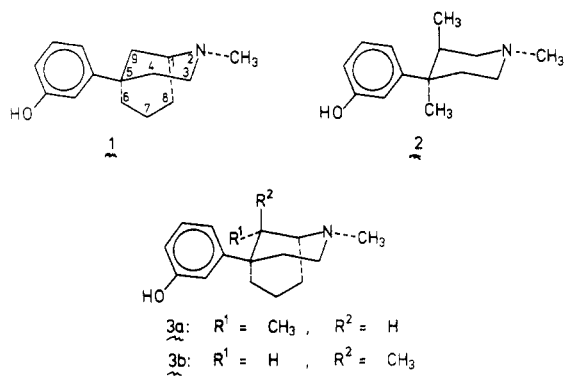
2,9α-Dimethyl-5-(*m*-hydroxyphenyl)morphan (**3a**) has been synthesized from 5-(*m*-methoxyphenyl)-2-methyl-9-oxomorphan (**4**) and resolved into its enantiomers (+)-**3a** and (−)-**3a**. The assigned α-orientation of the 9-methyl group was derived from studies of induced NMR shifts using Eu(fod)$_3$-d_{27}. Compound (+)-**3a** has inappreciable agonist (antinociceptive) activity in mice, and (−)-**3a** shows codeine-like potency in the hot-plate and writhing tests only. The 9-demethyl homologues, (+)-**1** and (−)-**1**, are strong agonists, about as potent as morphine in these tests as well as in the tail-flick assay. The racemic compound **3a** and (+)-**3a**, but not (−)-**3a**, exhibit low-potency, narcotic-antagonist activity in mice (tail-flick test, vs. morphine). All three, however, precipitate abstinence in nonwithdrawn, morphine-dependent rhesus monkeys. Monkey studies with the 9-demethyl homologues confirmed earlier results showing that (+)-**1**, suppressing abstinence in withdrawn animals, has high physical dependence capacity, while (−)-**1** has none. Instead, (−)-**1** precipitates abstinence in nonwithdrawn animals. Studies in rats and isolated organs (guinea pig ileum and mouse vas deferens) and receptor-binding assays confirm the quite different opioid-action profiles of (+)-**1** and (−)-**1**, which thus might interact with different opioid receptors. Catalytic hydrogenation of the methiodide (**7**) of **5** gave, instead of the expected epimer of **3a**, ring-opened compound **8**.

5-(*m*-Hydroxyphenyl)-2-methylmorphan[1] (**1**, Chart I) and its enantinomers[2-4] [(+)-**1** and (−)-**1**] have been shown to possess antinociceptive potency comparable to that of morphine in the mouse hot-plate test. The (+) isomer completely supports morphine dependence in rhesus monkeys, in contrast to the (−) isomer, which, instead, precipitates withdrawal symptoms. A few years ago, Zimmerman et al.[5] demonstrated that 4β-(*m*-hydroxyphenyl)-1,3β,4α-trimethylpiperidine (**2**) is a "pure" antagonist (apparently by virtue of the 3-methyl substituent), unique at that time, for *N*-methyl compounds of the 4-phenylpiperidine series. These observations prompted us to introduce a methyl group into **1** in a position corresponding to the 3-position of **2**. Of the alternatives, i.e., 4- or 9-methyl derivative of **1**, we chose the latter because of the availability of 5-(*m*-methoxyphenyl)-2-methyl-9-oxomorphan[1,2] (**4**, Scheme I) as a suitable intermediate. We now describe the synthesis of 2,9α-dimethyl-5-(*m*-hydroxyphenyl)morphan (**3a**; obtained under the employed experimental conditions) and its resolution into its enantiomers, (+)-**3a** and (−)-**3a**, and present the results of pharmacological studies of these compounds and appropriate reference substances. Also included are additional pharmacological studies and receptor-binding data for (+)-**1** and (−)-**1** of known stereochemistry.[4]

Chart I



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Scheme I

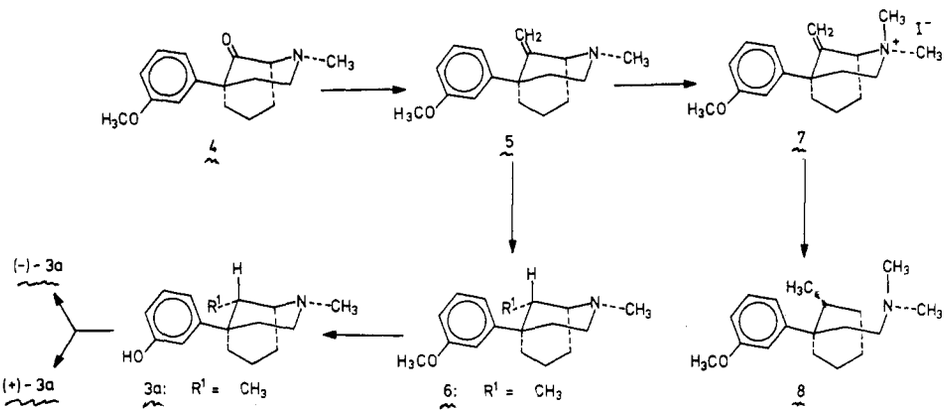

Table I. Narcotic Agonist (Antinociceptive) and Antagonist Activities of Some 5-Phenylmorphans and Appropriate Standards in Mice[a]

compd	antinociceptive act. (ED_{50}, mg/kg sc)			antagonist act. (AD_{50}, mg/kg sc):
	tail flick	PPQ	hot plate	tail flick
6·HBr	I	I	I	I
3a·HCl	I	I[b]	9.3 (6.4-13.5)	5.0 (2.0-12.8)
(+)-3a·HCl	I	I	I[c]	4.5 (1.7-11.8)
(−)-3a·HCl	I	1.9 (0.4-8.5)	10.0 (7.2-13.9)	I
(+)-1·HBr	1.1 (0.7-1.7)	0.5 (0.3-0.9)	0.4 (0.3-0.5)	I
(−)-1·HBr	5.4 (2.1-13.9)	0.9 (0.4-2.0)	1.7 (1.2-2.4)	I
morphine[d]	5.8 (5.7-5.9)	0.2 (0.2-0.3)	1.0 (0.8-1.1)	I
codeine[e]	14.5 (8.1-20.0)	1.4 (0.5-2.5)	6.8 (4.5-10.2)	I
nalorphine[d]	I	0.6 (0.3-1.4)	9.9 (5.7-17.1)	2.6 (0.7-9.8)

[a] I means inactive to 30 mg/kg. [b] 30% at 30 mg/kg. [c] 60% at 50 mg/kg. [d] Sulfate. [e] Phosphate. [f] Hydrochloride.

Chemistry. Using a modification of previously published methods,[6,7] the Wittig reaction of 5-(*m*-methoxyphenyl)-2-methyl-9-oxomorphan (**4**, Scheme I) gave the corresponding 9-methylene compound (**5**), which was isolated as the hydrobromide (**5**·HBr). Hydrogenation of the latter (PtO_2) resulted in absorption of 1 molecular equiv of H_2, yielding 2,9α-dimethyl-5-(*m*-methoxyphenyl)morphan hydrobromide (**6**·HBr) in over 90% yield. No diastereoisomer was detected. That the 9-methyl group occupies the 9α-position[8] (cis orientation of the 9-methyl group and the 1,5-diaxial-fused cyclohexane ring) has been demonstrated by NMR spectroscopy. In $CDCl_3$, the 9-CH_3 signal appears as a doublet centered at δ 0.78 in accordance with an expected diamagnetic shift of about 0.4 ppm due to the anisotropic effect of the phenyl.[9] However, because of the very similar orientations of the 9α- and 9β-methyl groups with respect to the freely rotating 5-phenyl ring (Dreiding models), either methyl group should experience about the same anisotropic effect. Strong evidence of the assigned 9α-position of the methyl group, however, is furnished by data obtained with the lanthanide shift reagent Eu(fod)$_3$-d_{27}.[10] NMR shifts induced by such reagents (Δ_{Eu}) can be calculated from $\Delta_{Eu} = (3\cos\theta - 1)/r^3$, where r is the separation of the nucleus from the paramagnetic ion, and θ is the angle between the vector joining the metal atom to the nucleus and the principal magnetic axis of the molecular complex.[11] With data from Dreiding models, the predicted induced shifts are Δ_{Eu} 9β-CH_3 > Δ_{Eu} N-CH_3 > Δ_{Eu} 9α-CH_3. As noted in the Experimental Section, Δ_{Eu} has been found to be 1.27 ppm for N-CH_3 and 0.67 ppm for 9-CH_3. These findings leave little doubt that the 9-methyl compound obtained from the hydrogenation of **5** has a 9α-orientation, as shown in **6**.

Attempts to obtain the corresponding 9β-CH_3 stereoisomer with 15–17% ethanolic HCl or HBr or AcOH as solvent in hydrogenations with PtO_2 or Pd/C at atmospheric pressure or 30 psig gave also **6** and/or starting material (**5**). When the methiodide (**7**) of **5** was hydrogenated (PtO_2, EtOH), 2 molecular equiv of H_2 was consumed to give N-ring-opened compound **8**. Presumably, to relieve steric crowding, the initially formed 9β-methyl compound (9-methyl group oriented toward the quaternary nitrogen) underwent Hoffmann elimination, followed by hydrogenation of the resulting olefin, to give **8**.

Conversion of **6** to the corresponding phenolic compound **3a** with HBr was routine. Optical resolution of **3a** into its enantiomers (+)-**3a** and (−)-**3a** was accomplished with di-*p*-toluoyl-D- and -L-tartaric acids.

Pharmacology. Opioid agonist activity was studied in the antinociceptive tail-flick[12] (TF), *p*-phenylquinone-writhing[12] (PPQ), and hot-plate[13] (HP) assays in mice; opioid antagonist activity (vs. morphine) was studied in the TF antagonism[12] test. The results obtained with the 5-phenylmorphans and appropriate standards are shown in Table I.

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The intermediate **6** exhibited neither agonist nor antagonist properties. The racemic 9α-methyl compound (**3a**) is an agonist–antagonist, about as potent as nalorphine as an agonist in the HP test and approximately half as potent as the standard as an antagonist in the TF antagonism test. Its dextro form [(+)-**3a**] shows about the same antagonist potency but lacks agonist activity in all three assays, being perhaps a "pure" antagonist. The levo counterpart [(−)-**3a**], on the other hand, has about the same agonist potency as the racemic compound (**3a**) in the HP test and is active in the PPQ test but devoid of antagonist activity in the TF-antagonism assay. Thus, (−)-**3a** is an agonist of codeine-like potency. Although (−)-**3a** seems to have a disproportionately high agonist potency (low ED_{50}) in the PPQ test considering the weak agonist activity of the racemic compound (**3a**), we point out that the confidence limits for the former are rather broad and, thus, the dose–response curve shallow. However, these findings might also reflect a counteraction between the agonistic (−)-**3a** and the antagonistic (+)-**3a**, resulting in the observed exceedingly decreased agonist potency of the racemic compound, **3a**. In morphine-dependent rhesus monkeys, neither racemic **3a** nor its enantiomers (+)-**3a** and (−)-**3a** suppressed abstinence in withdrawn animals at any dose tested.[14] Thus, these compounds have no morphine-like physical dependence capacity in this animal model. On the contrary, all three of them precipitated abstinence in nonwithdrawn, morphine-dependent monkeys, being $^1/_{80}$ to $^1/_{200}$ as potent as the reference standard, naloxone.[15]

The enantiomeric 9-demethyl homologues [(+)-**1** and (−)-**1**] are strong agonists, showing activity in all three antinociceptive assays with potencies comparable to morphine and lacking antagonist properties. In morphine-dependent monkeys, (+)-**1** substituted for morphine, whereas (−)-**1**, instead, precipitated abstinence.[2,3,14] Similarly, in rats made dependent on morphine by continuous infusion for 6 days,[16] (+)-**1** nearly suppressed withdrawal signs, while (−)-**1** did not readily substitute for morphine. Moreover, (+)-**1** showed high receptor-binding affinity with an EC_{50} of 85.7 nmol in the presence and an EC_{50} of 56.6 nmol in the absence of NaCl (sodium response ratio 1.51). The corresponding data for (−)-**1** are 443 and 487 nmol, respectively (sodium response ratio 0.94). Finally, (+)-**1** resembled morphine in the guinea pig ileum (GPI) and in the mouse vas deferens (MVD), whereas (−)-**1** had only slight activity in the GPI and low activity in the MVD.[15]

Two points in the above-described data are worthy of emphasis. Firstly, the introduction of a 9α-methyl group into the strong antinociceptive agents (+)-**1** and (−)-**1** affords compounds [(+)-**3a** and (−)-**3a**] with markedly decreased agonist potency. On the other hand, the structural change from (+)-**1** to (+)-**3a** induces antagonist activity in the TF-antagonism test, and the change from (−)-**1** to (−)-**3a** does not affect antagonist activity in the monkey. Thus, the overall trend of this structural alteration is a decrease of agonist and an increase of antagonist properties. This parallels the results of Zimmerman et al.[5] in the 4-phenylpiperidine series, where introduction of a methyl substitutent into the comparable 3-position surprisingly yielded potent, pure antagonists. Their 3β-methyl compound (**2**) was roughly 40 times more potent than its 3α-methyl stereoisomer, which was still about half as potent as nalorphine in mice. Thus, in the 5-phenylmorphan series, the unknown 9β-methyl compound (**3b**) might also be much more potent as an antagonist than its 9α-methyl stereoisomer (**3a**).

Secondly, (+)-**1** is a potent agonist with morphine-like properties in all respects discussed. The enantiomer [(−)-**1**] is a potent agonist in the antinociceptive assays too, but it is not morphine-like in many other respects. It seems probable therefore, that (+)-**1** and (−)-**1** interact with different opioid receptors and that optical resolution of **1** has effected a favorable dissociation of opioid properties.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover capillary apparatus. IR spectra (Beckman Acculab 8) are consistent with structures shown. NMR data were obtained with a 60-MHz Hitachi Perkin-Elmer Model R-24; optical rotations were obtained with a Perkin-Elmer 141 polarimeter. Mass and analytical data (values for C, H, and N within ±0.4% of theory) are from the Section on Microanalytical Services and Instrumentation (Dr. David Johnson Chief), National Institutes of Health.

5-(*m*-Methoxyphenyl)-2-methyl-9-methylenemorphan (5) Hydrobromide. To the Wittig reagent,[6,7] prepared from 0.3 g (11.6 mmol) of NaH, 4.5 g (11.6 mmol) of methyltriphenylphosphonium iodide, and 50 mL of dry Me_2SO (N_2 atmosphere, 20 min stirring at room temperature) was added, dropwise during 10 min (stirring), 1.5 g (5.8 mmol) of **4** in 20 mL of dry Me_2SO. The mixture was stirred for 6 h at 45–50 °C (bath temperature, N_2), cooled, poured into ice–H_2O, acidified with 10% HCl, and extracted with 160 mL of Et_2O in four portions. The aqueous layer was made alkaline with NH_4OH and extracted with Et_2O (4 × 30 mL). The combined extracts were washed with 10 mL of H_2O and dried ($MgSO_4$), giving, after evaporation of the Et_2O, 1.2 g of hygroscopic solid, which in Me_2CO with HBr gas gave 1.5 g (78%) of **5**·HBr as colorless needles: mp 199–200 °C after a recrystallization from Me_2CO; NMR ($CDCl_3$) δ 5.33 (s, 2 H, C=CH_2); EIMS, *m/e* 257 (M^+). Anal. ($C_{17}H_{24}BrNO$) C, H, N.

2,9α-Dimethyl-5-(*m*-methoxyphenyl)morphan (6) Hydrobromide.[8] The hygroscopic **5** (ca. 1 g), prepared from 1.3 g (3.9 mmol) of the HBr salt, was hydrogenated (60 mL of MeOH, 0.15 g of PtO_2) for 1 h in a Parr apparatus (25 °C, 30 psig). The filtered solution was evaporated to dryness in vacuo, giving 0.96 g of base, mp 147–148 °C (from Me_2CO), which was converted to the HBr salt (30% HBr–AcOH, Me_2CO, Et_2O). It was recrystallized from Me_2CO–Et_2O, giving colorless needles: mp 228–230 °C; NMR ($CDCl_3$, free base) δ 0.78 (d, 3 H c-9 Me), 2.88 (s, 3 H, *N*-Me), 3.80 (s, 3 H, *O*-Me); NMR [Eu(fod)$_3$, $CDCl_3$] δ 1.45 (d, 3 H C-9 Me, Δ_{Eu} 0.42), 4.15 (s, 3 H, *N*-Me, Δ_{Eu} 1.27), 4.22 (s, 3 H, *O*-Me, Δ_{Eu} 0.42); EIMS, *m/e* 259 (M^+). Anal. ($C_{17}H_{26}BrNO$) C, H, N.

2,9α-Dimethyl-5-(*m*-hydroxyphenyl)morphan (3a) Hydrochloride.[8] The HBr salt of **6** (1.0 g) and 10 mL of 48% HBr were refluxed for 3 h, cooled, poured into ice–H_2O, made alkaline with NH_4OH, and extracted with Et_2O (4 × 30 mL). The combined extracts were washed with H_2O, dried, and evaporated, giving 0.66 g of **7**, mp 199–205 °C (pink melt), and 0.72 g (87%) of the **HCl salt** as colorless needles mp: 193–195 °C after a recrystallization from Me_2CO; EIMS, *m/e* 245 (M^+). Anal. ($C_{16}H_{24}ClNO\cdot H_2O$) C, H, N.

Optical Resolution of 3a. Me_2CO (30 mL), 10 mL of MeOH, and 1.7 g (7 mmol) of **7** were warmed to solution and treated with 2.7 g (7 mmol) of di-*p*-toluoyl-D-tartaric acid. After slight warming, the mixture was filtered, and the flask and filter were washed with 5 mL of Me_2CO. The combined filtrates were concentrated to 10 mL and cooled for 3 h at room temperature and overnight at 0 °C, giving 2.6 g of colorless precipitate. This was recrystallized 4 times from Me_2CO to yield 2.2 g, mp 151–154 °C dec, which was dissolved in 10 mL of saturated saline. The extracts were washed with H_2O (2 × 3 mL), dried ($MgSO_4$), and evaporated, giving 0.8 g (96%) of base (+)-**3a**: mp 175–176 °C after recrystallization from Me_2CO; $[\alpha]^{19}_D$ +49.5° (*c* 1.03, EtOH); EIMS, *m/e* 245 (M^+). Anal. ($C_{16}H_{23}NO$) C, H, N.

The **HCl salt** of (+)-**3a** (from Me_2CO–HCl gas) crystallized from Me_2CO: mp 205–207 °C; $[\alpha]^{19}_D$ +36.9° (*c* 1.02, EtOH). Anal. ($C_{16}H_{24}ClNO$) C, H, N.

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The combined filtrates from the isolation and recrystallization of the above (+)-**3a** di-*p*-toluoyl-D-tartrate were evaporated to dryness in vacuo. The residue was dissolved in 30 mL of H_2O and made alkaline with NH_4OH. Extraction with Et_2O and evaporation of the dried extracts left 0.86 g (3.5 mmol) of base, principally (−)-**3a**, which was warmed to solution with 20 mL of Me_2CO and 5 mL of MeOH containing 1.42 g (3.5 mmol) of di-*p*-toluoyl-L-tartaric acid hydrate. The filtered solution, combined with 5 mL of Me_2CO "washing", was concentrated to 5 mL and cooled overnight at 0 °C, giving 1.8 g of salt. It was recrystallized twice from MeOH, yielding 1.65 g (75%), mp 151–154 °C dec. This was converted to (−)-**3a** (H_2O–NH_4OH–Et_2O) as described in the isolation of (+)-**3a**, giving, after recrystallization from Me_2CO, 0.6 g: mp 175–176 °C; $[\alpha]^{25}_D$ −49.0° (*c* 1.05, EtOH). Anal. ($C_{16}H_{23}NO$) C, H, N.

Methiodide (7) of 5. Base **5** [ca. 1 g, prepared from 1.3 g (3.9 mmol) of HBr salt] in 30 mL of dry Et_2O was treated dropwise with 0.66 g (4.6 mmol) of MeI in 20 mL of dry Et_2O during 10 min at 0 °C. After the mixture was stirred overnight at room temperature, the precipitated **7** was collected and recrystallized from Me_2CO: yield 1.7 g (86%); mp 197–199 °C (colorless needles); NMR (Me_2SO-d_6) δ 3.20 and 3.32, (2 s, 6 H, NMe_2) 4.62 and 5.28 (2 s, 2 H, C=CH_2). Anal. ($C_{18}H_{26}INO$) C, H, N.

Hydrogenation of 7. PtO_2 (0.5 g), 2.0 g (5 mmol) of **7**, and 60 mL of 95% EtOH were shaken together at 25 °C and 30 psig for 12 h and then filtered. The filtrate was evaporated to dryness in vacuo to give 2.0 g of an oil, which was partitioned between 5% HCl and Et_2O. The Et_2O layer was extracted with 5% HCl. The combined aqueous acid layers were washed with Et_2O and made basic with NH_4OH. Et_2O extraction, drying (Na_2SO_4), and evaporation of the Et_2O gave 0.62 g (45%) of what appears to be compound **8**, 1-[2-(dimethylamino)ethyl]-1-(*m*-methoxyphenyl)-2-methylcyclohexane, resulting from absorption of 1 mol of H_2, Hofmann elimination, and absorption of a 2nd mol of H_2. The **HBr salt** of **8** (HBr gas–Me_2CO) crystallized from Me_2CO in prisms: mp 223–224 °C; NMR ($CDCl_3$) δ 0.65 (d, 3 H, *C*-Me), 2.24 and 2.30 (2 s, 6 H, NMe_2), 4.83 (s, 3 H, *O*-Me), 6.70 and 7.35 (m, 4 H, phenyl); EIMS, *m/e* 275. Anal. ($C_{18}H_{30}BrNO$) C, H, N.

Acknowledgment. We are indebted to Dr. Arthur E. Jacobson, National Institutes of Health, for arranging for C, H, and N analyses and mass spectral determinations and for hot-plate data. This research was supported by NIDA Grant DA-00490 and Contract 271-81-3830.

Registry No. (+)-**1**, 28623-81-6; (+)-**1**·HBr, 88588-34-5; (−)-**1**, 28623-84-9; ()-**1**·HBr, 53467-24-6; (±)-**3a**, 88550-29-2; (+)-**3a**, 88550-30-5; (+)-**3a**·HCl, 88550-31-6; (−)-**3a**, 88550-32-7; (−)-**3a**·HCl, 88550-33-8; **4**, 88550-34-9; **5**, 88550-35-0; **5**·HBr, 88550-36-1; **6**, 88550-37-2; **6**·HBr, 88550-38-3; **7**, 88550-39-4; **8**, 88550-40-7; **8**·HBr, 88550-41-8; methyltriphenylphosphonium iodide, 2065-66-9.

Studies on Heterocyclic Compounds. 6.[1] Synthesis and Analgesic and Antiinflammatory Activities of 3,4-Dimethylpyrano[2,3-*c*]pyrazol-6-one Derivatives

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A series of new 1- and 2-substituted 3,4-dimethylpyrano[2,3-*c*]pyrazol-6-one derivatives and 1-substituted 1,6-dihydro-4-methyl-6-oxopyrano[2,3-*c*]pyrazole-3-acetic acids were synthesized and examined for their analgesic and antiinflammatory activities. Most of these compounds showed more prominent analgesic activities than antiinflammatory activities, and this result was similar to that of aminopyrine. Among these compounds, 1,3,4-trimethylpyrano[2,3-*c*]pyrazol-6(1*H*)-one and 2,3,4-trimethylpyrano[2,3-*c*]pyrazol-6(2*H*)-one showed more potent analgesic activity than aminopyrine.

Recently, 3,4-dimethylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (**1**) has been synthesized[1,2] and found to possess analgesic and antiinflammatory activities. However, neither the synthesis nor the biological activity of its N-substituted derivatives has been studied. We therefore carried out the synthesis of a series of N-substituted 3,4-dimethylpyrano[2,3-*c*]pyrazol-6-one derivatives in order to evaluate their biological activities. This report describes the synthetic results and the analgesic and antiinflammatory activities of these derivatives.

Chemistry. N-Alkylation of Compound 1. When compound **1** was treated with NaH in dry DMF, followed by reaction with methyl iodide at room temperature, two products (**3a** and **4a**) were obtained. The relative yield of the two products (**3a** and **4a**) was around 1:2. Based on mass spectra (M^+ *m/e* 178) and elemental analysis, the molecular formulas of both compounds were determined to be $C_9H_{10}N_2O_2$, which indicated that the two products could be isomers of *N*-methyl-3,4-dimethylpyrano[2,3-*c*]-pyrazol-6-ones. A similar result was realized when compound **1** was reacted with methyl iodide in dry DMF in the presence of K_2CO_3 under reflux.

The proposed isomeric products (**3a** and **4a**) could not be distinguished by the IR, UV, mass, and ^1H NMR spectral data (Table I). In order to ascertain the position of the *N*-methyl groups, the application of the method of $^1H\{^1H\}$ nuclear Overhauser effect in ^1H NMR spectroscopy was attempted. Unfortunately, no effect was observed upon the irradiation of the proton signals of the *N*-methyl protons [δ 3.80 (**3a**) and 3.85 (**4a**)]. We then investigated their ^{13}C NMR spectra. As shown in Table II, from the difference of chemical shifts between C-3 [δ 153.46 (**3a**), 150.67 (**4a**)] and C-9 [δ 151.07 (**3a**), 158.09 (**4a**)], the two structures could be tentatively assigned. The assignment was further confirmed by long-range coupling (J_{CNCHn} obtained by employing ^1H-gated decoupling method) between the protons of the *N*-methyl groups [δ 3.80 (**3a**), 3.85 (**4a**)] and C-9. The splittings of the signals of C-9 were quite different between those two isomers. The C-9 signal of compound **3a** is a quartet (J_{CNCH_3}) and that of **4a** is a

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0022-2623/84/1827-0539$01.50/0