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Various 5-Substituted and 2,5-Disubstituted 1,3-Dioxanes, a New Class of Analgesic Agents

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A series of 5-substituted and 2,5-disubstituted 1,3-dioxanes was prepared and evaluated for analgesic activity in mice and rats. Some of the compounds possessed significant analgesic effects; their structure-activity relationships and chemistry are discussed. These compounds represent a unique series of analgesic agents.

The compound 5-benzoyl-5-methyl-1,3-dioxane $(8)^1$ was determined to be an impurity in the Mannich reaction of propiophenone. The acid-catalyzed reaction of phenyl alkyl ketones with formaldehyde will provide compounds such as 8 and 5-benzoyl-1,3-dioxane (6a).² During the course of preparing various derivatives of 6a and 8 for broad pharmacological screening, a new class of analgesics was found.

We wish to report this new class of analgesics which is represented by the following general formula



The substitutents Ar and R are illustrated in Table IV.

Chemistry. Most of the 5-substituted 1,3-dioxanes 4a-t (Table IV) and 2,5-disubstituted 1,3-dioxanes 5a-g (Table IV) were prepared as outlined in Scheme I. The Knoevenagel condensation³ of arylaldehydes with diethyl malonate provided diethyl (arylmethylene)malonates 1a-p (Table I). A Michael addition of secondary amines to



1a-p gave substituted diethyl malonates 2a-t (Table II) in quantitative yields. These products 2a-t were viscous

Table I. Diethyl (Arylmethylene)malonates

| | | $ArCH = C(CO_2C_2H)$ | ₅) ₂ | | |
|------------|--|----------------------|-----------------------------|---|--|
| No. | Ar | Yield, % | Bp (mm), $^{\circ}C$ | $Formula^m$ | |
| 1a | C, H, | 38 | $120 (0.1)^a$ | $C_{14}H_{16}O_4$ | |
| 1b | $2 - C C C_6 H_4$ | 8 | $142(0.7)^{b}$ | $C_{14}H_{15}ClO_4$ | |
| 1c | $3-ClC_{6}H_{4}$ | 16 | $150(0.7)^{c}$ | $C_{14}H_{15}ClO_4$ | |
| 1d | $4 - ClC_{6}H_{4}$ | 53 | $144 (0.7)^d$ | $C_{14}H_{15}ClO_4$ | |
| 1e | 2,4-Cl,C,H, | 43 | 132 (0.05) | $C_{14}H_{14}Cl_{2}O_{4}$ | |
| 1 f | 4-FC, H | 24 | $152 (0.5)^{e}$ | $C_{14}H_{15}FO_4$ | |
| 1g | 3-CH ₃ OC ₆ H ₄ | 42 | $154(0.7)^{f}$ | $\mathbf{C}_{15}\mathbf{H}_{18}\mathbf{O}_{5}$ | |
| 1ĥ | 4-CH ₃ OC ₆ H ₄ | 20 | $162 (0.7)^{g}$ | $\mathbf{C}_{15}\mathbf{H}_{18}\mathbf{O}_{5}$ | |
| 1i | $2 - CH_3C_5H_4$ | 19 | $142(0.7)^{h}$ | $C_{15}H_{18}O_{4}$ | |
| 1j | 3-CH ₃ C ₆ H ₄ | 27 | 138 (0.7) | $C_{15}H_{18}O_{4}$ | |
| 1 k | $4-CH_{3}C_{6}H_{4}$ | 40 | $140(0.7)^{i}$ | $C_{15}H_{18}O_{4}$ | |
| 11 | 3-C, H, ČH, OC, H, | 9 | Oil | $C_{21}H_{22}O_{5}$ | |
| 1m | $4 - C_6 H_5 CH_7 OC_6 H_4$ | 75 | 222(0.1) | $C_{21}H_{22}O_{5}$ | |
| 1n | $2 - C_4 H_4 N$ | 30 | $140(0.05)^{j}$ | $\mathbf{C}_{13}\mathbf{H}_{15}\mathbf{NO}_{4}$ | |
| 10 | $3 - C_4 H_4 N$ | 79 | $150 \ (0.1)^{k}$ | $\mathbf{C}_{13}\mathbf{H}_{15}\mathbf{NO}_{4}$ | |
| 1p | $4 - C_4 H_4 N$ | 45 | $138 (0.05)^l$ | C ₁₃ H ₁₅ NO ₄ | |

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| | | R ₂ | | | | | | | | | | |
|--|---|--|--|--|--|--|--|--|--|--|--|--|
| | $\operatorname{ArCHCH}(\operatorname{CO}_2 \operatorname{C}_2 \operatorname{H}_5)_2$ | | | | | | | | | | | |
| No. | Ar | $\mathbf{R}_{1}, \mathbf{R}_{2}$ | Formula ^a | | | | | | | | | |
| 2a 2b 2c 2d 2e 2f 2g 2h 2i 2j 2k 2l 2n 2o 2p 2q | $\begin{array}{c} C_{e}H_{s}\\ 2\text{-}ClC_{e}H_{4}\\ 3\text{-}ClC_{e}H_{4}\\ 4\text{-}ClC_{e}H_{4}\\ 2,4\text{-}ClC_{e}H_{4}\\ 3\text{-}CH_{3}OC_{e}H_{4}\\ 4\text{-}CH_{3}OC_{e}H_{4}\\ 4\text{-}CH_{3}OC_{e}H_{4}\\ 4\text{-}CH_{3}C_{e}H_{4}\\ 3\text{-}CH_{3}C_{e}H_{4}\\ 3\text{-}CH_{3}C_{e}H_{4}\\ 4\text{-}CH_{3}C_{e}H_{4}\\ 4\text{-}CH_{3}C_{e}H_{4}\\ 4\text{-}CH_{3}C_{e}H_{4}\\ 4\text{-}CH_{3}C_{e}H_{4}\\ 4\text{-}CH_{3}CH_{2}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{2}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{2}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{2}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{2}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{3}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{2}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{4}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{4}OC_{e}H_{4}OC_{e}H_{4}\\ 4\text{-}Ce_{H_{3}}CH_{4}OC_{e}H_{4}\\ 4\text{-}Ce_{$ | CH ₃ ,CH ₃ CH ₃ ,CH ₃ | C ₁₆ H ₂₃ NO ₄ C ₁₆ H ₂₂ ClNO ₄ C ₁₆ H ₂₁ Cl _{NO₄} C ₁₇ H ₂₅ NO ₅ C ₁₇ H ₂₅ NO ₅ C ₁₇ H ₂₅ NO ₄ C ₁₇ H ₂₅ NO ₅ C ₁₃ H ₂₉ NO ₅ C ₁₃ H ₂₉ NO ₅ C ₁₅ H ₂₂ N ₂ O ₄ C ₁₅ H ₂₂ N ₂ O ₄ | | | | | | | | | |
| 2r 2s 2t | C, H, C, H, C, H, | $\hat{C}_{2}H_{s}^{2},\hat{C}_{2}H_{s}$ (CH_{2}) ₄ ^c (CH_{2}) ₂ O(CH_{2}) ₂ ^d | $\begin{array}{c} C_{18}^{19}H_{27}^{2}NO_{4}\\ C_{18}^{18}H_{25}NO_{4}\\ C_{18}^{18}H_{25}NO_{5} \end{array}$ | | | | | | | | | |

^a All compounds were viscous oils and were characterized by NMR. ^b Piperidino. ^c Pyrrolidino. ^d Morpholino.

oils which were characterized by NMR absorption spectra. Reduction of 2a-t with a 70% solution of sodium bis(2methoxyethoxy)aluminum hydride in benzene afforded 2-substituted 1,3-propanediols 3a-t (Table III). An acid-catalyzed condensation of formaldehyde with 3a-tprovided 5-substituted 1,3-dioxanes 4a-t (Table IV). Similarly, the condensation of aliphatic aldehydes or ketones with 3a or 3k gave 2,5-disubstituted 1,3-dioxanes 5a-g (Table IV).

Compounds 4u and 4v were prepared by the respective catalytic hydrogenation of 4l and 4m. The acylation of 4v with acetic anhydride provided 4w. Demethylation of







4a with diethyl azodicarboxylate gave 4x. Compound 4x was alkylated with allyl bromide to provide 4y (Table IV).

Alternatively, 4a can be prepared through an enamine intermediate of 6a. A mixture of 6a and dimethylamine at 0 °C was allowed to react upon addition of titanium tetrachloride.⁴ The resulting enamine was catalytically hydrogenated to yield 4a. The above enamine method was also followed for the preparation of 7 from 6b.⁵ Reduction of 6a with lithium aluminum hydride gave 4z (Scheme II).

Compound 8 was allowed to react with hydroxylamine hydrochloride in pyridine and the oxime of 8 was reduced with lithium aluminum hydride to provide 9. Compound 9 was subjected to the Eschweiler-Clarke modification of the Leuckart reaction to afford 10 (Scheme III).

Two of the biologically more active compounds, 4a and

| Table III. | 2-[(α-Dialk | ylamino)(ar | yl)methyl |]-1,3-pr | opanediols |
|------------|-------------|-------------|-----------|----------|------------|
|------------|-------------|-------------|-----------|----------|------------|

| | | $\mathbf{R}_{\mathbf{N}_{2}}$ | | | | | | | | |
|------------|--|--|-----------|----------|---|---|--|--|--|--|
| | | IN I | | | | | | | | |
| | ArCHCH(CH ₂ OH) ₂ | | | | | | | | | |
| No. | Ar | $\mathbf{R}_{1},\mathbf{R}_{2}$ | Mp, °C | Yield, % | Formula ^a | | | | | |
| 3a | C ₆ H ₅ | CH ₃ ,CH ₃ | 82-83 | 29 | $C_{12}H_{19}NO_{2}$ | _ | | | | |
| 3b | $2-ClC_6H_4$ | CH ₃ ,CH ₃ | Oil | 53 | $C_{12}H_{18}CINO_{2}$ | | | | | |
| 3c | $3-ClC_6H_4$ | CH_3, CH_3 | 90-91 | 55 | $C_{12}H_{18}CINO_{2}$ | | | | | |
| 3d | $4-ClC_{6}H_{4}$ | CH_3, CH_3 | 102-103 | 59 | $C_{12}H_{18}CINO_{2}$ | | | | | |
| 3e | $2,4-Cl_2C_6H_3$ | CH ₃ ,CH ₃ | Oil | 87 | $C_{12}H_{17}Cl,NO_{7}$ | | | | | |
| 3f | 4-FC, H | CH_3, CH_3 | 85-86 | 40 | C ₁ ,H ₁₈ FNO, | | | | | |
| 3g | 3-CH ₃ OC ₅ H ₄ | CH [°] ₃ ,CH [°] ₃ | 92-93 | 27 | C ₁₃ H ₂ NO ₃ | | | | | |
| 3 h | 4-CH ₃ OC ₆ H ₆ | CH, CH, | 102-103 | 27 | C ₁₃ H ₂₁ NO ₃ | | | | | |
| 3 i | 2-CH ₃ C ₆ H ₄ | CH ₃ ,CH ₃ | Oil | 74 | C, H, NO, | | | | | |
| 3j | 3-CH ₃ C ₆ H ₄ | CH, CH, | 100-101 | 25 | C ₁₃ H ₂ NO | | | | | |
| 3k | 4-CH ₃ C ₆ H ₄ | CH, CH, | 125 - 126 | 16 | C ₁₃ H ₂ NO | | | | | |
| 31 | 3-C, H, CH, OC, H, | CH, CH, | 114-115 | 32 | C ₁₀ H ₁₀ NO | | | | | |
| 3m | 4-C, H, CH, OC, H, | CH, CH, | 176-177 | 45 | C, H, NO | | | | | |
| 3n | 2-C,H,N | CH, CH | Oil | 94 | C.H.N.O. | | | | | |
| 30 | 3-C,HN | CHĴCHĴ | 89-90 | 60 | C.H.N.O. | | | | | |
| 3p | $4-C_{H}$ | CHICH | 110-111 | 17 | C.H.N.O. | | | | | |
| 3a | 4-CIC, H. | $(CH_{a}), b^{a}$ | Oil | 52 | C.H.CINO. | | | | | |
| 3r | C.H. | C.H.C.H. | Oil | 56 | C.H.NO. | | | | | |
| 3s | C, H, | (CH_3) | Oil | 85 | $C_{14}H_{23}NO_{2}$ | | | | | |
| 3t | C ₆ H ₅ | $(CH_2)_2^2O(CH_2)_2^d$ | Oil | 85 | $C_{14}H_{21}NO_{3}$ | _ | | | | |

^a All crystalline compounds were analyzed for C, H, and N. Both crystalline and noncrystalline compounds were characterized by NMR. ^{b-d} See corresponding footnotes in Table II.

40, were resolved to provide their respective optical isomers. Resolution of 4a with (-)- and (+)-dibenzoyltartaric acids in ethyl acetate gave (+)-4a and (-)-4a. The (+) and (-) isomers of 40 were obtained by resolution with (+)- and (-)-10-camphorsulfonic acids in acetone, respectively.

Structure–Activity Relationships. Analgesic activity was determined following subcutaneous injection using the mouse writhing and the rat tail jerk tests.⁶ The ED₅₀ (dose required for a 50% reduction in the frequency of writhing in mice) and ED_{2s} (dose required for a 2-s increase in reaction time in rats) along with their 95% confidence limits were computed by "The Use of the Regression Line in Reverse".⁷ The results for the inhibition of acetic acid induced writhing are presented in Table IV. Each ED₅₀ was determined at approximately the time of peak effect, which was usually 15–30 min after injection. Racemates 40, 5a, and 5g and optical isomers (-)-4a and (-)-40 were as potent as meperidine and codeine. The narcotic antagonist naloxone effectively blocked the analgesic activity of this series in the mouse writhing test.

As indicated in Table IV, substituents on the phenyl ring of 4a did not significantly increase analgesic potency and in some instances the potency was decreased in relation to the unsubstituted phenyl ring of 4a. With regard to the amino portion, the most potent compounds were those with a dimethylamino group. Alkyl substitution at the 4 and 5 positions of the dioxane ring decreased activity as in the cases of compounds 6a and 6b, with respect to the unsubstituted dioxane ring of 4a. A methyl group at position 2 of the dioxane ring increased activity over that of 4a, e.g., compounds 5a and 5g. Higher alkyl or aromatic groups at position 2 gave compounds which were less active than 4a. Also, the 2-pyridyl (4n) and 4-pyridyl (4p) compounds were much less potent than the 3-pyridyl (40) compound. The levorotary isomers, (-)-4a and (-)-4o, were more potent than their respective racemates.

The results from the rat tail jerk test for several of the more interesting compounds are shown in Table V. The relative potencies for these compounds in this test are similar to those found in the mouse writhing test. The analgesic effects of the more active compounds were comparable to those of morphine, codeine, and meperidine. Naloxone completely antagonized the activity in this test also.

This class of compounds represents a unique structure containing potent analgesic properties.

Experimental Section

All compounds had NMR spectra consistent with their respective structures. Where analyses are indicated by symbols of the elements, the microanalytical results were within $\pm 0.4\%$ of the theoretical values. Melting points and boiling points are uncorrected.

Diethyl (Phenylmethylene)malonate (1a). In a flask fitted with a Dean-Stark water trap a mixture of benzaldehyde (212 g, 2.0 mol), diethyl malonate (320 g, 2.0 mol), and 10 mL of piperidine in 500 mL of C_6H_6 was refluxed for 16 h. The reaction mixture was poured into cold H_2O and the aqueous mixture was extracted with Et_2O . The Et_2O extract was washed with 10% NaHCO₃ and then with H_2O . The Et_2O solution was dried (MgSO₄) and evaporated to dryness in vacuo. The residual oil was distilled to afford 190 g (38%) of 1a: bp 120 °C (0.1 mm).

By the same method, starting with the appropriate arylaldehyde, the compounds in Table I were prepared.

Diethyl (α -Dimethylaminobenzyl)malonate (2a). A solution of 1a (24.8 g, 0.1 mol) in 100 mL of Et₂O was added dropwise to anhydrous dimethylamine (13.5 g, 0.3 mol) at 0 °C. The reaction mixture was allowed to stand at room temperature for 16 h. The reaction mixture was concentrated to dryness in vacuo to provide 29.3 g (100%) of 2a: NMR (CDCl₃) δ 1.3 (6, 2 t, CCH₃), 2.2 [6, s, N(CH₃)₂], 2.3 (1, m, C₃CH), 4.2 (1, m, C₂CHN), 4.3 (4, 2 q, OCH₂C), 7.2-7.6 (5, m, aromatic).

By the same method, using the appropriate diethyl (arylmethylene)malonate and secondary amine, the compounds in Table II were prepared.

2-(α -Dimethylaminobenzyl)-1,3-propanediol (3a). A solution of 2a (10 g, 0.034 mol) in 50 mL of C₆H₆ was added dropwise over a 30-min period to a solution of NaAlH₂(OCH₂CH₂OCH₃)₂ (33 mL, 0.12 mol) in 50 mL of C₆H₆ with external cooling in an ice-water bath. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured into an ice-20% NaOH mixture. The basic mixture was extracted with CHCl₃. The CHCl₃ extract was washed with H₂O, dried (MgSO₄), and concentrated to dryness in vacuo to provide 3.6 g of an oil. The oil was crystallized with EtOAc-Skelly B to give 2.1 g (29%) of **3a**: mp 82-83 °C. Anal. (C₁₂H₁₉NO₂) C, H, N.

| | Analgesic act. ^g ED _{so} , ^j mg/kg sc ^h | 14 (11-18) | 6.2(4.3-9.1) | >50 | ~ 48 | >50 | ~ 39 | 7 20 / 50 | ~ 30 | | | 20 | 503 / FD | 00 (14-97) | 20 (14-21) > 50 | 200 | 200 200 | 6 1 (4 4-8 6) | 2 6 (9 8 4 5) | 0.0 (2.0 ⁻⁴ .0) > 50 | 200 | m m \ \ | ~ 50 | >50 | >50 | >50 | 13 (6.1-29) | 11 (8.4-14) | ~21 | >50 | >50 | 3.9(2.8-5.3) | ~19 | >50 | >50 | \sim 45 | >502.9 (2.4-3.5) |
|--------------------------------|--|---------------|---------------|------------|--------------|------------------|---------|----------------|------------|-----------|-----------|-----------|-------------|------------|--------------------|----------|--------------------------|--|---------------|--|-------------|------------------|-------------|------------|-----------------------------|------------|--------------|--|--------------|---------------------|------------|---|----------------------|------------------|---|---|---|
| | Formula ^a | C, H, NO, HCI | C, H, NO, HCI | C,H,NO,HCI | C.H.CINO.HCI | C H CINO C H O I | | | TH FNO HCI | | | | | | | | C_{10} H N O C H O f | $O_{12} H_{18} N_{2} O_{2} O_{4} H_{14} O_{4}$ | | $C_{12}H_{18}H_{20}C_{12}H_{21}C_{12}$ | | C H CINO ·HCI | C H NO HCIO | C.H.NO.HCI | C, H, NO, HCI | C,H,NO,HCI | CIAH, NO HCI | C ₁ ,H ₂ ,NO ₄ .HCl | C,,H,,NO,HCI | C,H"NO, HCI | C,H,NO,HCI | C ₁₄ H ₂₁ NO ₂ | C,H ₃ NO, | CI,H,NO,HCI | C ₁ ,H ₂ ,NO ₂ HCI | C ₁₉ H ₂₃ NO ₂ | C ₂₁ H ₂₇ NO ₂ ·C ₄ H ₄ O ₄ ' C ₁₅ H ₂₃ NO ₂ ·HCl |
| | Yield, % | 70 | | | 48 | 60 | 48 | 17 | - 67 | 55 | 49 | 1 C | 09 | 200 | - 0 0 | 29 | 94 | 50 | 4 | | α | - 6 | 47 | 17 | 30 | 53 | 25 | 51 | 18 | 59 | 42 | 21 | 30 | 12 | 15 | 9 | $\frac{15}{25}$ |
| | Mp, °C | 169-170 | 201 - 202 | 201 - 202 | 220 dec | 170-171 | 219 dec | 920 dec | 105_106 | 134-135 | 104-105 | 920 doo | 146_167 | 138-130 | 905 der | 910 dec | 134-135 | 106-107 | 108 400 | 108 dec | 146-147 | 207 dec | 175 dec | 207 dec | 191 dec | 235 dec | 175-176 | 182-183 | 183 - 184 | 193 - 195 | 205 dec | 142 - 143 | 95-98 | 196-197 | 222 dec | 105 - 108 | 120–121 188 dec |
| $\overset{R_3}{\sim}_{R_4}$ | Method | A, B | | | V | | | | < < | < < | 4 ⊲ | : < | ۲ < | ¢ < | 4 | 4 | | | 2 | | Ċ |) 4 | 4 | A | Α | D | D | ы | Ч | IJ | Н | C | ပ | с С | 0 | c | 00 |
| R ₁ -N-R2 ArcH-0 | ${f R}_3, {f R}_4$ | H.H | H,H | Н,Н | H,H | НН | нн | пп | цц | ц, ц ц | н н | ц ц | п,п | п п | цп | н н | нн | цці | п,п п п | п,п | ц, ц ц ц | н н | нн | H.H | H,H | H,H | H,H | H,H | H,H | H,H | Н,Н | CH ₃ ,H | С, Н, , Н | <i>i</i> -Ċ,Ĥ,,H | C,H.,H | С,н,н | C,H,,C2H CH3,H |
| | $\mathbf{R}_1, \mathbf{R}_2$ | CH., CH. | CH, CH, | CH, CH | CH, CH, | CH CH | CH CH | | | | | | | | | | | | | | | CH) b | | $(CH_1)^c$ | $(CH_{a})^{2}O(CH_{a})^{d}$ | ĊH, ĊH, | CH, CH | CH ₃ ,CH ₃ | CH, H | $CH_{i}C_{i}H_{i}e$ | н,Н | CH.,CH. | CH, CH | CH, CH, | CH ₃ ,CH ₃ | CH ₃ ,CH ₃ | CH,,CH, CH,,CH, |
| | Ar | C.H. | C, H, | Ċ,H, | 2-CIC H. | 3-CIC H | 4-CIC H | | | | | | | | | | | | | 3.7 H N | | | | C.H. | C,H, | 3-HÔC, H, | 4-HOC,H | 4-CH,CO,C,H4 | C,H, | C,H, | C,H, | C, H, | C, H, | C,H, | C H | C ₆ H ₅ | $C_{c}H_{s}$ 4-CH, $C_{s}H_{a}$ |
| | No. | 4a | ()-4a | (+)-4a | 40 | Ar Ar | 24 | n 1 | 46 | 14 | 48 Al- | 11. 1. | 41 | 41. 41. | 4.K A1 | ±1 // | 4m | 40 | 40 | $0^{+}(-)$ | (+)-40 | 44 | -4V | 48 | 4t | 4u | 4v | 4w | 4x | 4y | 4ž | $5a^i$ | 5b ⁱ | 5c ⁱ | 5d ¹ | 5e [/] | 57 57 51 51 51 51 51 51 51 51 51 51 51 51 51 |

Table IV. N.N-Dialkyl- α -aryl- α -(1, 3-dioxan-5-yl)methylamines

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| Table V. | Analgesic Activity in the Rat Tail Jerk | Test |
|-----------|---|------|
| Following | Subcutaneous Administration | |

| Compd no. | Peak time, min | ED ₂₈ , mg/kg |
|--------------------------|----------------------|-----------------------------|
| 4a | 15 | 4.0 (2.7-5.8) |
| (-)- 4 a | 15 | 2.4(1.7-3.5) |
| (+)-4a | 15 | ~ 69 |
| 4k | 15 | 7.9 (4.4-14) |
| 40 | 15 | 9.6(5.6-17) |
| (-) -4o | 15 | 5.7(4.2-7.6) |
| (+)-4o | 15 | >80 |
| 4v | 15 | 12(7.1-20) |
| 4w | 15 | 7.3 (5.2-10) |
| 5a | 15 | 6.3(5.0-8.1) |
| 5g | 15 | 7.9 (4.4-14) |
| Morphine sulfate | 30 | 1.8(1.1-3.2) |
| Codeine sulfate | 30 | 4.2(2.9-5.9) |
| Meperidine hydrochloride | 15 | 1.9(1.0-3.5) |

^{*a*} The ED_{2s} is defined as the dose required for a 2-s increase in reaction time above that of the saline-treated control rats. The compounds were given as aqueous solutions, except for 5a which was solublized in 0.01 N HCl. 95% confidence limits are given in parentheses.

By the same method, the compounds of Table II were used to prepare the corresponding compounds in Table III.

Procedures for the Preparation of Compounds in Table IV are Illustrated by the Following Methods. Method A. N, N-Dimethyl- α -(1,3-dioxan-5-yl)benzylamine (4a). To a stirred mixture of 3a (20.9 g, 0.1 mol) and paraformaldehyde (60 g, 2.0 mol) in 300 mL of CH₃CN was added dropwise during a 1-h period 100 mL of BF_3 ·Et₂O. The reaction mixture became slightly exothermic upon addition of the $BF_3 \cdot Et_2O$. The reaction mixture was refluxed for 3 h and then poured slowly into an ice-saturated aqueous NaHCO3 mixture. The basic mixture was extracted with Et₂O. The Et₂O extract was washed with H₂O and dried (MgSO₄). The Et_2O solution was saturated with anhydrous HCl to give a precipitate which was recrystallized from MeOH-EtOAc to provide 18 g (70%) of 4a hydrochloride: mp 169-170 °C. Anal. (C13H20CINO2) C, H, N.

Method B. A mixture of 5-benzoyl-1,3-dioxane (6a, 9.7 g, 0.05 mol) and excess dimethylamine (20 mL) in 150 mL of C_6H_6 was cooled to 5 °C with an ice bath. To the cooled mixture was added a solution of TiCl₄ (4.75 g, 0.025 mol) in 50 mL of C_6H_6 dropwise with stirring. The reaction mixture was cooled at 5 °C for an additional 30 min and then was allowed to warm to room temperature over a 1-h period. The reaction mixture was filtered through a sintered glass funnel and the filtrate was evaporated to dryness in vacuo to yield 10 g of enamine. The enamine in 100 mL of EtOH was hydrogenated for 16 h at 37 psi of H_2 over 5% Pd on carbon (0.5 g). The catalyst was removed from the reaction mixture and the solvent was evaporated in vacuo. The residual oil was suspended in 50 mL of 5 N HCl and the mixture was extracted with Et₂O. The acidic solution was made alkaline with excess NH₄OH and the basic mixture was extracted with Et_2O . The Et_2O solution was washed with H_2O and dried $(MgSO_4)$. The Et₂O solution was saturated with anhydrous HCl to afford a precipitate which was recrystallized with MeOH-EtOAc to provide 2.2 g (17%) of 4a hydrochloride: mp 169-170 °C. Anal. $(C_{13}H_{20}ClNO_2)$ C, H, N.

Method C. 3-[(Dimethylamino)(1,3-dioxan-5-yl)methyl]pyridine (40). A mixture of 2-[(dimethylamino)(3-pyridyl)methyl]-1,3-propanediol (30, 90 g, 0.428 mol), s-trioxane (90 g, 1.0 mol), and p-toluenesulfonic acid monohydrate (171 g, 0.9 mol) in 1.5 L of CHCl₃ was refluxed in a flask fitted with a Soxhlet extractor containing 3A molecular sieves for 16 h. The reaction mixture was extracted with H_2O . The aqueous solution was made alkaline with excess 5 N NaOH and the resultant basic solution was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with saturated NaCl solution, dried $(MgSO_4)$, and evaporated to dryness in vacuo to yield an oil. Vacuum distillation of the oil afforded 40 (40 g, 42%): bp 125-130 °C (0.5 mm). The distilled product 40 was dissolved in 300 mL of EtOAc and the solution was saturated with anhydrous HCl to give a precipitate. The precipitate was recrystallized with MeOH-EtOAc to yield 50 g

| ~ 32 | > 50 | $\begin{array}{c} 0.97 & (0.84-1.1) \\ 6.7 & (5.1-8.7) \\ 2.9 & (2.4-3.5) \end{array}$ | The salts were given as an in parentheses. |
|--|--|--|--|
| C ₁₄ H ₂ NO ₂ HCI | C ₁₄ H ₂₁ NO ₂ ·HCl | | id writhing in mice. h |
| 14 | 86 | | l induce 95% co |
| 213-214 | 195-196 | | ion of acetic acic was isolated. |
| в | I | | Inhibiti acemate |
| NICH-J2 OH3 OH3 | MicH-Jk | | • corresponding footnotes in Table II. ^e Allyl. ^f Maleate. n in 0.01 N HCl. ^f In all instances only one diastereomeric |
| Дi | 10 | Morphine sulfate Codeine sulfate Meperidine hydrochloride | ^{<i>a</i>} Analyzed for C, H, N. b^{-d} See a aqueous solutions. The bases given |

(95%) of 4o dihydrochloride: mp 196–197 °C. Anal. $(C_{12}H_{20}\text{-}Cl_2N_2O_2)$ C, H, Cl, N.

Method D. N, N-Dimethyl- α -(1,3-dioxan-5-yl)-4hydroxybenzylamine (4v). A mixture of N,N-dimethyl- α -(1,3-dioxan-5-yl)-4-benzyloxybenzylamine hydrochloride (4m, 28 g, 0.77 mol) and 5% Pd on carbon (0.5 g) in 200 mL of EtOH was shaken under 27 psi of H₂ for 18 h. The catalyst was removed from the reaction mixture and the solvent was evaporated in vacuo. The residue was crystallized with MeOH-EtOAc to provide 5.3 g (25%) of 4v hydrochloride: mp 175-176 °C. Anal. (C₁₃H₂₀-ClNO₃) C, H, N.

Method E. N,N-Dimethyl- α -(1,3-dioxan-5-yl)-4-acetoxybenzylamine (4w). A mixture of 4v hydrochloride (3.2 g, 0.012 mol), 30 mL of acetic anhydride, and 30 mL of pyridine was allowed to stand at room temperature for 16 h. The reaction mixture was diluted with Et₂O. The resultant precipitate was recrystallized with MeOH-EtOAc to yield 1.9 g (51%) of 4w hydrochloride: mp 182-183 °C. Anal. (C₁₅H₂₂ClNO₄) C, H, N.

Method F. N-Methyl- α -(1,3-dioxan-5-yl)benzylamine (4x). To a solution of 4a (5.5 g, 0.025 mol) in 100 mL of C_6H_6 was added at once diethyl azodicarboxylate (4.5 g, 0.025 mol). The reaction mixture was allowed to stand at room temperature for 16 h. The reaction mixture was concentrated to dryness in vacuo and to the residual oil was added 50 mL of EtOH and 50 mL of saturated NH₄Cl solution. The reaction mixture was refluxed for 2 h and then concentrated to 0.5 vol in vacuo. To the concentrate was added 100 mL of H₂O and the aqueous mixture was extracted with Et₂O. The acidic solution was made alkaline with excess NH_4OH and the basic mixture was extracted with Et_2O . The Et_2O solution was washed with H_2O , dried (MgSO₄), and evaporated to dryness in vacuo to provide 5 g of an oil. Chromatography of this reaction product on silica gel by eluting with C₆H₆ containing increasing amount of EtOAc gave two components. Elution with C_6H_6 -EtOAc (4:1) gave 3 g of recovered 4a. Elution with C_6H_6 -EtOAc (1:4) gave 2 g of an oil which was dissolved in Et₂O. The Et₂O solution was saturated with anhydrous HCl to give a precipitate. The precipitate was recrystallized with MeOH-EtOAc to provide 1.1 g (18%) of 4x hydrochloride: mp 183-184 °C. Anal. $(C_{12}H_{18}ClNO_2)$ C, H, N.

Method G. N-Allyl-N-methyl- α -(1,3-dioxan-5-yl)benzylamine (4y). A mixture of 4x (2.1 g, 0.009 mol), allyl bromide (1.05 g, 0.009 mol), and K₂CO₃ (0.6 g, 0.0045 mol) in 100 mL of Me₂CO was refluxed for 16 h. The reaction mixture was concentrated to dryness in vacuo. The residual oil was suspended in H₂O and the aqueous mixture was extracted with Et₂O. The Et₂O solution was dried (MgSO₄) and saturated with anhydrous HCl to afford a precipitate. The precipitate was recrystallized with MeOH-EtOAc to yield 1.2 g (59%) of 4y hydrochloride: mp 193-195 °C. Anal. (C₁₅H₂₂ClNO₂) C, H, N.

Method H. α -(1,3-Dioxan-5-yl)benzylamine (4z). A mixture of 6a (7g, 0.036 mol), hydroxylamine hydrochloride (7 g, 0.1 mol), and 10 mL of pyridine in 10 mL of EtOH was refluxed for 3 h. The reaction mixture was evaporated to dryness in vacuo and the residue was triturated with H₂O. The residue was crystallized with EtOH-H₂O to provide 5.3 g (83%) of 6a oxime: mp 142-143 °C. Anal. (C₁₁H₁₃NO₃) C, H, N.

Compound 6a oxime (2 g, 0.01 mol) in 25 mL of THF was added dropwise to a stirred suspension of LiAlH₄ (0.76 g, 0.02 mol) in 100 mL of THF. The reaction mixture was refluxed for 3 h, decomposed by careful addition of a saturated NH₄Cl solution, and filtered through a sintered glass funnel. The filtrate was concentrated to dryness in vacuo and the residual oil was dissolved in Et₂O. The Et₂O solution was extracted with 5 N HCl. The acidic extract was made alkaline with excess NH₄OH and the basic mixture was extracted with Et₂O. The Et₂O solution was washed with H₂O, dried (MgSO₄), and saturated with anhydrous HCl to give a precipitate. The precipitate was recrystallized with MeOH-EtOAc to yield 1 g (42%) of 4z hydrochloride: mp 205 °C dec. Anal. (C₁₁H₁₆ClNO₂) C, H, N.

In a similar manner the oxime of 8 was prepared: 91%; mp 144-145 °C. Anal. (C₁₂H₁₅NO₃) C, H, N. The compound 8 oxime

was reduced as above to provide 31% of 9 hydrochloride: mp 235 °C dec. Anal. ($C_{12}H_{18}ClNO_2$) C, H, N.

Method I. N, N-Dimethyl- α -(5-methyl-1,3-dioxan-5-yl)benzylamine (10). To a solution of α -(5-methyl-1,3-dioxan-5-yl)benzylamine (9, 4.1 g, 0.02 mol) in 25 mL of cold 90% HCO₂H was added 25 mL of 38% aqueous HCHO. The reaction mixture was warmed to 100 °C for 16 h. The reaction mixture was poured into an ice-water mixture. The aqueous solution was made alkaline with excess 2 N NaOH. The basic mixture was extracted with Et₂O. The Et₂O solution was washed with H₂O, dried (MgSO₄), and saturated with anhydrous HCl to provide a precipitate. The precipitate was recrystallized with MeOH-EtOAc to yield 4.5 g (86%) of 10 hydrochloride: mp 195-196 °C. Anal. (C₁₄H₂₂ClNO₂) C, H, N.

Resolution of *N*,*N*-Dimethyl- α -(1,3-dioxan-5-yl)benzylamine (4a). A solution of 4a (8 g, 0.036 mol) in 100 mL of EtOAc was mixed with a solution of (+)-dibenzoyltartaric acid monohydrate (6.8 g, 0.018 mol) in 100 mL of EtOAc. The mixture was allowed to stand at room temperature for 16 h. A crystalline product was collected: 6.5 g; mp 127-129 °C; $[\alpha]^{25}_{D} + 58.8^{\circ}$ (c 1, EtOH). Three recrystallizations with MeOH-EtOAc gave 2.7 g (26%) of (-)-4a (+)-dibenzoyltartrate: mp 129-130 °C; $[\alpha]^{25}_{D}$ +64.5° (c 1, EtOH). The above product was suspended in H₂O and excess NH₄OH was added to the mixture. The basic mixture was extracted with Et₂O. The Et₂O solution was washed with H₂O, dried (MgSO₄), and saturated with anhydrous HCl to afford a precipitate. The precipitate was recrystallized with MeOH-EtOAc to provide 0.8 g (67%) of (-)-4a hydrochloride: mp 201-202 °C; $[\alpha]^{25}_{D}$ -3.6° (c 1, H₂O). Anal. (C₁₃H₂₀ClNO₂) C, H, N.

In a similar manner the resolution of **4a** (11 g, 0.05 mol) with (-)-dibenzoyltartaric acid monohydrate (9.45 g, 0.025 mol) in 200 mL of EtOAc gave 2.2 g (15%) of (+)-**4a** (-)-dibenzoyltartrate: mp 129–130 °C; $[\alpha]^{25}_{D}$ -64.9° (c 1, EtOH). From this product was obtained 0.5 g (51%) of (+)-**4a** hydrochloride: mp 201–202 °C; $[\alpha]^{25}_{D}$ +4.0° (c 1, H₂O). Anal. (C₁₃H₂₀ClNO₂) C, H, N.

Resolution of 3-[(Dimethylamino)(1,3-dioxan-5-yl)methyl]pyridine (40). A warm solution of 40 (54 g, 0.243 mol) in 200 mL of Me₂CO was mixed with a warm solution of (-)-10-camphorsulfonic acid (27.8 g, 0.12 mol) in 200 mL of Me₂CO. The mixture was allowed to stand at room temperature for 16 h. A crystalline product was collected: 17 g; mp 167–169 °C; $[\alpha]^{25}$ -15.8° (c 1, H₂O). Recrystallization with EtOAc gave 16 g (29%) of (-)-40 (-)-10-camphorsulfonate: mp 170-171 °C; $[\alpha]^{25}_{D}$ -16.2° $(c 1, H_2O)$. The above product was suspended in H_2O and excess NH₄OH was added to the mixture. The basic mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O_3 . dried (MgSO₄), and concentrated to dryness in vacuo to provide an oil. The oil was dissolved in EtOAc and the solution was saturated with anhydrous HCl to yield a precipitate. The precipitate was recrystallized with MeOH–EtOAc to give 7 g (68%) of (-)-40 dihydrochloride: mp 198 °C dec; $[\alpha]^{25}_{D}$ -17.0° (c 1, MeOH). Anal. $(C_{12}H_{20}Cl_2N_2O_2)$ C, H, Cl, N.

In a similar manner, the resolution of **40** (18 g, 0.08 mol) with (+)-10-camphorsulfonic acid (9.3 g, 0.04 mol) in 200 mL of Me₂CO gave 4.2 g (23%) of (+)-**40** (+)-10-camphorsulfonate: 170–171 °C; $[\alpha]^{25}_{\rm D}$ +15.5° (c 1, H₂O). From this product was obtained 1.1 g (40%) of (+)-**40** dihydrochloride: mp 198 °C dec; $[\alpha]^{25}_{\rm D}$ +16.8° (c 1, MeOH). Anal. (C₁₂H₂₀Cl₂N₂O₂) C, H, Cl, N.

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