Acknowledgment. This work was supported by a U.S. Public Health Service Research Grant (GM-20 357) and NIGMS Research Career Development Award (1-K04-GM-70023), 1971–1976, to W.L.N. and by grants from the Washington and Iowa Heart Association to D.C.D.

References and Notes

(1) For paper 3 in this series, see W. L. Nelson, J. E. Wennerstrom, and S. R. Sankar, *J. Org. Chem.*, **42**, 1006 (1977).
(2) A portion of this work was presented at the 172nd National Meeting of the American Chemical Society, Fall 1976, San Francisco, Calif., Abstracts, MEDI 12. A communication concerning chemical aspects of this work has appeared: W. L. Nelson and J. E. Wennerstrom, *J. Chem. Soc., Chem. Commun.*, 921 (1976).
(3) For a review of antihypertensive adrenergic blocking agents, see L. H. Werner and W. E. Barrett in "Antihypertensive Agents", E. Schlittler, Ed., Academic Press, New York, N.Y., 1967, Chapter X, pp 331–392.
(4) (a) E. Forneau, D. Bovet, and P. Maderni, *J. Pharm. Chim.*, 18, 185 (1933); (b) E. Fourneau and D. Bovet, *C. R. Seances Soc. Biol., Ses Fil*, 113, 388 (1933).
(5) (a) M. Nickerson, *Pharmacol. Rev.*, **9**, 246 (1957); (b) A. B. Demson, Jr., S. Bardhanabaedyna, and H. D. Green, *Circ. Res.*, **2**, 537 (1954); (c) W. Rosenblatt, T. M. Haymond, S. Bellet, and G. Koelle, *Am. J. Med. Sci.*, **227**, 179 (1954).
(6) (a) E. Fourneau and D. Bovet, *Arch. Int. Pharmacodyn. Ther.*, 46, 178 (1933); (b) D. Bovet and A. Simon, *ibid.*, **55**, 15 (1937); (c) A. P. Swain, U.S. Patent 2 695 294 (1954); *Chem. Abstr.*, **49**, 14039 (1955); (d) C. E. Rapela and H. O. Green, *J. Pharmacol. Exp. Ther.*, 132, 29 (1961).
(7) J. Augstein and A. M. Green, *Nature (London)*, **201**, 628 (1964).
(8) C. J. E. Niemegen, J. C. Vergauggen, F. J. Van Neuten, and P. A. J. Janssen, *Int. J. Neutopharmacol.*, **2**, 349 (1963).
(9) W. K. A. Schapers, A. H. M. Jageneau, and P. A. J. Janssen, *Arzneim.-Forsch.*, 13, 579 (1963).
(10) D. Bovet and A. Simon, *Bull. Sci. Pharmacol.*, **42**, 466 (1935); *Chem. Abstr.*, **30**, 769 (1936).
(11) E. Baer, *Biochem. Prep.*, **2**, 31 (1952).
(12) (a) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939); (b) J. C. Sowden and H. O. L. Fischer, *J. Am. Chem. Soc.*, **64**, 1291 (1942).
(13) The absolute stereochemistry as designated by the Cahn–Ingold–Prelog system changes with different substituents from **7** to **8**, **11** to **12** (or **2–4**), and **16** to **11**, although no stereochemical change at the asymmetric carbon has occurred. In the synthetic steps, a single inversion occurs in each sequence, **10** to **11** and **14** to **15**: R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956); *Angew. Chem., Int. Ed. Engl.*, 5 385 (1966).
(14) R. R. Ruffolo, Jr., J. W. Fowble, D. D. Miller, and P. N. Patil, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 3730 (1976).
(15) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961).
(16) G. G. Lyle and L. F. Keifer, *J. Org. Chem.*, 31, 3921 (1966).
(17) P. S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967).
(18) B. Belleau, *Pharmacol. Rev.*, 18, 131 (1966).
(19) A. F. Casy in "PMR Spectroscopy in Medicinal and Biological Chemistry", Academic Press, London, 1971, pp 254–255.
(20) E. Klarmann, L. W. Gates, and V. A. Shternov, *J. Am. Chem. Soc.*, **54**, 1204 (1932).
(21) (a) E. Fourneau, P. Maderni, and Y. de Lestrange, *J. Pharm. Chim.*, 18, 185 (1933); (b) J. Trepouel and Y. Dunant, *Bull. Sci. Pharmacol.*, **42**, 459 (1935).
(22) E. Fourneau, U.S. Patent 2 056 046; *Chem. Abstr.*, **30**, 8530 (1936).
(23) (a) B. Belleau and J. Puranen, *J. Med. Chem.*, **6**, 325 (1963); (b) D. Triggle and B. Belleau, *Can. J. Chem.*, **40**, 1201 (1962).
(24) J. Frefouel and Y. Dunant, *Bull. Sci. Pharmacol.*, **42**, 459 (1935).
(25) A. Grün, U.S. Patent 2366102; *Chem. Abstr.*, **40**, 2271 (1946).
(26) O. Arunlakshana and H. O. Schild, *Br. J. Pharmacol.*, 14, 48 (1959).

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

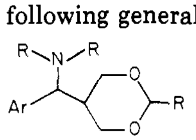
Richard N. Booher,* Stephen E. Smits, William W. Turner, Jr., and Albert Pohland

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206. *Received November 19, 1976*

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.

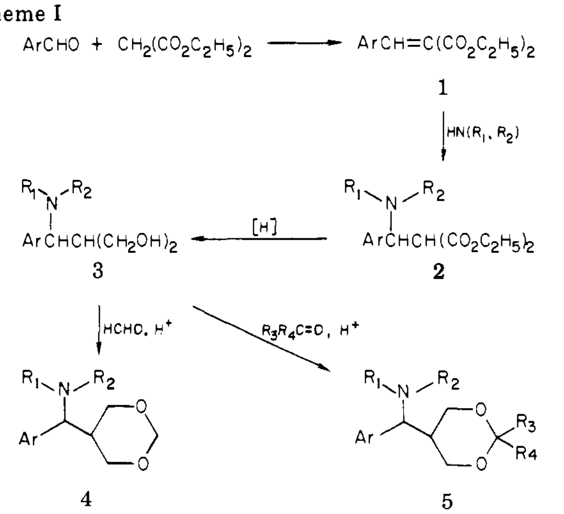
We wish to report this new class of analgesics which is represented by the following general formula



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 condensation[3] of arylaldehydes with diethyl malonate provided diethyl (arylmethylene)malonates **1a–p** (Table I). A Michael addition of secondary amines to

Scheme I



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), °C	Formula[m]
1a	C_6H_5	38	120 (0.1)[a]	$C_{14}H_{16}O_4$
1b	$2\text{-}ClC_6H_4$	8	142 (0.7)[b]	$C_{14}H_{15}ClO_4$
1c	$3\text{-}ClC_6H_4$	16	150 (0.7)[c]	$C_{14}H_{15}ClO_4$
1d	$4\text{-}ClC_6H_4$	53	144 (0.7)[d]	$C_{14}H_{15}ClO_4$
1e	$2,4\text{-}Cl_2C_6H_3$	43	132 (0.05)	$C_{14}H_{14}Cl_2O_4$
1f	$4\text{-}FC_6H_4$	24	152 (0.5)[e]	$C_{14}H_{15}FO_4$
1g	$3\text{-}CH_3OC_6H_4$	42	154 (0.7)[f]	$C_{15}H_{18}O_5$
1h	$4\text{-}CH_3OC_6H_4$	20	162 (0.7)[g]	$C_{15}H_{18}O_5$
1i	$2\text{-}CH_3C_6H_4$	19	142 (0.7)[h]	$C_{15}H_{18}O_4$
1j	$3\text{-}CH_3C_6H_4$	27	138 (0.7)	$C_{15}H_{18}O_4$
1k	$4\text{-}CH_3C_6H_4$	40	140 (0.7)[i]	$C_{15}H_{18}O_4$
1l	$3\text{-}C_6H_5CH_2OC_6H_4$	9	Oil	$C_{21}H_{22}O_5$
1m	$4\text{-}C_6H_5CH_2OC_6H_4$	75	222 (0.1)	$C_{21}H_{22}O_5$
1n	$2\text{-}C_4H_4N$	30	140 (0.05)[j]	$C_{13}H_{15}NO_4$
1o	$3\text{-}C_4H_4N$	79	150 (0.1)[k]	$C_{13}H_{15}NO_4$
1p	$4\text{-}C_4H_4N$	45	138 (0.05)[l]	$C_{13}H_{15}NO_4$

[a] H. Staudinger, *Justus Liebigs Ann. Chem.*, 341, 110 (1905), gave bp 185–186 °C (17 mm). [b] Gagnon and L. Gravel, *Can. J. Res.*, **8**, 600 (1933), gave bp 182–183 °C (5 mm). [c] N. Vul'fson, F. Zhurina, and L. Senyavina, *Zh. Obshch. Khim.*, 36 (4), 609 (1966), gave bp 133 °C (0.01 mm). [d] E. F. Pratt and E. Werble, *J. Am. Chem. Soc.*, **72**, 4638 (1950), gave bp 156–158 °C (1.5 mm). [e] T. Urbanski and J. Lange, *Rocz. Chem.*, 33, 197 (1959), gave bp 140–142 °C (0.2 mm). [f] D. Hey and K. Nagdy, *J. Chem. Soc.*, 1894 (1953), gave bp 160 °C (0.3 mm). [g] E. Bowden and H. Adkins, *J. Am. Chem. Soc.*, 62, 2422 (1940), gave bp 167 °C (0.3 mm). [h] K. Mori, M. Matsui, and Y. Sumiki, *Agric. Biol. Chem.*, **27** (1), 27 (1963), gave bp 148–149 °C (4 mm). [i] A. Cope, *J. Am. Chem. Soc.*, 56, 721 (1934), gave mp 50–51 °C. [j] R. Mohrbacker, U.S. Patent 3 274 202 (1966), gave bp 157 °C (0.5 mm). [k] A. Dornow and F. Boberg, *Justus Liebigs Ann. Chem.*, **578**, 107 (1952), gave bp 140 °C (4 mm). [l] M. Rubtsov, E. Nikitskaya, and A. Yanina, *Dokl. Akad. Nauk SSSR*, **89**, 81 (1953), gave bp 162–164 °C (5 mm). [m] The structures of all compounds were confirmed by NMR spectra.

Table II. Diethyl [(α-Dialkylamino)(aryl)methyl]malonates

$ArCH(NR_1R_2)CH(CO_2C_2H_5)_2$

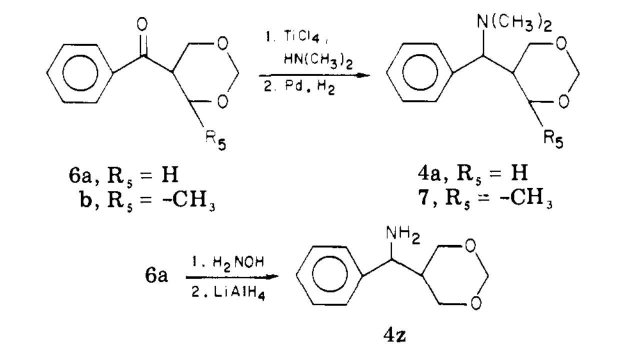
No.	Ar	R_1,R_2	Formula[a]
2a	C_6H_5	CH_3,CH_3	$C_{16}H_{23}NO_4$
2b	$2\text{-}ClC_6H_4$	CH_3,CH_3	$C_{16}H_{22}ClNO_4$
2c	$3\text{-}ClC_6H_4$	CH_3,CH_3	$C_{16}H_{22}ClNO_4$
2d	$4\text{-}ClC_6H_4$	CH_3,CH_3	$C_{16}H_{22}ClNO_4$
2e	$2,4\text{-}Cl_2C_6H_3$	CH_3,CH_3	$C_{16}H_{21}Cl_2NO_4$
2f	$4\text{-}FC_6H_4$	CH_3,CH_3	$C_{16}H_{22}FNO_4$
2g	$3\text{-}CH_3OC_6H_4$	CH_3,CH_3	$C_{17}H_{25}NO_5$
2h	$4\text{-}CH_3OC_6H_4$	CH_3,CH_3	$C_{17}H_{25}NO_5$
2i	$2\text{-}CH_3C_6H_4$	CH_3,CH_3	$C_{17}H_{25}NO_4$
2j	$3\text{-}CH_3C_6H_4$	CH_3,CH_3	$C_{17}H_{25}NO_4$
2k	$4\text{-}CH_3C_6H_6$	CH_3,CH_3	$C_{17}H_{25}NO_4$
2l	$3\text{-}C_6H_5CH_2OC_6H_4$	CH_3,CH_3	$C_{23}H_{29}NO_5$
2m	$4\text{-}C_6H_5CH_2OC_6H_4$	CH_3,CH_3	$C_{23}H_{29}NO_5$
2n	$2\text{-}C_5H_4N$	CH_3,CH_3	$C_{15}H_{22}N_2O_4$
2o	$3\text{-}C_5H_4N$	CH_3,CH_3	$C_{15}H_{22}N_2O_4$
2p	$4\text{-}C_5H_4N$	CH_3,CH_3	$C_{15}H_{22}N_2O_4$
2q	$4\text{-}ClC_6H_4$	$(CH_2)_5$[b]	$C_{19}H_{26}ClNO_4$
2r	C_6H_5	C_2H_5,C_2H_5	$C_{18}H_{27}NO_4$
2s	C_6H_5	$(CH_2)_4$[c]	$C_{18}H_{25}NO_4$
2t	C_6H_5	$(CH_2)_2O(CH_2)_2$[d]	$C_{18}H_{25}NO_5$

[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(2-methoxyethoxy)aluminum hydride in benzene afforded 2-substituted 1,3-propanediols **3a–t** (Table III). An acid-catalyzed condensation of formaldehyde with **3a–t** provided 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).

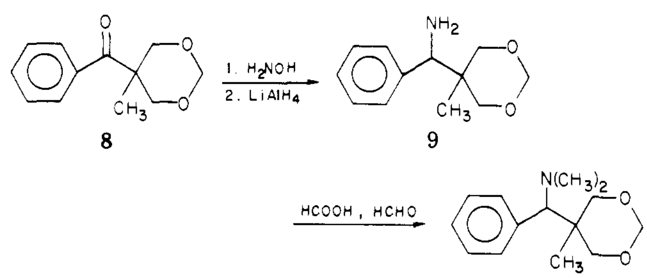
Compounds **4u** and **4v** were prepared by the respective catalytic hydrogenation of **4l** and **4m**. The acylation of **4v** with acetic anhydride provided **4w**. Demethylation of

Scheme II



6a, R_5 = H; b, R_5 = $-CH_3$ → 4a, R_5 = H; 7, R_5 = $-CH_3$; 6a → 4z

Scheme III



8 → 9 → 10

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-Dialkylamino)(aryl)methyl]-1,3-propanediols

R_1R_2N–$CH(Ar)CH(CH_2OH)_2$ (ArCHCH(CH_2OH)$_2$ with NR_1R_2 on the benzylic carbon)

No.	Ar	R_1,R_2	Mp, °C	Yield, %	Formula[a]
3a	C_6H_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	$C_{12}H_{18}ClNO_2$
3c	3-ClC_6H_4	CH_3,CH_3	90-91	55	$C_{12}H_{18}ClNO_2$
3d	4-ClC_6H_4	CH_3,CH_3	102-103	59	$C_{12}H_{18}ClNO_2$
3e	2,4-$Cl_2C_6H_3$	CH_3,CH_3	Oil	87	$C_{12}H_{17}Cl_2NO_2$
3f	4-FC_6H_4	CH_3,CH_3	85-86	40	$C_{12}H_{18}FNO_2$
3g	3-$CH_3OC_6H_4$	CH_3,CH_3	92-93	27	$C_{13}H_{21}NO_3$
3h	4-$CH_3OC_6H_6$	CH_3,CH_3	102-103	27	$C_{13}H_{21}NO_3$
3i	2-$CH_3C_6H_4$	CH_3,CH_3	Oil	74	$C_{13}H_{21}NO_2$
3j	3-$CH_3C_6H_4$	CH_3,CH_3	100-101	25	$C_{13}H_{21}NO_2$
3k	4-$CH_3C_6H_4$	CH_3,CH_3	125-126	16	$C_{13}H_{21}NO_2$
3l	3-$C_6H_5CH_2OC_6H_4$	CH_3,CH_3	114-115	32	$C_{19}H_{25}NO_3$
3m	4-$C_6H_5CH_2OC_6H_4$	CH_3,CH_3	176-177	45	$C_{19}H_{25}NO_3$
3n	2-C_5H_4N	CH_3,CH_3	Oil	94	$C_{11}H_{18}N_2O_2$
3o	3-C_5H_4N	CH_3,CH_3	89-90	60	$C_{11}H_{18}N_2O_2$
3p	4-C_5H_4N	CH_3,CH_3	110-111	17	$C_{11}H_{18}N_2O_2$
3q	4-ClC_6H_4	$(CH_2)_5$[b]	Oil	52	$C_{15}H_{22}ClNO_2$
3r	C_6H_5	C_2H_5,C_2H_5	Oil	56	$C_{14}H_{23}NO_2$
3s	C_6H_5	$(CH_2)_4$[c]	Oil	85	$C_{14}H_{21}NO_2$
3t	C_6H_5	$(CH_2)_2O(CH_2)_2$[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.

4o, 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 **4o** 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 ED_{50} (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 ED_{50} was determined at approximately the time of peak effect, which was usually 15–30 min after injection. Racemates **4o**, **5a**, and **5g** and optical isomers (−)-**4a** and (−)-**4o** 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 (**4o**) 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 ±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% $NaHCO_3$ and then with H_2O. The Et_2O solution was dried ($MgSO_4$) and evaporated to dryness in vacuo. The residual oil was distilled to afford 190 g (38%) of **1a**: bp 120 °C (0.1 mm).

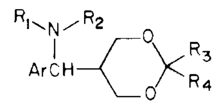
By the same method, starting with the appropriate arylaldehyde, the compounds in Table I were prepared.

Diethyl (α-Dimethylaminobenzyl)malonate (2a). A solution of 1a (24.8 g, 0.1 mol) in 100 mL of Et_2O 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 ($CDCl_3$) δ 1.3 (6, 2 t, CCH_3), 2.2 [6, s, $N(CH_3)_2$], 2.3 (1, m, C_3CH), 4.2 (1, m, C_2CHN), 4.3 (4, 2 q, OCH_2C), 7.2–7.6 (5, m, aromatic).

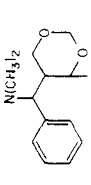
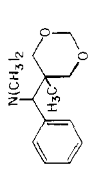
By the same method, using the appropriate diethyl (arylmethylene)malonate and secondary amine, the compounds in Table II were prepared.

2-(α-Dimethylaminobenzyl)-1,3-propanediol (3a). A solution of **2a** (10 g, 0.034 mol) in 50 mL of C_6H_6 was added dropwise over a 30-min period to a solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (33 mL, 0.12 mol) in 50 mL of C_6H_6 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 $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), 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. ($C_{12}H_{19}NO_2$) C, H, N.

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



No.	Ar	R_1,R_2	R_3,R_4	Method	Mp, °C	Yield, %	Formula[a]	Analgesic act.,[g] ED_{50},[j] mg/kg sc[h]
4a	C_6H_5	CH_3,CH_3	H,H	A, B	169-170	70	$C_{13}H_{19}NO_2 \cdot HCl$	14 (11-18)
(−)-4a	C_6H_5	CH_3,CH_3	H,H		201-202		$C_{13}H_{19}NO_2 \cdot HCl$	6.2 (4.3-9.1)
(+)-4a	C_6H_5	CH_3,CH_3	H,H		201-202		$C_{13}H_{19}NO_2 \cdot HCl$	>50
4b	2-ClC_6H_4	CH_3,CH_3	H,H	A	220 dec	48	$C_{13}H_{18}ClNO_2 \cdot HCl$	~48
4c	3-ClC_6H_4	CH_3,CH_3	H,H	A	170-171	60	$C_{13}H_{18}ClNO_2 \cdot C_4H_4O_4$[f]	>50
4d	4-ClC_6H_4	CH_3,CH_3	H,H	A	219 dec	48	$C_{13}H_{18}ClNO_2 \cdot HCl$	~32
4e	2,4-$Cl_2C_6H_3$	CH_3,CH_3	H,H	A	230 dec	17	$C_{13}H_{17}Cl_2NO_2 \cdot HCl$	>50
4f	4-FC_6H_4	CH_3,CH_3	H,H	A	195-196	43	$C_{13}H_{18}FNO_2 \cdot HCl$	~30
4g	3-$CH_3OC_6H_4$	CH_3,CH_3	H,H	A	134-135	27	$C_{14}H_{21}NO_3 \cdot C_4H_4O_4$[f]	>50
4h	4-$CH_3OC_6H_4$	CH_3,CH_3	H,H	A	194-195	42	$C_{14}H_{21}NO_3 \cdot HCl$	>50
4i	2-$CH_3C_6H_4$	CH_3,CH_3	H,H	A	230 dec	25	$C_{14}H_{21}NO_2 \cdot HCl$	~39
4j	3-$CH_3C_6H_4$	CH_3,CH_3	H,H	A	166-167	60	$C_{14}H_{21}NO_2 \cdot C_4H_4O_4$[f]	>50
4k	4-$CH_3C_6H_4$	CH_3,CH_3	H,H	A	138-139	67	$C_{14}H_{21}NO_2 \cdot C_4H_4O_4$[f]	20 (14-27)
4l	3-$C_6H_5CH_2OC_6H_4$	CH_3,CH_3	H,H	A	205 dec	38	$C_{20}H_{25}NO_3 \cdot HCl$	>50
4m	4-$C_6H_5CH_2OC_6H_4$	CH_3,CH_3	H,H	A	210 dec	56	$C_{20}H_{25}NO_3 \cdot HCl$	>50
4n	2-C_5H_4N	CH_3,CH_3	H,H	C	134-135	24	$C_{12}H_{18}N_2O_2 \cdot C_4H_4O_4$[f]	>50
4o	3-C_5H_4N	CH_3,CH_3	H,H	C	196-197	42	$C_{12}H_{18}N_2O_2 \cdot 2HCl$	6.1 (4.4-8.6)
(−)-4o	3-C_5H_4N	CH_3,CH_3	H,H		198 dec		$C_{12}H_{18}N_2O_2 \cdot 2HCl$	3.6 (2.8-4.5)
(+)-4o	3-C_5H_4N	CH_3,CH_3	H,H		198 dec		$C_{12}H_{18}N_2O_2 \cdot 2HCl$	>50
4p	4-C_5H_4N	CH_3,CH_3	H,H	C	146-147	8	$C_{12}H_{18}N_2O_2 \cdot C_4H_4O_4$[f]	>50
4q	4-ClC_6H_4	$(CH_2)_5$[b]	H,H	A	207 dec	19	$C_{16}H_{22}ClNO_2 \cdot HCl$	~33
4r	C_6H_5	C_2H_5,C_2H_5	H,H	A	175 dec	47	$C_{15}H_{23}NO_2 \cdot HClO_4$	>50
4s	C_6H_5	$(CH_2)_4$[c]	H,H	A	207 dec	17	$C_{15}H_{21}NO_2 \cdot HCl$	>50
4t	C_6H_5	$(CH_2)_2O(CH_2)_2$[d]	H,H	A	191 dec	30	$C_{15}H_{21}NO_3 \cdot HCl$	>50
4u	3-HOC_6H_4	CH_3,CH_3	H,H	D	235 dec	53	$C_{13}H_{19}NO_3 \cdot HCl$	>50
4v	4-HOC_6H_4	CH_3,CH_3	H,H	D	175-176	25	$C_{13}H_{19}NO_3 \cdot HCl$	13 (6.1-29)
4w	4-$CH_3CO_2C_6H_4$	CH_3,CH_3	H,H	E	182-183	51	$C_{15}H_{21}NO_4 \cdot HCl$	11 (8.4-14)
4x	C_6H_5	CH_3,H	H,H	F	183-184	18	$C_{12}H_{17}NO_2 \cdot HCl$	~21
4y	C_6H_5	CH_3,C_3H_5[e]	H,H	G	193-195	59	$C_{15}H_{21}NO_2 \cdot HCl$	>50
4z	C_6H_5	H,H	H,H	H	205 dec	42	$C_{11}H_{15}NO_2 \cdot HCl$	>50
5a[i]	C_6H_5	CH_3,CH_3	CH_3,H	C	142-143	21	$C_{14}H_{21}NO_2$	3.9 (2.8-5.3)
5b[i]	C_6H_5	CH_3,CH_3	C_2H_5,H	C	95-98	30	$C_{15}H_{23}NO_2$	~19
5c[i]	C_6H_5	CH_3,CH_3	*i*-C_3H_7,H	C	196-197	12	$C_{16}H_{25}NO_2 \cdot HCl$	>50
5d[i]	C_6H_5	CH_3,CH_3	C_6H_{11},H	C	222 dec	15	$C_{19}H_{29}NO_2 \cdot HCl$	>50
5e[i]	C_6H_5	CH_3,CH_3	C_6H_5,H	C	105-108	6	$C_{19}H_{23}NO_2$	~45
5f[i]	C_6H_5	CH_3,CH_3	C_6H_5,C_2H_5	C	120-121	15	$C_{21}H_{27}NO_2 \cdot C_4H_4O_4$[f]	>50
5g[i]	4-$CH_3C_6H_4$	CH_3,CH_3	CH_3,H	C	188 dec	25	$C_{15}H_{23}NO_2 \cdot HCl$	2.9 (2.4-3.5)

7[i]		B	213–214	14	$C_{14}H_{21}NO_2\cdot HCl$	~32
10		I	195–196	86	$C_{14}H_{21}NO_2\cdot HCl$	>50
Morphine sulfate						0.97 (0.84–1.1)
Codeine sulfate						6.7 (5.1–8.7)
Meperidine hydrochloride						2.9 (2.4–3.5)

[a] Analyzed for C, H, N. [b-d] See corresponding footnotes in Table II. [e] Allyl. [f] Maleate. [g] Inhibition of acetic acid induced writhing in mice. [h] The salts were given as aqueous solutions. The bases given in 0.01 N HCl. [i] In all instances only one diastereomeric racemate was isolated. [j] 95% confidence limits are given in parentheses.

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

Compd no.	Peak time, min	ED_{2s}, mg/kg
4a	15	4.0 (2.7–5.8)
(−)-4a	15	2.4 (1.7–3.5)
(+)-4a	15	~69
4k	15	7.9 (4.4–14)
4o	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 CH_3CN was added dropwise during a 1-h period 100 mL of $BF_3\cdot Et_2O$. 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 $NaHCO_3$ mixture. The basic mixture was extracted with Et_2O. The Et_2O extract was washed with H_2O and dried ($MgSO_4$). 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. ($C_{13}H_{20}ClNO_2$) 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 $TiCl_4$ (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 Et_2O. 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 and dried ($MgSO_4$). The Et_2O 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 (4o). A mixture of 2-[(dimethylamino)(3-pyridyl)methyl]-1,3-propanediol (**3o**, 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 $CHCl_3$ 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 **4o** (40 g, 42%): bp 125–130 °C (0.5 mm). The distilled product **4o** 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

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

Method D. *N,N*-Dimethyl-α-(1,3-dioxan-5-yl)-4-hydroxybenzylamine (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 H_2 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. ($C_{13}H_{20}ClNO_3$) 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 Et_2O. The resultant precipitate was recrystallized with MeOH–EtOAc to yield 1.9 g (51%) of **4w** hydrochloride: mp 182–183 °C. Anal. ($C_{15}H_{22}ClNO_4$) 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 NH_4Cl 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 H_2O and the aqueous mixture was extracted with Et_2O. 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 ($MgSO_4$), and evaporated to dryness in vacuo to provide 5 g of an oil. Chromatography of this reaction product on silica gel by eluting with C_6H_6 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 Et_2O. The Et_2O 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 K_2CO_3 (0.6 g, 0.0045 mol) in 100 mL of Me_2CO was refluxed for 16 h. The reaction mixture was concentrated to dryness in vacuo. The residual oil was suspended in H_2O and the aqueous mixture was extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) 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. ($C_{15}H_{22}ClNO_2$) 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 H_2O. The residue was crystallized with EtOH–H_2O to provide 5.3 g (83%) of **6a** oxime: mp 142–143 °C. Anal. ($C_{11}H_{13}NO_3$) C, H, N.

Compound **6a** oxime (2 g, 0.01 mol) in 25 mL of THF was added dropwise to a stirred suspension of $LiAlH_4$ (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 NH_4Cl solution, and filtered through a sintered glass funnel. The filtrate was concentrated to dryness in vacuo and the residual oil was dissolved in Et_2O. The Et_2O solution was extracted with 5 N HCl. The acidic extract 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 ($MgSO_4$), 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. ($C_{11}H_{16}ClNO_2$) C, H, N.

In a similar manner the oxime of **8** was prepared: 91%; mp 144–145 °C. Anal. ($C_{12}H_{15}NO_3$) 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% HCO_2H 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 Et_2O. The Et_2O solution was washed with H_2O, dried ($MgSO_4$), 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. ($C_{14}H_{22}ClNO_2$) 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° (*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 H_2O and excess NH_4OH was added to the mixture. The basic mixture was extracted with Et_2O. The Et_2O solution was washed with H_2O, dried ($MgSO_4$), 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, H_2O). Anal. ($C_{13}H_{20}ClNO_2$) 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, H_2O). Anal. ($C_{13}H_{20}ClNO_2$) C, H, N.

Resolution of 3-[(Dimethylamino)(1,3-dioxan-5-yl)methyl]pyridine (4o). A warm solution of **4o** (54 g, 0.243 mol) in 200 mL of Me_2CO was mixed with a warm solution of (–)-10-camphorsulfonic acid (27.8 g, 0.12 mol) in 200 mL of Me_2CO. The mixture was allowed to stand at room temperature for 16 h. A crystalline product was collected: 17 g; mp 167–169 °C; $[\alpha]^{25}{}_D$ –15.8° (*c* 1, H_2O). Recrystallization with EtOAc gave 16 g (29%) of (–)-**4o** (–)-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 NH_4OH was added to the mixture. The basic mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried ($MgSO_4$), 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 (–)-**4o** 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 **4o** (18 g, 0.08 mol) with (+)-10-camphorsulfonic acid (9.3 g, 0.04 mol) in 200 mL of Me_2CO gave 4.2 g (23%) of (+)-**4o** (+)-10-camphorsulfonate: 170–171 °C; $[\alpha]^{25}{}_D$ +15.5° (*c* 1, H_2O). From this product was obtained 1.1 g (40%) of (+)-**4o** dihydrochloride: mp 198 °C dec; $[\alpha]^{25}{}_D$ +16.8° (*c* 1, MeOH). Anal. ($C_{12}H_{20}Cl_2N_2O_2$) C, H, Cl, N.

References and Notes

(1) B. Wesslén and L. Ryrfors, *Acta Chem. Scand.*, **22**, 2071 (1968).
(2) A. Terada, *Nippon Kagaku Zasshi*, 81, 612 (1960).
(3) G. Jones, *Org. React.*, **15**, 204 (1967).
(4) W. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).
(5) B. Wesslén, *Acta Chem. Scand.*, **23**, 1033 (1969).
(6) S. Smits and M. Myers, *Res. Commun. Chem. Pathol. Pharmacol.*, **7**, 651 (1974).
(7) K. A. Brownlee, "Statistical Theory and Methodology in Science and Engineering", 2nd ed, Wiley, New York, N.Y., 1965.