Articles

1-Aryl-3-azabicyclo[3.1.0]hexanes, a New Series of Nonnarcotic Analgesic Agents

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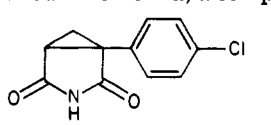
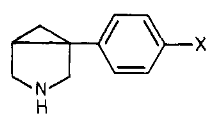
A series of 1-aryl-3-azabicyclo[3.1.0]hexanes was synthesized by hydride reduction of 1-arylcyclopropanedicarboximides. Hydroxyphenyl analogues **20**, **22**, and **24** were prepared by EtSNa-DMF ether cleavage of the corresponding methoxyphenyl analogues **2m**, **2n**, and **23**, respectively, with the secondary amines **20** and **22** going through the *N*-formyl intermediates **19** and **21**. The *p*-ethoxy analogue **26** was obtained by O-ethylation of **19**, followed by base hydrolysis of the amide **25**. The greatest analgesic potency in mouse writhing and rat paw-pain assays was observed for para-substituted compounds. Bicifadine, 1-(4-methylphenyl)-3-azabicyclo[3.1.0]hexane (**2b**), was the most potent member of the series and is presently undergoing clinical trials in man. Analgesic activity of **2b** is limited to the (+) enantiomer **2v**, which has the 1*R*,5*S* absolute configuration as determined by single-crystal X-ray analysis. The *N*-methyl analogue (**27d**) of **2b** showed significant analgesic potency, whereas the *N*-allyl (**27a**), *N*-(cyclopropylmethyl) (**27b**), and *N*-(*n*-hexyl) (**27c**) analogues were inactive. Bicifadine (**2b**) showed a nonnarcotic profile different from analogous azabicycloalkane and 3-phenylpyrrolidine analgesics.

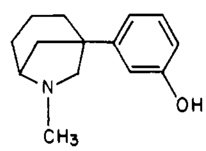
The reduction of **1a**, a compound previously under study



1a



2a, X = Cl
b, X = CH_3



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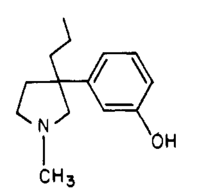

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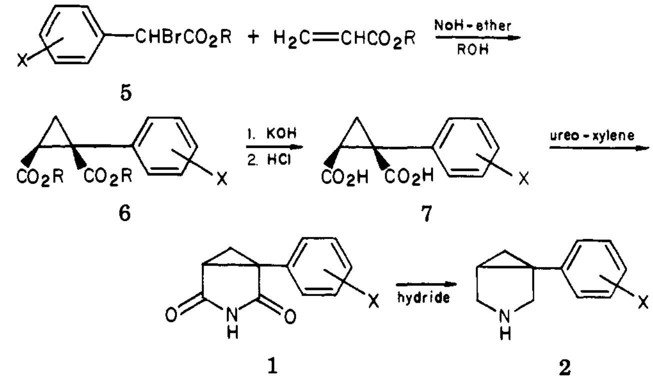
in these laboratories as a potential anxiolytic agent, gave 1-(4-chlorophenyl)-3-azabicyclo[3.1.0]hexane (**2a**), which exhibited analgesic activity in rats. Thus, a series of 1-phenyl-3-azabicyclo[3.1.0]hexanes was synthesized,[1] and many of the compounds, particularly the *p*-methylphenyl analogue **2b**,[2] bicifadine[3] (CL 220 075), showed analgesic activity in rats and mice. This study defines the structure-activity relationships in this series of compounds due to variations on the phenyl ring, substitution on the nitrogen atom, and optical resolution.

Various azabicycloalkane systems, such as **3**,[4] and phenylpyrrolidines, such as profadol (**4**),[5] have been reported as analgesic agents having mixed agonist-antagonist properties. The common features of these compounds for significant activity is the presence of a *m*-hydroxyphenyl group and *N*-alkyl substitution. The compounds of this study do not adhere to this set of structural requirements and they do not show narcotic-type activity in rats and mice.

Scheme I. General Procedure



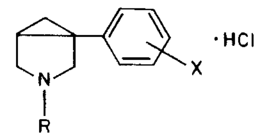
Chemistry. The azabicyclohexanes **2a-y**, **36**, and **37** (Table I) were synthesized via the hydride reduction of the corresponding cyclopropanedicarboximides **1a-y** (Table V), **34**, and **35** using either sodium bis(2-methoxyethoxy)aluminum hydride or borane-tetrahydrofuran (Schemes I and VI). Whereas the former reagent caused extensive dechlorination of the 3,4-dichlorophenyl derivative **1t**, BH_3-THF gave the desired **2t** in excellent yield with no evidence of any dechlorination. The synthetic route to the precursor 1-aryl-1,2-cyclopropanedicarboximides was first reported from these laboratories by Izzo and Safir. Their initial syntheses of imides of this type involved the reaction of 2-arylmaleimides with diazomethane[6] or with trimethylsulfoxonium chloride-sodium hydride.[7]

The α-bromophenylacetates **5** (Table II) were reacted with acrylic esters in a sodium hydride-alcohol-ether mixture by the method originally reported by McCoy[8,9] to

(1) Epstein, J. W.; Brabander, H. J.; Fanshawe, W. J.; McKenzie, T. C.; Osterberg, A. C.; Safir, S. R. "Abstracts of Papers", 175th National Meeting of the American Chemical Society, Anaheim, CA, Mar 1978; American Chemical Society: Washington, D.C., 1978; Abstr MEDI 17.
(2) Osterberg, A. C.; Regan, B. A.; Patel, G. J. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1978**, *37*, 769.
(3) United States Adopted Name: *J. Am. Med. Assoc.* **1979**, *242*, 1912.
(4) Takeda, M.; Inoue, H.; Noguchi, K.; Honma, Y.; Kawamori, M.; Tsukamoto, G.; Yamawaki, Y.; Saito, S.; Aoe, K.; Date, T.; Nurimoto, S.; Hayashi, G. *J. Med. Chem.* **1977**, *20*, 221.
(5) Bowman, R. E. *Chem. Ind. (London)* **1969**, 1077.
(6) Izzo, P. T.; Safir, S. R. U.S. Patent 3 166 571, 1965.
(7) Izzo, P. T. *J. Org. Chem.* **1963**, *28*, 1713.
(8) McCoy, L. L. *J. Am. Chem. Soc.* **1958**, *80*, 6568. *Ibid.* **1962**, *84*, 2246.
(9) McCoy, L. L. *J. Org. Chem.* **1960**, *25*, 2078.

0022-2623/81/1824-0481$01.25/0

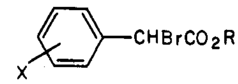
Table I. Physical Properties and Biological Activity of 1-Aryl-3-azabicyclo[3.1.0]hexanes



compd	X	R	mp, °C	recrystn solvent	yield, % (procedure)	formula[a]	$[\alpha]^{25}_D$ (c 1, MeOH), deg	3-legged gait ED_{50} (95% CL), mg/kg po[b]	paw pressure ED_{50} (95% CL), mg/kg po[c]	PPQ ED_{50} (95% CL), mg/kg po[d]
2a	p-Cl	H	215–217	EtOH	65 (E)	$C_{11}H_{12}ClN{\cdot}HCl$		31 (21–45)	21 (15–28)	21 (13–34)
2b	p-CH_3	H	207–208	MeCN	58 (E)	$C_{12}H_{15}N{\cdot}HCl$		18 (11–31) [4 (3–7) sc]	11 (3–28)	13 (6–29)
2c	H	H	166–168	MeCN	34 (E)	$C_{11}H_{13}N{\cdot}HCl$		70 (44–111)	71 (24–206)	<100
2d	m-Cl	H	182–184	i-PrOH	70 (E)	$C_{11}H_{12}ClN{\cdot}HCl$		>50[e]	~50	34 (24–48)
2e	o-Cl	H	188–190	i-PrOH	50 (E)	$C_{11}H_{12}ClN{\cdot}HCl$		>100[f]	NT[g]	NT
2f	p-Br	H	231–233	EtOH	68 (F)	$C_{11}H_{12}BrN{\cdot}HCl$		~141	NT	NT
2g	p-CF_3	H	249–251	MeCN	56 (E)	$C_{12}H_{12}F_3N{\cdot}HCl$		38 (28–52)	~40	>100[f]
2h	m-CF_3	H	146–148	MeCN	47 (E)	$C_{12}H_{12}F_3N{\cdot}HCl$		28 (21–37)	~50	29 (13–64)
2i	p-F	H	170–172	MeCN	81 (E)	$C_{11}H_{12}FN{\cdot}HCl$		>50[e]	14 (6–33)	34 (19–60)
2j	m-F	H	140–146	MeCN	33 (E)	$C_{11}H_{12}FN{\cdot}HCl$		>50[e]	~67	21 (13–34)
2k	o-CH_3	H	204–206	MeCN	42 (E)	$C_{12}H_{15}N{\cdot}HCl$		>50[f]	NT	>50[f]
2l	m-CH_3	H	164–166	MeCN	46 (E)	$C_{12}H_{15}N{\cdot}HCl$		>50[e]	~25	18 (13–25)
2m	p-OCH_3	H	174–175	i-PrOH	65 (E)	$C_{12}H_{15}NO{\cdot}HCl$		24 (11–61)	49 (27–86)	4 (2–9)
2n	m-OCH_3	H	150–152	MeCN	24 (E)	$C_{12}H_{15}NO{\cdot}HCl$		~177	NT	NT
2o	p-C_2H_5	H	207–209	MeCN	56 (E)	$C_{13}H_{16}N{\cdot}HCl$		13 (9–19)	~25	24 (13–45)
2p	p-$CH(CH_3)_2$	H	231–232	i-PrOH	71 (E)	$C_{14}H_{19}N{\cdot}HCl$		9 (6–15) sc	>25 sc[f]	30 (22–40)
2q	p-$C(CH_3)_3$	H	263–265	MeCN–MeOH	45 (E)	$C_{15}H_{21}N{\cdot}HCl$		>200[f]	NT	NT
2r	p-(n-C_6H_{13})	H	181–183	MeCN	56 (E)	$C_{17}H_{25}N{\cdot}HCl$		>50[f]	NT	NT
2s	3-CF_3, 4-Cl	H	164–166	MeCN	73 (F)	$C_{12}H_{11}ClF_3N{\cdot}HCl$		~177	NT	NT
2t	3,4-Cl_2	H	180–181	i-PrOH	65 (F)	$C_{11}H_{11}Cl_2N{\cdot}HCl$		~141	NT	NT
2u	3-Br, 4-OCH_3	H	208–211	MeCN	43 (F)	$C_{12}H_{14}BrNO{\cdot}HCl$		>25[f]	NT	NT
2v	(+)-p-CH_3	H	210–212	MeCN–MeOH	73 (E)	$C_{12}H_{15}N{\cdot}HCl$	+66	17 (10–31)	<25[e]	NT
2w	(−)-p-CH_3	H	204–207	MeCN	37 (E)	$C_{12}H_{15}N{\cdot}HCl$	−64	>200[e]	>25[e]	NT
2x	(+)-p-Cl	H	190–192	MeCN	46 (E)	$C_{11}H_{12}ClN{\cdot}HCl$	+63	25 (17–37)	~13	19 (14–25)
2y	(−)-p-Cl	H	197–200	MeCN	58 (E)	$C_{11}H_{12}ClN{\cdot}HCl$	−67	>150[f]	>50[f]	<100[e]
20	p-OH	H	195–196	EtOH–Et_2O	33 (H)	$C_{11}H_{13}NO{\cdot}HCl$		>200[e]	NT	NT
22	m-OH	H	209–210	EtOH–MeCN	48 (H)	$C_{11}H_{13}NO{\cdot}HCl$		16 (11–23) sc	>25 sc[f]	NT
23	m-OCH_3	CH_3	148–150	MeCN	47 (E)	$C_{13}H_{17}NO{\cdot}HCl$		>100[f]	NT	NT
24	m-OH	CH_3	180–181	i-PrOH	15 (G)	$C_{12}H_{15}NO{\cdot}HCl$		>50[f]	~25 sc[e]	>50[f]
26	p-OC_2H_5	H	192–193	i-PrOH	55 (I)	$C_{13}H_{17}NO{\cdot}HCl$		~29	NT	NT
27a	p-CH_3	allyl	168–170	MeCN	76 (J)	$C_{15}H_{19}N{\cdot}HCl$		>50[f]	NT	NT
27b	p-CH_3	c-PrMe	187–189	MeCN	95 (J)	$C_{16}H_{21}N{\cdot}HCl$		>50[f]	NT	NT
27c	p-CH_3	n-C_6H_{13}	182–184	MeCN	92 (J)	$C_{18}H_{27}N{\cdot}HCl$		>50[f]	NT	NT
27d	p-CH_3	CH_3	197–198	i-PrOH	44 (K)	$C_{13}H_{17}N{\cdot}HCl$		20 (16–25)	24 (18–34)	16 (11–23)
29	p-Cl	CH_3	180–182	MeCN	55 (E)	$C_{12}H_{14}ClN{\cdot}HCl$		>50[f]	~60	<100[e]
36	(+)-H	H	169–171	MeCN	60 (E)	$C_{11}H_{13}N{\cdot}HCl$	+68	~125	~79	NT
37	(−)-H	H	170–172	MeCN	67 (E)	$C_{11}H_{13}N{\cdot}HCl$	−67	>200[f]	~43	<50[e]
ASA[h]								74 (60–93)	150 (118–193)	29 (19–42)
codeine phosphate								51 (33–81)	43 (29–62)	9 (7–11)
control[i]										

[a] The analyses of all new compounds were within 0.4% of the theoretical value for C, H, N, Br, Cl, and F. [b] Inflamed rat-paw reversal of abnormal (three-legged) gait. [c] Inflamed rat-paw pressure threshold method. [d] Mouse antiwrithing method. [e] Highest dose tested, active. [f] Highest dose tested, inactive. [g] Not tested. [h] Acetylsalicylic acid (aspirin). [i] The vehicle for oral (po) controls and solutions of test compounds was a 2% starch suspension in distilled water, containing 5% polyethylene glycol 400 and a drop of Tween 80. For subcutaneous administrations (sc), normal saline was used.

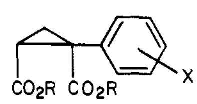
Table II. Physical Properties of Bromophenylacetates 5



no.	X	R	bp (mm Hg), °C	% yield (procedure)	formula[a]
5a	p-Cl	Et	107-113 (0.5)	79 (A)	$C_{10}H_{10}BrClO_2$
5b	p-CH_3	Me	115-120 (0.05)	57	$C_{10}H_{11}BrO_2$
5c	H	Et	138-145 (12)	85 (A)	$C_{10}H_{11}BrO_2$ [b]
5d	m-Cl	Et	86-95 (0.3)	80 (A)	$C_{10}H_{10}BrClO_2$
5e	o-Cl	Et	88-90 (0.1)	40 (A)	$C_{10}H_{10}BrClO_2$
5f	p-Br	Me	c	97 (A)	$C_9H_8Br_2O_2$
5g	p-CF_3	Me	92-95 (0.4)	39 (A)	$C_{10}H_8BrF_3O_2$
5h	m-CF_3	Et	75-77 (0.5)	83 (A)	$C_{11}H_9BrF_3O_2$
5i	p-F	Me	88-92 (0.15)	75 (A)	$C_9H_8BrFO_2$
5j	p-F	Et	140-143 (13)	70 (A)	$C_{10}H_{10}BrFO_2$
5k	o-CH_3	Me	115-120 (3.5)	60 (D)	$C_{10}H_{11}BrO_2$
5l	m-CH_3	Me	c	48 (D)	$C_{10}H_{13}BrO_3$
5m	p-OCH_3	Et	c	90 (A)	$C_{11}H_{13}BrO_3$ [d]
5n	m-OCH_3	Me	108-111 (0.3)	40 (D)	$C_{10}H_{11}BrO_3$
5o	p-C_2H_5	Et	135-140 (2.5)	62 (D)	$C_{12}H_{15}BrO_2$ [e]
5p	p-$CH(CH_3)_2$	Et	c	92 (D)	$C_{13}H_{17}BrO_2$ [f]
5q	p-$C(CH_3)_3$	Me	104-110 (0.03)	65 (A)	$C_{13}H_{17}BrO_2$
5r	p-(n-C_6H_{13})	Et	c	82 (D)	$C_{16}H_{23}BrO_2$
5s	3-CF_3, 4-Cl	Me	115-122 (0.75)	69 (A)	$C_{11}H_9BrClF_3O_2$
5t	3,4-Cl_2	Et	118-120 (0.05)	80 (A)	$C_{10}H_9BrCl_2O_2$
5u	3-Br, 4-OCH_3	Me	c	70 (A)	$C_{10}H_{10}Br_2O_3$

[a] The analyses were generally not within 0.4% of the calculated values for C, H, Br, Cl, and F. Compounds were used in subsequent reactions without further purification. [b] Lit.[34] bp 150-152 °C (13 mm). [c] Not purified. [d] Lit.[12] bp 150 °C (3 mm). [e] Lit.[12] bp 125 °C (4 mm). [f] Lit.[10] bp 142 °C (6 mm).

Table III. Physical Properties of 1-Aryl-1,2-cyclopropanedicarboxylates 6



no.	X	R	bp (mm Hg) or mp, °C	% yield	formula[a]
6a	p-Cl	Et	134-140 (0.5)	48	$C_{15}H_{17}ClO_4$
6b	p-CH_3	Me	58-59	86	$C_{14}H_{16}O_4$
6c	H	Et	124-130 (0.7)	53	$C_{15}H_{18}O_4$
6d	m-Cl	Et	128-132 (0.25)	60	$C_{15}H_{17}ClO_4$
6e	o-Cl	Et	130-135 (0.4)	40	$C_{15}H_{17}ClO_4$
6f	p-Br	Me	71-72	50	$C_{13}H_{13}BrO_4$
6g	p-CF_3	Me	128-135 (2)	66	$C_{14}H_{13}F_3O_4$
6h	m-CF_3	Et	107-111 (0.2)	50	$C_{16}H_{17}F_3O_4$
6i	p-F	Me	105-108 (0.3)	57	$C_{13}H_{13}FO_4$
6j	m-F	Et	115-120 (0.4)	47	$C_{15}H_{17}FO_4$
6k	o-CH_3	Me	98-103 (0.3)	67	$C_{14}H_{16}O_4$
6l	m-CH_3	Me	120-124 (0.5)	55	$C_{14}H_{16}O_4$
6m	p-OCH_3	Et		70	$C_{14}H_{16}O_5$ [b]
6n	m-OCH_3	Me	147-148 (0.5)	25	$C_{14}H_{16}O_5$
6o	p-C_2H_5	Et	120-125 (0.25)	25	$C_{17}H_{22}O_4$
6p	p-$CH(CH_3)_2$	Et		73	$C_{18}H_{24}O_4$ [b]
6q	p-$C(CH_3)_3$	Me, Et	145-160 (0.05)	60	$C_{19}H_{26}O_4$ [c]
6r	p-(n-C_6H_{13})	Et	187-192 (1)	50	$C_{21}H_{30}O_4$
6s	3-CF_3, 4-Cl	Me	115-120 (0.1)	66	$C_{14}H_{12}ClF_3O_4$
6t	3,4-Cl_2	Et	152-160 (0.5)	29	$C_{15}H_{16}Cl_2O_4$
6u	3-Br, 4-OCH_3	Me		30	$C_{14}H_{15}BrO_5$ [b]

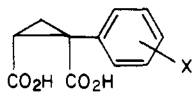
[a] The analyses were generally not within 0.4% of the calculated values for C, H, Br, Cl, and F. The ^{1}H NMR spectra were consistent with the assigned structures. The diesters were hydrolized to the diacids 7 without further purification. [b] Not purified. [c] Mixture of methyl and ethyl esters due to ester interchange during workup: mass spectrum, m/e 318, 304, 290.

give the *cis*-diesters **6** (Table III) as the major products. GLC analysis of some of the diesters (**6a,c,d**) showed a greater than 9:1 cis/trans ratio. The 1-aryl-1,2-cyclopropanedicarboxylates **6** were hydrolyzed to the corresponding diacids **7** (Table IV), and these were cyclized to the imides **1a–y** (Table V) using urea in refluxing xylene.

The required α-bromophenylacetates were prepared as follows (Scheme II): (1) Bromo esters **5a,c–j,m,q,s–u** were prepared by the reaction of an equimolar amount of *N*-bromosuccinimide (NBS) and the corresponding phenylacetate in carbon tetrachloride containing a catalytic amount of HBr[10] or benzoyl peroxide. In scale-up experiments, however, methyl *p*-methoxyphenylacetate (**9**) underwent bromination in the phenyl ring to give the 3-bromo-4-methoxy derivative **10**. (2) The *p*-methyl-

(10) Trust, R. I.; McEvoy, F. J.; Albright, J. D. *J. Med. Chem.* **1979**, *22*, 1068.

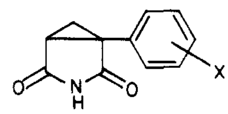
Table IV. Physical Properties of 1-Arylcyclopropanedicarboxylic Acids 7



no.[a]	X	mp, °C	recrystn solvent	% yield	formula[b]
7a	p-Cl	162-163	EtOAc-PE	54	$C_{11}H_9ClO_4$
7b	p-CH_3	188-190	EtOAc-Hex	80	$C_{12}H_{12}O_4$
7c	H	153-154	EtOAc-PE	80	$C_{11}H_{10}O_4$
7d	m-Cl	141-143	EtOAc-PE	36	$C_{11}H_9ClO_4$
7e	o-Cl				$C_{11}H_9ClO_4$[c]
7f	p-Br	72-74	H_2O	98	$C_{11}H_9BrO_4$
7g	p-CF_3	161-162	EtOAc-Hex	48	$C_{12}H_9F_3O_4$
7h	m-CF_3	198-200	EtOAc-Hex	60	$C_{12}H_9F_3O_4$
7i	p-F	175-176	EtOAc-Hex	45	$C_{11}H_9FO_4$
7j	m-F	142-143	EtOAc-PE	21	$C_{11}H_9FO_4$
7k	o-CH_3	165-167	EtOAc-Hex	33	$C_{12}H_{12}O_4$
7l	m-CH_3	158-160	MeCN	37	$C_{12}H_{12}O_4$
7m	p-OCH_3	184-186	EtOAc-PE	40	$C_{12}H_{12}O_5$
7n	m-OCH_3			59[d]	$C_{12}H_{12}O_5$
7o	p-C_2H_5	183-185	EtOAc-Hex	44	$C_{12}H_4O_4$
7p	p-$CH(CH_3)_2$	179-181	EtOAc	61	$C_{14}H_{16}O_4$[e]
7q	p-$C(CH_3)_3$	186-188	EtOAc-Hex	96	$C_{15}H_{18}O_4$
7r	p-(n-C_6H_{13})			84[d]	$C_{17}H_{22}O_4$
7s	3-CF_3, 4-Cl	167-169	EtOAc-Hex	33	$C_{12}H_8ClF_3O_4$
7t	3,4-Cl_2	170-174	EtOAc-Hex	40	$C_{11}H_8Cl_2O_4$
7u	3-Br, 4-OCH_3	188-192	H_2O	44	$C_{12}H_{11}BrO_5$

[a] Compounds 7v-y are described under Experimental Section. [b] The analyses of all new compounds were within 0.4% for C, H, Br, Cl, and F, except as otherwise noted. [c] Not isolated. [d] Yield of crude diacid. [e] H: calcd, 6.50; found, 6.04.

Table V. Physical Properties of 1-Aryl-1,2-cyclopropanedicarboximides 1



no.	X	mp, °C	recrystn solvent[a]	% yield	formula[b]
1a	p-Cl	141-143	EtOH	85	$C_{11}H_8ClNO_2$
1b	p-CH_3	114-116	EtOH	70	$C_{12}H_{11}NO_2$
1c	H	135-136[c]	EtOH-H_2O	85	$C_{11}H_9NO_2$
1d	m-Cl	131-133	EtOH	82	$C_{11}H_8ClNO_2$
1e	o-Cl	154-156	EtOAc-Hex	40	$C_{11}H_8ClNO_2$
1f	p-Br	150-151	MeOH	40	$C_{11}H_8BrNO_2$
1g	p-CF_3	164-165	EtOAc-Hex	30	$C_{12}H_8F_3NO_2$
1h	m-CF_3	113-115	EtOAc-PE	73	$C_{12}H_8F_3NO_2$
1i	p-F	146-148	EtOAc-PE	58	$C_{11}H_8FNO_2$
1j	m-F	123-125	EtOAc-PE	50	$C_{11}H_8FNO_2$
1k	o-CH_3	156-157	EtOAc-Hex	22	$C_{12}H_{11}NO_2$
1l	m-CH_3	129-131	EtOAc	50	$C_{12}H_{11}NO_2$
1m	p-OCH_3	129-130	EtOH-H_2O	60	$C_{12}H_{11}NO_3$
1n	m-OCH_3	125-127	i-Pr_2O	40	$C_{12}H_{11}NO_3$
1o	p-C_2H_5	102-104	EtOAc-Hex	44	$C_{13}H_{13}NO_2$
1p	p-$CH(CH_3)_2$	147-148	EtOAc-Hex	79	$C_{14}H_{15}NO_2$
1q	p-$C(CH_3)_3$	164-168	EtOAc-Hex	37	$C_{15}H_{17}NO_2$
1r	p-(n-C_6H_{13})	115-117	EtOAc-Hex	25	$C_{17}H_{21}NO_2$
1s	3-CF_3, 4-Cl	123-124	EtOAc-PE	43	$C_{12}H_7ClF_3NO_2$
1t	3,4-Cl_2	119-120	EtOAc-PE	84	$C_{11}H_7Cl_2NO_2$
1u	3-Br, 4-OCH_3	182-184	MeOH	51	$C_{12}H_{10}BrNO_3$
1v	(+)-p-CH_3	161-162	EtOAc-Hex	85	$C_{12}H_{11}NO_2$[d]
1w	(−)-p-CH_3	153-157	EtOAc-Hex	85	$C_{12}H_{11}NO_2$[e]
1x	(+)-p-Cl	172-173	EtOH	83	$C_{11}H_8ClNO_2$[f]
1y	(−)-p-Cl	172-173	EtOH	77	$C_{11}H_8ClNO_2$[g]

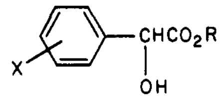
[a] PE, petroleum ether (30-60 °C). [b] The analyses of all new compounds were within 0.4% of the theoretical value for C, H, N, Br, Cl, and F. Optical rotations: c 1, MeOH. [c] Lit.[35] mp 130 °C. [d] $[\alpha]^{25}_D$ +77°. [e] $[\alpha]^{25}_D$ −74°. [f] $[\alpha]^{25}_D$ +61.9°. [g] $[\alpha]^{25}_D$ −62.3°.

phenylbromo ester **5b** was prepared from p-methylphenylacetic acid (**18**) by the method of Harpp[11] using thionyl chloride and NBS, followed by the reaction of the α-bromo acid chloride with cold methanol. No concomitant bromination of the methyl group was observed by NMR. (3) The preferred method for the synthesis of bromo esters **5k,l,n–p,r** was the reaction of phosphorus tribromide with mandelates **15a–f**[12] (Table VI). This

(11) Harpp, D. N.; Bao, L. Q.; Black, C. J.; Gleason, J. G.; Smith, R. A. J. Org. Chem. 1975, 40, 3420.

(12) Beletskaya, I.; Artamkina, G.; Shevlyagina, E.; Reutov, O. Zh. Obshch. Khim. 1964, 34, 321; Chem. Abstr. 1964, 60, 10707.

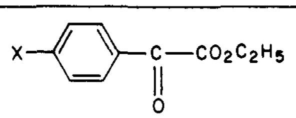
Table VI. Physical Properties of Substituted Mandelates 15



no.	X	R	bp (mmHg) or mp, °C	% yield (procedure)	formula[a]
15a	*o*-CH_3	CH_3	115-120 (2)	70 (B)[g]	$C_{10}H_{12}O_3$[b]
15b	*m*-CH_3	CH_3	50-52	66 (B)[g]	$C_{10}H_{12}O_3$
15c	*m*-OCH_3	CH_3	122-124 (0.3)	25 (B)[g]	$C_{10}H_{12}O_4$[c]
15d	*p*-C_2H_5	C_2H_5	108-112 (0.2)	70 (C)	$C_{12}H_{16}O_3$[d]
15e	*p*-$CH(CH_3)_2$	C_2H_5	38-40	94 (C)	$C_{13}H_{18}O_3$[e]
15f	*p*-(*n*-C_6H_{13})	C_2H_5	29-31	94 (C)	$C_{16}H_{24}O_3$[f]

[a] The analyses of all new compounds were within 0.4% for C and H, except as otherwise noted. [b] C: calcd, 66.6; found, 65.6. [c] C: calcd, 61.2; found, 60.4. [d] Lit.[12] bp 155 °C (11 mm). [e] Lit.[15] mp not given. C: calcd, 70.2; found, 71.1. [f] C: calcd, 72.4; found, 72.9. H: calcd, 9.50; found, 8.87. [g] Based on starting benzaldehyde.

Table VII. Physical Properties of (4-Alkylphenyl)glyoxylates 17



no.	X	bp (mmHg), °C	% yield	formula[a]
17a	C_2H_5	115-120 (0.4)	38	$C_{12}H_{14}O_3$[b]
17b	$CH(CH_3)_2$	130-135 (0.75)	60	$C_{13}H_{16}O_3$
17c	*n*-C_6H_{13}	130 (0.3)	66	$C_{16}H_{22}O_3$

[a] The analyses of all new compounds were within 0.4% for C and H. [b] Lit.[14] bp 161 °C (11 mm).

method avoids the bromination of activated carbon atoms elsewhere in the molecule. The mandelates **15a–c** were prepared by the conversion of the appropriate benzaldehyde **11** to the cyanohydrin, followed by hydrolysis[13] to the mixed amide–acid and then esterification.[14] The *p*-alkylmandelates **15d–f** were prepared by Friedel–Crafts acylation of the appropriate alkylbenzene **16a–c** with ethyl oxalyl chloride–aluminum chloride to give glyoxylates **17a–c** (Table VII), which were catalytically hydrogenated to the mandelates.[15]

Demethylation of the methoxyl derivatives (Scheme III) **2m** and **2n** with sodium ethyl mercaptide in DMF[16] gave the *N*-formyl phenols **19** and **21**, respectively.[17] Alkaline hydrolysis of the formamides gave the desired phenolic amines **20** and **22**. This procedure was used to convert the *N*-methyl-*m*-methoxyphenyl derivative **23** to the phenol **24**. The *N*-formyl-*p*-hydroxyphenyl derivative **19** was alkylated with ethyl iodide to give **25**, followed by alkaline hydrolysis of the amide to give the *p*-ethoxyphenyl derivative **26**.

The *N*-allyl, *N*-(cyclopropylmethyl), and *N*-(*n*-hexyl) derivatives **27a–c**, respectively, were prepared by the reaction of the secondary amine **2b** with the appropriate alkyl bromide (Scheme IV). The *N*-methyl derivative **27d** was prepared by Eschweiler–Clarke methylation[18] of **2b**.

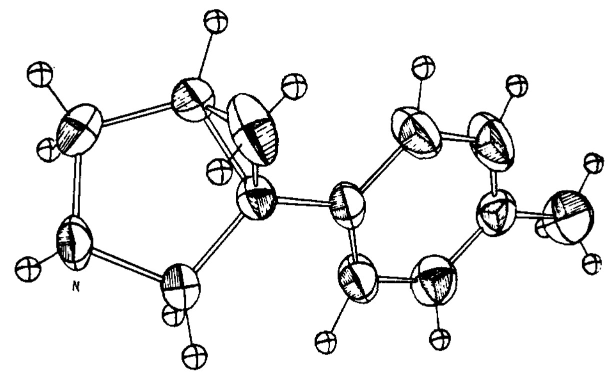


Figure 1. ORTEP drawing of **2v** showing 1*R*,5*S* absolute configuration.

Table VIII. Coordinates of 2v

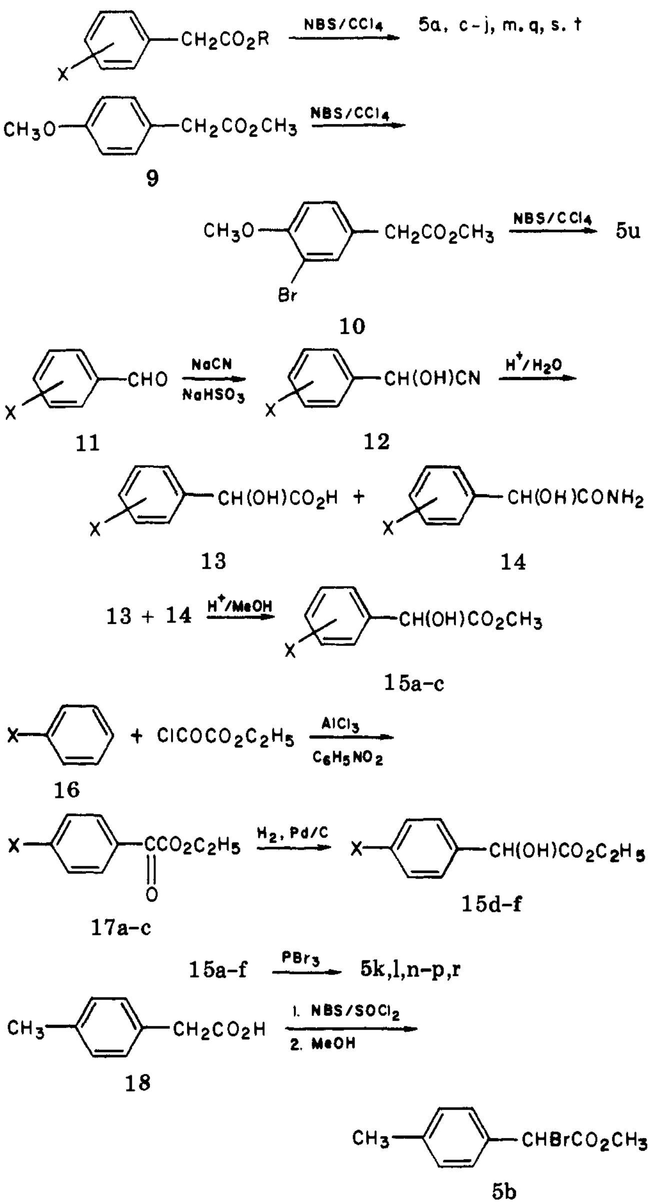
atom	*X*	*Y*	*Z*
Cl-1	0.2402	0.6865	−0.8808
C-1	−0.0519	0.1766	0.0985
C-2	0.0308	0.3567	−0.1076
C-3	0.1191	0.1996	0.4051
C-4	−0.0670	0.2692	−0.0852
C-5	0.1059	0.2551	0.1641
C-6	−0.1281	0.2730	−0.1730
C-7	0.0046	0.1687	0.1807
C-8	−0.0257	0.3635	−0.1889
C-9	0.0455	0.2624	0.0739
N-1	0.2058	0.2902	0.1121
C-10	0.1961	0.1110	0.1179
C-11	0.1490	0.3661	0.0555
C-12	0.1359	0.0946	0.2094

The *p*-chlorophenyl imide **1a** was treated with sodium hydride in DMF and then with methyl iodide to give the *N*-methyl derivative **28**. This was subsequently reduced to **29** with sodium bis(2-methoxyethoxy)aluminum hydride.

The resolutions (Scheme V) of the *p*-methyl (**2b**) and the *p*-chloro (**2a**) congeners were accomplished at the diacid stage. Thus, the *p*-methylphenyl diacid **7b** with (−)-α-methyl-1-naphthalenemethylamine gave the resolved salt **30** and then the (+)-diacid **7v**, while (−)-diacid **7w** was obtained via the resolved brucine salt **31**. The (+)-*p*-chlorophenyl diacid **7x** was obtained from **7a** with (−)-2-aminobutanol [(−)-2AB] via the salt **32**, and the (−)-enantiomer **7y** was obtained with (+)-2AB via the salt **33**.[19] The (+)-*p*-chlorophenyl imide **1x** was dechlorinated with palladium on charcoal and hydrogen (Scheme VI) to the

(13) Corson, B. B.; Dodge, R. A.; Harris, S. A.; Yeaw, J. S. In "Organic Syntheses"; Wiley: New York, 1941; Collect. Vol. I, p 336.
(14) Kindler, K. *Chem. Ber.* **1941**, *74B*, 315.
(15) Kindler, K. *Chem. Ber.* **1943**, *76B*, 308.
(16) Mirrington, R. N.; Fuetrill, G. I. *Org. Synth.* **1973**, *53*, 90.
(17) N-Formylation has been observed for *N*-methylaniline in the presence of NaH–DMF: Pettit, G. *J. Org. Chem.* **1959**, *24*, 895. *Ibid.* **1961**, *26*, 2563.
(18) Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571.
(19) Hofmann, C. M.; Osterberg, A. C.; Greenblatt, E. N.; Tedeschi, D. H. U.S. Patent 3892772, 1975.

Scheme II. Synthesis of Bromo Esters



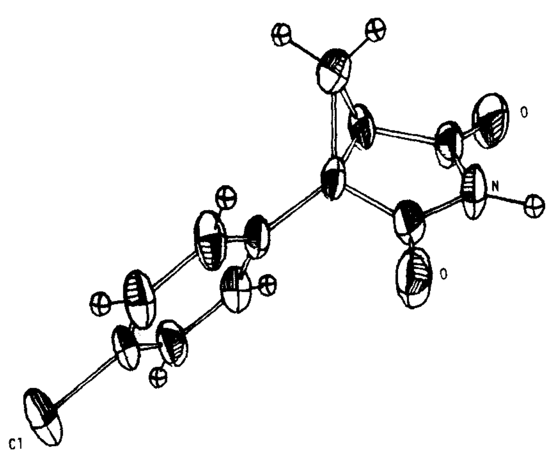
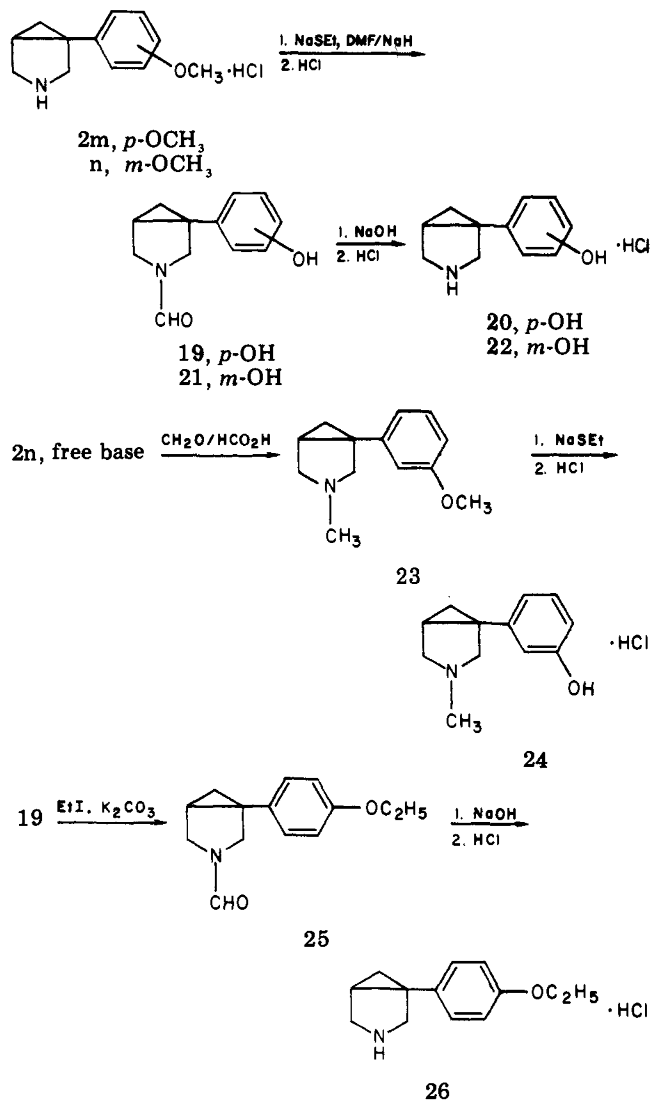


Figure 2. ORTEP drawing of 1y showing 1S,2R absolute configuration.

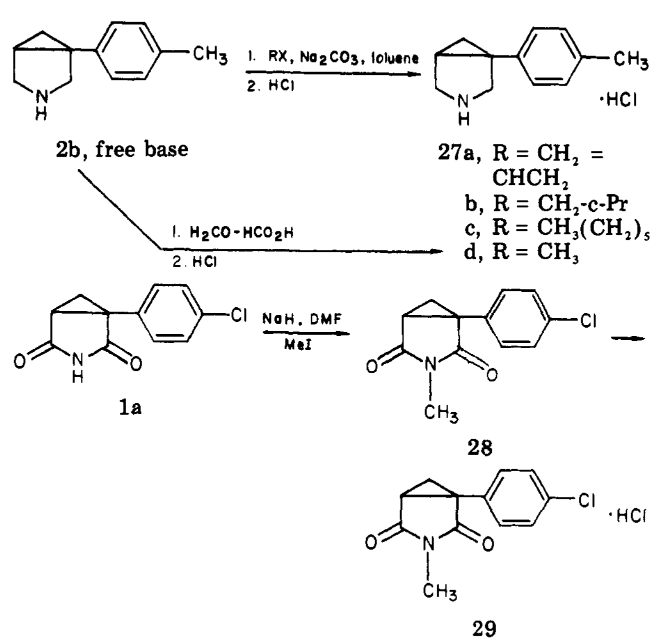
(+)-phenyl imide 34. Likewise, (−)-p-chlorophenyl imide 1y was converted to the (−)-phenyl imide 35.

X-ray Crystallography. The absolute configuration of the (+)-p-methylphenyl enantiomer 2v was found to be 1R,5S by single-crystal X-ray analysis. An ORTEP[20] drawing of the molecule showing the nonhydrogen atoms is depicted in Figure 1. The final coordinates for nonhydrogen

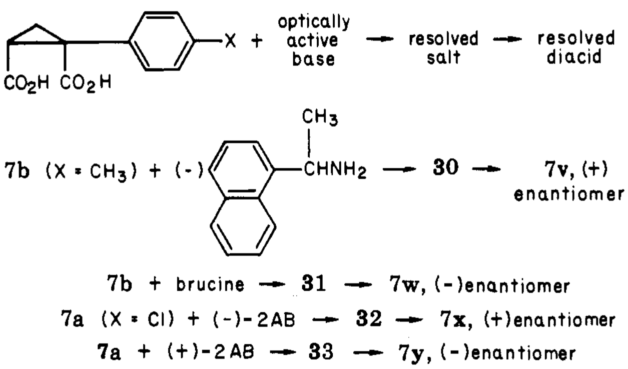
Scheme III



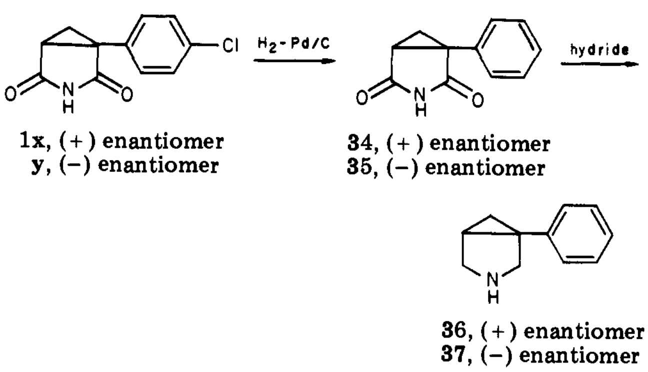
Scheme IV. Alkylations



Scheme V. Resolution



Scheme VI. Enantiomers of Phenyl Analogue 2c



atoms with their standard deviations are listed in Table VIII. Similarly, the absolute configuration of the (-)-*p*-chlorophenyl imide **1y** was found to be 1*S*,2*R*. An ORTEP[20] drawing of **1y** is depicted in Figure 2, with the coordinates for nonhydrogen atoms appearing in Table IX. On this basis, the (+)-*p*-chlorophenyl- and (+)-phenylazabicyclo-[3.1.0]hexanes, **2x** and **36**, respectively, have the 1*R*,5*S* absolute configuration.

Pharmacology. The potential analgesic activity of the azabicyclohexanes was assessed by their ability to reverse the abnormal (three-legged) gait in rats.[21] Selected compounds having an $ED_{50} < 100$ mg/kg were than tested by the inflamed rat paw pressure threshold method[22] and the mouse antiwrithing method[23] using phenyl-*p*-quinone. Activities of azabicyclohexanes, as well as the reference agents acetylsalicylic acid (aspirin) and codeine, are listed in Table I.

A structure–activity relationship was derived by examining the "abnormal gait" data of Table I. For the substituents Cl, CH_3, and OCH_3 the para-substituted compounds **2a**,**b**,**m**, respectively, were more potent than the corresponding meta-substituted **2d**,**l**,**n**. The ortho-substituted **2e** and **2k** were inactive. The particular substituent effect that governs potency in this test is not evident; however, it can be seen that *p*-alkyl substituents, such as CH_3 (**2b**) and C_2H_5 (**2o**), impart the greatest degree of activity of the substituents studied. Potency diminished for compounds in which the alkyl group was larger than ethyl, while the *p*-*tert*-butyl analogue **2q** was inactive. The effect of optical isomerism is clearly discernible from the greater potencies of the 1*R*,5*S*-(+) enantiomers **2v** and **2x**, as compared to the relative inactivity of the 1*S*,5*R*-(-) antipodes **2w** and **2y**.

(20) Johnson, C. K. "ORTEP"; Oak Ridge National Laboratory: Oak Ridge, TN, 1965; Report ORNL-3794.
(21) Atkinson, D. C.; Cowan, A. *J. Pharm. Pharmacol.* **1974**, *26*, 727.
(22) Randall, L. O.; Selitto, J. J. *Arch. Int. Pharmacodyn. Ther.* **1957**, *111*, 409.
(23) Hendershot, L. C.; Forsaith, J. *J. Pharmacol. Exp. Ther.* **1958**, *125*, 237.

Table IX. Coordinates of 1y

atom	X	Y	Z
Cl-1	0.175900	0.242680	0.156900
C-1	0.269170	0.325920	0.154110
C-2	0.282170	0.397370	0.337360
C-3	0.357190	0.464360	0.339900
C-4	0.414530	0.456970	0.152590
C-5	0.398200	0.383840	-0.035740
C-6	0.324170	0.316850	-0.036120
C-7	0.497510	0.524790	0.172010
C-8	0.500610	0.653970	-0.152590
C-9	0.541770	0.581320	-0.038790
C-10	0.565500	0.474370	0.329050
C-12	0.635220	0.556350	0.007810
N-1	0.643270	0.503310	0.223400
O-1	0.556720	0.418170	0.503680
O-2	0.693990	0.580570	-0.126620

The effects of N-alkylation are not uniform. For the *p*-Cl analogue **2a**, activity is diminished in going to the *N*-Me derivative **29**, whereas for the *p*-CH_3 analogue **2b**, conversion to the *N*-Me derivative **27d** is accompanied by no loss in potency. However, when the allyl, cyclopropylmethyl, and *n*-hexyl groups were incorporated into **2b** to give **27a–c**, respectively, there was a considerable loss of analgesic potency, and these compounds were not morphine antagonists. These groups are generally used as N-substituents for narcotic–antagonist type analgesics.[24]

The *p*-tolyl analogue **2b** was chosen for further study as an analgesic based on its uniform potency in all three screening tests. It was essentially inactive in the high-intensity rat tail-flick procedure[25] and by the mouse hot plate method.[26] It did not show physical dependence liability when tested by a subcutaneous pellet implant procedure[27] using an incremental intraperitoneal dosing schedule[28] (with naloxone challenge). Single-dose substitution studies in morphine-dependent rhesus monkeys[29] produced transitory effects that did not necessarily imply morphine-like properties. Primary dependence studies in rhesus monkeys over a period of 40 days did not produce morphine-like physical dependence.[30] Relatively little tolerance was seen to develop.

Experimental Section

Melting points were determined in open capillary tubes with a Mel-Temp apparatus and are uncorrected. Elemental analyses are within ±0.4% of theory except where indicated. ^1H NMR

(24) Bowman, R. E.; Collier, H. O. J.; Hattersley, P. J.; Lockhart, I. M.; Peters, D. J.; Schneider, C.; Webb, N. E.; Wright, M. *J. Med. Chem.* **1973**, *16*, 1177. Bowman, R. E.; Collier, H. O. J.; Lockhart, I. M.; Schneider, C.; Webb, N. E.; Wright, M. *Ibid.* **1973**, *16*, 1181.
(25) Gray, W. D.; Osterberg, A. C.; Scuto, T. J. *J. Pharmacol. Exp. Ther.* **1970**, *172*, 154.
(26) Eddy, N. E.; Touchberry, C. F.; Lieberman, J. E. *J. Pharmacol. Exp. Ther.* **1950**, *98*, 121.
(27) Way, E. L.; Loh, M. M.; Shen, F. S. *J. Pharmacol. Exp. Ther.* **1969**, *167*, 1.
(28) Saelens, J. K.; Granat, F. R.; Sawyer, W. K. *Arch. Int. Pharmacodyn. Ther.* **1971**, *190*, 213.
(29) Aceto, M. D.; Harris, L. S.; Dewey, W. L.; May, E. L. Proceedings of the 41st Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Addendum; Philadelphia, PA, June 6–9, 1979; National Research Council, Committee on Problems of Drug Dependence: Washington, DC, 1979; p 341.
(30) Aceto, M. D.; Harris, L. S.; Dewey, W. L.; May, E. L., Committee on Problems of Drug Dependence, private communication, 1979.

measurements were obtained on Varian Associates HA-100A and A60 spectrometers, and chemical shifts are reported in δ downfield from tetramethylsilane as the internal standard. ^{1}H NMR spectra were obtained for all intermediates and final products and were consistent with the assigned structures. Where noted, specific synthetic procedures are representative of general methods used for the preparation of the compounds in Tables I–VII. Vitride is a trade name for sodium bis(2-methoxyethoxy)aluminum hydride in benzene or toluene.

Bromo Esters 5a,c–j,m,q,s–u. Procedure A (Table II). To a mixture of 0.79 mol of arylacetic acid ester and 146 g (0.82 mol) of NBS in 2 L of CCl_4 was added 3 drops of 48% HBr, and this mixture was refluxed until the starting material was consumed (NMR). The cooled solution was filtered through a pad of magnesium silicate to remove crystallized and dissolved succinimide, and the filtrate was evaporated in vacuo to give the bromo ester, which could be used in the subsequent step without further purification.

Methyl (3-Bromo-4-methoxyphenyl)acetate (10). The above procedure, using 395 g (2.19 mol) of methyl *p*-methoxyphenylacetate and 403 g (2.26 mol) of NBS in 3 L of CCl_4 containing 0.5 mL of 48% HBr, gave the ring-brominated product 10: bp 176–178 °C (13 mm); ^{1}H NMR (CCl_4) δ 3.44 (s, 2, CH_2), 3.64 (s, 3, ester OCH_3), 3.83 (s, 3, phenyl OCH_3), 6.74 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 7.10 (dd, 1, $J_{5,6}$ = 8 Hz, $J_{2,6}$ = 3 Hz, H-6), 7.38 (d, 1, $J_{2,6}$ = 3 Hz, H-2). Anal. ($C_{10}H_{11}BrO_3$) H; C: calcd, 46.4; found, 47.4. Br: calcd, 30.8; found 31.9.

Methyl Bromo(4-methylphenyl)acetate (5b). To 120 g (0.80 mol) of *p*-tolylacetic acid was added 230 mL (1.6 mol) of $SOCl_2$, and this solution was allowed to stand at room temperature for 2 h, after which it was warmed to 60 °C for 1 h. To this solution was added 285 g (1.60 mol) of NBS and 10 drops of 48% HBr, and this mixture was refluxed in an oil bath at 90 °C for 1 h. An additional 90 mL of $SOCl_2$ was added and refluxing was continued for 45 min, at which time bromine evolution had ceased (exothermic at this point). The mixture was distilled in vacuo to remove 250 mL of $SOCl_2$, and the residual liquid was poured into 500 mL of cold MeOH with stirring and ice cooling over 15 min. This solution was evaporated in vacuo to give a dark oil, which was then dissolved in 100 mL of $CHCl_3$. The solution was washed with 500 mL of H_2O, dried over $MgSO_4$, and filtered through magnesium silicate. The filtrate was evaporated in vacuo to give a dark oil, which was distilled to give 110.6 g (57%) of **5b** as a pale yellow liquid: bp 115–120 °C (0.05 mm); ^{1}H NMR (CCl_4) δ 2.28 (s, 3, CH_3), 3.66 (s, 3, OCH_3), 5.22 (s, 1, CHBr), 7.06 and 7.31 (m, 4, arom H). Anal. ($C_{10}H_{11}BrO_2$) H; C: calcd, 49.4; found, 51.8. Br: calcd, 32.9; found, 31.5.

Ethyl (4-Alkylphenyl)glyoxylates (17a–c; Table VII). Alkylbenzenes (ethylbenzene, cumene, and *n*-hexylbenzene) were acylated with ethyloxalyl chloride and $AlCl_3$ in nitrobenzene to give **17a–c**, respectively.

Methyl Mandelates (15a–c). Procedure B (Table VI). The appropriate benzaldehyde, 11, was converted to the cyanohydrin with KCN–$NaHSO_3$, and this product was hydrolyzed to an acid (13)–amide (14) mixture, which was then esterified with MeOH–H_2SO_4 to give **15a–c**.

Ethyl 4′-Alkylmandelates (15d–f). Procedure C (Table VI). Glyoxylates **17a–c** were hydrogenated over Pd/C (10%) in EtOH to give **15d–f**.

Bromo Esters 5k,l,n–p,r. Procedure D (Table II). Mandelates **15a–f** were converted to the corresponding bromo esters with PBr_3 in $CHCl_3$. The reaction mixture, after being washed with water and dried over $MgSO_4$, was filtered through a pad of magnesium silicate. Evaporation of the solvent gave **5k,l,n–p,r**, which were suitable for further reactions with no additional purification.

Diethyl and Dimethyl 1-Arylcyclopropanedicarboxylates (6a–u; Table III). To a stirred slurry of 17 g (0.35 mol) of NaH (50% in mineral oil) in 1 L of anhydrous Et_2O was added 1 mL of alcohol, followed by a solution of 0.35 mol of bromo ester **5** in 0.70 mol (100% excess) of methyl or ethyl acrylate (depending on the alcohol moiety of the bromo ester) and 10 mL of alcohol over a 2-h period during which the temperature was maintained between 25 and 30 °C. The mixture was stirred at room temperature for 24 h, and then unreacted NaH was decomposed with 10 mL of the initially used alcohol; 250 mL of H_2O was added. The organic layer was dried over $MgSO_4$ and filtered, and the ether was removed in vacuo to give **6a–u**.

1-Arylcyclopropanedicarboxylic Acids (7a–u; Table IV). A mixture of 0.45 mol of diesters **6a–u** and 66 g (1.0 mol) of KOH (85%) in 1 L of 1:1 EtOH–H_2O was heated at reflux for 6 h and then was evaporated to one-half volume. The aqueous solution was extracted with Et_2O, chilled in ice, and then made acidic with 100 mL of 12 N HCl. Crystalline product was collected by filtration and was recrystallized to give the diacid **7a–u**. Compounds **7v–y** are described below.

1-Arylcyclopropanedicarboximides (1a–y; Table V). A mixture of 0.038 mol of **7a–y** and 3.5 g (0.079 mol) of urea in 250 mL of xylene was heated at reflux for 6–20 h and was then evaporated to dryness in vacuo to give **1a–y**.

1-(4-Methylphenyl)-3-azabicyclo[3.1.0]hexane Hydrochloride (2b; Table I). Procedure E. To a stirred slurry of 20.1 g (0.100 mol) of **1b** in 600 mL of benzene or toluene was added 160 mL of Vitride (70% in benzene or toluene) under N_2 over 10 min. This solution was stirred at room temperature for 0.5 h and at reflux for 2 h. To the cooled solution was cautiously added 160 mL of 10 N NaOH (evolution of H_2 occurs initially), and the organic layer was washed with two portions of water and dried over $MgSO_4$. This solution was filtered and the filtrate was evaporated in vacuo to give the amine as an oil. A solution of the amine in 250 mL of ether was saturated with HCl gas, and the precipitated solid was recrystallized from MeCN to give 12.1 g (58%) of **2b**: mp 207–208 °C; ^{1}H NMR (D_2O) δ 1.28 (m, 2, cyclopropyl CH_2), 2.15 (m, 1, cyclopropyl CH), 2.41 (s, 3, CH_3), 3.82 (m, 4, CH_2NCH_2), 7.28 (s, 4, aromatic H).

Procedure F. To 40 mL (0.040 mol) of 1 M BH_3–THF, stirred at 0 °C under N_2, was added a solution of 0.010 mol of the imide in 50 mL of dry THF over 15 min. This solution was stirred at room temperature for 15 min and then warmed on a steam bath for 1 h. The solution was then cooled in ice, 20 mL of 6 N HCl was added cautiously, and solvent was then removed in vacuo. The residual material was combined with 75 mL of 5 N NaOH and the mixture was extracted with ether. The ether extract was washed twice with water, dried over $MgSO_4$, and filtered. The filtrate was saturated with HCl gas and the precipitated solid was recrystallized to give the amine hydrochloride.

1-(4-Hydroxyphenyl)-3-azabicyclo[3.1.0]hexane-3-carboxaldehyde (19). Procedure G. To a slurry of 7.2 g (0.15 mol) of NaH (50% oil dispersion) in 170 mL of DMF at 0–5 °C was added a solution of 10.1 mL of EtSH in 85 mL of DMF over a 15-min period. An additional 3.16 g (0.07 mol) portion of NaH was added, followed by 14.4 g (0.064 mol) of the amine hydrochloride **2m**. After the addition of 40 mL of DMF, the mixture was refluxed for 4 h and the solvent was then removed in vacuo. The residue was dissolved in 150 mL of H_2O and mineral oil was extracted with ether. The aqueous solution was made acidic with AcOH and the precipitated crystals were collected by filtration to give 9.8 g (75%) of **19** as tan crystals: mp 166–167 °C; IR (KBr) 1640 (CHO) cm^{-1}. Anal. ($C_{12}H_{13}NO_2$) C, H, N.

1-(3-Hydroxyphenyl)-3-azabicyclo[3.1.0]hexane-3-carboxaldehyde (21). The above procedure with **2n** gave **21** as colorless crystals (77%), mp 129–130 °C. Anal. ($C_{12}H_{13}NO_2$) C, H, N.

1-(4-Hydroxyphenyl)-3-azabicyclo[3.1.0]hexane Hydrochloride (20). Procedure H. A solution of 4.50 g (0.022 mol) of **19** in 40 mL of 1.25 N NaOH was heated on a steam bath for 3 h under N_2. The chilled solution was neutralized with AcOH and filtered to give 3.30 g of the amine as a tan powder, mp 174–177 °C. This was dissolved in 20 mL of absolute EtOH, and HCl gas was bubbled into the solution. Evaporation of the solvent gave 3.78 g (81%) of tan crystals, mp 193–195 °C. A sample was recrystallized from EtOH to give **20** as tan crystals: mp 195–196 °C; ^{1}H NMR (D_2O) δ 1.00 (dd, 1, *J* = 4 and 8 Hz, cyclopropyl CH_2), 1.20 (t, 1, *J* = 8 Hz, cyclopropyl CH_2), 2.40 (quint, 1, *J* = 4 Hz, cyclopropyl CH), 3.65 (m, 4, CH_2NCH_2), 6.87 (d, 2, arom H), 7.22 (d, 2, arom H). Anal. ($C_{11}H_{13}NO\cdot HCl$) C, H, N, Cl.

1-(4-Ethoxyphenyl)-3-azabicyclo[3.1.0]hexane-3-carboxaldehyde (25). To a stirred mixture of 1.0 g (0.005 mol) of **19** and 0.7 g (0.005 mol) of K_2CO_3 in 25 mL of absolute EtOH was added a solution of 3.2 g (0.02 mol) of EtI in 10 mL of absolute EtOH. The mixture was refluxed for 2 h and then was filtered and evaporated. The residual mixture of crystals and liquid was combined with H_2O, this was extracted with $CHCl_3$, and the extract was dried over $MgSO_4$ and evaporated to give 1.0 g (86%) of **25** as colorless crystals. Recrystallization from hexane gave 0.31 g of colorless crystals: mp 48–51 °C; ^1H NMR ($CDCl_3$) δ 0.74 (t, 1, J = 5 Hz, cyclopropyl CH_2), 1.06 (dd, 1, J = 5 and 8 Hz, cyclopropyl CH_2), 1.38 (t, 3, CH_3), 1.76 (quint, 1, cyclopropyl CH), 3.3–4.3 (m, 6, CH_2NCH_2 and OCH_2), 6.82 (d, 2, arom H), 7.14 (d, 2, arom H), 8.16 and 8.20 (s, 1, CHO); IR (KBr) 1670 (C=O) cm^{-1}. Anal. ($C_{14}H_{17}NO_2$) C, H, N.

1-(4-Ethoxyphenyl)-3-azabicyclo[3.1.0]hexane Hydrochloride (26). Procedure I. Hydrolysis of **25**, as above, gave **26**, free base, as colorless crystals (55%), mp 48–49 °C. This was combined with EtOH–HCl to give **26** as colorless crystals from EtOH–Et_2O, mp 192–193 °C. Anal. ($C_{13}H_{18}NOCl$) C, H, N, Cl.

1-(4-Methylphenyl)-3-alkyl-3-azabicyclo[3.1.0]hexanes (27a–c; Table I). Procedure J. A mixture of 7.8 g (0.045 mol) of **2b** (free base), 0.05 mol of the alkyl bromide, and 9.4 g (0.06 mol) of Na_2CO_3 in 60 mL of toluene was stirred and heated under reflux for 17–20 h. The reaction mixture was cooled and treated with 10 mL of 5 N NaOH. The phases were separated and the alkaline layer was extracted twice with toluene. The combined toluene phases were washed with water, dried over Na_2SO_4, filtered, and concentrated to remove the solvent. The residual oil was acidified with 25 mL of 3 N HCl–EtOH and diluted with ether. The crystalline hydrochloride was collected, washed with ether, and dried. The hydrochlorides were purified by recrystallization from MeCN or MeOH.

3-Methyl-1-(4-methylphenyl)-3-azabicyclo[3.1.0]hexane Hydrochloride (27d). Procedure K. A solution of 10.0 g (0.060 mol) of **2b** (free base) in 120 mL of 97% HCO_2H and 105 mL 37% formaldehyde was heated on a steam bath for 3 h and then was evaporated to a white paste. This was combined with an excess of 5 N NaOH, the mixture was extracted with ether, and the extract was dried over Na_2SO_4. The filtered ether solution was saturated with HCl gas to give 12.5 g (93%) of **27d**, mp 193–197 °C. Recrystallization from *i*-PrOH gave 9.5 g of **27d** as colorless crystals, mp 195–198 °C. Anal. ($C_{13}H_{19}NCl$) C, H, N, Cl.

***N*-Methyl-1-(4-chlorophenyl)-1,2-cyclopropanedicarboximide (28).** To a stirred solution of 11.1 g (0.050 mol) of **1a** in 50 mL of anhydrous DMF was added 2.5 g (0.05 mol) of NaH (54% in mineral oil) over 15 min. To this solution was added 5 mL of MeI, and the solution was stirred for 1 h and then poured into 125 mL of H_2O. The crystals which formed were collected by filtration, washed with cold hexane, and recrystallized from EtOAc–heptane to give 8.05 g of **28** (70%) as colorless crystals, mp 103.5–105.5 °C. Anal. ($C_{12}H_{10}ClNO_2$) C, H, N, Cl.

(1*R*,2*S*)-(+)-1-(4-Methylphenyl)-1,2-cyclopropanedicarboxylic Acid Monosalt with (−)-α-Methyl-1-naphthalenemethylamine (30). A solution of 94.8 g (0.43 mol) of racemic **7b** and 73.8 g (0.43 mol) of (−)-α-methyl-1-naphthalenemethylamine in 300 mL of THF was diluted with 300 mL of Et_2O and was left at room temperature until crystallization was complete to give 49.5 g (59%) of salt **30**: mp 85–88 °C; $[\alpha]^{25}_D$ +25° (MeOH). Anal. ($C_{24}H_{25}NO_4$) H, N; C: calcd, 73.6; found, 72.9.

(1*R*,2*S*)-(+)-1-(4-Methylphenyl)-1,2-cyclopropanedicarboxylic Acid (7v). Liberation of the acid from **30** gave **7v** (92%): mp 192–193 °C; $[\alpha]^{25}_D$ +196° (MeOH) (unchanged by recrystallization from MeCN). Anal. ($C_{12}H_{12}O_4$) C, H.

(1*S*,2*R*)-(−)-1-(4-Methylphenyl)-1,2-cyclopropanedicarboxylic Acid Monosalt with Brucine (31). Resolution of racemic **7b** with brucine tetrahydrate in absolute EtOH gave the salt **31**: mp 145–150 °C; $[\alpha]^{25}_D$ −47° (MeOH). Anal. ($C_{35}H_{40}N_2O_9 \cdot H_2O$) C, N; H: calcd, 6.37; found, 5.89.

(1*S*,2*R*)-(−)-1-(4-Methylphenyl)-1,2-cyclopropanedicarboxylic Acid (7w). The acid was liberated from the salt **31** to give **7w** (57%): mp 192–193 °C; $[\alpha]^{25}_D$ −189°. (MeOH) (96.3% optical purity based on **7v**). Anal. ($C_{12}H_{12}O_4$) C, H.

(1*S*,2*R*)-(−)-1-(4-Chlorophenyl)-1,2-cyclopropanedicarboxylic Acid Salt with (+)-2-Aminobutanol (1:2) (33). Racemic **7a** was combined with 2 molar equiv of (+)-2-aminobutanol in acetone to give **33** (93%): mp 153–154 °C; $[\alpha]^{25}_D$ −99° (H_2O). Anal. ($C_{19}H_{31}ClN_2O_6$) C, H, N, Cl.

(1*R*,2*S*)-(+)-1-(4-Chlorophenyl)-1,2-cyclopropanedicarboxylic Acid Salt with (−)-2-Aminobutanol (1:2) (32). The residue on evaporation of the filtrate in the preceding resolution was combined with 2 molar equiv of (−)-2-aminobutanol to give **32** (90%): mp 154–155 °C; $[\alpha]^{25}_D$ +96° (H_2O). Anal. ($C_{19}H_{31}ClN_2O_6$) C, H, N, Cl.

(1*R*,2*S*)-(+)-1-(4-Chlorophenyl)-1,2-cyclopropanedicarboxylic Acid (7x). Liberation of the acid from the salt **32** gave **7x** (80%) as colorless crystals: mp 173.5–175.5 °C dec; $[\alpha]^{25}_D$ +183° (EtOH). Anal. ($C_{11}H_9ClO_4$) C, H, Cl.

(1*S*,2*R*)-(−)-1-(4-Chlorophenyl)-1,2-cyclopropanedicarboxylic Acid (7y). Liberation of the acid from the salt **33** gave **7y** (41%) as colorless crystals: mp 173–175 °C dec; $[\alpha]^{25}_D$ −187° (EtOH). Anal. ($C_{11}H_9ClO_4$) C, H, Cl.

(1*R*,2*S*)-(+)-1-Phenyl-1,2-cyclopropanedicarboximide (34). The imide **1x** was dechlorinated with H_2 at 2 atm over 10% Pd/C in EtOH–NH_4OH to give **34** (38%): mp 138–138.5 °C; $[\alpha]^{25}_D$ +74° (MeOH). Anal. ($C_{11}H_9NO_2$) C, H, N.

(1*S*,2*R*)-(−)-1-Phenyl-1,2-cyclopropanedicarboximide (35). The imide **1y** was dechlorinated with H_2 at 2 atm over 10% Pd/C in EtOH–NH_4OH to give **35** (43%): mp 137.5–138.5 °C; $[\alpha]^{25}_D$ −75° (MeOH). Anal. ($C_{11}H_9NO_2$) C, H, N.

Pharmacological Testing Methods. Analgesic activity was determined in the following manner (Table I).

(1) Inflamed Rat Paw-Pressure Threshold Method. A modification of the method of Randall and Selitto[22] was used to measure the pain threshold of rats whose paws were made sensitive to pressure by the injection of a 20% aqueous suspension (0.1 mL) of brewers' yeast into the plantar surface of the left hind paw. Pressure-pain thresholds were always recorded 2 h after brewers' yeast. Analgesic agents were administered at various times before or after the yeast, depending on the duration of action and time of peak effect. A ≥100% elevation in pressure threshold was considered a positive analgesic response; the dose estimated to cause a ≥100% elevation in 50% of the animals tested was defined as the ED_{50}. ED_{50} values and 95% confidence limits were calculated according to the linear arc sine transformation method of Finney.[31]

(2) Inflamed Rat Paw-Reversal of Abnormal (Three-Legged) Gait. A modification of the procedure of Atkinson and Cowan[21] was used. Brewers' yeast was injected into the plantar surface of the left hind paw of each rat and 3 h later a predrug assessment was determined for each rat. The assessment was based on a scale of 0 (normal gait) to 2 (maximum abnormal walking behavior). Rats with a gait score of 2 were then treated with vehicle or test compound, and postdrug scores were determined at selected time intervals. A ≥50% reduction of abnormal gait was considered a positive analgesic response; the dose estimated to reduce the gait score from 2 to 1 in 50% of the rats was defined as the ED_{50}.

(3) Mouse Antiwrithing Method. A modification of the procedure of Hendershot and Forsaith[23] was used. The method is based on the antagonism of a writhing syndrome (abdominal contractions and twisting of the body) produced by the intraperitoneal injection of 1 mg/kg of phenyl-*p*-quinone (PPQ). ED_{50} values were calculated[31] as the dose required to reduce the number of writhes to <18 in 50% of the pairs of mice.

X-ray Crystallography. A crystal of **2v** suitable for X-ray analysis was obtained by recrystallization from acetonitrile. The crystal is orthorhombic, space group $P2_12_12_1$ (noncentrosymmetric) with a = 23.611 (6), b = 8.248 (3), and c = 5.733 (3) Å. For one molecule in the asymmetric unit, the calculated density is 1.247 g cm^{-3}. The observed density by flotation in carbon tetrachloride–hexane is 1.242 g cm^{-3}. Intensity data were collected in the range 6° ≤ 2θ ≤ 120° with Cu Kα radiation (λ = 1.5418 Å) and of the 1031 reflections measured, 844 were considered observed by the criterion $I \geq 2.0\ \sigma(I)$.

Direct methods[32] revealed the positions of the chlorine and 9 carbon atoms. Alternate structure factor and difference map calculations gave the remaining atoms. Refinement of the trial structure with an anomalous dispersion correction for chlorine

(31) D. J. Finney, "Statistical Methods in Biological Assay", 2nd ed.; Hafner: New York, 1964; p 454.
(32) Germain, G.; Main, P.; Woolfson, M. H. *Acta Crystallogr., Sect. B.* **1970**, *26*, 274. *Acta Crystallogr., Sect. A.* **1971**, *27*, 368.
(33) Gerrard, W. *J. Chem. Soc.* **1945**, 848.
(34) Anschutz, R. *Justus Liebigs Ann. Chem.* **1907**, *354*, 127.
(35) Fraisse, R. *Bull. Soc. Chim. Fr.* **1959**, 1102.

and anisotropic temperature factors for the heavier atoms converged at $R = 5.5\%$.

A crystal of **1y** suitable for X-ray analysis was obtained from the analytical sample. The crystal is orthorhombic, space group $P2_12_12_1$ (noncentrosymmetric) with $a = 15.677$ (10), $b = 11.625$ (10), and $c = 5.654$ (9) Å. For one molecule in the asymmetric unit, the calculated density is 1.45 g cm^{-3}. The observed density by flotation in bromobenzene–heptane is 1.414 g cm^{-3}. Intensity data were collected in the range $6° \leq 2\theta \leq 120°$ with Cu Kα radiation ($\lambda = 1.5418$ Å) and of the 937 reflections measured, 738 were considered observed by the criterion $I \geq 2.0\ \sigma(I)$.

The chlorine atom was located by the Patterson method and alternate structure factor and difference map calculations revealed the remaining heavier atoms. The hydrogen atoms were placed at the calculated positions and the structure refined with an anomalous dispersion correction for chlorine and anisotropic temperature factors for the heavier atoms. The refinement converged at $R = 6.0\%$.

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Supplementary Material Available: Tables X–XIII containing hydrogen coordinates and temperature parameters of **2v** and **1y** (4 pages). Ordering information is given on any current masthead page.

A Potent, New, Sedative–Hypnotic Agent: 5,7-Dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)furo[3,4-*e*]-*as*-triazine 4-Oxide

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A series of 3-phenylfuro[3,4-*e*]-*as*-triazines was prepared and their CNS sedative–hypnotic activity was measured. From this series, 5,7-dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)-furo[3,4-*e*]-*as*-triazine 4-oxide (**5b**) emerged as a potent sedative-hypnotic of unique pharmacological properties. A description of the syntheses and a discussion of the relationship between structure and CNS activity of these compounds, in particular of compound **5b**, are presented.

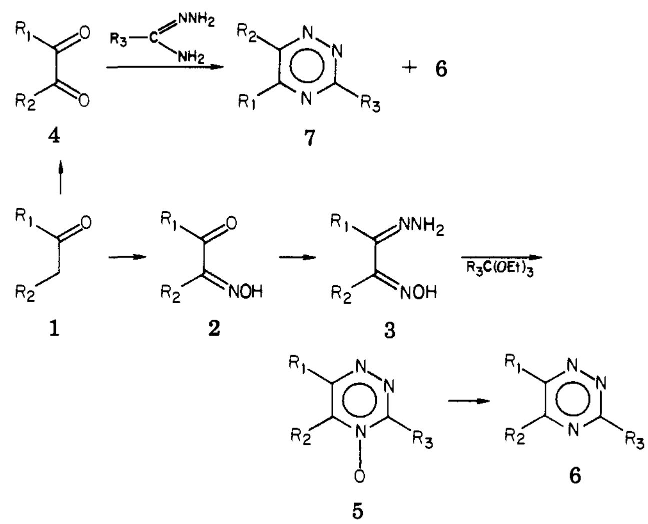
Despite the development of a number of safe and effective benzodiazepines,[1] the search for new and improved sedative–hypnotic agents continues. The longer-acting benzodiazepines tend to cause hangover, and at higher doses REM and slow-wave sleep deprivation occur, thereby affecting the quality of sleep they produce.[25] These side effects are of marginal importance, however, considered in relation to the exceptionally high safety margin the benzodiazepines display, and they are at present the safest drugs available for the induction and maintenance of sleep.[24] An ideal agent would reduce sleep latency and increase total sleep time while inducing a physiological sleep, i.e., one in which the architecture has not been skewed or disrupted.

To this end, a series of 3-phenylfuro[3,4-*e*]-*as*-triazines has been prepared and tested for sedative–hypnotic activity. From this series emerged compound **5b**, 5,7-dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)furo[3,4-*e*]-*as*-triazine 4-oxide, a potent sedative–hypnotic of novel chemical structure and unique pharmacological properties. A description of the syntheses and a discussion of the relationship between structure and CNS activity of these compounds, in particular of **5b**, are presented in this paper.

Chemistry. The parent compound in the series, triazine (**5a**), was prepared as part of our antiinflammatory program.[2] The synthesis via hydrazone oxime **3**, as outlined in Scheme I, was selected because of its general applicability to a variety of commercially available ketones, **1**, and diones, **4**, as well as the simple nature of the reactions. The preparation of the ketone **1** and dione **4** starting materials has been described.[3]

Pharmacology. The acute behavioral activity of these triazines as well as their ability to reinduce anesthesia were both measured in mice. The biological methods are discussed under Experimental Section. For comparison purposes, the discussion of biological activity and the compound tables use the hexobarbital reinduction ED_{50} values (mg/kg ip) as a relative measure of in vivo sedative–hypnotic activity.

Scheme I



Discussion

This presentation of the relationship between chemical structure and biological activity will look at the role of the 4-*N*-oxide, followed by A-ring (furan) analogues, B-ring (triazine) analogues, and finally C-3 analogues.

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(1) L. O. Randall and B. Kappell in "The Benzodiazepines", S. Garattini, E. Mussini, and L. O. Randall, Eds., Raven Press, New York, 1973, p 27.
(2) G. B. Bennett, R. B. Mason, L. J. Alden, and J. B. Roach, *J. Med. Chem.*, 21, 623 (1978).
(3) G. B. Bennett, W. J. Houlihan, R. B. Mason, and R. G. Engstrom, *J. Med. Chem.*, 19, 709 (1976).