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Studies on Analgesic Agents. 1.[1a] Preparation of 1,2-Diphenyl-2-(4-substituted 1-piperazinyl)ethanol Derivatives and Structure–Activity Relationships

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The preparation and analgesic activity of a series of the title compounds (**8–55** and **57**) are described. The intermediates, 2-phenyl-2-(1-piperazinyl)acetophenones **5** and **6**, were prepared from benzyl phenyl ketones **3** via their bromides **4**. On reduction, compounds **5** afforded the titled compounds **8–12**, **16**, and **26–48**. Compounds **13–15** and **17–25** were obtained by alkylation or benzylation of 1,2-diphenyl-2-(1-piperazinyl)ethanols **7** derived from **6** by reduction. The reduction of **5** and **6** with metal hydrides predominantly gave the erythro isomers. The erythro isomers were remarkably more active than their threo isomers. The more active members in this series of compounds were **16** and derivatives **35** and **37–44** of *dl-erythro*-1-phenyl-2-(substituted phenyl)-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]ethanol. Compounds **16**, **43**, and **44** were the most active with a potency of about two to three times that of codeine. Racemates **16** and **38** were resolved into their optical isomers and it was found that (−)-**16** and (+)-**38** were more potent than their antipodes. Structure–activity relationships are discussed.

The analgesic activity of lefetamine (**1**) is known to be about one-tenth as potent as that of (-)-morphine.[2] Recently Natsuka et al. reported that a related compound, (*S*)-(+)-1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (**2**), is approximately equipotent to (−)-morphine as an analgesic and that the absolute configuration of its asymmetric carbon is opposite to that of both **1** and (−)-morphine (C^9).[3] It is notable that the replacement of the dimethylamino moiety of **1** by a cyclohexylpiperazinyl group caused such a significant increase in activity. On the other hand, it might be expected that the conformation of two phenyl rings in **1** and **2** also plays an important role for the appearance of the activity. It is assumed that **1** takes an eclipsed conformation in which two phenyl rings are perpendicular to each other.[4] Thus the introduction of a hydroxyl group at position C^2 of **2** to create a new asymmetric center adjacent to the original one might have effects on the conformation of the two phenyl rings leading to altered activity. In fact, Yamakawa had reported that *dl*-1,2-diphenyl-2-(dimethylamino)ethanol showed no analgesic activity by the Haffner method while only the levo form possessed weak activity and that, as a conclusion, the introduction of a hydroxyl group to **1** caused a marked decrease in activity.[5] Therefore, it was deemed of interest to synthesize new types of compounds containing both the piperazinyl and hydroxyl groups—1,2-diphenyl-2-piperazinylethanol derivatives. Based on the above considerations, a number of the title compounds were prepared and tested for analgesic activity in experimental animals. Some of these compounds were found to possess potent activity.

Chemistry. The titled compounds were prepared by the methods shown in Scheme I. Benzyl phenyl ketones **3** used as starting materials were prepared by Grignard reaction of benzyl halides with benzonitriles in ether or by Friedel–Crafts reaction of phenylacetyl chlorides with benzene, toluene, or phenol in good yields. Bromination of **3** with bromine in $CHCl_3$, followed by amination with N-substituted piperazines or piperazine, gave **5** or **6**, respectively, which was reduced by metal hydrides such as $NaBH_4$ and $LiAlH_4$ to give the amino alcohols **8–12**, **16**, and **26–48** or **7** (see Table I). Compounds **13–15** and **17–25** were obtained from **7** by alkylation with alkyl halides or by heating with benzaldehydes in the presence of formic acid.[6]

On acylation with the corresponding acid anhydrides in pyridine at room temperature, the amino alcohols **16** and **38** gave the acyl derivatives **49–51**. For comparison of the analgesic activity, the dehydroxylated compound **57** was prepared by reaction of *N*,*N*-bis(2-chloroethyl)(1,2-diphenylethyl)amine **56** with (*p*-methoxybenzyl)amine in DMF (see Scheme II).[3] On reduction of **5** or **6** with metal hydrides as described above, erythro isomers were obtained predominantly according to Cram's rule.[7] Diastereoisomers were separated by recrystallization of the dihydrochloride salts of the amino alcohol from 80% EtOH or by column chromatography of the free base on silica gel (3% MeOH–$CHCl_3$). The stereochemical assignments were confirmed by NMR and in particular by the chemical shift and the coupling constant of the C^1 proton (-OCH=). The erythro isomers showed a doublet at δ 5.25–5.35 (J = 4.4–5.0 Hz) and the threo isomers showed a doublet at δ 4.95–5.05 (J = 10.1–10.3 Hz) which corresponded with those reported by Munk et al.[8] for 1,2-diphenyl-2-aminoethanol derivatives. The total yield of the titled compounds from **3** was 30–40%.

Optical resolution of racemic compounds **16** and **38** was accomplished by the formation of salts with (+)-2'-

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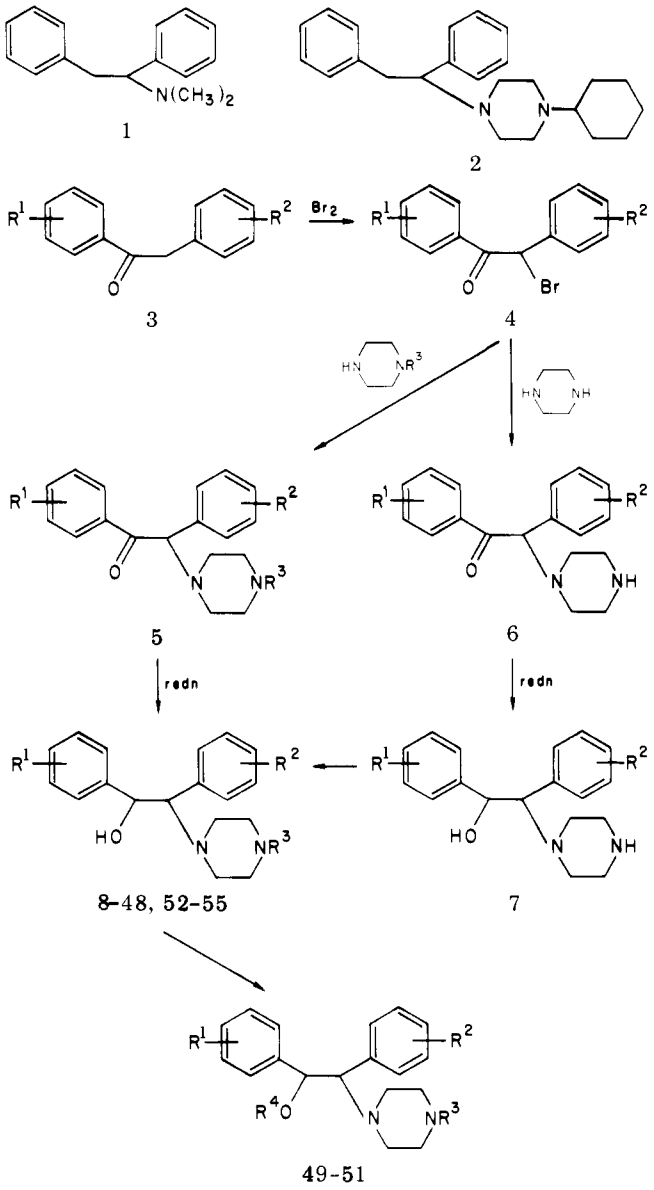
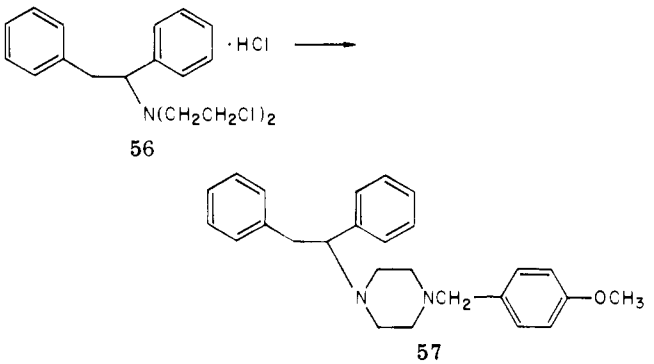
Scheme I



Scheme II



nitrotartranilic acid or (−)-2′-nitrotartranilic acid[9] in EtOH. Optically pure (+)-16, (−)-16, (+)-38, and (−)-38 were obtained by selective crystallizations.

Pharmacological Results and Discussion. Analgesic ED_{50} values of the compounds are shown in Table II. The details of the test procedure are given in the Experimental Section.

As shown in Table II, the introduction of a hydroxyl group to 2 resulted in a marked decrease in activity. To the contrary, the introduction of a hydroxyl group to 1-(*p*-methoxybenzyl)-4-(1,2-diphenylethyl)piperazine (57) caused a marked increase in activity.

As in the case for most potent analgesics which have an asymmetric carbon, analgesic activity largely resides in one member of each enantiomorphic pair.[10] In the case of 16 and 38, (−)-16 and (+)-38 were more potent than their antipodes (Table III). It is of much interest that the sign of rotation of the more potent optical isomers is altered by the presence of the ortho substituent on the C^2 phenyl ring. The absolute configuration of (−)-16 and (+)-38 is under investigation.

From the results by the D'Amour-Smith method in Table II it can be seen that various benzyl groups at position N^4 in *dl-erythro*-1,2-diphenyl-2-(4-substituted 1-piperazinyl)ethanol are preferred for activity. Of these, the compound (16) with a *p*-methoxybenzyl group at position N^4 shows marked activity and is approximately 15 times as potent as aminopyrine and two times as potent as codeine. However, multiple and *o*- or *m*-CH_3O substitution of the benzyl group at position N^4 causes a marked decrease in activity (19–25). Compounds with other groups such as phenyl, pyridyl, phenethyl, and cyclohexyl at position N^4 are all less active. With the exception of *m*- and *p*-methyl groups (32 and 33) the introduction of a substituent such as OCH_3, Cl, CH_3, and OH on the phenyl ring at position C^1 in *dl-erythro*-1,2-diphenyl-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]ethanol causes a remarkable decrease in activity compared with 16 (data not shown). Substitution at the ortho or meta position on the C^2 phenyl ring causes only a slight decrease in activity while para substitution on the C^2 phenyl ring results in a retention (37 and 40) or an enhancement (43 and 44) in the activity. Substitution on both phenyl rings diminishes the activity. As for diastereoisomers, the erythro isomers 16, 38, 41, and 44 are found to be remarkably more potent than their corresponding threo isomers 52–55. Acyl derivatives 49–51 are less active than their corresponding amino alcohols 16 and 38. Thus the most active members in this series of compounds are 16, 43, and 44 with a potency of about two to three times that of codeine.

Compounds 35, 38, and 41 were found to have no significant physical dependence liability by both the jumping test[11] in mice and the substitution test[12] in the morphine-dependent rats.

In addition, compound 38 (DU-608) was also found to have no physical dependence liability by a single dose suppression test in the morphine-dependent monkeys.[13] Analgesic activity of 38 was antagonized by naloxone hydrobromide like codeine, pentazocine, and 1.

As shown in Tables IV and V, 38 was much more active than aminopyrine and half as potent as codeine when tested by oral administration in mice and rats, and the acute lethal toxicity of 38 was very low. It has, therefore, been selected for further study as an analgesic.

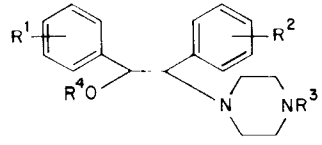
From the results described above, it may be concluded that the SAR of the title compounds is different from 1 and 2.

Experimental Section

Melting points, determined on a Yanagimoto micromelting point apparatus, are uncorrected. The reactions were monitored routinely on TLC with Merck F 254 silica gel plates, which were generally developed with 5 or 10% MeOH in $CHCl_3$. Organic extracts were washed with water and dried over anhydrous Na_2SO_4 or K_2CO_3.

Synthetic methods A–E are representatives for compounds reported in Table I. Benzyl phenyl ketones 3 were prepared by Grignard reaction in ether (26, 28, 29, 31, 32, 35–39, 41–43, and 45–48) or by Friedel–Crafts reaction in benzene (8–16, 25, 40, and 44), toluene (23), chlorobenzene (30), carbon disulfide (27), and

Table I. *dl*-1,2-Diphenyl-2-(4-substituted 1-piperazinyl)ethanols and Their Esters



compd	R^1	R^2	R^3	R^4	isomer[a]	synth method[b]	mp, °C[c]	recrystn solvent[d]	formula[e]
8	H	H	C_6H_4-*o*-Cl	H	E	A	165-167	F	$C_{24}H_{25}N_2OCl$
9	H	H	C_6H_4-*o*-OCH_3	H	E	A	163-165	F	$C_{25}H_{28}N_2O_2$
10	H	H	2-C_5H_4N[f]	H	E	A	166-169	G	$C_{23}H_{25}N_3O$
11	H	H	C_6H_{11}[g]	H	E	A	268-271	G	$C_{24}H_{32}N_2O\cdot 2HCl$
12	H	H	$CH_2C_6H_5$	H	E	A	230-235	H	$C_{25}H_{28}N_2O\cdot 2HCl$
13	H	H	$CH_2CH_2C_6H_5$	H	E	B	134-137	F	$C_{26}H_{30}N_2O$
14	H	H	$CH_2C_6H_4$-*p*-CH_3	H	E	B	228-230	H	$C_{26}H_{30}N_2O\cdot 2HCl\cdot H_2O$
15	H	H	$CH_2C_6H_4$-*p*-NO_2	H	E	B	240-242	H	$C_{25}H_{27}N_3O_3\cdot 2HCl$
16	H	H	$CH_2C_6H_4$-*p*-OCH_3	H	E	A	117-119	F	$C_{26}H_{30}N_2O_2$
17	H	*o*-Cl	$CH_2C_6H_4$-*p*-OCH_2CH_3	H	E	B	220-222	H	$C_{27}H_{31}N_2O_2Cl\cdot 2HCl$
18	H	*o*-Cl	$CH_2C_6H_4$-*p*-$OCH_2C_6H_5$	H	E	B	208-211	H	$C_{32}H_{33}N_2O_2Cl\cdot 2HCl$
19	H	H	$CH_2C_6H_4$-*o*-OCH_3	H	E	C	214-220	H	$C_{26}H_{30}N_2O_2\cdot 2HCl\cdot 0.5H_2O$
20	H	*o*-Cl	$CH_2C_6H_4$-*o*-OCH_3	H	E	C	225-228	H	$C_{26}H_{29}N_2O_2Cl\cdot 2HCl\cdot H_2O$
21	H	*o*-Cl	$CH_2C_6H_4$-*m*-OCH_3	H	E	C	240-244	H	$C_{26}H_{29}N_2O_2Cl\cdot 2HCl$
22	H	*o*-CH_3	$CH_2C_6H_4$-*m*-OCH_3	H	E	C	220-223	H	$C_{27}H_{32}N_2O_2\cdot 2HCl\cdot H_2O$
23	H	*o*-Cl	$CH_2C_6H_3$-3,4-$(OCH_3)_2$[h]	H	E	C	225-229	H	$C_{27}H_{31}N_2O_3Cl\cdot 2HCl$
24	H	*o*-Cl	$CH_2C_6H_3$-3,4-(-OCH_2O-)[i]	H	E	C	231-235	H	$C_{26}H_{27}N_2O_3Cl\cdot 2HCl$
25	H	H	$CH_2C_6H_2$-3,4,5-$(OCH_3)_3$[j]	H	E	B	225-228	H	$C_{28}H_{34}N_2O_4\cdot 2HCl\cdot H_2O$
26	*o*-OCH_3	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	206-210	H	$C_{27}H_{32}N_2O_3\cdot 2HCl$
27	*p*-OCH_3	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	198-202	H	$C_{27}H_{32}N_2O_3\cdot 2HCl\cdot H_2O$
28	*o*-Cl	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	206-208	H	$C_{26}H_{29}N_2O_2Cl\cdot 2HCl$
29	*m*-Cl	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	216-221	H	$C_{26}H_{29}N_2O_2Cl\cdot 2HCl\cdot H_2O$
30	*p*-Cl	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	207-211	H	$C_{26}H_{29}N_2O_2Cl\cdot 2HCl$
31	*o*-CH_3	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	211-217	H	$C_{27}H_{32}N_2O_2\cdot 2HCl$
32	*m*-CH_3	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	228-232	H	$C_{27}H_{32}N_2O_2\cdot 2HCl$
33	*p*-CH_3	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	239-240	H	$C_{27}H_{32}N_2O_2\cdot 2HCl$
34	*p*-OH	H	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	185-188	H	$C_{26}H_{30}N_2O_3\cdot 2HCl$
35	H	*o*-OCH_3	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	211-219	H	$C_{27}H_{32}N_2O_3\cdot 2HCl$
36	H	*m*-OCH_3	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	243-245	H	$C_{27}H_{32}N_2O_3\cdot 2HCl$
37	H	*p*-OCH_3	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	202-207	H	$C_{27}H_{32}N_2O_3\cdot 2HCl$
38	H	*o*-Cl	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	215-216	H	$C_{26}H_{29}N_2O_2Cl\cdot 2HCl$
39	H	*m*-Cl	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	215-220	H	$C_{26}H_{29}N_2O_2Cl\cdot 2HCl$
40	H	*p*-Cl	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	205-209	H	$C_{26}H_{29}N_2O_2Cl\cdot 2HCl$
41	H	*o*-CH_3	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	211-217	H	$C_{27}H_{32}N_2O_2\cdot 2HCl$
42	H	*m*-CH_3	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	224-228	H	$C_{27}H_{32}N_2O_2\cdot 2HCl$
43	H	*p*-CH_3	$CH_2C_6H_5$-*p*-OCH_3	H	E	A	224-232	H	$C_{27}H_{32}N_2O_2\cdot 2HCl$

44	H	p-NO_2	$CH_2C_6H_5$-p-OCH_3	H	E	A	192–196	H	$C_{26}H_{29}N_3O_4 \cdot 2HCl$
45	p-CH_3	o-Cl	$CH_2C_6H_5$-p-OCH_3	H	E	A	216–222	H	$C_{27}H_{31}N_2O_2Cl \cdot 2HCl$
46	p-CH_3	p-Cl	$CH_2C_6H_5$-p-OCH_3	H	E	A	209–212	H	$C_{27}H_{31}N_2O_2Cl \cdot 2HCl$
47	p-CH_3	o-OCH_3	$CH_2C_6H_5$-p-OCH_3	H	E	A	223–228	H	$C_{28}H_{34}N_2O_3 \cdot 2HCl$
48	p-CH_3	p-CH_3	$CH_2C_6H_5$-p-OCH_3	H	E	A	228–234	H	$C_{28}H_{34}N_2O_2 \cdot 2HCl$
49	H	H	$CH_2C_6H_5$-p-OCH_3	$COCH_3$	E	D	148–153	H	$C_{28}H_{32}N_2O_3 \cdot 2HCl$
50	H	H	$CH_2C_6H_5$-p-OCH_3	COC_2H_5	E	D	161–165	H	$C_{29}H_{34}N_2O_3 \cdot 2HCl$
51	H	o-Cl	$CH_2C_6H_5$-p-OCH_3	COC_2H_5	E	D	168–172	H	$C_{29}H_{33}N_2O_3Cl \cdot 2HCl$
52	H	H	$CH_2C_6H_5$-p-OCH_3	H	T	E	132–134	F	$C_{26}H_{30}N_2O_2$
53	H	o-Cl	$CH_2C_6H_5$-p-OCH_3	H	T	E	200–206	H	$C_{26}H_{29}N_2O_2Cl \cdot 2HCl$
54	H	o-CH_3	$CH_2C_6H_5$-p-OCH_3	H	T	E	219–223	H	$C_{27}H_{32}N_2O_2 \cdot 2HCl$
55	H	p-NO_2	$CH_2C_6H_5$-p-OCH_3	H	T	E	218–223	H	$C_{26}H_{29}N_3O_4 \cdot 2HCl$

[a] Diastereoisomer: E = erythro, T = threo. [b] Capital letters refer to synthetic methods A–E in the Experimental Section. [c] All melting points of dihydrochlorides are decomposed ones. [d] F = EtOH, G = MeOH, H = 80% EtOH. [e] All compounds analyzed for C, H, N, and, where present, Cl within ±0.4% of the calculated values. [f] 2-Pyridyl. [g] Cyclohexyl. [h] 3,4-Dimethoxybenzyl. [i] 3,4-(Methylenedioxy)benzyl. [j] 3,4,5-Trimethoxybenzyl.

Table II. Analgesic Activity (ED_{50}) of Test Compounds in Mice

compd[a]	ED_{50}, mg/kg (95% CL)[c] D'Amour-Smith method, sc	phenylquinone method, po
11	>80,[b] inactive	32.4 (12.2-85.6)
12	>160	20.6 (6.68-63.7)
14	>160	43.7
15	>160	40.0 (9.82-125)
16	15.2 (11.5-20.1)[b]	31.1 (19.6-49.2)
31	120	100
32	26.4 (12.0-39.9)	18.5 (8.1-32.1)
33	31.7 (14.0-59.4)	85.9 (49.3-117.0)
35	32.5 (25.8-40.5)	28.6 (12.9-63.5)
37	37.4 (24.6-54.6)	24.1 (9.6-60.2)
38	79.0 (61.0-102.2)	20.9 (11.9-36.6)
39	48.1 (30.3-76.5)	27.2 (14.2-52.3)
40	39.7 (23.2-68.1)	16.4 (7.61-35.1)
41	65.2 (42.3-100)	30.2 (14.5-54.8)
42	28.0 (11.6-67.6)	27.7 (17.9-42.8)
43	14.1 (8.44-23.7)	16.8 (7.34-28.9)
44	8.11 (5.19-12.7)	10.2 (4.96-20.8)
48	98.6 (74.9-128)	55.6 (31.7-82.8)
49	80-160	46.3 (23.6-90.7)
50	73.1 (38.3-139.8)	44.3 (21.8-90.4)
51	>160	90
57	>240, inactive	
codeine phosphate	28.1 (19.9-39.8)	8.21 (4.6-14.5)
aminopyrine	233 (185-348)	53.3 (33.8-72.8)

[a] ED_{50} values of other compounds listed in Table I were >160 mg/kg sc by the D'Amour-Smith method. [b] Toxic dose. [c] CL = confidence limits.

Table III. Analgesic Activity (ED_{50}) of Optical Isomers in Mice

compd	ED_{50}, mg/kg sc (95% CL),[a] D'Amour-Smith method
(·)-16	15.2 (11.5-20.1)
(+)-16	40.1 (28.9-55.5)
(-)-16	13.5 (10.3-17.7)
(±)-38	79.0 (61.0-102.2)
(+)-38	58.4 (46.4-73.4)
(-)-38	>160
codeine	28.1 (19.9-39.8)

[a] CL = confidence limits.

Table IV. Analgesic Activity (ED_{50}) of 38 and Other Analgesics in Mice and Rats

drugs	ED_{50}, mg/kg po (95% CL)[a] D'Amour-Smith method, mice	Haffner method, rats
38	165 (123-222)	228 (180-289)
codeine phosphate	98.4 (61.4-158)	196 (164-234)
aminopyrine	>640, inactive	>2560, inactive

[a] CL = confidence limits.

Table V. Acute Lethal Toxicity (LD_{50}) of 38 and Other Analgesics in Mice and Rats

drugs	route	LD_{50},[a] mg/kg (95% CL)[b] male mice	male rats
38	po	509 (469-554)	>3200
	sc	431 (371-500)	584 (471-726)
codeine phosphate	po	574 (552-597)	1178 (925-1501)
	sc	271 (232-326)	365 (283-470)
aminopyrine	po	523 (477-572)	>2000
	sc	385 (349-425)	511 (568-572)

[a] One-week observation. [b] CL = confidence limits.

nitrobenzene (34) according to known methods.[14,15]

General Procedure for Preparation of 4. To a solution of 3 (20 mmol) in $CHCl_3$ (30 mL) kept at 50 °C was added dropwise bromine (22 mmol) with stirring. After being stirred at 50 °C

for 0.5 h, the mixture was washed successively with aqueous 10% hyposolution and water. The solvent was removed in vacuo to yield **4** as an oily substance or crystals.

General Procedure for Preparation of 6. A solution of **4** (30 mmol) and piperazine hexahydrate (90 mmol) in EtOH (50 mL) was heated at 60 °C for 4 h. After the solvent was evaporated in vacuo, water was added to the residue. The resulting oily substance was extracted with benzene. The solvent was evaporated in vacuo to give an oily substance which was solidified with ethanolic HCl. The resulting hydrochloride was recrystallized from 80% EtOH.

Method A. *dl-erythro*-1-Phenyl-2-(*o*-chlorophenyl)-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]ethanol (38) Dihydrochloride. A solution of 2-(*o*-chlorophenyl)-2-bromoacetophenone (**4**) (26.8 g, 87 mmol), *N*-(*p*-methoxybenzyl)-piperazine (17.9 g, 87 mmol), and triethylamine (10.5 g, 104 mmol) in EtOH (100 mL) was heated at 60 °C for 3 h. After the solution was cooled and filtered, the filtrate was concentrated to dryness in vacuo. The residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water and dried. The solvent was removed to yield 37.1 g of **5** as an oily substance: IR 2800 (CH of piperazine), 1690 cm^{-1} (C=O).

A solution of **5** (37.1 g, 85 mmol) in MeOH (200 mL) was made weakly basic with aqueous 5% NaOH. To the solution was added $NaBH_4$ (6.4 g, 170 mmol) in small portions with stirring. After being kept at room temperature overnight, the mixture was concentrated to dryness in vacuo. The residue was taken up in $CHCl_3$. The solvent was removed to give an oily substance which was solidified with ethanolic HCl. The crude hydrochloride was recrystallized from 80% EtOH to give 25.8 g of **38**·2HCl.

Method B. *dl-erythro*-1,2-Diphenyl-2-[4-(*p*-methylbenzyl)-1-piperazinyl]ethanol (14) Dihydrochloride. To a solution of *dl-erythro*-1,2-diphenyl-2-(1-piperazinyl)ethanol (**6**) (0.8 g, 2.8 mmol) and *p*-methylbenzyl chloride (0.43 g, 3.1 mmol) in EtOH (20 mL) was added K_2CO_3 (1.2 g, 8.4 mmol), and the mixture was heated to reflux for 4 h with stirring. After cooling, the mixture was poured into cold water. The resulting oil was extracted with $CHCl_3$. After removal of the solvent, the residue was solidified with ethanolic HCl. The crude hydrochloride was recrystallized from 80% EtOH to give 0.5 g of **14**·2HCl.

Method C. *dl-erythro*-1-Phenyl-2-(*o*-chlorophenyl)-2-[4-(3,4-dimethoxybenzyl)-1-piperazinyl]ethanol (23) Dihydrochloride. A mixture of *dl-erythro*-1-phenyl-2-(*o*-chlorophenyl)-2-(1-piperazinyl)ethanol (**7**) (2.3 g, 7.3 mmol), 3,4-dimethoxybenzaldehyde (1.8 g, 11 mmol), and formic acid (0.5 g, 11 mmol) was heated at 160 °C for 1 h. After the mixture was dissolved in benzene, the solution was shaken with aqueous 5% HCl. The precipitated oil and the aqueous layer were separated from the benzene layer, and a mixture of them was made basic with aqueous 5% NaOH. The resulting oil was extracted with $CHCl_3$. After removal of the solvent, the residue was solidified with ethanolic HCl. The crude hydrochloride was recrystallized from 80% EtOH to give 0.35 g of **23**·2HCl.

Method D. *dl-erythro*-1-Acetoxy-1,2-diphenyl-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]ethane (49) Dihydrochloride. A solution of **16** (1.0 g, 2.5 mmol), acetic anhydride (1.0 g, 10 mmol), and anhydrous pyridine (5 mL) was allowed to stand at room temperature overnight and then poured onto ice water. After the mixture was neutralized with aqueous 5% K_2CO_3, the resulting oil was extracted with $CHCl_3$. After removal of the solvent, the residue was solidified with ethanolic HCl. The crude hydrochloride was recrystallized from 80% EtOH to give 0.8 g of **49**·2HCl.

Method E. *dl-threo*-1,2-Diphenyl-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]ethanol (52). A solution of 2-phenyl-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]acetophenone (**51**) dihydrochloride prepared according to method A in MeOH (300 mL) was made weakly basic with aqueous 5% NaOH. To the solution was added $NaBH_4$ (4.8 g, 126.9 mmol) in small portions with stirring. After being kept at room temperature overnight, the mixture was concentrated to dryness in vacuo. The residue was extracted with $CHCl_3$. The solvent was removed to give 12 g of crude product **16** which was recrystallized from EtOH. The oily substance (8.5 g) obtained from the mother liquor was chromatographed on silica gel (Merck Kieselgel 60) with 3% MeOH in $CHCl_3$. The product obtained from the first fraction was recrystallized from MeOH to yield 2 g of **52**.

1-(*p*-Methoxybenzyl)-4-(1,2-diphenylethyl)piperazine (57) Dihydrochloride. In DMF (40 mL) was dissolved *N*,*N*-bis(2-chloroethyl)(1,2-diphenylethyl)amine hydrochloride[3] (3.0 g, 9.3 mmol), and (*p*-methoxybenzyl)amine (5.1 g, 37.2 mmol) was added to the mixture. The mixture was heated to reflux for 5 h with stirring. After the solvent and excess amine were removed, the residue was dissolved in aqueous 10% HCl and the solution was cooled. The resulting crystals were recrystallized from 80% EtOH to give 1.05 g of **57**·2HCl: mp 209–214 °C. Anal. ($C_{26}H_{30}N_2$·2HCl) C, H, N, Cl.

Optical Resolution of (±)-*erythro*-1,2-Diphenyl-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]ethanol (16) and (±)-*erythro*-1-Phenyl-2-(*o*-chlorophenyl)-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]ethanol (38). To a warm solution of (±)-**16** (14.1 g, 35 mmol) in EtOH (50 mL) was added a warm solution of (−)-2′-nitrotartranilic acid (9 g, 70.3 mmol) in EtOH (150 mL). After being cooled, the precipitates were collected and recrystallized from 80% EtOH several times to give (+)-**16** di-(−)-2′-nitrotartranilate (6.4 g) as pale yellow crystals: mp 185–186 °C; $[\alpha]^{25}_D$ −34.7° (c 1.0, MeOH). Anal. ($C_{26}H_{30}N_2O_2$·$2C_{10}H_{10}N_2O_7$) C, H, N.

The above salt was dissolved in H_2O, aqueous 10% Na_2CO_3 was added to the solution, and the liberated base was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried. The solvent was removed and the residue was solidified with ethanolic HCl. The resulting hydrochloride was recrystallized from 80% EtOH to give 2.1 g of (+)-**16**·2HCl as colorless needles: mp 230–232 °C dec; $[\alpha]^{25}_D$ +44.3° (c 1.0, MeOH); ORD $[\phi]^{25}$ (nm) +170° (650), +210 (589), +2050 (285). Anal. ($C_{26}H_{30}N_2O_2$·2HCl) C, H, N, Cl.

The first mother liquor from the (−)-2′-nitrotartranilate formation was evaporated to dryness. To the residue was added aqueous 10% Na_2CO_3, and the liberated base was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried, and evaporated to dryness in vacuo. The residue was dissolved in EtOH (30 mL) and treated with a warm solution of (+)-2′-nitrotartranilic acid (9.5 g, 35.1 mmol) in EtOH (80 mL). After being cooled, the precipitates were collected and recrystallized from 80% EtOH several times to give (−)-**16** di-(+)-2′-nitrotartranilate (4.1 g) as pale yellow crystals: mp 185–186 °C; $[\alpha]^{25}_D$ +34.0° (c 1.0, MeOH). Anal. ($C_{26}H_{30}N_2O_2$·$2C_{10}H_{10}N_2O_7$) C, H, N.

Treatment of the salt with alkali in a similar manner as described above gave the free base, which was converted to its hydrochloride. The hydrochloride was recrystallized from 80% EtOH to give 1.2 g of (−)-**16**·2HCl as colorless needles: mp 230–232 °C dec; $[\alpha]^{25}_D$ −45.0° (c 1.0, MeOH); ORD $[\phi]^{25}$ (nm) −160° (650), −214 (589), −2090 (285). Anal. ($C_{26}H_{30}N_2O_2$·2HCl) C, H, N, Cl.

Optical resolution of (±)-**38** was accomplished in a similar manner as described above. (+)-**38** di-(+)-2′-nitrotartranilate: mp 155–157 °C; $[\alpha]^{25}_D$ +55.7° (c 1.0, MeOH). Anal. ($C_{26}H_{29}N_2O_2Cl$·$2C_{10}H_{10}N_2O_7$) C, H, N, Cl. (+)-**38**·2HCl: mp 254–255.5 °C dec; $[\alpha]^{25}_D$ +30.3° (c 1.0, MeOH); ORD $[\phi]^{25}$ (nm) +110° (650), +153 (589), +930 (300). Anal. ($C_{26}H_{29}N_2O_2Cl$·2HCl) C, H, N, Cl. (−)-**38** di-(−)-2′-nitrotartranilate: mp 155–157 °C; $[\alpha]^{25}_D$ −57.3° (c 1.0, MeOH). Anal. ($C_{26}H_{29}N_2O_2Cl$·$2C_{10}H_{10}N_2O_7$) C, H, N, Cl. (−)-**38**·2HCl: mp 254–255 °C dec; $[\alpha]^{25}_D$ −31° (c 1.0, MeOH); ORD $[\phi]^{25}$ (nm) −119° (650), −158 (589), −955 (300). Anal. ($C_{26}H_{29}N_2O_2Cl$·2HCl) C, H, N, Cl.

Analgesic Assay. The compounds listed in Table I were tested for analgesic activity by the following methods. (1) D'Amour-Smith method:[16] thermal pain was induced by radiating heat light on the tail of male mice (9–12 g) of ddN strain using the modified apparatus of D'Amour-Smith according to the procedure of Nakamura et al.[16b] (2) Phenylquinone writhing method:[17] chemical pain was induced by intraperitoneal injection of phenylquinone in female mice (18–22 g) of ddN strain. (3) Haffner method:[18] mechanical pain was induced by pressing the tail of male rats (90–110 g) of Wistar strain using the modified apparatus of Haffner.

Six to twelve animals were used for a dose, and the value of ED_{50} was calculated according to the Litchfield-Wilcoxon method.

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Synthesis and Evaluation of the Antiovulatory Activity of a Variety of Melatonin Analogues

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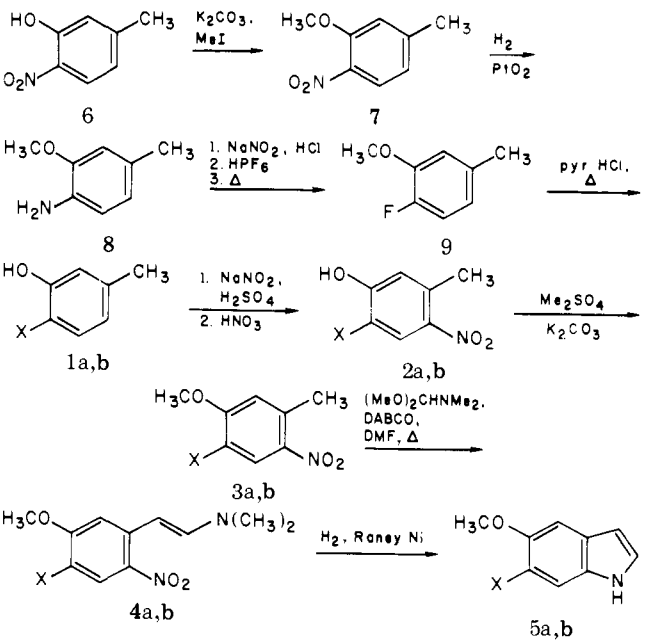
A series of melatonin analogues was synthesized and examined for ovulation-blocking activity. Deviation from the 5-methoxy group or substitution of the 1 position prevented activity. Activity was not particularly sensitive to minor variations in the *N*-acyl group nor was it significantly altered by methylation of position 2 or the α-methylene; however, a pronounced enhancement resulted from halogenation of the 6 position.

Since the first isolation of melatonin (**15a**) in 1959,[1] interest in this hormone has grown steadily. Of particular interest are the reports that melatonin has the ability to inhibit LH secretion.[2] A major difficulty in assessing the physiological properties of melatonin is its very rapid metabolism. This rate of metabolism combined with the polyphasic nature of the process complicates estimation of a biological half-life for melatonin. Kopin et al.[3] estimate that exogenously administered melatonin disappears from whole mice with a half-life of about 2 min through the first 10 min following injection but that after 40 min the half-life has grown to about 35 min. In this same report, data are presented indicating a plasma half-life in rats through the first 30 min of about 15 min. Maickel et al.[4] have estimated the plasma half-life in rats to be about 12 min through the first 2 h following administration.

We undertook the synthesis of a variety of melatonin analogues with the intention of producing compounds with similar physiological properties but greater resistance to metabolism. A more general goal was to establish which features of the melatonin molecule are essential for activity and which sites will tolerate structural modification. In view of the evidence that the major route in the metabolism of melatonin is hydroxylation at the 6 position,[3] we were particularly interested in synthesizing analogues bearing substituents in that position.

Chemistry. The synthetic work is described in three parts: (1) preparation of the indoles, (2) attachment of the side chain at the 3 position, and (3) preparation of analogues starting from serotonin.

Scheme I



a, X = Cl; b, X = F

Indoles. The versatile indole synthesis developed by

0022-2623/79/1822-0063$01.00/0