References and Notes

(1) J. M. Buchanan and S. C. Hartman, *Adv. Enzymol.*, **21**, 199 (1959).
(2) A. Hoshi, F. Kanzawa, K. Kumagai, and K. Kuretani, *Cancer Chemother. Rep.*, **53**, 165 (1969).
(3) A. Hoshi, Y. Ohsaka, T. Nishimoto, F. Kanzawa, and K. Kuretani, *Gann*, **61**, 383 (1970).
(4) A. Hoshi, F. Kanzawa, and K. Kuretani, *Cancer Chemother. Rep.*, **55**, 229 (1971).
(5) A. Bloch, "Drug Design", Vol. IV, E. J. Ariens, Ed., Academic Press, New York, N.Y., 1973.
(6) J. R. McCarthy, Jr., M. J. Robins, and R. K. Robins, *Chem. Commun.*, 536 (1967).
(7) D. H. Murray, J. Prokop, and A. Bloch, *J. Pharm. Sci.*, **58**, 1275 (1969).
(8) A. Bloch and C. A. Nichol, *Biochem. Biophys. Res. Commun.*, **16**, 400 (1964).
(9) J. F. Henderson, *ACS Monogr.*, **No. 170** (1972).
(10) Commercially available from ICN Pharmaceuticals, Inc., Life Science Group, Cleveland, Ohio 44128.
(11) A. Yamazaki, T. Meguro, I. Kumashiro, and T. Takenishi, U.S. Patent 3332935 (1967).
(12) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970).
(13) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953). (The reagent was best obtained by the procedure of Verheyden and Moffatt.[12])
(14) Methylene chloride has recently been used instead of DMF as the solvent for the successful synthesis of 5′-deoxy-5′-iodopurine nucleosides: J. G. Moffatt and coworkers, unpublished results.
(15) Obtained from Matheson Coleman and Bell.
(16) R. P. Panzica and L. B. Townsend, *J. Heterocycl. Chem.*, **9**, 623 (1972).
(17) M. Kawana, G. A. Ivanovics, R. J. Rousseau, and R. K. Robins, *J. Med. Chem.*, **15**, 841 (1972).
(18) G. A. Ivanovics, R. J. Rousseau, M. Kawana, P. C. Srivastava, and R. K. Robins, *J. Org. Chem.*, **39**, 3651 (1974).
(19) J. Mai, *Ber.*, **35**, 162 (1902).
(20) R. W. Sidwell and J. H. Huffman, *Appl. Microbiol.*, **22**, 797 (1971).

Studies on 1-Substituted 4-(1,2-Diphenylethyl)piperazine Derivatives and Their Analgesic Activities. 1[1]

Kagayaki Natsuka,* Hideo Nakamura, Hitoshi Uno, and Susumu Umemoto

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., 33-94, Enoki-cho, Suita, Osaka, Japan.

Received May 27, 1975

The preparation and analgesic activities of a series of the entitled compounds (**5–22**) and the optical isomers of the 1-cyclohexyl derivative **5** are described. Reactions of *N,N*-bis(2-chloroethyl)-1,2-diphenylethylamine (**3**) with ammonia and primary amines gave *N*-(1,2-diphenylethyl)piperazine (**4**) and N[1]-substituted derivatives (**5–20, 22**), respectively. The alkylation of **4** afforded **12–21**. Compounds **5–18** and **22** were also obtained by the reactions of 1,2-diphenylethylamine (**23**) and N-substituted 2,2′-dichlorodiethylamine. Racemate **5** was resolved with (+)- or (−)-2′-nitrotartranilic acid into its optical isomers [(+)-**5** and (−)-**5**], and the absolute configuration of (+)-**5** was determined to be *S* configuration by the synthesis and optical rotatory dispersion measurements. The most active members in this series of compounds were **5–7**, which were approximately as potent as (−)-morphine. In the case of **5**, the more potent enantiomer (*S*)-(+)-**5** has the opposite configuration to that of (−)-*N,N*-dimethyl-1,2-diphenylethylamine (Spa) or (−)-morphine with respect to the (C-9) asymmetric center and belongs to a new series of compounds having potent analgesic activity.

It is well known that certain derivatives of 10,11-dihydrodibenzo[*b,f*]thiepine having a piperazinyl group at position 10 exhibit a number of interesting effects on the central nervous system.[2] Among them perathiepine [10-(4-methylpiperazinyl)-10,11-dihydrodibenzo[*b,f*]thiepine] (**1**)[2] has been used clinically as a major tranquilizer. After considering structural modifications of **1**, it appeared that an investigation of derivatives of 1-piperazinyl-1,2-diphenylethane, which were derived from **1** by opening the central seven-membered ring with the loss of the sulfur atom, might lead to compounds with useful pharmaceutical properties.

On the other hand, Fujimura et al.[3] reported syntheses of 1,2-diphenylethylamine derivatives, and they found that (−)-*N,N*-dimethyl-1,2-diphenylethylamine (Spa) was about one-tenth as potent as (−)-morphine. Since 1-piperazinyl-1,2-diphenylethane derivatives bear a close structural resemblance to Spa, they might be also interesting as analgesics.

In order to investigate the activities on the central nervous system and analgesic activities, we have synthesized a number of 1-substituted 4-(1,2-diphenylethyl)piperazine derivatives[4] and found that some of these compounds were highly active as analgesics in animal tests.[5]

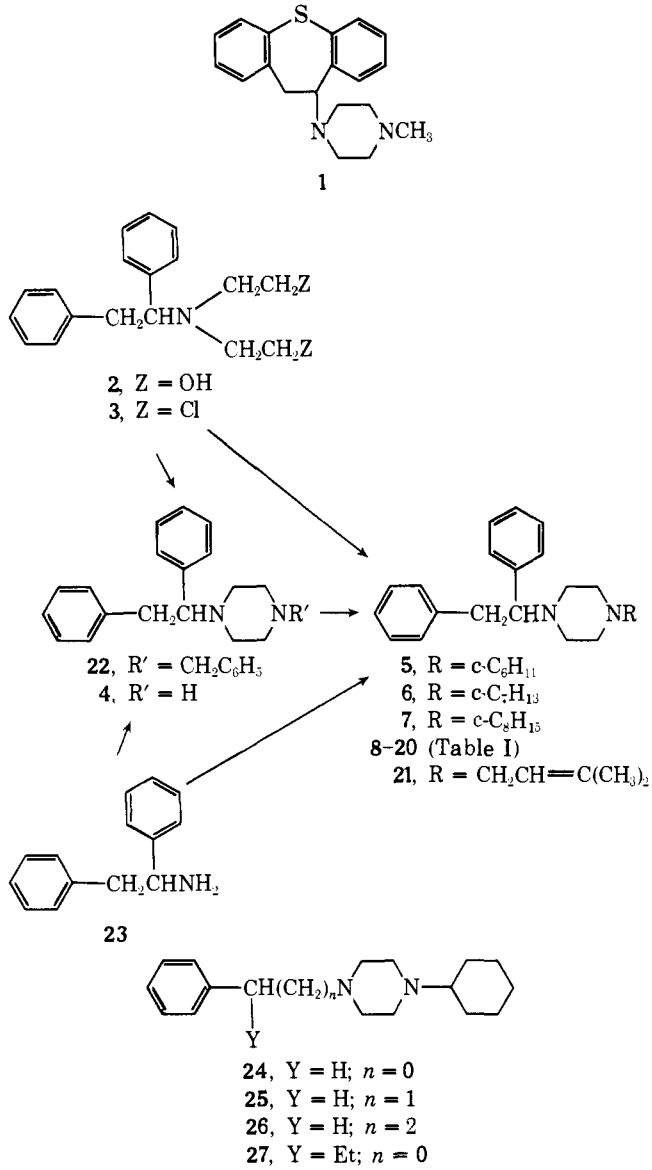
Chemistry. 1-Substituted 4-(1,2-diphenylethyl)piperazine derivatives were prepared by several procedures as shown in Scheme I. *N,N*-Bis(2-hydroxyethyl)-1,2-diphenylethylamine (**2**), which was prepared according to the method of Goodson et al.,[6] was chlorinated with thionyl chloride to give *N,N*-bis(2-chloroethyl)-1,2-diphenylethylamine (**3**) hydrochloride. Reactions of **3** with primary amines gave several 1-substituted 4-(1,2-diphenylethyl)piperazine derivatives (**5–20** and **22**). The catalytic hydrogenolysis of 1-benzyl-4-(1,2-diphenylethyl)piperazine (**22**) on palladium/carbon gave the debenzylated compound, *N*-(1,2-diphenylethyl)piperazine (**4**). Although the reaction of **3** and ammonia also gave **4**, the yield was very poor.

The alkylation of **4** afforded 1-substituted 4-(1,2-diphenylethyl)piperazine derivatives (**12–21**). Compounds **5–18** and **22** were also obtained by the reactions of 1,2-diphenylethylamine (**23**) and N-substituted 2,2′-dichlorodiethylamine.[8] Synthesized compounds are summarized in Table I.

It is well known that steric factors are important in analgesics. In most potent analgesics which have an asymmetric center, analgesic activity largely resides in one member of each enantiomorphic pair. The difference in potency between enantiomorphs is very likely due to the asymmetric topography of the receptor.[9,20]

Since 1-substituted 4-(1,2-diphenylethyl)piperazine has an asymmetric carbon, the 1-cyclohexyl derivative **5**, which showed a strong analgesic activity,[5] was resolved into its optical isomers and the absolute configuration of each enantiomorph was determined to assess the structure–activi-

Scheme I



ty relationship.

Optical resolution of racemic compound **5** was accomplished by the formation of salts with (+)-2′-nitrotartranilic acid[10] or (−)-2′-nitrotartranilic acid in 95% ethanol and optically pure (+)-**5** and (−)-**5** were obtained.[11]

In order to determine the absolute configurations of these compounds, (*R*)-(−)-1,2-diphenylethylamine (**23**)[12] was treated with *N*-cyclohexyl-2,2′-dichlorodiethylamine hydrochloride.[8] Since the product of this reaction was identical with (−)-**5**, the configuration of (−)-**5** was determined to be the *R* configuration.[4b] Moreover, the optical rotatory dispersion (ORD) of (−)-**5**, (*R*)-(−)-**23**,[13] and Spa which has also the *R* configuration showed negative plain curves. This fact confirmed the absolute configuration of (−)-**5** to be the *R* configuration. On the other hand, (+)-**5** was obtained from (*S*)-(+)-1,2-diphenylethylamine (**23**)[13] in the same way and (+)-**5** showed a positive plain curve in the ORD. Therefore the configuration of (+)-**5** was determined to be the *S* configuration.

Pharmacological Results and Discussion. The compounds listed in Table I were tested for analgesic activity as described in the Experimental Section.[14-16] Analgesic ED_{50} values are summarized in Tables II and III.

The structure of 1-substituted 4-(1,2-diphenylethyl)piperazine may be divided into two parts: the diphenylethyl moiety and the piperazinyl moiety. Initial studies focused on changes in analgesic activity as a function of the substituents at position N^1 in 1-substituted 4-(1,2-diphenylethyl)piperazine (**5–22**). As shown in Table II, compounds with a cyclohexyl,[5] cycloheptyl, or cyclooctyl group showed marked activities. They were approximately as potent as (−)-morphine, but the compounds with a cyclopentyl or a cyclododecyl group showed weak or no activity. Replacement of these cycloalkyl groups by linear or branched chain alkyl groups caused an appreciable decrease in activity. When the substituent at position N^1 is a phenyl or a benzyl group, the resulting compound shows only weak activity. On the other hand, 1-cyclohexyl-4-phenylalkylpiperazine derivatives (**24–27**), 1-cyclohexylpiperazine (**28**),[17] 1-cyclohexyl-4-methylpiperazine (**29**),[17] which have a cyclohexylpiperazinyl group but lack the diphenylethyl moiety in their molecule, or *N*,*N*-dimethylcyclohexylamine (**30**) were almost inactive.

These results seemed to suggest that the cycloalkylpiperazinyl group might have an important role in analgesic activity, but cycloalkylpiperazine itself could not display analgesic activity and the 1,2-diphenylethyl moiety may be necessary for the appearance of potent activity in these compounds.

Fujimura et al.[3] showed that in the case of Spa, only the (−) enantiomer showed analgesic activity. Its mirror image form showed no activity and the racemic compound was less active than the (−) isomer. Nakazaki[12] reported that Spa has the *R* configuration and bears the same absolute configuration to (−)-morphine with respect to the (C-9) asymmetric center of the latter.[18] Nakazaki[12] also assumed from the activity of Spa that it might interact with the analgesic receptor[20] in a similar manner as (−)-morphine. Sasaki et al.[13] studied the absolute configuration and the conformation of Spa and assumed that the analgesic activity of Spa is consistent with its stereochemical resemblance to (−)-morphine.

Therefore it is very interesting that in the case of **5**, the racemic compound showed marked activity and the (+) enantiomer of **5**, which has the *S* configuration, is more potent than its mirror image form, which has the same configuration as Spa.

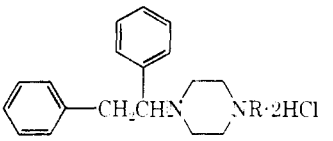
Generally, in most potent analgesics which have an asymmetric center, analgesic activity largely resides in one member of each enantiomorphic pair.[9,19,20] In the case of **5**, the more potent enantiomer (+)-**5** has the opposite configuration to that of Spa or (−)-morphine with respect to the (C-9) asymmetric center, and even (−)-**5** shows activity approximately comparable to that of Spa. Since the racemic **5** is as potent as (+)-**5** in some assay methods, it could be possible that (−)-**5** potentiates the activity of (+)-**5** or in **5** the stereosensitivity is decreased.[9]

These results may suggest that the asymmetric center of (+)-**5** does not correspond to the (C-9) asymmetric center of (−)-morphine and the mode of interaction of (+)-**5** with the receptor[20] differs from that of Spa.[21]

It may be concluded from the results of this investigation that a piperazinyl moiety substituted with a cycloalkyl group having 6–8 carbon atoms may be essential for analgesic activity and for the appearance of potent activity a 1,2-diphenylethyl moiety may be necessary. These compounds belong to a new series of analgesics.

In order to get a more consistent correlation between structure and activity, changes in activity as a function of substituents at position 1 of the piperazinyl moiety and effects on the activity of substituents on both of the phenyl rings in the diphenylethyl moiety are under investigation

Table I. 1-Substituted 4-(1,2-Diphenylethyl)piperazine Dihydrochlorides



Compd	R	Procedure[a]	Mp, °C	Recrystn solvent	Yield, %	Formula[b]
4	H	A	265–267 dec	MeOH	7	$C_{18}H_{22}N_2 \cdot 2HCl$
5	C_6H_{11}[c]	A	270–271 dec	MeOH	66	$C_{24}H_{32}N_2 \cdot 2HCl$
6	C_7H_{13}[d]	A	273–277 dec	MeOH	71	$C_{25}H_{34}N_2 \cdot 2HCl$
7	C_8H_{15}[e]	A	268–272 dec	MeOH	67	$C_{26}H_{36}N_2 \cdot 2HCl$
8	$C_{12}H_{23}$[f]	A	249–254	EtOH	61	$C_{30}H_{44}N_2 \cdot 2HCl$
9	C_5H_9[g]	A	254–258 dec	MeOH	58	$C_{23}H_{30}N_2 \cdot 2HCl$
10	C_6H_5	B	216–218	EtOH	47	$C_{24}H_{26}N_2 \cdot 2HCl \cdot C_2H_5OH$[h]
11	o-$CH_3OC_6H_4$	B	268–270 dec	MeOH	69	$C_{25}H_{28}N_2O \cdot 2HCl \cdot 0.5H_2O$[i]
12	$CH_2C_6H_4$-p-Cl	A	258–259	MeOH	44	$C_{25}H_{27}N_2Cl \cdot 2HCl$
13	$(CH_2)_2C_6H_5$	A	270–271	AcOH	66	$C_{26}H_{30}N_2 \cdot 2HCl$
14	$(CH_2)_3C_6H_5$	A	239–245	MeOH	58	$C_{27}H_{32}N_2 \cdot 2HCl$
15	C_6H_{13}	A	257–259	EtOH	60	$C_{24}H_{34}N_2 \cdot 2HCl$
16	$CH_2CH(CH_3)_2$	B	254–255 dec	MeOH	55	$C_{22}H_{30}N_2 \cdot 2HCl$
17	CH_3[j]	B	262–263	EtOH	32	$C_{19}H_{24}N_2 \cdot 2HCl$
18	$CH_2CH{=}CH_2$	B	240–241 dec	MeOH	57	$C_{21}H_{26}N_2 \cdot 2HCl$
19	CH_2CH_2OH	B	245–246	EtOH	50	$C_{20}H_{26}N_2O \cdot 2HCl$
20	$(CH_2)_3N(CH_3)_2 \cdot HCl$	B	252–254 dec	MeOH	53	$C_{23}H_{33}N_3 \cdot 3HCl$
22	$CH_2C_6H_5$	A	250–251	MeOH	60	$C_{25}H_{28}N_2 \cdot 2HCl$

[a] Capital letters refer to procedures in the Experimental Section. [b] All compounds were analyzed for C, H, N, and Cl; analytical results were within ±0.4% of the theoretical values. [c] Cyclohexyl. [d] Cycloheptyl. [e] Cyclooctyl. [f] Cyclododecyl. [g] Cyclopentyl. [h] Mass spectrum m/e 342 (M^+). [i] Mass spectrum m/e 372 (M^+). [j] Maleate.[7]

in our laboratory. The absolute configuration and the conformation of potent compounds are also being investigated. Results of these investigations will be reported in successive papers.

Experimental Section

All melting points were taken in a capillary and were uncorrected. Optical rotatory dispersion measurements were carried out in MeOH (c 0.10) at 22–24° with an automatic recording spectropolarimeter Model ORD/UV-5, Japan Spectroscopic Co., Ltd. Mass spectra were taken with a Hitachi RMU-6L mass spectrometer using the direct insert probe, an ionizing potential of 70 eV. Organic extracts were dried over anhydrous Na_2SO_4.

***N,N*-Bis(2-chloroethyl)-1,2-diphenylethylamine (3) Hydrochloride.** In $CHCl_3$ (150 ml) was suspended *N,N*-bis(2-hydroxyethyl)-1,2-diphenylethylamine (**2**) hydrochloride[6] (80.5 g, 0.25 *mol*), and a solution (150 ml) of $SOCl_2$ (90 g, 0.75 mol) in $CHCl_3$ was added dropwise to the mixture. The mixture was refluxed for 2 hr and the excess of $SOCl_2$ and the solvent were removed in vacuo. The residue was recrystallized from acetone to give 79.5 g (89%) of **3**·HCl as colorless needles: mp 130–131°. Anal. ($C_{18}H_{21}NCl_2 \cdot HCl$) C, H, N, Cl.

1-Substituted 4-(1,2-Diphenylethyl)piperazine (5–20, 22) Dihydrochlorides (Table I). Procedure A. 5–9, 12–15, and 22 Dihydrochlorides. In DMF (30–40 ml) was dissolved **3**·HCl (20 mmol) and the appropriate primary amine (80 mmol) was added to the mixture. The mixture was refluxed for 5 hr with stirring. After the solvent and excess of amine were removed, the residue was dissolved in aqueous 10% HCl and the solution was cooled. The resulting crystals were collected, washed with a small amount of cold H_2O and acetone, and dried. The product was recrystallized from MeOH or EtOH.

Procedure B. 10, 11, and 16–20 Dihydrochlorides. In DMF (30 ml) were dissolved **3**·HCl (20 mmol) and the appropriate primary amine (25–40 mmol), and $NaHCO_3$ (6.8 g, 81 mmol) was added to the solution. The mixture was heated at 80–100° for 24 hr with stirring. The solvent and excess of amine were removed, and to the residue was added aqueous 10% Na_2CO_3. The mixture was extracted with Et_2O, the Et_2O extract was washed with H_2O and dried, and the solvent was removed. The residue was treated with methanolic HCl, and the resulting crystals were recrystallized from MeOH or EtOH.

***N*-(1,2-Diphenylethyl)piperazine (4) Dihydrochloride (Table I). Procedure A.** In MeOH (300 ml) was added **3**·HCl (11 g, 30 mmol) and 28% NH_4OH (60 ml) was added to the solution. The mixture was refluxed for 48 hr. After the reaction, the solvent was distilled off and to the residue was added aqueous 5% NaOH. The mixture was extracted with AcOEt, and the AcOEt extracts were dried. After the solvent was removed, the oily residue was purified by chromatography on a column of neutral alumina. The product was eluted with $CHCl_3$. The oily base was converted to its hydrochloride with methanolic HCl.

Procedure B. In AcOH (90 ml) was dissolved **22**·2HCl (4.3 g, 10 mmol), and 10% Pd/carbon (2.2 g) was added to the solution. The mixture was subjected to catalytic reduction. When about 1 molar equiv of hydrogen (250 ml) was absorbed, the reaction was stopped and the catalyst was filtered off. The filtrate was concentrated under reduced pressure and the residue was washed with Et_2O and then dissolved in H_2O. The mixture was made alkaline with NaOH and extracted with Et_2O. The Et_2O extract was washed with H_2O and dried and the solvent was removed. The residue was treated with methanolic HCl and the resulting crystals were collected and recrystallized from MeOH to give 2.9 g (86%) of **4**·2HCl: mp 265–267° dec.

1-(3-Methyl-2-butenyl)-4-(1,2-diphenylethyl)piperazine (21) Dihydrochloride. In DMF (30 ml) were dissolved **4** (2.7 g, 10 mmol) and 1-bromo-3-methyl-2-butene (1.8 g, 12 mmol) and $NaHCO_3$ (1.4 g, 17 mmol) was added to the mixture. The mixture was refluxed for 8 hr with stirring. The solvent was removed in vacuo, and to the residue was added aqueous 10% NaOH. The mixture was extracted with Et_2O. The Et_2O extract was dried and the solvent was removed. The residue was treated with methanolic HCl and the resulting crystals were recrystallized from MeOH to give 2.6 g (64%) of **21**·2HCl as colorless needles: mp 232–234° dec. Anal. ($C_{23}H_{30}N_2 \cdot 2HCl$) C, H, N, Cl.

1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine (5). In DMF (45 ml) were dissolved *N*-cyclohexyl-2,2′-dichlorodiethylamine hydrochloride[8] (9.0 g, 34 mmol) and 1,2-diphenylethylamine (**23**) (6.8 g, 34 mmol) and $NaHCO_3$ (10 g, 119 mmol) was added to the solu-

Table II. Analgesic Activity of Test Compound in Mice

Compd[a]	ED_{50}, mg/kg: D'Amour–Smith method sc	ED_{50}, mg/kg: Phenylquinone method po
4	>160	65.0
5	3.09 (2.21–4.95)[c]	12.5 (6.29–21.8)
6	5.45 (2.98–9.95)	10.4 (6.21–17.4)
7	3.45 (2.06–5.80)	8.98 (4.03–20.0)
8	>160	>100
9	36.9	41.6
10	>160	
14	>160	60.0
15	>160	
16	≥70[b]	≥100
22	>160	65.0
24	>160	>100
25	~120[b] (inactive)	
26	>160	>100
27	>160	>100
28·2HBr	>160	>100
29	>160	78
30·HCl	>160	>100
2·HCl	>160	>100
Spa·HCl	46.6	52.3
Morphine·HCl	2.39 (1.78–3.20)	4.20 (2.61–6.77)

[a]Dihydrochloride unless otherwise stated. [b]Toxic dose. [c]95% confidence limits.

tion. The mixture was refluxed for 10 hr with stirring. After being cooled, the inorganic materials were filtered off and the solvent was removed. To the residue was added aqueous 10% HCl and the mixture was cooled. The resulting crystals were collected, washed with a small amount of cold H_2O and acetone, dried, and recrystallized from MeOH to give 8.5 g (59%) of **5**·2HCl: mp 270–271° dec. The base (**5**), prepared from the dihydrochloride with aqueous 5% NaOH, crystallized from 95% EtOH in colorless prisms: mp 94–95°. Anal. ($C_{24}H_{32}N_2$) C, H, N.

1-Benzyl-4-(1,2-diphenylethyl)piperazine (22) Dihydrochloride. In EtOH (200 ml) were dissolved **23** (7.5 g, 38 mmol) and *N*-benzyl-2,2′-dichlorodiethylamine hydrochloride[8] (10.2 g, 38 mmol), and $NaHCO_3$ (11.5 g, 137 mmol) was added to the solution. The mixture was refluxed for 24 hr with stirring. After being cooled, the inorganic materials were filtered off and the solvent was removed. To the residue was added aqueous 10% NaOH and the mixture was extracted with Et_2O. The Et_2O extract was washed with H_2O and dried and the solvent was removed. The residue was treated with methanolic HCl, and the resulting crystals were recrystallized from MeOH to give 9.0 g (55%) of **22**·2HCl: mp 250–251°.

4-Benzyl-, 4-(2-Phenethyl)-, 4-(3-Phenylpropyl)-, and 4-(1-Phenylpropyl)-1-cyclohexylpiperazine (24–27) Dihydrochloride. A mixture of benzyl chloride (or 2-phenethyl chloride, 3-phenylpropyl chloride, or 1-phenylpropyl chloride) (10 mmol), *N*-cyclohexylpiperazine (**28**)[17] (10 mmol), $NaHCO_3$ (1.6 g, 19 mmol), and DMF (15–20 ml) was refluxed for 20 hr and the solvent was removed in vacuo. To the residue was added aqueous 10% Na_2CO_3 and the mixture was extracted with AcOEt. The AcOEt extract was washed with H_2O and dried. The solvent was removed and the residue was treated with methanolic HCl. The resulting crystals were recrystallized from MeOH. The yield of **24**·2HCl ranged from 50 to 65%. **24**·2HCl: colorless scales; mp 261–264° dec Anal. ($C_{17}H_{26}N_2$·2HCl) C, H, N, Cl. **25**·2HCl: colorless prisms; mp 296–299° dec. Anal. ($C_{18}H_{28}N_2$·2HCl) C, H, N, Cl. **26**·2HCl: colorless pillars; mp 268–272° dec. Anal. ($C_{19}H_{30}N_2$·2HCl) C, H, N, Cl. **27**·2HCl: colorless prisms; mp 267–269° dec. Anal. ($C_{19}H_{30}N_2$·2HCl) C, H, N, Cl.

Optical Resolution of (±)-1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine (5). To a warm solution of (±)-**5** (14.2 g, 41 mmol) in 95% EtOH (103 ml) was added a warm solution of (+)-2′-nitrotartranilic acid[10] (22.1 g, 82 mmol) in 95% EtOH (103 ml). After being cooled, the precipitates were collected and recrystallized several times from methyl ethyl ketone to give (+)-**5** di-(+)-2′-nitrotartranilate (12.3 g) as pale yellow crystals: mp 132–134°, $[\alpha]^{30}D$ +61.0° (*c* 2.0, MeOH). Anal. ($C_{24}H_{32}N_2$·$2C_{10}H_{10}N_2O_7$) C, H, N.

The above salt was dissolved in H_2O and aqueous 10% Na_2CO_3 was added to the solution and the liberated base was extracted with AcOEt. The AcOEt extract was washed with H_2O and dried and the solvent was removed. The residue was treated with methanolic HCl and the resulting crystals were recrystallized from MeOH to give 4.5 g [26% based on (±)-**5**] of (+)-**5**·2HCl as colorless needles: mp 275–276.5° dec; $[\alpha]^{22}D$ +56.3° (c 2.0, MeOH); ORD $[\phi]^{24}$ (nm) +150° (650), +205° (589), +2850° (275). Anal. ($C_{24}H_{32}N_2$·2HCl) C, H, N, Cl.

The free base [(+)-**5**], prepared from the dihydrochloride with aqueous 10% Na_2CO_3, crystallized from *n*-hexane in colorless needles: mp 96–97°; $[\alpha]^{22}D$ +62.7° (*c* 2.0, MeOH); ORD $[\phi]^{23}$ (nm) +171° (650), +220° (589), +3950° (275). Anal. ($C_{24}H_{32}N_2$) C, H, N.

The first mother liquor from the (+)-2′-nitrotartranilate formation was evaporated to dryness. The residue was taken up in AcOEt, and the solution was washed with aqueous 10% Na_2CO_3 and H_2O, dried, and evaporated to dryness in vacuo. The residue was dissolved in 40 ml of 95% EtOH and treated with a warm solution of (−)-2′-nitrotartranilic acid (11.1 g, 41 mmol) in 95% EtOH (50 ml). After being cooled, the precipitates were collected and recrystallized several times from methyl ethyl ketone to give (−)-**5** di-(−)-2′-nitrotartranilate (9.0 g) as pale yellow crystals: mp 132–134°; $[\alpha]^{22}D$ −61.5° (*c* 2.0, MeOH). Anal. ($C_{24}H_{32}N_2$·$2C_{10}H_{10}N_2O_7$) 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 MeOH to give 3.4 g [20% based on (±)-**5**] of (−)-**5**·2HCl as colorless needles: mp 275–276.5° dec; $[\alpha]^{29}D$ −56.0° (c 1.0, MeOH); ORD $[\phi]^{24}$ (nm) −150° (650), −203° (589), −2840° (275). Anal. ($C_{24}H_{32}N_2$·2HCl) C, H, N, Cl.

The free base [(−)-**5**], prepared from the dihydrochloride, crystallized from *n*-hexane in colorless needles: mp 96–97°; $[\alpha]^{30}D$ −63.0° (c 2.0, MeOH). Anal. ($C_{24}H_{32}N_2$) C, H, N.

Table III. Analgesic Activity of 1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine and Its Enantiomorphs in Mice and Rats

Compd[a]	Confign	ED_{50}, mg/kg: D'Amour–Smith method (mice, sc)	ED_{50}, mg/kg: Phenylquinone method (mice, po)	ED_{50}, mg/kg: Haffner method (rats, sc)
(±)-5		3.09 (2.21–4.95)[b]	12.5 (6.29–21.8)	0.73 (0.37–1.17)
(+)-5	*S*	1.92 (1.35–2.73)	10.6 (5.30–19.5)	0.73 (0.37–1.17)
(−)-5	*R*	50.7	73.3	
Spa·HCl	*R*	46.6	52.3	
Morphine·HCl	9*R*	2.39 (1.78–3.20)	4.20 (2.61–6.77)	1.17 (0.65–2.28)

[a]See footnote *a* in Table II. [b]See footnote *c* in Table II.

Synthesis of (−)-1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine [(−)-5] Dihydrochloride from (*R*)-(−)-1,2-Diphenylethylamine. In EtOH (30 ml) were dissolved (*R*)-(−)-1,2-diphenylethylamine[12] (1.1 g, 5.6 mmol) and *N*-cyclohexyl-2,2′-dichlorodiethylamine hydrochloride (1.3 g, 5 mmol) and $NaHCO_3$ (1.4 g, 17 mmol) was added to the solution. The mixture was refluxed for 24 hr with stirring and the solvent was removed in vacuo. To the residue was added aqueous 10% Na_2CO_3 and the mixture was extracted with AcOEt. The organic layer was washed with H_2O and dried and the solvent was removed. The residue was treated with methanolic HCl, and the resulting crystals were recrystallized from MeOH to give 1.2 g (57%) of colorless needles: mp 275–277° dec; $[\alpha]^{28}D$ −54.6° (*c* 1.0, MeOH). By mixture melting point measurement and ir spectrum, this compound was identified with (−)-5·2HCl, previously described.

Synthesis of (+)-1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine [(+)-5] Dihydrochloride from (*S*)-(+)-1,2-Diphenylethylamine. To a solution of *N*-cyclohexyl-2,2′-dichlorodiethylamine hydrochloride (0.99 g, 3.8 mmol) in $CHCl_3$ was added (*S*)-(+)-1,2-diphenylethylamine[13] (1.5 g, 7.6 mmol). After the solvent was removed, the mixture was heated at 110–120° for 2.5 hr and then at 120–130° for 0.5 hr. After being cooled, to the mixture was added aqueous 10% HCl and the mixture was cooled and the resulting crystals were collected, washed with a small amount of cold H_2O and acetone, and dried. The crystals were recrystallized from MeOH to give 0.64 g of colorless needles: mp 275.5–277° dec; $[\alpha]^{19}D$ +54.5° (*c* 2.0, MeOH). By mixture melting point measurement and ir spectrum, this compound was identified with (+)-5·2HCl previously described.

(*R*)-(−)-*N,N*-Dimethyl-1,2-diphenylethylamine hydrochloride:[3] ORD $[\phi]^{22}$ (nm) −258° (610), −273° (589), −3560° (275).

Analgesic Assay. The compounds listed in Table I were tested for analgesic activity by the following methods. D'Amour-Smith method.[14] 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.[14b] Phenylquinone writhing method.[15] Chemical pain was induced by an intraperitoneal injection of phenylquinone in female mice (18–22 g) of ddN strain. Haffner method.[16] Mechanical pain was induced by pressing the tail of male rats (90–110 g) of Wister strain using the modified apparatus of Haffner.

Six to twelve animals were used for a dose, and the values of ED_{50} were calculated according to the Litchfield–Wilcoxon method.[22]

Acknowledgment. The authors are grateful to Dr. H. Takamatsu, the director of these laboratories, Dr. H. Nishimura, and Dr. M. Shimizu for their encouragement throughout the course of this work. Thanks are also due to Mr. T. Negoro for his technical assistance and members of the analytical section of these laboratories for elemental analysis and spectral measurements.

References and Notes

(1) K. Natsuka, H. Nakamura, and S. Umemoto, Abstracts, 21st Meeting of Kinki Branch, Pharmaceutical Society of Japan, Osaka, Nov 1971, p 14.
(2) M. Protiva, J. O. Jílek, J. Metyšová, V. Seidlová, I. Jirkovský, J. Metyš, E. Adlerová, I. Ernest, K. Pelz, and J. Pomykáček, *Farmaco., Ed. Sci.*, **20**, 721 (1965).
(3) (a) H. Fujimura and K. Kawai, *Nippon Yakurigaku Zasshi*, **56**, 514 (1960); (b) K. Ogiu, H. Fujimura, and Y. Yamakawa, *Yakugaku Zasshi*, **80**, 283 (1960); (c) H. Fujimura and Y. Yamakawa, *ibid.*, **80**, 286 (1960).
(4) (a) S. Umemoto, K. Natsuka, and H. Nakamura, Japanese Patent 6304 (1972) [*Chem. Abstr.*, **77**, 5521 (1972)]; (b) S. Umemoto, K. Natsuka, and H. Nakamura, Japanese Patent 49071 (1972) [*Chem. Abstr.*, **78**, 124634 (1973)].
(5) H. Nakamura, Y. Masuda, Y. Soji, and K. Kawashima, *Jpn. J. Pharmacol.*, **22**, 88 (1972).
(6) L. H. Goodson and H. Christopher, *J. Am. Chem. Soc.*, **72**, 358 (1950).
(7) V. Seidlová, K. Pelz, E. Adlerová, I. Jirkovský, J. Metyšová, and M. Protiva, *Collect. Czech. Chem. Commun.*, **34**, 2258 (1969).
(8) (a) E. Wilson and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3635 (1951); (b) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).
(9) A. F. Casy in "Medicinal Chemistry", Part I, A. Burger, Ed., Wiley-Interscience, New York and London, 1970, pp 81.
(10) T. A. Montzka, T. L. Pindell, and J. D. Matiskella, *J. Org. Chem.*, **33**, 3993 (1968).
(11) S. Umemoto, K. Natsuka, and H. Nakamura, Japanese Patent 188 (1974); *Chem. Abstr.*, **81**, 37579 (1974).
(12) M. Nakazaki, I. Mita, and N. Toshioka, *Bull. Chem. Soc. Jpn.*, **36**, 161 (1963).
(13) T. Sasaki, K. Kanematsu, Y. Tsuzuki, and T. Tanaka, *J. Med. Chem.*, **9**, 847 (1966).
(14) (a) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exp. Ther.*, **72**, 74 (1941); (b) H. Nakamura, T. Kadokawa, K. Nakatsuji, and K. Nakamura, *Arzneim.-Forsch.*, **20**, 1032 (1970).
(15) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957).
(16) F. Haffner, *Dtsch. Med. Wochenschr.*, **55**, 731 (1929).
(17) K. Nakajima, *Bull. Chem. Soc. Jpn.*, **34**, 651, 655 (1961).
(18) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **38**, 2038 (1955).
(19) K. Takagi, H. Fukuda, M. Watanabe, and M. Sato, *Yakugaku Zasshi*, **80**, 1506 (1957).
(20) (a) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954); (b) A. H. Beckett and A. F. Casy in "Progress in Medicinal Chemistry", Vol. 4, G. P. Ellis and G. B. West, Ed., Butterworths, London, 1965, p 195.
(21) (a) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965); (b) *J. Pharm. Sci.*, **55**, 865 (1966).
(22) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

Antagonism of Luteinizing Hormone Release and of Ovulation by an Analog of the Luteinizing Hormone-Releasing Hormone

John P. Yardley,* Theodore J. Foell, Craig W. Beattie, and Norman H. Grant

Wyeth Laboratories Inc., Philadelphia, Pennsylvania 19101. *Received May 7, 1975*

Two varients of LH-RH, <Glu-D-Phe-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly-NH_2 (I) and <Glu-D-Phe-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-$NHCH_2CH_3$ (II), have been synthesized by solid-phase methods. Both peptides strongly inhibit the LH-RH induced secretion of LH in an in vitro assay; however, only I proved effective in preventing ovulation in the 4-day cycling rat.

Antagonists of the luteinizing hormone releasing factor (LH-RH) offer a basis for the design of a contraceptive agent.[1] A successful candidate would be expected to inhibit pituitary secretion of the gonadotropins FSH and LH which normally induce ovarian functions such as follicular development, ovulation, and gonadal steroid production.

The route taken by leading groups in this field involves the design of more potent agonists of LH-RH which could themselves form the basis for antagonist design, e.g., by deletion of histidine at position 2.[2-4] The potentiating effects of D-alanine at position 6 and of the N-terminal ethylamide modifications on agonist activity have been reported[3,4] and