Stereochemical Studies on Medicinal Agents I

Absolute Configuration of Certain Analgesic (−)-*N*-[2-(Phenalkylmethylamino)propyl]propionanilides

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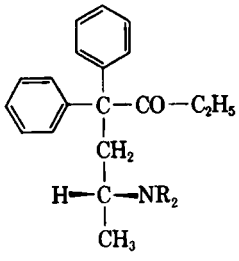
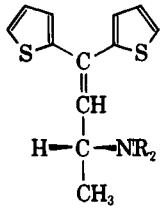
The absolute configuration of certain (−)-*N*-[2-(phenalkylmethylamino)propyl]-propionanilides has been determined by relating them to D-(−)-alanine. The compounds corresponding to the L-configuration have greater analgesic potency than those with the D-configuration. An interpretation of the significance of the relationship of absolute configuration to analgesic activity is discussed in terms of an analgesic receptor surface.

THE RELATIONSHIP of the absolute spatial geometry of medicinal agents to their pharmacological potency has received serious attention only in the past 10 years. There are numerous observations recorded in the literature on the optical specificity of enzymes and on the unequal distribution of pharmacological activity between (+)- and (−)-enantiomers of many types of drugs (1).

One of the few classes of drugs which has been systematically investigated from a three-dimensional point of view is the narcotic analgesic group. Though there has been a considerable research effort devoted to the elucidation of the optimum structural requirements for analgesic molecules, only the methadone-type (including its isosteres) and thiambutene-type compounds have been studied from an absolute configurational approach. In such experiments Beckett and co-workers have shown that most of the analgesic activity resides in the enantiomorphs possessing the D-configuration. A hypothesis



D-Methadone Series



D-Thiambutene Series

was advanced in an attempt to explain this antipodal specificity on the basis of three point contact with a receptor in which only one antipode can fit properly (1).

The need for more information concerning the relationship of configuration to analgesic activity has prompted us to determine the absolute configuration of certain potent analgesics of the basic anilide type (II and IV) (2). We have reported some of our experiments in prior preliminary communications (3, 4) and now wish to present a detailed description and interpretation of our results.

The configuration of the (−)-enantiomers of II and IV have been related to D-(−)-alanine by an unambiguous sequence in which the stereochemical integrity of the asymmetric carbon in question was at all times preserved.

In preliminary experiments, attempts at direct optical resolution of racemic II and IV were not successful. Therefore, we turned to the resolution of the (±)-diamine (I) which is an intermediate in the synthesis of racemic basic anilide analgesics containing the phenalkyl moiety (2). This was accomplished by mixing equivalent amounts of the (±)-diamine (I) and (+)-tartaric acid in 95% ethanol. Several recrystallizations afforded a salt of high purity which, on treatment with aqueous sodium hydroxide, yielded optically pure (+)-diamine (I). The enantiomeric (−)-diamine (I) was obtained in pure form by triangular crystallization of a second crop of crystals obtained from the alcoholic mother liquor. The (+)-diamine (I) was converted to the (−)-propionanilide (II) by heating in propionic anhydride. Catalytic hydrogenolysis of (−)-II produced the debenzylated (+)-intermediate (III) which was subsequently phenethylated to give the (−)-propionanilide (IV).

Catalytic hydrogenolysis of the resolved (+)-diamine (I) produced the debenzylated (−)-diamine (VII). This compound was shown to have the D-configuration through an unambiguous synthetic procedure. D-(−)-Alanine was converted to (+)-carbobenzoxy-D-alanine (V) (5) by treating with benzyl chloroformate. This intermediate (V) was transformed to the (+)-anilide (VI) in high yield by allowing a tetrahydrofuran solution of compound V, aniline, and dicyclohexylcarbodiimide to stand for several hours. Reduction of VI with lithium alumi-

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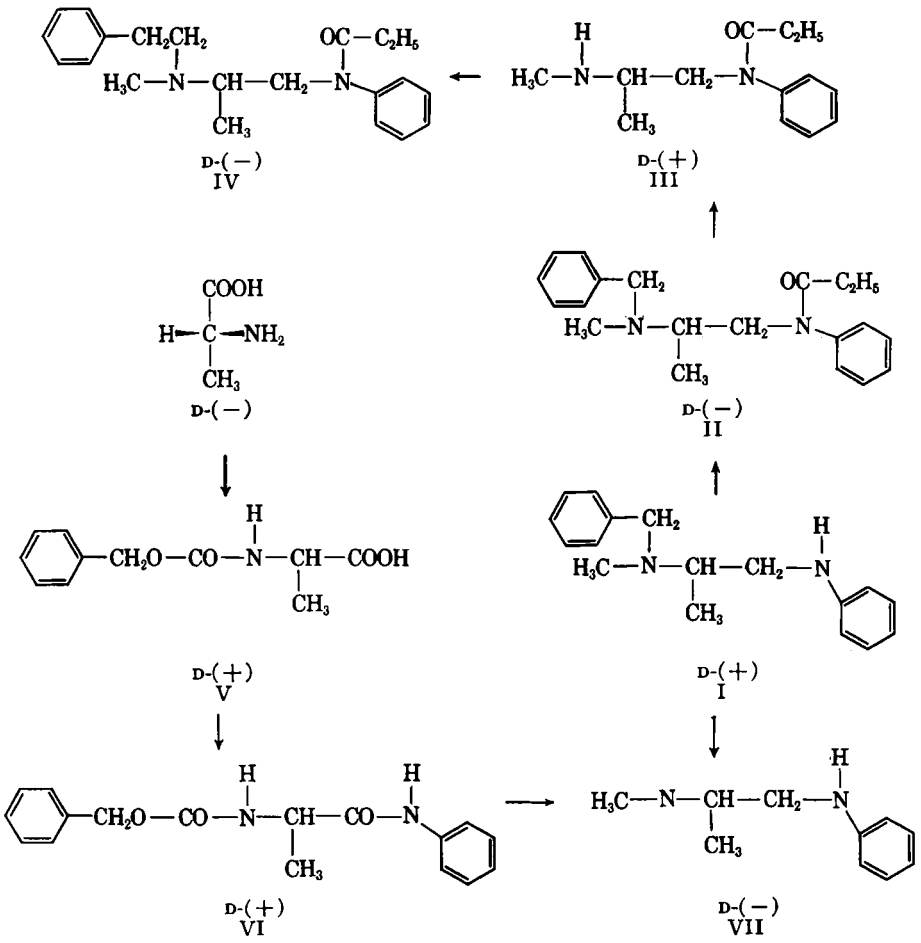

num hydride afforded D-(−)-N^2-methyl-N^1-phenyl-1,2-propanediamine, whose physical properties are identical with the (−)-diamine (VII) derived from the catalytic hydrogenolysis of (+)-I.

The preceding sequence of transformations, therefore, unequivocally demonstrates that the (−)-enantiomers of II and IV are stereochemically related to D-(−)-alanine.

The (+)- and (−)-enantiomers of analgesics II and IV have been tested by others (6) on rats by a modification of the rat tail heat response method. As illustrated in Table I, the L-isomers of II and IV possess activity comparable to that of morphine, whereas the D-isomers are less active. These pharmacological results are quite unexpected, as it has been demonstrated that the more active enantiomorphs of methadone-type and thiambutene-type analgesics have the D-configuration (1). The addictive properties of II and IV (7) and their antagonism by nalorphine (8) suggest that they are acting on the same analgesic receptor through which methadone and other potent analgesics exert their activity, despite the fact that the more active enantiomorphs of these compounds (II and IV) are related to L-(+)-alanine.

These results are in disagreement with the hypothesis that all highly active analgesics possessing an asymmetric carbon have the D-configuration (1). Moreover, the apparent inversion of antipodal specificity in an analgesic receptor is not without precedent. It has been reported that (−)-α-methadol derived from the catalytic reduction of L-(+)-methadone is seven times more active than (+)-α-methadol obtained from D-(−)-methadone (9). Interestingly, the sodium-in-propanol reduction of D-(−)-methadone affords a preponderance of the diastereomeric (−)-β-methadol which has seven times greater potency than (+)-β-methadol derived by reducing L-(+)-methadone (9). These results are summarized in Table II.

The preceding example is highly significant because it serves to illustrate how a reversal in potency ratio between D- and L-isomers of diastereomeric methadols can be effected by merely altering the stereochemistry of the hydroxyl group.

It has been postulated (1) that an aromatic ring, basic nitrogen, and a hydrocarbon moiety interact with the analgesic receptor in a certain conformation. Accordingly, the receptor can make contact with analgesics of the D-configuration in such manner as to accommodate all three of the aforementioned groups, whereas the L-configuration could not easily fit the receptor because the hydrocarbon moiety no longer can fill a suitably oriented "cavity" on the receptor surface.

Since the basic anilide analgesics (II and IV) and the α-methadols do not conform to the above hypothesis, there may be certain additional require-

TABLE I.—RELATIONSHIP OF ABSOLUTE CONFIGURATION TO ANALGESIC POTENCY

Configuration	Compd.	AD_{50}[a,b] (mg./Kg.)
D	II[c]	Inactive at 50
L	II[c]	4.3
D	IV[d]	11.7
L	IV[d]	3.6
	Meperidine	11.0
	Morphine	3.0

[a] We thank Dr. W. B. Wright and Dr. R. A. Hardy for forwarding us their pharmacological data prior to publication. [b] AD_{50} = the subcutaneous dose which elevates the rat tail radiant heat response time by 100% in 50% of the animals. [c] Tested as the hydrochloride salt. [d] Tested as the free base.

ments which must be considered in the depiction of an analgesic receptor surface.

In comparing the potency ratios of the D- and L-isomers of the basic anilide type (II and IV) to those in the methadone series, it is tempting to speculate that, as in the case of the optically active methadols, the reversal in potency ratio on going from the anilides to the methadones is due to a difference in the orientation of the oxygen function. Inspection of Dreiding stereomodels of anilide analgesics (II and IV) and methadone-type compounds reveal that there is a distinct difference in the position of the carbonyl oxygen relative to the rest of the molecule. The amide moiety is planar due to partial sp^2 character in the bond connecting the nitrogen and carbonyl carbon. In contrast to compounds II and IV, the quaternary carbon in the methadone series is tetrahedral. The planarity of the amide moiety consequently causes the orientation of the amide carbonyl oxygen (relative to the rest of the molecule) to differ from that of the ketonic oxygen in the methadone compounds.

If the relative position of the oxygen function does influence the optical specificity of an analgesic receptor, the stereochemical course of binding of certain analgesic molecules to the active site may in part be governed by the orientation of the oxygen function (hydroxyl, amide carbonyl oxygen, and ketonic oxygen) which would be capable of interacting with a secondary site of the analgesic receptor.

We are presently engaged in stereochemical studies on the methadols, methadones, and basic anilides in order to gain further insight into factors which may alter the stereochemical course of molecular binding to an analgesic receptor.

EXPERIMENTAL

(+)-N²-Benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine (I).—A solution of 34.66 Gm. (0.136 mole) of (±)-diamine (I) (2) in 70 ml. of 95% ethanol was mixed with 280 ml. of an ethanolic solution containing 20.48 Gm. (0.136 mole) of (+)-tartaric acid. The combined solution was allowed to stand at 25° for 24 hours. The crystals were collected and recrystallized four times from 95% ethanol to afford 17.3 Gm., m.p. 101–103°,[1] of the tartrate salt, $[\alpha]_D^{27}$ − 16.0° (*c* 5% in water).

Anal.—Calcd. for $C_{21}H_{28}N_2O_6 \cdot H_2O$: C, 59.98; H, 7.17; N, 6.64. Found: C, 60.01; H, 7.13; N, 6.72.

[1] All melting points are uncorrected and were obtained with a "Hoover" capillary melting point apparatus.

TABLE II.—ANALGESIC ACTIVITY OF ISOMERIC METHADOLS (9)

Parent Methadone	ED_{50}[a]	Methadol Isomer	ED_{50}[a]
L-(+)	25.7	(−)-α	3.5
D-(−)	0.8	(+)-α	24.7
L-(+)	...	(+)-β	63.7
D-(−)	...	(−)-β	7.6

[a] Values are mg./Kg. administered subcutaneously in mice.

To 16.4 Gm. of the above salt there was added 80 ml. of 1 *N* sodium hydroxide and 100 ml. of water; the mixture was extracted with ether and dried over sodium sulfate. On removal of the solvent *in vacuo*, 9.1 Gm., m.p. 59–61°, of (+)-I crystallized, $[\alpha]_D^{27°}$ + 31.2° (*c* 5% in ethanol). This compound was analyzed as the monopicrate, m.p. 168–169°.

Anal.—Calcd. for $C_{27}H_{29}N_5O_7$: C, 57.11; H, 5.21; N, 14.48. Found: C, 56.84; H, 5.33; N, 14.38.

(−)-N²-Benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine.—The combined mother liquor from the preceding resolution was concentrated and allowed to stand 12 hours at 25°. The crystalline product was collected and purified by triangular crystallization from water. There was obtained 8.5 Gm., m.p. 82–84°, of tartrate salt, $[\alpha]_D^{25°}$ + 30.0° (*c* 2% in water).

Anal.—Calcd. for $C_{21}H_{28}N_2O_6 \cdot 2H_2O$: C, 57.29; H, 7.12; N, 6.37. Found: C, 57.18, H, 7.39; N, 6.47.

The (+)-salt (7.6 Gm.) was converted to 3.8 Gm. of (−)-*N*²-benzyl-*N*²-methyl-*N*¹-phenyl-1,2-propanediamine, m.p. 59–60°, $[\alpha]_D^{30°}$ − 30.8° (*c* 5% in ethanol) by the procedure described for the (+)-diamine (I).

(−)-N-[2-(Benzylmethylamino)propyl]propionanilide (II).—A mixture of 5.08 Gm. (0.02 mole) of (+)-diamine (I) and 10 ml. of propionic anhydride was heated on a steam bath for 2 hours. The propionic acid and propionic anhydride were removed by distillation and the residue fractionated through a spinning band column to give 4.9 Gm. (80% yield) of (−)-anilide (II), b.p. 152–157° (0.3 mm.), $[\alpha]_D^{32°}$ − 45.7° (*c* 5% in ethanol). This compound exhibited an infrared spectrum and gas chromatographic retention time which are identical with that of racemic II (2).

(+)-N-[2-(Methylamino)propyl]propionanilide (III).—The preparation of (+)-III was similar to the procedure employed in the synthesis of racemic III (2). A mixture of 18.0 Gm. (0.058 mole) of (−)-anilide (II), 14.5 ml. of 4 *N* HCl, 115 ml. of 95% ethanol, and 1.2 Gm. of 10% palladium-on-carbon was shaken in a hydrogen atmosphere at a pressure of 40 p.s.i. for 24 hours. The mixture was filtered, evaporated *in vacuo* to an oil, basified with aqueous sodium hydroxide, and extracted with ether. After the ether extract was dried over sodium sulfate, the solvent was removed *in vacuo* and the residue distilled. The yield of (+)-III, b.p. 110–114° (0.1 mm.), $n^{25°}$ 1.5214, $[\alpha]_D^{25°}$ + 14° (*c* 5% in ethanol), was 8.1 Gm. (69%). The infrared spectrum of (+)-III is identical with that of racemic III.

(−)-N-[2-(Phenethylmethylamino)propyl]-propionanilide (IV).—A mixture of 1.75 Gm. (0.008 mole) of (+)-III, 1.48 Gm. (0.008 mole) of phen-

ethyl bromide and 0.85 Gm. of anhydrous sodium carbonate was refluxed in 12 ml. of benzene for 48 hours. The mixture was extracted with water and the benzene solution concentrated *in vacuo*. Distillation through a spinning band column gave 2.0 Gm. (77%) of product, b.p. 159–163° (0.1 mm.), $n^{28°}$ 1.5440, $[\alpha]_D^{28°}$ − 26.4° (*c* 5% in ethanol). The infrared spectrum and gas chromatographic retention time are identical with that of racemic IV (2).

Preparation of (−)-N²-Methyl-N¹-phenyl-1,2-propanediamine (VII) from (+)-N²-Benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine (I).—A mixture of 2.54 Gm. (0.01 mole) of (+)-diamine (I), 2.5 ml. of 4 *N* HCl, 20 ml. of 95% ethanol, and 0.2 Gm. of 10% palladium-on-carbon was shaken in an atmosphere of hydrogen at a pressure of 40 p.s.i. When the theoretical amount of hydrogen was absorbed, the mixture was filtered and the ethanol removed *in vacuo*. The remaining liquid was made basic with aqueous sodium hydroxide, extracted with ether, and dried over sodium sulfate. Removal of the solvent afforded an oil which on distillation through a spinning band column yielded 1.2 Gm. (73%) of hygroscopic (−)-VII, b.p. 75–78° (0.3 mm.), m.p. 34–35°, $[\alpha]_D^{27°}$ − 29.5° (*c* 5% in ethanol). The dipicrate, infrared spectrum, and gas chromatographic retention time of this compound (VII) are identical with those of the (−)-diamine derived from D-(−)-alanine.

(+)-Carbobenzoxy-D-alanine (V).—This was prepared (5) by reacting D-(−)-alanine and benzylchloroformate in sodium bicarbonate solution (10).

(+)-Carbobenzoxy-D-alanine Anilide (VI).—To a mixture of 30 Gm. (0.13 mole) of (+)-carbobenzoxy-D-alanine and 12.1 Gm. (0.13 mole) of aniline dissolved in 200 ml. of tetrahydrofuran there was added a solution of 29.5 Gm. (0.143 mole) of dicyclohexylcarbodiimide in an equal volume of tetrahydrofuran. After allowing the mixture to stand 6 hours, the solution was concentrated to 200 ml. Five milliliters of acetic acid was added and the solution was again filtered. Removal of all the solvent produced 36 Gm. (93%) of crude (+)-anilide (VI). Recrystallization from 95% ethanol produced crystals, m.p. 162–164°, $[\alpha]_D^{30°}$ + 28.4°. An infrared spectrum of the product exhibited bands at 3.0 μ (—NH), 5.92 μ (—OCO—N), and 6.03 μ (amide).

Anal.—Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.33. Found: C, 68.19; H, 6.13; N, 9.66.

Synthesis of D-(−)-N²-Methyl-N¹-phenyl-1,2-propanediamine (VII) from (+)-Carbobenzoxy-D-alanine Anilide (VI).—To a stirred mixture of 10.64 Gm. (0.28 mole) of lithium aluminum hydride and 200 ml. tetrahydrofuran, there was added (over a 30-minute period) a solution of 20.88 Gm. (0.07 mole) of VI in an equal volume of tetrahydrofuran. The mixture was refluxed for 5.5 hours, cooled, and treated successively with 11 ml. of water, 28 ml. of 15% sodium hydroxide, and 28 ml. of water. The mixture was filtered, dried over sodium sulfate, and the solvent removed *in vacuo*. Ethyl acetate was added to the residue, and it was extracted with 100 ml. 1 *N* HCl. The aqueous solution was made basic with 1 *N* sodium hydroxide and extracted with ethyl acetate. After removal of solvent *in vacuo*, the residue was distilled through a spinning band column. There was collected 9.0 Gm. (78% yield) of D-(−)-diamine (VII), b.p. 67–71° (0.1 mm.), $[\alpha]_D^{30}$ − 29.2° (*c* 5% in ethanol), which crystallized, m.p. 35–36.5°, on cooling. This compound is very hygroscopic and quickly liquifies on exposure to moist air. The product was analyzed as the dipicrate.

Anal.—Calcd. for $C_{22}H_{22}N_8O_{14}$: C, 42.43; H, 3.56; N, 18.00. Found: C, 42.49; H, 3.60; N, 18.23.

The infrared spectrum, gas chromatographic retention time, and dipicrate were found to be identical with those of (−)-diamine VII derived from the catalytic hydrogenolysis of (+)-*N*²-benzyl-*N*²-methyl-*N*¹-phenyl-1,2-propanediamine (I).

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