Stereochemical Studies on Medicinal Agents III. Influence of Length of *N*-Aralkyl Group on Configurational Selectivity of Receptors Toward Enantiomeric Basic Anilide Analgesics

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Enantiomers of *N*-[2-(*p*-methylbenzylmethylamino)propyl]propionanilide and of the *N*-phenylpropyl analog have been prepared, and the S−(+)-isomers were found to possess greater analgesic potency. When the number of methylene groups in the *N*-aralkyl substituent is increased from one to three, the changes in the enantiomeric potency ratio which occur are considered as being reflective of a diminution in the stereoselectivity of the analgesic receptors. The decrease in stereoselectivity is attributed to differing modes of analgesic-receptor binding.

It is well known (1) that among the narcotic analgesics one enantiomer is usually more active than its mirror image, although the more active enantiomers may not necessarily be configurationally related (2). For example, the more active enantiomers of methadone and thiambutane are stereochemically related to R−(−)-alanine (1), whereas the more potent optical isomers of α-methadol (3) and the carbethoxy analog of methadone (4) are of opposite configuration. Moreover, the authors have recently found (5) that the more active antipodes of certain basic anilide analgesics, having an asymmetric carbon atom in common with methadone, are also in the (S)–rather than in the (R)–series. Such changes or inversion in the enantiomeric potency ratio recently (2) have been rationalized as being reflective of differing modes of interaction of narcotic analgesics with receptors. Certain aspects of this concept are of great interest, because it is known that, in some cases, a minor alteration in the molecule may result in a profound change in the configurational selectivity. This was seen in the case of basic anilide compounds I and III where, although the (+)-isomers are more active, the enantiomeric potency ratios differ markedly (6). Since it appeared that the stereoselectivity of the receptors was diminishing as the length of the aralkyl chain increased, it was of interest to see if a further lowering of the potency ratio would occur in the phenylpropyl compound (IV). A report follows on the determination of the configuration of basic anilide analgesics II and IV and on the activity of these enantiomers.

Configurational Studies.—The authors have prepared enantiomers of II and IV *via* two routes, starting with diamines (V and VI), whose absolute stereochemistry previously has been established (5). (Scheme I.) The sequence is similar to that employed by Wright and Hardy (6) in the preparation of optically active I and III and to that of Portoghese and Larson (5) in the establishment of the configuration of the latter compounds.

Intermediate (+)−VIII was derived from R−(+)−V *via* propionylation to (−)−I, followed by catalytic hydrogenolysis of the benzyl group. This anilide was then converted to the R−(−)-enantiomers of II and IV by reaction with the appropriate aralkyl bromide. Similarly, (−)−VIII was transformed to S−(+)−II. An alternate procedure was employed in the preparation of S−(+)−IV, since it was ascertained that the prolonged reaction time necessary for phenylpropylation in the synthesis of the corresponding (−)-enantiomer had led to some $N^1 \rightarrow N^2$ acyl migration (7) of the starting material (VIII) and consequently afforded low yields of the desired product. The procedure involved phenylpropylation of S−(+)−VI to afford (−)−VII, which subsequently was propionylated to (+)−IV.

This established the more active (+)-enantiomers[1] of II and IV as being in the (S)-series. A similar relationship was previously found (5) in the case of I and III.

Pharmacology.—The analgesic activity of the racemates and optical antipodes of II and IV, together with the previously reported pharmacological data for the racemates and enantiomers of I and III (6), are shown in Table I. These compounds were tested using a modification of the rat tail radiant heat procedure of D'Amour and Smith (8) as described by Osterberg and Rauh (9). The AD_{50} values for racemic II and IV are somewhat more potent than the figures reported (10) earlier, although the same method[2] was employed for both determinations. These changes, however, do not appear to be statistically significant.

DISCUSSION

It can be seen in Table I that the S−(+)-enantiomer of II possesses high potency, while the R−(−)-isomer is devoid of activity at 50 mg./Kg. This parallels the data on the (+)- and (−)-enantiomers of I (6). The figures for the phenylpropyl compound (IV) indicate that the (+)- is slightly more active than the (−)-isomer. Although this conforms with the rest of the data which show the S−(+)-compounds to be more potent, the difference in activity between enantiomers may not be statistically significant. In either case, it appears that the analgesic receptors have lost most of their configurational selectivity for the phenylpropyl compound. Phenampromide (III) (6) displays an enantiomeric potency ratio which is between the

Received August 30, 1965, from the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota, Minneapolis.

Accepted for publication September 28, 1965.

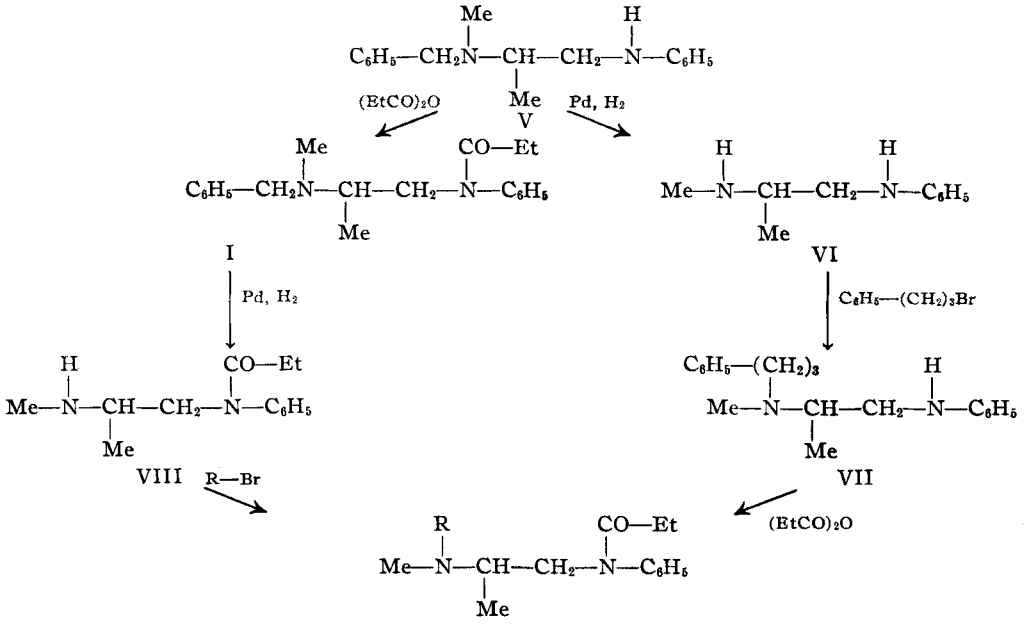
This investigation was supported by grant NB 05192 from the Institute of Neurological Diseases and Blindness, U. S. Public Health Service, Bethesda, Md.

The authors express their appreciation to Dr. R. A. Hardy, Jr., and Dr. A. C. Osterberg, Lederle Laboratories, Pearl River, N. Y., for their cooperation and aid in connection with the analgesic testing.

Previous paper: Portoghese, P. S., *J. Med. Chem.*, **8**, 147 (1965).

[1] Optical rotation of the free bases; the hydrochloride salts of the (+)-bases are levorotatory.

[2] Since the heat source equipment was not the same, small differences in the heat stimulus may account for the apparent changes in AD_{50} values.



II, R = *p*-Me—C_6H_5—CH_2
III, R = C_6H_5—$(CH_2)_2$
IV, R = C_6H_5—$(CH_2)_3$

Scheme I

TABLE I.—RELATIONSHIP OF ABSOLUTE CONFIGURATION TO ANALGESIC POTENCY

Compd.	Enantiomer[a]	Configuration	AD_{50}[b, c] mg./Kg.
I[d]	(±)	...	8
	(+)	(S)	4.3
	(−)	(R)	Inactive at 50
II	(±)	...	1.6 (1.2–2.3)[e]
	(+)	(S)	1.4 (1.0–2.1)
	(−)	(R)	Inactive at 50
III[d]	(±)	...	3.7
	(+)	(S)	3.6
	(−)	(R)	11.7
IV	(±)	...	12.5 (7.9–19.8)
	(+)	(S)	8.9 (6.9–11.5)
	(−)	(R)	11.9 (10.0–14.2)

[a] Optical rotation of the free base. [b] The subcutaneous dose which elevates the rat tail radiant heat response time by 100% in 50% of the animals. [c] The authors thank Dr. A. C. Osterberg and associates, Lederle Laboratories, for testing the (+)- and (−)-enantiomers of II and IV and for retesting the racemates. [d] *Reference 6.* [e] The figures in parentheses are 95% confidence limits, as calculated by the method of Litchfield and Wilcoxon (12).

benzyl analogs (I and II) and IV. Hence, the apparent configurational selectivity of the analgesic receptors diminishes when the number of methylene groups in the aralkyl substituent is increased from one to three.

It has been suggested, in a recently developed concept (2) concerning the interaction of narcotic analgesics with receptors, that similar modes of binding of compounds in different series are characterized by parallelism (11) of analgesic potency when the *N*-substituent is varied in the same way in both series. The high degree of nonparallelism between identically substituted basic anilide analgesics and methadone-type compounds is very likely a consequence of dissimilar binding modes between identically *N*-substituted compounds in the two series and is consistent with the stereochemical data.

Inasmuch as the analgesic receptors appear to be less stereoselective as the aralkyl chain length (I–IV) is increased, it is probable that transitions in the mode of binding occur even among members of a single series. Since it is possible that the mode of binding among basic anilide analgesics having *N*-aralkyl groups of varying length is not identical, and inasmuch as it is not entirely clear whether more than one type of narcotic analgesic receptor exists, several mechanisms that can contribute to changing the enantiomeric potency ratio (*i.e.*, at the receptor level) will be discussed. These are as follows.

(*a*) Differences in the position of molecular binding, among basic anilide analgesics, to a single species of receptors. If different aralkyl *N*-substituents interact with different parts of the analgesic receptors, the position of binding may be altered and consequently be manifested as a change in the enantiomeric potency ratio.

(*b*) Differences in the distribution of molecular binding of various basic anilide analgesics to two or more common species of receptors possessing differing stereoselectivities. If various analgesics are bound in different proportions to two or more common species of receptors whose steric requirements vary, then this will be reflected as a difference in the enantiomeric potency ratio.

(*c*) Binding of various basic anilide analgesics to different species of receptors having dissimilar stereoselectivities. If different analgesics interact with two or more species of receptors which are not

common to all of these analgesics, then a difference in the enantiomeric potency ratio will be observed if the steric requirements of the receptors are dissimilar.

Various combinations of the above can also account for a variation of the potency ratio among the analgesics. Investigations to distinguish between some of the above possibilities are presently underway.

EXPERIMENTAL

(−) - N - [2 - (p - Methylbenzylmethylamino)-propyl]propionanilide (II).—A mixture of 3.30 Gm. (0.015 mole) of R−(+)−VIII (5, 6), 2.78 Gm. (0.015 mole) of α-bromoxylene, and 1.60 Gm. (0.015 mole) of anhydrous sodium carbonate were refluxed in 25 ml. of benzene for 48 hr. Water was added to the mixture and the benzene phase separated. After removing the solvent *in vacuo*, the residue was distilled through a spinning band column to afford 3.15 Gm. of II, b.p. 170–173° (0.1 mm.), $[\alpha]_D^{29°}$ −49.3° (c 5% in ethanol). An infrared spectrum of IV was identical to that of authentic racemic II (9).

(−) - N - [2 - (Phenylpropylmethylamino)propyl]-propionanilide (IV).—A mixture of 3.30 Gm. (0.015 mole) of R−(+)−VIII, 2.90 Gm. (0.015 mole) of phenylpropyl bromide, and 1.60 Gm. (0.015 mole) of anhydrous sodium carbonate was refluxed in 25 ml. of benzene for 72 hr. The reaction mixture was worked up according to the preceding procedure. Distillation through a spinning band column afforded a 1.5-Gm. fraction at 170–175° (0.1 mm.), $[\alpha]_D^{28°}$ −34.8° (c 5% in ethanol), whose infrared and ultraviolet spectra were identical to that of racemic IV (9).

S - (−) - N - [2 - (Methylamino)propyl]propion-anilide (VIII).—The preparation was similar to the procedure employed in the synthesis of (+)−VIII (5, 6). The undistilled product, $[\alpha]_D^{32°}$ −11° (c 5% in ethanol), possessed an infrared spectrum which was identical to (+)−VIII.

(+) - N - [2 - (p - Methylbenzylmethylamino)-propyl]propionanilide (II).—This enantiomer was prepared from S−(−)−VIII, using the procedure employed in the preparation of (−)−II. The product, $[\alpha]_D^{25°}$ +43° (c 5% in ethanol), had an infrared spectrum which was identical to that of racemic II (9).

S - (+) - N^2 - Methyl - N^1 - phenyl - 1,2 - propanediamine (VI).—This enantiomer was derived from (−)−V by employing a procedure which is identical to the synthesis of (−)−VI (5, 6). The infrared spectrum of the product, $[\alpha]_D^{25°}$ +28° (c 5% in ethanol), is identical to that of the (−)-enantiomer.

(−) - N^2 - Phenylpropyl - N^2 - methyl - N^1-phenyl-1,2-propanediamine (VII).—A mixture of 6.0 Gm. (0.039 mole) of (+)−VI, 6.2 Gm. (0.039 mole) phenylpropyl bromide, 6.8 Gm. anhydrous sodium carbonate, and 55 ml. of toluene was refluxed for 72 hr. The mixture was then cooled, and enough water was added to dissolve all the solid material. The organic phase was separated, and the aqueous layer was extracted with ether. The combined nonaqueous extract was dried and the solvent removed *in vacuo*. Distillation through a spinning band column afforded 5.3 Gm. of product, b.p. 158–164° (0.2 mm.), $[\alpha]_D^{28°}$ −28° (c 5% in ethanol), whose infrared and ultraviolet spectra were identical to (±)−VII (9).

(+) - N - [2 - (Phenylpropylmethylamino)propyl]-propionanilide (IV).—A mixture of 5.2 Gm. (0.015 mole) of (−)−VII and 23 ml. of propionic anhydride was heated on a steam bath for 4 hr. The mixture then was distilled through a spinning band column to yield 5.4 Gm. of product, b.p. 132–139° (0.02 mm.), $[\alpha]_D^{26°}$ +35.8°, whose infrared and ultraviolet spectra were identical with the racemic product (9).

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