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Review Article

Stereochemical Factors and Receptor Interactions Associated with Narcotic Analgesics

By PHILIP S. PORTOGHESE

STEREOCHEMICAL studies on narcotic analgesics can be considered an outgrowth of earlier chemical investigations which were concerned primarily with the elucidation of structural moieties necessary for analgesic activity. During this period, which spans about 50 years, considerable attention had been focused on the design and synthesis of analgesics. The role of steric factors, however, was not well understood and was largely unexplored.

The major advances in configurational and conformational analysis which occurred approximately 15 years ago set the stage for various stereochemical studies on narcotic analgesics which were soon to follow. These studies have drawn attention to the importance of steric factors in analgesia and have provided greater insight into the nature of the analgesic–receptor interaction.

This review is organized into three main sections: (*a*) absolute configurational studies, (*b*) conformational factors, and (*c*) concepts on analgesic–receptor interactions. No attempt has been made to give an exhaustive coverage of the chemical and pharmacological literature on this subject, but rather, discussion has been restricted to key developments and recent research related to the steric aspects of analgetically active compounds.

ABSOLUTE CONFIGURATIONAL STUDIES

One of the best approaches to delineating the steric requirements for analgesia involves the correlation of enantiomeric potency with absolute spatial geometry. In most cases one enantiomer possesses greater analgesic activity than its mirror image form. Since the lipid solubility and dissociation constant of enantiomeric bases are identical, differences in distribution are minimized and the variation in analgesic activity may be ascribed more confidently to events at the receptor level. The difference in potency between enantiomorphs is very likely due to the asymmetric topography of the receptors. In such a dissymmetric environment, (+)- and (−)-antipodes behave differently. Thus, one enantiomer may be more potent by virtue of its greater affinity and/or intrinsic activity (1, 2).

Inasmuch as optical rotation of structurally diverse compounds possessing a common asymmetric center is not necessarily indicative of absolute stereochemistry, correlations of optical rotation with analgesic activity are devoid of

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any meaning other than being an expression of differences in the stereoselectivity of analgesic receptors for (+)- and (−)-enantiomers. In order to correlate molecular spatial geometry with analgesic potency, the configuration of the enantiomers must be established. Most of the methods employed for this purpose have involved chemically relating one of the optical antipodes to a compound of known configuration. The analgesics which have received greatest attention are those which possess an asymmetric center in common with methadone and with isomethadone.

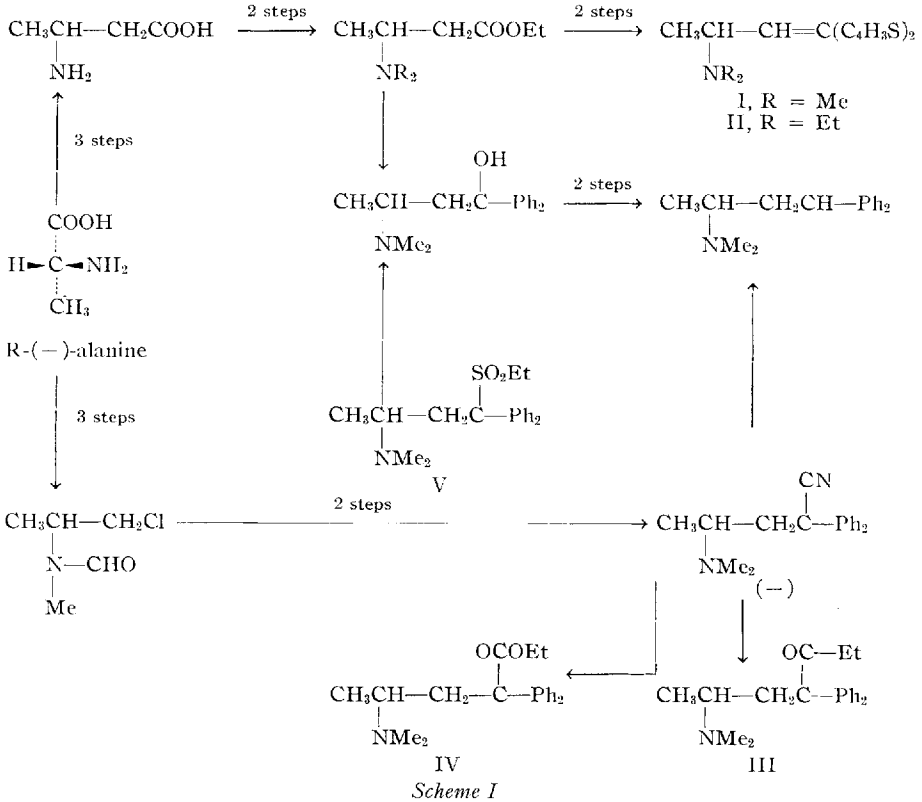
Structures Possessing an Asymmetric Center in Common with Methadone.—The first reported investigation on the configuration of synthetic narcotic analgesics of the methadone type was carried out by Beckett and Casy (3) who related the (+)-thiambutenes (I and II: *Scheme I*) (4) and the (−)-enantiomers of methadone (III: *Scheme I*) (5–8) and analogous structures (IV and V: *Scheme I*) (8, 9) to R(−)-alanine by the route outlined in *Scheme I*. The key reaction in this sequence was the transformation of R-alanine to β-aminobutyric acid *via* the Wolf rearrangement. Since this reaction was generally known to proceed with retention of configuration, the butyric acid intermediate was assumed to be stereochemically related to its precursor. Aminobutyric acid was then converted in several steps to (+)-thiambutene (I: *Scheme I*) and its diethyl homolog (II: *Scheme I*). The configuration of (−)-methadone (III: *Scheme I*) was established by converting the (−)-nitrile, which is a precursor of III: *Scheme I*, to 1,1-diphenyl-3-dimethylaminobutane derived from R-alanine. Since all of these stereochemical interrelationships were based on the assumption that the Wolf rearrangement had proceeded in the usual way, the configuration of III: *Scheme I* was subsequently confirmed unequivocally by converting R-alanine to the (−)-nitrile without involving the asymmetric center in question. The (−)-nitrile was also transformed to the (−)-carbethoxy analog of methadone (IV: *Scheme I*). The (−)-sulfone analog (V: *Scheme I*) was hydrolyzed to the same aminobutanol derivative which was derived from R-alanine.

From molecular rotation studies (−)-phenadoxone (Table III, *2*) (10) was also determined to be configurationally related to R-(−)-methadone.

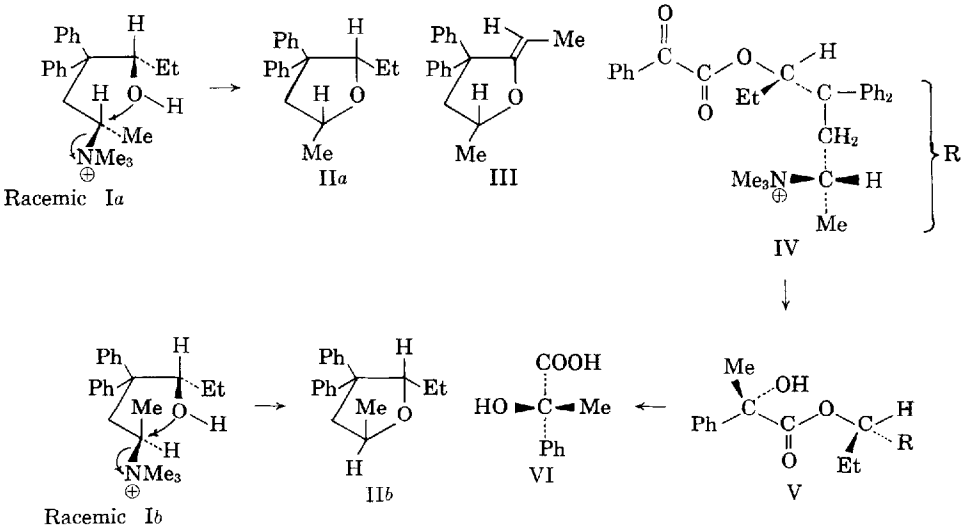
It has been pointed out by Beckett and Casy (11) that the (+)-enantiomers of I and II: *Scheme I* and the (−)-enantiomers of III, V: *Scheme I* and Table III, *2*, are all more active and configurationally related to R-alanine. Equally significant, however, is the fact that the more active enantiomer of IV: *Scheme I* is in the (S)- rather than in the (R)-series.

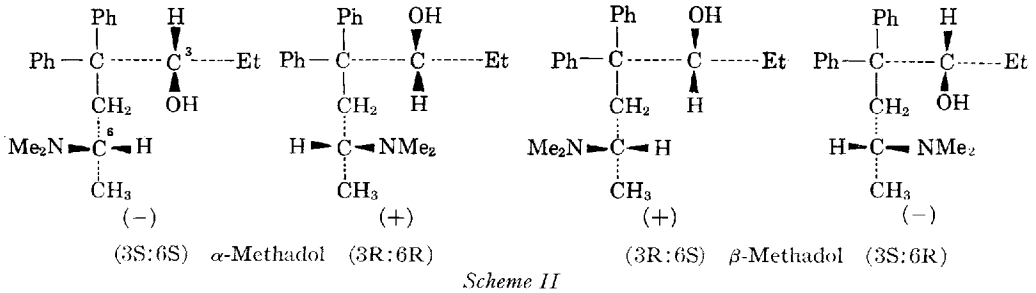
Pohland (8) and Eddy (12) have described the synthesis of optically active diastereomers of methadol (Table I, *1*) and acetylmethadol (Table I, *2*). Catalytic hydrogenation of methadone afforded only α-methadol (Table I, *α-1*), whereas sodium and propanol reduction yielded a mixture of diastereomers in which the β-isomer (Table I, *β-1*) predominated. The absolute stereochemistry at C-6 is now known because the diastereomers were derived from enantiomers of methadone, whose configuration (3) was subsequently determined. The stereochemistry of the C-3 hydroxyl group had not been reported, however. The absolute stereochemistry of the methadols is of particular interest because of the inversion of configurational selectivity[1] of analgesic receptors which occurs on transforming methadone to α-methadol (Table I). Interestingly, no such inversion occurs in the case of Table I, *β-1*. Upon acetylation of Table I, *α-1*, to form Table I, *α-2*, the potency ratio becomes inverted, so that the (6R)-series is once again more active. Portoghese and Williams (13) have investigated the stereochemistry of the methadols and have assigned the configuration at C-3 as designated in *Scheme II*. These assignments were based on the ability of racemic α- and β-methadol methiodide (I*a* and I*b*: *Scheme II*, respectively) to undergo stereospecific ring closure to isomeric tetrahydrofurans II*a* and II*b*: *Scheme II*. It was found that catalytic hydrogenation of the ethylidene compound (III: *Scheme II*) gave rise to II*a*: *Scheme II* as the preponderant isomer. Molecular models indicated that adsorption by the catalyst would occur on the less hindered top face of III: *Scheme II* to afford the *cis* isomer (II*a*: *Scheme II*). Since ring closure occurs with inversion at the C-6 center of I, the relative stereochemistry of the α- and β-isomers was deduced. Inasmuch as the configuration at C-6 is known (3), the absolute stereochemistry at C-3, therefore, was established. Additional proof was obtained from the dissociation constants of α- and β-methadol. The α-isomer was found to be a stronger base. This indicated less steric hindrance of the α-compound to intramolecular hydrogen bond formation be-

[1] The term "selectivity" rather than "specificity" is employed throughout. The former signifies that pharmacological activity is found predominantly in one isomer, though not exclusively, while the latter implies that activity resides in only one isomer. This definition is adapted from Eliel, E. L., "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 436.



Scheme I



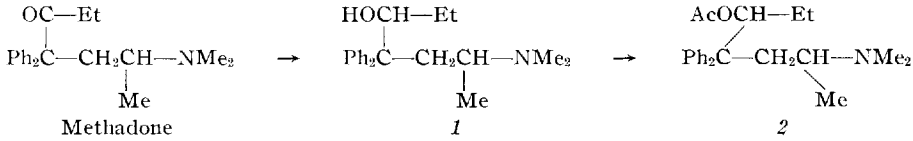


Scheme II

tween the protonated amine function and the oxygen atom of the hydroxyl group (14). Molecular models of α-methadol show that it is less hindered in the internally bonded form than is the β-isomer. Asymmetric induction studies utilizing Prelog's rule confirmed the above stereochemical assignment. Thus, treatment of (3S:6S)-methadol benzoylformate methiodide (IV: *Scheme II*) with methylmagnesium iodide gave the atrolactate ester (V: *Scheme II*) which on basic hydrolysis afforded S-atrolactic acid (VI: *Scheme II*) in 8% optical purity. A knowledge of the stereochemistry of the methadols made possible the complete configurational assignment of the acetate esters (Table I, *2*) and other related compounds. (See also Table III.)

The configuration of several basic anilide analgesics (15, 16), which have an asymmetric center in common with methadone, has been investigated by Portoghese and co-workers (17, 18). The (−)-enantiomers of these compounds were related to R-alanine by the route outlined in *Scheme III*. The (+)-diamine (V: *Scheme III*) was converted to the (−)-antipodes of I through IV: *Scheme III*. The stereochemistry of (+)-V: *Scheme III*, was determined by transforming it to (−)-VI: *Scheme III*, whose configuration was established by synthesis from R-alanine. Significantly, the more

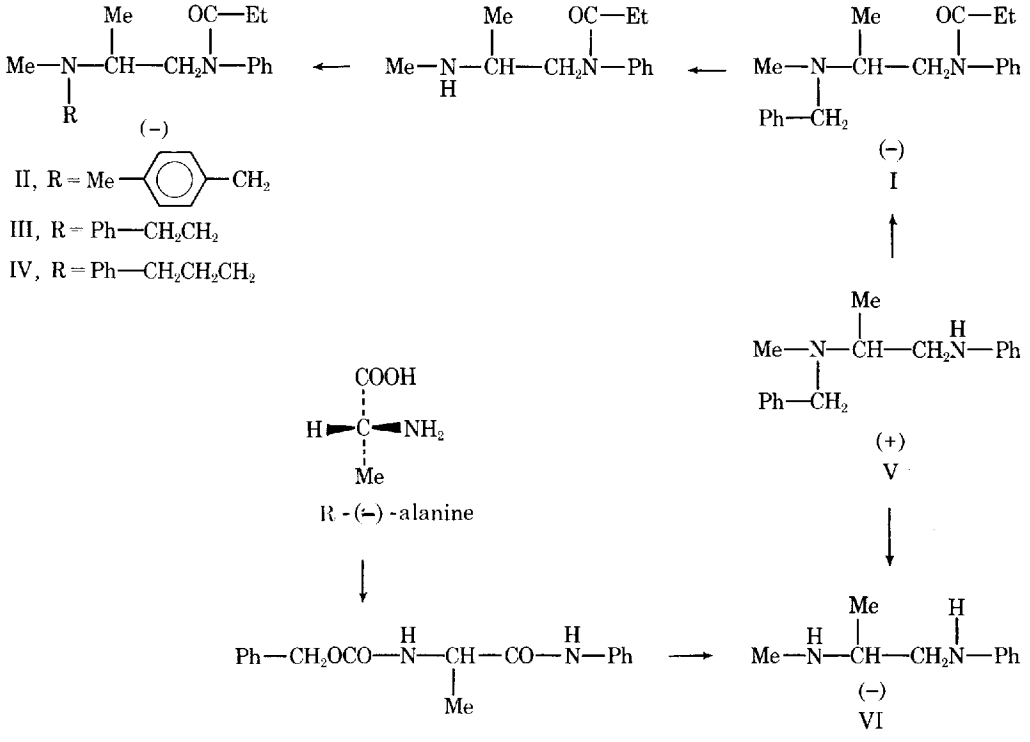
Table I.—Analgesic Potency of Isomeric Methadols and Acetylmethadols[a]



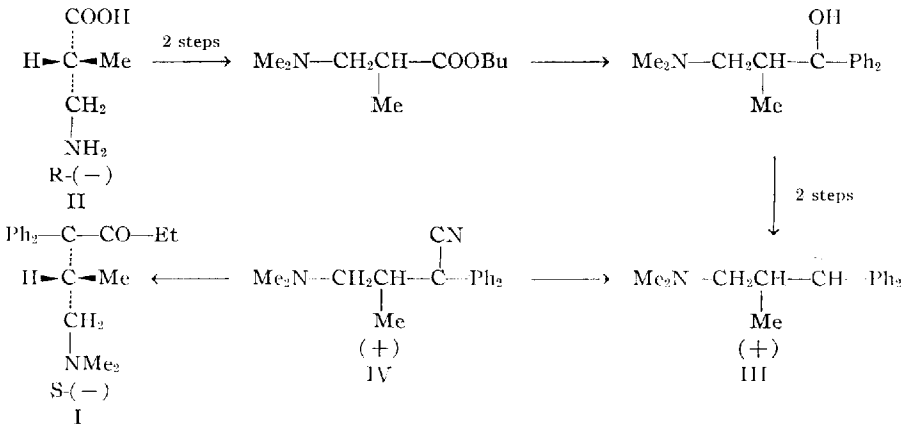
Methadone *1* *2*

Configuration	ED_{50}, mg./Kg.[b]	Isomer	ED_{50}, mg./Kg.[b]	ED_{50}, mg./Kg.[b]
S-(+)	25.7	(−)-α	3.5	1.8
		(+)-β	63.7	4.1
R-(−)	0.8	(+)-α	24.7	0.3
		(−)-β	7.6	0.4

[a] Data from *Reference 12*. [b] Administered subcutaneously in mice.

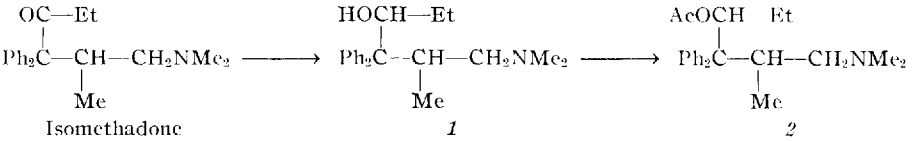


Scheme III



Scheme IV

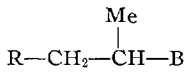
TABLE II.—ANALGESIC POTENCY OF ISOMERIC ISOMETHADOLS AND ACETYLISOMETHADOLS[a]

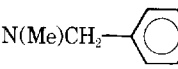
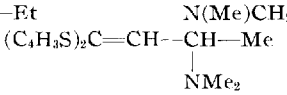
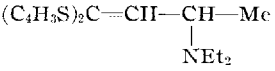


Configuration	ED_{50},[b] mg./Kg.	Isomer	ED_{50}[b], mg./Kg.	Isomer	ED_{50}[b], mg./Kg.
R-(+)	49.8	(+)-α	60.7	(−)-α	62.7
		(−)-β	58.7	(+)-β	70.6
S-(−)	1.2	(−)-α	91.7	(+)-α	2.7
		(+)-β	6.2	(−)-β	10.9

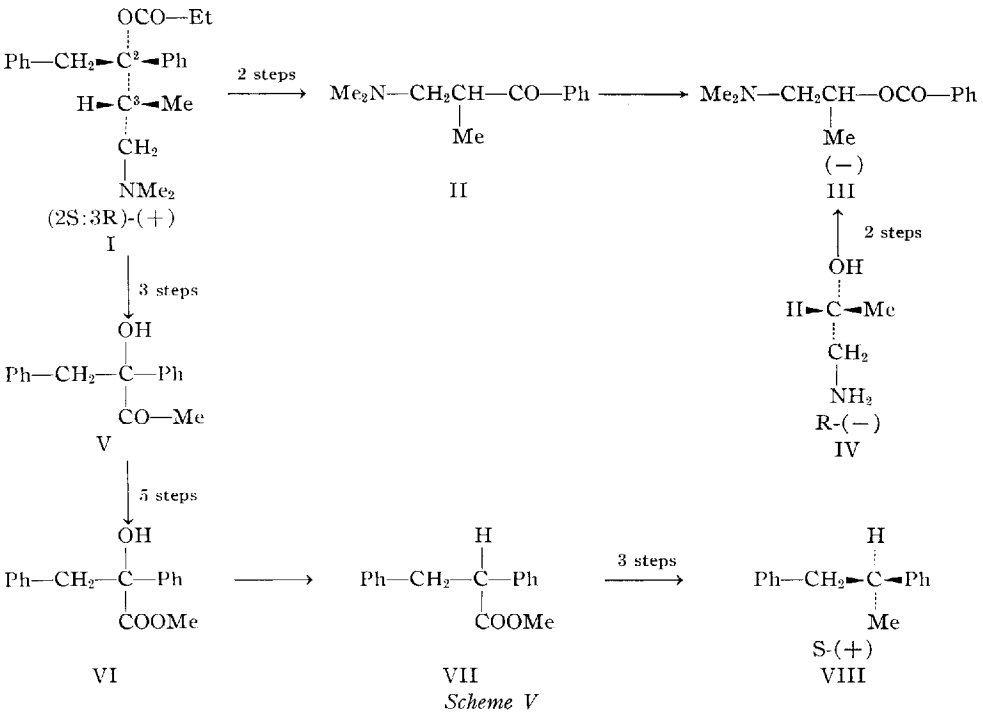
[a] Data from *Reference 19*. [b] Administered subcutaneously in mice.

TABLE III.—CONFIGURATIONAL SELECTIVITY OF ANALGESIC RECEPTORS TOWARD COMPOUNDS HAVING AN ASYMMETRIC CENTER IN COMMON WITH METHADONE

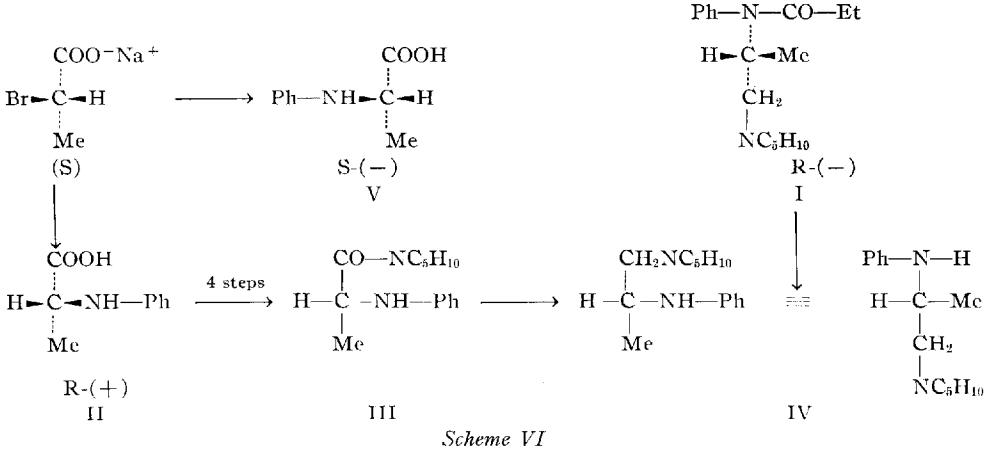


	R	B	Configuration[a]	Ref.
1	Ph_2C—CO—Et	NMe_2	(R)	(3, 6–8)
2	Ph_2C—CO—Et	NC_4H_8O	(R)	(10)
3	Ph_2C—SO_2Et	NMe_2	(R)	(3, 9)
4	Ph_2C—COOEt	NM_2	(S)	(3, 8)
5	Ph_2C—CH(OH)Et	NMe_2	(3S : 6S)	(8, 12, 13)
6	Ph_2C—CH(OH)Et	NMe_2	(3S :6R)	(12, 13)
7	Ph_2C—CH(OAc)Et	NMe_2	(3R:6R)	(8, 12, 13)
8	Ph_2C—CH(OAc)Et	NMe_2	(3S :6R)	(12, 13)
9	Ph_2C—CH(OAc)Et	NHMe	(3R:6R)	(13, 81)
10	Ph—N—CO—Et	$N(Me)CH_2Ph$	(S)	(15–18)
11	Ph—N—CO—Et		(S)	(15–18)
12	Ph—N—CO—Et	$N(Me)CH_2CH_2Ph$	(S)	(15–18)
13	Ph—N—CO—Et	$N(Me)CH_2CH_2CH_2Ph$	(S)[b]	(15–18)
14			(R)	(3, 4)
15			(R)	(3, 4)

[a] Configuration of the more active enantiomer. [b] The S-enantiomer is slightly more potent, although this may not be statistically significant.



Scheme V



Scheme VI

active (+)-enantiomers of the aforementioned compounds are related to S-alanine (Table III) and hence possess a configuration opposite to that of the active antipodes of methadone. Moreover, the stereoselectivity of the receptors decreases (enantiomeric potency ratio approaches unity) as the length of the aralkyl chain is increased. This phenomenon is discussed further in a subsequent section (Table XII).

Structures Possessing an Asymmetric Center in Common with Isomethadone. — Most of the analgesic activity of isomethadone has been found to reside in the (−)-enantiomer (I: *Scheme IV*) (19). The absolute stereochemistry of this compound was elucidated by Beckett *et al.* (20) by the pathway outlined in *Scheme IV*. R(−)-α-Methyl-β-alanine (II: *Scheme IV*) was transformed to (+)-III: *Scheme IV*, which was also derived from the (−)-isomethadone precursor, (+)-IV: *Scheme IV*. This establishes the stereochemical relationship between II: *Scheme IV* and (−)-isomethadone (I: *Scheme IV*) whose configuration is designated as S-isomethadone.

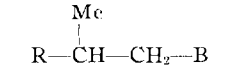
May and Eddy (19) have reduced the carbonyl group of optically active isomethadone to produce isomeric isomethadols. Reduction with lithium aluminum hydride proceeded stereospecifically to give the α-isomer (Table II, *α-1*). Treatment with sodium in propanol

afforded a mixture of Table II, *α-1* and *β-1*, with the latter as the predominant isomer. The analgesic activity of these optical isomers and their stereochemical relationship to (+)- and (−)-isomethadone are shown in Table II. All of the enantiomers in the α- and β-series, which are related to R-isomethadone, have a low order of activity. With isomers derived from S-isomethadone, however, Table II, (+)-*β-1*, is much more potent than Table II, (−)-*α-1*. The reverse is true for the acetate esters, in that Table II, (+)-*α-2*, is more active than Table II, (−)-*β-2*. It can be noted that there is an inversion in the enantiomeric potency ratio of the type seen in the α-methadol compounds (Table I), although in this case, a large diminution of analgesic potency and of stereoselectivity is observed.

(+)-Propoxyphene (I: *Scheme V*) is the only one of four optical isomers which has significant analgesic activity (21). Sullivan, Beck, and Pohland (22) have determined its absolute stereochemistry as (2S:3R) *via* an elegant series of transformations (*Scheme V*). Establishment of the configuration at C-3 was accomplished by converting I to the Mannich base (II: *Scheme V*) and then carrying out a Baeyer-Villiger oxidation to give the (−)-ester (III: *Scheme V*). The identical ester was prepared from R(−)-propanolamine (IV: *Scheme V*). Since the oxidation is known to proceed with retention of configuration, the C-3 center was designated as being in the R-series. Casy and Myers (23) subsequently have confirmed this configurational assignment by a route which did not involve the C-3 asymmetric center. Elucidation of the stereochemistry at C-2 was carried out by transforming (+)-propoxyphene to S(+)-1,2-diphenylpropane (VIII: *Scheme V*). The reaction sequence involved the degradation of I: *Scheme V*, to the methyl ketone (V) which was subsequently converted to VIII *via* intermediates VI and VII. The assignment of the stereochemistry at C-2 is based upon the fact that the steric course of hydrogenolysis of a benzylic hydroxyl group proceeds with high retention of configuration.

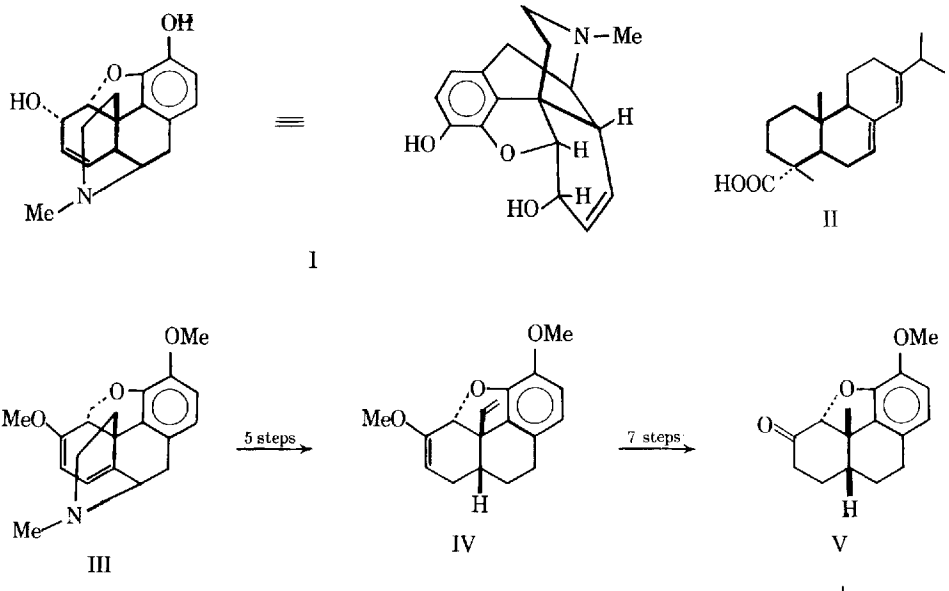
Phenampromide (I: racemic *Scheme VI*) (24), a basic anilide analgesic which can be considered structurally related to isomethadone and propoxyphene, has been resolved and the (−)-enantiomer found to be four times more active than the (+)-isomer. The configuration of I was determined by Portoghese (25) to be related to R-(+)-*N*-phenylalanine (II: *Scheme VI*). The absolute stereochemistry of II: *Scheme VI* was established (26) by studying the steric course of the interaction of aniline with S-2-bromopropionate. When the reaction was carried out in pure or 4 *M* aniline the (+)-amino acid (II: *Scheme VI*) was produced, whereas in a 0.1 *M* aniline solution the (−)-enantiomer (V) was formed. According to the established mechanism (27) of displacement reactions on sodium 2-bromopropionate, the former reaction should take place with net inversion and the latter with net retention of configuration. Since the inverted product (II: *Scheme VI*) is derived from S-2-bromopropionate, II: *Scheme VI*, therefore, possesses the R-configuration. The optically pure amino acid (II: *Scheme VI*), obtained by deracemization, was transformed to the amide (III) and this was reduced to the diamine (IV). The identical diamine was derived from the hydrolysis of (−)-phenampromide (I: *Scheme VI*). It should be pointed out that the more active enantiomers, R-phenampromide, S-isomethadone, and (2S:3R)-propoxyphene, are all stereochemically related at their common asymmetric center (Table IV). This may mean that the aforementioned analgesics are interacting with common receptors, although

TABLE IV.—CONFIGURATIONAL SELECTIVITY OF ANALGESIC RECEPTORS TOWARD COMPOUNDS HAVING AN ASYMMETRIC CENTER IN COMMON WITH ISOMETHADONE



	R	B	Configuration[a]	Ref.
1	Ph_2C—CO—Et	NMe_2	(S)	(19, 20)
2	Ph_2C—CH(OH)Et	NMe_2	α-(6R)[b]	(19)
3	Ph_2C—CH(OH)Et	NMe_2	β-(6S)	(19)
4	Ph_2C—CH(OAc)Et	NMe_2	α-(6S)	(19)
5	Ph_2C—CH(OAc)Et	NMe_2	β-(6S)	(19)
6	Ph—CH_2(Ph)C—OCO—Et	NMe_2	(2S:3R)	(21–23)
7	Ph—N—CO—Et	NC_5H_{10}	(R)	(24, 25)

[a] Configuration of the more active enantiomer. [b] The (6R)-isomer has a very low order of activity and is only 1.5 times more potent than its enantiomer.



Scheme VII

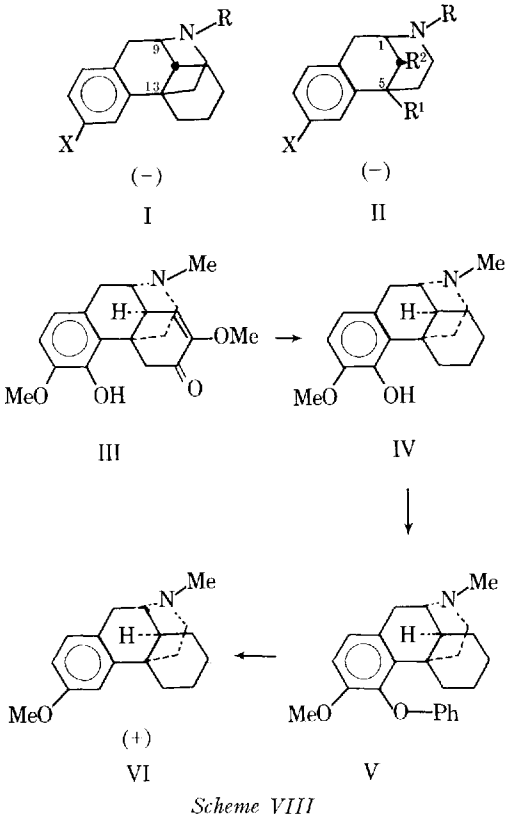
it is also possible that such stereochemical equivalence may be entirely fortuitous.

The relationship between configuration and analgesic activity of compounds having an asymmetric center in common with methadone and with isomethadone are summarized in Tables III and IV, respectively. The data compiled in Table III show an apparent lack of consistency, inasmuch as the more active enantiomers are not all configurationally related. The constitution of the R group appears to play a key role in determining the configurational selectivity of analgesic receptors. Such changes in stereoselectivity recently have been interpreted as being reflective of differing modes of analgesic–receptor interactions (28). (See under *Concepts on Analgesic-Receptor Interactions.*) A much more consistent correlation is shown in Table IV where the more active enantiomers, with one possible exception (Table IV, *2*), are all stereochemically related at a common asymmetric center.

Morphine and Related Structures.—The absolute configuration of (−)-morphine (I: *Scheme VII*) was determined by Jeger and collaborators (29) who converted thebaine (III: *Scheme VII*) to a degradation product (VII) of abietic acid (II) of known absolute stereochemistry (30). The route which was employed is outlined in *Scheme VII*. Hydrogenation of III, followed by exhaustive methylation and degradation, gave the vinyl intermediate (IV). This was transformed, in a series of reactions, to the tetracyclic ketone (V), which was then converted to intermediate (VI). Ozonization of VI afforded the (−)-diacid (VII) which was identical to that obtained from II. MacKay and Hodgkins (31) have come to the same conclusion by means of X-ray crystallography.

It has been determined that unnatural (+)-morphine is inactive as an analgesic (32). Similarly, the activity of optically active morphinans (I: *Scheme VIII*) and benzomorphans (II: *Scheme VIII*) has been found to reside principally in the (−)-enantiomers (33). This strongly suggested that the (−)-isomers of these compounds are configurationally related to (−)-morphine. Chemical evidence in the morphinan series for such a relationship was obtained by degradation of I: *Scheme VIII* (R = Me, X = OH), to VII: *Scheme VII via* a scheme (34) which is similar to the procedure employed in establishing the configuration of morphine. Sawa *et al.* (35) have also related sinomenine (III: *Scheme VIII*), which is enantiomeric to (−)-morphine at the C-9 and C-13 asymmetric centers, to (+)-3-methoxy-*N*-methylmorphinan (VI: *Scheme VIII*). Clemmensen reduction of III: *Scheme VIII*, afforded IV. This compound was converted to

the phenyl ether (V) and subsequently reduced to VI. In accord with the above stereochemical assignment, Beckett (36) has reported that silica gel which has been pretreated with levorphanol (I: *Scheme VIII;* R = Me, X = OH) has greater adsorptive capacity for (−)-morphine than silica gel that has been treated with the corresponding (+)-morphinan.

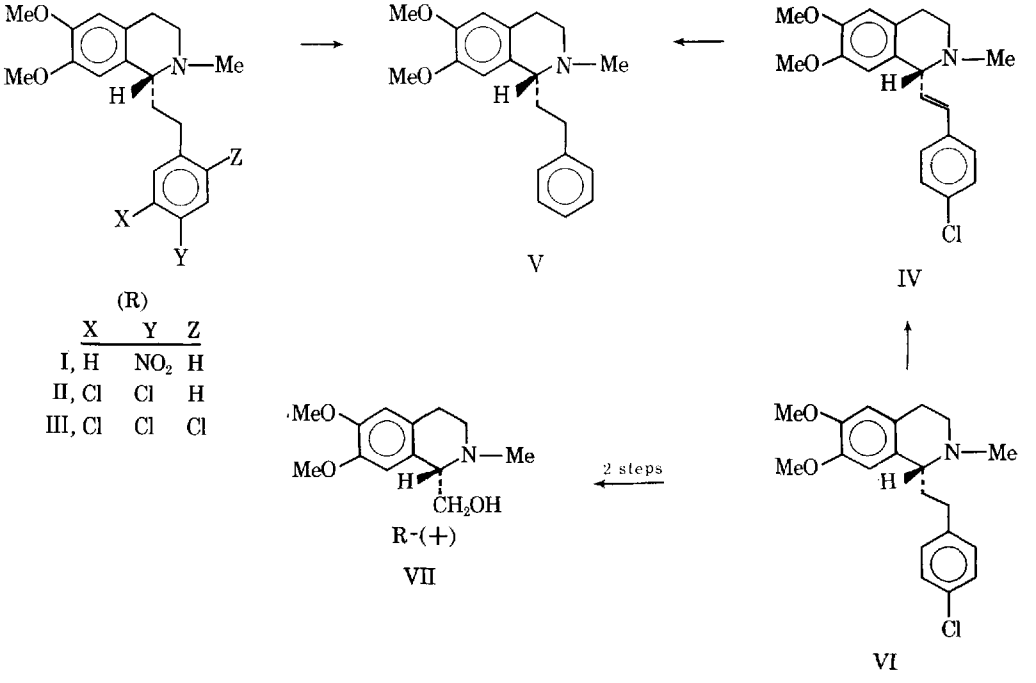


Scheme VIII

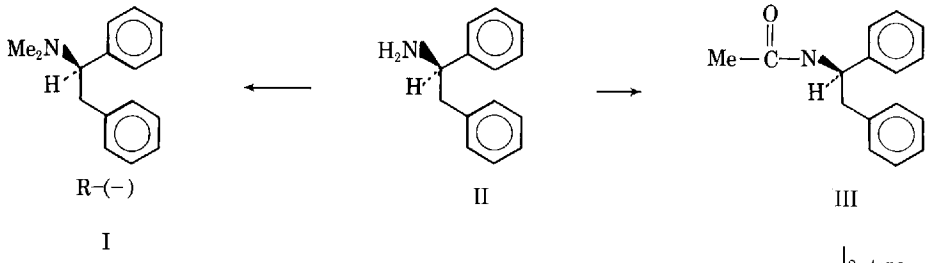
No direct chemical proof of the absolute configuration of benzomorphan derivatives (II: *Scheme VIII*) is available. Beckett (36) has furnished evidence, from stereoselective adsorption studies on silica gel, which suggests that II: *Scheme VIII* (R = R^1 = R^2 = Me, X = OH), is configurationally related to I: *Scheme VIII* (R = Me, X = OH), and hence to (−)-morphine (I: *Scheme VII*). The optical rotatory dispersion (ORD) characteristics of the above compounds have been studied (37), and it has been found that the free bases and salts all exhibit Cotton effects of the same sign. This provides strong evidence that the C-1 and C-5 centers in (−)-II: *Scheme VIII*, are identical to the C-9 and C-13 centers of (−)-morphine.

Miscellaneous Structures.—These compounds are grouped together under this classification because they have no obvious common centers of asymmetry and/or do not bear close structural resemblance to the previously discussed analgesics.

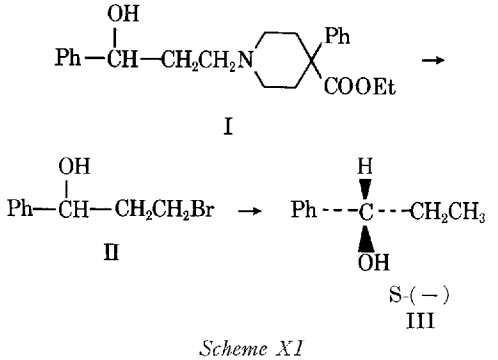
The phenethyltetrahydroquinolines (*Scheme IX*) represent a relatively new class of analgesics having activity in the range of codeine (38). These compounds have been resolved (38, 39)



Scheme IX



Scheme X



Scheme XI

and activity found to reside mainly in one antipode. The absolute stereochemistry of these analgesics has recently been determined by Rheiner and Brossi (39) (*Scheme IX*). The (−)-enantiomers, II and IV: *Scheme IX*, and the (+)-antipode (III) were all converted to the same product (V) by reductive dehalogenation. Reduction of the (−)-nitro compound (I) to the amine followed by deamination also afforded V. Since IV previously (40) had been related to R-(+)-calycotomine (VII) *via* VI, compounds I through IV possess the R-configuration. All of the analgesically more active enantiomers are in the R-series.

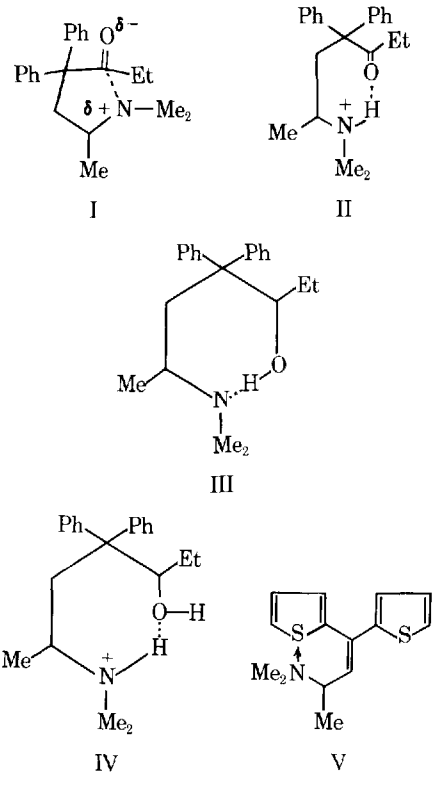
The (−)-enantiomer of *N,N*-dimethyl-1,2-diphenethylamine (I: *Scheme X*) has been reported (41) to be approximately half as active as morphine, while the (+)-antipode is virtually inactive. Nakazaki *et al.* (42) have determined the stereochemistry of I: *Scheme X*, by the procedure shown in *Scheme X*. The amide (III: *Scheme X*), which was derived from the precursor (II) of I, was subjected to exhaustive ozonolysis. The ozonolysis product ultimately was converted to R-aspartic acid (IV). It has been noted (42) that there is a stereochemical resemblance between I and the C-9 asymmetric center of (−)-morphine.

Mazur (43) has resolved the highly potent analgesic, phenoproperidine (I: *Scheme XI*) and found the (−)-isomer to be 4 times more potent than its enantiomer. This suggests that the *N*-aralkyl group is contributing to the pharmacological effect by interacting with a dissymmetric portion of the receptor surface. The configuration of the (−)-isomer was determined by dealkylating with cyanogen bromide to yield the aralkyl bromide (II: *Scheme XI*) and then reducing to the (−)-enantiomer of 1-phenylpropanol (III: *Scheme XI*), whose stereochemistry is known to be in the S-series.

CONFORMATIONAL FACTORS

The relationship between conformational preference and analgesic activity is difficult to assess because differences in conformation *in vivo* can be brought about only by structural variation of the molecule. Since the physical and chemical properties of such compounds may be different enough so that their distribution characteristics are not identical, a knowledge of the relative concentrations of analgesics in the biophase would be needed before differences in potency could be attributed to phenomena related to drug–receptor complex formation. In view of this major drawback, a small difference in potency between diastereomeric compounds, for example, may be difficult to interpret. In spite of the above pitfalls, such correlations appear to be of value, if not for elucidating the optimal conformational requirements for analgesia, then most certainly for determining which conformational species are active.

Open-Chain Analgesics.—It has been postulated (11, 44) that open-chain analgesics such as methadone form ring-like conformations, thereby approximating the over-all geometry



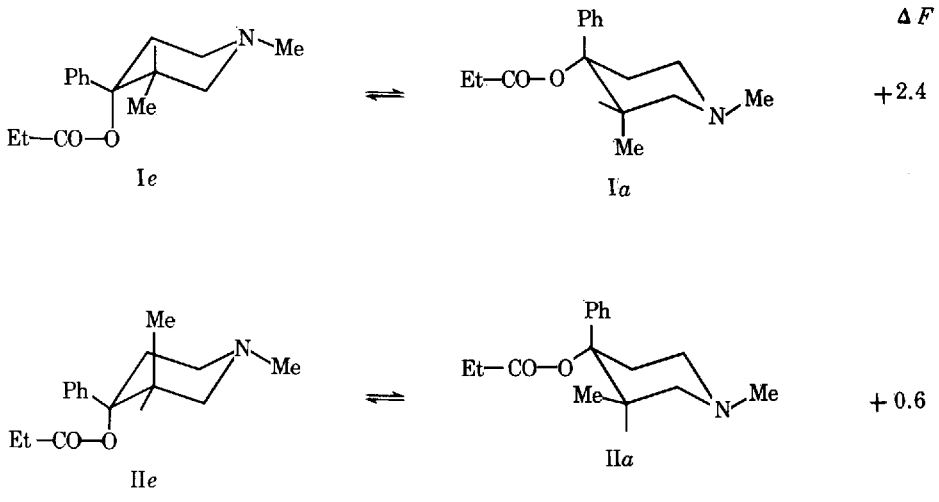
of the piperidine moiety in morphine. Subsequent investigation led Beckett (45) to conclude that such a quasi ring conformation (I) occurs by virtue of an interaction of the basic nitrogen with the carbonyl carbon atom. It has recently been reported by Smith (46) that the NMR spectrum of methadone hydrochloride in chloroform shows magnetically nonequivalent *N*-methyl groups. This has been interpreted as being caused by the molecular asymmetry inherent in the methadone molecule and by intramolecular association between the protonated amine function and the carbonyl oxygen (II). An infrared study of methadol diastereomers has indicated that both the α- and β-isomers (III) are internally hydrogen bonded (13). The protonated forms also are intramolecularly hydrogen-bonded as represented by IV. The α-isomer has been determined to form a stronger hydrogen bond than its diastereomer. (See under *Structures Possessing an Asymmetric Center in Common with Methadone.*) Gero (44) has postulated that thiambutene exists in a conformation (V) which allows intramolecular association between the basic nitrogen and the sulfur atom in the thiophene ring.

Cyclic Analgesics. Cyclic analgesics are restricted to far fewer possible conformations than are open-chain compounds. Moreover, in compounds containing the piperidine ring, the position of equilibria between flip conformational species can be estimated by assuming that the nonbonded interactions are similar to those in cyclohexane.

Among the simplest diastereomeric phenylpiperidine analgesics of known stereochemistry (47–49) are α- and β-prodine (I and II: *Scheme XII*, respectively) (50, 51). β-Prodine is approximately 7 times more potent than the α-isomer. A similar relationship holds for the *N*-phenethyl analogs (52). Estimates of the relative amounts of conformational isomers (I and II: *Scheme XII*) in solution can be obtained if it is assumed that the nonbonded interactions in the solvated free base and cyclohexane are similar. This is a valid assumption in view of the recent report (53) that hydrogen–solvated electron pair and hydrogen–hydrogen interactions differ by only a small factor. It is also reasonably assumed that the *N*-methyl group exists primarily in the equatorial orientation (54) in both flip conformations. The free energy differences between axial- and equatorial-phenyl species have been calculated from average values[2] obtained from the literature (55). It should be emphasized that the ΔF values are approximations, and that small differences ($\Delta\Delta F$) between diastereomers cannot meaningfully be assessed by this method. The ΔF for the conformational equilibrium of the α-isomer (I: *Scheme XII*) has been calculated to be +2.4 Kcal./mole, while that of the β-compound has been estimated to be +0.6 Kcal./mole. This means that the equilibrium for α-prodine is about 98% in the direction of Ie: *Scheme XII*, and that the β-isomer contains approximately 75% of IIe: *Scheme XII*.

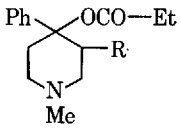
Beckett and Casy (11) have postulated that II: *Scheme XII*, is more active than I: *Scheme XII* by virtue of its greater ability to adopt the axial conformation (IIa: *Scheme XII*) which would be similar to the orientation of the phenylpiperidine moiety in morphine (I: *Scheme VII*). Ziering and co-workers (51) have noted, however, that there is little relationship between stereochemistry and analgesic activity, since other 3-substituted compounds in the prodine series (Table V) do not display parallel activity. The α- and β-isomers of the 3-ethyl compound have about equal activity, and in the 3-allyl analog the α- is more active than the β-isomer. The conformational equilibria of the ethyl and allyl compounds should be comparable to that

[2] The average values employed for ΔF/interaction (in Kcal./mole) are as follows: OCO-Et:H, 0.4; Ph:H, 1.4; Me:H and Me: solvated *N*, 0.9; Me:Me, 3.7; Me:OCO-Et, 2.2.



Scheme XII

TABLE V.—ANALGESIC ACTIVITY OF ISOMERIC PRODINES AND RELATED COMPOUNDS[a]



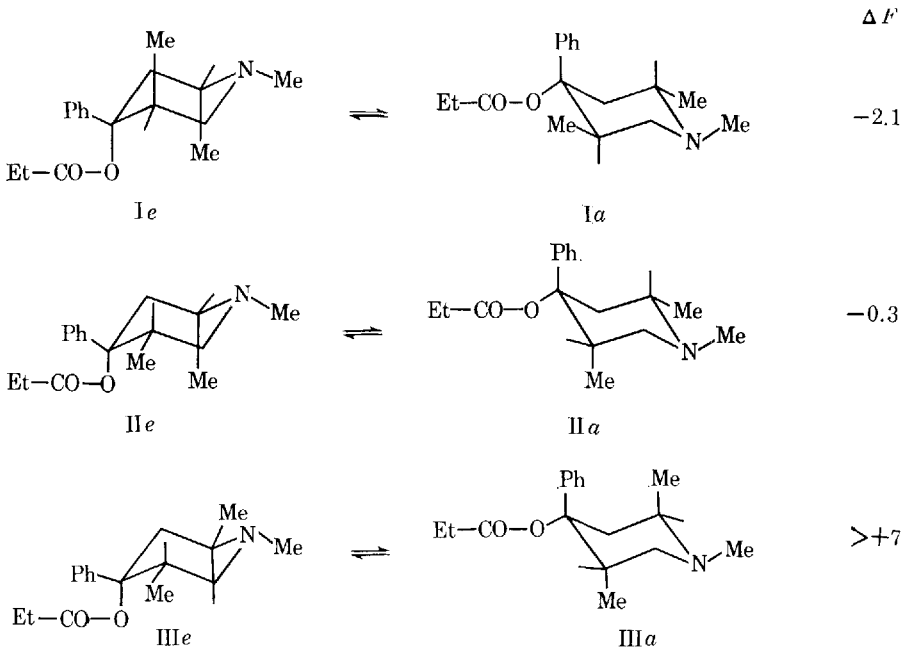
Isomer[b]	R	Relative Activity[c]
α	Me	1.0
β	Me	7.0
α	Et	1.1
β	Et	1.25
α	Allyl	11.0
β	Allyl	3.0

[a] Data from *Reference 51.* [b] α = *trans* Ph:R; β = *cis* Ph:R. [c] Activity relative to meperidine.

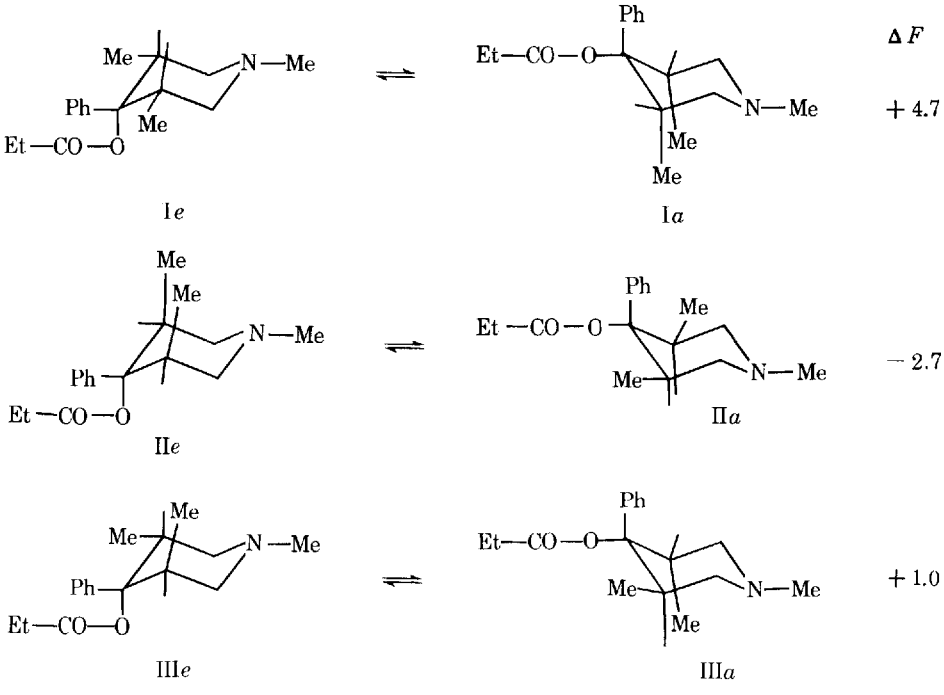
of the 3-methyl diastereomers (I and II: *Scheme XII*), inasmuch as the steric bulk (55) of these groups do not differ substantially. It seems that studies on the distribution and metabolism of these compounds are warranted in order to determine whether the differences in the α/β potency ratio are reflective primarily of events at the receptor level or rather due mainly to concentration differences in the brain. If it is found that differences in activity are related to drug–receptor phenomena, this could also mean that the 3-substituent, rather than the orientation of the phenyl group, exerts a primary influence on drug–receptor association. In any case, it is apparent that an answer to the question of the importance of conformational factors remains highly speculative and awaits experimental clarification.

Nazarov and co-workers (56) have prepared three of the four possible racemates of 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine. The complete stereochemical assignment of these diastereomeric racemates has been reported (57) to be as illustrated in *Scheme XIII*. [In *Schemes XIII* and *XIV*, ΔF values (Kcal./mole) are approximations only. See *Footnote 2* for information on the calculation of these values.] The γ-isomer (III: *Scheme XIII*), which is known as promedol, exceeds the potency of morphine by about threefold, while the β-racemate (II) is about twice as effective as promedol. The most active compound is the α-isomer (I) which has twice the potency of the β-compound. Calculation of the free energy differences between conformational isomers gives an approximation of the positions of the equilibria. Thus, with the α-, β-, and γ-isomers, the values are −2.1, −0.3, and >+7 Kcal./mole, respectively. This indicates that Ia and IIa: *Scheme XIII* are present to the extent of about 97 and 62%, respectively, while IIIa is virtually absent. It appears therefore that I and II: *Scheme XIII* are exerting their action in both flip conformations and that promedol is acting in the equatorial conformation (IIIe: *Scheme XIII*). The positions of the conformational equilibria correlate with the relative analgesic potency of the diastereomers in that increasing axial character parallels analgesic activity. This is consistent with the ideas expressed by Beckett and Casy (11) in connection with the prodines (I and II: *Scheme XII*), although alternate possibilities for the above correlation, which have already been discussed in relation to the prodines, also should be considered.

The three theoretically possible diastereomers of 1,3,5-trimethyl-4-propionoxy-4-phenylpiperidine (*Scheme XIV*) have been prepared by Sorokin (58). The γ-racemate (III: *Scheme*



Scheme XIII

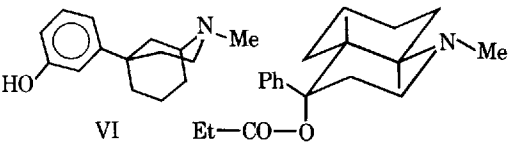


Scheme XIV

XIV) has activity comparable to promedol (III: *Scheme XIII*), whereas the α- and β-isomers are inactive. Conformational analysis indicates no parallelism between potency and the relative amounts of axial-phenyl species in equilibrium with the equatorial form, as has been observed for the prodines (*Scheme XII*) and promedols (*Scheme XIII*). Thus, the inactive β-isomer has a calculated ΔF of −2.7 Kcal./mole, which means that approximately 99% is present as the axial-phenyl conformation (II*a*: *Scheme XIV*). The α-diastereomer, which is also inactive,

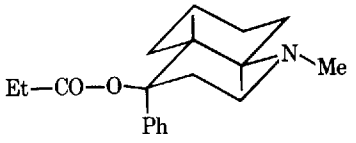
has a value of +4.7 Kcal./mole, which suggests that virtually all of it exists as Ie. On the other hand, the highly potent γ-racemate has a conformational free energy difference (+1 Kcal./mole), which is between the values calculated for I and II: *Scheme XIV*, corresponding to about 15% of IIIa. The preceding analysis suggests that the inactivity of the α- and β-diastereomers (I and II) is related to the 3,5-diequatorial methyl groups which are present in the more stable conformations (Ie and IIa). The active γ-diastereomer (III) is incapable of disposing both the 3- and 5-methyl groups in a similar orientation when in a chair conformation. If the inactivity of I and II are reflective of phenomena at the receptor level, this may be caused by steric hindrance of the 3,5-diequatorial methyl groups to analgesic–receptor association (59).

Although it cannot be stated unequivocally that variation in potency among diastereomeric structures is a direct consequence of the analgesic–receptor interaction, it has been suggested by conformational analysis of flexible phenylpiperidine diastereomers (*Schemes XII–XIV*) that both equatorial- and axial-phenyl conformations have the ability to produce high analgesic activity when other groups on the piperidine ring do not prevent drug–receptor association. Molecules having structural features which prevent conformational inversion can furnish further insight into the nature of the pharmacophoric species. It is well known, for example, that morphine (I: *Scheme VII*), morphinans (I: *Scheme VIII*), and benzomorphans (II: *Scheme VIII*) are all conformationally homogeneous by virtue of the methylene bridge which connects the axial aromatic group to the piperidine ring. The equatorial counterpart to the above compounds is found in the azabicyclononane derivative (VI) (60). The trimethylene bridge prevents conformational inversion and therefore precludes the presence of an axial aromatic ring. This compound has activity comparable to the phenolic benzomorphan structure (II: *Scheme VIII*; R = R^1 = R^2 = Me, X = OH). In a recent study, Smissman and Steinman (61) have prepared two isomeric decahydroquinoline analogs (VII and VIII) of the prodine type analgesics. The *trans* ring juncture in these structures prevents inversion of the piperidine moiety and, thereby, ensures conformational homogeneity. Since both the equatorial (VII) and axial (VIII) isomers were equally potent, it was concluded that no definite conformational requirements of the aromatic ring are necessary for analgesic activity. This is inconsistent with



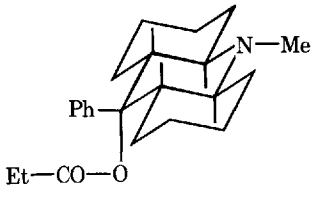
VI

VII



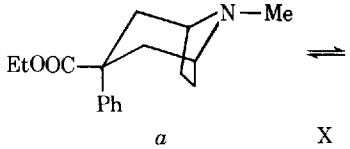
VIII

Beckett's hypothesis (11) which states that analgesics containing an axially oriented aromatic ring should be more potent than those possessing the equatorial conformation. The perhydroacridine analog (IX) was also prepared (62) and found to be inactive. This has been attributed to steric hindrance of the carbocyclic moieties attached to both sides of the piperidine ring, and is consistent with the results obtained from conformational analysis of I and II: *Scheme XIV*.

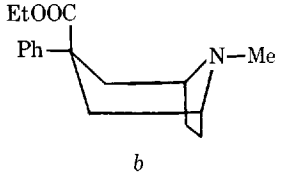


IX

The tropane analog (X) of meperidine was prepared by Bell and Archer (63) and found to be slightly more potent than meperidine (XI). Although inversion of the piperidine moiety cannot occur because of the restriction imposed by the ethylene bridge, spectral evidence (63, 64) suggests that there is a substantial amount of the boat conformation (X*b*) present. This is to be expected in view of the severe diaxial interactions between the phenyl group and the



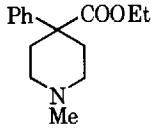
a X



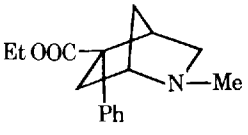
b

ethylene bridge when in the chair conformation (X*a*). Unequivocal evidence demonstrating that

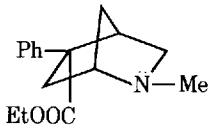
a boat conformation is active has been provided by Portoghese and co-workers (65), who have synthesized and tested bicycloheptane analogs (XII and XIII) of meperidine. In these diastereomers, the piperidine ring is rigidly held in a boat conformation by the C-7 methylene group. The *endo*-phenyl compound (XII), which is about 6 times more potent than the corresponding *exo*-isomer (XIII), is about twice as active as meperidine (XI). The difference in activity between isomers may be due in part to distribution since XIII is a stronger base than XII and hence would not be expected to reach the site of action in the same concentration as its isomer.



XI



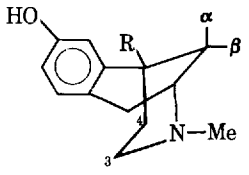
XII



XIII

From all the available data it appears that the conformational requirements for most of the 4-phenylpiperidine type analgesics are minimal. It is rather paradoxical that in certain cases high optical selectivity of the analgesic receptors is observed, whereas a variety of compounds in different conformations are capable of producing analgesia. This paradox can be resolved if it is assumed that differing modes of analgesic–receptor binding (28) occur. (See under *Concepts on Analgesic–Receptor Interactions.*)

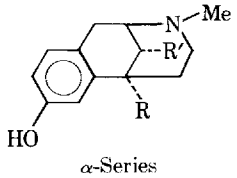
In the preceding discussion the possibility was considered that disposition of groups other than the aromatic ring could also influence analgesic activity. Thus, the activity of prodine-type diastereomers (*Schemes XII–XIV*) could depend in part on the orientation of alkyl groups attached to the piperidine ring. In order to limit the number of variables, it would be informative to examine the effect of a configurational change at a single asymmetric center in analgesics whose geometry is largely restricted to a single conformation. Inasmuch as such compounds are epimeric rather than enantiomeric, it should be mentioned that the observed differences in activity between epimers cannot unequivocally be attributed to events at the receptor level when differences in potency are small. Much of the work on compounds which fall into this category has been carried out by May and co-workers (66–70), who have prepared a variety of epimeric benzomorphans. The conclusions derived from these correlations cannot be extrapolated to the prodines, however, because the modes of interaction of the benzomorphans and the former compounds are most probably different. (See under *Concepts on Analgesic–Receptor Interactions.*) The data presented in Table VI show that compounds in the β-series are consistently more potent than the corresponding α-isomers. Furthermore, it appears that when R = R′ = propyl, the α-compound shows a large decrease in potency while the β-epimer exhibits a relatively small decrease. It can be seen from the three-dimensional representation (XIV) of these isomers



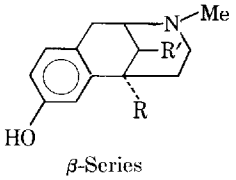
XIV

that the α-series possesses an equatorial C-9 alkyl group, whereas the isomeric β-series has

TABLE VI.– ANALGESIC ACTIVITY OF ISOMERIC BENZOMORPHANS



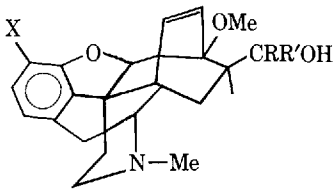
α-Series



β-Series

α-Series ED_{50}	R	R′	β-Series ED_{50}[a]	Ref.
3.0	Me	Me	0.44	(66)
4.9	Et	Me	0.07	(66, 68)
1.5	Me	Et	0.47	(66, 68)
4.2	Et	Et	0.28	(66, 67, 69)
2.9	Pr	Me	0.12	(66, 70)
71.2	Pr	Pr	0.87	(66, 70)

[a] mg./Kg. subcutaneously in mice.



XV

this group oriented in the axial conformation. This suggests that when the C-9 substituent is in the equatorial conformation and beyond a certain size, it may adversely affect drug–receptor association. An equatorial C-9 group would be expected to have little effect on analgesic activity if association with a receptor involved contact only with the C-3,4 hydrocarbon moiety and aromatic ring. Since this is not the case, it appears as if other portions of the molecule are also involved in the receptor interaction. A somewhat related situation exists in certain highly potent analgesics derived from Diels-Alder adducts of thebaine (XV) (71, 72). The —CRR'OH group, which is on the top face of the molecule, can enhance analgesic activity by a factor of up to 7800 times the potency of morphine. Moreover, it has been reported that when the carbinol group is asymmetric (XV; R = Me, R′ = Pr, X = OMe), the activity of one of the isomers is about 90 times that of morphine and approximately 130 times more potent than its epimer. This remarkable difference in potency is probably related, in some way, to the ability of CRR'OH in one of the epimers to enhance receptor binding when in a preferred conformation.

CONCEPTS ON ANALGESIC–RECEPTOR INTERACTIONS

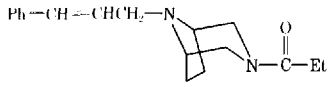
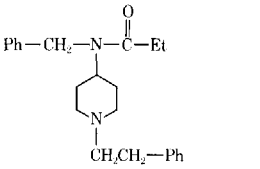
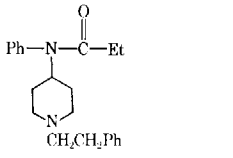
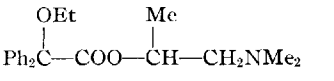
Since isolation and visualization of narcotic analgesic receptors presently is not possible, the medicinal chemist is naturally dependent on the relationship between molecular structure and analgesic activity in order to obtain some insight into the nature and dimensions of such receptors.

The process of determining the pharmacophoric groups necessary for analgesic action evolved slowly and can be traced back to Whalen (73), who in 1902, proposed that the properties of morphine (I: *Scheme VII*) were due to the phenanthrene skeleton. This idea prevailed (74) until 1939, when Eisleb and Schaumann (75) discovered that meperidine (XI) possessed substantial analgesic activity. The structural relationship between morphine and meperidine was realized and it was postulated (76) that the 4-phenylpiperidine moiety was necessary for analgesic activity. With the advent of the methadones (Table X, series 1 and 2) (77), Schaumann (78) modified and generalized his hypothesis by suggesting the structural requirements to be an aromatic ring attached to a quaternary carbon atom two carbons removed from a tertiary amine function. The requirements for analgesic activity, however, were once again outmoded with the appearance of the thiambutenes (Table X, series 5) (4, 79). Gero (44) attempted to rationalize the activity of the thiambutenes and methadones by postulating that these open-chain analgesics formed pseudo-ring conformations.

Beckett and Casy (11) sought to elucidate the receptor requirements for analgesic activity through stereochemical studies of the methadones and thiambutenes. The fact that the more active enantiomers of some of these structures were found to be configurationally related, supported the idea that "fit" at an analgesic receptor is important for activity. A receptor surface was formulated whose dimensions were complementary to certain elements of the phenylpiperidine moiety in morphine. Hence, it was postulated that an analgesic receptor possessed a flat surface, a cavity, and an anionic site which were envisaged to accommodate an aromatic ring, a hydrocarbon moiety, and a protonated basic nitrogen, respectively. These features were depicted as being in a particular sequence, the active enantiomers being capable of three-point contact while the inactive or less active enantiomers were capable of presenting only two of the three essential groups for orientation at the receptor surface. According to this concept, specific orientations of the various pharmacophoric groups in an analgesic molecule are required in order that they may conform to the above receptor dimensions. It was suggested that meperidine and the prodines (*Scheme XII*) were able to associate with this receptor with greater facility when in the axial-phenyl conformation and that the methadones interact by assuming a cyclic conformation. Subsequent studies on the dissociation constants of methadone-type compounds led Beckett (45) to conclude that methadone and related compounds form ring-like conformations by virtue of an interaction of the basic nitrogen with the carbonyl carbon atom. It was concluded (80) from correlations of analgesic activity with the widths of the basic groups, that the anionic site has a width of 7.5–8.5 Å.[3]

[3] This is based on the assumption that the distribution and metabolism of the methadones containing different basic groups are approximately the same. If this is indeed found to be the case by determining the concentration of these compounds in the brain, then their correlation would receive much stronger support.

TABLE VII.—SOME POTENT ANALGESICS OF DIVERSE CONSTITUTION

Compd.	Activity[a, b]
	10 (82)
	2.3 (83)
	~2000 (84)
	5 (85)

[a] Relative to meperidine. [b] References in parentheses.

As more compounds were synthesized and found to possess analgesic activity, it soon became evident that the requirements which were summarized by Braenden, Eddy, and Halbach (60) in 1955 were once again violated (81). It is now known, for example, that there may be as many as five atoms between the aromatic ring and basic nitrogen and still have compounds which are at least as potent as meperidine. Some structurally diverse analgesics, to list only a few, are compiled in Table VII. Other radical departures recently have been reported (86). It is apparent that this presents quite a perplexing problem. Can all of these structures fit a receptor surface having dimensions which have been postulated (11) to be complementary to portions of the morphine molecule while still maintaining high activity? It seems quite probable that this is not the case. Other aspects of the relationship between structure and analgesic activity which are not adequately explained by the Beckett hypothesis are found in Table III, where it can be seen that there is no consistent correlation between the configuration of the more active enantiomers and analgesic activity. It is obvious that the constitution of the R moiety has an important bearing on the configurational selectivity of the receptors. Still another puzzling phenomenon was the ability of identical *N*-substituents to either enhance or diminish analgesic activity when attached to different analgesiophores.[4] For example, replacing the *N*-methyl group in meperidine by the cinnamyl substituent enhances activity by thirty to forty-fold while an identical change in morphine causes a loss of potency (see Table VIII). Along these same lines, it is well known that replacement of the *N*-methyl in morphine by an allyl group results in a compound which has low activity in rodents and morphine antagonist properties. Significantly, similar replacement in meperidine (Table VIII) or in methadone-type analgesics (Table X) results neither in a drastic diminution of potency nor in a compound which has antagonistic properties (87).

Quite recently, Portoghese (28) has introduced a new concept on the mode of interaction of narcotic analgesics with receptors in order to explain all of the above phenomena. It has been postulated that complex formation of different narcotic analgesics with receptors may, in many cases, involve differing modes of interaction rather than a single type of drug–receptor interaction involving binding to the same sites on the receptors. The possibility of induced fit as a factor contributing to receptor binding of diverse analgesics was also recognized (2, 28). Within the framework of this concept the possible modes of interaction were outlined as follows.

Case 1.—Interaction of different analgesics with a single species of receptors; (*a*) identical interaction; (*b*) differing interaction.

Case 2.—Interaction of different analgesics with two or more species of receptors common to the different analgesics; (*a*) identical partitioning on the receptors by different analgesics, (*b*) dissimilar partitioning on the receptors by different analgesics.

Case 3.—Interaction of different analgesics with two or more species of receptors not common to the different analgesics.

Different molecules may interact with identical sites [Case 1(*a*)] or with different sites [Case 1(*b*)] on the same receptor species. Case 1(*b*) is schematically illustrated in Fig. 1. The molecule outlined by the solid line depicts one position of binding, while the dashed line denotes a second position. It is assumed that the steric environment presented to different molecules in different binding positions are not identical.

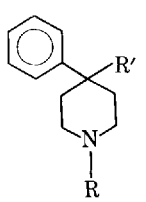
The second case is symbolized by the following equations:

$$\begin{aligned} A + \alpha + \beta &\rightleftharpoons (A\alpha) + (A\beta) \\ B + \alpha + \beta &\rightleftharpoons (B\alpha) + (B\beta) \end{aligned}$$

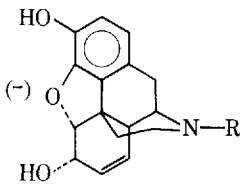
Different analgesics (A and B) and species of receptors (α and β) common to A and B may interact so that the ratios, $(A\alpha):(A\beta)$ and $(B\alpha):$

[4] Analgesiophore is defined as the analgesic molecule less the substituent on the basic nitrogen.

TABLE VIII.—RELATIVE ANALGESIC ACTIVITY OF STRUCTURES CONTAINING THE PHENYLPIPERIDINE MOIETY[a]



1,R′ = CO_2Et
2,R′ = OCOEt
3,R′ = OCOMe



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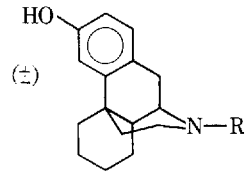

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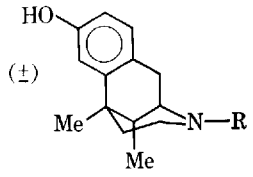


6

R	Relative Activity[b] 1[c,d,e] H.P.[l]	1[c,d,e] R.H.[m]	2[c,f] H.P.[l]	2[c,f] R.H.[m]	3[c,f] H.P.[l]	3[c,f] R.H.[m]	Relative Activity[h] 4[g] R.H.[l]	5[i,j] H.P.[l]	6[j,k] H.P.[l]
Me	1.0	1.0	7.4	26	1.0	2.4	1.0	2	0.7
Et	...	0.5	...	...	...	...	<0.1	0.1	0
n-Pr	...	1.5	...	...	...	...	0	...	0
Allyl	...	0.8[n]	...	...	...	...	<0.1	0	...
n-Bu	...	1.5	...	...	...	...	<0.1	...	0
n-Amyl	...	1.5	...	...	...	...	0.7	~2	~1
$C_6H_5CH_2$	<0.3	<0.5	1.5	1.4	1.0	1.1	<0.1	0	...
	0.15	0.32	3.8	...	...	...	...	...	...
$C_6H_5(CH_2)_2$	2.3	2.6	25	110	12	60	6	~10	~10
	2.7	...	66	69	66	72	...	...	...
$C_6H_5(CH_2)_3$	23	20	162	572	62	265	...	...	0.15
	27	18	318	637	90	142	...	...	...
$C_6H_5(CH_2)_4$	1.6	2.8	54	108	32	39	...	~0.3	...
$C_6H_5CH{=}CHCH_2$	32	40	261	1100	82	376	<0.1	0	...
	61	39	650	785	...	189	...	...	...

[a] Adapted from *Reference 28*. [b] Analgesic activity relative to meperidine; a value of 10 signifies the compound is 10 times more potent than the reference compound. [c] *Reference 90*. [d] Thorpe, R. H., and Walton, E., *J. Chem. Soc.*, **1948**, 559. [e] Elpern, B., Gardner, L. N., and Grumbach, L., *J. Am. Chem. Soc.*, **79**, 1951(1957). [f] Elpern, B., Wetterau, W., Carbateas, P., and Grumbach, L., *ibid.*, **80**, 4916(1958). [g] Winter, C. A., Orahovats, P. D., and Lehman, E. G., *Arch. Intern. Pharmacodyn.*, **110**, 186(1957). [h] Analgesic activity relative to morphine in the same sense as in *Footnote a*. [i] Eddy, N. B., Besendorf, H., and Pellmont, B., *Bull. Narcotics, U. N. Dept. Social Affairs*, **10**, 23(1958). [j] *Reference 33*, p. 157. [k] Ager, J. H., and May, E. L., *J. Org. Chem.*, **25**, 984(1960). [l] Hot plate method using mice. [m] Rat tail radiant heat method. [n] Administered intraperitoneally.

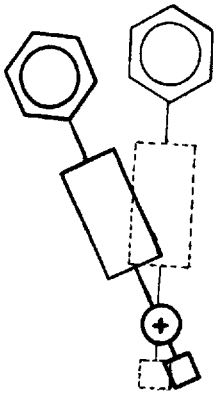


Fig. 1.—A schematic representation of Case 1(*b*). The protonated amine nitrogen is represented by ⊕, the square denotes an *N*-substituent, and the rectangle depicts another portion of the molecule. The different positions of molecular binding are represented by the heavy and dashed lines.

(Bβ), are similar [Case 2(*a*)] or different [Case 2(*b*)].

The third possibility is illustrated by the equations below. In this case α and β are not common to A and B. If different receptor species

$$A + \alpha + \beta \rightleftharpoons (A\alpha)$$
$$B + \alpha + \beta \rightleftharpoons (B\beta)$$

have dissimilar steric requirements in Cases 2(*b*) and 3, then this would be manifested by a difference in the stereoselectivity of the receptors for analgesics A and B.

Combinations of the above cases may also exist, thus creating a much more complex situation. It is probable that Cases 1 and 2 may be the most prevalent types of interaction.

This concept is capable of explaining the lack of correlation between configuration and analgesic activity (Table III). If, for example, methadone (Table III, *1*) and α-methadol (Table III, *5*) are interacting with different patterns of sites on a single species of receptors [Case 1(*b*)] then the steric requirements for the analgesic molecules may not be identical. The fact that the more active enantiomers of the above compounds possess the opposite configuration supports the contention that at least a portion of these analgesic molecules are in different physicochemical environments on the receptors. Figure 2 illustrates schematically how R-methadone and (3S:6S)-methadol, with opposite configuration at C-6, may interact with analgesic receptors. Dipoles conceivably can be sites which are hydrogen bonding donors (X) or acceptors (Y). Interaction of methadone with an analgesic

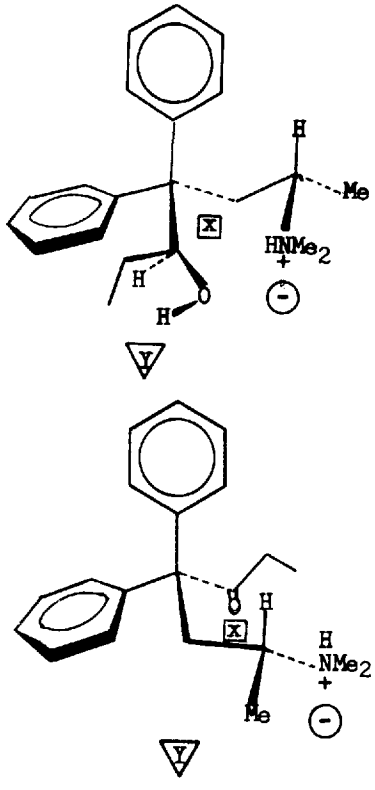


Fig. 2.—One possible mechanism whereby different polar groups in analgesic molecules may cause inversion in the configurational selectivity of analgesic receptors. Hydrogen bonding proton donor and acceptor dipoles are noted by X in square and Y in triangle, respectively. The anionic site is represented by ⊖. Top: (3S:6S)-methadol; bottom: R-methadone.

receptor may involve hydrogen bonding of the ketonic carbonyl group by X, whereas with α-methadol, OH...Y could occur. According to the above interpretation, alteration of a polar group in an analgesic molecule may afford a compound which can interact with dipolar sites and hydrophobic areas that differ from those involved in the binding of the unaltered structure. An alternate explanation can be found in Case 2(*b*). In this case, methadone and α-methadol would interact in different ratios with two or more species of receptors having dissimilar steric requirements. This too could bring about an inversion in configurational selectivity if the steric requirements of the different receptor species common to both analgesics are dissimilar.

The well-known ability of the basic group to influence analgesic activity has been utilized as a means of detecting similarities or differences in the mode of binding to receptors (28, 88). If the mode of interaction between various analgesics and receptors is similar [Cases 1(*a*) and 2(*a*)], then the *N*-substituent should be positioned in a similar physicochemical environment on the receptors and, therefore, contribute to the analgesic effect quantitatively in the same way. Thus, if identical changes of the *N*-substituent in two or more series of compounds produce parallel changes in potency, the mode of binding of the different analgesiophores should be similar. Conversely, dissimilar modes of interaction [Cases 1(*b*), 2(*b*), and 3] should produce nonparallel changes in potency. This is exemplified in Table VIII where parallel relationships can be seen between the meperidines (series 1) and the acyloxy analogs (series 2 and 3). Parallelism is also exhibited among the compounds in the morphine (series 4), morphinan (series 5), and benzomorphan (series 6) series. Comparison of the former (series 1, 2, and 3) with the latter (series 4, 5, and 6), however, shows that there is no parallelism. The correlations in Table VIII indicate that the analgesiophores in series 1, 2, and 3 are binding to receptors by similar modes and that an analogous situation exists among the latter series. On the other hand, lack of parallelism between the phenylpiperidines and structures related to morphine suggested that the binding mode of identically substituted compounds in the former series is different from those in the latter.

If identically *N*-substituted compounds in two different series are interacting with receptors in a similar manner, then the quantitative contribution to the analgesic effect by various substituents should produce, under steady-state conditions, proportionate variations of activity in both series. Such a proportionality is reflective of a linear free energy relationship. The slope of such a regression should be near unity, since identical basic groups are expected to contribute to the pharma-

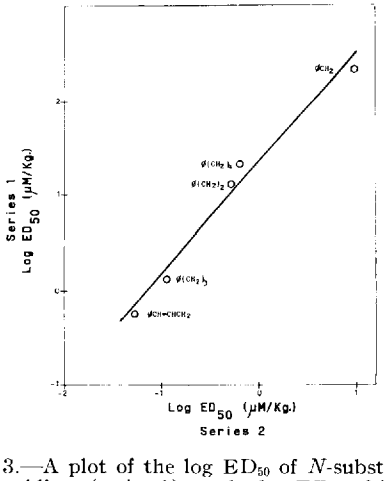
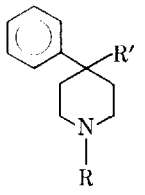


Fig. 3.—A plot of the log ED_{50} of *N*-substituted normeperidines (series 1) *vs.* the log ED_{50} of identically substituted reversed esters (series 2).

TABLE IX.—REGRESSION ANALYSIS OF THE LOGARITHM OF THE ANALGESIC ACTIVITY IN VARIOUS *N*-SUBSTITUTED PHENYLPIPERIDINE SERIES[a]

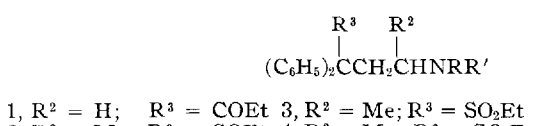


1, R′ = CO_2Et
2, R′ = OCO—Et
3, R′ = OCO—Me

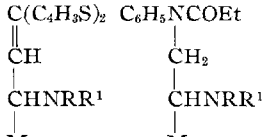
Correlation[b]	Slope[c]	S.E.	S.D.	r[d]	n[e]	Data Source[f]
1 *vs.* 2[i]	1.20	0.09	0.16	0.99	5	*g*
	1.01	0.13	0.25	0.96	6	*h*
1 *vs.* 3[j]	0.93	0.24	0.37	0.90	4	*g*
	0.87	0.21	0.42	0.87	6	*h*
3 *vs.* 2[k]	1.09	0.20	0.27	0.96	4	*g*
	1.06	0.19	0.25	0.94	5	*h*

[a] Adapted from *Reference 28*. [b] Series 1, 2, and 3 were plotted as the logarithm of the activity (μm./Kg.). [c] Values were calculated by the method of least squares. [d] Represents the linear correlation coefficient; when $r = 1$ there is a perfect correlation; if $r = 0$ there is no correlation. [e] Denotes the number of points in the regression. [f] All data were obtained from *Reference 90*; mice were the test animals. [g] Eddy's data. [h] Janssen's data. [i] R=φCH=CHCH₂; φ(CH₂)₃; φ(CH₂)₂; φ(CH₂)₄; φCH₂ · R=φCH(OCOEt)CH₂CH₂; φCH=CHCH₂; φ(CH₂)₃; φCH=CH(CH₂)₂; CH₃. [j] R=φ(CH₂)₃; φ(CH₂)₂; φ(CH₂)₄; φCH₂ · R=φCH(OAc)CH₂CH₂; φCH=CHCH₂; φ(CH₂)₃; φ(CH₂)₂; φCH=CH(CH₂)₂; CH₃. [k] R=φ(CH₂)₃; φ(CH₂)₂; φ(CH₂)₄; φCH₂ · R=φCH=CHCH₂; φ(CH₂)₃; φ(CH₂)₂; φCH=CH(CH₂)₂; CH₃.

TABLE X.—RELATIVE ANALGESIC ACTIVITY[a,b] OF STRUCTURES RELATED TO METHADONE[c]



1, R^2 = H; R^3 = COEt 3, R^2 = Me; R^3 = SO_2Et
2, R^2 = Me; R^3 = COEt 4, R^2 = Me; R^3 = CO_2Et



R	R^1	1[d]	2[d]	3[d]	4[d]	5[e]	6[f]
Me	Me	1.2[g], 2.5[g,h]	7.8,[g] 5.6[g,h]	6	1.3,[g] 0.55[h]	5	0
Me	Benzyl	0, 0[h]	...	..	...	<0.1	1.4[i]
Et	Et	0.3,[g] 0.82[h]	8.1	..	...	5	0
n-Pr	*n*-Pr	<0.33, <0.25[h]	...	..	...	<0.1	...
Allyl	Allyl	0.5[j]	...	..	...	0.7	...
C_4H_8		4.0, 1.9[g,h]	4,[k] 5.7[g,h]	..	...	3.5	0
C_4H_8O		7.0, 8.5[g,h]	19,[g] 4.5[g,h]	..	<0.1[h]	1	0
C_5H_{10}		2.6,[g] 2.5[g,h]	20, 5.4[g,h]	6	0.2[h]	5.5	0

[a] Analgesic activity relative to meperidine; a value of 10 signifies the compound is 10 times more potent than the reference compound. [b] Unless otherwise specified compounds were administered subcutaneously to rats. [c] Adapted from *Reference 28*. [d] Data were obtained from Janssen, P. A. J., "Synthetic Analgesics," Part I, Pergamon Press, Inc., New York, N. Y., 1960, Table V, p. 63. [e] Values were calculated from *Reference 4*. [f] With the exception of the methyl benzyl analog, the above compounds were inactive at 25 mg./Kg. The authors thank Dr. W. Wright, Jr., Lederle Laboratories, Pearl River, N. Y., for providing this information. [g] Average value. [h] Mice were employed as test animals. [i] Calculated from *Reference 15*. [j] Animal species not revealed. [k] Administered intraperitoneally.

cological effect by the same mechanism. The above quantitative relationship is, of course, dependent on the assumption that identical changes in substituents on two different analgesiophores will affect the distribution of the compounds in a similar fashion. This assumption is quite reasonable in view of the successful application of substituent constants for predicting drug availability at the site of action (89). When the mode of binding is not similar, a nonparallel relationship should be obtained which may be characterized by point scattering and the absence of a regression.

It is important to point out that a regression cannot be properly constructed unless the pharmacological data have well-defined confidence limits and are derived from a single source. The analgesic data of Janssen and Eddy (90) appeared to fulfill these requirements. The regressions obtained from these data are shown graphically (Fig. 3) and in Table IX. The high correlation coefficients (r) corroborate the postulate that parallelism in activity is indicative of similar modes of binding and that this concept (28, 87) is of utility in distinguishing between similar [Cases 1(*a*) and 2(*a*)] and different modes [Cases 1(*b*),

2(*b*), or 3] of drug–receptor interactions. Although series 3, 4, and 5 (Table VIII) also display parallelism, these data cannot be quantitated because the activities were obtained from different literature sources.

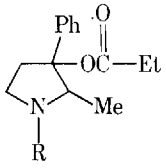
It was discussed earlier that inversion of configurational selectivity is indicative of differences in the mode of interaction between analgesic molecules and receptors. Further support for this proposal was obtained by qualitatively assessing whether parallelism exists between different series of open-chain compounds (Table X) whose *N*-substituents were varied in the same way. Because these data were obtained from a variety of sources, only substantial changes in potency were interpreted as being meaningful.

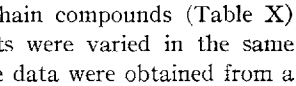
Qualitative inspection suggests that series 1, 2, 3, and 5 exhibit a roughly parallel variation of analgesic activity. This has been interpreted as being reflective of similar modes of interaction with receptors [Cases 1(*a*) or 2(*a*)] and is consistent with the fact that, among the series containing an asymmetric center (series 2, 3, and 5) the more active enantiomers are configurationally related to R-alanine (Table III). Since series 4 and 6 (Table X) show little correlation with series 2, 3, and 5, the mode of interaction of compounds in the former series is probably different from those in the latter. Significantly, the more active enantiomers (series 4 and 6) possess the S-configuration. In the above case, dissimilar binding modes are characterized by both inversion in the stereoselectivity of the receptors and by nonparallel variations in activity. It is important to realize that an identical stereochemical relationship between more active enantiomers does not necessarily imply that analgesic molecules are interacting with receptors in a similar fashion, since this may be coincidental. A more rigorous procedure would, in addition, involve the correlative procedures discussed above. For example, the more active enantiomers of the carbethoxy analog of methadone (series 4; R = R^1 = Me) and the basic anilide compounds (series 6; R = Me, R^1 = benzyl) possess identical configuration but variation of the *N*-substituent does not appear to affect analgesic activity in the same way. This is suggestive of different binding modes despite the fact that the more active optical isomers have the same configuration.

Similar analysis on phenolic and nonphenolic morphinans (I: *Scheme VIII*) and benzomorphans (II: *Scheme VIII*) has also been carried out by the substituent variation method (28). The phenolic compounds show an enhancement of activity on replacing an *N*-methyl with a phenethyl group, while the nonphenolic structures exhibit a decrease in activity when an identical change is made (81). This suggests that the phenolic and nonphenolic compounds are binding to analgesic receptors by different modes. Lack of correlation with other series is also seen among the tetrahydroisioquinoline analgesics (*Scheme IX*), where it has been reported (91) that replacement of the *N*-methyl group by a variety of substituents causes a loss of activity. The pyrrolidine analgesics (Table XI) exhibit a pattern of activities on substituent variation, which is unlike its close relative, the prodines (92). Nonparallelism is also found in the highly potent benzimidazole analgesics (XVI) (93) where variation of the basic group causes changes in activity unlike those seen in other types of analgesic compounds. All of the above phenomena can be rationalized in terms of differing modes of drug–receptor binding. These possibilities include Cases 1(*b*), 2(*b*), and 3, which were described earlier.

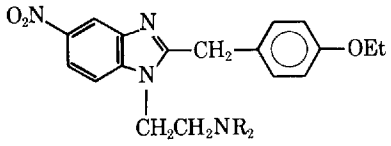
It has also been mentioned (28) that differing modes of interaction were likewise possible among compounds in a single series. In such a case, the binding mode of an analgesiophore would be modified when the basic group is changed. One criterion for detecting transitions in the mode of binding is a large change in enantiomeric potency ratio. It has been shown (18) recently that as the number of methylenes in the *N*-aralkyl group of the basic anilide analgesics (Table XII) is increased from one to three, the enantiomeric potency ratio approaches unity. These marked

TABLE XI.—PYRROLIDINE ANALGESICS[a]



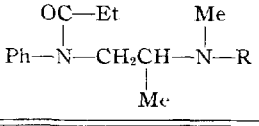
R	Activity[b]
Me	0.8
Ph—CH_2CH_2	0.4
Ph—CH=CH—CH_2	0.4
	1.3
Ph—CH(OH)CH_2CH_2	0.8

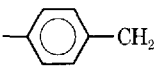
[a] *Reference 92.* [b] Relative to codeine (base/base), 30 min. after i.p. injection.



XVI

TABLE XII.—RELATIONSHIP OF LENGTH OF THE *N*-ARALKYL GROUP ON CONFIGURATIONAL SELECTIVITY OF ANALGESIC RECEPTORS[a]



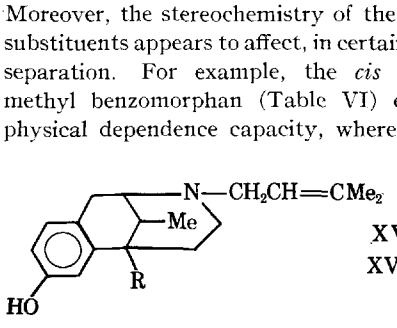
R	Enantiomer[b]	Configuration	AD_{50}[c]
Ph—CH_2	(+)	(S)	4.3[d]
	(−)	(R)	Inactive at 50
Me—  —CH_2	(+)	(S)	1.6
	(−)	(R)	Inactive at 50
Ph—CH_2CH_2	(+)	(S)	3.6[d]
	(−)	(R)	11.7
Ph—$CH_2CH_2CH_2$	(+)	(S)	8.9
	(−)	(R)	11.9

[a] Adapted from *Reference 18*. [b] Optical rotation of the free base. [c] The subcutaneous dose which elevates the rat tail radiant heat response time by 100% in 50% of the animals. [d] *Reference 16*.

changes in potency ratio, which were observed on increasing the chain length, represent a decrease in the stereoselectivity of the receptors which is attributed to differing modes of analgesic–receptor binding [possibilities are Cases 1(*b*), 2(*b*), or 3].

Archer (94, 95) has reported a significant observation regarding the effect of stereochemistry on analgesic antagonist activity. The *cis* and *trans* 5,9-dimethyl (XVII) and the *cis*-5-ethyl-9-methyl (XVIII) compounds all show antagonism against narcotic analgesics, while *trans* XVIII is a meperidine antagonist but does not antagonize morphine. This suggests that the mode of interaction of *trans* XVIII differs from that of the other dimethallyl benzomorphans and provides support that more than one receptor species (Cases 2 or 3) may be involved in analgesic action.

It is conceivable that the great variability in the physical dependence associated with various narcotic analgesics could be related to differing modes of interaction. May (66, 70) has shown that analgesic activity can be separated from physical dependence by merely altering the 5,9-dialkyl substituents in *N*-methylbenzomorphans. Moreover, the stereochemistry of the 5,9-dialkyl substituents appears to affect, in certain cases, this separation. For example, the *cis* 5-propyl-9-methyl benzomorphan (Table VI) exhibits no physical dependence capacity, whereas the corresponding *trans* isomer shows high physical dependence capacity (70).



XVII, R = Me
XVIII, R = Et

CONCLUDING REMARKS

Modification of the pain threshold by strong analgesics is a complex phenomenon which is not well understood. The large variety of structurally unrelated compounds which possess morphine-like activity attests to the complexity of this phenomenon. The structural diversity of compounds having high analgesic potency may be due to a combination of factors. Induced fit (2, 28, 94, 96) and differing modes of analgesic-receptor association (2, 28) have been discussed as possible contributing causes for the apparent overall lack of consistency in the relationship between structure and activity. For this reason the topographical characteristics of analgesic receptors remain obscure. The problem of delineating the geometry of analgesic receptors and ideally, elucidating the chemical components which comprise such entities, will challenge the best efforts of the medicinal chemist for years to come.

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