SYNTHETIC ANALGESICS: STEREOCHEMICAL CONSIDERATIONS

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In a review article[1] in 1952 on "Analgesics," one of the present authors stated "it appears probable from a consideration of the diverse types of compounds which have an analgesic activity equal to, or greater than, that of pethidine, that the minimum requirement for activity may be a hydrophobic group (or collection of groups) containing a basic centre with an overall optimum spatial arrangement." Further "it is possible that the stereochemical configuration of the drug must be complementary to that of a certain tissue surface or enzyme system." Since the appearance of this article, much evidence has been forthcoming supporting the above statements. The purpose of this paper is to correlate the relevant information, to present stereochemical evidence obtained in our own laboratories, and to postulate the type of drug-receptor mechanism involved and the nature of the receptor surface.

The importance of the spatial configuration in analgesics is most clearly demonstrated in those compounds possessing one asymmetric carbon atom. In all cases where optical enantiomorphs have been prepared and tested, one is always more active than the other of each pair, and, in many cases, the whole of the activity of the racemic mixture resides in one of the isomers. In Table I the analgesic activities of a number of enantiomorphic pairs and the nature of their rotations are presented.

The significance of the difference in activities of optical isomers in drug-receptor mechanisms only becomes established when the configurations of the isomers are elucidated. We have determined the configurations of a number of these optical isomers, some of varying chemical types; the more analgesically active isomers of each enantiomorphic pair have identical spatial configurations which are related to that of D-(−)-alanine (see Fig. 1). (Figure 2 shows the outline of the reactions used in establishing the configurational relationships; full chemical details will be published elsewhere.)

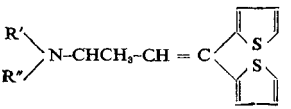
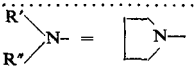
The difference in biological activity exhibited by isomers of enantiomorphic pairs can be attributed to one or more of the following factors:

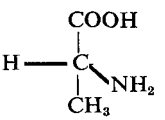
1. difference in their distribution;
2. difference in their rates of metabolism;
3. preferential adsorption of one of the isomers by an optically active constituent in the body before it can reach the site of action;
4. difference in their ease of adsorption upon a complementary receptor surface;
5. difference in the nature of the drug receptor combination.

TABLE I

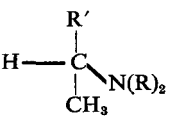
ANALGESIC ACTIVITIES OF ENANTIOMORPHIC PAIRS OF COMPOUNDS

The figures given for analgesic activity are approximate and relate to the activity measured on rats. They have been calculated from results published by various workers (see references 2 to 9).

Analgesic compound	Configuration	Rotation	Analgesic activity (Related to (±)-methadone = 100)
R_2N–$CHCH_3$–CH_2–$C(C_6H_5)_2$–R′			
Methadone: R = CH_3, R′ = $-COC_2H_5$	D	−	180
	L	+	10
Sulphone analogue of methadone: R = CH_3; R′ = $-SO_2C_2H_5$	D	−	180
	L	+	10
			
R′ = CH_3 R″ = CH_3	D	+	170
	L	−	30
R′ = C_2H_5 R″ = C_2H_5	D	+	120
	L	−	20–50
		+	90
		−	50
Isomethadone		−	80
		+	5
3-hydroxy-*N*-methyl morphinan: levorphan		−	400
3-hydroxy-*N*-methyl morphinan: dextrorphan		+	0
3-methoxy-*N*-methyl morphinan: levomethorphan		−	40
3-methoxy-*N*-methyl morphinan: dextromethorphan		+	0



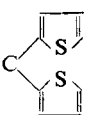
D-(−)-alanine



Optically active analgesics (D-configuration)

(*a*) ((−)-isomer) R = CH_3; R′ = $-CH_2(C_6H_5)_2COC_2H_5$.

(*b*) ((−)-isomer) R = CH_3; R′ = $-CH_2(C_6H_5)_2SO_2C_2H_5$.

(*c*) ((+)-isomer) R = CH_3; R′ = 

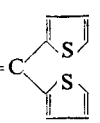
(*d*) ((+)-isomer) R = C_2H_5; R′ = 

FIG. 1.

The possibility of the first 3 factors being involved in the difference of activity amongst enantiomorphs with analgesic action appears remote, because it has been shown that the distribution of (+)-and (−)-methadone within the body is the same[10], and that the excretion of (+), (−) and (±) 3-hydroxy-*N*-methylmorphinan is similar[11]. Furthermore, rat

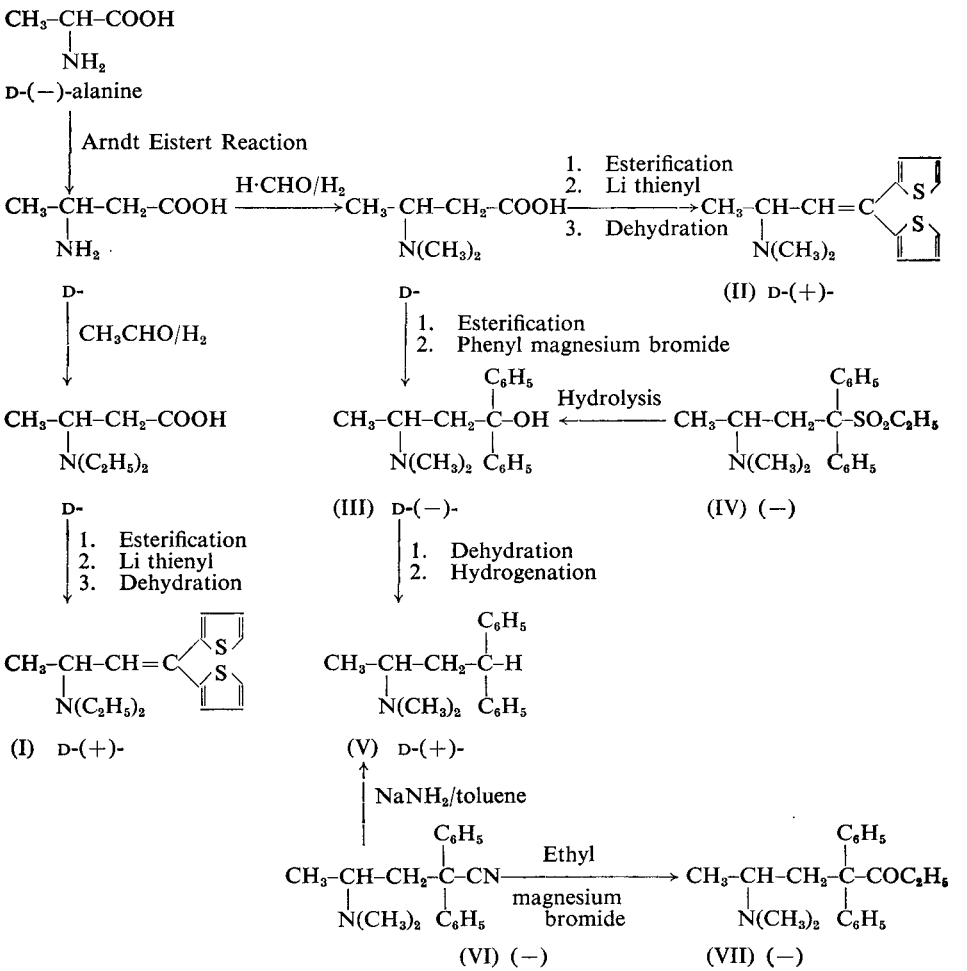


FIG. 2. The determination of the configuration of certain analgesically active isomers.

liver slices (the liver being the chief organ for the metabolism of methadone) have the same effect upon both methadone isomers[10].

Indications that a particular receptor surface is involved in the mediation of analgesic action by a drug can also be obtained by consideration of analgesic antagonists. *N*-allylnormorphine (nalorphine) has been shown to antagonise the analgesic action of compounds of various chemical structures, i.e., morphine, methadone, isomethadone, the

dithienylbutenylamines, acetylmethadols, phenadoxone, 3-hydroxy-*N*-methylmorphinan, pethidine[12,13,14,15,16]. Nalorphine possesses slight analgesic action itself and, when injected into mice after a dose of morphine, rapidly abolishes the analgesic effect of the latter and reduces the pain perception to the level given by nalorphine alone[17]. It also antagonises the respiratory depressant properties of morphine[18]. The replacement of the CH_3– of the N–CH_3 group of morphine by various alkyl groups yields compounds showing a gradation of analgesic and anti-analgesic action; some exhibited both effects[19]. *N*-propylnormorphine, and its diacetyl derivative, antagonised the analgesic action of methadone, pethidine and thiambutene in addition to that of morphine[19]. Substitution of allyl, methallyl, *n*-propyl and *iso*butyl groups for methyl in morphine, dihydro-, desoxy- and dihydrodesoxymorphines and various dihydromorphinones give compounds which antagonised the analgesic effect of morphine[20]. 3-Hydroxy-*N*-allylmorphinan (racemic mixture and (−)-isomer) antagonise the actions of morphine and synthetic analgesics[21,22].

The stereochemical factors involved in the "fit" upon the complementary receptor surface are further emphasised by the following facts concerning analgesic antagonists:

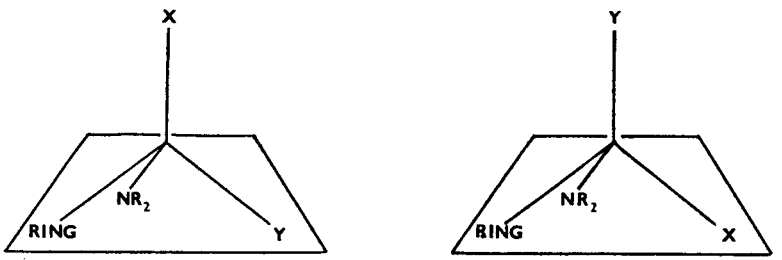
1. Morphine and its antagonist nalorphine have identical configurations.

2. (−)-3-Hydroxy-*N*-methylmorphinan (levorphan), a potent analgesic, is antagonised by (−)-3-hydroxy-*N*-allylmorphinan of identical configuration but not by the (+)- allyl compound possessing the same configuration as the almost inactive (+)-3-hydroxy-*N*-methylmorphinan (dextrorphan)[21].

3. *N*-Methyl*iso*morphinan, essentially without analgesic activity, yields a *N*-allyl compound which is inactive as an anti-analgesic[20].

It may be assumed, therefore, that a "fit" at a receptor surface is involved in analgesic action and that stereochemical factors are extremely important. However, it is not intended to imply that adsorption at a particular receptor site, of necessity, mediates an analgesic effect. It is postulated that analgesic compounds, and their antagonists, "fit" the receptor surface, the former initiating a reaction sequence (or interfering with a reaction sequence), the outcome of which effect is analgesic action, while the latter, because of slight difference in their structure, fail to evoke, or only partially evoke, the reaction sequence. An antagonist can thus compete with an analgesic for the receptor site and, in suitable concentration, completely prevent the analgesic being adsorbed upon the essential site with consequent blocking of its pharmacological effect. By considering the structural surfaces common to different chemical types of analgesics, by bearing in mind the established stereochemical requirement of the synthetic analgesics, and assuming that there is no deformation on adsorption on the receptor surface, certain tentative conclusions can be drawn as to the complementary fine structure of the latter.

Features which are common to all analgesics and their antagonists are (1) a tertiary basic group and (2) a flat aromatic ring structure, e.g., a 6-membered ring possessing 3 double bonds or a 5-membered ring with 2 double bonds. It is probable that these two essential groupings become associated with specific receptor sites in a cellular boundary representing the primary site of action. Substituent groups are not essential because *N*-methylmorphinan, an analgesic, is simply a three dimensional structure of aromatic and hydroaromatic rings possessing one basic centre. Because in certain enantiomorphic pairs, one isomer is analgesically active while the other is inactive, a third grouping consisting of a hydrocarbon moiety must be involved to form a third reaction point at the surface, with the result that only one of the stereoisomers presents the three groups in the correct relative positions. (Figure 3 illustrates that if the (−)-isomer is analgesically active and structure X is involved at the surface as well as the basic group and the aromatic ring, then the (+)-isomer can only present two of the three essential groups in the correct orientation to the receptor surface.)



(+)− isomer (−)− isomer

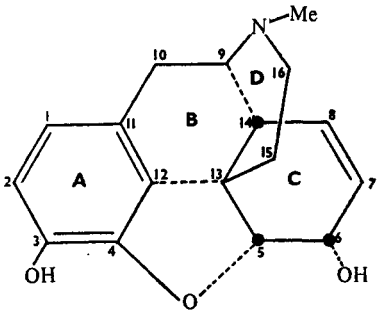
FIG. 3.

Both ease of attachment of the drug to the receptors and the nature of the drug-receptor combination appear to be important in analgesic activity. Inactive isomers, although incapable of coming into 3-point contact with the receptors, can reduce the activity of the active isomers, when added together, by a partial "blocking" effect. It has been shown, for instance, that dextrorphan tartrate and (+)-methadone (inactive isomers) can reduce the analgesic effects of their respective active enantiomorphs[23,24]. Furthermore, the analgesic effects of levorphan and (−)-methadone hydrochloride are inhibited by the inactive (+)-isomers of the other compound to the same degree as by their own inactive isomers, while the combination of half the effective dose of each (−)-isomer is additive in nature[24].

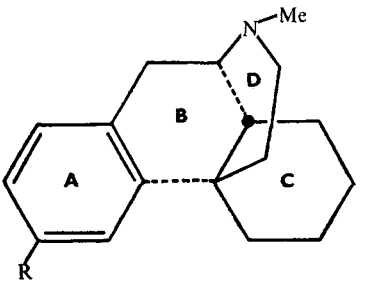
Morphine and the morphinans have rigid structures in which the relationships of the various asymmetric centres have been established[25,26] (see VIII and IX for conventional line representation). They were used as models for a consideration of the most probable surface for presentation to a receptor (a flat ring and the basic centre being regarded as two essential moieties).

The nature of the conformation of the reduced rings of these substances is therefore important. Bose[27] has presented evidence from which he has

concluded that, in morphine (VIII) the alicyclic rings B, C and the piperidine ring D are all in the chair form. Although agreeing with his general conclusions, the present authors consider that ring C in morphine is a boat form and not a chair, because of the steric requirements of the 4 — 5 ether bridge. This steric constraint is not present in the morphinans



(VIII)
morphine

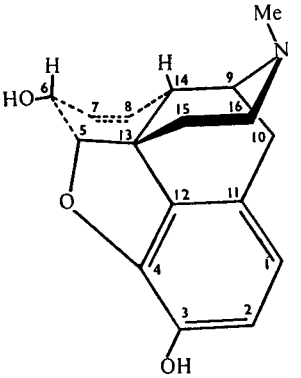


(IX)
N-methyl morphinan (R = H)
racemorphan (dromoran) (R = OH)

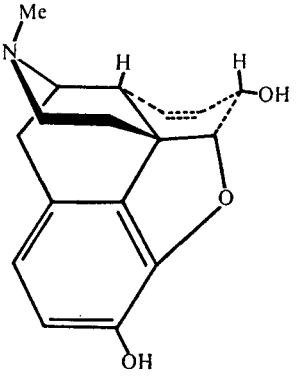
(IX) where it is concluded that rings B, C and D are of the chair conformation. Either conformation of ring C, however, satisfies the points raised in the following discussion. Figure 4 shows a diagramatic representation of the three dimensional arrangement of these structures. Because the relationship of the configuration of morphine and the morphinans to the amino-acids has not been established, morphine can be represented by structure (X) or (XI) and (—)-3-hydroxy-*N*-methyl morphinan by (XII) or (XIII). It is concluded that the structures, as shown (X and XI), represent the surface of the drug which can fit at a complementary receptor surface. The flat aromatic ring A and the basic group lie in almost the same plane, with the $-\overset{15}{C}H_2-\overset{16}{C}H_2-$ part of the piperidine ring D projecting slightly in front, and to the side, of the line between the centre of ring A and the basic group. If a cavity is present in the receptor to accommodate the projecting $-CH_2-CH_2-$ portion, then the electrostatic attraction for the basic group as a cation (at physiological *p*H morphine (pK_a 7·88)[28] will be approximately 80 per cent. ionised) for an anionic site in the receptor could be reinforced by the collective van de Waals' forces between benzene ring A and a flat portion of the receptor surface (e.g. see Albert[41]). If it is assumed that the configuration of morphine is (X) rather than (XI), its mirror image, then (XIV) would represent a diagramatic representation of the complementary surface of the receptor. (If morphine is configuration (XI) then the receptor surface will be the mirror image of the one shown.)

It is postulated, therefore, that the receptor surface by which analgesic action is mediated has the following three essential sites:

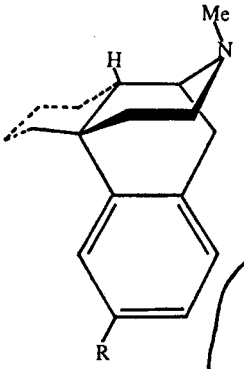
1. A flat portion allowing of van de Waals' forces binding the aromatic ring of the analgesic drug;
2. An anionic site;



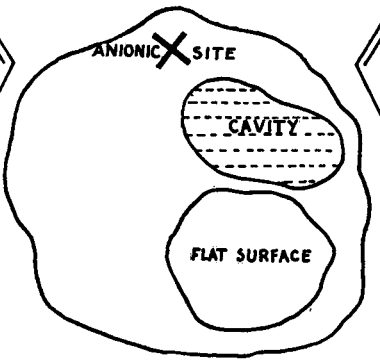
(X) Morphine



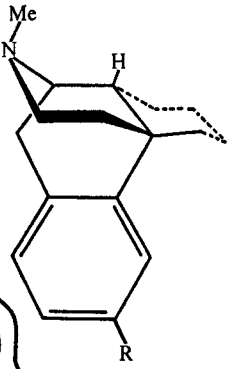
(XI)



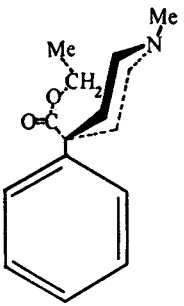
Levorphan (XII)



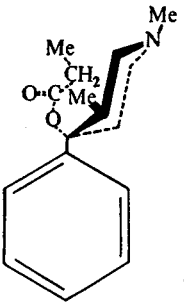
(XIV) Receptor surface



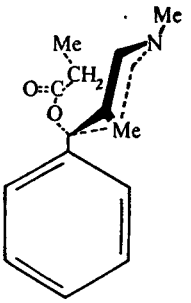
(XIII)



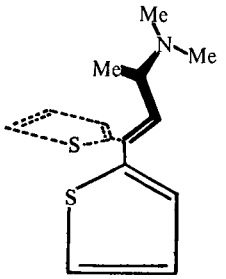
(XV) Pethidine



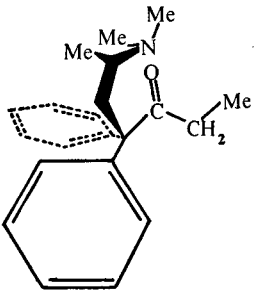
(XVI)



(XVII)



(XVIII)



(XIX) Methadone

FIG. 4. Diagrammatic representation of the three dimensional arrangement of analgesics and the "analgesic receptor surface." The diagrams represent the lower surface of the drug and the upper surface of the receptor, i.e., complementary surfaces. In front of, behind, and in the plane of the paper are represented by ———, ·····, and ——— respectively.

3. A cavity suitably orientated with sites 1 and 2 as diagramatically represented in (XIV).

The association of drug donor groupings with sites 1 and 2 then represents the primary site of analgesic action whereas correct alignment of a projecting hydrocarbon residue with the cavity in one enantiomorph can enhance the drug-receptor contact and consequently the analgesic activity, and, in the opposite enantiomorph, the projecting group will impair the drug receptor contact. The difference in activity between levorphan (XII; R = OH) and dextrorphan (XIII; R = OH) is explicable in terms of the above receptor surface hypothesis. The replacement of the *N*-methyl group of morphine or levorphan by the *N*-allyl group will not impair the fit at the receptor surface. Yet the alteration in structure is enough to make these substances sufficiently dissimilar from their parent compounds to cause them to fail to carry out the normal reaction of the latter when adsorbed. The reason for the simultaneous mild analgesic and anti-analgesic action exhibited by certain of the *N*-allyl*nor*morphine type compounds and the lack of anti-analgesic action in (+)-*N*-allyl-3-hydroxymorphinan is also explicable.

The implications of the presence or absence of phenolic or other groups and their effect upon partition coefficients and dissociation constants, etc., will be described in detail in a subsequent publication.

The synthetic analgesics of less rigid structures may be considered in terms of association with the essential receptor sites specified above.

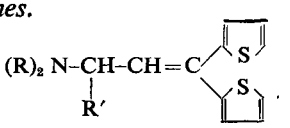
Pethidine and related structures.

The most stable conformation of pethidine will be a chair form for the piperidine ring with the large phenyl group probably in the equatorial and the ester group in the axial position. This structure fits the essential three receptor sites (see XV and XIV). The greater activity exhibited by the pethidine type compound (XVI), in which the methyl and propionoxy groups are *cis*, compared with compound (XVII) in which they

are *trans*[29] becomes explicable in terms of the *cis* methyl (equatorial) fitting the receptor cavity better than the *trans* methyl (axial).

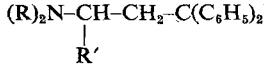
The configuration of the two isomers XVI and XVII was not established unequivocally. If the assignments are incorrect, compound XVII would be the more active isomer and its most stable conformation would probably be that in which the phenyl group was in the axial, and the propionoxy and methyl groups in the equatorial positions. The resulting three dimensional arrangement would be nearer to that of morphine than the one diagrammatically represented in XVII. This point will be discussed more fully in a later publication when further experimental evidence has been obtained.

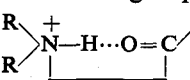
Dithienylbutenylamines.



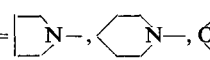
(XX)

The use of molecular models (Catalin) clearly reveals that, if R and R′ = CH_3, the D-(+)-isomer can have one thienyl ring and the basic group fitting at the flat surface and the anionic site of the receptor respectively, while the methyl group will fit into the cavity (see Fig. 4, XVIII and XIV). In the L-(−)-isomer the methyl group is not quite correctly orientated although there is not a great difference between the "fit" of the two isomers. These facts are compatible with the fact that the D-(+)-isomer is more active than the L-(−)-isomer although both exhibit analgesic activity. The same explanation and correlation applies to the observed structure and activities when R = C_2H_5 and R′ = CH_3. The use of molecular models also revealed that increase in size of group R′ would result in a less favourable alignment of the thienyl ring and basic centre with the receptor sites; this observation is compatible with the pharmacological results of decrease in activity with increasing size of group R′[6].

Methadone and related structures.  (XXI).

In methadone (XXI; R = CH_3; R′ = CH_3; R″ = COC_2H_5) the bulky groups attached to the quaternary carbon atom impose severe restraint to free rotation in the molecule. The planar phenyl groups will tend to positions of maximum clearance, that is to positions corresponding to the sides of a trihedral angle with the quaternary carbon at the apex (an effect termed "trihedralisation"[30]). The other bulky groups impart a certain rigidity to the molecule, especially since the carbonyl oxygen atom and the nitrogen atom can approach so close to each other that it seems probable that, when this basic group is in the cationic form, hydrogen bonding of the type  occurs. The molecule can be regarded

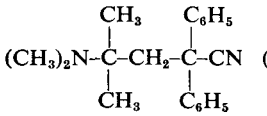
as semi-rigid and the D-(−)-isomer of methadone has then a correct alignment if one phenyl ring, the basic group and the CH_3– group fit the flat surface, the anionic site and the cavity of the receptor surface respectively (see Fig. 4, XIX and XIV). Models reveal that the L-(+)-isomer would be expected to fit at the same receptor surface, although not so well as the D-(−). It is significant that, although the former isomer is almost completely devoid of analgesic activity, it reduces the activity of the latter when both are given together, indicating that both ease of attachment and the nature of the drug–receptor combination are important in analgesic activity. The difference in activities between the D-(−)- and the L-(+)-isomers of the sulphone analogue of methadone (XXI; $R = CH_3$, $R' = CH_3$, $R'' = SO_2C_2H_5$) and of the (+)- and (−)-isomers of isomethadone can also be explained as above. Reduction of isomethadone yields the isomethadols which would be expected to fit the same receptor surface as the active analgesic. This conclusion is supported by the fact that analgesically inactive α-isomethadol, in large doses, partially blocks the analgesic activity of isomethadone; if methadone and the slightly active α-methadol are given together a sum of the effects of the two compounds given separately is obtained.[31] In methadone compounds, the significance of the dependence of analgesic effect upon configuration of the isomer is not so clear as in the cases which have been discussed previously, e.g., α-(−)-methadol, α-(−) and β-(+)-acetylmethadol, all derived from the relatively inactive L-(+)-methadone, possess a fair degree of activity[32]; the L-(+)-ester (XXI; $R = CH_3$, $R' = CH_3$, $R'' = COOC_2H_5$), although possessing only weak analgesic activity, is more active than its D-(−)-isomer.[5] However, these compounds can "fit" the analgesic receptor surface (Fig. 4. XIV) and consequently the nature of the drug–receptor combination is the most important factor involved in their activity. There are indications that there are limitations to the size of basic groups permissible if the drug is to combine with the receptor because, although 5- and 6-membered basic ring structures (XXI);

$(R)_2N =$  , in amidone analogues are active, 7- and

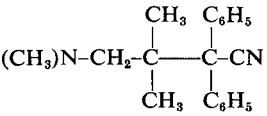
8-membered rings yield inactive products[33].

The fact that D-(−)-methadone possesses high analgesic activity while its L-(+)-isomer is almost inactive made the preparation of "6-methylmethadone" (6-dimethylamino-6-methyl-4:4-diphenylheptan-3-one) (XXIV) of interest. If one phenyl group, the basic group and one methyl group (on C 6) in this compound are correctly orientated towards the receptor surface (as in D-(−)-methadone) then the other C 6 methyl group will be positioned as in L-(+)-methadone with phenyl and basic group fitting at the appropriate receptor sites. This substance has been prepared and has been shown to be devoid of analgesic activity indicating that, despite the correct configurational arrangement of the 3 essential analgesic groupings, an incorrectly positioned methyl group can prevent the correct drug–receptor combination.

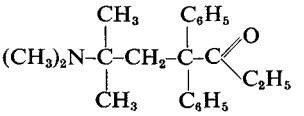
"6-Methylmethadone" (XXIV) was prepared by treating 3-dimethylamino-3-methyl-1 : 1-diphenyl-butyl cyanide (XXII) with ethyl magnesium bromide. This cyanide was formed together with the isomeric 3-dimethylamino-2 :2-dimethyl-1 : 1-diphenyl-propyl cyanide (XXIII) by the condensation of 1-chloro-2-dimethylamino-2-methyl propane with diphenylmethylcyanide.



(XXII)



(XXIII)



(XXIV)

It has been observed that condensations between 2-amino-1-chloropropanes, or 1-amino-2-chloropropanes (e.g., $(CH_3)_2N\,CH_2{\cdot}CH(Cl){\cdot}CH_3$, and diphenylmethyl cyanide yield pairs of isomeric cyanides[33,34,35,36], the cyanide group of one member being hindered as shown by the isolation of a stable ketimine from the cyanide-Grignard complex and the difficulty of hydrolysis of the cyanide group. The two cyanides obtained in the present work (XXII and XXIII) varied greatly in their reactions. Ethylmagnesium bromide yielded a ketone with one cyanide (A) but failed to react with cyanide (B). The latter was also recovered unchanged after treatment with lithium ethyl and attempted hydrolysis with 20 per cent. hydrobromic acid. These facts demonstrate the hindered nature of the cyanide group in (B) and consequently structure (XXII) has been allocated to the less hindered cyanide (A) and structure (XXIV) "6-methylmethadone" to the derived ketone.

Conclusion

It is postulated that, if an organic compound is to exhibit high analgesic activity, the following essential features are necessary:

1. A basic centre which is ionised as a cation at physiological *p*H, in order that it may be able to associate with an anionic site in the receptor surface.
2. A flat aromatic structure in the molecule to allow of a strong collective van der Waals' force bonding to a flat portion of the receptor reinforcing the ionic bond mentioned in (1) which otherwise would not be sufficiently permanent because of ion exchange under biological conditions.
3. The basic group and the flat structure to be almost in the same plane; this to be accomplished by a completely rigid molecule or a slightly less rigid one held in the correct configuration by steric or other constraints.
4. A suitably positioned projecting hydrocarbon moiety to form, with the basic centre and flat aromatic structure, a three dimensional geometric pattern indicated in Fig. 4.

EXPERIMENTAL

All m.pts. are uncorrected.

Equivalent weights of the bases were determined by titration with 0·02N perchloric acid in glacial acetic acid using crystal violet as indicator. Titration of the hydrohalide salts was carried out in non-aqueous media in the presence of mercuric acetate by the method described by Pifer and Wollish[37].

Configuration of certain analgesics. (−)-Methadone, (−)-ethyl 3-dimethylamino-1 : 1-diphenylbutyl sulphone, (+)-3-dimethylamino-1 : 1-di-(2′-thienyl)-but-1-ene and (+)-3-diethylamino-1 : 1-di-(2′-thienyl)-but-1-ene have been shown to possess identical configurations related to that of D-(−)-alanine (full details will be published elsewhere).

2-*Dimethylamino-2-methylpropan-1-ol.* This was prepared in 83 per cent. yield by the method described by Rosnati[38]; Equiv. wt. 117 (theory 120), methiodide m.pt. 237° to 238° C. (decomp.).

1-*Chloro-2-dimethylamino-2-methylpropane hydrochloride.* Thionyl chloride (7·5 ml.) was added slowly, with stirring, to a solution of 2-dimethylamino-2-methylpropan-1-ol (5·85 g.) in benzene (50 ml.) cooled in ice, and the mixture then refluxed for 1 hour. The crystals (7 g.) which separated upon cooling were washed with benzene and recrystallised from acetone-methanol to yield 1-*chloro-2-dimethylamino-2-methylpropane hydrochloride* as colourless platelets m.pt. 166° to 167° C. Found: C, 41·9; H, 8·5; N, 8·5; Cl, 41·2 per cent. Equiv. wt., 168. $C_6H_{15}NCl_2$ requires C, 41·8; H, 8·7; N, 8·1; Cl, 41·3 per cent. Equiv. wt., 172.

Condensation of 1-*chloro-2-dimethylamino-2-methylpropane with diphenylmethyl cyanide.*

Sodamide (4 g.) was added to a solution of diphenylmethyl cyanide (19·3 g.) in dry benzene (150 ml.) and the mixture stirred until no further darkening occurred. A solution in benzene (150 ml.) of 1-chloro-2-dimethylamino-2-methylpropane, freshly liberated from the hydrochloride (17·2 g.), was added drop by drop and the mixture stirred overnight. The bases were extracted with dilute hydrochloric acid, the acidic extracts made alkaline with solution of ammonia, and the liberated bases extracted with ether. The ethereal extract was dried (sodium sulphate), and the solvent removed to yield a yellow oil (23 g.) which, after dissolving in boiling light petroleum (b.pt. 40° to 60° C.) (10 ml.) and then cooling, gave pale yellow crystals of *cyanide A*, m.pt. 73° C. Found: C, 82·4; H, 8·25; N, 9·4 per cent. Equiv. wt., 290. $C_{20}H_{24}N_2$ requires C, 82·2; H, 8·2; N, 9·6 per cent. Equiv. wt., 292. The *hydrobromide* crystallised from acetone/ether as colourless needles mp.t 183° C. Found: C, 63·7; H, 6·7; N, 7·2; Br 21·0 per cent. Equiv. wt., 367. $C_{20}H_{25}N_2Br$ requires C, 64·3; H, 6·7; N, 7·5; Br, 21·5 per cent. Equiv. wt., 373.

The mother liquors, after removal of the solvent, were treated with excess of ethanolic hydrobromic acid. A white solid precipitated and was recrystallised from acetone to yield *cyanide B hydrobromide* (10·5 g.), m.pt. 239° C. (d). Found: C, 64·0; H, 6·7; N, 7·7; Br, 21·4 per cent.

Equiv. wt., 376. $C_{20}H_{25}N_2Br$ requires C, 64·3; H, 6·7; N, 7·5; Br, 21·5 per cent. Equiv. wt., 373.

6-Dimethylamino-6-methyl-4:4-diphenylheptan-3-one (XXIV).

Cyanide A (2 g.) in dry toluene (15 ml.) was added to ethylmagnesium bromide in ether (10 ml.) prepared from magnesium (0·75 g.) and ethyl bromide (3·4 g.). The ether was distilled off, the mixture refluxed for 3 hours and then added to crushed ice and concentrated hydrochloric acid (8 ml.). The solid which separated was washed, the base liberated with dilute solution of ammonia and extracted with ether. After drying (sodium sulphate) the solvent was removed to yield a pale yellow oil (1·6 g.) which crystallised on standing, and was recrystallised from ethanol to give colourless crystals of *6-dimethylamino-6-methyl-4:4-diphenylheptan-3-one*, m.pt. 81 to 82° C. Found: C, 82·1; H, 8·95; N, 4·3 per cent. Equiv. wt., 320. $C_{22}H_{29}NO$ requires C, 81·7; H, 9·0; N, 4·3 per cent. Equiv. wt., 323.

Reactions of cyanide B. The cyanide was recovered unchanged when subjected to the above reaction, and when treated with a fourfold equivalent of lithium ethyl. It was not hydrolysed upon boiling with 20 per cent. aqueous hydrobromic acid for 3 hours.

Pharmacological results.

The method of testing used was a tail reflex method[39] which gives results exactly corresponding to the tail pain method described by Grewal[40].

(+)-3-Diethylamino-1:1-di-(2′-thienyl)-but-1-ene is as active, and the (±)-compound slightly more than 50 per cent. as active, as (±)-methadone. 6-Dimethylamino-6-methyl-4:4-diphenylheptan-3-one is devoid of analgesic activity.

Summary

1. The evidence is presented for the probability of the activity exhibited by analgesics and their antagonists being due to their association with a specific receptor surface.

2. The configurations of those isomers exhibiting nearly all the activity of certain racemic mixtures are identical, and related to that of D-(−)-alanine; the stereochemical requirements of analgesics are considered.

3. Active analgesics are shown to have structures which enable them to present similar surfaces to allow of their association with a proposed "analgesic receptor surface," the essential features of which are described.

4. A number of essential structures are outlined as prerequisites for compounds designed as analgesics.

The authors wish to express their thanks to Dr. M. F. Lockett for carrying out the pharmacological testing.

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DISCUSSION

The paper was presented by DR. A. H. BECKETT.

DR. F. HARTLEY (London) said that many denied that any substantial correlation had been found between chemical structure and physiological action, but it was desirable that, as far as possible, attempts should be made to correlate some aspects of chemical structure, however simple, with activity, in order to formulate a working hypothesis. The authors had selected an excellent test case in 6-methylmethadone. The extra methyl group should interfere with the analgesic behaviour, and, as had been shown, the compound was inactive. This might be regarded as a critical test, but it was unfortunate that in preparing 6-methylmethadone the reaction of the diphenylacetonitrile with the chlorodimethylamino-alkyl-derivative was ambiguous, as the reaction could proceed in two ways. Although Dr. Beckett had advanced *prima facie* evidence as to why the structure he had assigned to the compound was correct, it was important that the critical example should be beyond reproach. In order to establish the structure with certainty Dr. Beckett should degrade his compound to establish the position of the methyl groups beyond doubt.

DR. G. E. FOSTER (Dartford) said he was not clear how the authors explained why nalorphine was an antagonist to morphine and other synthetic analgesics when they all fitted the proposed receptor surface.

DR. J. B. STENLAKE (Glasgow) expressed the opinion that the conformations suggested for pethidine and the two esters XVI and XVII were open to question on the grounds that the propionoxy and phenyl groups were of comparable size. A pethidine molecule with a conformation having an axial 4-phenyl group bore a far more striking resemblance to the 3-dimensional structure of morphine than did the alternative conformation in which the 4-phenyl group was equatorial. He considered that the conformation suggested for the ester XVII with an axial 3-methyl group was improbable, and that in fact the most likely stable conformation would be the alternative one in which both methyl and propionoxy groups were equatorial and the phenyl group axial. He agreed that in XVI the phenyl group was most probably equatorial. He went on to point out that the configurations of XVI and XVII had not been rigidly assigned, and suggested that the known greater ease of hydrolysis of the least active isomer was open to the alternative interpretation that in this isomer (actually XVI) the propionoxy group was axial. In consequence the phenyl group would be equatorial and the molecule would be in an unmorphine-like conformation. Its more stable and more active isomer would then be that in which the phenyl group was axial with the molecule in a morphine-like conformation (XVII). He expressed the hope that the authors would seek further experimental evidence of the configuration of these two isomers.

DR. G. BROWNLEE (London) said that although nalorphine antagonised some of the effects of morphine, it did not antagonise all of them, which seemed to indicate that there was more than one receptor site. This did not detract from the value of the hypothesis that there was not a single simple receptor site for morphine. It was possible that 6-methylmethadone should also have some functions which might be measured. Did it reverse the action of morphine? What action did it have on smooth muscle?

DR. BECKETT, in reply to Dr. Hartley, said that work was in progress to establish the constitution of the product obtained by the condensation of diphenylacetonitrile with 1-chloro-2-dimethylamino-2-methylpropane in an unequivocal manner. The lack of analgesic activity of the final ketone, however, supported the hypothesis irrespective of whether it was 6-methyl methadone or 6-methyl-*iso*methadone. Replying to Dr. Foster, he said that nalorphine and certain other substances in which the *N*-methyl group of morphine and related compounds was replaced by *N*-allyl and other groups could 'fit' the proposed receptor site. A gradation of analgesic and anti-analgesic action was produced. Replying to Dr. Stenlake, he said that he agreed that there was some doubt concerning the correctness of the configuration assigned by the American workers to the isomers XVI and XVII. Work was in progress to establish their configurations. If the configurational assignments were in fact reversed, it would then

be reasonable to postulate the most stable conformation for the more active isomer with an axial phenyl and the methyl and propionoxy groups in the equatorial position. It could then be postulated that the phenyl group of pethidine was axial when the molecule was adsorbed on the receptor surface because "fit" at the surface under biological conditions could favour the adoption of the authors' conformation in preference to an alternative one of approximately equal stability as the contact points were coming together. However, the general hypothesis was unaffected by the problems still requiring solution in connection with these pethidine type compounds. In reply to Dr. Brownlee, he said that he would be disappointed if 6-methylmethadone reversed the activity of morphine because the evidence suggested that it did not "fit" at the proposed analgesic receptor surface.