REVIEW ARTICLE

ANALGESICS—A GENERAL SURVEY

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SYNTHETIC analgesics were reviewed comprehensively in 1948 by Bergel and Morrison,[1] especially from the chemical point of view. Since that time, other reviews[2,3,4,5,6,7,8,9,10] have appeared dealing with various aspects of the problem of producing compounds with the analgesic activity of morphine but without its undesirable side-effects. The research in this important field of medicinal chemistry continues with little sign of reduction in its volume, although its emphasis changes from time to time as fresh clues to analgesic activity are unearthed, or new theories for activity proposed. The present article will survey the whole field of analgesics briefly, and emphasise especially:—1. The chemical aspect of the work since 1948. 2. The absorption, distribution, metabolism and excretion of analgesics. 3. The theories relating to the mode of action, and the attempts to relate chemical structure and analgesic activity. Compounds of weak activity such as aspirin, phenacetin, phenazone, and related substances, called by Fourneau[11] "antalgics," will not be included.

MODIFICATIONS OF THE MORPHINE MOLECULE

The structure for morphine (I) put forward by Gulland and Robinson[12] has recently been proved conclusively to be correct by the synthesis of tetrahydrodesoxycodeine[13] and of morphine[14] itself. Morphine has been modified chemically in many ways in attempts to reduce its undesirable side effects, the chief of which are its great liability to produce addiction and its depressant effect upon the respiratory centre. Summaries of the results of this work have been presented elsewhere[1,3,11,15] and only the more important or newer compounds derived from morphine-type alkaloids are described here. Table I shows the structure of many of these compounds and the approximate analgesic activities.

6-*Acetylmorphine* (II). This substance, although 4 times as active as morphine, exhibits a 4-fold increase in the unwanted side effects.

Diacetylmorphine (*Diamorphine*; *Heroin*). (C-OH in position 3 and 6 replaced by C-$OCOCH_3$). Although possessing a higher analgesic activity than morphine, it is more toxic and possesses a greater liability to habitation, and its manufacture has been prohibited in many countries.

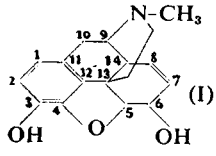
Dihydromorphinone (*Dilaudid*) (IV). Unfortunately an increased toxicity accompanies its increased analgesic action. However, it is said to be less habit forming, and to have less emetic action than morphine.

Methyldihydromorphinone (*Metopon*) (V). This compound was prepared by Small *et al.*[16] in the course of a fundamental study of the reaction of thebaine with organomagnesium halides. Its structure has not yet

TABLE I

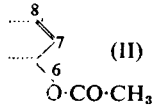
MORPHINE AND ITS DERIVATIVES

The relative analgesic activities are given as numbers in parenthesis



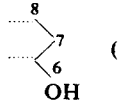
(I)

Morphine (100)



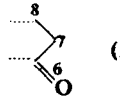
(II)

6-Acetylmorphine (400)



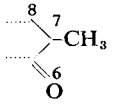
(III)

Dihydromorphine (200)



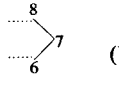
(IV)

Dihydro-morphinone (500) (Dilaudid)



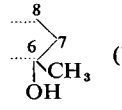
(V)

Methyldihydromorphinone (1000) (Metopon)



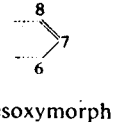
(VI)

Dihydrodesoxymorphine-D (900) (Desomorphine)



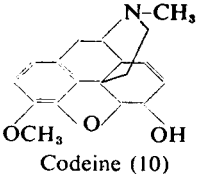
(VII)

6-Methyldihydromorphine (100)



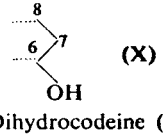
(VIII)

Δ^7— Desoxymorphine (800)



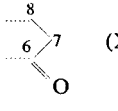
(IX)

Codeine (10)



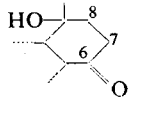
(X)

Dihydrocodeine (15)



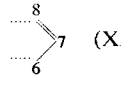
(XI)

Dihydrocodeinone (50) (Dicodid)



(XII)

Dihydrohydroxycodeinone (50) (Eucodal)



(XIII)

Δ^7—Desoxycodeine (5)

been rigidly established. In America, metopon has been studied clinically in cases of inoperable cancer[17,18] and the results indicate that it is a more powerful analgesic than morphine, with apparently fewer undesirable side effects. Metopon can be administered orally, but unfortunately it is difficult and expensive to make.

Dihydrodesoxymorphine-D (*Desomorphine*) (VI). Although about 10 times as active as morphine as an analgesic, and only possessing about 3 times its toxicity, this compound has only a short duration of action.

6-*Methyldihydromorphine* (VII). This compound was synthesised recently by Small and Rapoport[19] by the action of methyl-lithium upon dihydromorphine. It possesses about the same analgesic action as morphine, but the duration of the action is almost doubled, and its addictive tendencies seem to be less than that of morphine.[17] However, it has been classified as an addiction-producing drug.[20]

Δ^7-*Desoxymorphine* (VIII). Preliminary pharmacological tests[21] indicate that it is about 8 times as active as morphine and that the onset of the effect is very rapid but the duration of the effect is short.

Codeine (IX) *and phenolic ethers of morphine.* The blocking of the phenolic hydroxyl group of morphine produced a reduction in analgesic activity and toxicity. Codeine, ethylmorphine (dionine) and benzylmorphine (peronine) have been used in medicine. Codeine, unlike morphine, does not have a depressant action on the respiratory centre, and because it has also little action on the intestine and is not such a powerful drug of addiction as morphine, it is of value as a mild analgesic and cough sedative. Ethylmorphine and benzylmorphine are more active than codeine but also more toxic.

Dihydrocodeinone (*Dicodid*) (XI). This substance has been used in Germany and America principally for cough relief, although apparently there is more danger of addiction than with codeine.

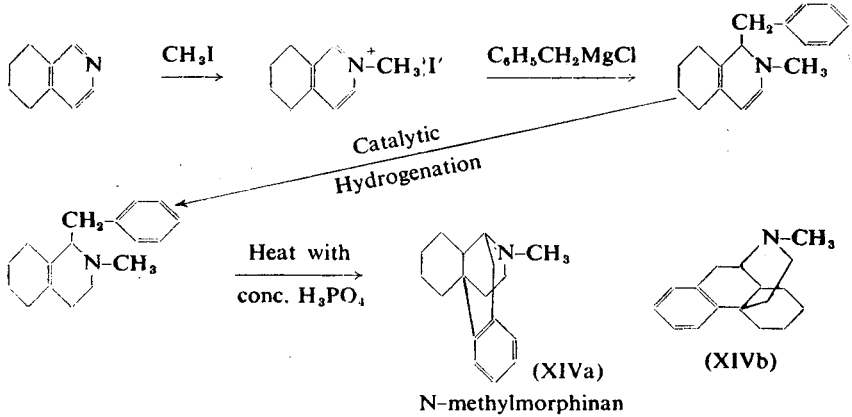
Dihydro-hydroxycodeinone (*Eucodal*) (XII). Results indicate that it has a lower toxicity than dicodid but a higher addiction liability.

Δ^7-*Desoxycodeine* (XIII). This substance was prepared in 1951 by Karrer and Widmark[22] and by Rapoport and Bonner[23] independently. Its analgesic action is about half that of codeine.[22]

The Morphinans and Synthesis of the Morphine Structure

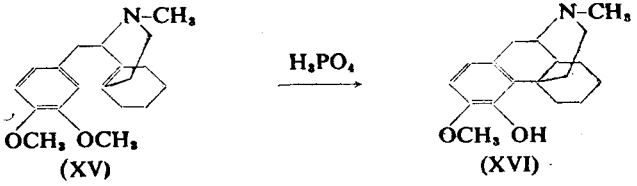
The synthetic approaches to the morphine structure have been reviewed recently by Stern.[24] Grewe's fundamental studies in this field led to the preparation of *N*-methylmorphinan from 5:6:7:8-tetrahydro*iso*quinoline as follows[25,26,27] (Chart I).

CHART I

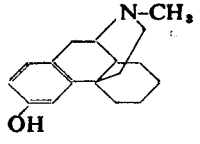


N-Methylmorphinan is usually written as (XIVb) which illustrates graphically its relationship to morphine. Pharmacological animal tests showed that this substance possessed morphine-like properties.[26] The steric identity of *N*-methylmorphinan with morphine was shown by Grewe *et al.*[28] in the synthesis of tetrahydro-desoxycodeine (XVI) by

cyclisation of compound (XV), the *lævo* isomer being identical with *l*-tetrahydrodesoxycodeine,



prepared from codeine. This was the first total synthesis of a compound in the morphine series. The same workers also prepared 3-hydroxy-N-methylmorphinan (XVII) by a similar cyclisation procedure.



(XVII) (HBr salt is Dromoran)

Schnider and Grussner[29] had also prepared this compound by a number of methods, and reported that it had an intensive and long-lasting analgesic effect on oral as well as parenteral administration and that its ethers and acyl derivatives were also active. Later pharmacological and clinical reports on the hydrobromide of (XVII) (called *Dromoran*)[30,31,32,33,34,35] demonstrated that it was about 4 times as potent an analgesic as morphine, with a greater duration of effect, and less frequent or severe side reaction .

The optically active isomers of dromoran have been prepared[36] and the *l*-isomer has approximately the same toxicity but a higher analgesic action than the racemic compound, while the *d*-isomer is less toxic and inactive.[37] *l*-Dromoran is also a greater respiratory depressant than the *d*-isomer, and *d*-, *l*- and *dl*-methyl ethers of dromoran exhibit parallel analgesic characteristics, although they are less potent and more toxic than the parent compounds.[38] Schnider *et al*[29,36,39] have prepared other derivatives related to dromoran and state that the replacement of the *N*-methyl group by *N*-ethyl, *N*-allyl, or *N*-benzyl reduces activity, and the same effect is produced by the introduction of an hydroxyl group at C_2. The 2 (or 4)-hydroxy derivative of *N*-methylmorphinan is inactive. Recent patents[40] cover the synthesis of many derivatives belonging to the morphinans. In Grewe's synthesis of *N*-methylmorphinan,[27] small quantities of two by-products were obtained. Gates *et al.*[41,42,43] have synthesised a morphinan-type structure by a totally different synthetic approach, and have shown it to be identical with one of Grewe's by-products. It has been called *N*-methyl*iso*morphinan,[43] and is stated to show considerable analgesic activity in animal tests. The successful synthesis of racemic β-Δ^6-desoxydihydrocodeine methyl ether[44] confirms that the steric configuration of these *iso*morphinan compounds is epimeric at

C_{14} to that of the morphinans and morphine itself. A prediction in Stern's recent review[24] that "within the next few years the synthesis of morphine, and with it a most interesting and difficult chapter of alkaloid chemistry, will be brought to a successful conclusion" has been justified by the recent preliminary communication by Gates and Tschudi[45] of the total synthesis of morphine.

Partial Structures of Morphine and Miscellaneous Substances

While the previously described approach to the synthesis of a new drug *via* the route of "operation upon the alkaloid" was in progress, the alternative route of synthesis of fragments of the parent molecule, to emphasise certain structural features, was not ignored. Hundreds of compounds have been prepared as partial structures of morphine, and Table II gives some of these basic structures. The formulae are drawn to indicate their relationship to morphine.

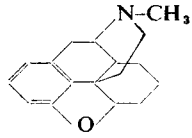
Phenanthrenes (XVIII), *dibenzofurans* (XIX) *and carbazoles* (XX). Under the auspices of the Drug Addiction Committee of the National Research Council of America, systematic work on synthetic analgesics was commenced in 1929, and although many derivatives of these compounds were prepared, none had a greater analgesic activity than codeine. This work has been summarised.[15]

Aralkylamines. In 1943, Dodds *et al*[46,47] reported that diphenylethylamines (XXII) relieved pain, and that α:β-diphenylethanolamine produced definite analgesic effects in cancer patients, but later[48] it was stated that it would only relieve the particular pain associated with pressure upon nerve, and was inactive in animals compared with pethidine or morphine. A similar line of approach has been investigated by other workers[49,50,51,52,53,54,55,56,57] but compounds have not been produced which possess significant analgesic activity. Kulz[58] claimed analgesic activity in phenolic bisphenylethylamines (XXI) and Lee *et al.*[59] prepared substances in which one of the phenyl groups was replaced by the *cyclo*hexyl group, and methyl-2-*p*-hydroxy-phenylethyl-2′-*cyclo*hexylethylamine was stated to have 1/7th the activity of morphine. Ullyot and co-workers[60,61,62] prepared a series of aminophthalidylalkanes, and 1-amino-1-phthalidylpropane was shown to possess considerable activity.[63,64] Because of reports of analgesic activity found for sympathomimetic amines, and the implied significance of adrenaline in analgesia, Fellows and Ullyot[5] undertook a systematic investigation of aralkylamines, and although some of these showed analgesic activity, three of the most promising ones, when subjected to clinical trials, were found to have only a low order of potency. For a more comprehensive treatment of the aralkylamines see the review by Fellows and Ullyot.[5] Recently the preparation of the four isomers of α:β-diphenyl-β-hydroxyethylamine has been reported[65] but the pharmacological data was not given. Burckhalter and Johnson[66] have prepared a series of di- and tri-phenylpropylamines and state that α-(benzhydrylmethyl)-benzylamine exhibits activity approaching that of morphine. Little activity was

TABLE II

PARTIAL STRUCTURES RELATED TO MORPHINE

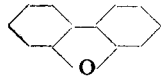
Basic structures



Morphine

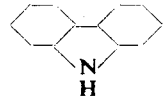
(XVIII)

Phenanthrene



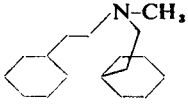
(XIX)

Dibenzofuran



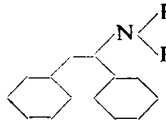
(XX)

Carbazole



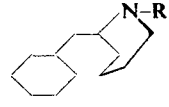
(XXI)

Bisphenylethylamines



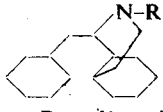
(XXII)

Diphenylethylamines



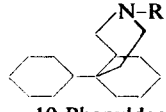
(XXIII)

2-Benzylpiperidines



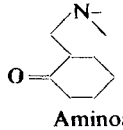
(XXIV)

Benzyl*iso*quinolines



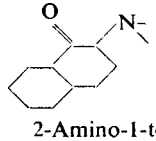
(XXV)

10-Phenyldecahydroquinoline



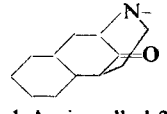
(XXVI)

Aminoalkyl-*cyclo*hexanones



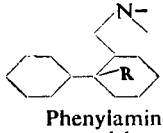
(XXVII)

2-Amino-1-tetralones



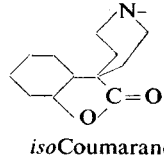
(XXVIII)

1-Aminoalkyl-2-tetralones



(XXIX)

Phenylaminoalkyl-*cyclo*hexanes



(XXX)

*iso*Coumaranones

obtained in a number of α-methylbenzylamines prepared by McCoubrey.[67,68]

2-*Benzylpiperidines* (XXIII), *benzyl*isoquinolines (XXIV), 10-*phenyldecahydroquinolines* (XXV) *and related substances.* Many compounds of this type have been prepared[59,69,77] but little analgesic activity was obtained. (See Suter[5] pp. 443 to 451). Smith *et al.*[78] prepared α-aminophenacylpyridines and quinolines and some of the derivatives were equal to codeine in analgesic activity. The work was continued by the preparation of 2- and 5-phenacylpyrimidines.[79] The benzyl*iso*quinolines prepared by Shapiro[80,81] were devoid of analgesic action.

*Aminoalkyl*cyclo*hexanones* (XXVI), *tetralones* (XXVII) *and hydrindones.* Lee *et al.*[59] found that 2-aminomethyl-1-tetralone and derivatives possessed analgesic properties, the most active having about 1/7th the activity of morphine. Reduction of the compounds had but little effect, while acetylation of these alcohols reduced the activity. The corresponding *cyclo*hexanone derivatives were without significant activity. Scheuing and Walach[82] had previously claimed that 2-alkylamino-1-tetralones had analgesic properties. Barltrop[73] prepared hydrindones and aminoalkyl derivatives of 2-tetralone, and *cyclo*hexanones containing phenyl groups and basic groups have also been prepared,[83,84] but either no analgesic properties have been reported or else they are of a low order.

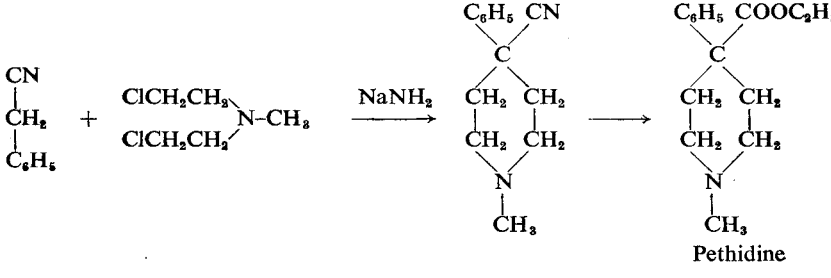
*Phenylaminoalkyl*cyclo*hexanes* (XXIX) *and related compounds.* Compounds prepared by Lee *et al.*[59] and by Goldschmidt *et al.*[85,86] showed little analgesic activity.

iso*Coumaranones* (XXX) *and related substances where the oxygen containing ring system of morphine is considered.* The *iso*coumarones and lactones prepared by Bergel *et al.*[87] were shown to be inactive by Macdonald *et al.*[88] Bovet and Simon[89] found that diethylaminomethylbenzodioxan and related compounds showed some analgesic properties. A study of condensed cyclic aryl ethers[90,91] and sulphides[92] carrying alkylamine side chains has been carried out, but little activity resulted. Compounds emphasising the ether ring of morphine prepared by other workers[93,94,95,96,97,98] possessed little activity.

From the above brief account of synthetic fragments of the morphine molecule, it is apparent that morphine has been mentally dissected in almost every conceivable way, in the hope that analgesically active compounds would result. Despite the thoroughness and comprehensive character of this attack, it has not yielded compounds with significant activity comparable with morphine. However, fortuitous events are not unknown in the field of scientific endeavour, and the fact is emphasised in the search for analgesics. The discovery by Eisleb and Schaumann[99] in 1938, that pethidine had analgesic activity was the necessary clue to guide the search into more profitable channels, and pethidine was prepared by these workers in a search for spasmolytic agents, regarding atropine as the parent structure.

Pethidine and Related Compounds

Pethidine was synthesised originally as follows:[100]



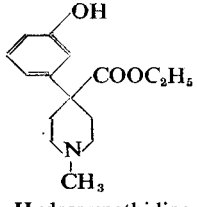
Pethidine

but because this route involved the use of the dangerous vesicant methylbis-2-chloroethylamine, other synthetic routes were devised (see reviews[1,2] for routes and references). Although pethidine is not so powerful an analgesic as morphine (about 1/5th in animal tests and 1/8th in humans) it rarely depresses the respiratory centre and has less powerful addictive properties than morphine (see Yonkman[101] for a review of the pharmacology). Since the discovery of pethidine, much work has been performed in preparing modifications of the molecule in attempts to increase the activity and lower the incidence of side effects (for reviews see references[1,5,102]). These modifications include moving, removing, and substituting the phenyl group, substituting and breaking open the piperidine ring, replacing the *N*-methyl group by other alkyl groups, and replacing the ethyl ester by other ester groups, hydrogen, ketonic and reversed ester groupings.

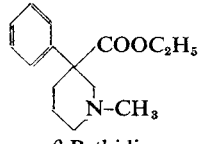
Only the most important compounds are considered here, the structures of which are given in Table III.

TABLE III

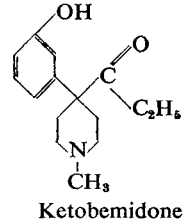
PETHIDINE-TYPE COMPOUNDS



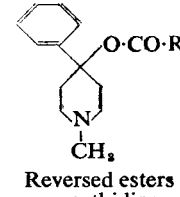
Hydroxypethidine (XXXI)



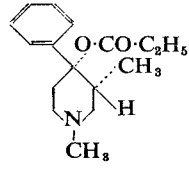
β-Pethidine (XXXII)



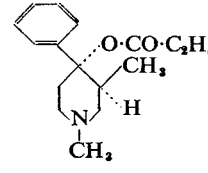
Ketobemidone (XXXIII)



Reversed esters of pethidine (XXXIV)



Alphaprodine (XXXVa)



Betaprodine (XXXVb)

Hydroxypethidine (XXXI) (bemidone). This substance has about the same analgesic activity as pethidine[88] and is reported to have given promising clinical results when used as a general anæsthetic by intravenous injection.[103]

β-Pethidine (XXXII). Bergel *et al.*[104] prepared this compound and it has been studied pharmacologically[88] and clinically.[105] It has only a low toxicity, but it is a less potent and shorter-acting analgesic than pethidine.

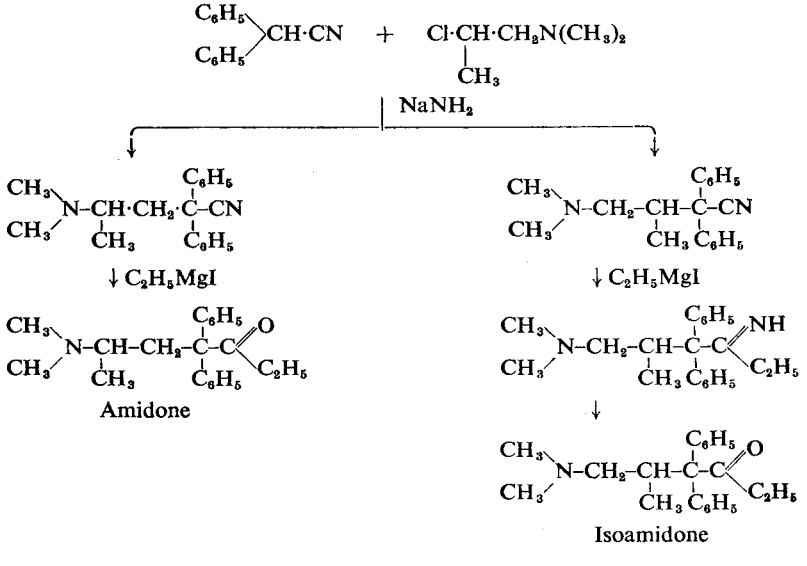
Ketobemidone (XXXIII). The change from the ester group of hydroxypethidine to the ethyl ketone was reported to give a compound with 20 times the activity of pethidine,[103] and although clinical trials by

Kirchoff[106] showed that it had excellent analgesic properties, it has proved to be a powerful drug of addiction,[107] comparable with heroin in this respect.

Reversed ester of pethidine (XXXIV). In 1943, Jensen *et al.*[108] reported that these compounds were more active than pethidine, especially the propionoxy derivative (R = C_2H_5), which was stated to have 5 times the activity of pethidine. Independently, workers in the Roche laboratories (for references see review[1]) prepared many compounds of this type. Ziering and Lee[109] obtained compound (XXXV) in its *cis*-(XXXVa) and *trans*-(XXXVb) modifications (configurations assigned only provisionally) and resolved the *trans*-form into its optical enantiomorphs. Randall and Lehmann[110] obtained the following pharmacological results on rats, morphine being taken as 100, Nu 1196 (*cis*-form racemate) 97, Nu 1779 (*trans*-form racemate) 550, Nu 1831 (*l*-form *trans*-) 350, Nu 1832 (*d*-form *trans*-) 790, but in man the difference in action between the *cis*- and *trans*-racemates is not so pronounced.[111] The World Health Organisation has recognised Alphaprodine and Betaprodine as international non-proprietory names, for the *cis*- and *trans*-racemate respectively. Gross *et al.*[112] investigated Nu 1196 and Nu 1779 in man, and Houde *et al.*[18] reported that Nu 1196 had a weaker analgesic action than morphine and showed side effects in 10 per cent. of the patients. Evidence that these substances show addiction properties has been obtained by Isbell.[107]

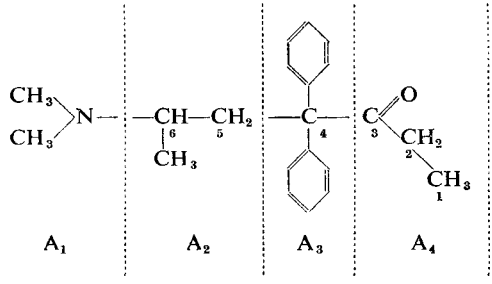
Amidone and Related Substances

The synthesis of amidone proceeds as follows and results in two products, amidone and isoamidone.



For further references to synthetic routes and the mechanism of the above sodamide condensation, see the review by Bergel.[1] Early reports published after the war,[103,113] gave the information that amidone was 5 to 10 times as active as pethidine. The literature on the pharmacology of amidone and related compounds is too extensive to be dealt with here (for detailed accounts see references[114,115,116,119]).

Since 1945, many workers have investigated modifications of the amidone structure, and the results of these modifications are discussed briefly below.



AMIDONE

Modification of the Basic Group (A_1). Various basic groups have been tried[103,117,118,119,120,121,122] and, in general, a decrease in activity is produced except in the case of the morpholino (O N–) or piperidino (N–) analogues. The morpholino compound[117,118] (CB. 11, heptalgin, *phenadoxone*) was reported by Wilson and Hunter[123] and Hewer *et al.*[124] to be at least as potent as amidone in human subjects, but Winter and Flataker[125] found that in rats it was shorter-acting than amidone. Its detailed pharmacological actions have been described by Basil *et al.*[126] Isbell and Fraser[127] state that its addiction liability is quite low, but "the drug is a relatively ineffective and short-acting analgesic." The piperidino analogues of amidone and isoamidone have received a favourable report by Ofner *et al.*,[128] and Prescott *et al.*[129] have found that the isoamidone analogue has less respiratory depressant effect than morphine, amidone or pethidine in man. Removal of the basic group results in a complete loss of analgesic activity[119] while quaternisation of the group markedly decreases activity.[115,130]

Modifications in A_2. The effects of length, branching and position of branching in the carbon atoms joining the tertiary nitrogen atom and quaternary carbon atom have been investigated. A methyl group on C_6, as in amidone, is advantageous,[103,117,131] and when the methyl group is on C_5, as in isoamidone, some reduction of activity occurs[118,119,112] (exception is the piperidyl analogue). Isoamidone has been studied in some detail[133,134] and is reported to have less respiratory depressant activity than amidone. Lengthening or shortening the chain results in reduction or complete loss of activity.[117,120]

The presence of a methyl group on C_6 (amidone) or C_5 (isoamidone)

introduces an asymmetric carbon atom in the molecule, and many of the compounds have been resolved (amidone,[120,135,136,137,138] isoamidone,[137] sulphone analogue of amidone[139]) into their optical enantiomorphs, and pharmacological studies have shown that one enantiomorph is always much more active than the other.[116,119,139] This point will be considered in more detail later.

Modifications of A_3. The phenyl groups have been substituted,[103,117,119] one or both groups replaced by *cyclo*hexyl,[119] alkyl,[119,140] thiazole,[141] benzyl,[120] pyridyl[142] or thienyl[143,144] groups, but a reduction or complete loss of activity occurs. The migration of one phenyl group to the neighbouring carbon atom (C_5) resulted in loss of activity.[119,120] The replacement of the whole group by the fluorenyl group[120,145] led to reduced activity.

Modifications of A_4—*the ketonic portion.* 1. Other ketones were less effective.[103,120,121] 2. Replacement by

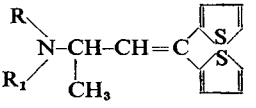
$$\text{-COOH, -COOR, -CH}_2\text{OH, -CHO, -O·CO·R, -CH = CH·CH}_3\text{,}$$
$$\text{-CH}_2\text{O·COR, -CONH}_2\text{, H, -OH, -CH}\begin{matrix}\text{Cl}\\ \text{C}_2\text{H}_5\end{matrix}$$

led to a reduction or complete loss of activity.[115,118,119,120,121,146,147,148] 3. Reduction of the ketonic group of amidone, and related compounds, to a secondary alcohol[118,149,150,151] led, in general, to a reductionof toxicity and also of activity which can be restored by acetylation. The platinum oxide hydrogenation or the lithium aluminium hydride reduction of *dl*-amidone (or *dl*-isoamidone) only gave one of the two possible racemic alcohols in each case. Pohland *et al.*[153] obtained the optically active forms of the same isomer (designated the α-isomer) by hydrogenation of *d*- and *l*-amidone. The name methadol has been approved for α-*dl*-methadol (one of the secondary alcohols from *dl*-amidone), and methadyl acetate for the acetyl ester of α-*dl*-methadol. By the use of sodium/propanol reduction of *d*-, *l*-, and *dl*-amidone Eddy *et al.*[152] have obtained α-*dl*- and β-*dl*-methadol and the four corresponding optical isomers (α-*d*-; α-*l*-; β-*d*-; β-*l*-), and have converted them to the acetyl esters. Both α- and β-*dl*-methadols were less effective than *dl*-amidone, the parent compound, but the acetyl esters were similar to *dl*-amidone in toxicity, but had greater analgesic effect. The corresponding compounds (α-*d*-, β-*l*-) obtained from *l*-amidone showed similar results to the above. Rather remarkably, α-*l*-methadol, and α-*l*- and β-*d*-acetylmethadols, derived from the only weakly analgesic *d*-amidone, showed very high analgesic activity both orally and subcutaneously, and are now being tried clinically. Chen[119] has reported that in rats, by subcutaneous injection, α-*d*-acetylmethadol is about 5 times as active as the α-*l*-isomer and twice as active as *dl*-amidone, but the α-*l*-isomer shows a long duration of action (see also Sherrod *et al.*[154]). The analgesic effects in man[155] and the addiction potentialities[156] of the α-acetylmethadol isomers have been reported. It is possible that some of the reduction products, and their esters, derived from amidone-type compounds may prove to be of great importance.

4. Compounds obtained by replacements of the ketonic group by ketimine $-C\begin{matrix}NH\\C_2H_5\end{matrix}$ and acyl ketimine $-C\begin{matrix}NCOR\\C_2H_5\end{matrix}$ groups, have been described by various workers.[157,158,159] Cheney *et al.*[159] stated that the order of decreasing toxicity and increasing therapeutic index was ketone: ketimine: acetylketimine in both the amidone and isoamidone series.

5. The replacement of $-C\begin{matrix}O\\C_2H_5\end{matrix}$ by the sulphone ($-SO_2-R$) group[160] leads to active compounds, especially when $R = C_2H_5$, and this substance was claimed to have the analgesic activity of amidone but only half its toxicity. Resolution into the optical isomers was accomplished[139] and the *l*-form was 20 times as active as the *d*-form, and has been claimed to be one of the most powerful analgesics.[161]

Miscellaneous compounds related to amidone. The ketonic group of amidone has been incorporated into one of the reduced phenyl groups,[162] the arrangement of the two phenyl groups, ketone and basic side chain about the quaternary carbon atom has been altered,[84] basic and ketonic groups have been introduced into the fluorene molecule,[145,163] but little analgesic activity has been obtained. However, Adamson[164,165] has reported high analgesic activity in compounds of type (XXXVI).

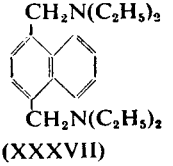


(XXXVI)

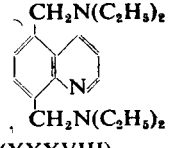
Despite the absence of a ketonic group and a quaternary carbon atom, the compounds are stated to be as active as morphine in the rat with undesirable side-effects (in the dog) at a minimum. Two of these compounds have been resolved and the analgesic activity has been shown to be present mainly in the *d*-isomer.[166] Reduction of the double bond reduces the analgesic activity.[166] Some of the compounds have been tested in man, and they appear to be more active than pethidine but less active than amidone.[167]

Other Series of Miscellaneous Compounds

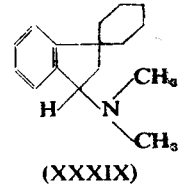
Compound (XXXVII) has been claimed by Badger *et al.*[75] in a



(XXXVII)



(XXXVIII)



(XXXIX)

preliminary communication to be as active as pethidine, and further details of compounds of this type, which are so completely different from previous analgesics, are awaited with interest. Martin and Hanslick[168] have described salts of the closely related compound

(XXXVIII) as analgesic agents. Horning and Rutenberg,[169] stressing the importance in analgesics of a quaternary C atom attached to an aromatic ring with an amino *N* in β-relationship to it, have prepared a series of oxindoles, but the pharmacological results were not recorded. A similar approach has been made by Schwartzman[170,171] in preparing *spirocyclo*hexyl quinolines and indanes (XXXIX) and activity has been obtained in some of the compounds. *Spiro*piperidino-*iso*quinolines have been described by Kägi and Miescher.[172] Close *et al.*[173] prepared benzoxazolones but they were found to possess much less analgesic activity than pethidine. The bispidines prepared by Kyi and Wilson[174] and the dihydroglyoxaline derivatives prepared by Wilson[175] were shown to be devoid of analgesic activity by Marshall *et al.*[176]

The Absorption, Distribution, Fate and Excretion of Analgesics

The study of the distribution and fate of analgesics is one approach to the problem of elucidating the mechanism of action of these drugs which is already of importance. It may well yield more important results in the future, now that techniques have been perfected for detecting and separating small quantities of drugs in tissues and body fluids. The analgesics which have received attention up to the present have been morphine, codeine, pethidine, and amidone. The absorption and fate of morphine and codeine was reviewed comprehensively in 1941 by Krueger *et al.*,[177] but since that time important publications have appeared as the more powerful analytical methods have been applied.

Morphine. The information which had been accumulated up to 1940 indicated that an animal which absorbs a dose of morphine begins to excrete the unchanged drug in urine and fæces at once, but only about 15 to 35 per cent. could be accounted for. It was presumed that the rest was destroyed or eliminated promptly by unknown chemical processes. However, in 1941 Gross and Thompson[178] showed that previous workers had only measured "free" morphine and that in dogs both "free" and "combined" morphine was present in the urine, and they were able to account for 80 to 85 per cent. of a given dose by this route of excretion. Oberst[179] showed that in man a large percentage of morphine was excreted in the urine, chiefly as the "combined" form. It had previously been suggested[180] that morphine was possibly conjugated with glucuronic acid, but Gross and Thompson[178] failed to find any evidence of morphine glucuronate in urine. These workers also showed that a smaller percentage of a given dose of morphine appears in the urine of the tolerant than of the non-tolerant dog. Later work of Bernheim and Bernheim[181,182] established that the liver is the only organ which conjugates morphine. Zauder[183] has shown that, in rats, 80 per cent. of the administered dose is excreted as free and combined morphine, and that in tolerant rats less of the conjugated form appears in the urine. He further showed that liver slices conjugated morphine, but, unlike Abord and Koon[184] he could not demonstrate any oxidation of morphine by these slices, and concluded that the mechanism responsible for the destruction of morphine is extrahepatic.

Recently, radioactive morphine (morphine -N-$C^{14}H_3$) has been prepared[185] and its tissue distribution, metabolic fate and excretion studied in rats.[186] All the radioactivity disappeared from the animal within 48 hours, about 2/3rds *via* the urine and 1/3rd *via* the gastrointestinal tract, and the results indicated that a greater part was excreted by the liver into the bile. A small percentage of radioactivity was excreted *via* the respiratory route indicating an *N*-demethylation process. The central nervous system contained a negligible amount of radioactivity.

Thus, from the evidence at present available, it appears that about 70 to 80 per cent of the morphine is excreted in the urine in free or conjugated form, and a small percentage is excreted in the fæces. The conjugation occurs in the liver and excretion *via* the bile occurs. A small percentage is *N*-demethylated, but the mechanism by which the rest of the morphine (probably less than 10 per cent.) is destroyed is not yet known. A fairly rapid removal of morphine from the body occurs and only very small traces of morphine (or metabolic product) ever reach the central nervous system.

Codeine. By the use of C^{14}-methoxy-labelled codeine synthesised by Chang *et al.*,[187] Latham and Elliot[188] showed that there was a general distribution of codeine (or metabolite) in rats, and that no "site of action" could be inferred as might be evidenced by excessive concentration in any tissue. Only a small percentage reached the brain or central nervous system. A consideration of the results of the radio-active tracer work, and the publications in which other techniques have been applied, indicate that a number of different mechanisms and routes of excretion come into operation after codeine has been administered:—1. Conjugation to a more water-soluble form excreted, along with unchanged codeine, in the urine. Oberst[189] showed that about 11 per cent. of free base and 32 per cent. of conjugated base was excreted in humans. Latham and Elliot[188] showed similar results in rats. 2. Formation of codeine -X, a biologically inactive metabolite excreted *via* the bile into the intestinal tract from which it is apparently later reabsorbed.[188,190] 3. Demethylation to form morphine has been shown to occur using rat liver slices[182,191,192] and *in vivo* in rats.[192] When radio-active codeine (C^{14} methoxy) was used, radio-active carbon dioxide was found in the expired air.[188] Under *in vitro* conditions approximately 1/3rd of the metabolised codeine appears as morphine, both in free and combined forms.[193] The site of demethylation is the liver.[181,192,193] 4. Conjugation of the liberated morphine[191] and excretion in the urine in this form.[193]

Pethidine. The study of the metabolism of pethidine using the N-$C^{14}H_3$ labelled material has shown that only very small amounts of pethidine (or metabolite) reach the brain or cerebrospinal fluid.[194,195] After oral administration, over 90 per cent is absorbed from the gut within 4 hours.[194] If a subcutaneous injection is used, radio-activity is present at the site after 12 hours, which indicates slow absorption from a subcutaneous depot.[195] In human subjects it has been shown that there is no pethidine in the milk of lactating mothers within 1 to 6 hours after injection, and very little in the urine of new-born infants whose mothers had received

injections of the drug.[194] Plotnikoff[196] has reported that, after a subcutaneous injection of radio-active pethidine in rats, 50 per cent. of the radio-activity could be recovered in the urine and 4 per cent. in the fæces. This radio-activity is a measure of both unchanged pethidine and some of the metabolic products because the combined results of other workers[197,198,199] indicate that less than 10 per cent. of a given dose is excreted as pethidine in the urine. The liver has been shown to be the main organ for metabolising pethidine by hydrolysis in *vitro* and in *vivo*, the enzyme responsible being an unknown esterase.[194,200,201] When radio-active pethidine (N-$C^{14}H_3$) was used, radio-activity was found in the expired air,[196] indicating *N*-demethylation. A recent publication by Plotnikoff *et al.*[195] confirmed that one metabolic route involves hydrolysis of the ester group and another pathway involves *N*-demethylation, because pethidine, hydrolysed pethidine and nor-pethidine were identified in human and rat urine. However, the sum total of these substances did not account for all the radio-activity in the urine. They also showed that the liver was probably responsible for the demethylation because $C^{14}O_2$ was evolved from rat liver slices in the presence of pethidine (N-$C^{14}H_3$).

Amidone. As in the case of the analgesics already mentioned, only very small concentrations of amidone reach the brain and central nervous system.[202,203,204] The drug is fairly rapidly mobilised from the site of a subcutaneous injection,[203,205] is carried by the blood plasma,[206] and 10 minutes after an injection radio-activity is found in the bile.[207] When radio-active amidone was used, high radio-activity was found in the adrenals[203] and this fact may be significant because of the reports which implicate adrenaline as a mediator of the analgesic effects of certain drugs. Many publications have appeared dealing with the metabolism and excretion of amidone. Elliot *et al.*[203] showed that C^{14} labelled amidone (-C(=O)$C^{14}H_2 \cdot CH_3$) may be recovered as radio-active material to the extent of 80 per cent. in the fæces and 20 per cent. in the urine, and a later publication[207] indicated that biliary excretion was chiefly responsible for the radio-activity appearing in the gastro-intestinal tract. The whole of the radio-activity did not represent unchanged amidone because other workers[202,208] found that about 10 per cent. was excreted in urine and 10 to 20 per cent. in fæces, and it was suggested that the methods appeared to measure degradation products in addition to amidone itself. Subsequent work by Way *et al.*[209] showed that amidone was excreted unchanged in about 8 to 10 per cent. in the urine and 8 to 10 per cent. in the fæces. These results agree well with those obtained by Richards *et al.*[204] using a different method. Way *et al.*[209,210] partially separated and characterised a basic amino metabolic product from the bile of rats and dogs, and also indicated that there is possibly another metabolic product in the fæces. Richards *et al.*[204] considered that one possible metabolic pathway could involve the introduction of hydroxyl groups into the phenyl rings of amidone. The liver has been shown[204,211,212]

to be the chief organ for metabolising amidone *in vitro* and *in vivo*, and it has been recently reported[213] that liver slices from tolerant rats appeared to metabolise the drug less rapidly than slices from normal rats. The tissue distribution and excretion of the optical isomers of amidone has been studied.[214,215] Rat liver slices have the same effect upon both isomers.[214] Although the two isomers differ so markedly in pharmacological activity, the distribution in the various tissues follows the same pattern as that of racemic amidone, and *l*-amidone is not localised to any higher degree than the *d*-isomer in the brain.

Hypothesis Concerning the Mode of Action of Analgesics

This section of the work on analgesics will only be considered very briefly because the theories are highly speculative, and the search for clues to the explanation of activity in the investigation of effects upon enzyme systems or biochemical processes has not proved very fruitful (Krueger *et al.*[177]). The effect of analgesics upon the enzyme cholinesterase has received some attention. Bernheim and Bernheim[216] showed that morphine strongly inhibited cholinesterase in *vitro* and work in this direction has been performed using both morphine and other analgesics.[217,218,219,220] Thus, the effect of this inhibition would be to block the hydrolysis of acetylcholine, and this leads to speculation as to whether this may be connected with the action of analgesics on the central nervous system. On the other hand, Burn[221] has suggested that analgesics may be substances which antagonise acetylcholine in parts of the central nervous system, and has presented evidence in support of this hypothesis. Analgesics have been shown to inhibit the oxygen uptake of brain tissue.[222,223,224,225,226] However, in general, the concentrations of analgesics which have been required to produce a significant inhibition have been far in excess of the concentrations which have been shown to reach the brain in the intact animal, and so the results are of little practical significance. Other workers[227,228] have shown that the oxidation of glucose, succinate, ascorbate, lactate, etc., by brain tissue is inhibited by analgesics. Because of this inhibition of oxidation processes, Wang and Bain[229] have investigated the sensitivity to morphine of the various steps in the cytochrome system.

Pero[230] has advanced the hypothesis that pain is a cholinergic, and analgesia is an adrenergic phenomenon (stimulation of secretion of adrenaline at the synapses), and numerous reports (see Ivy *et al.*[231]) state that adrenaline and sympathomimetric amines have analgesic action. However, it has been shown[232,233] that an injection of morphine results in the liberation of adrenaline from the adrenals—a cholinergic phenomenon! Furthermore, when the adrenals are removed, the analgesic response to a given dose of morphine is below normal.[234,235] In connection with this possible implication of adrenaline as a mediator of the analgesic effect of drugs, the relatively high concentration of radio-activity in the adrenals after the subcutaneous injection of radioactive amidone may be of significance.[203] The effect of certain analgesics and adrenal cortical hormone on the brain of normal and hypophy-

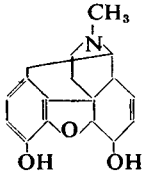
sectomised rats, as measured by the thiobarbituric acid reagent, has been investigated by Zauder.[236] His results seem to indicate that these analgesics, *via* the mechanism of adrenaline release, induce a release of adrenocorticotrophic hormone from the hypophysis with a consequent stimulation of the adrenal cortex, but the recent report by Irwin and Shideman[237] does not support these results.

Morphine and other opium derivatives produce hyperglycæmia[177] and the newer analgesics have also been shown to do the same.[238,241] The effect is possibly due to the stimulation of a supraspinal centre with the subsequent release of adrenaline and then mobilisation of liver glycogen.[177,242] It is of interest that *l*-amidone produces a much greater hyperglycæmia in dogs than does the *d*-isomer,[242] whereas the two isomers affect *in vitro* tissue respiration to the same extent.[227] Pfeiffer *et al.*[243] have suggested that analgesics specifically block certain metabolites such as amino-acids which are essential for the central nervous system, but experimental evidence is lacking. Schueler *et al.*[244] state that the activity of analgesics may be traced to effects involving the autonomic nervous system.

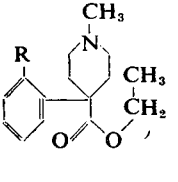
It is therefore apparent that a clear picture of the mode of action of analgesics is, as yet, a distant goal, despite the multitudinous array of facts which have been collected.

Chemical Constitution and Analgesic Action

Many of the workers engaged in the search for synthetic analgesics have tried to explain any analgesic activity in their compounds in terms of a relationship with the morphine molecule. This is not unexpected when the basic plan underlying much of the research was the synthesis of partial fragments of the morphine structure. The publications of Fourneau[11] and Small *et al.*[15] illustrate this approach. After the discovery of the analgesic activity of pethidine and related compounds, these structures were related to the structure of morphine,[88,245,246] and this relationship has been illustrated as follows:—



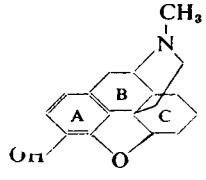
Morphine



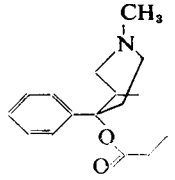
Pethidine series

Macdonald *et al.*[88] stated that their results seemed to indicate that "the shape or fit of the molecule as a whole is more important in determining its analgesic value than any precise duplication of any one fraction of the morphine structure." Ziering and Lee[109] suggested that the *trans*-isomer (XLI) was more closely related to dihydrodesoxymorphine (XL) than the *cis*-isomer (XLII) (see Randall and Lehmann[110] also) and that this accounted for the *trans*-isomer being more active than the *cis*-. The propionoxy chain and the methyl group in the piperidine ring are together

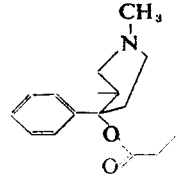
supposed to simulate ring C of dihydrodesoxymorphine, and the carbonyl oxygen atom of the propionoxy group is said to occupy spatially the exact position of the ether oxygen in (XL).



(XL)



XLI (*trans-*)



(XLII) (*cis-*)

According to Bergel and Morrison[1] (excluding diphenylpropylamine derivatives) "those substances which contain almost unimpaired certain elements of morphine, such as the phenyl and piperidine rings and an appropriate chain or ring on the quaternary carbon, are true morphine-like analgesics." After previously emphasising the steric arrangement and compactness of the morphine molecule, they state, concerning the diphenylpropylamine derivatives such as amidone, "when an atomic model is made, the spatial compactness of amidone and its close similarity to morphinan and the phenylpiperidines becomes evident." However, as Adamson and Green[164] have pointed out, it is difficult to discern any structural similarity between analgesically active dithienylbutenylamines and morphine. Furthermore, Eddy[3] and Bochmühl[120] state that they fail to see any direct relationship between the structures of amidone and morphine. Even if amidone and other analgesics show some similarity to morphine, dealing in terms of the relationship alone does not carry us much further forward towards a statement as to the simplest pharmacodynamic group required for analgesic activity. However, the approach does emphasise the necessity of stereochemical considerations in the treatment of the problem. It has been repeatedly emphasised in many publications (e.g.,[84,169,170,247]) that morphine, pethidine and amidone possess in common a tertiary nitrogen group and a quaternary carbon atom separated by a $-CH_2 \cdot CH_2-$ linkage. Eddy,[3] in a recent review, has stated that a tertiary nitrogen seems to be essential for analgesic action and a $-CH_2 \cdot CH_2-$ link joining tertiary nitrogen and quaternary carbon seems to be desirable and perhaps optimal for analgesic action. A different approach to the problem has been made by Schueler *et al*,[244] who suggested that the presence of both sympathomimetic and parasympathomimetic moieties, connected (in general) by the same nitrogen atom, was necessary for analgesic action. A subsequent publication[248] indicated that this was not likely to be a fruitful approach.

One important factor which undoubtedly emerges from any consideration of chemical structure and analgesic activity is the importance of the stereochemical configuration. *N*-methylmorphinan, for instance, is just a collection of aromatic and hydroaromatic rings, joined together in a certain way, and possessing a basic centre, and yet this compound is analgesically active. However, the fact that *N*-methyl*iso*morphinan also

possesses activity suggests that more than one spatial arrangement may be permissible for activity. The importance of spatial configuration is also seen in the difference of activity between the diastereoisomers of 1-amino-1-phthalidyl propane,[60] and the diphenylethanolamines[52] and the *cis*- and *trans*-isomers of the pethidine type compounds.[109] The clearest examples are provided by the analgesics containing one asymmetric carbon atom, where in all cases in which the optical enantiomorphs have been prepared, one enantiomorph is always very much more active than the other (e.g., amidone, amidone-type esters and sulphones, isoamidone, β-pethidine, dithienylbutenylamines). The distribution within the body of the *d*- and *l*-isomers of amidone is the same,[215] and although these measurements of tissue distribution are on a macroscopical level, and specific agents act on a molecular level, the possibility of a stereochemical fit upon a certain receptor surface of one isomer, and not the other, does receive some support. Thus, before analgesic action can be mediated directly or indirectly, it is possible that the stereochemical configuration of the drug must be complementary to that of a certain tissue surface or enzyme system.

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. Once this essential minimum is present, functional groups can increase or decrease the effect because of affecting the distribution, the metabolism, or the fit at a particular receptor surface.

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