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SYNTHETIC SUBSTANCES WITH MORPHINE-LIKE EFFECT

Relationship between Chemical Structure and Analgesic Action *

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SYNOPSIS

For morphine-, morphinan-, pethidine-, methadone-, and dithienylbutenylamine groups of analgesic compounds a systematic survey is given of how analgesic activity is quantitatively affected by alteration of the chemical constitution. Features common to the structural formulae of substances with morphine-like analgesic effect are pointed out.

Morphine has been the standard of comparison in most studies of analgesic action and must again be the starting-point in the present discussion. Structurally, morphine consists of a complex five-ring system, with certain peripheral groups, which is subject to attack at many points. Also, one can see within its structure any one of several basic ring-systems and postulate that the molecule as a whole is built upon that basic pattern. One can, therefore, look for clues to the relationship between structure and action in the modifying effect of attack on essential portions of the molecule or in the appearance of a characteristic action at some point in a build-up from a basic moiety identifiable within the morphine molecule. The latter

* This is the second of a series of studies on synthetic drugs with morphine-like effect, undertaken in accordance with resolution No. 505 (XVI) C adopted at the sixteenth session (30 June to 5 August 1953) of the United Nations Economic and Social Council. The first study of the series deals with "Chemical aspects".[14]

has been, in some instances at least, a matter of reasoning backwards when analgesic action has been demonstrated in a new type of structure and one has found that such a structure is a recognizable moiety in the morphine molecule.

Modifications of the Morphine Molecule (Table I)

1. *The hydroxyl groups*

Either the phenolic hydroxyl at position 3 or the alcoholic hydroxyl at position 6 is converted readily to an ether or ester: OH to OCH_3, OC_2H_5, $OCOCH_3$, $OCH_2C_6H_5$, etc. The effect, however, is not only different but opposite in direction according to whether the phenolic or the alcoholic group is modified. If the change is at position 3 activity is decreased, sometimes to one tenth of that of morphine; if the change is at position 6 activity is increased to 2 to 4 times that of morphine. If an ether or ester is formed at each position simultaneously, as in diacetylmorphine, codeine methyl ether, etc., the decreasing effect of muzzling the phenolic hydroxyl would seem to predominate, except in the case of diacetylmorphine. The resulting compounds are less effective than morphine but are more effective than the analogue in which the phenolic hydroxyl only is covered. The greater activity of diacetylmorphine may be due to the ease with which the acetyl group may be removed from the phenolic hydroxyl *in vivo*, probably allowing the substance to act as 6-monoacetylmorphine. An exception of opposite kind is benzylmorphine myristyl ester, in which analgesic activity is markedly reduced, perhaps because the large fatty acid (myristic acid, $C_{14}H_{16}O_2$) radical attached to the alcoholic hydroxyl interferes with absorption.

Other modifications at the alcoholic hydroxyl have been effected: substitution by chlorine, oxidation to a ketone, and replacement by hydrogen. Each of these changes has increased activity: chlorine substitution, two- or three-fold; oxidation to a ketone, four- or five-fold; and replacement by hydrogen, ten-fold. Removal of the phenolic hydroxyl from the morphine molecule has not been accomplished, but the effect of such removal, or conversely the effect of the introduction of a phenolic hydroxyl, has been demonstrated in other groups of analgesic compounds. In other words, *a free phenolic hydroxyl enhances and a free alcoholic hydroxyl interferes with analgesic activity in the morphine group and, as will be shown later, also in synthetic analgesics of different types.*

2. *Saturation of the alicyclic ring*

Only a few compounds in which the double bond in the alicyclic ring has been removed by hydrogenation are listed in Table I. Many others

have been studied, and there is in addition a group of isomeric compounds in which the double bond is between carbons 6 and 7, and with which the effect of hydrogenation has been determined. The effect of the change is variable, usually an increase in activity, but it depends in some manner on the rest of the molecule. It is particularly noteworthy, even though its significance is not clear, that hydrogenation of monoacetylmorphine or of diacetylmorphine reduces activity markedly, but hydrogenation of acetylcodeine increases activity significantly.

3. *Modification at the nitrogen*

Morphine has a tertiary nitrogen carrying a methyl group in a piperidine-like ring structure. The tertiary character of the nitrogen, the methyl substituent, and the ring structure are all intimately associated with analgesic action, because disruption of any one of these characteristics markedly reduces, and in many instances practically abolishes, analgesic action.

The tertiary character of the nitrogen is most critical; *a tertiary nitrogen will be found in every potent analgesic, whatever other chemical characteristics may be present.* A potent analgesic in this connexion is understood to be one developing analgesic action comparable to that of morphine. The nitrogen cannot be made quaternary, as in the formation of an N-oxide or a methochloride, without very great diminution in analgesic action.

In morphine and its derivatives the methyl substituent on nitrogen seems essential because its substitution by other alkyl groups reduces or abolishes analgesic action. It is most interesting that, if the N-alkyl substituent consists of a three-carbon chain, with or without an additional methyl group in branched form, not only may analgesic action be virtually lost, but the compound antagonizes or is able to suppress the analgesic action of morphine or of other morphine-like analgesics. Other N-alkyl substituents containing more or less than 3 carbons in a straight chain diminish or abolish this antagonistic action.

The piperidine-like ring in morphine and its derivatives is essential. If the ring is opened, as in the methylmorphimethines, analgesic action is reduced to such an extent as to be of no practical value. The general importance of the nitrogen ring structure for analgesic action will be discussed more fully later in this report.

4. *New substituent on the aromatic or alicyclic ring*

The addition of new substituents to the aromatic or alicyclic portions of the morphine molecule generally results in a decrease in analgesic effectiveness. There are, however, some notable exceptions. A halogen or NH_2 attached to the aromatic ring (position 1 or 2) decreases effectiveness in each instance.

A hydroxyl at position 10 reduces the activity of codeine to one fourth. An alkyl group on the alicyclic ring (position 7 or 6) is variable in its effect. Methyl added to dihydromorphinone at position 7,* producing metopon, increases activity significantly, but added to other molecular species, dihydromorphine, dihydrocodeine, etc., either fails to modify or decreases analgesic action. Increasing the size of the alkyl group added at position 7 decreases the analgesic effect of the compound. Methyl added at position 6 may increase or decrease the intensity of analgesic action, but tends to maintain or prolong duration of such action in contrast to the shortening effect of all other changes at position 6. The action of 6-methyl-Δ^6-desoxymorphine compared to that of desoxymorphine is not prolonged, but is at least equally intense.

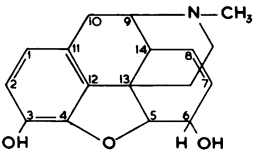
The addition of a hydroxyl at carbon 14 in two instances increases analgesic effectiveness significantly. The new hydroxyl creates a tertiary alcohol; its acetylation, like acetylation of the alcoholic hydroxyl at position 6, increases effectiveness.

5. *Opening the oxygen bridge*

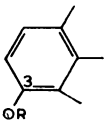
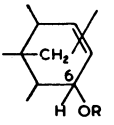
The effect of this change appears to be to decrease analgesic action, but it should be pointed out that a new hydroxyl group is also formed at position 4. A clearer delineation of the effect of the cleavage of the oxygen bridge alone is obtainable in the morphinan group of compounds (see page 949).

* Recent work by Stork & Bauer [93] would indicate that the position of alkyl substitution in metopon and related substances is most likely at position 5.

TABLE I. MODIFICATIONS OF THE MORPHINE MOLECULE *



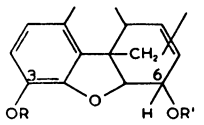
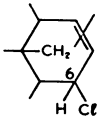
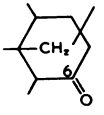
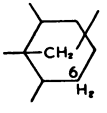
Morphine

Structural change			*Effect on analgesic action*
Etherification or esterification of the phenolic hydroxyl			
	Codeine	$R=CH_3$	Decreased to one tenth
	Dihydrocodeine	$R=CH_3$	Decreased to one tenth [a]
	Ethylmorphine	$R=C_2H_5$	Decreased to one tenth
	Methoxymethyl-dihydro-morphine	$R=CH_2OCH_3$	Decreased to one sixth [a]
	Benzylmorphine	$R=CH_2C_6H_5$	Decreased to one tenth
	Benzyldihydro-morphine	$R=CH_2C_6H_5$	Decreased to one tenth [a]
	Pholcodine	$R=C_2H_4N$⟨O⟩	Decreased very markedly
Etherification or esterification of the alcoholic hydroxyl			
	Heterocodeine	$R=CH_3$	Increased 2 times
	Dihydrohetero-codeine	$R=CH_3$	Increased 1.5 times [a]
	Morphine alcoholic ethyl ether	$R=C_2H_5$	Increased 2.5 times
	Dihydro-morphine alcoholic ethyl ether	$R=C_2H_5$	No change [a]
	Monoacetyl-morphine	$R=COCH_3$	Increased 4 times

* In this and subsequent tables, the structural formula of the parent compound is given at the top, and for each structural change only that portion of the molecule undergoing change is reproduced. The change is either shown directly or its position is indicated by R. The meaning of R is given after the name of the compound. It is to be understood that the rest of the molecule is as in the parent compound unless otherwise indicated. The effect on analgesic action is shown as a directional change, with the approximate quantitative relationship whenever possible. Table I is derived from the report by Small et al.[89] and from unpublished work of the Section on Analgesics, Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md., USA.

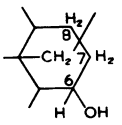
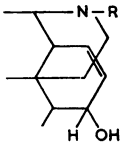
[a] Comparison with dihydromorphine

TABLE I (*continued*)

Structural change		*Effect on analgesic action*
Modification of both hydroxyls simultaneously		
		
Codeine methyl ether	R,R′=CH_3	Decreased
Dihydrocodeine methyl ether	R,R′=CH_3	Decreased [a]
Diacetylmorphine	R,R′=$COCH_3$	Increased
Benzylmorphine myristyl ester	R=$CH_2C_6H_5$ R′=myristic acid	Decreased very markedly
Benzylmorphine methyl ether	R=$CH_2C_6H_5$ R′=CH_3	Decreased
Acetylcodeine	R=CH_3 R′=$COCH_3$	Decreased
Chlorine substitution for the alcoholic hydroxyl		
		
Chloromorphide		Increased
Chlorodihydromorphide		Increased [a]
Chlorocodide		Increased [b]
Chlorodihydrocodide		Increased [c]
Oxidation of the alcoholic hydroxyl to a ketone		
		
Dihydromorphinone		Increased 1.5 times [a]
Dihydrocodeinone		Increased 6 times [c]
Methyldihydromorphinone		Increased 50 times [d]
Methyldihydrocodeinone		Increased 25 times [e]
Removal of the alcoholic hydroxyl		
		
Dihydrodesoxymorphine-D (desomorphine)		Increased 3 times [a]
Dihydrodesoxycodeine-D		Increased 3.5 times [c]

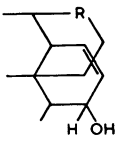
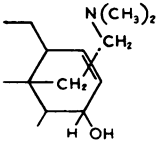
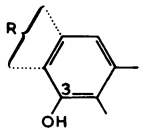
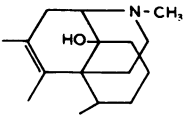
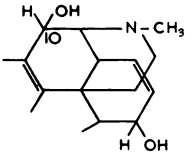
[b] Comparison with codeine
[c] Comparison with dihydrocodeine
[d] Comparison with methyldihydromorphine
[e] Comparison with methyldihydrocodeine

TABLE I (*continued*)

Structural change		*Effect on analgesic action*
	Saturation of the alicyclic ring	
	Dihydromorphine	Increased 3 times
	Dihydrocodeine	Increased slightly [b]
	Dihydroheterocodeine	Increased 3 times [f]
	Benzyldihydromorphine	Increased 3 times [g]
	Monoacetyldihydromorphine	Decreased to one seventh [h]
	Diacetyldihydromorphine	Decreased to one fourth [i]
	Acetyldihydrocodeine	Increased 2 times [j]
	Chlorodihydromorphide	Increased 20 times [k]
	Removal or substitution of the N-alkyl group	
	Normorphine R=H	Decreased markedly
	N-Ethylnor-morphine R=C_2H_5	Decreased
	N-Propylnor-morphine R=C_3H_7	Nearly abolished
	N-Isopropylnor-morphine R=$CH(CH_3)_2$	Nearly abolished
	N-Allylnor-morphine R=$CH_2CH{:}CH_2$	Nearly abolished *
	N-Methylallyl-normorphine R=$CH(CH_3)CH{:}CH_2$	Nearly abolished
	N-Isobutylnor-morphine R=$CH_2CH(CH_3)_2$	Nearly abolished
	N-Butenylnor-morphine R=$CH_2CH{:}CHCH_2$	No analgesic effect
	N-Propargylnor-morphine R=$CH_2C{\vdots}CH$	Decreased

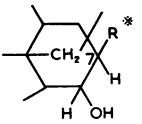
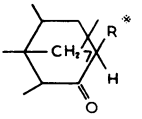
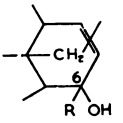
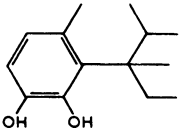
f Comparison with heterocodeine
g Comparison with benzylmorphine
h Comparison with monoacetylmorphine
i Comparison with diacetylmorphine
j Comparison with acetylcodeine
k Comparison with chloromorphide
* See page 991 for further comments.

TABLE I (*continued*)

Structural change			*Effect on analgesic action*
	Tertiary nitrogen changed to quaternary		
	Morphine N-oxide	$R=NCH_3\rightarrow O$	Decreased markedly
	Morphine methochloride	$R=\overset{+}{N}(CH_3)_2Cl^-$	Decreased markedly
	Codeine methochloride	$R=\overset{+}{N}(CH_3)_2Cl^-$	Decreased markedly [b]
	Opening the nitrogen ring		
	α-Methylmorphimethine		Decreased markedly [b]
	β-Methylmorphimethine		Decreased markedly [b]
	New substituents on the aromatic or alicylic ring		
	Aminomorphine	$R=NH_2$	Decreased markedly
	Chlorocodeine	$R=Cl$	Decreased to one half [b]
	Bromocodeine	$R=Br$	Decreased to one half [b]
	Acetocodeine	$R=COCH_3$	Decreased markedly [b]
	Acetodihydrocodeine	$R=COCH_3$	Decreased markedly [c]
	Dihydrohydroxymorphinone		Increased [l]
	Dihydrohydroxycodeinone		Unchanged [m]
	Acetylhydroxycodeinone		Increased 16 times [n]
	Dihydrohydroxycodeine		Increased 3 times [c]
	10-Hydroxycodeine		Decreased to one fourth [b]

[l] Comparison with dihydromorphinone
[m] Comparison with dihydrocodeinone
[n] Comparison with hydroxycodeinone

TABLE I (*concluded*)

Structural change			*Effect on analgesic action*
New substituents on the aromatic or alicyclic ring (*continued*)			
	Methyldihydro-morphine	$R=CH_3$	Decreased to one twelfth [a]
	Methyldihydro-codeine	$R=CH_3$	Decreased to one third [c]
	Methyldihydro-morphinone	$R=CH_3$	Increased 2.5 times [l]
	Methyldihydro-codeinone	$R=CH_3$	Increased slightly [m]
	Ethyldihydro-morphinone	$R=C_2H_5$	Unchanged [l]
	Isopropyldihydro-morphinone	$R=CH(CH_3)_2$	Decreased to one eighth [l]
	Amyldihydro-morphinone	$R=C_5H_{11}$	Decreased to one half [l]
	6-Methylmorphine	$R=CH_3$	Decreased to one half
	6-Methyldihydro-morphine	$R=CH_3$	Decreased to one third [a]
	6-Methylcodeine	$R=CH_3$	Unchanged [b]
	6-Methyldihydro-codeine	$R=CH_3$	Unchanged [c]
	6-Methyl-Δ^6-desoxymorphine	$R=CH_3$	Increased 2 times [o]
Opening the oxygen bridge			
	Tetrahydrodesoxymorphine		Decreased to one eighth [p]
	Tetrahydrodesoxycodeine		Decreased to one half [q]

[o] Comparison with desoxymorphine; other compounds of this type have been described by Orahovats et al.[70]

[p] Comparison with dihydrodesoxymorphine

[q] Comparison with dihydrodesoxycodeine

* See footnote, page 940.

Moieties in the Morphine Molecule

As pointed out in the opening paragraph, it is possible to see within the morphine molecule moieties, or simpler structures, which can be seen also in other analgesic compounds. As in the morphine series modifications of these several basic structures have been made and each group will be described in turn, the structure and activity being related back to that of morphine whenever possible. The basic structures themselves superimposed upon the morphine molecule are shown in Table II.

Phenanthrene

It has long been recognized that a major portion of the morphine molecule may be characterized as a partially hydrogenated phenanthrene, and many attempts have been made to synthesize from phenanthrene compounds with significant analgesic action. Phenanthrene, dihydro-, tetrahydro-, and octahydro-phenanthrene (Table II, 2, 3, 4, 5) are relatively inert so far as analgesic action is concerned. The tetrahydro-compound has some effect, but the dose required is large and the action may be only an indirect result of toxicity. The addition of substituents increases the action of these compounds, especially of tetrahydrophenanthrene. The greatest analgesic action appears when the substituent is an amine or an amino alcohol. The most active compound, however, in which a diethylaminoethanol side-chain is introduced at position 3, is only one twenty-fifth as effective as morphine. Introduction of an amine at position 9, which would most closely resemble the morphine structure, does not evoke the greatest analgesic action, and simultaneous addition of a hydroxyl at position 3 in a 9-aminophenanthrene reduces rather than enhances the action of the compound.

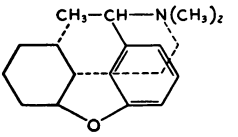
Dibenzofuran and carbazole

Looking again at the morphine molecule one can see in it a partially hydrogenated morphenol (Table II, 6), a morphinan (Table II, 7), or a dibenzofuran (Table II, 8). Morphenol has not been shown to have significant analgesic activity. Derivatives of dibenzofuran, however, and of carbazole (Table II, 10), which is not a part of the morphine molecule but bears some resemblance to dibenzofuran, carrying substituents similar to those of the more active phenanthrene compounds, are as active as the phenanthrenes and in some instances are more effective. The analgesic effectiveness of aminoethyldibenzofuran (Table II, 9), which would more closely resemble the morphine structure, has not been determined.

Phenyl- and diphenyl-ethylamines

One can recognize in morphine still simpler portions than those already considered; e.g., one in which an amine is attached through a CH_2-CH_2 linkage to a phenyl group. This disregards the greater part of the ring

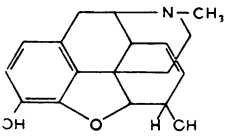
structure of morphine, but weak analgesic action has been demonstrated with compounds of this type. Some analgesic activity has been shown also with diphenylethylamines,[22] whose structure can be superimposed on the morphine molecule if one does not take into account the degree of unsaturation. Activity is enhanced in the diphenylethylamines by the addition of a hydroxyl to the ethyl linkage. Recently some degree of analgesic action has been described for phenylethylamines in which a cyclohexyloxy group is introduced *para* or *meta* to the ethylamine.[64] Disregarding the degree of saturation of the respective ring structures, it is possible to superimpose such a structure on the morphine molecule.



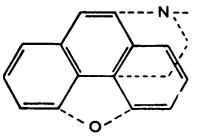
m-cyclohexyloxy-α-phenylethyldimethylamine

Only the compound in which the cyclohexyloxy is in *meta*-position to the ethylamine will fit the morphine molecule, and this is less effective as an analgesic than the one in which the substituents are in *para*-position.

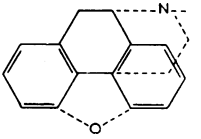
TABLE II. MOIETIES IN THE MORPHINE MOLECULE



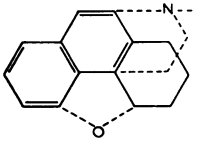
1. Morphine



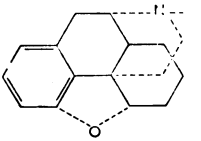
2. Phenanthrene



3. Dihydrophenanthrene

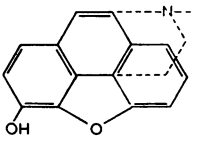


4. Tetrahydrophenanthrene

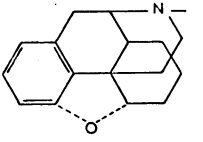


5. Octahydrophenanthrene

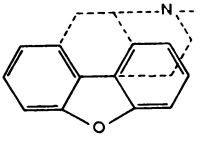
TABLE II (*continued*)



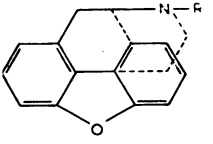
6. Morphenol



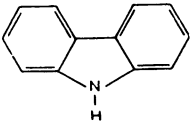
7. Morphinan



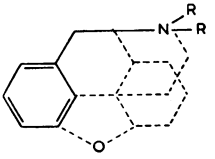
8. Dibenzofuran



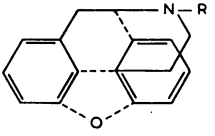
9. Aminoethyldibenzofuran



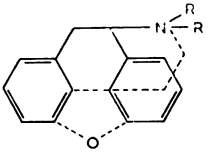
10. Carbazole *



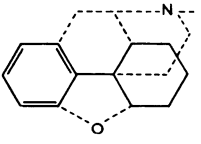
11. Phenylethylamines



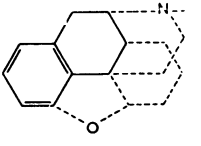
12. Bisphenylethylamines



13. Diphenylethylamines



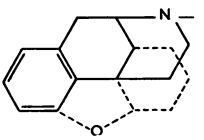
14. Phenylcyclohexane



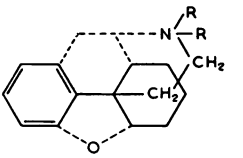
15. Tetrahydronaphthalene

* Not a moiety, but introduced for comparison with dibenzofuran.

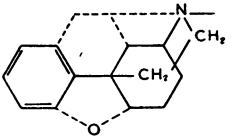
TABLE II (*concluded*)



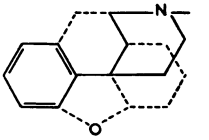
16. Benzmorphan



17. Aminoethylphenylcyclohexane



18. Phenylmorphan *



19. 4-Phenylpiperidine

* Note difference in position of heterocyclic ring from that of morphine.

Morphinan Derivatives

Greater similarity of structure and a higher degree of analgesic activity have been attained in the synthesis of morphinan and its derivatives (Table III). Morphinan exhibits only weak analgesic action. Methylation of the nitrogen enhances activity definitely; N-methylmorphinan has about one fifth the analgesic effect of morphine. The further addition of a hydroxyl at position 3 raises the activity of the compound at least to the level of that of morphine. It should be emphasized at this point that the synthetic compound, 3-hydroxy-N-methylmorphinan (racemorphan) is a racemate, whereas natural morphine is a *laevo*-isomer. The former has been resolved into its *l*- and *d*-components so that, in relating activity to that of morphine, one should more properly compare *l*-3-hydroxy-N-methylmorphinan (levorphan). In such a comparison the synthetic compound is more than twice as effective as morphine. The *d*-isomer of 3-hydroxy-N-methylmorphinan (dextrorphan) has practically no analgesic effect; on the contrary an antagonistic action of the *d*-isomer towards the analgesic effect of the *l*-isomer or of morphine has been described.[88]

3-Hydroxy-N-methylmorphinan differs from morphine by the absence of the oxygen bridge, by the absence of the alcoholic hydroxyl, and by the saturation of the 7-8 double bond. Its closest analogue in the morphine series is dihydrodesoxymorphine-D (desomorphine), from which it differs

only by the absence of the oxygen bridge. *l*-3-Hydroxy-N-methylmorphinan has less than half the analgesic potency of desomorphine (laevorotatory),* establishing more firmly the conclusion stated previously that abolition of the oxygen bridge decreases analgesic activity.

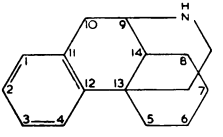
An isomer of N-methylmorphinan has been made in which the isomerism is dependent upon the position of the hydrogen on carbon 14, *cis* to the ethanamine system in N-methylmorphinan, *trans* in N-methylisomorphinan. The *trans* isomeric compound is devoid, or very nearly devoid, of analgesic activity. Another isomer of N-methylmorphinan has also been made in which the closure of the nitrogen ring is at carbon 8 (Table IV). Again analgesic activity is markedly reduced.

Opening the nitrogen ring of N-methylmorphinan reduces analgesic activity to one third if the amine continues to be tertiary, $N(CH_3)_2$, to zero if the amine becomes $NHCH_3$ or NH_2.

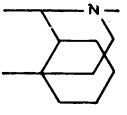
Shifting the position of the hydroxyl of 3-hydroxy-N-methylmorphinan to 2 or 4 abolishes analgesic activity. Muzzling the hydroxyl with CH_3 or $COCH_3$ decreases activity to about one tenth, as in the morphine series. If the racemic 3-methoxy-N-methylmorphinan (racemethorphan) is resolved, one finds that analgesic activity is again exhibited only by the *l*-isomer, levomethorphan; the *d*-isomer, dextromethorphan, has no analgesic effect.

Again as in the morphine series, analgesic activity is reduced by the addition of a substituent, CH_3, to the aromatic ring at position 2, and is reduced or very nearly abolished by substituting allyl or propargyl for methyl on the nitrogen. The N-allyl compound is antagonistic to morphine and morphine-like substances, including the morphinans, to an extent nearly equal to N-allylnormorphine.

TABLE III. MORPHINAN DERIVATIVES

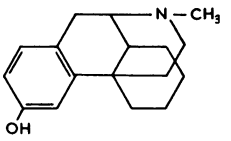
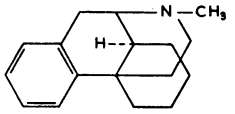
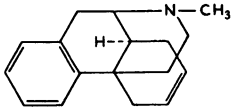
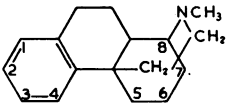
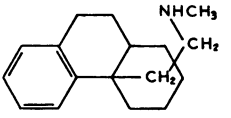
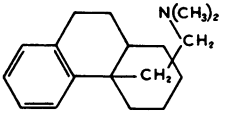
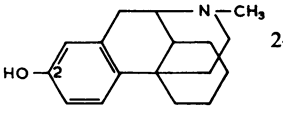


Morphinan

Structural change		*Analgesic action*
	Morphinan	Very weak [25]
	N-Methylmorphinan	Increased to one fifth that of morphine [41, *]

* Eddy, N. B., unpublished results

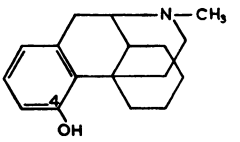
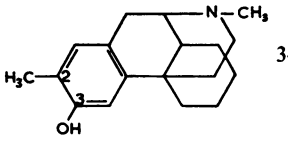
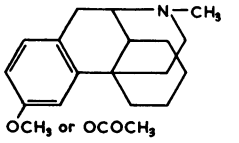
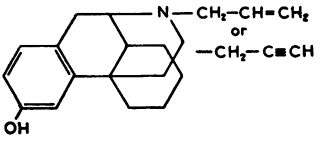
TABLE III (*continued*)

Structural change		*Analgesic action*
	*dl*-3-Hydroxy-N-methylmorphinan (racemorphan)	Increased to that of morphine or a little greater [33, 49, 88]
	l-3-Hydroxy-N-methylmorphinan (levorphan)	More than twice that of morphine [33, 49, 88]
	d-3-Hydroxy-N-methylmorphinan (dextrorphan)	Almost none [33, 49, 88]
	N-Methylisomorphinan	Almost none [16, **]
	N-Methyl-Δ^6-dehydroisomorphinan	About one fourth that of morphine [16]
	Structural isomer of N-methylmorphinan	One eighth that of N-methylmorphinan *
		None *
		One third that of N-methylmorphinan *
	2-Hydroxy-N-methylmorphinan	None [33]

* Eddy, N. B., unpublished results

** Gates et al.[35] previously reported that this compound had appreciable analgesic activity.

TABLE III (*concluded*)

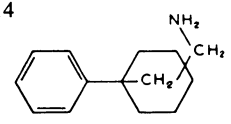
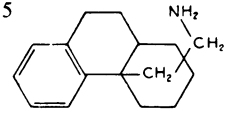
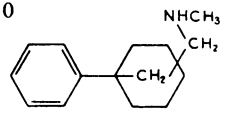
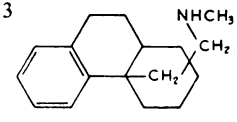
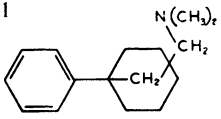
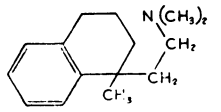
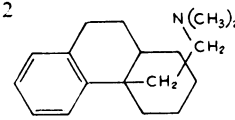
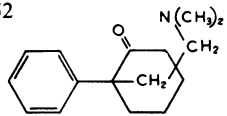
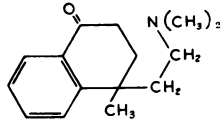
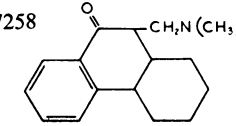
Structural change		*Analgesic action*
	4-Hydroxy-N-methyl-morphinan	None [33]
	3-Hydroxy-2,N-dimethyl-morphinan	Reduced *
	*dl*-3-Methoxy-(or acetoxy-) N-methylmorphinan	Reduced to one tenth that of racemorphan [9, 10, 76, 87]
	l-3-Methoxy-N-methyl-morphinan	Twice that of its racemate [9, 10, 76]
	d-3-Methoxy-N-methyl-morphinan	None [9, 10, 76]
	*l*-3-Hydroxy-N-allyl-(or-N-propargyl-) morphinan	Nearly abolished ; [8] compounds are antagonists to morphine, etc.*

* Eddy, N. B., unpublished results

Phenylcyclohexanes, Phenylmorphans, and Benzmorphans

It is convenient to consider at this point some compounds related in some respects to the morphinans, and with ring structures which can be superimposed upon the morphine molecule (see Table IV). Unfortunately the programme of synthesis, of which these compounds are a part, has not progressed far enough for more than a preliminary comparison of the four types of ring structure. However, some important trends have appeared already. *A high degree of analgesic activity, even equivalent to that of morphine, can be attained with a simpler ring structure than that of morphine or morphinan.* It does not appear essential that nitrogen be in cyclic structure; the introduction of a hydroxyl when nitrogen is cyclic enhances very significantly the analgesic action, but the position of the hydroxyl is important. As in other series, muzzling the hydroxyl with CH_3 again reduces activity. The failure of the acetyl group to have a similar effect (Table IV, 7252) is probably due to the easy removal of the acetyl group by hydrolysis as compared with the resistant character of a methoxyl.

TABLE IV. PHENYLCYCLOHEXANES, PHENYLMORPHANS, BENZMORPHANS, ETC. *

Phenylcyclohexanes	*Tetrahydronaphthalenes and benzmorphans*	*Octahydrophenanthrenes*	
		leading to isomorphinans	*leading to morphinans*
5914  **80**		5915  **None**	
5910  **63**		5913  **None**	
5701  **25**	6068  **25**	5912  **36**	
5352  **None**	6047  **None**		7258  **24**

* All the compounds shown in this table have been made (except 6017 and 3537) and evaluated in the laboratories of the National Institutes of Health, USA. The number to the left of the formula is the identification code number. The figure in bold type to the right is the analgesic effectiveness in mg/kg when administered subcutaneously to mice. The corresponding figure for morphine is 2, for codeine is 14, and for pethidine is 10. The chemistry of these compounds has been described by May & Murphy,[62, 63] and the method of evaluation of analgesic action has been described by Eddy & Leimbach.[26, 55]

TABLE IV (*continued*)

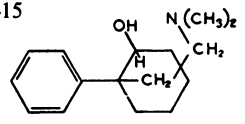
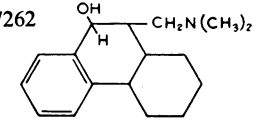
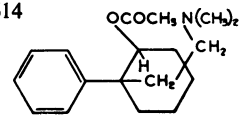
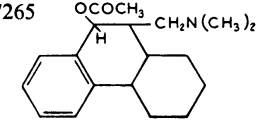
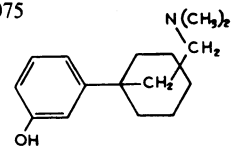
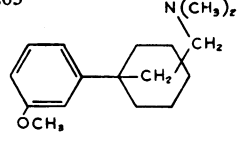
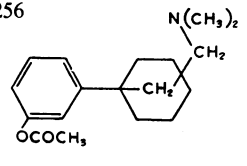
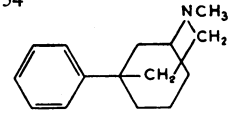
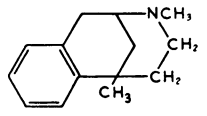
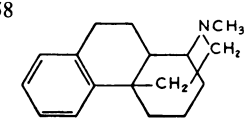
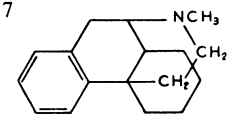
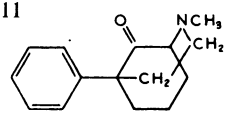
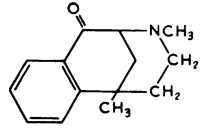
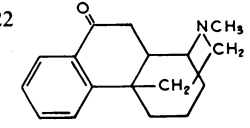
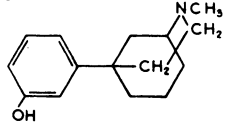
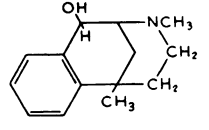
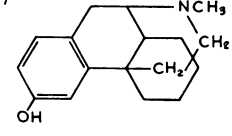
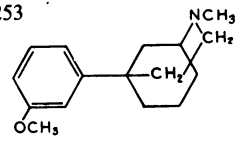
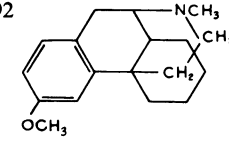
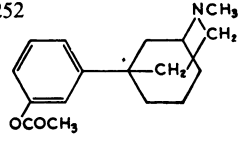
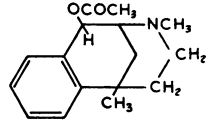
Phenylcyclohexanes	*Tetrahydronaphthalenes and benzmorphans*	*Octahydrophenanthrenes*	
		leading to isomorphinans	*leading to morphinans*
5415  **None**			7262  **50**
5614  **95**			7265  **65**
7075  **89**			
7263  **45**			
7256  **83**			

TABLE IV (*concluded*)

Phenylcyclohexanes		*Tetrahydronaphthalenes and benzmorphans*		*Octahydrophenanthrenes*			
				leading to isomorphinans		*leading to morphinans*	
5754		6048		5758		6017	
	21		**22**		**91**		**11**
5711		6049		5822			
	160		**225**		**19**		
7215		6044				3537	
	2.7		**29**				**0.9**
7253						4592	
	28						**8**
7252		7216					
	2.1		**32**				

Pethidine and its Derivatives

The synthetic work which led to the preparation of pethidine had another objective than analgesic activity, and the thought that the pethidine structure was related to that of morphine did not emerge until the analgesic effect of the former was discovered, as a by-product so to speak. That discovery, however, was of tremendous importance to future developments. The original investigators as well as others made many modifications of the phenylpiperidine carboxylate structure and all of these, at least as to type, are illustrated in Table V.

1. *Addition of a substituent to the phenyl group*

Not only the nature but also the position of the substituent is important. A substituent in the *para*-position always decreased, and sometimes abolished, analgesic action, but a hydroxyl in the *meta*-position or a methyl group *ortho* to the piperidine-ring linkage increased analgesic activity about one and a half times. Phenylpiperidine is a recognizable part of the morphine molecule (Table II, 19), and the *meta*-position on the phenyl ring corresponds to position 3 of the morphine structure. Also, as in the morphine series, muzzling the hydroxyl with a methyl group decreased activity and acetylation of the hydroxyl did not, probably again because the acetyl group is more easily removed *in vivo*.

2. *Shift in position, substitution, or removal of the phenyl group*

Attention has been drawn repeatedly to the presence in morphine and pethidine (as well as in other structures, as will appear later) of a quaternary carbon atom separated from a tertiary amine by two CH_2 groups. Disturbance of this relationship in pethidine by shifting the phenyl group to position 3 of the piperidine ring, as in isopethidine, by the interposition of an additional CH_2 between the phenyl and the piperidine ring, or by removal of the phenyl group, greatly decreases analgesic activity. The quaternary carbon and the CH_2–CH_2 linkage to the amine are still present if the phenyl is replaced by cyclohexyl or naphthyl, but analgesic action is decreased markedly. It would seem, therefore, that *a phenyl group attached to the quaternary carbon is the optimal if not the essential configuration.* Norisopethidine was synthesized as a racemate. When resolved into the optical isomers, analgesic activity was exhibited almost exclusively by the *laevo*-form; the *dextro*-form was practically inactive.

3. *Change in the substituent on the nitrogen*

Removal of the methyl group (norpethidine) or its replacement by larger groups reduces analgesic effectiveness; likewise, the nitrogen cannot be changed from tertiary to quaternary without loss of analgesic action. *NCH_3, therefore, is the optimal formulation.*

4. *Addition of a substituent to the piperidine ring*

Only a methyl group at position 3 has increased analgesic activity significantly, and this effect has been attained only when an ethyl carboxylate is attached at position 4. If the carboxylate is changed to propionoxy and a methyl group is then introduced at position 3, either *cis* (betaprodine) or *trans* (alphaprodine) to the substituents at position 4, a further increase in analgesic activity, over that effected by the change to propionoxy, is not obtained. Nor is a further increase in analgesic activity attained with methyl groups at positions 2 and 5 in a propionoxy-substituted compound (Promedol).

5. *Piperidine ring changed to hexamethyleneimine or pyrrolidine*

Increasing or decreasing the size of the heterocyclic ring decreases analgesic effectiveness. The hexamethyleneimines will be discussed a little later. *Activity is abolished if the ring consists of less than 6 or more than 7 members.*

6. *Opening the nitrogen ring*

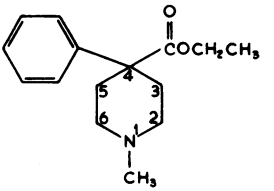
Again as in the morphine series, *opening the nitrogen ring decreases activity very considerably*—a result apparently in marked contrast to the effectiveness of the methadones and dithienylbutenylamines. In the latter, however, steric forces seem to produce a pseudopiperidine ring structure; that is, a carbon of the amino group adjacent to the nitrogen is forced into juxtaposition to an aromatic-ring carbon, giving the appearance in molecular models of a piperidine ring without actual ring closure (see page 995). When the piperidine ring of pethidine is opened no such pseudopiperidine arrangement is retained, and when the nitrogen ring is opened in morphine a pseudopiperidine structure is possible but the juxtaposition is to carbon 12, altering significantly the character of the molecule.

7. *Changes in the carboxylate portion of the molecule*

Changing the size or character of the group forming the carboxylic acid ester, or changing the carboxylate to an amide, to a ketoxime, to a ketone, or to a carbinol, or replacing it with an alcohol which is esterified, almost invariably decreases, and often abolishes, analgesic action. Among the esters the ethyl ester is optimal, and in other configurations the greatest activity is shown with two- or three-carbon systems. Among the ketones the propyl ketone is the most active, the ethyl ketone being only half as effective. However, when the change to the ethyl ketone is accompanied by the addition of a hydroxyl in *meta*-position on the phenyl group, a very powerful analgesic (ketobemidone) results. Among the alcohols the propionoxy derivative is the most active and this activity is not enhanced, in some instances it is even decreased, by other changes in the molecule.

To summarize, advantageous changes in the pethidine molecule include only a substituent in *meta*- or *ortho*-position on the phenyl group, a substituent at position 3 in the piperidine ring, and substitution of propionoxy for the ethyl carboxylate. Only the first of these changes increases the similarity between the pethidine and morphine molecules.

TABLE V. PETHIDINE DERIVATIVES



Pethidine

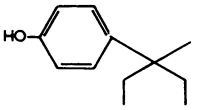
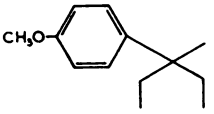
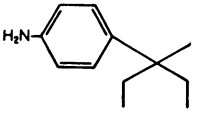
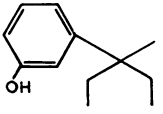
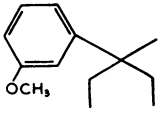
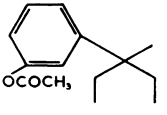
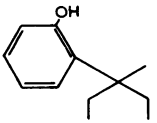
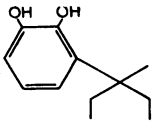
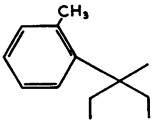
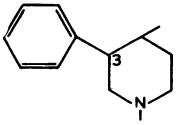
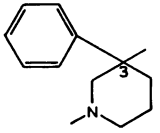
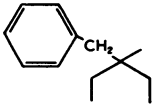
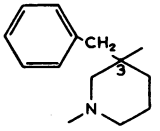
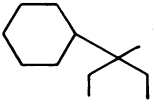
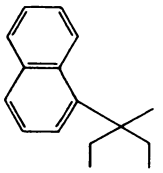
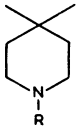
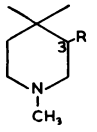
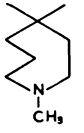
Structural change		*Analgesic action*
Addition of substituent to phenyl group		
		Decreased to one fifth [96]
		None [96]
		Decreased markedly [96]
	Bemidone	Increased 1.5 times [96]
		Decreased to one half [104]
		Unchanged [59]

TABLE V (*continued*)

Structural change		*Analgesic action*
Addition of substituent to phenyl group (*continued*)		
		None [59]
		None [59]
		Increased 1.5 times [59]
Shift in position, substitution, or removal of phenyl group		
		Decreased [25]
	Isopethidine	Decreased to one half [59]
		Decreased markedly [25]
		None [59]
		Decreased to one fourth *

* Eddy, N. B., unpublished results

TABLE V (*continued*)

Structural change	*Analgesic action*
Shift in position, substitution, or removal of phenyl group (*continued*)	
	None [96]
	Decreased markedly [96]
Change in substituent on the nitrogen	
	R=H Norpethidine — Decreased markedly [96]
	$R=CH_2CH_3$ — Decreased slightly [96]
	$R=(CH_2)_2CH_3$ — Decreased to one half [96]
	$R=(CH_2)_3CH_3$ — Decreased [96]
	$R=CH_2CH:CH_2$ — Decreased markedly [21]
	R=  — None [96]
	$R=CH_2CH_2OH$ — Decreased slightly [96]
	$R=NH_2$ — Decreased markedly [96]
	$R=CH_2CH_2N(C_2H_5)_2$ — Decreased markedly [96]
Addition of substituent to piperidine ring	
	R=  — None [96]
	R=OC  — Decreased [30]
	$R=CH_3$ — Increased [75]
Piperidine ring changed to hexamethyleneimine or pyrrolidine	
	Decreased to one half to one fourth *

* Seifter, J. & Glassman, J., personal communication

TABLE V (*continued*)

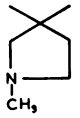
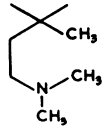
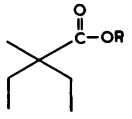
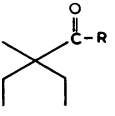
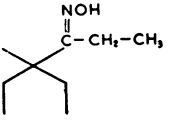
Structural change	*Analgesic action*
Piperidine ring changed to hexamethyleneimine or pyrrolidine (*continued*)	
	None [59]
Opening the piperidine ring	
	Decreased to one sixth [59]
Change in the ester group	
	
R=H	None [96]
$R=CH_3$	Decreased to one sixth [96]
$R=CH(CH_3)_2$	Decreased to one half [96]
$R=(CH_2)_2CH_3$	Decreased to one third [96]
$R=CH_2CH:CH_2$	Decreased to one half [96]
$R=C_4H_9$	Decreased markedly [96]
$R=CH_2$ 	Decreased markedly [96]
R= 	Decreased markedly [96]
$R=CH_2CH_2N(C_2H_5)_2$	None [96]
Carboxylate changed to amide	
	
$R=NH_2$	None [96]
$R=NH\cdot CH_2CH_2N(C_2H_5)_2$	None [96]
$R=NH\cdot CONH_2$	None [96]
$R=N(C_2H_5)_2$	None [96]
Carboxylate changed to ketoxime	
	Decreased [96]

TABLE V (*continued*)

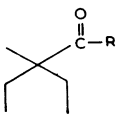
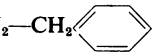
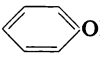
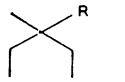
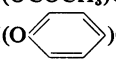
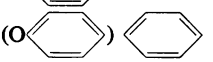
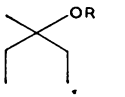
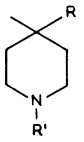
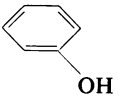
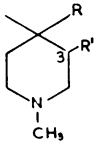
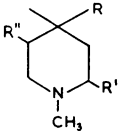
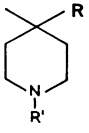
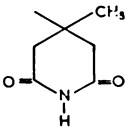
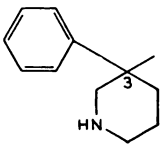
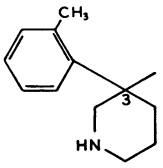
Structural change		*Analgesic action*
	Carboxylate changed to ketone	
	$R=CH_3$	Decreased markedly [96]
	$R=CH_2CH_3$	Decreased to about one half [96]
	$R=CH(CH_3)_2$	Decreased to one half [96]
	$R=(CH_2)_2CH_3$	Unchanged [96]
	$R=(CH_2)_6CH_3$	None [96]
	R= 	Decreased markedly [96]
	R= 	Decreased markedly [96]
	R= 	Decreased markedly [96]
	R= 	Decreased markedly [96]
	R= 	Decreased markedly [96]
	R= 	Decreased to one half [96]
	Carboxylate changed to carbinol	
	$R=CH_2OH$	None [79]
	$R=CHOHCH_3$	None [59]
	$R=CH(OCOCH_3)CH_3$	None [59]
	R= 	Decreased markedly [96]
	R= 	None [96]
	Carboxylate changed to alcohol and esterified	
	$R=H$	None [50]
	$R=COCH_3$	Decreased to about one half [50]
	$R=COCH_2CH_3$	Increased 5 to 10 times [50]
	$R=CO(CH_2)_2CH_3$	Decreased slightly [50]
	$R=CO(CH_2)_3CH_3$	Decreased slightly [50]
	$R=COCH_2CH(CH_3)_2$	Decreased slightly [50]

TABLE V (*continued*)

Structural change			*Analgesic action*
	Molecule changed at two points simultaneously		
	R = $COCH_2CH_3$ R′ = H		Decreased markedly [96]
	R = $COCH_2CH_3$ R′ = $CH(CH_3)_2$		Increased 10 times [86]
	R = $COCH_2CH_3$ R′ = 		Decreased to one half [96]
	R = $COCH_2CH_3$ R′ = $(CH_3)_2I$		None *
	R = $COCH_2CH_3$ R′ = 	Ketobemidone	Increased 10 times [17]
	R = $OCOCH_2CH_3$ R′ = CH_3(*trans*)	Alphaprodine	Increased 3 to 5 times [106]
	R = $OCOCH_2CH_3$ R′ = CH_3(*cis*)	Betaprodine	Increased 2 to 4 times [106]
	R = $OCOCH_2CH_3$ R′ = C_2H_5(*trans*)	Alphameprodine	Increased [75]
	R = $OCOCH_2CH_3$ R′ = C_2H_5(*cis*)	Betameprodine	Increased [75]
	R = $OCOCH_2CH_3$ R′, R″ = CH_3	Promedol	Increased 3 to 5 times [38, 67]
	R = CH_3 R′ = H		Decreased to one third *
	R = CH_3 R′ = CH_3		Decreased to one third *

* Eddy, N. B., unpublished results

TABLE V (*concluded*)

Structural change	*Analgesic action*
Molecule changed at two points simultaneously (*continued*)	
	None *
 *dl*-Norisopethidine	Decreased to one fourth [59]
l-Norisopethidine	Decreased to one half [59]
d-Norisopethidine	None [59]
	Decreased to three fourths [59]

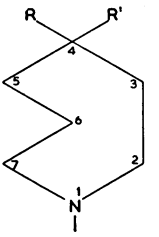
* Eddy, N. B., unpublished results

Hexamethyleneimines

As indicated in Table V, substituting a seven-membered heterocyclic ring for the piperidine of pethidine decreases analgesic activity;** similar substitution of hexamethyleneimine for piperidine in the ketobemidone type of compound decreased activity, but did not do so in an alphaprodine analogue. The method of synthesis of the hexamethyleneimines has thus far limited the production of derivatives comparable to those which have been made in the pethidine series. For the most part, however, the same type of modification has effected the same directional change in analgesic action whether the molecule contained a six- or a seven-membered heterocyclic ring (compare Table VI with Table V). This is true for changing the ester group of the carboxylate (except the methyl ester), for the change from carboxylate to ketone or from carboxylate to hydroxyl plus esterification, for the removal of the carboxylate part of the molecule, for the introduction of a methyl group at position 3 of the nitrogen ring, and for the formation (except in one instance) of a quaternary ammonium salt. It is noteworthy also that substitution of a thienyl for the phenyl group in the hexamethyleneimine analogue abolishes analgesic action.

** To one third in rats (Seifter, J. & Glassman, J., personal communication) and to one fourth in mice (Eddy, N. B., unpublished results). In man the two compounds are about equally effective orally for some types of pain; pethidine is more effective parenterally for severe pain [37] (Batterman, R. C., personal communication).

TABLE VI. HEXAMETHYLENEIMINES



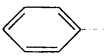
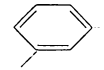
R	*R'*	*Ring substituents*		*Analgesic action**
	$COOCH_2CH_3$	NCH_3	— [a]	33.5
,,	,,	,,	2-CH_3	13
,,	,,	,,	3-CH_3	4.9
,,	,,	,,	5-CH_3	>32
,,	,,	,,	6-CH_3	Almost none
,,	,,	,,	7-CH_3	>50
,,	$COOCH_3$	,,	2-CH_3	10.5
,,	$COOCH_2CH_2CH_3$	,,	,,	>32
,,	$COOCH(CH_3)_2$	,,	,,	10 to 32
,,	$COOCH_2CH_2N(C_2H_5)_2$	,,	—	32
,,	$COCH_2CH_3$	,,	—	>50
,,	$COCH_2CH_2CH_3$	,,	—	>50
,,	$COCH_2CH_3$	,,	2-CH_3	20
,,	$SO_2CH_2CH_3$	,,	—	32
,,	$OCOCH_3$	,,	2-CH_3	>32
,,	,,	,,	3-CH_3	60
,,	$OCOCH_2CH_3$	,,	2-CH_3	18
,,	,,	,,	3-CH_3 [b]	1.1
,,	H	,,	—	None

* Analgesic action is expressed as ED_{50} (mg/kg of base, intraperitoneally in rats, radiant-heat stimulus); the corresponding dose for pethidine is 11.2 and for morphine is 1.4 [85] (Seifter, J. & Glassman, J., personal communication).

a Pethidine analogue

b Alphaprodine analogue

TABLE VI (*concluded*)

R	*R'*	*Ring substituents*		*Analgesic action*
	H	NCH_3	$2\text{-}CH_3$	>32
,,	,,	,,	$3\text{-}CH_3$	>32
,,	$COOCH_2CH_3$	$\overset{+}{N}(CH_3)_2\overset{-}{Br}$	—	30
,,	,,	$\overset{+}{N}(CH_3)_2\overset{-}{I}$	$2\text{-}CH_3$	None
,,	H	,,	—	None
,,	C ⋮ N	$\overset{+}{N}(CH_3)_2\overset{-}{Cl}$	—	>80
,,	,,	$\overset{+}{N}(CH_3)_2\overset{-}{Br}$	—	None
	$COCH_2CH_3$	NCH_3	— [c]	16.5
	$COOCH_2CH_3$	,,	—	None

[c] Ketobemidone analogue

Methadone, Isomethadone, and their Derivatives

According to the method of synthesis, methadone or isomethadone may be the predominant or sole final product. These two compounds differ with respect to the position of a methyl group in the R″ portion of the molecule (Table VII). Methadone is the stronger analgesic. Both compounds are synthesized as racemates, both have been resolved into their optical components, and in both cases analgesic activity is exhibited almost entirely by the *laevo*-isomer. Methadone and isomethadone, like pethidine, contain a quaternary carbon separated from a tertiary amine by two methylene groups, and according to Gero [36] steric forces create a pseudo-piperidine structure by approximation of an amino alkyl carbon towards a carbon of a phenyl group. Since its discovery, hundreds of modifications of the structure of methadone have been made by attacking the molecule at all points. All types of change, but not nearly all the individual modifications of the methadone molecule, are illustrated in Table VII.

1. *Variation in the basic group of R″*

Almost all changes in the basic group effect a decrease in analgesic activity. The exceptions, constituting maintenance of, or only a slight

increase in, analgesic action, are the exchange of piperidino or morpholino for dimethylamino when the rest of the molecule has the methadone constitution or is a straight-chain hexanone. The piperidino and morpholino derivatives of isomethadone are less effective than isomethadone. Changing the tertiary nitrogen of methadone or isomethadone to quaternary almost abolishes analgesic action.

2. *Variation in the aliphatic portion of R″*

This portion of the molecule has been changed by increasing or decreasing the number of carbon atoms between the quaternary carbon and the amine and by increasing or decreasing the number of carbons in chain beyond the amine. All of these modifications decrease analgesic activity. It has already been pointed out that shifting a methyl group to carbon 5 (isomethadone) decreases effectiveness significantly, and cyclization in this portion of the molecule (Table VII, 40, 41, and 42) abolishes analgesic action.

3. *Variation in the hydrocarbon portion of R′*

Again, increasing or decreasing the hydrocarbon chain decreases or abolishes analgesic action; $COCH_2CH_3$ is a sharply critical structure. Only one exception has been described—an allyl ketone (No. 58), which is said to have the same analgesic action as the corresponding compound containing $COCH_2CH_3$ (No. 24).

4. *Reduction of the ketone to a carbinol and acylation*

The formation of a secondary alcohol introduces a new asymmetric carbon and hence makes possible additional isomeric forms.[27, 55, 60, 61] With only one exception—No. 76, the alcohol derived from the *d*-isomer of methadone—the analgesic action of the alcohols in both the methadone and the isomethadone series is markedly less than that of the corresponding ketones. Acetylation of the alcohol always increases analgesic action, to or more often to a little above that of the ketone in the methadone series and nearly to that of the ketone in the isomethadone series. If acylation of the alcohol is effected by a smaller or larger group than $COCH_3$, or if chlorine is substituted in the acylating group, the increase in analgesic effect is less than in the acetoxy compounds. The few primary alcohols which have been examined are less effective than the ketones, but again acetylation (No. 73) increases analgesic effect.

5. *Ketone of R′ changed to a sulfone or to a ketimine*

The C=O group has been replaced by SO_2, or its oxygen by NH, in some instances without loss or even with a slight increase in analgesic effectiveness. This is particularly true when the amine is piperidine or

morpholine. At other times the sulfone or ketimine is less active than the corresponding ketone. The results of this type of change have been too variable for more specific generalization.

6. *Ketone changed to carboxylate or acid amide*

Changing the ketone to an acid with esterification or with the formation of an amide has always been disadvantageous with respect to analgesic activity. The formation of the amide abolishes analgesic effect in a dozen different compounds varying with respect to the amine portion of the molecule.

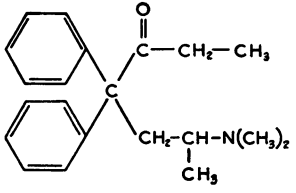
7. *Complete reduction of the ketone or removal of the ketone side-chain*

Reduction of the ketone markedly decreases, and removal of the ketone side-chain usually abolishes, analgesic effect. Also, if the side-chain is replaced by OH or by $OCOCH_3$ activity is usually abolished. The compounds in which CH_2NH_2 or $CH_2NHCOCH_3$ is substituted for the ketone side-chain are also without analgesic effect, even when the rest of the compound has the methadone or isomethadone constitution.

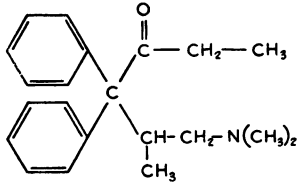
8. *Addition of substituents to, substitution, or removal of the phenyl groups*

The addition of a substituent to one or both phenyl groups, whether in *ortho-*, *meta-*, or *para*-position, to the extent that it has been investigated, has decreased markedly or abolished analgesic action. Also, shifting a phenyl group to a different carbon, which abolishes the quaternary carbon, or substitution of one or both phenyl groups by thienyl, by fluorene, or by ethyl, which does not abolish the quaternary carbon, decreases or abolishes analgesic effect. Again one must conclude that *a phenyl group, a quaternary carbon, and a tertiary amine at a suitable distance are optimal if not essential configurations for analgesic action.*

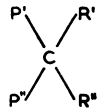
TABLE VII. METHADONE, ISOMETHADONE, AND THEIR DERIVATIVES



Methadone



Isomethadone



	P′	*P″*	*R′*	*R″*	*Analgesic activity* *
1	*dl*-C_6H_5	C_6H_5	$COCH_2CH_3$	$CH_2CH(CH_3)N(CH_3)_2$	Equivalent to that of morphine [55, 84]
2	*l*- ,,	,,	,,	,,	Twice that of 1 [55]
3	*d*- ,,	,,	,,	,,	One sixteenth that of 1 [55]
4	*dl*- ,,	,,	,,	$CH(CH_3)CH_2N(CH_3)_2$	Two thirds that of 1 [55]
5	*l*- ,,	,,	,,	,,	Twice that of 4 [55]
6	*d*- ,,	,,	,,	,,	One twentieth that of 4 [55]
			Variation in the basic group of R″		
7	C_6H_5	C_6H_5	$COCH_2CH_3$	$CH_2CH(CH_3)N(C_2H_5)_2$	Less than that of 1 [68]
8	,,	,,	,,	$CH_2CH(CH_3)N$ 	Less than that of 1 [13]
9	,,	,,	,,	$CH_2CH(CH_3)N$ 	Same as or greater than that of 1 [13]

* Many of the compounds in this table differ from methadone (or isomethadone) in more than one respect. Therefore, to represent more clearly the effect of a single change, the compounds have been numbered on the left, and each compound is compared with another from which it differs in one particular only. This also permits direct or indirect comparison with methadone (or isomethadone). For another extensive review of methadone- and isomethadone-like compounds, see Sander.[78]

TABLE VII (*continued*)

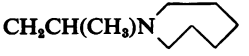
	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Variation in the basic group of R″ (*continued*)		
10	C_6H_5	C_6H_5	$COCH_2CH_3$	$CH_2CH(CH_3)N$ 	Slightly greater than that of 1 [28]
11	,,	,,	,,	$CH_2CH(CH_3)N$ 	None [12]
12	,,	,,	,,	$CH(CH_3)CH_2N(C_2H_5)_2$	Less than that of 4 [68]
13	,,	,,	,,	$CH(CH_3)CH_2N$ 	Less than that of 4 [68]
14	,,	,,	,,	$CH(CH_3)CH_2N$ 	Much less than that of 4 [92]
15	,,	,,	,,	$CH(CH_3)CH_2N$ 	None [12]
16	,,	,,	,,	$CH(CH_3)CH_2N$ 	None [12]
17	,,	,,	,,	$CH_2CH_2N(C_2H_5)_2$	Less than that of 34 [24]
18	,,	,,	,,	$CH_2CH_2N(C_3H_7)_2$	Much less than that of 34 [24]
19	,,	,,	,,	$CH_2CH_2NCH_3 \cdot C_3H_7$	Greater than that of 18; less than that of 34 [96]
20	,,	,,	,,	$CH_2CH_2NCH_3 \cdot CH_2$ 	None [13]
21	,,	,,	,,	$CH_2CH_2NCH_3 \cdot CH_2CH{:}\ CH_2$	About one half that of 34 [65]
22	,,	,,	,,	$CH_2CH_2N(CH_2CH{:}\ CH_2)_2$	Much less than that of 34 [65]
23	,,	,,	,,	CH_2CH_2N 	Less than that of 34 [13]

TABLE VII (*continued*)

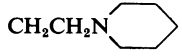
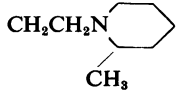
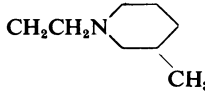
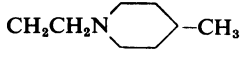
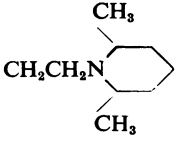
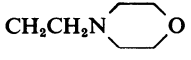
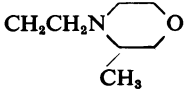
	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Variation in the basic group of R″ (*continued*)		
24	C_6H_5	C_6H_5	$COCH_2CH_3$		Same as that of 34 [92, 95]
25	,,	,,	,,		None [24]
26	,,	,,	,,		Much less than that of 34 [24]
27	,,	,,	,,		Less than that of 34 [21]
28	,,	,,	,,		Much less than that of 34 [24]
29	,,	,,	,,		Slightly less than that of 34 [92]
30	,,	,,	,,		One fourth that of 34 [24]

TABLE VII (*continued*)

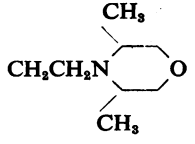
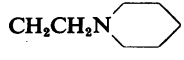
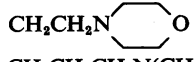
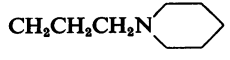
	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Variation in the basic group of R″ (*continued*)		
31	C_6H_5	C_6H_5	$COCH_2CH_3$		One fourth that of 34 [24]
			Variation in the aliphatic portion of R″		
32	C_6H_5	C_6H_5	$COOCH_2CH_3$	CH_2NH_2	Less than that of 34 [13]
33	,,	,,	,,	$CH_2N(CH_3)_2$	Less than that of 34 [24]
34	,,	,,	$COCH_2CH_3$	$CH_2CH_2N(CH_3)_2$	One half that of 1 ; two thirds that of 4 [28]
17	,,	,,	,,	$CH_2CH_2N(C_2H_5)_2$	Much less than one half that of 1 [68]
23	,,	,,	,,		Less than one half that of 1 [24]
24	,,	,,	,,		One half that of 1 [92, 95]
29	,,	,,	,,		One eighth that of 1 [92]
35	,,	,,	,,	$CH_2CH_2CH_2N(CH_3)_2$	One tenth that of 1 [28]
36	,,	,,	,,	$CH_2CH_2CH_2N(C_2H_5)_2$	None [24]
37	,,	,,	,,		None [68]
38	,,	,,	,,		None [24]

TABLE VII (*continued*)

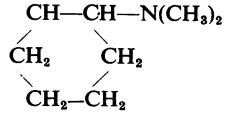
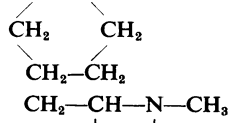
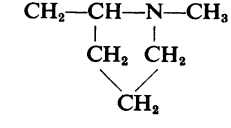
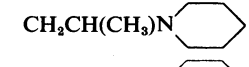
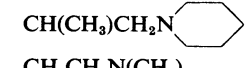
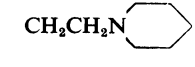
	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Variation in the aliphatic portion of R″ (*continued*)		
39	C_6H_5	C_6H_5	$COCH_2CH_3$	$CH_2CH(C_2H_5)N(CH_3)_2$	None [13]
40	,,	,,	,,		None [13]
41	,,	,,	,,		None [13]
42	,,	,,	,,		None [13]
			Variation in the hydrocarbon portion of R′		
43	C_6H_5	C_6H_5	$COCH_3$	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 1 [98]
44	,,	,,	,,		Much less than that of 9 [68]
45	,,	,,	,,		Much less than that of 13 [68]
46	,,	,,	,,	$CH_2CH_2N(CH_3)_2$	Much less than that of 34 [98]
47	,,	,,	,,	$CH_2CH_2N(C_2H_5)_2$	Less than that of 17 [13]
48	,,	,,	,,		None [98]

TABLE VII (*continued*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Variation in the hydrocarbon portion of R′ (*continued*)		
49	C_6H_5	C_6H_5	$COCH_3$	CH_2CH_2N⟨O⟩	Much less than that of 29 [13]
50	,,	,,	,,	$CH_2CH_2CH_2N$⟨⟩	None [68]
51	,,	,,	$COCH_2CH_2CH_3$	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 1 [98]
52	,,	,,	,,	$CH_2CH(CH_3)N$⟨⟩	Much less than that of 9 [98]
53	,,	,,	,,	$CH_2CH_2N(CH_3)_2$	None [98]
54	,,	,,	,,	$CH_2CH_2N(C_2H_5)_2$	None [96]
55	,,	,,	,,	CH_2CH_2N⟨⟩	Much less than that of 24 [98]
56	,,	,,	,,	CH_2CH_2N⟨O⟩	Much less than that of 29 [24]
57	,,	,,	,,	$CH_2CH_2CH_2N$⟨⟩	None [68]
58	,,	,,	$COCH_2CH{:}\,CH_2$	CH_2CH_2N⟨⟩	Same as that of 24 [13]
59	,,	,,	$COCH(CH_3)_2$	$CH_2CH(CH_3)N(CH_3)_2$	None [98]
60	,,	,,	,,	$CH(CH_3)CH_2N(CH_3)_2$	None [98]
61	,,	,,	,,	$CH_2CH_2N(CH_3)_2$	None [13]
62	,,	,,	,,	CH_2CH_2N⟨⟩	Much less than that of 24 [68]
63	,,	,,	$COCH_2CH_2CH_2CH_3$	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 1 [98]

TABLE VII (*continued*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Variation in the hydrocarbon portion of R′ (*continued*)		
64	C_6H_5	C_6H_5	$COCH_2CH(CH_3)_2$	CH_2CH_2N⟨⟩	Slightly less than that of 24 [13]
65	,,	,,	CO⟨⟩	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 1 [98]
66	,,	,,	,,	$CH_2CH_2N(CH_3)_2$	None [24]
67	,,	,,	,,	CH_2CH_2N⟨⟩	Much less than that of 24 [98]
68	,,	,,	,,	CH_2CH_2N⟨O⟩	None [13]
			Reduction of ketone to carbinol and acylation		
69	C_6H_5	C_6H_5	CH_2OH	$CH_2CH(CH_3)N(CH_3)_2$	Decreased to one fifth that of 1 [92]
70	,,	,,	,,	$CH(CH_3)CH_2N(CH_3)_2$	None [105]
71	,,	,,	,,	CH_2CH_2N⟨O⟩	Much less than that of 29 [92]
72	,,	,,	,,	CH_2CH_2N⟨⟩	Less than that of 24 [13]
73	,,	,,	CH_2OCOCH_3	CH_2CH_2N⟨O⟩	Greater than that of 71 [92]
74	,,	,,	$CHOHCH_3$	CH_2CH_2N⟨⟩	None [13]
75	*α-dl-* ,,	,,	$CHOHC_2H_5$	$CH_2CH(CH_3)N(CH_3)_2$	Less than one tenth that of 1 [55]
76	*α-l-* ,,	,,	,,	,,	7 times that of 3 [55]

TABLE VII (*continued*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Reduction of ketone to carbinol and acylation (*continued*)		
77	*α-d*-C_6H_5	C_6H_5	$CHOHC_2H_5$	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 2 [55]
78	*β-dl-* ,,	,,	,,	,,	Less than one fourth that of 1 [55]
79	*β-l-* ,,	,,	,,	,,	One ninth that of 2 [55]
80	*β-d-* ,,	,,	,,	,,	One half that of 3 [55]
81	*α-dl-* ,,	,,	$CH(OCOH)C_2H_5$	,,	4.5 times that of 75 [55]
82	*α-dl-* ,,	,,	$CH(OCOCH_3)C_2H_5$	,,	15 times that of 75 [55]
83	*α-l-* ,,	,,	,,	,,	2 times that of 76 [55]
84	*α-d-* ,,	,,	,,	,,	80 times that of 77; greater than that of 1 [55]
85	*β-dl-* ,,	,,	,,	,,	10 times that of 78 [55]
86	*β-l-* ,,	,,	,,	,,	20 times that of 79 [55]
87	*β-d-* ,,	,,	,,	,,	10 times that of 80 [55]
88	*α-dl-* ,,	,,	$CH(OCOC_2H_5)C_2H_5$	,,	7 times that of 75 [55]
89	*α-dl-* ,,	,,	$CH(OCOC_3H_7)C_2H_5$	,,	3 times that of 75 [55]
90	*α-dl-* ,,	,,	$CH(OCOC_6H_5)C_2H_5$	,,	Less than that of 75; almost abolished [28]
91	*α-dl-* ,,	,,	$CH(OCOCH_2C_6H_5)C_2H_5$	,,	Much less than that of 82 [92]
92	*α-dl-* ,,	,,	$CH[OCO(p\text{-}NHC_6H_5)]C_2H_5$	,,	Much less than that of 82; almost abolished [92]
93	*α-dl-* ,,	,,	$CH(OCOCH_2Cl)C_2H_5$	,,	Greater than that of 82 [91]
94	*α-dl-* ,,	,,	$CH(OCOCH_2Br)C_2H_5$	,,	Much less than that of 82 [91]
95	*α-dl-* ,,	,,	$CHOHC_2H_5$	$CH(CH_3)CH_2N(CH_3)_2$	Less than one twentieth that of 4 [55]
96	*α-l-* ,,	,,	,,	,,	Much less than that of 5 [55]
97	*α-d-* ,,	,,	,,	,,	Three fourths that of 6 [55]

TABLE VII (*continued*)

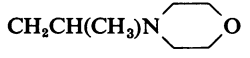
	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Reduction of ketone to carbinol and acylation (*continued*)		
98	*β-dl*-C_6H_5	C_6H_5	$CHOHC_2H_5$	$CH(CH_3)CH_2N(CH_3)_2$	One fifth that of 4 [55]
99	*β-l-* ,,	,,	,,	,,	Three fourths that of 6 [55]
100	*β-d-* ,,	,,	,,	,,	One fifth that of 5 [55]
101	*α-dl-* ,,	,,	$CH(OCOCH_3)C_2H_5$	,,	15 times that of 95 [55]
102	*α-l-* ,,	,,	,,	,,	Same as that of 97 [55]
103	*α-d-* ,,	,,	,,	,,	Much greater than that of 96 [55]
104	*β-dl-* ,,	,,	,,	,,	Slightly less than that of 98 [55]
105	*β-l-* ,,	,,	,,	,,	Two thirds that of 100 [55]
106	*β-d-* ,,	,,	,,	,,	Two thirds that of 99 [55]
107	*α-dl-* ,,	,,	$CH(OCOC_2H_5)C_2H_5$	,,	4 times that of 95 [55]
108	*α-dl-* ,,	,,	$CH(OCOC_6H_5)C_2H_5$	,,	Less than that of 95; almost abolished [28]
109	,,	,,	$CHOHC_2H_5$		None [92]
110	,,	,,	$CH(OCOCH_3)C_2H_5$	,,	Compare 109; greater than that of 10 [92]
111	,,	,,	$CH(OCOCH_2Cl)C_2H_5$	,,	Less than that of 110 [91]
112	,,	,,	$CH(OCOCH_2Cl)C_2H_5$	$CH(CH_3)CH_2N(CH_3)_2$	Less than that of 101 [91]
113	,,	,,	$CH(OCOC_2H_4Cl)C_2H_5$	,,	Less than that of 112 [91]
114	,,	,,	$CHOHC_2H_5$	$CH_2CH_2N(CH_3)_2$	Slightly less than that of 34 [92]
115	,,	,,	,,		Less than that of 29 [92]
116	,,	,,	$CH(OCOCH_3)C_2H_5$	,,	3 times that of 115 [92]
117	,,	,,	$CH(OCOCH_2Cl)C_2H_5$	,,	Much less than that of 116 [91]

TABLE VII (*continued*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Ketone of R′ changed to sulfone		
118	C_6H_5	C_6H_5	SO_2CH_3	CH_2CH_2N⟨⟩	Less than that of 24 [51]
119	〃	〃	$SO_2CH_2CH_3$	$CH_2CH(CH_3)N(CH_3)_2$	Two thirds that of 2 [51]
120	〃	〃	〃	$CH_2CH(CH_3)N$⟨⟩	Greater than that of 9 [51]
121	〃	〃	〃	$CH_2CH_2CH_2N$⟨⟩	Greater than that of 37 [51]
122	〃	〃	〃	CH_2CH_2N⟨⟩	Less than that of 24 [51]
123	〃	〃	〃	$CH_2CH_2N(CH_3)_2$	Less than that of 34 [51]
124	〃	〃	〃	$CH_2CH_2N(C_2H_5)_2$	Same as that of 17 [51]
125	〃	〃	$SO_2CH_2CH_2CH_3$	$CH_2CH(CH_3)N(CH_3)_2$	None [51]
126	〃	〃	SO_2⟨⟩CH_3	〃	None [51]
127	〃	〃	〃	CH_2CH_2N⟨⟩	None [51]
			Ketimines and their acyl derivatives		
128	C_6H_5	C_6H_5	$C(:NH)C_2H_5$	$CH_2CH(CH_3)N(CH_3)_2$	Same as that of 1 [19]
129	〃	〃	〃	$CH(CH_3)CH_2N(CH_3)_2$	One sixth that of 4 [28]
130	〃	〃	〃	$CH(CH_3)CH_2N(C_2H_5)_2$	Less than that of 12 [24]
131	〃	〃	〃	$CH(CH_3)CH_2N$⟨⟩	Much less than that of 13 [24]

TABLE VII (*continued*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Ketimines and their acyl derivatives (*continued*)		
132	C_6H_5	C_6H_5	$C(:NH)C_2H_5$	$CH(CH_3)CH_2N$ 	Slightly greater than that of 14 [5]
133	,,	,,	,,	CH_2CH_2N 	Greater than that of 24 [19]
134	,,	,,	,,	CH_2CH_2N 	Greater than that of 29 [19]
135	,,	,,	$C(:NH)C_3H_7$	$CH_2CH(CH_3)N$ 	Less than that of 9 [24]
136	,,	,,	$C(:NH)$ 	$CH_2CH(CH_3)N(CH_3)_2$	None [98]
137	,,	,,	$C(:NCOCH_3)C_2H_5$	,,	Much less than that of 128 [28]
138	,,	,,	,,	$CH(CH_3)CH_2N(CH_3)_2$	None [28]
139	,,	,,	,,	CH_2CH_2N 	Less than that of 133 [19]
140	,,	,,	,,	CH_2CH_2N 	Less than that of 134 [19]
141	,,	,,	$C(:NCOC_2H_5)C_2H_5$	,,	Same as that of 134 [19]
142	,,	,,	,,	$CH_2CH(CH_3)N(CH_3)_2$	Less than that of 128 [19]
			Ketone of R′ changed to carboxylate		
143	C_6H_5	C_6H_5	$COOCH_3$	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 1 [28]
144	,,	,,	,,	CH_2CH_2N 	Less than that of 24 [98]

TABLE VII (*continued*)

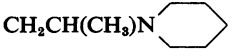
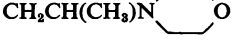
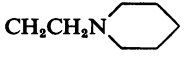
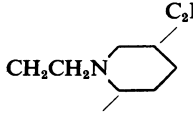
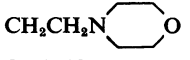
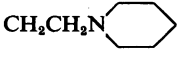
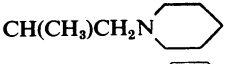
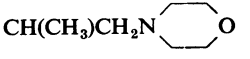
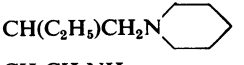
	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Ketone of R′ changed to carboxylate (*continued*)		
145	C_6H_5	C_6H_5	$COOCH_2CH_3$	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 1 [28]
146	,,	,,	,,	$CH_2CH(CH_3)N$ 	Much less than that of 9 [13]
147	,,	,,	,,	$CH_2CH(CH_3)N$ 	Much less than that of 10 [13]
148	,,	,,	,,	$CH_2CH_2N(CH_3)_2$	Less than that of 34 [24]
149	,,	,,	,,	$CH_2CH_2N(C_2H_5)_2$	Less than that of 17 [24]
150	,,	,,	,,	CH_2CH_2N 	Less than that of 24 [98]
151	,,	,,	,,	C_2H_5  CH_3	Much less than that of 24 [13]
152	,,	,,	,,	CH_2CH_2N 	Same as that of 29 [92]
33	,,	,,	,,	$CH_2N(CH_3)_2$	Less than that of 34 [13]
32	,,	,,	,,	CH_2NH_2	Same as that of 33 [13]
153	,,	,,	$COOCH(CH_3)_2$	$CH_2CH(CH_3)N(CH_3)_2$	None [28]
154	,,	,,	,,	CH_2CH_2N 	Less than that of 150 [13]
155	,,	,,	$COO(CH_2)_3CH_3$	,,	Less than that of 150 [13]

TABLE VII (*continued*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Ketone of R′ changed to carboxylate (*continued*)		
156	C_6H_5	C_6H_5	$COOCH_2CH(CH_3)_2$	CH_2CH_2N⟨O⟩	Less than that of 152 [13]
157	,,	,,	$COOCH_2$⟨⟩	CH_2CH_2N⟨⟩	Less than that of 150 [13]
			Ketone of R′ changed to acide amide		
158	C_6H_5	C_6H_5	$CONH_2$	$CH_2CH(CH_3)N(CH_3)_2$	None [20]
159	,,	,,	,,	$CH_2CH(CH_3)N(C_2H_5)_2$	None [20]
160	,,	,,	,,	$CH_2CH(CH_3)N$⟨⟩	None [20]
161	,,	,,	,,	$CH_2CH_2CH_2N(CH_3)_2$	None [20]
162	,,	,,	,,	$CH_2CH_2CH_2N$⟨⟩	None [20]
163	,,	,,	,,	$CH_2CH_2N(CH_3)_2$	None [20]
164	,,	,,	,,	$CH_2CH_2N(C_2H_5)_2$	None [68]
165	,,	,,	,,	CH_2CH_2N⟨⟩	None [20]
166	,,	,,	,,	CH_2CH_2N⟨⟩	None [20]
167	,,	,,	,,	CH_2CH_2N⟨O⟩	None [20]
168	,,	,,	,,	$CH_2N(CH_3)_2$	None [13]
169	,,	,,	,,	CH_2N⟨⟩	None [13]

TABLE VII (*continued*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Other changes in R′		
170	C_6H_5	C_6H_5	$CH_2CH_2CH_3$	$CH_2CH(CH_3)N(CH_3)_2$	One twentieth that of 1 *
171	,,	,,	$CH_2CH_2CH_2OH$	,,	Less than that of 170 *
172	,,	,,	$CH_2CH_2CH_2OCOCH_3$	,,	Same as that of 171 *
173	,,	,,	$CH_2CH_2COOCH_3$	,,	Nearly abolished *
174	,,	,,	$CH_2CH_2CH_3$	$CH(C_2H_5)N(CH_3)_2$	None *
175	,,	,,	,,	CH_2NH_2	None [83]
176	,,	,,	$CH(CH_3)_2$	,,	None [83]
177	*dl-* ,,	,,	H	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 1 [55]
178	*l-* ,,	,,	,,	,,	1.5 times that of 177 [55]
179	*d-* ,,	,,	,,	,,	None *
180	*dl-* ,,	,,	,,	$CH(CH_3)CH_2N(CH_3)_2$	Nearly abolished [55]
181	,,	,,	OH	,,	None [66]
182	,,	,,	,,	$CH(CH_3)CH_2N(C_2H_5)_2$	None [77]
183	,,	,,	,,		None [77]
184	,,	,,	,,		None [77]
185	,,	,,	,,	$CH(C_2H_5)CH_2N(CH_3)_2$	None [77]
186	,,	,,	,,		None [77]
187	,,	,,	,,	$CH_2CH_2NH_2$	None [1]
188	,,	,,	,,	$CH_2CH_2N(CH_3)_2$	None [56]

* Eddy, N. B., unpublished results

TABLE VII (*continued*)

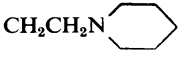
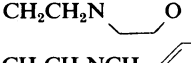
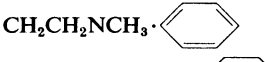
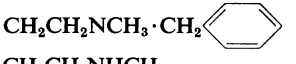
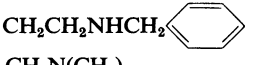
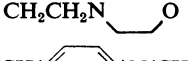
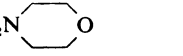
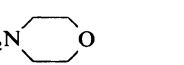
	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Other changes in R′ (*continued*)		
189	C_6H_5	C_6H_5	OH	$CH_2CH_2N(C_2H_5)_2$	None [1]
190	,,	,,	,,	$CH_2CH_2N(C_3H_7)_2$	None [1]
191	,,	,,	,,	$CH_2CH_2N(C_4H_9)_2$	None [1]
192	,,	,,	,,	$CH_2CH_2N(CH_2CH{:}CH_2)_2$	None [1]
193	,,	,,	,,		None [77]
194	,,	,,	,,		None [7]
195	,,	,,	,,		None [1]
196	,,	,,	,,		None [65]
197	,,	,,	,,	$CH_2CH_2NHCH_3$	None [65]
198	,,	,,	,,	$CH_2CH_2NHC_2H_5$	None [1]
199	,,	,,	,,		None [1]
200	,,	,,	,,	$CH_2N(CH_3)_2$	None [56]
201	,,	,,	,,		None [56]
202	,,	,,	$OCOCH_3$	$CH_2CH_2N(CH_3)_2$	None [65]
203	,,	,,	,,		None [7]
204	,,	,,	,,		None [56]

TABLE VII (*continued*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Other changes in R′ (*continued*)		
205	C_6H_5	C_6H_5	$OCOCH_2CH_3$	$CH_2CH(CH_3)N(CH_3)_2$	One twelfth that of 1 *
206	,,	,,	,,	$CH_2CH_2N(CH_3)_2$	None [65]
207	,,	,,	,,		None [7]
208	,,	,,	CH_2NH_2	$CH_2CH(CH_3)N(CH_3)_2$	None [83]
209	,,	,,	,,	$CH(CH_3)CH_2N(CH_3)_2$	None [83]
210	,,	,,	$CH_2NHCOCH_3$	$CH_2CH(CH_3)N(CH_3)_2$	None [68]
211	,,	,,	,,	$CH(CH_3)CH_2N(CH_3)_2$	None [68]
212	,,	,,		$CH_2CH(CH_3)N(CH_3)_2$	None [68]
213	,,	,,	,,	$CH(CH_3)CH_2N(CH_3)_2$	None [68]
			Variations in P′ and P″		
214	C_6H_5	*p*-$CH_3C_6H_4$	COC_2H_5		None [24]
215	,,	*p*-ClC_6H_4	,,	$CH_2CH(CH_3)N(CH_3)_2$	None [91]

* Eddy, N. B., unpublished results

TABLE VII (*continued*)

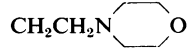
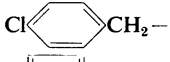
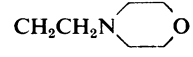
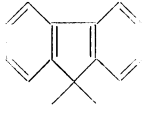
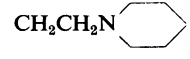
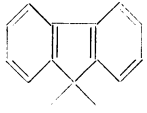
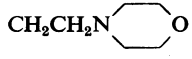
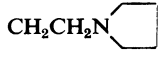
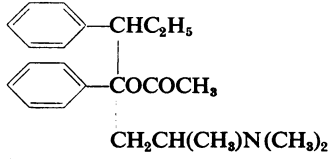
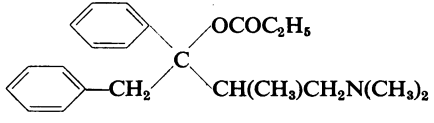
	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Variations in P′ and P″ (*continued*)		
216	*p*-ClC_6H_4	*p*-ClC_6H_4	COC_2H_5	$CH_2CH(CH_3)N(CH_3)_2$	None [99]
217	C_6H_5	,,	,,	$CH_2CH_2N(CH_3)_2$	None [13]
218	,,	,,	$CHOHC_2H_5$	$CH_2CH(CH_3)N(CH_3)_2$	None [91]
219	,,	,,	$CH(OCOCH_3)C_2H_5$	,,	None [91]
220	,,	*p*-BrC_6H_4	COC_2H_5	$CH(CH_3)CH_2N(CH_3)_2$	None [91]
221	,,	*o*-$CH_3C_6H_4$	,,		Much less than that of 29 [24]
222	,,	*m*-OHC_6H_4	,,	,,	Much less than that of 29 [13]
223	,,	*m*-$OCH_3C_6H_4$	,,	,,	Much less than that of 29 [13]
224	,,		,,	$CH_2CH(CH_3)N(CH_3)_2$	None [99]
225	,,		$COOC_2H_5$		Less than that of 152 [15]
226		,,	,,	,,	Much less than that of 152 [58]
227	,,	,,	COC_2H_5	$CH_2CH(CH_3)N(CH_3)_2$	Much less than that of 1 [69, 81]
228			$COOC_2H_5$		Much less than that of 150 [96]

TABLE VII (*concluded*)

	P′	*P″*	*R′*	*R″*	*Analgesic activity*
			Variations and P′ in P″ (*continued*)		
229			$COOC_2H_5$		Less than that of 152 [96]
230	C_2H_5	C_2H_5	$COOCH(CH_3)_2$		None [96]
231					Much less than that of 82 *
232					One tenth that of 4 [42]

* Eddy, N. B., unpublished results

Dithienylbutenylamine Derivatives

The report of Adamson & Green [3] in 1950 that morphine-like analgesic action was produced by dithienylbutenylamines seemed at first a radical departure from any suggestions that had been made with respect to the relation of structure to analgesic action. A closer inspection of the group indicates, however, that the most active compounds possess characteristics which bring them into harmony in several respects with other morphine-like analgesics. The variations which have been described in this group of compounds are illustrated in Table VIII.

1. *Variations in the amino substituents*

Whether the compounds contain an allyl or a butenyl chain, maximum activity is attained with a tertiary amine in which the amino substituents are dimethyl, methylethyl, or diethyl. Activity is closely similar when the tertiary amine is formed by pyrrolidine, piperidine, or diethyl in the butenyl compounds. Molecular models of these compounds indicate that in each of these cases steric forces create a pseudopiperidine ring by approximation of a carbon of the amine and a carbon of one of the thienyl groups (see page 995).

2. *Variation in the carbon chain between the dithienyl and the amine*

The highest degree of activity is attained when the hydrocarbon is butenyl, the amine remaining the same. Activity is reduced markedly by the removal or addition of a single carbon, and abolished by the addition of more than one carbon. Effectiveness is also decreased if a methyl group is attached to the β-carbon ($>C=\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}CH_2N<$).

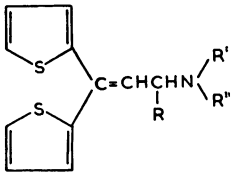
Strictly speaking there is no quaternary carbon in this group of compounds. There is, however, what might be called a quasiquaternary carbon in those compounds in which a double bond exists between carbons 1 and 2, since carbon 1 is then joined only to other carbon atoms. This semblance of a quaternary carbon is lost when the double bond is saturated, and concomitantly analgesic activity is reduced markedly whatever the nature of the amine.

3. *Substitution or modification of the dithienyl groups*

Analgesic activity is decreased by substitution in the thienyl groups and by replacement of one or both thienyls by phenyl.[2] It is most surprising that phenyl cannot be substituted for thienyl in the dithienylbutenylamines nor thienyl for phenyl in the methadone series without marked loss of analgesic effectiveness.

Two of the dithienylbutenylamines ($NR'R''=N(CH_3)_2$ or N ) have been resolved into their optical isomers.[2]

TABLE VIII. DITHIENYLBUTENYLAMINE DERIVATIVES



Structural change	*Analgesic action*
Variation in the amino substituents (R′, R″) when R = H *	
$NR'R'' = N(CH_3)_2$	Less than one tenth
„ $= NCH_3 \cdot CH(CH_3)_2$	None
„ $= N(C_2H_5)_2$	About one fifth
„ $= N$ 	About one tenth
„ $= N$ 	About one tenth
Variation in the amino substituents (R′, R″) when R = CH_3 *	
$NR'R'' = NH_2$	None
„ $= NHCH_3$	Less than one tenth
„ $= NHC_2H_5$	Slightly less than one tenth
„ $= NHC_4H_9$	None
„ $= N(CH_3)_2$	Equivalent to that of morphine
„ $= NCH_3 \cdot C_2H_5$	Slightly greater than that of morphine
„ $= NCH_3 \cdot C_3H_7$	About one tenth
„ $= NCH_3 \cdot CH(CH_3)_2$	About three tenths
„ $= NCH_3 \cdot CH_2$ 	None
„ $= N(C_2H_5)_2$	Equivalent to that of morphine
„ $= N(C_3H_7)_2$	None
„ $= N(CH_2CH : CH_2)_2$	About one fifth
„ $= N$ 	Slightly less than that of morphine
„ $= N$ 	Equivalent to that of morphine
„ $= N$ 	About one fifth
„ $= N$ 	About one fifth

* Analgesic action is expressed as the ratio of activity to that of morphine as 1, based on the work of Green.[19]

TABLE VIII (*concluded*)

Structural change	*Analgesic action*
Variation in R when NR′R″ is $N(CH_3)_2$ *	
R = H	Less than one tenth
,, = CH_3	Equivalent to that of morphine
,, = C_2H_5	Less than one tenth
,, = C_3H_7	None
,, = $CH(CH_3)_2$	None
,, = CH_2–C$_6$H$_5$	None
,, = CH_2OCH_3	None
,, = –C$_6$H$_5$	Slightly less than one tenth
Saturation of the double bond between carbon 1 and carbon 2 **	
R = CH_3 ; NR′R″ = $N(CH_3)_2$	About one half
,, ,, = $NCH_3 \cdot C_2H_5$	About one fifth
,, ,, = $N(C_2H_5)_2$	Slightly less than one fifth
,, ,, = N(C$_4$H$_8$)	One half
,, ,, = N(C$_6$H$_{10}$)	One seventh
Substitution of phenyl for thienyl	
C$_6$H$_4$(CH)–C=CHCH(CH$_3$)N(CH$_3$)$_2$	Decreased [71]
C$_4$H$_2$S(CH)–C=CHCH(CH$_3$)N(CH$_3$)$_2$	Decreased [2]

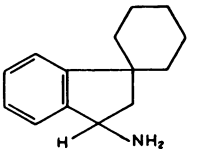
* Analgesic action is expressed as the ratio of activity to that of morphine as 1, based on the work of Green. [39]

** Analgesic action is expressed as the ratio of activity to that of the corresponding unsaturated compound (Eddy & Leimbach [26]). A similar relationship was described by Adamson, Duffin & Green.[2]

Spirocyclohexylindanes

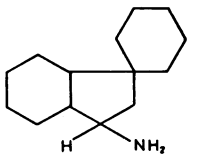
Schwartzman,[82] working on the hypothesis that a quaternary carbon separated by CH_2–CH_2 from an amino group is an essential structure for significant analgesic action, synthesized a group of spirocyclohexylindanes. Some of these compounds have been examined for analgesic activity.* The formulae of these compounds are shown in Table IX. In each case the figure in bold type on the right of the formula is the dose in mg/kg which produces an analgesic effect in 50% of the animals (mice) tested. The results support the hypothesis to the extent that an analgesic effect as great as, or a little greater than, that of codeine was demonstrated in at least two instances. The points of similarity between the structure of the more active compounds in this group and the structure of morphine are a quaternary carbon with a phenyl group attached, and a tertiary amine separated by a CH_2–CH_2 linkage from the quaternary carbon.

TABLE IX. SPIROCYCLOHEXYLINDANE DERIVATIVES [82,*]



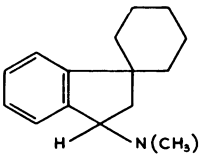
35

Spiro-(1,1′-cyclohexyl-3′-aminoindane)



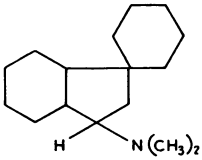
30

Spiro-(1,1′-cyclohexyl-3′-aminohexahydroindane)



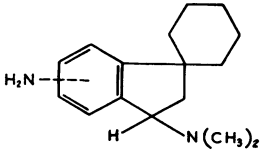
40

Spiro-(1,1′-cyclohexyl-3′-dimethylaminoindane)



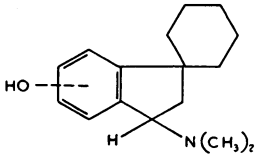
25

Spiro-(1,1′-cyclohexyl-3′-dimethylaminohexahydroindane)



10

Spiro-(1,1′-cyclohexyl-3′-dimethylamino-X′-aminoindane)



12.5

Spiro-(1,1′-cyclohexyl-3′-dimethylamino-X′-hydroxyindane)

* Eddy, N. B., unpublished results

Antagonistic Effect of N-Allylnormorphine

In 1914, Pohl [73] showed that N-allylnorcodeine could antagonize significantly the respiratory depressant effect of morphine. Little notice was taken of this report, and nearly thirty years passed before Hart,[45] Hart & McCawley,[46] and Unna [97] demonstrated a similar effect with N-allylnormorphine. This drug exhibits some morphine-like effects when given alone in animals or man, but when administered shortly before or after morphine diminishes or suppresses most of the latter's effects. There are species differences in the effects of N-allylnormorphine and quantitative differences in its antagonism to morphine. For example, N-allylnormorphine has little analgesic action in animals,[90, 97] but may be analgesic in man;[54] it readily antagonizes the analgesic action of morphine in animals,[90, 97] but in suitable dose ratios permits morphine to exhibit its full analgesic action in man.[54] N-allylnormorphine has no effect on the convulsant action of morphine [52] and in most experiments has had little influence on the lethal effect of morphine in animals;[34] its antagonism to respiratory depression has been most striking and has been of life-saving importance in man.[4, 18, 32, 94] In suitably designed experiments N-allylnormorphine has antagonized the exciting effect of morphine in cats,[97] its narcotic effect in animals and man,[4, 90, 97] and its effect on the heart-rate and blood-pressure,[90] on the pupil,[90] on the intestine,[43] on urinary output,[103] and on body temperature.[90] N-allylnormorphine does not produce a morphine-like euphoric effect in post-addicts,[101] rather it is dysphoric, especially on repeated administration, and when administered to an addicted individual (man [101] or monkey [48]) it promptly precipitates a typical abstinence syndrome, which is related in its intensity to the duration of an addiction. The precipitation of the abstinence syndrome may be interpreted as an effect of antagonism to the drug of addiction; it has been demonstrated as early as 48 hours after the beginning of narcotic administration.[101]

N-allylnormorphine exerts its antagonistic action not only against morphine but, as one might expect, against similar actions of morphine derivatives.[18, 47, 94] It also antagonizes the morphine-like effects of the several classes of potent analgesics—methadone,[32, 47, 90] pethidine, [21, 74] N-methylmorphinan,[18, 23] and dithienylbutenylamine [21, 29] derivatives. This broad range of antagonism is further demonstrated by the precipitation of abstinence phenomena by N-allylnormorphine, when the addicting agent belongs to any one of these classes of compounds and the addicted individual is man [102,*] or monkey.[48]

* Isbell, H., personal communication

The antagonistic action to morphine-like effects is possessed by other N-alkyl derivatives of morphine, particularly when there are three carbons in a straight chain in the alkyl group.[40, *] It is exhibited also by similar N-alkyl derivatives in the morphinan series, such as the N-allyl derivative of 3-hydroxy- or 3-methoxy-morphinan and the N-propyl and N-propargyl derivatives of 3-hydroxymorphinan.[44, **] The N-allyl derivative of pethidine has limited antagonistic effect on the respiratory depression produced by morphine, levorphan, and methadone, but does not antagonize the analgesic action of these compounds.[21]

Discussion

As early as 1902 Whalen [100] linked the analgesic properties of morphine to a phenanthrene skeleton, and this was the general conception for nearly 40 years. On this basis many phenanthrene derivatives were made, but disappointingly little analgesic effect was found.[31, 89]

A new direction to the line of thought was given by the discovery of pethidine, a 4-phenylpiperidine, and it was very shortly pointed out that a phenylpiperidine moiety is clearly recognizable in the morphine structure (see Table II, 19, page 949). This led Schaumann [79, 80] to introduce the term " analgiphoric " group and to postulate that for a substance to possess morphine-like analgesic activity, a 1-methyl-4-phenylpiperidine system containing a quaternary carbon at position 4 is necessary. Rupture of the piperidine ring nearly abolishes analgesic activity in the morphine or pethidine series (see Tables I and V, pages 944 and 961). Schaumann's theory seemed to break down when high analgesic activity was found for the methadones (see Table VII, page 969), which do not contain a piperidine ring. Schaumann[80] met this situation with the suggestion that perhaps the analgiphoric groups of the methadones are: (1) a quaternary carbon atom; (2) a benzene nucleus attached to the quaternary carbon; and (3) a tertiary amino group separated from that carbon by two methylene groups. These features he pointed out are held in common with morphine and pethidine.

The dithienylbutenylamines (see Table VIII, page 988), appeared to constitute a greater departure in structure than the methadones, but Lapière [53] pointed out that the phenyl groups of methadone had been replaced by isosteres and that the central carbon atom, although no longer truly quaternary, was nevertheless linked only to other carbon atoms. Supporting Schaumann's 4-phenylpiperidine theory, Gero [36] recently postulated that in both methadone and the dithienylbutenylamines, there were certain steric factors operative which forced a part of the molecule

* Pfister, C. & Winter, C. A., personal communication

** Eddy, N. B. unpublished results; Silberschmidt, R., personal communication

into a position resembling a piperidine ring, a so-called "pseudopiperidine ring". Molecular models illustrate this possibility. Compare photographs of such models for methadone and dithienylbutenylamine with those of morphine, morphinan, and pethidine (see pages 994-995). These photographs show the existence of such a piperidine or pseudopiperidine system in all of these compounds.

Beckett & Casy,[6] also approaching the problem from a stereochemical viewpoint, have suggested that potent analgesic compounds must have an over-all structure which results in a close surface fit with an analgesic receptor.* On the other hand, Pfeiffer [72] calls attention to the distance between the essential elements of prosthetic groups on analgesic compounds and believes that potency is related to a specific spatial relationship of these groups. In other words, Beckett seems to emphasize the semi-rigidity of the molecule and Pfeiffer the spatial relationship of prosthetic groups as the basis for a fit with the receptor surface. There is still lacking, as Bergel [11] points out, adequate knowledge of the physicochemical properties of analgesic substances, as well as of receptor surfaces, and especially of the effect on such properties of what appear to be minor changes in structure.

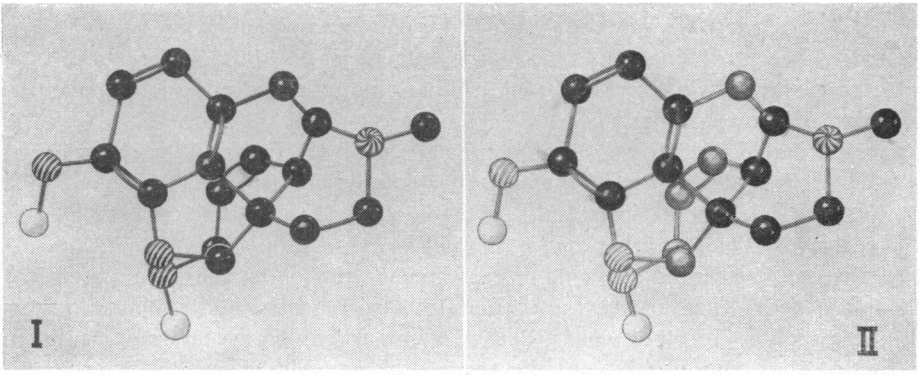
Molecular Models

As a means of illustrating the similarities of the relationships of the atoms in the various groups of morphine-like substances, molecular models (see pages 994-995) have been made of morphine, racemorphan, pethidine, methadone, and 3-dimethylamino-1,1-di-(2′-thienyl)-1-butene. In these models the hydrogen atoms have not been included, except in the OH groups of morphine and racemorphan, because they would unduly complicate the model and are not essential for the present purpose.

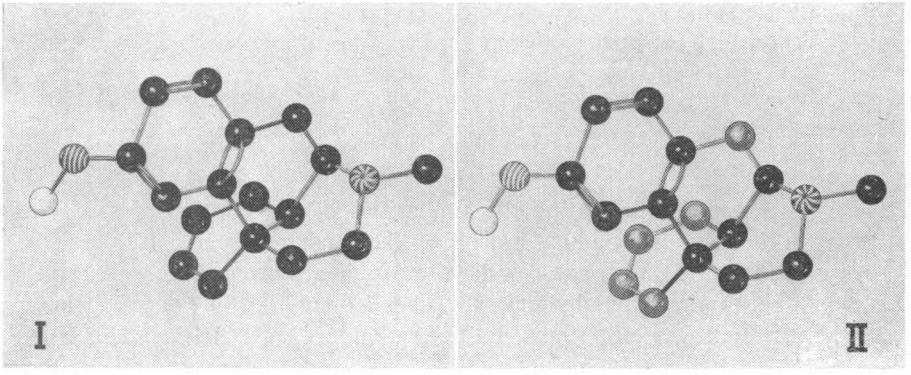
Each of the models has been photographed, and two copies of each photograph, differently prepared, have been reproduced. In all cases photograph I has been taken from essentially the same angle, and has only been retouched to show the difference between the carbon, hydrogen, nitrogen, oxygen, and sulfur atoms. In photograph II certain parts have been under-developed in order to make it easier to visualize the phenylpiperidine (or simulated piperidine) similarity in these compounds.

* Compare the recent work of Lindsey & Barnes [67] on the stereochemical configuration of codeine.

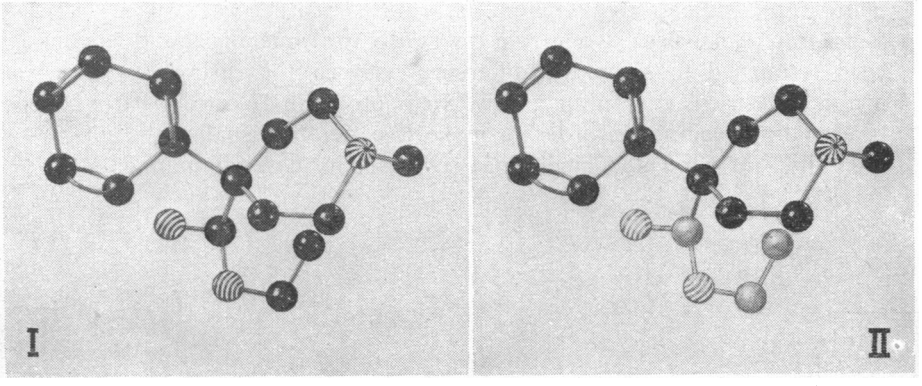
FIG. 1. MOLECULAR MODELS



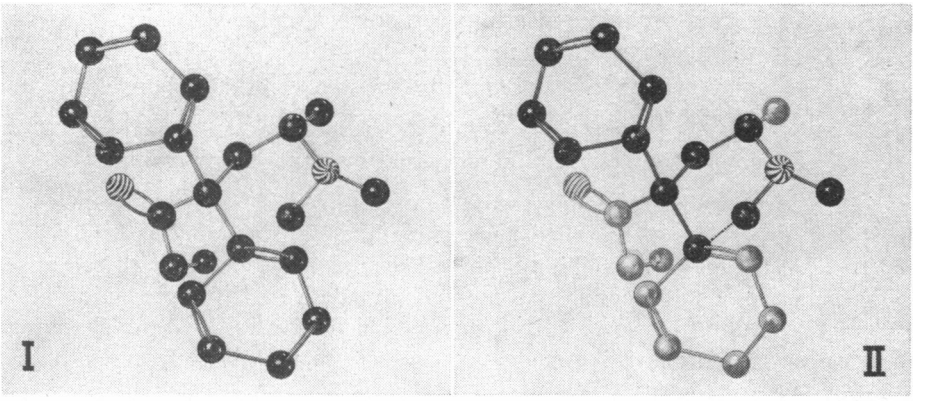
Morphine



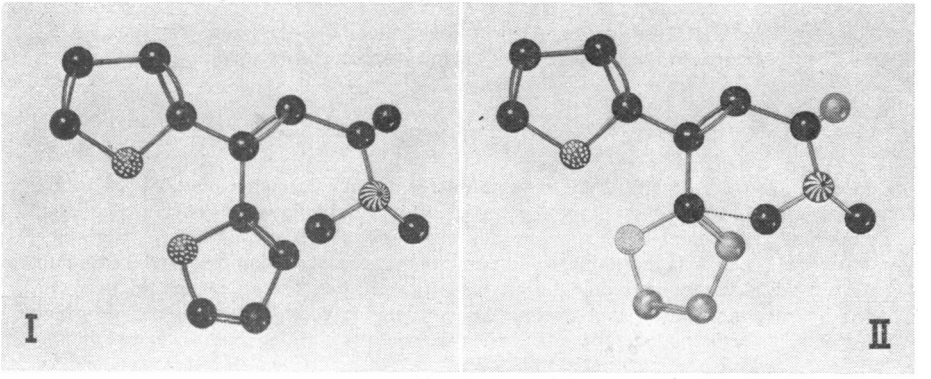
3-Hydroxy-N-methylmorphinan



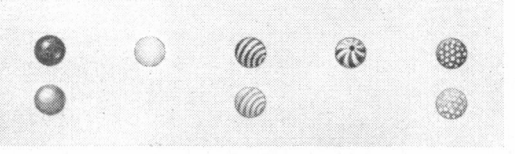
1-Methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester



4,4-Diphenyl-6-dimethylaminoheptanone-3



3-Dimethylamino-1,1-di-(2'-thienyl)-1-butene



KEY: Carbon Hydrogen Oxygen Nitrogen Sulfur

Conclusions

1. The following features seem to stand out for known compounds possessing morphine-like analgesic activity:

(*a*) A tertiary nitrogen, the group on the nitrogen being relatively small;

(*b*) A central carbon atom none of whose valences are connected with hydrogen;

(*c*) A phenyl group, or a group isosteric with phenyl, which is connected with the central carbon atom;

(*d*) Maximum activity is obtained when the central carbon atom is connected with the nitrogen by a two-carbon chain.

2. All potent analgesics are antagonized by N-allylnormorphine.

3. Compounds possessing the features outlined in 1, including many among the groups of so-called " morphine-like " analgesics (see Tables I, V, VII, VIII), may not exhibit morphine-like analgesic action and, therefore, the presence of those conditions cannot be made a basis for prediction of analgesic action. However, all substances which have justified the characterization of morphine-like analgesics conform to the above features.

ACKNOWLEDGEMENT

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RÉSUMÉ

Cet article est le second d'une série consacrée aux médicaments synthétiques à effet morphinique. Il traite des rapports entre la structure chimique et l'effet analgésique. Comparant et étudiant les structures des composés possédant un effet analgésique comparable à celui de la morphine, les auteurs concluent que ces composés ont en commun les caractères suivants: un atome d'azote tertiaire auquel est fixé un groupe relativement petit; un carbone central dont aucune des valences ne porte un atome d'hydrogène; un groupe phényle ou isostérique du phényle relié au carbone central. L'activité du composé est maximum lorsque l'atome de carbone central est lié à l'azote par une chaîne dicarbonique. Tous les analgésiques très actifs ont pour antagoniste la N-allylnormorphine.

Les composés possédant les caractères énumérés ci-dessus, y compris plusieurs de ceux qui appartiennent au groupe des substances dites analogues de la morphine, ne présentent pas des propriétés analgésiques analogues à celles de la morphine. Il n'est donc pas possible de prévoir si des substances présentant ces caractères auront des propriétés analgésiques. Cependant, toutes les substances analgésiques à effet morphinique les possèdent.

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