SYNTHETIC ANALGESICS

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I. *Introduction*

(a) *Pain and Analgesia.*—The distressing and isolating effect of pain [1, 2, 3] has made its removal or alleviation one of the main objectives of medicine throughout the ages. From very early times the use of opium as an analgesic was widely recognised, and, even at the present day, morphine is still the mainstay of the doctor's armoury in his fight against pain in all its most distressing forms.

Morphine was first isolated from opium by Sertuerner in 1805, and was recognised as being the main analgesic constituent of the mixture of alkaloids present in the natural extract of poppy seeds. Since that date the chemist has played his part in the war against pain by the elucidation of the chemical structure of morphine, the preparation of more active derivatives, and the total syntheses of compounds possessing true analgesic activity.

Analgesics are considered pharmacologically as belonging to the class of symptomatic drugs, having mainly a depressant action on the central nervous system (C.N.S.). There are some indications that the autonomic nervous system may also be involved.[4, 5, 6] They differ from other members of this group such as general anæsthetics, hypnotics, sedatives, and anti-epileptics in that they diminish or abolish the sensation of pain without stupefaction or loss of consciousness. In non-toxic quantities they do not, however, lower the threshold for touch, vibration, 2-point discrimination, smell, and hearing.[7] The quantitative testing of analgesia in animals and man has been thoroughly investigated in recent years, many species of animals and a variety of pain-stimuli having been employed.[8, 9, 10, 11, 12, 13, 14] So far, no one method has been accepted as being markedly superior to all

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[1] E. D. Adrian, "The Physiology of Pain", *Practitioner*, 1947, **158**, 76.

[2] H. G. Wolff and J. D. Hardy, "The Nature of Pain", *Physiol. Rev.*, 1947, **27**, 167.

[3] K. D. Keele, *Lancet*, 1948, II, 6.

[4] A. C. Ivy, F. R. Goetzl, S. C. Harris, and D. Y. Burrill, *Quart. Bull. Northwestern Univ. Med. School*, 1944, **18**, 298.

[5] E. G. Gross, E. M. Christensen, H. Holland, and H. R. Carter (in the press).

[6] F. J. Friend and S. C. Harris, *J. Pharm. Exp. Ther.*, 1948, **93**, 161.

[7] A. Wickler, H. Goodell, and H. G. Wolff, *ibid.*, 1945, **83**, 294.

[8] H. Kreuger, N. B. Eddy, and M. Sumwalt, "The Pharmacology of the Opium Alkaloids", U.S. Public Health Service Suppl. 165, Table 3, p. 20.

[9] H. G. Wolff, J. D. Hardy, and H. Goodell, *J. Clin. Invest.*, 1940, **19**, 649.

[10] *Idem, ibid.*, p. 659.

[11] G. Woolfe and A. D. Macdonald, *J. Pharm. Exp. Ther.*, 1944, **80**, 300.

[12] N. Ercoli and M. N. Lewis, *ibid.*, 1945, **84**, 301.

[13] O. L. Davies, J. Raventos, and A. L. Walpole, *Brit. J. Pharmacol.*, 1946, **1**, 255.

[14] C. C. Pfeiffer, R. R. Sonnenschein, L. Glassman, E. H. Jenney, and S. Bogolub, *Ann. New York Acad. Sci.*, 1948, **51**, 21.

others, and, as various animal species exhibit varying sensitivity to different analgesics, results obtained in such animal experiments must be submitted to the final clinical test in man. Moreover, in evaluating the relative potencies of two drugs, unless the log. dose–response graphs are parallel, the ratio will vary for all dose levels and it is impossible to predict which dose level in an animal is equivalent to a clinical dose in man.[13, 14a] Nevertheless the screening tests now at the disposal of the pharmacologist are invaluable in guiding chemical research and sparing clinical trials.

(b) *General Physical and Biochemical Properties of Analgesics.*—While the general anæsthetics and hypnotics belong mainly to the chemical class of neutral or slightly acidic compounds such as hydrocarbons, alcohols, ethers, aldehydes, alkyl halides, and aliphatic and alicyclic amides, all well-established potent analgesics, both natural and synthetic, are characterised by a tertiary nitrogen atom. Their strongly basic properties are of great clinical importance, as it makes possible their parenteral administration in the form of water-soluble salts. Recently analgesic properties have been claimed for 3 : 3-diphenyl-1-ethyl-2-pyrrolidone [15], but it remains to be seen whether this non-basic compound belongs to the same class as morphine, amidone, pethidine, etc., or to the much less potent class of " antalgics " and the " euphorigenics " of the cannabinol family (cf. I, c) which are all non-basic in nature.

The physicochemical significance of other functional groups in the morphine series and in some of the new synthetic drugs, such as the phenolic hydroxyl, ether, carbonyl, or carboalkoxyl groups, has not so far been fully clarified. The rôle of these groups and of the aromatic and hydroaromatic ring systems in the production of pharmacological effects will be considered later. There is no doubt that analgesic activity is closely linked with spatial molecular configuration, and marked differences can be noted between both geometrical and optical isomers. Such relationships are difficult to resolve in the complex morphine structure but have been successfully studied in the much simpler synthetic analgesics. A short discussion on the geometrical isomerism introduced by condensed ring systems, such as that of morphine, will be dealt with under the appropriate heading. We will also consider later (cf. IV) the general relationship between chemical constitution and analgesic action, but here it may be said that it is probable that a more complete elucidation of this problem will only be arrived at through systematically extended physicochemical investigations such as comparative *X*-ray crystallographic studies, measurements of the inter-atomic distances, and evaluation of the electrostatic effects of the functional groups. The last two, indeed, have been made the subject of preliminary speculation by C. C. Pfeiffer.[16, 17]

[14a] R. H. K. Foster and A. J. Carman, *J. Pharm. Exp. Ther.*, 1947, **91**, 195.

[15] F. F. Blicke and A. J. Zambito, Abstract of Papers Presented at the 113th Meeting of the American Chemical Society, Chicago, Ill., April 19—23, 1948, Div. Med. Chem., 1K—3K.

[16] C. C. Pfeiffer, J. Santos-Martinez, and T. R. Sherrod, *Fed. Proc.*, 1948, **7**, 248.

[17] C. C. Pfeiffer, *Science*, 1948, **107**, 94.

Moreover, as the effect of a drug is not only determined by its own chemical and physical properties but also by those of the substances of the tissue interacting with it, a more intensive study of the biochemistry of analgesics appears to be necessary. Up to the present, we only know that, in difference from the effect of narcotics such as barbiturates and gaseous anæsthetics, analgesics do not appear to exercise measurable influence on the oxygen metabolism of the C.N.S. when used in physiological concentrations.

Although it was reported by J. H. Quastel and A. H. M. Wheatley [18] that higher concentrations of morphine under certain conditions affected the oxygen uptake of brain tissue, results obtained by other investigators,[19, 20, 21, 22] using in addition newer synthetic analgesics, confirmed the statement of A. D. Welch and E. Bueding [23] that analgesic action cannot yet be correlated with any effect on the respiratory system of the C.N.S. Studies with other enzyme systems such as cholinesterase [24, 25] present a similar state of affairs. Pfeiffer's hypothesis [16] that analgesics specifically block certain metabolites essential for the C.N.S., such as amino-acids, awaits further proof.

(c) *Antalgics and Euphorigenics.*—Before proceeding to the chemistry of the true analgesics, we wish to mention briefly two groups of compounds which undoubtedly possess low analgesic activity, but are mainly characterised by other pharmacological effects. The first are the well-known antipyretics (such as aspirin, phenacetin, and antipyrine), products of earlier synthetic efforts in pharmaceutical chemistry which furnished until quite recently the only class of totally synthesised pain relievers. While nobody will deny the therapeutic effect of these compounds, E. Fourneau's [26] suggestion to separate them from true analgesics and call them " antalgics " has been justified by later pharmacological evaluation of their relatively low analgesic potency when compared with opiates.[13, 27] The second group of substances are the tetrahydrocannabinols, the first of which was isolated from natural cannabis resin ; but many other members have since been synthesised, mainly by A. R. Todd and his collaborators [28] in this country and R. Adams and his collaborators [29] in America.

The analgesic action of synthetic representatives of this class was established in rats for the first time by Raventos [13] and later by Avison *et al.*[30]

[18] *Biochem. J.*, 1932, **26**, 725 ; *Proc. Roy. Soc.*, 1932, *B*, **112**, 60.

[19] M. H. Seevers and F. E. Shideman, *J. Pharm. Exp. Ther.*, 1940, **71**, 373.

[20] E. G. Gross and I. H. Pierce, *ibid.*, 1935, **53**, 156.

[21] H. W. Elliott, A. E. Warrens, and H. P. James, *ibid.*, 1947, **91**, 98.

[22] R. H. Thorpe, E. Walton, and P. Ofner, *Nature*, 1947, **160**, 605.

[23] " Currents in Biochemical Research : Biochemical Aspects of Pharmacology ", Interscience Publishers, New York, 1946, p. 404.

[24] C. I. Wright and J. C. Sabine, *J. Pharm. Exp. Ther.*, 1943, **78**, 375.

[25] M. E. Greig and R. S. Howell, *Proc. Soc. Exp. Biol. Med.*, 1948, **68**, 352.

[26] *Chim. et Ind.*, 1938, **39**, 1043.

[27] H. G. Wolff, J. D. Hardy, and H. Goodell, *J. Clin. Invest.*, 1941, **20**, 63.

[28] See A. R. Todd, *Experientia*, 1946, **2**, 55.

[29] See R. Adams, " Harvey Lectures ", 1941, 1942, Series 37, 168.

[30] A. W. D. Avison, A. L. Morrison, and M. W. Parkes (in the press).

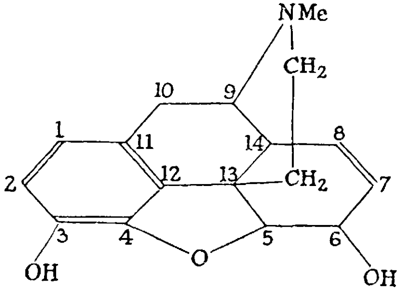
In contrast to the morphine series and most of the synthetic analgesics, these compounds show only slight increase of potency with increase of dosage. In view of their euphorigenic properties, the extracts from natural cannabis have been classed with the morphine alkaloids under the internationally accepted Dangerous Drugs Act.

II. *Morphine and Related Compounds*

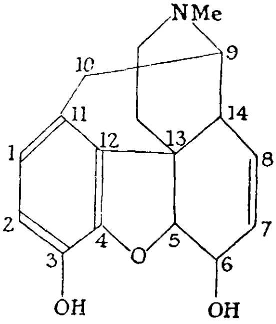
(a) *Structural Problems.*—In 1938, in his article on "Analgesic Power and Chemical Constitution", E. Fourneau [26] said: "Morphine and a few of its derivatives alone can be considered as true analgesics. . . ." But, just at that time, the first synthetic "true analgesic" was discovered in form of a phenylpiperidine derivative. This, with other compounds, we will discuss later. Before doing so, it seems appropriate to recapitulate briefly the chemistry of morphine, and with it that of closely related alkaloids, as it forms the historic starting point for further developments.

The structural formula generally accepted at present is that of J. M. Gulland and R. Robinson [31] (I) which was supported by C. Schoepf [32]; it is based on the chemistry of codeine (III) and thebaine (II). The elaborate work which led to its establishment is adequately reviewed, for instance, by T. A. Henry [33] and by L. F. Small and R. E. Lutz.[34]

The American authors say: "The formula of Gulland and Robinson, while as yet not proved beyond dispute, probably accounts best, on the whole, for the complicated facts of morphine chemistry, and until further more definite evidence is available, may be accepted as representing the true structure of the morphine alkaloids." It is, however, understood that this formula, which emphasises the phenanthrene portion of the total structure, is a two-dimensional representation of a three-dimensional arrangement. The same applies to the variation (I*a*) which O. Schaumann [35]



(I.)



(I*a*.)

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[31] *Mem. Proc. Manchester Lit. Phil. Soc.*, 1924—25, **69**, 79.

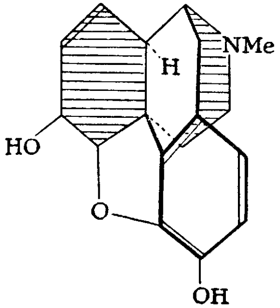
[32] *Annalen*, 1927, **452**, 211.

[33] "The Plant Alkaloids", 3rd Edit., J. & A. Churchill Ltd., London, 1939, p. 223 *et seq.*

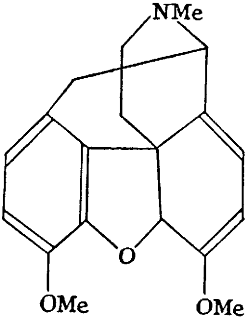
[34] "The Chemistry of Opium Alkaloids", Suppl. 103 to Public Health Reports, U.S. Treasury Department, 1932, p. 336 *et seq.*

[35] *Arch. Exp. Path. Pharm.*, 1940, **196**, 109.

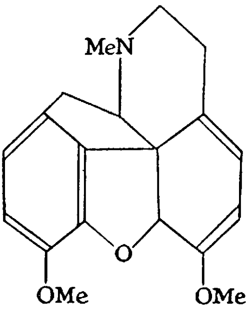
and later F. Bergel, J. W. Haworth, A. L. Morrison, and H. Rinderknecht [36] adopted in view of more recent synthetic developments and which stresses the 4-phenylpiperidine fragment.



(I*b*.)



(II.)



(II*a*.)

On C. Schoepf and Th. Pfeiffer's [37] assumption that the spatial arrangement of the hydroaromatic rings is analogous to that of *cis*-decalin and that consequently the piperidine ring is joined in *trans*-position to the unsaturated hydroaromatic ring, the phenanthrene structure of the morphine molecule, to quote R. Grewe's [38] vivid description, is folded along the bond 13 : 14. This means that a part of the tetralin fragment formed by the benzene and the other hydroaromatic ring is nearly at right angles to the practically planar *iso*quinoline ring formed by the piperidine and the unsaturated nucleus, and that the ether–oxygen bridge is arranged in *cis*-position (I*b*).

H. L. Holmes *et al.*,[39] starting from the assumption that complete evidence as to the true location of the ethanamine chain between position 9 and 13 was still lacking, reinvestigated the so-called hydroxycodeine of F. Ach and L. Knorr [40] and found that it did not behave like a compound with a

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[36] *J.*, 1944, 261.

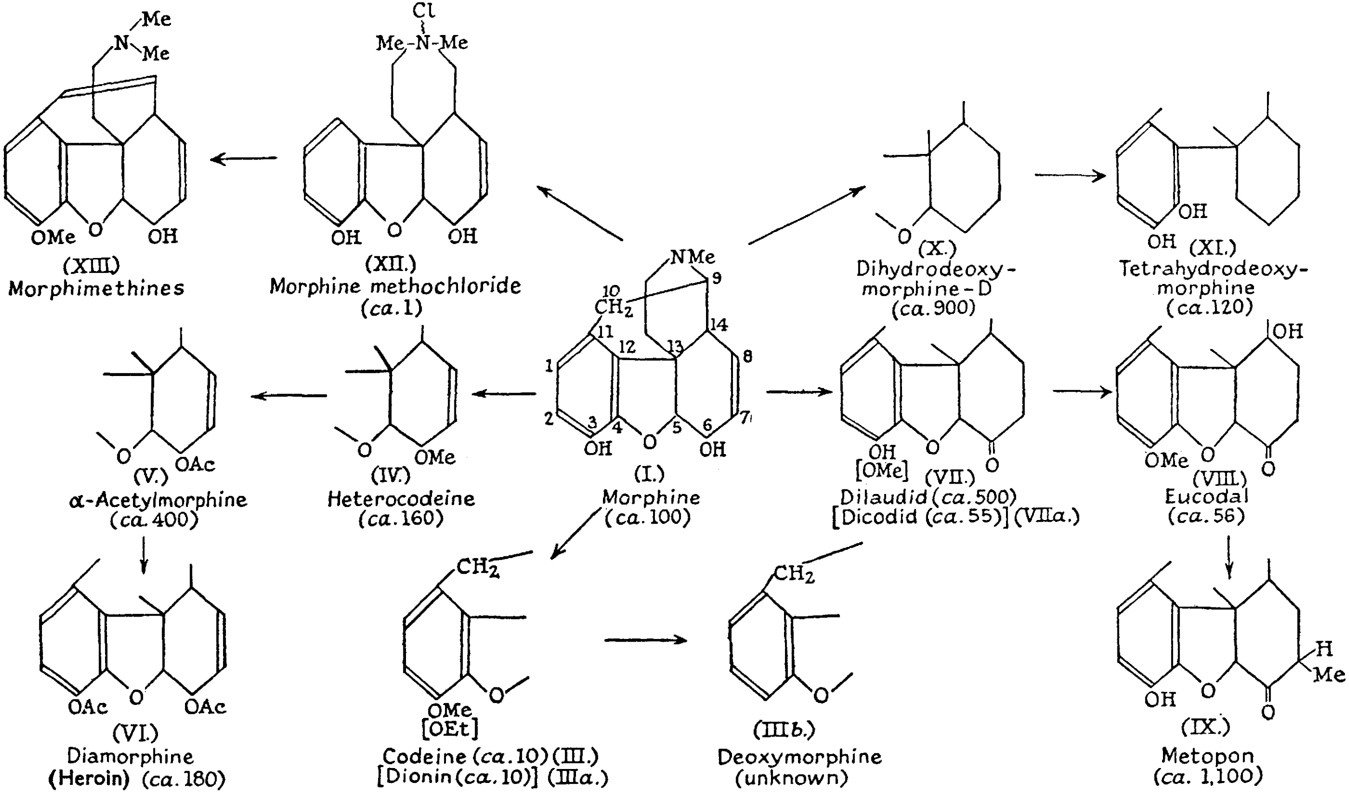
[37] *Annalen*, 1930, **483**, 157.

[38] *Naturwiss.*, 1946, **33**, 333.

[39] H. L. Holmes and C. C. Lee, *J. Amer. Chem. Soc.*, 1947, **69**, 1996 ; H. L. Holmes, C. C. Lee, and A. Mooradian, *ibid.*, p. 1998 ; H. L. Holmes and K. M. Mann, *ibid.*, p. 2000.

[40] *Ber.*, 1903, **36**, 3067.

Morphine and its Derivatives.



Figures in parentheses express relative analgesic activities.

hydroxyl group and a nitrogen atom attached to the same carbon atom. This would be difficult to reconcile with the structure of the alkaloid as a 9-hydroxycodeine derivative of (I) or (III).

A more recent contribution by R. Robinson himself[41] supports strongly structure (I) or (I*a*), although this past-master of morphine chemistry, in complete fairness to existing chemical evidence, considers one other alternative for thebaine, namely (II*a*). In the light of his own arguments and of the pharmacological properties of synthetic compounds belonging to the group of 3-phenylpiperidine derivatives (cf. page 366), there appears to be little support for its existence.

(b) *Piecemeal Syntheses in the Morphine Series.*—This Review would not be complete without a reference to products which have been obtained by part-synthesis from morphine or related alkaloids. Summaries of the results can be found in Part I of " Studies in Drug Addiction ", by L. F. Small, N. B. Eddy, E. Mosettig, and C. K. Himmelsbach,[42] and in E. Fourneau's paper.[26]

This recapitulation will also provide a clearer picture of the effects on analgesic power produced by modifications of the morphine molecule.

(i) *Phenolic group.* The naturally occurring methyl ether (codeine, III) is much less active than morphine, and this is also true of the synthetic ethyl ether, Dionin (III*a*). As deoxymorphine (III*b*) is unknown, it is probable that the determination of the contribution of the phenolic hydroxyl group to the analgesic power of morphine must await future synthetic work.

(ii) *Alcoholic hydroxyl group.* Methylation of the alcoholic group as in heterocodeine (IV) increases activity and toxicity. A similar change in the pharmacological properties occurs if morphine is acylated. α-Acetylmorphine (V), in which only the alcoholic group is esterified, and diacetylmorphine (diamorphine or heroin, VI) are both more potent but also more toxic. Early views that heroin was free from habit-forming action were soon disproved. Replacement of the alcoholic hydroxyl group by halogen, leading to halogeno-morphides, produced very much the same effect as acylation, but these compounds were never used practically.

(iii) *Oxidation or reduction of the alcoholic hydroxyl group.* When the alcoholic hydroxyl group is oxidised to a keto-group or transformed into a methylene group, usually in conjunction with saturation of the double bond 7 : 8, considerable increase of activity is noted, together with greater toxicity and sometimes decrease of duration of action.

Dihydromorphinone or Dilaudid (VII) and the corresponding codeine derivative dihydrocodeinone or Dicodid (VII*a*), produced by catalytic rearrangement of morphine and codeine, in presence of excess of palladium, have gained considerable recognition as therapeutics. Another representative of the dihydrocodeinone series is Eucodal or 14-hydroxydihydrocodeinone (VIII) which is obtained from thebaine, *via* either bromocodeinone or

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[41] *Nature*, 1947, **160**, 815.

[42] Suppl. No. 138 to Public Health Reports, U.S. Treasury Department, Washington, 1938, p. 1 *et seq.*

hydroxycodeinone. Thus the more toxic and therapeutically useless thebaine can be transformed into a valuable substance.

A more recent addition to this group, methyldihydromorphinone or metopon (IX) has found great favour in America as it is a very powerful analgesic and shows less undesirable side effects.[43] Tolerance to and dependence upon metopon are less pronounced than with morphine. It is prepared in a complicated manner from dihydrothebaine [44] by introduction of a methyl group with methylmagnesium iodide, thus giving two isomeric phenolic ketones, methyldihydrothebainone and *iso*methyldihydrothebainone, in which the oxygen ring 4 : 5 is broken. The former, on re-formation of the oxygen bridge *via* bromomethyldihydrocodeinone gives, after reduction, methyldihydrocodeinone which, on demethylation, yields metopon.

Of the reduction products, the most interesting is dihydrodeoxymorphine-D (desmorphine or Permonid, X). Whereas dihydromorphine or paramorphan shows some increase of analgesic activity, desmorphine in the cat is more than nine times as effective and about five times as toxic as morphine. Clinically its action is of shorter duration.[45]

(iv) *Ether–oxygen bridge.* When the ether bridge between carbon atoms 4 and 5 is opened, which happens with ease when reductive processes are applied, compounds of decreased activity and toxicity are obtained, *e.g.*, (XI).[46]

(v) *Changes at the nitrogen atom.* Transformation of the tertiary nitrogen atom of morphine or codeine into quaternary goes hand-in-hand with a considerable decrease of activity (XII) ; a certain curare-like activity is brought about.[47, 48] Exchange of the *N*-methyl group for other alkyl or alkenyl groups has only in *N*-allylnorcodeine and *N*-allylnormorphine [49] produced substances with improved pharmacological properties, especially in regard to respiration and movements of the intestinal tract.[50] Rupture of the piperidine ring in the morphine alkaloids, as in α-methylmorphimethine (XIII),[51] leads to an almost complete loss of true analgesic potency. Apomorphine, which is produced by a deep-set rearrangement of morphine by concentrated hydrochloric acid, excels in emetic but shows only weak analgesic action. Many other derivatives have been made, and more details can be found in the surveys 34, 42, 52.

III. *Synthetic Analgesics*

(a) *The Significance of the Pharmacodynamic Group.*—The organic chemist, in his search for synthetic compounds to replace naturally occurring

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[43] L. E. Lee, National Research Council, Report of Committee on Drug Addiction, 1929—41, 1550.

[44] L. Small, H. M. Fitch, and W. E. Smith, *J. Amer. Chem. Soc.*, 1936, **58**, 1457.

[45] Cf. ref. 42, p. 33.

[46] L. Small and F. L. Cohen, *J. Amer. Chem. Soc.*, 1931, **53**, 2227.

[47] Cf. ref. 42, pp. 33 and 81.

[48] N. B. Eddy, *J. Pharm. Exp. Ther.*, 1933, **48**, 183.

[49] E. L. McCawley, E. R. Hart, and D. F. Marsh, *J. Amer. Chem. Soc.*, 1941, **63**, 314.

[50] E. R. Hart and E. L. McCawley, *J. Pharm. Exp. Ther.*, 1944, **82**, 339.

[51] Cf. ref. 34, p. 268 *et seq.*

pharmacologically active substances, may have several objectives in view. He may simply be seeking to replace a natural drug which has become unobtainable, but more usually he is endeavouring to synthesise compounds with improved pharmacological action, *viz.*, enhanced and clear-cut main potency and diminished undesirable side-effects. Of absorbing theoretical interest, and possible practical importance, is the tracking down in the original natural substance of the simplest pharmacodynamic group which is responsible for the desirable pharmacological effect.

In the case of analgesics, the primary necessity was to find a drug which, unlike morphine, would not produce tolerance or addiction. Reviews on this subject have already been given,[52] and more recently by A. L. Morrison and H. Rinderknecht,[53] Lee and his colleagues,[54], Dodds and his collaborators [55] and Grewe.[120]

Systematic work on synthetic analgesics did not begin until 1929 when, under the auspices of the Committee on Drug Addiction of the American National Research Council, a campaign was started with the object of finding a substitute for morphine which would be free from all the undesirable side-effects of the natural drug, while still retaining the full analgesic action. The American team, under the leadership of L. F. Small, concentrated mainly on the conception of morphine as a phenanthrene or dibenzfuran derivative, and prepared a large number of related compounds, none of which, however, surpassed codeine in analgesic action.

It was not until 1938 that the first true synthetic analgesic was made, when O. Eisleb and O. Schaumann [35, 56] observed that ethyl 4-phenyl-1-methylpiperidine-4-carboxylate, originally designed as a spasmolytic, possessed definite analgesic properties, and it was probably only then realised that in its structure of a 4-phenylpiperidine derivative it constituted a fragment of the morphine molecule. This fortuitous discovery gave an impetus to the search for analgesics of a similar simple structure, and considerable success has crowned these efforts. In this intensive search, the morphine molecule has been dissected to provide the framework of new synthetic compounds, and in the following table the fragments are set out together with compounds built up from them.

It is now proposed to discuss in greater detail the chemistry and pharmacological properties of these compounds, and to report on the latest views as to the essential pharmacodynamic group responsible for analgesic action. The formulæ given are shown only in their two-dimensional aspect and little is known of the extent to which the workers who synthesised the compounds used three-dimensional models in deciding which molecular arrangement would most closely approach that of morphine.

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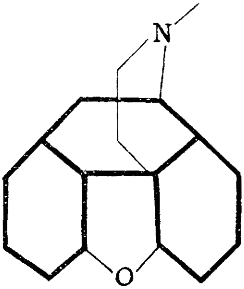
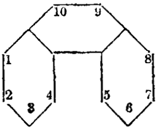
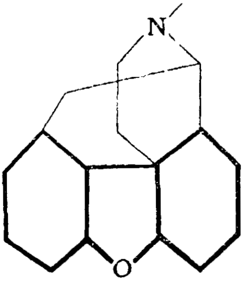
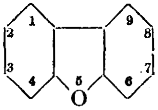
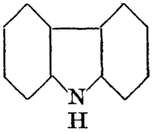
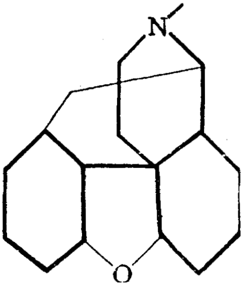
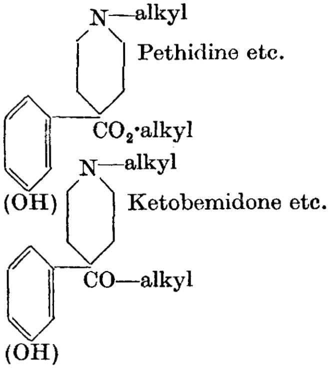
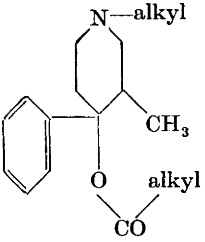
[52] National Research Council, Report of Committee on Drug Addiction, 1929—41, Washington, D.C.

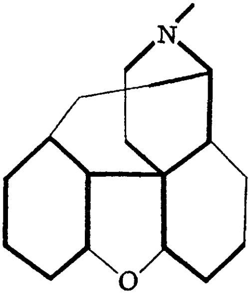
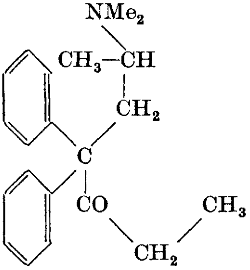
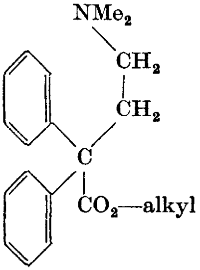
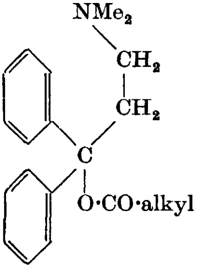
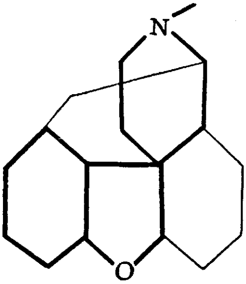
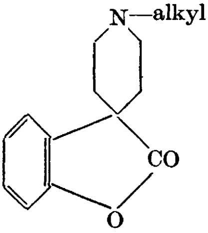
[53] Jubilee Vol. Emil Barell, 1946, 253.

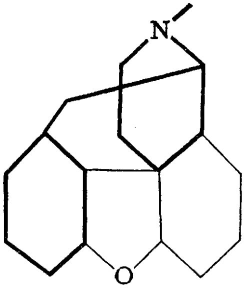
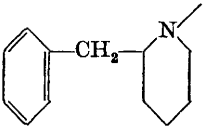
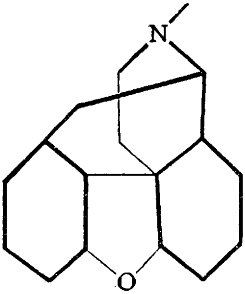
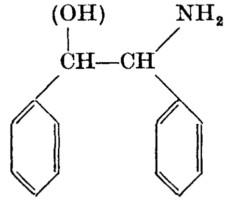
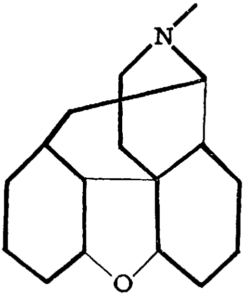
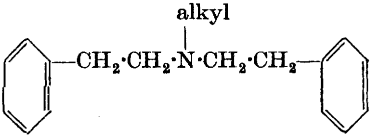
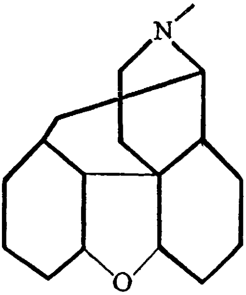
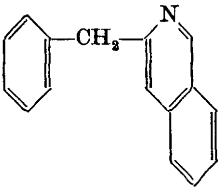
[54] J. Lee, A. Ziering, L. Berger, and S. D. Heineman, *ibid.*, p. 264.

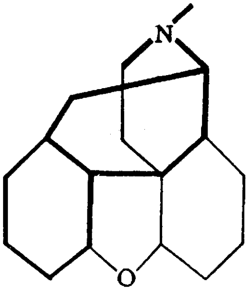
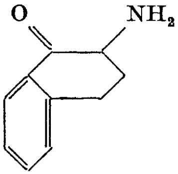
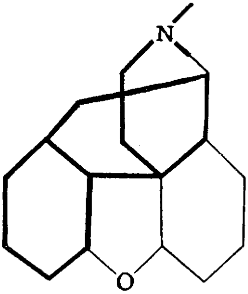
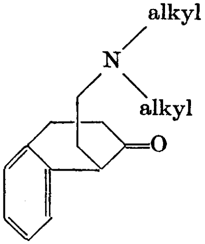
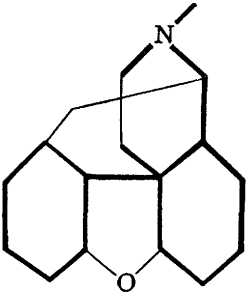
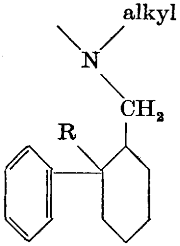
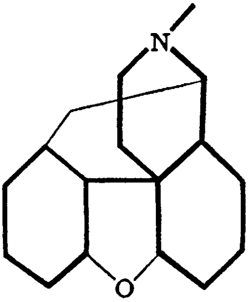
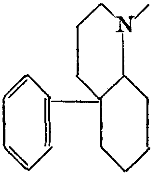
[55] E. C. Dodds, W. Lawson, and P. C. Williams, *Proc. Roy. Soc.*, 1944, *B*, **132**, 119.

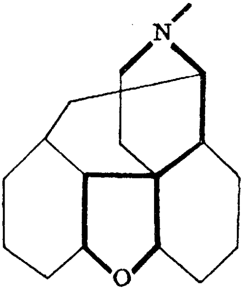
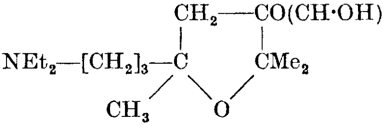
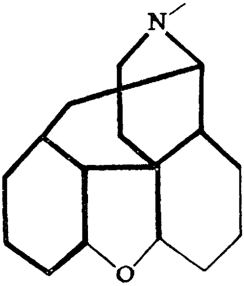
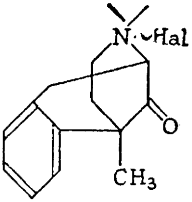
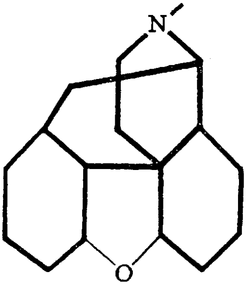
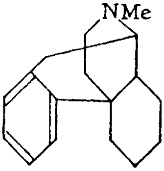
[56] O. Eisleb and O. Schaumann, *Deut. Med. Woch.*, 1939, **65**, 967.

Group.	Morphine fragment.	Synthetic compounds.	Refs.
1	 	Phenanthrene derivatives  	42 52
2	 	Dibenzfuran derivatives  Carbazole derivatives  	42 52
3	 	Phenylpiperidine derivatives  Pethidine etc. Ketobemidone etc.	35 68 57 69 58 70 59 77 60 78 61 79 62 64 65 57 66 68
3b		 	14*a* 54 71 72 73 74 75

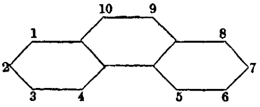
Group.	Morphine fragment.	Synthetic compounds.	Refs.
4		Diphenylpropylamines  Amidone, etc.	22 87 66 88 82 89 83 90 84 91 85 92 86
4*a*			67 80
4*b*			94
5		*iso*Coumaranone 	95 96 97

Group.	Morphine fragment.	Synthetic compounds.	Refs.
6		2-Benzylpiperidines 	54 75 98
7		Diphenylethylamines 	55 100 101 102 103
8		Bisphenylethylamines 	54 104
9		Benzyl*iso*quinolines 	99

Group.	Morphine fragment.	Synthetic compounds.	Refs.
10		2-Amino-1-tetralone 	105
11		1-Dialkylaminoethyl-2-tetralone 	106
12		Phenylaminomethyl*cyclo*hexane  (R = OH = O·CO·alkyl)	54 94
13		Phenyldecahydroquinoline 	107

Group.	Morphine fragment.	Synthetic compounds.	Refs.
14		Tetrahydrofuran derivatives 	108 109
15			119
16	Morphinan 	*N*-Methylmorphinan 	38 120 128 129

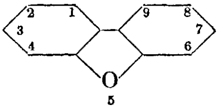
(b) *Phenanthrenes and Dibenzfurans* (*Groups* 1 *and* 2).—In 25 chemical papers [52] and eight pharmacological publications,[52] as well as in a summarising report,[42] the team of American workers who began work on the synthesis of phenanthrene derivatives in 1929 laid down their results which, although producing most interesting serial studies, did not lead to the



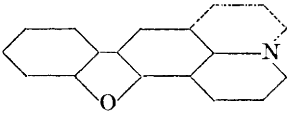
(XIV.)

discovery of a potent analgesic. It would duplicate their own writing if we attempted to present the details of this work. It suffices to say that they investigated relatively simple phenanthrene or hydrogenated phenanthrene derivatives (XIV), substituted mostly in positions 2, 3 or 9 by hydroxyl, amino-, aminomethyl, carboxyl, formyl, acyl, and carbinyl groups, or a combination of these groups. It is remarkable that even the hydrocarbons, especially 1 : 2 : 3 : 4-tetrahydrophenanthrene, show a weak, " antalgic "-like, but measurable analgesic effect. Speculating on the fact that morphine is an amino-alcohol, Mosettig and his colleagues prepared a series of 3- and 9-derivatives of phenanthrene and 9 : 10-dihydro- and octahydro-phenanthrenes. In addition, cyclic amino-alcohols and amino-ketones of tetrahydrophenanthrenes were investigated.

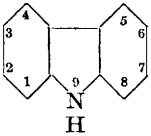
No more promising results were obtained when the same team concentrated on the preparation of dibenzfuran (XV) and benzofuroquinoline derivatives (XVI). Again 2- and 3-amino-, acyl, carboxyl, etc., derivatives of (XV) and of the corresponding tetrahydrodibenzfuran and substances carrying amino-alcohol side chains were made. Unfortunately, because of preparative difficulties, in none of the numerous derivatives do the positions of the substituents approximate to those of the morphine peripheral groups. From 3-aminodibenzfuran by the Skraup method, isomeric benzofuroquinolines (XVI) were obtained which after reduction of the pyridine nucleus in presence of chromite catalyst yielded the corresponding tetrahydro-compounds. Relatively speaking the dibenzfuran derivatives, especially the amino-alcohols, showed more analgesic activity, but at the same time greater toxicity than the corresponding phenanthrene derivatives. Finally, by changing the oxygen of the dibenzfuran nucleus into the nitrogen of carbazoles (XVII), Small and colleagues made 3-amino-9-alkyl- or -9-acetyl-carbazoles and a number of amino-alcohol derivatives. Nearly all of them had a phenylpyrazolone-like antalgic effect with low toxicity. None of the phenanthrene, dibenzfuran, and carbazole derivatives so far prepared and tested represents the true pharmacological grouping for analgesic effect.



(XV.)

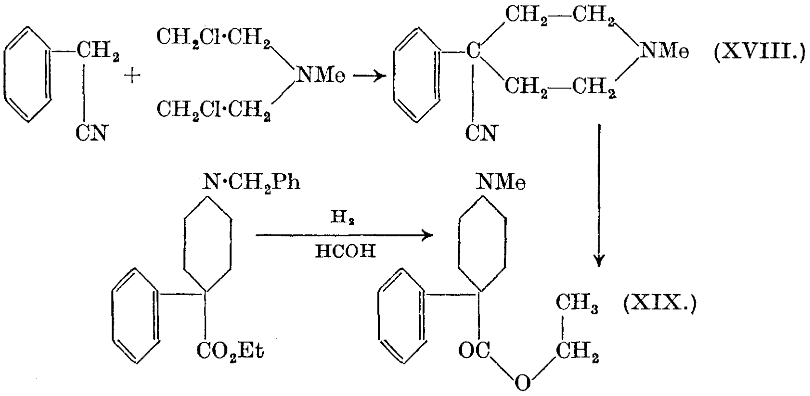


(XVI.)



(XVII.)

(c) 4-*Phenylpiperidine Derivatives* (*Groups* 3, 3a, 3b).—The compound Dolantin (known later as Dolantal, pethidine, Demerol, etc.) was prepared by O. Eisleb.[57] Benzyl cyanide was condensed with methylbis-2-chloroethylamine to give 4-cyano-4-phenyl-1-methylpiperidine (XVIII), and replacement of the cyano-group by a carbethoxy-group either directly or through the intermediate acid gave the analgesic (XIX).



(XVIII.)

(XIX.)

The Eisleb synthesis of pethidine involved the use of the well-known vesicant, methylbis-2-chloroethylamine, and it was not surprising to learn from B.I.O.S. reports [58] that the Germans never used this method for large-scale manufacture but made use of the much less dangerous benzylbis-2-chloroethylamine, and as a final stage in the synthesis removed the benzyl group and replaced it by a methyl group by hydrogenation in the presence of formaldehyde.

The promising early clinical reports on pethidine led many workers to seek for alternative methods of synthesis, which would obviate completely the use of bis-2-chloroethylalkylamines; subsequent publications have shown that this search was successful.

F. Bergel, A. L. Morrison, and H. Rinderknecht [59] evolved a new piperidine synthesis by condensing benzyl cyanide with 2-chloroethyl vinyl ether, and hydrolysing the resulting product to the di-alcohol, which on chlorination and condensation with methylamine gave 4-cyano-4-phenyl-1-methylpiperidine.

2-Chloroethylalkylformals which like the vinyl ethers are easily hydrolysed to the free alcohols can equally well be used in the above synthesis.

Syntheses of pethidine starting from 2-alkoxyethyl derivatives of benzyl cyanide or from 4-cyano-4-phenyl-pentamethylene 1-oxide, in which the very unstable phenylbis-2-bromoethylacetic acid is an intermediate, have been reported,[60, 61, 62] but the methods do not appear to be of technical importance.

I.G. Farbenindustrie developed another pethidine synthesis [58] in which

[57] *Ber.*, 1941, **74**, 1433.

[58] B.I.O.S. Final Report No. 766, Item Nos. 22 and 24, p. 60.

[59] *J.*, 1944, 265.

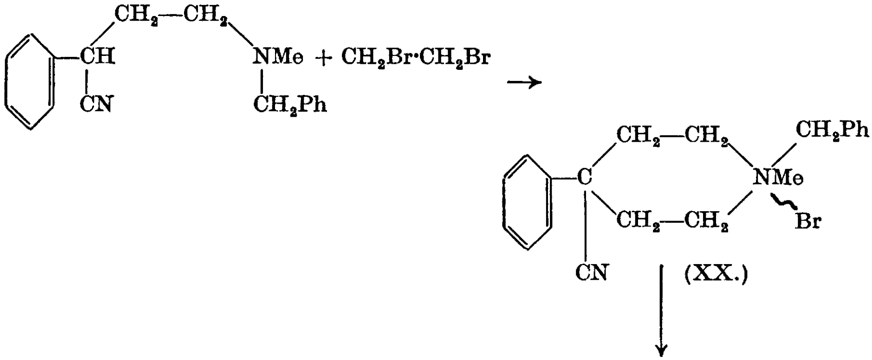
[60] F. Bergel, A. L. Morrison, and H. Rinderknecht, *J.*, 1944, 267.

[61] U.S.P. 2,242,575.

[62] E. Walton and M. B. Green, *J.*, 1945, 315.

they started from phenyl-2-chloroethylmethyl cyanide originally prepared by E. C. Knowles and J. B. Cloke.[63] This compound was condensed with 2-methylaminoethanol, the hydroxyl group replaced by chlorine, and ring closure to (XVIII) brought about by treatment with sodamide.

A recent patent [64] has shown that Ciba Ltd. evolved an original method of preparing pethidine, using quaternary salts as intermediates. 1-Phenyl-3-(benzylmethylamino)propyl cyanide was condensed with ethylene dibromide in the presence of sodamide to give 4-cyano-4-phenyl-1-benzyl-1-methylpiperidinium bromide (XX) which on hydrogenolysis gave (XVIII).



(XX.)

(XVIII.)

As a modification of the above process, the cyano-derivatives of the quaternary salts[65] were hydrolysed to give betaines which decomposed on dry distillation to give tertiary base esters. For example : 4-phenyl-1 : 1-dimethylpiperidine-4-carboxylic acid betaine gave methyl 4-phenyl-1-methylpiperidine-4-carboxylate. The 1-methyl-1-ethyl betaine gave, not pethidine, but the isomeric methyl 4-phenyl-1-ethylpiperidine-4-carboxylate.

O. Eisleb [57] also prepared a large number of compounds derived from 4-cyano-4-phenyl-1-methylpiperidine including ketones formed by the action of an alkyl- or aryl-magnesium halide. All these compounds were tested pharmacologically by O. Schaumann [35] but at that time none proved better in spasmolytic and analgesic properties than pethidine.

Following on the success of such a simple compound as pethidine as an analgesic, it was natural that many attempts would be made to modify the pethidine molecule in all possible ways. It was reported after the war that the introduction of a *m*-hydroxyl group into the phenyl ring of pethidine gave a compound (known in Germany as bemidone) which had given promising clinical results when used as a general anæsthetic by intravenous administration.[66] A. D. Macdonald, G. Woolfe, F. Bergel, A. L. Morrison, and H. Rinderknecht [67] had previously stated that its analgesic potency was of the same order as that of pethidine.

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[63] *J. Amer. Chem. Soc.*, 1932, **54**, 2028.

[64] B.P. 591,992.

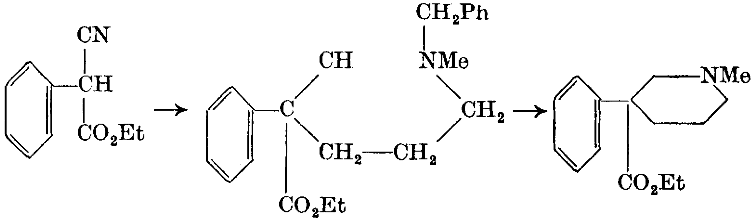
[65] Ciba Ltd., B.P. 597,794.

[66] U.S.A. Office of the Publ. Board, Department of Commerce, Report No. PB-981.

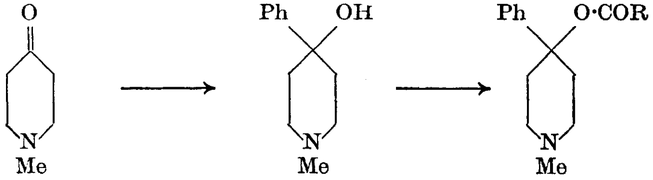
[67] *Brit. J. Pharmacol.*, 1946, **1**, 4.

While the introduction of a *m*-hydroxyl group into the phenyl ring of pethidine did not produce a marked change in analgesic potency, the corresponding ethyl ketone (ketobemidone; Hoechst No. 10720)[66] was twenty times as active as the ethyl ketone which did not carry a *m*-phenolic group, and ten times as active as pethidine. A recent exploratory clinical trial would indicate that this compound, in view of the excellent analgesia obtained with minimal side-actions, merits further study.[68]

An isomer of pethidine, ethyl 3-phenyl-1-methylpiperidine-3-carboxylate (β-pethidine; XXI), was prepared by F. Bergel, N. C. Hindley, A. L. Morrison, and H. Rinderknecht,[69] by condensation of ethyl phenylcyanoacetate with benzylmethyl-3-chloropropylamine and reduction of the product. This change of the phenyl ring from the 4 to the 3 position of the piperidine ring leads to a reduction in analgesic action,[67, 70] but it is interesting to note that in the β-pethidine series, as in the pethidine series of esters, the ethyl ester is the most active.[67]


(XXI.)

In 1943, K. A. Jensen, F. Lindquist, E. Rekling, and C. G. Wolffbrandt[71] reported the analgesic and spasmolytic properties of a group of compounds related to pethidine, namely 4-acyloxy-4-phenyl-1-methylpiperidines, which were prepared by the action of phenylmagnesium halide on 1-methyl-4-piperidone, followed by acylation of the tertiary carbinol so formed.


(XXII.)

Besides the carbinol itself, the Danish workers tested the series of compounds where R = Me, Et, or Pr, and found that the propionoxy-derivative (XXII, R = Et) was the most active, being about five times as potent as pethidine.

More recently research workers of Hoffman-La Roche, Inc., have

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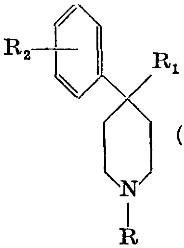
[68] A. C. Kirchhof, *Fed. Proc.*, 1948, **7**, 234.

[69] *J.*, 1944, 269.

[70] A. J. Glazebrook and A. W. Branwood, *Lancet*, 1945, **249**, 528.

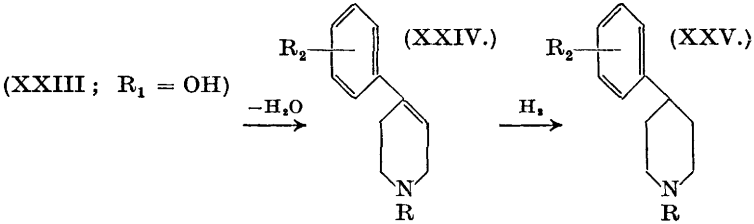
[71] *Dansk Tids. Farm.*, 1943, **17**, 173 (*Chem. Abs.*, 1945, **39**, 2506).

reported[14a, 54, 72, 73, 74, 75, 76] as part of a comprehensive study of the relationship between chemical structure and analgesia the results of a more detailed examination of this group of compounds, carried out independently of the Danish workers. They found that in the general formula (XXIII), maximum activity was found when in (XXIII) R = Me, R_2 = H and R_1 = Et·CO_2, thus confirming the findings of Jensen and collaborators. Lengthening of R led to a decrease in potency and also toxicity, while branching of it led to an increase in stability of the ester grouping in aqueous solution, the 1-*iso*propyl compound being stable for months while the corresponding 1-methyl compound was rapidly hydrolysed. Substitution in the phenyl ring by R_2 = methoxyl or methyl group led to a decrease in analgesic potency.



(XXIII.)

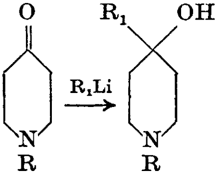
The properties of the tetrahydropyridines obtained by dehydration of the arylcarbinols (XXIII, R_1 = OH) and the corresponding saturated piperidines were also examined.



(XXIV.) (XXV.)

The piperidols (XXIII, R_1 = OH) themselves were practically inactive, while the tetrahydropyridines (XXIV) had distinct activity ; 4-*p*-methoxyphenyl-1-ethyl-1 : 2 : 5 : 6-tetrahydropyridine, for example, having about $\frac{1}{30}$th of the potency of morphine. The saturated piperidines (XXV) had about the same order of potency.

The American workers next turned their attention to the effect of replacing the phenyl group by other groups such as alkyl, *cyclo*alkyl, heterocyclyl, and heterocyclylalkyl. All these compounds with the exception of *cyclo*alkyl were prepared generally by the action of the appropriate lithium compound on 1-alkyl-4-piperidone :



(R_1 = Me, *n*-hexyl, *n*-butyl, 2-pyridyl, 3-pyridyl, 2-furyl, 2-picolyl, 2-lutidyl, or 2-thienyl.)

(XXVI.)

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[72] J. Lee, A. Ziering, S. D. Heineman, and L. Berger, *J. Org. Chem.*, 1947, **12**, 885.

[73] *Idem, ibid.*, p. 894.

[74] L. Berger, A. Ziering, and J. Lee, *ibid.*, p. 904.

[75] A. Ziering and J. Lee, *ibid.*, p. 911.

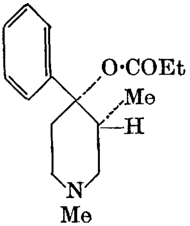
[76] L. O. Randall and G. Lehmann, *J. Pharm. Exp. Ther.*, 1948, **93**, 314.

The *cyclo*hexylcarbinols were obtained by catalytic hydrogenation of the phenylcarbinols under acid or neutral conditions. The corresponding esters on hydrogenation eliminated a molecule of acid yielding 4-*cyclo*hexyl-1-alkylpiperidines.

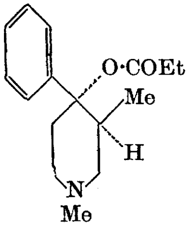
None of the propionates of the new carbinols proved to be more potent than the 4-propionoxy-4-phenyl-1-alkylpiperidines. The methyl and hexyl compounds were completely inactive, while the butyl was slightly active. Of the heterocyclic compounds, the β-pyridyl was the most active at $\frac{1}{30}$th of the activity of the corresponding phenyl compound.

The most remarkable result was that obtained with 4-propionoxy-4-*cyclo*hexyl-1-methylpiperidine, which was shown to have one-third of the activity of 4-propionoxy-4-phenyl-1-methylpiperidine. This is the first analgesic reported with a potency of the same order as morphine and not containing a phenyl ring.

J. Lee and his co-workers[75] from theoretical considerations, which will be fully discussed in IV, arrived at the conclusion that one of the isomers of 4-propionoxy-4-phenyl-1 : 3-dimethylpiperidine should have outstanding analgesic properties. This was found to be the case, one isomer to which they ascribed the *trans*-structure (XXVII) approaching dihydrodeoxymorphine-D in potency while the other with the *cis*-structure (XXVIII) was about as active as morphine.[76]



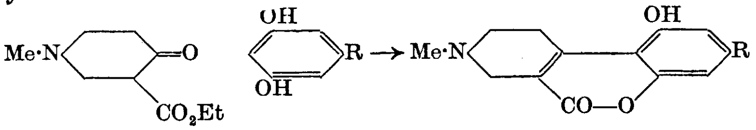
(XXVII.)



(XXVIII.)

J. W. Cook *et al.*[77, 78] have prepared various 3- and 4-phenylpiperidines, 3-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines, and 4-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines, but none of the compounds possessed any marked analgesic action.

R. M. Anker and A. H. Cook[79] made interesting 4-phenylpiperidine derivatives, which are closely related to the euphorigenic tetrahydrocannabinols, by condensing 4-keto-1-methylpiperidine-3-carboxylates with 5-alkylresorcinols :



(R = Me, *n*-amyl.) (XXIX.)

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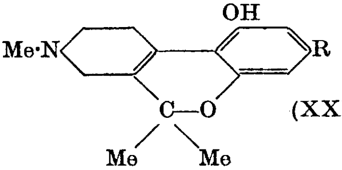
[77] J. W. Cook and W. Barr, *J.*, 1945, 438.

[78] G. M. Badger, J. W. Cook, G. M. S. Donald, J. D. P. Graham, and T. Walker, *Nature*, 1948, **162**, 21.

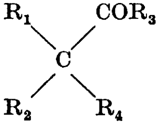
[79] *J.*, 1946, 58.

Treatment of (XXIX) with methylmagnesium iodide gave the benzpyran derivatives (XXX, R = Me, *n*-amyl) ; these compounds were not active as analgesics, even when the double bond in the nitrogen ring of the *n*-amyl compound was hydrogenated.



(XXX.)

(d) *Diphenylpropylamines* (*Group* 4, 4a, 4b).—It might have been concluded from the known loss of analgesic action brought about by the opening of the piperidine ring in morphine (cf. page 356), and from the activity of certain 4-phenylpiperidine derivatives, that the piperidine ring was an essential feature of an analgesic. I.G. Farbenindustrie workers at Hoechst discovered a new class of potent analgesics which do not contain such a ring : M. Bockmuehl and G. Ehrhart [80] claimed that esters (Group 4*a*) of diphenylacetic and of fluorenecarboxylic acid, carrying 2-dialkylaminoalkyl radicals in the α-positions, possessed analgesic and spasmolytic properties. A. D. Macdonald *et al.*[67] reported that a representative of this class, ethyl $\alpha\alpha$-diphenyl-γ-*N*-piperidinobutyrate, had about half of the activity of pethidine. During the war the Hoechst laboratories extended this work to the preparation of ketones corresponding to the above esters of the type (XXXI ; R_1 and R_2 = Ph, R_3 = alkyl or aryl, R_4 = 2-dialkylaminoalkyl).[66] Of 23 compounds prepared, the greatest activity was present when R_1 = R_2 = Ph, R_3 = Et, and R_4 = 2-dimethylaminopropyl. This compound (Hoechst No. 10820) was reported to be 5—10 times as active as pethidine and was given the name amidone. Other compounds of high activity were Hoechst Nos. 10582 (XXXI, R_1 = R_2 = Ph ; R_3 = Et; R_4 = 2-dimethylaminopropyl), 10581 (XXXI, R_1 = R_2 = Ph ; R_3 = Et ; R_4 = 2-morpholinoethyl), 10819 (XXXI, R_1 = R_2 = Ph ; R_3 = Et ; R_4 = 2-pyrrolidinoethyl), 10503 (XXXI, R_1 = R_2 = R_3 = Ph ; R_4 = 2-piperidinoethyl), 10515 (XXXI, R_1 = R_2 = R_3 = Ph ; R_4 = 2-morpholinoethyl), and 10505 (XXXI, R_1 = R_2 = R_3 = Ph ; R_4 = 2-dimethylaminoethyl). In contrast to the pethidine series, the introduction of a *m*-hydroxyl group into one of the phenyl rings led to a marked fall in analgesic action, compound 10802 (XXXI, R_1 = *m*-OH·C_6H_4; R_2 = Ph ; R_3 = Et ; R_4 = 2-morpholinoethyl) possessing only $\frac{1}{25}$th of the potency of compound 10581. The methyl homologue of 10581 (XXXI, R_1 = R_2 = Ph ; R_3 = Et ; R_4 = 2-morpholinopropyl) prepared by the Glaxo Laboratories has recently been assessed clinically.[81]



(XXXI.)

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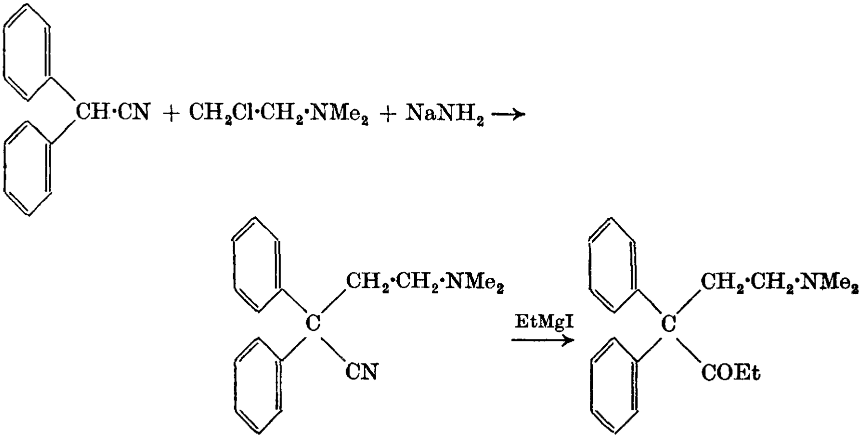
[80] D.R.-P. 711,069.

[81] W. M. Wilson and R. B. Hunter, *Brit. Med. J.*, 1948, No. 4576, 553.

The preparation of the above compounds where R_4 was a β-dialkylaminoethyl group proceeded in a straightforward manner by condensing diphenylmethyl cyanide with the appropriate β-halogenoethyldialkylamine, and treating the basic cyanide so formed with the desired alkylmagnesium halide to give the ketone. The preparation of compound 10582 exemplifies the general reaction :



In the preparation of amidone, the base prepared from 2-chloro-1-dimethylaminopropane hydrochloride was condensed with diphenylmethyl cyanide in the presence of sodamide [66, 82, 83] or potassium butoxide [83] to give equal amounts of the two isomeric cyanides (XXXII) and XXXIII). Treatment of (XXXII) and (XXXIII) with ethylmagnesium halide yielded amidone [66, 82, 83] and the isomeric *iso*amidone [84] respectively.

$CPh_2(CN){\cdot}CH_2{\cdot}CHMe{\cdot}NMe_2$	$CPh_2(CN){\cdot}CHMe{\cdot}CH_2{\cdot}NMe_2$
(XXXII.)	(XXXIII.)

Explanations of the mechanism of the above condensations have been put forward by E. M. Schulz and J. M. Sprague [85] and W. R. Brode and M. W. Hill.[86]

The constitution of amidone has also been proved by an unambiguous synthesis by N. R. Easton, J. H. Gardner, and J. R. Stevens,[87] who condensed diphenylmethyl cyanide with propylene oxide, treated the iminoether so formed with phosphorus tribromide, and condensed the product with dimethylamine to give (XXXII).

Details of the resolution of (XXXII) with D-tartaric acid, and the formation of *dextro* and *lævo*-amidone have been reported.[22] It is interesting

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[82] B.I.O.S. Final Report No. 1404, Item Nos. 22 and 24, p. 141.

[83] E. M. Schulz, C. M. Robb, and J. M. Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454.

[84] N. R. Easton, J. H. Gardner, M. L. Evanick, and J. R. Stevens, *ibid.*, 1948, **70**, 76.

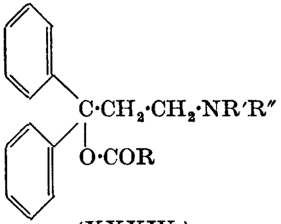
[85] *Ibid.*, p. 48. [86] *Ibid.*, 1947, **69**, 724. [87] *Ibid.*, p. 2941

to note that more recent publications[88] claim *iso*amidone (XXXI, $R_1 = R_2 = Ph$; $R_3 = Et$; R_4 = 2-dimethylamino*iso*propyl) to approach the activity of amidone, although, according to Dr. Bockmühl of Hoechst, it was much less active, and therefore discarded.[82]

A comparison of the pharmacological properties of the optical isomers of amidone and *iso*amidone showed that the *lævo*-isomers are both much more potent analgesics than the *dextro*-isomers, and very recently it has been suggested that *lævo-iso*amidone should be tested clinically.[89]

A very important discovery in this field was that the acyl derivatives of the alcohols prepared from the ketones of the amidone type, such as 2-dimethylamino-5-acetoxy-4 : 4-diphenylheptane hydrochloride and the 2-morpholino-analogue were equal to amidone in analgesic potency but produced less undesirable side-effects.[90, 91, 92] More recently still it has been reported that dialkylaminoalkylbenzhydryl sulphones also possess high activity.[93]

A. L. Morrison and H. Rinderknecht[94] speculated from a consideration of the structure of amidone and of 4-propionoxy-4-phenyl-1-methylpiperidine that acyl derivatives of 3-dialkylamino-1 : 1-diphenylpropan-1-ol



(R = Me, Et; R′ = R″ = Me;
R′R″ = pentamethylene.)

(XXXIV.)

(XXXIV), which would combine features of both these powerful analgesics, might also possess comparable activity. None of the compounds, however, possessed any marked analgesic action.

(e) *Miscellaneous Syntheses.*—Apart from the syntheses described above, numerous attempts in different directions have been undertaken.

As representatives of Group 5, F. Bergel, J. W. Haworth, A. L. Morrison, and H. Rinderknecht[95] prepared 4-(2-hydroxyphenyl)-1-methylpiperidine-4-carboxylic acid lactone (XXXV, R = H), and its methoxy-derivative (XXXV, R = OMe) while later J. A. Barltrop[96] prepared the acetoxy-

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[88] F. P. Luduena, L. C. Miller, E. Ananenko, and J. D. Frick, *Fed. Proc.*, 1948, **7**, 241.

[89] J. E. Denton, O. H. Straus, W. E. Waddell, and H. K. Beecher, *ibid.*, p. 214.

[90] T. R. Sherrod, R. Kaiser, J. Santos-Martinez, and C. C. Pfeiffer, *ibid.*, p. 255.

[91] E. L. May and E. Mosettig, *J. Org. Chem.*, 1948, **13**, 459.

[92] *Idem, ibid.*, p. 663.

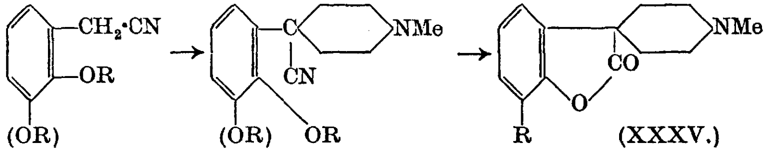
[93] C. M. Suter, M. M. Klenk, W. F. Wetterau, B. F. Tullar, and S. Archer, Abstracts of Papers 114th Meeting of the American Chemical Society, Washington, August—September 1948, 9K.

[94] Private communication.

[95] *J.*, 1944, 261.

[96] *J.*, 1946, 958.

derivative (XXXV, R = OAc) by the general method used by the first authors, who condensed 2-alkoxy- and 2 : 3-dialkoxyphenylmethyl cyanide with methylbis-2-chloroethylamine, and hydrolysed the resulting cyanides

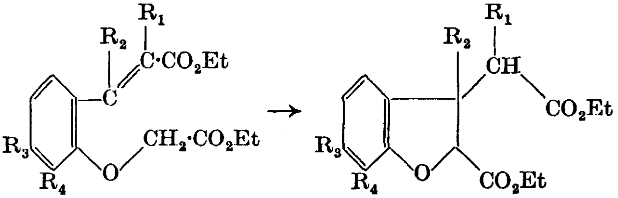


(XXXV.)

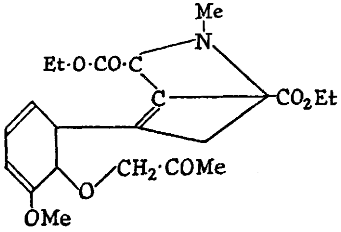
(R = H, OMe.) (R = H, OMe.) (R = H, OMe, OAc.)

with acid to give the lactones (XXXV). Compounds (XXXV ; R = H, and R = OMe) did not possess any analgesic properties.[67]

C. F. Koelsch [97] had also envisaged a synthesis of coumarin derivatives which would carry such substituents as to make possible the formation of additional rings. He showed that a compound of type (XXXVI) could by cyclised by a Michael reaction to (XXXVII), which he planned to extend by the use of (XXXVIII).

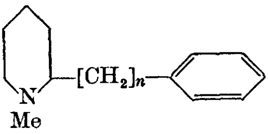


(XXXVI.) (XXXVII.)

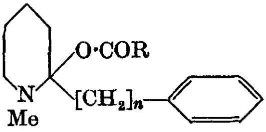


(XXXVIII.)

Although certain 4-substituted 4-phenylpiperidines were found to be effective analgesics, the corresponding 2-phenyl- and 2-aralkyl-piperidine derivatives (Group 6) were found by J. Lee *et al.*[54, 75] to be without action. Compounds of types (XXXIX and XL, $n = 0$, 1, or 2) were made



(XXXIX.)



(XL.)

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[97] *J. Amer. Chem. Soc.*, 1945, **67**, 569.

by the action of aryl- and aralkyl-magnesium halides on 2-ketopiperidines followed by direct acylation of the Grignard complex to give (XL) or by spontaneous dehydration of the carbinol and hydrogenation to give (XXXIX).

R. M. Anker, A. H. Cook, and I. M. Heilbron [98] also prepared a number of 2-benzylpiperidines, carrying different substituents on the nitrogen atom, but none possessed analgesic potency.

Related to the above compounds and in certain features to papaverine which is devoid of analgesic action are 1-aralkyltetrahydro*iso*quinoline derivatives (Group 9) prepared by F. Külz and C. A. Hornung [99] and claimed to have analgesic properties.

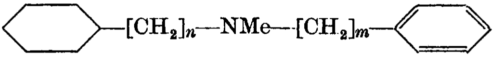
No doubt encouraged by their success in designing the stilboestrols as synthetic equivalents of oestradiol, E. C. Dodds and his collaborators [55, 100] applied similar reasoning to synthetic attempts in the analgesic field, and concluded that, as 1 : 2-diarylethanes had proved to be equivalent to the phenanthrene molecule of oestradiol, 1 : 2-diarylethylamines (Group 7) might replace the aminophenanthrene ring system of morphine. Although it was originally reported that 2-hydroxy-1 : 2-diphenylethylamine had definite analgesic properties in clinical trials, afterwards, when tested on animals with pethidine and morphine as standards, it was found to be devoid of any measurable analgesic action (cf. also refs. 101, 102, 103).

If we consider in the morphine molecule both the piperidine and furan ring systems as being opened, compounds of Group 8, bisphenylethylamines, are produced. F. Külz [104] prepared and tested such compounds of the general formula :

$$(OH)_2C_6H_3—[R_1]—NR_3—[R_2]—C_6H_4{\cdot}OH$$

where R_1, R_2, and R_3 are straight or branched radicals, and found that certain members of the series had analgesic properties.

More recently J. Lee *et al.*[54] have investigated compounds of similar nature but differing in having a *cyclo*hexyl group replacing one phenyl group. Their compounds had the general formula :



where $n = 1$ or 2 and $m = 2$ or 3.

The most active compound in this series is that most closely related to the dissected portion of the morphine skeleton, namely methyl-2-*p*-hydroxyphenylethyl-2′-*cyclo*hexylethylamine, which however had only $\frac{1}{7}$th of the potency of the natural prototype.

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[98] *J.*, 1945, 917.

[99] B.PP. 512,560, 513,512 ; U.S.P. 2,223,373.

[100] E. C. Dodds, W. Lawson, S. A. Simpson, and P. C. Williams. *J. Physiol.*, 1945, **104**, 47.

[101] L. H. Goodson, C. J. W. Wiegand, and J. S. Splitter, *J. Amer. Chem. Soc.*, 1946, **68**, 2174.

[102] W. D. McPhee, E. S. Erickson, and U. J. Salvador, *ibid.*, p. 1866.

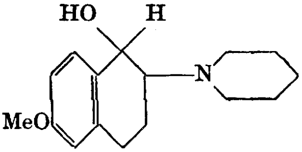
[103] R. B. Moffett and W. M. Hoehn, *ibid.*, 1947, **69**, 1792.

[104] U.S.PP. 2,276,618, 2,276,619 ; *Chem. Abs.*, 1942, **36**, 4672.

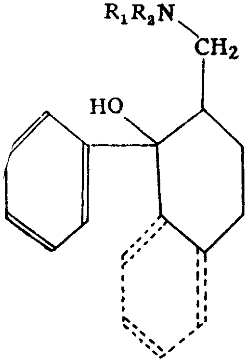
In 1938—39, G. Scheuing and B. Walach[105] claimed that compounds (Group 10) possessing distinct analgesic properties were formed by condensing β-bromotetralones with organic bases such as piperidine and tetrahydro*iso*quinoline. Reduction of the keto-group to a secondary alcohol seemed to increase the analgesic properties; 1-hydroxy-6-methoxy-2-*N*-piperidyl-1 : 2 : 3 : 4-tetrahydronaphthalene (XLI) was reported to be particularly effective.

J. A. Barltrop[106] condensed β-tetralone with dialkylaminoalkyl halides and prepared 1-(2-diethylaminoethyl)-2-tetralone, the corresponding piperidino-compound, and 1-(3-piperidinopropyl)-2-tetralone (Group 11).

Compounds corresponding to Group 12 were investigated by J. Lee *et al.*[54] and by A. L. Morrison and H. Rinderknecht[94] who prepared them by the action of arylmagnesium halides on Mannich bases derived from *cyclo*hexanone and α-tetralone to give substances of type XLII.



(XLI.)



R_1 and R_2 = alkyl or ring.
(XLII.)

Contrary to the effect produced in 4-phenyl-4-piperidols (cf. Group 3*b*)› acylation of the tertiary carbinols of this group did not lead to an increase in analgesic effect which was low with the original carbinols.

It is interesting to note that 6-phenyl-3-methyloctahydro-5 : 6-benz-1 : 3-oxazine (XLIII), which is prepared by the action of formaldehyde on 1-phenyl-2-methylaminomethyl-*cyclo*hexan-1-ol (XLII; R_1 = H, R_2 = Me) and can be regarded as mimicking three rings of the morphine skeleton, did not possess any analgesic activity.[94]

V. Boekelheide[107] from the consideration of morphine as an octahydro-*iso*quinoline derivative having an angular aryl group (Group 13) prepared 10-phenyldecahydroquinoline (XLIV) as a simple model representative of such compounds.

H. Henecka[108] having in mind the indispensability of the oxygen bridge

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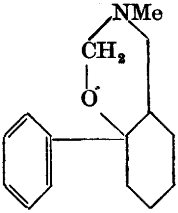
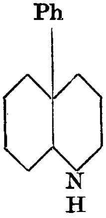
[105] U.S.PP. 2,369,611, 2,352,020.
[106] *J.*, 1946, 958.
[107] *J. Amer. Chem. Soc.*, 1947, **69**, 790.
[108] "Medicine in its Chemical Aspects", 1938, **3**, 280.

in morphine for analgesic action, prepared basic derivatives of tetrahydrofuran (Group 14) such as 1 : 4 : 4-trimethyl-1-(3-diethylaminopropyl)-tetrahydrofuran-3-one, and the corresponding alcohol. None of the compounds prepared, however, had any analgesic properties.



(XLIII.)



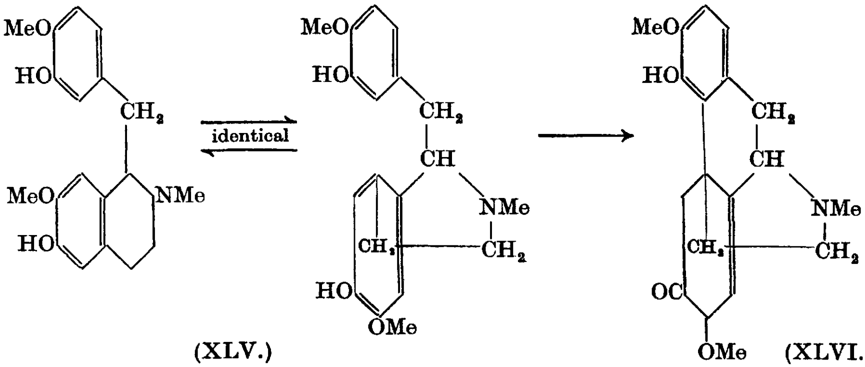
(XLIV.)

G. H. Harnest and A. Burger [109] from similar considerations prepared tetrahydropyranyl compounds and found 4-(1-hydroxy-2-piperidinoethyl)-tetrahydropyran hydrochloride to possess some analgesic activity.

Although many substances which do not bear any structural relationship to morphine have been stated to possess analgesic properties, only one, 1 : 4-bisdiethylaminomethylnaphthalene hydrochloride, according to a preliminary report by J. W. Cook *et al.*[78] approaches pethidine in potency.

(f) *Attempts at Morphine Synthesis.*—The crowning achievement would obviously be, from a chemical if not from a pharmacological point of view, a total synthesis of morphine. So far, nobody has succeeded in this, but various remarkable attempts have been made, at present culminating in the preparation of morphinan which contains four of the five rings of morphine.

In 1925, R. Robinson [110] suggested that the formation of the unique hydroaromatic structure of the alkaloids of the morphine–thebaine and sinomenine group had its biogenesis in a junction of the two aromatic nuclei of a base of the laudanosine type. Thus the phytosynthesis of sinomenine (XLVI) from a hypothetical protosinomenine (XLV) possibly followed this sequence :



(XLV.) (XLVI.)

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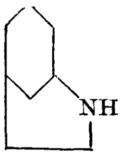
[109] *J. Amer. Chem. Soc.*, 1943, **65**, 370.

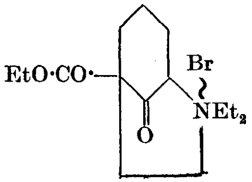
[110] See R. Robinson and Shigehiko Sugasawa, *J.*, 1931, 3163.

During the next few years this theory was pursued experimentally by Robinson and his collaborators [111, 112, 113, 114] in this country and by C. Schoepf *et al.*[115, 116, 117, 118] in Germany, but in 1933 Robinson [114] expressed the opinion that it was highly probable that only a fortunate and partly fortuitous discovery would reveal the appropriate conditions for the transformation of laudanosine types into bases containing a morphine-like nucleus. So far this discovery has not been made.

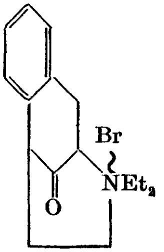
Some time later, J. A. Barltrop,[119] in Robinson's laboratory, approached the problem of a morphine synthesis in a different manner. He concentrated first on the preparation of the nitrogen-containing *m*-bridged ring system (XLVII) which forms part of the morphine alkaloid skeleton, to which he gave the trivial name "morphan". This he achieved by condensing ethyl *cyclo*hexanone-2-carboxylate with 2-dialkylaminoethyl chloride; after bromination and treatment of the bromo-intermediate with sodium hydrogen carbonate, he obtained the bicyclic quaternary nitrogen derivative (XLVIII). When this sequence of reactions was repeated with the corresponding β-tetralone derivative, a tricyclic compound (XLIX) was synthesised which contained those fragments of morphine as depicted by Figure 15 (see Table).



(XLVII.)



(XLVIII.)



(XLIX.)

The nearest approach, however, to a complete synthesis of the unique morphine ring structure has been achieved by R. Grewe,[38, 120] who by applying the Bogert reaction [121] to 1-benzyl-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro*iso*quinoline obtained a four-ring compound (see Table, Group 16) to which he first gave the name morphan [38], later amended to *N*-methylmorphinan.[120] He described the history of this work in an admirable

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[111] R. Robinson and Shigehiko Sugasawa, *J.*, 1931, 3173.

[112] Zenjiro Kitasato and R. Robinson, *J.*, 1932, 785.

[113] R. Robinson and Shigehiko Sugasawa, *ibid.*, p. 789.

[114] *Idem*, *J.*, 1933, 280.

[115] C. Schoepf and K. Thierfelder, *Annalen*, 1932, **497**, 22.

[116] C. Schoepf, H. Perrey, and I. Jäckh, *ibid.*, p. 47.

[117] *Idem, ibid.*, p. 59.

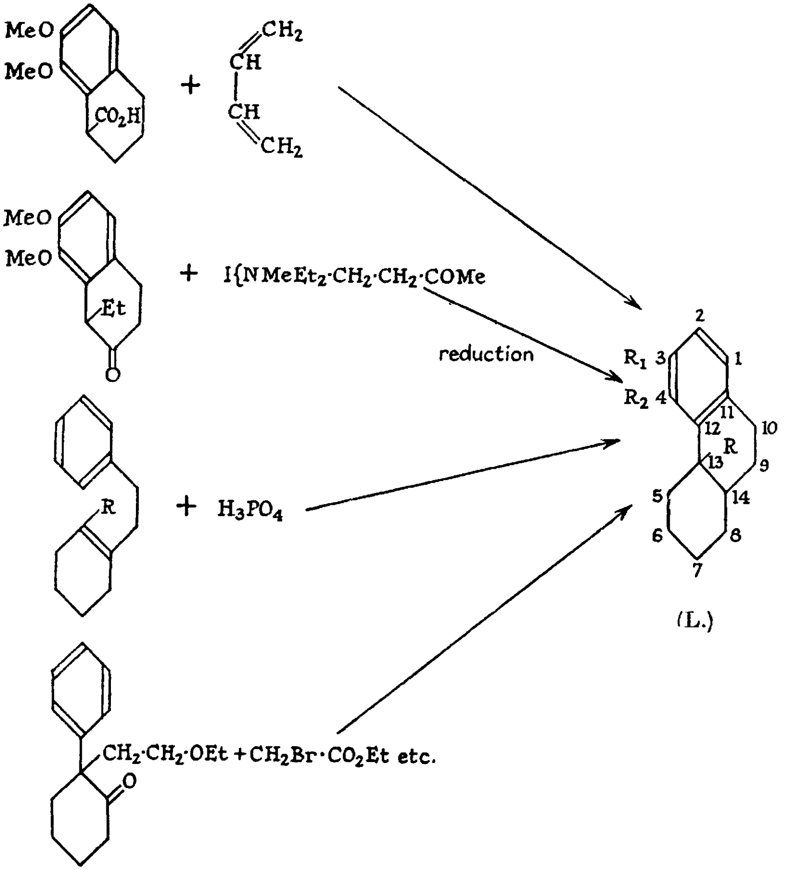
[118] C. Schoepf and K. Thierfelder, *ibid.*, 1939, **537**, 143.

[119] *J.*, 1947, 399.

[120] R. Grewe, *Z. angew. Chem.*, 1947, **59**, 194.

[121] D. Perlman, D. Davidson, and M. T. Bogert, *J. Org. Chem.*, 1936, **1**, 288.

lecture in Goettingen in 1946 [38] and later supplemented it in a survey " Synthetische Arzneimittel mit Morphin-Wirkung ".[120] Before proceeding to consider his work, of which we can give here only an outline, and that of O. Schnider and A. Grüssner on 3-hydroxymorphinan,[128, 129] we should like to mention three attempts by other authors in the same field. To obtain phenanthrene derivatives carrying angular substituents in position 13 (L), L. F. Fieser and H. L. Holmes [122, 123] used the addition of butadiene to dihydronaphthalene derivatives, and R. Ghosh and R. Robinson [124] the condensation of a tetralone derivative with 4-diethylaminobutan-2-one methiodide but no further progress towards the morphine structure has been



(L.)

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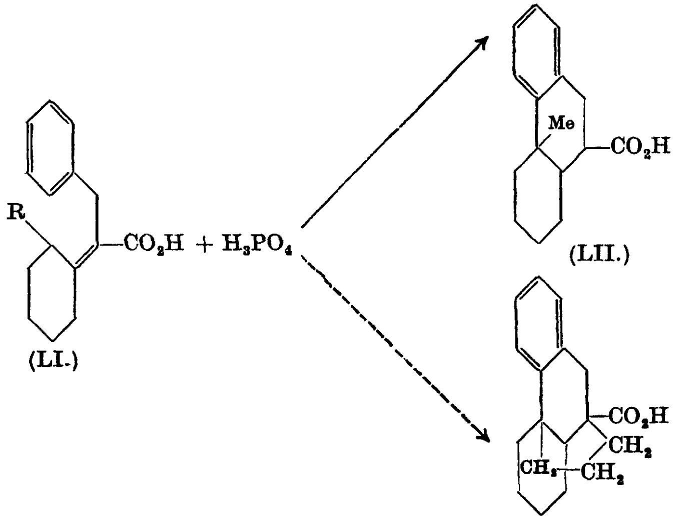
[122] *J. Amer. Chem. Soc.*, 1936, **58**, 2319.
[123] *Ibid.*, 1938, **60**, 2548.
[124] *J.*, 1944, 506.

reported. On the other hand, M. S. Newman and B. J. Magerlein,[125] starting from 2-phenyl-2-(2-ethoxyethyl)*cyclo*hexanone prepared 10-keto-13-(2-ethoxyethyl)-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthrene (L ; $R = CH_2{\cdot}CH_2{\cdot}OEt$; position 10 = $>CO$) which gave *via* the corresponding oxime and amine in very small yield a 4-ring compound which is isomeric with morphinan.

R. Grewe,[126, 127] likewise, first studied the synthesis of phenanthrene derivatives substituted in position 13 ; he treated phenylethyl*cyclo*hexene derivatives with warm phosphoric acid according to M. T. Bogert *et al.*,[121] and so obtained, especially when (L ; $R = CH_2{\cdot}CH{:}CH_2$), the desired phenanthrene compound with angular substituents on carbon 13. He then succeeded in the course of his investigations in bringing about a similar ring closure with the unsaturated acid (LI ; R = Me) to give 13-methyloctahydrophenanthrene-9-carboxylic acid with a reactive group in position 9 (LII) ; but if in place of the methyl group the starting material carried again an allyl side chain (LI ; $R = CH_2{\cdot}CH{:}CH_2$) the resulting product (LIII) was a four-ring system. Although this was encouraging as the substance showed similarity to the morphine skeleton, the compound itself was useless for further practical changes. This led Grewe to the conclusion that he would succeed in his aim if he started his reaction with 1-benzyl-2-methyloctahydro*iso*quinoline (LIV). This compound could be prepared



(LI.)

(LII.)

(LIII.)

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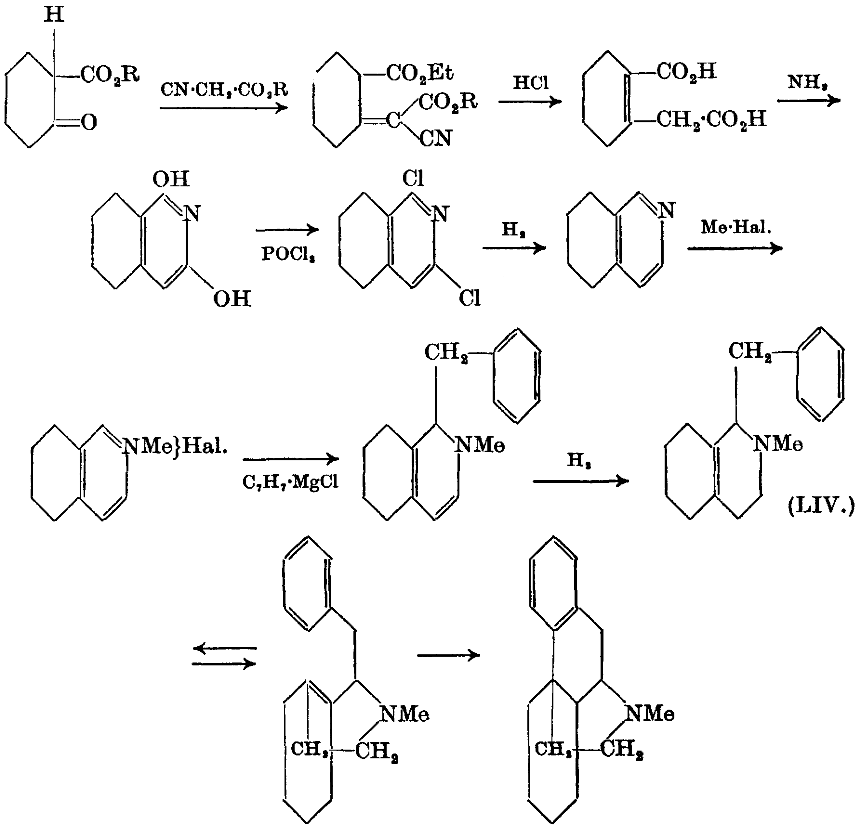
[125] *J. Amer. Chem. Soc.*, 1947, **69**, 942.
[126] *Ber.*, 1939, **72**, 426, 785, 1314.
[127] *Ibid.*, 1943, **76**, 1072, 1076.

in relatively good yield from ethyl*cyclo*hexanone-2-carboxylate *via* the following intermediates :



(LIV.)

(LV.)

When it was warmed with phosphoric acid, a new base, 2-methyl-5 : 9-tetramethylene-6 : 7-benzo-2-aza*bicyclo*(1 : 3 : 3)non-6-ene (*N*-methylmorphinan) was formed (LV). This obviously differs from deoxydihydromorphine (X) only through the lack of a phenolic hydroxyl group in position 3 and of the ether-oxygen bridge connecting carbons 4 and 5. It was a fitting climax to such an elegant synthesis that *N*-methylmorphinan on pharmacological testing was found to possess considerable analgesic activity. It has been found recently that 3-hydroxy-*N*-methylmorphinan, prepared by three different methods, and its ethers and acyl derivatives, possess considerable activity, while the 2- (or 4-) hydroxy-isomer and the *N*-ethyl homologues are useless as analgesics.[128, 129] In clinical trials 3-hydroxy-*N*-methylmorphinan surpasses morphine in the intensity and duration of the

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[128] Schweiz. PP. 252,755, 254,106.

[129] Jubilee Vol., P. Karrer, in the press.

analgesia produced, and has the added advantage of being equally effective when given by mouth.

IV. *Summary and Outlook*

(a) *Constitution and Activity.*—The problem of the relationship between constitution and activity in the field of analgesics is, as with many other branches of therapeutics, a very difficult one. The first period of synthetic work, after the recognition of the essential features of the morphine structure, was more directed towards alterations of the natural prototype than towards total synthesis. This was done without any preconceived idea as to the influence of the peripheral substituents on the efficacy of the drugs. Attempts at the total synthesis suffered from the extreme complexity of the morphine molecule, and it is in this light that we have to regard the earlier pioneer work of R. Robinson and his school and even the later success of R. Grewe.

When the American team started out on the search for the pharmacodynamic group of analgesic action, their method of preparing hundreds of compounds containing certain fragments of the morphine anatomy was the only possible one, as nobody knew at that time which were the essential elements for pharmacological potency and whether, indeed, the whole condensed ring system of the alkaloid was necessary. It is a fact that the discovery by Schaumann and Eisleb of the analgesic property of 4-phenylpiperidines was a fortuitous one, and it is also true that the remarkable development in recent years of still more potent substances was more stimulated by this chance discovery in 1938 than by a rational working hypothesis based on the morphine structure. Numerous surveys can be found in the literature on the subject of constitution and pharmacological action in this field. If we study these papers, such as those by E. Fourneau,[26] E. Mosettig,[42] A. D. Macdonald *et al.*,[67] A. L. Morrison and H. Rinderknecht,[53] J. Lee *et al.*,[54] R. Grewe,[38, 120] C. C. Pfeiffer,[16] and others, we can follow the historical development of theories, but are struck by the relatively slow progress made towards a simple answer to this question. This is partly due to the lack of a clear-cut idea as to the mechanism of analgesic action, and partly to the difficulty of collecting sufficient chemical, and the even greater difficulty of collecting sufficient physicochemical, data.

Where do we stand now ? We know that in *N*-methylmorphinan and in 3-hydroxy-*N*-methylmorphinan, which of all synthetic compounds approximate most closely to morphine, we have substances of distinct potency. According to Grewe the steric arrangement, which plays an all-important part in the opium alkaloid field, appears to be identical in morphine and morphinan. When one builds up an atomic model of *N*-methylmorphinan one is forcibly impressed by the ease with which the benzyl*iso*quinoline derivative forms a bond between the morphine positions 12 and 13 and produces the steric arrangements and compactness of the morphine molecule.

The phenanthrene and dibenzfuran fragments alone are not carriers of pronounced analgesic activity. It is, therefore, surprising that the 4-phenylpiperidines, having far less rigid steric properties than morphine alkaloids or morphinan, should exert such distinct action. This may be explained, of course, by the existence of a quaternary carbon atom which also carries a group simulating the hydroaromatic ring of morphine, as can be readily seen from an atomic model of pethidine. On changing the carbethoxy-group of this synthetic analgesic for the isomeric propionoxy-group, its carbonyl oxygen atom, according to J. Lee *et al.*,[75] occupies spatially the exact position of the ether-oxygen, while the two alkyl carbon atoms simulate carbon atoms 6 and 7 of the morphine molecule. The American workers, failing to obtain increased activity with the longer butyroxy-chain, speculated that position 8 of the morphine skeleton might be filled by a methyl group meta to the nitrogen in the piperidine ring and, furthermore, solely from stereochemical considerations of the morphine structure, one of the two possible stereoisomers should possess enhanced potency. This was found to be correct, as one possible form, the *trans*-isomer, of 4-propionoxy-4-phenyl-1 : 3-dimethylpiperidine, was more active than the other stereoisomer.

Up to this point, there seems to be no doubt that those substances which contain almost unimpaired certain elements of morphine, such as the phenyl and piperidine rings and an appropriate chain or ring on the quaternary carbon, are true morphine-like analgesics. One might have to be less dogmatic about the necessity for certain peripheral groups or for the aromatic ring, as J. Lee *et al.*[54] have shown that 4-propionoxy-4-*cyclohexyl*-1-methylpiperidine still possessed one-third of the activity of the phenyl analogue.

But, when we consider the case of diphenylpropylamine derivatives, such as amidone, we have here at first sight a molecule which differs widely from the natural prototype. This is often stressed in current literature, and it is true that no known derivatives of morphine in which the piperidine ring has been opened possess measurable activity ; yet when an atomic model is made, the spatial compactness of amidone and its close similarity to morphinan and the phenylpiperidines becomes evident. The function of the second phenyl group seems to be that of imparting spatial rigidity to the 2-dialkylaminopropyl side chain. Unless future *X*-ray measurements should produce a different picture of the atomic arrangements, one cannot deny that the amidone series falls into line with the other synthetic analgesics in their close relationship to the natural mother substance.

(b) *Future Trends.*—It is a common and understandable desire that the chemist who is engaged on the synthesis of therapeutically useful compounds, whether they are analgesics, spasmolytics, antibiotics, or any other, should look for a rational basis for his future work. It was mentioned in the introduction that C. C. Pfeiffer [16, 17] attempted to develop a theoretical background for such a planned approach. Whether his working hypothesis will help to speed up the development of more potent and less toxic compounds, only the future will show. True, one is tired of the " hit and miss " methods of the past and welcomes fervently a more ordered conception of the problem. Although Robinson's biogenetic theory has given to the alkaloid chemist a considerable stimulus, it must be admitted that more data will have to be collected empirically, particularly by the physicochemical and biochemical sciences, before the synthetic chemist can design his molecules to have specific pharmacological properties.

Apart from the total synthesis of morphine itself, which has still to be carried out, Grewe's morphinan synthesis promises, as he says himself, "The preparation of numerous substances of morphine-type which will be marked by a specific pharmacological effect." We may hope for a development of Barltrop's synthesis of meta-bridged nitrogen ring systems, and of Newman and Magerlein's efforts to give perhaps alternative preparations of compounds of the morphinan and morphine series.

When looking back at the analgesics belonging to the phenylpiperidine and diphenylpropylamine groups, there is every chance that addition of peripheral groups and slight variation in the skeleton may produce new active members of the existing family. In this connection one will remember that the acetylated alcohols corresponding to the ketones of the amidone group have recently been reported as possessing outstanding therapeutic effect.[90]

In spite of all the successes, especially during the last ten years, one goal appears to be so far unattainable, namely to produce an analgesic which is *completely* free from the danger of addiction. It is to be hoped that some of the newer representatives which, in contrast to pethidine, have not had their full share of intensive clinical evaluation, may turn out to be milestones on the road to this ideal.