SYNTHETIC APPROACHES TO THE MORPHINE STRUCTURE

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In recent years three broadly defined methods of approach to the chemistry of the morphine alkaloids have been clearly discernible. The older fields, elucidation of structure of the naturally occurring alkaloids by degradation and partial synthesis, and ultimate proof by total synthesis, have been supplemented, particularly since the discovery of Pethidine,[1] by the energetically pursued search for synthetic analgesics embodying those portions of the morphine molecule which give rise to its valuable properties, and lacking others which are pharmacologically undesirable.

This great amount of systematic work has led to the synthesis of a very large number of compounds bearing a steric rather than a chemical resemblance to morphine; the greater simplicity and accessibility of these series of "model" compounds did not, generally, require the development of synthetic methods directly applicable to syntheses of morphine alkaloids, and the chemistry of the synthetic analgesics is, therefore, generally considered as a subject only distantly related to the alkaloid field. The ample reviews [2, 3, 4] dealing with synthetic analgesics of necessity treat the attempted syntheses and recent developments in the morphine field only briefly, and the last complete review of this subject appears to be the monograph by Small and Lutz,[5] published before attempts at the rational synthesis of the morphine structure were far advanced. Later work in the United States, including reactions of the alkaloids, syntheses of simple phenanthrene and dibenzofuran derivatives, and pharmacological investigations of the products prepared, is summarised in another monograph [6] and requires no further review.

As recent synthetic work [7, 8] has at last proved the structure proposed by Gulland and Robinson [9] for morphine, the time is opportune for a review of the attempted syntheses of this most complex molecule which are now approaching fruition.

The unique fused-ring system of morphine (I) with its five asymmetric carbon atoms (cf. Small and Lutz [9a]) is, in theory, approachable by a large

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

[2] Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 349.

[3] Fourneau, *Chim. et Ind.*, 1938, **39**, 1043.

[4] Grewe, *Angew. Chem.*, 1947, **59**, 194.

[5] "The Chemistry of the Opium Alkaloids", Suppl. No. 103 to the Public Health Reports, U.S. Treasury Dept., 1932.

[6] Small, Eddy, Mosettig, and Himmelsbach, "Studies on Drug Addiction", Suppl. No. 138 to the Public Health Reports, U.S. Treasury Dept., 1938.

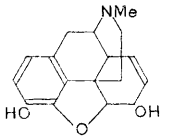
[7] Grewe, Mondon, and Nolte, *Annalen*, 1949, **564**, 161.

[8] Gates and Tschudi, *J. Amer. Chem. Soc.*, 1950, **72**, 4839.

[9] *J.*, 1923, **123**, 980; *Mem. Proc. Manchester Lit. Phil. Soc.*, 1924—5, **69**, 79.

[9a] Ref. 5, p. 354.

number of different synthetic routes and, whilst no synthesis of morphine has hitherto been published, several teams of workers have succeeded in obtaining polycyclic compounds bearing an obvious formal relation to morphine although lacking at least one of the five rings. These syntheses were undertaken generally with the intention of building up large parts of the morphine molecule, either as starting materials for the ultimate total synthesis of morphine, or for comparison with degradation products of morphine to establish the last doubtful feature of the Gulland–Robinson formula (I), the point of attachment of the ethanamine part of the nitrogenous ring to the phenanthrene nucleus.



(I)

Preliminary syntheses of small fragments of the morphine molecule for pharmacological evaluation (cf. Bergel and Morrison [2]) or for improved preparations of intermediates (cf., *e.g.*, Ginsburg and Pappo [10]; Soffer, Stewart, Cavagnol, Gellerson, and Bowler [11]) are so numerous that they must be considered outside the scope of this Review.

Syntheses in the Phenanthrene Field

The structural formula (I) proposed for morphine by Gulland and Robinson [9] had found general acceptance by 1932 (cf. Small and Lutz [5]); it was based entirely on degradations of morphine and related substances to phenanthrene derivatives, many of which had been identified and then synthesised by Pschorr's general methods.[12] In view of the importance of phenanthrene derivatives in the formulation of morphine, it is not surprising that several of the projected syntheses aimed in the first place at phenanthrene systems, particularly those substituted in the "angular" position at $C_{(13)}$, the expected position of attachment of the nitrogenous ring.

The first successful synthesis of this type of compounds, by Fieser and Holmes,[13] was based on the discovery [14] that an activated cyclic olefinic link can undergo the diene synthesis. Thus they prepared ethyl 3 : 4-dihydronaphthalene-1-carboxylate (II; R = H) (and 7-substituted compounds derived therefrom) by cyclisation of the condensation product of 3-phenylpropane-1-carboxylates and ethyl oxalate, and treated it with butadiene or 2 : 3-dimethylbutadiene under drastic conditions (*e.g.*, 41 hours at 150°). The product, obtained in about 25% yield, was a substituted hexahydrophenanthrene-13-carboxylate (III) and bore a close formal relation to morphine degradation products, such as the ethyloctahydroketomorphenol methyl ether (IV)[15] or deoxyhexahydromethylmorphimethine dimethyl ether (V).[16]

For a closer approach to the morphine molecule, suitable substituents

[10] *J.*, 1951, 516; cf. Bergmann, Pappo, and Ginsburg, *J.*, 1950, 1369.

[11] *J. Amer. Chem. Soc.*, 1950, **72**, 3704; cf. *ibid.*, 1949, **71**, 385.

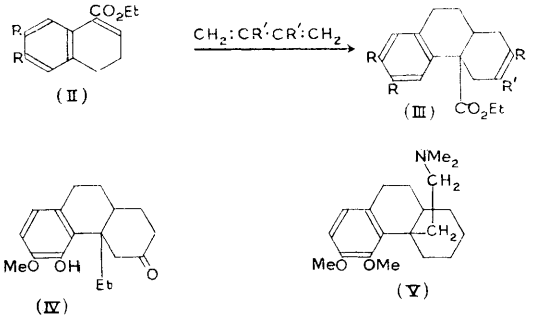
[12] Pschorr, *Ber.*, 1896, **29**, 496; 1900, **33**, 176; Pschorr and Sumuleanu, *ibid.*, p. 1810; Pschorr, Seydel, and Stöhrer, *ibid.*, 1902, **35**, 4400.

[13] Fieser and Holmes, *J. Amer. Chem. Soc.*, 1936, **58**, 2319; 1938, **60**, 2548.

[14] Fieser and Hershberg, *ibid.*, 1935, **57**, 2192.

[15] Cahn, *J.*, 1930, 702. [16] Speyer and Koulen, *Annalen*, 1924, **438**, 34.

had to be introduced into the phenanthrene system and the reactivity of the angular ester group examined. Although octahydro-2 : 3-dimethoxyphenanthrene-13-carboxylic acid was accessible [13] (in 35% overall yield), attempts at chain-lengthening at the 13-position were unsuccessful and compounds of the type (IV) or (V) could not be prepared from it. It



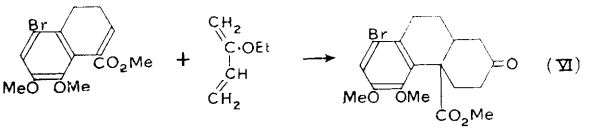
appeared that the angular carboxyl group was reactive to some extent, giving the acid chloride (which failed to undergo Rosenmund reduction to the aldehyde), and the ester which was reduced by sodium in amyl alcohol to the 13-hydroxymethyl derivative; reaction of this with acetic anhydride and phosphorus pentachloride gave the chloromethyl compound which, however, failed to react with potassium cyanide. This promising approach could thus not be fully exploited (cf. also Holmes and Trevoy [17]), and an alternative route through 4-alkyl-1 : 2-naphthaquinone [18] likewise appeared impracticable.

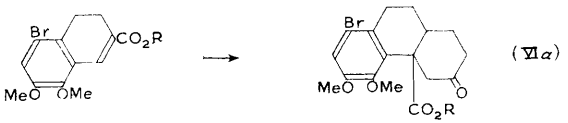
A later attempt by Holmes and Mann [19] to elucidate the position of attachment of the nitrogenous ring aimed at the synthesis of an octahydro-6-ketophenanthrene-13-carboxylate (VI*a*) which should be accessible also from the degradation of morphine or thebaine (cf. Cahn,[15] and substance IV). Diene reaction of methyl 5-bromo-3 : 4-dihydro-7 : 8-dimethoxynaphthalene-1-carboxylate with 2-ethoxybutadiene, however, gave the enol ether which, disappointingly, gave methyl 1-bromo-octahydro-7-keto-3 : 4-dimethoxyphenanthrene-13-carboxylate (VI) on hydrolysis; the desired 6-ketone (VI*a*) should be accessible from the corresponding dihydronaphthalene-2-carboxylate, a ready synthesis of which was not, however, available.

Phenanthrene derivatives closely related to these synthetic products and to possible degradation products of thebaine were prepared by Ghosh and Robinson.[20] They submitted substituted 3-phenylpropane-1-carboxylic acid to internal Friedel–Crafts reaction over stannic chloride, which gave 80—90% yields of the cyclic ketone; the ultimate " angular " alkyl group was then introduced (in good yield) by a Grignard reaction, and the dihydronaphthalene so obtained, on oxidation with hydrogen peroxide in acetic

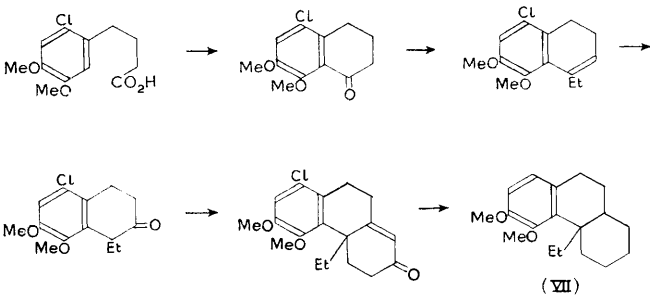
[17] *Canad. J. Res.*, 1944, **22**, *B*, 56, 109.
[18] Fieser and Bradsher, *J. Amer. Chem. Soc.*, 1939, **61**, 417.
[19] *Ibid.*, 1947, **69**, 2000. [20] *J.*, 1944, 506.

acid, gave the tetrahydroketonaphthalene (35% yield); this was condensed with 4-diethylaminobutan-2-one methiodide over sodamide, and the resultant $\alpha\beta$-unsaturated ketone was reduced to 13-ethyloctahydro-3 : 4-dimethoxy-





phenanthrene (VII). Again, the difficulties in the way of introducing an angular group capable of suitable modification prevented further exploitation of this route.

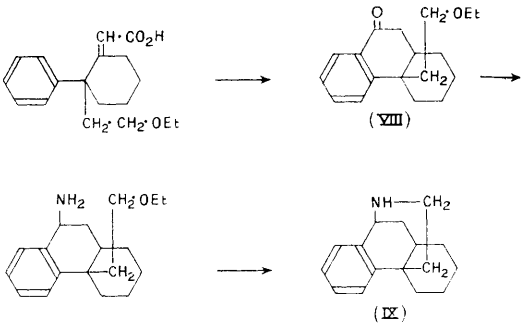


Heterocyclic Syntheses from Phenanthrenes

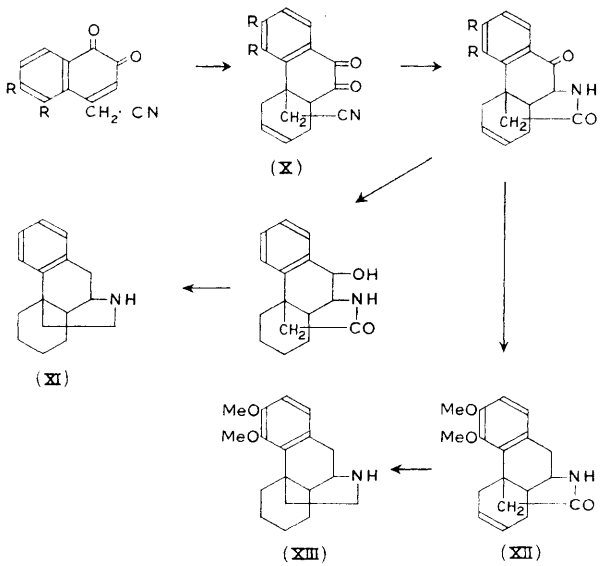
The difficulties connected with the introduction of suitable angular groups were first overcome by Newman and Magerlein[21] in an interesting synthesis of a tetracyclic compound related to morphine in structure. A 13-substituted phenanthrene was synthesised, the 13-substituent of which was capable of reacting with the nuclear substituent at $C_{(10)}$. As indicated in the reaction scheme below, Reformatzky reaction of 2-2′-ethoxyethyl-2-phenyl*cyclo*hexanone and bromoacetic ester, dehydration, and hydrolysis gave 2-2′-ethoxyethyl-2-phenyl*cyclo*hexylideneacetic acid, converted by reduction and internal Friedel–Crafts reaction into the 13-substituted phenanthr-10-one (VIII); the oxime of this ketone was reduced to the amine which cyclised, in poor yield, on treatment with hydrogen bromide to the tetracyclic compound (IX). This differed from the morphine skeleton only in containing a seven-membered (instead of the six-membered) nitrogenous ring and in lacking the oxygen bridge.

[21] *J. Amer. Chem. Soc.*, 1947, **69**, 942.

The nearest approach, however, to the morphine ring structure starting from phenanthrene derivatives has been achieved by Gates and his co-workers,[22, 23, 8] who succeeded in establishing the position of attachment



of the ethanamine chain of the morphine molecule at $C_{(13)}$ soon after this proof had been given by a different route by Grewe and his co-workers [7, 28] (see also below). The starting material used by Gates and Newhall [22] was 13-cyanomethyl-5 : 8 : 9 : 10 : 13 : 14-hexahydro-9 : 10-diketophenanthrene (X; R = H), obtained by diene synthesis from butadiene and 4-cyano-



methyl-1 : 2-naphthaquinone. An improved preparation of this diketone was given by Gates, Woodward, Newhall, and Künzli.[23] These authors also proved [23, 24] by infra-red spectrography that hydrogenation of the

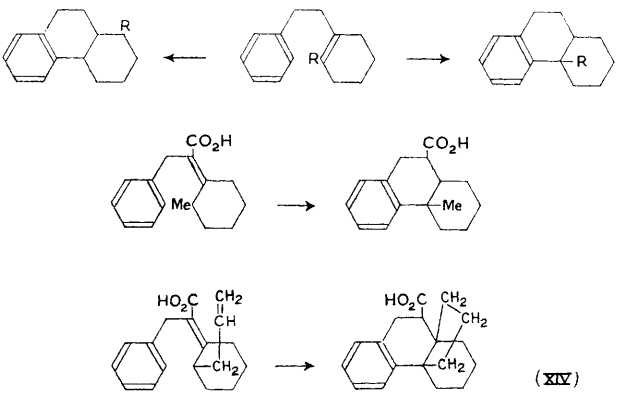
[22] Gates and Newhall, *J. Amer. Chem. Soc.*, 1948, **70**, 2261.
[23] Gates, Woodward, Newhall, and Künzli, *ibid.*, 1950, **72**, 1141.
[24] Gates and Newhall, *Experientia*, 1949, **5**, 285.

diketone (X; R = H) over copper chromite at moderate temperatures and pressures resulted in cyclisation to the lactam, and that hydrogenation of the dihydro-compounds produced over Raney nickel gave, ultimately, a tetracyclic hexahydro-compound which on hydrogenation over copper chromite under vigorous conditions (220° and 140 atm.) gave, in 80% yield, a compound (XI) with the basic morphine skeleton. This substance was shown, by direct comparison, to be isomeric with Grewe's morphinan [25] and was therefore called *iso*morphinan.

In the most recent paper of this series, Gates and Tschudi [8] disclosed the successful synthesis of *rac.*-β-Δ^6-deoxydihydrocodeine methyl ether (XIII), starting from the 3:4-dimethoxy-derivative (X; R = OMe). Cyclisation by hydrogenation over copper chromite gave the keto-lactam, reduced by the Kishner–Wolff procedure and remethylated to the lactam (XII); when this was reduced by lithium aluminium hydride, the olefinic linking was preserved, and *N*-methylation of the product gave the desired β-Δ^6-deoxydihydrocodeine methyl ether (XIII). Both epimers about $C_{(14)}$ of this were prepared for comparison purposes and it was thus found that the product (XIII) differed from the compounds obtained from dihydrothebainol [26] by methylation, esterification with toluene-*p*-sulphonyl chloride, and removal of toluene-*p*-sulphonic acid in boiling collidine. The product (XIII) was, however, identical with the substance obtained from β-dihydrothebainone [27] by reduction and subsequent methylation, etc., as above. This synthesis, therefore, not only proved the point of attachment of the ethanamine chain at $C_{(13)}$, but also confirmed the steric configuration of the synthetic material at $C_{(14)}$ as epimeric to that of natural morphine.

Other Syntheses of Heterocyclic Systems

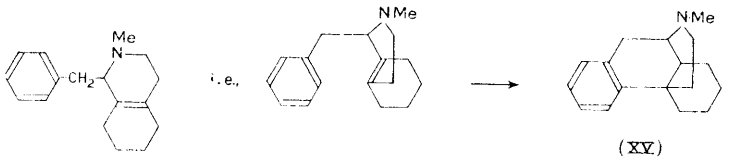
Grewe [28] studied the cyclisation of substituted 1-2′-phenylethyl*cyclo*hex-1-enes with phosphoric acid in attempts to prepare 13-substituted phenan-



(XIV)

[25] *Ber.*, 1948, **81**, 279.
[26] Skita, Nord, Reichert, and Stukart, *ibid.*, 1921, **54**, 1562.
[27] Small and Browning, jun., *J. Org. Chem.*, 1939, **3**, 618.
[28] *Ber.*, 1939, **72**, 426, 785, 1314; 1943, **76**, 1072, 1076.

threnes. He found that cyclisation proceeded in the desired direction when the 2-substituent R was methyl or allyl, but that a carbomethoxyl or 2-dimethylaminoethyl substituent appeared in the 8-position after cyclisation. Extension of this work to 1-(1-carboxy-2-phenylethylidene)*cyclo*hexane gave the 13-substituted octahydrophenanthrene-9-carboxylic acid when the substituent R was a methyl group, but, surprisingly, an allyl substituent gave a tetracyclic compound (XIV). These encouraging and partly fortuitous results led Grewe and Mondon [25] to investigate analogous ring-closures in the 1-benzyloctahydro*iso*quinoline series : these proceeded surprisingly cleanly under drastic acid conditions to give a tetracyclic compound (XV) containing, but for the oxygen bridge, the whole ring skeleton of morphine. The parent substance (XV) is called *N*-methylmorphinan.



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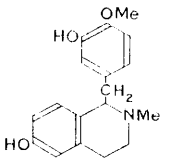


(XVI)

This cyclisation is reminiscent (cf. Grewe [4]) of the remarkable original theory of the biogenesis of morphine from 1-benzyl*iso*quinoline derivatives (such as XVI), formulated by Robinson and Sugasawa.[29] Early attempts to substantiate this hypothesis in the laboratory led to the laborious synthesis [29, 30] of 1 : 2 : 3 : 4-tetrahydro-6-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-7-methoxy-2-methyl*iso*quinoline (XVI) and of the closely related laudanosoline methyl and dimethyl ethers by Schöpf and his co-workers.[31] None of these tetrahydro*iso*quinolines could, however, be cyclised by any of the methods tried, and these " phytosynthetic " attempts had to be abandoned.

No further attempts at synthesising structures of the morphine type incorporating nitrogenous rings are on record before Koelsch's discovery [32] that an internal Michael condensation of substituted *o*-methoxycinnamates proceeded uninhibited by substituents at the ethylenic linking and gave a benzofuran. His attempted synthesis and use of the substituted tetrahydro-4-phenylpyridine (XVII) have not as yet been published, however (see also Koelsch and Lucht [33]).

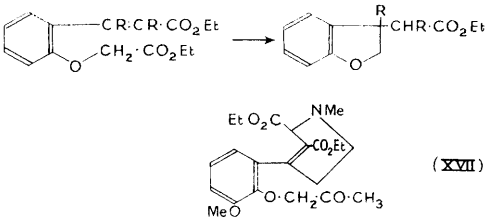
[29] *J.*, 1931, 3163, 3173 ; 1932, 789.

[30] Kitasato and Robinson, *J.*, 1932, 785.

[31] Schöpf and Thierfelder, *Annalen*, 1932, **497**, 22 ; 1939, **537**, 143 ; Schöpf, Perrey, and Jäckh, *ibid.*, 1932, **497**, 47 ; Schöpf, Jäckh, and Perrey, *ibid.*, p. 59.

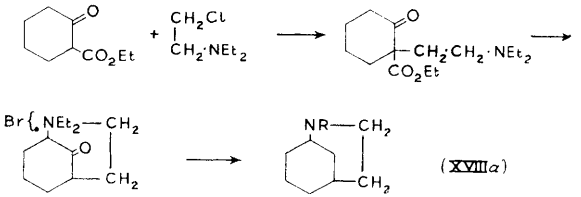
[32] *J. Amer. Chem. Soc.*, 1945, **67**, 569. [33] *Ibid.*, 1949, **71**, 3556.

In fact, it was not until recently [34] that the synthesis of the 2-aza*bicyclo*-[3 : 3 : 1]nonane system (XVIII; trivial name: morphan) present in the



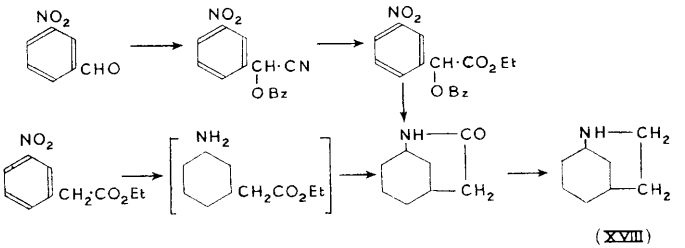
(XVII)

morphine structure was achieved by the condensation of ethyl *cyclo*hexanone-2-carboxylate with 2-diethylaminoethyl chloride and cyclisation of the product with bromine.



(XVIII*a*)

The synthesis of the parent substance morphan (XVIII) is also the subject of two more recent papers. Cronyn [35] condensed *m*-nitrobenzaldehyde with benzoyl chloride and sodium cyanide, hydrolysed the nitrile, and cyclised the resulting nitro-ester by hydrogenation over Raney nickel at 200°; finally hydrogenation of the lactam (obtained in 35% yield) over copper chromite gave morphan.



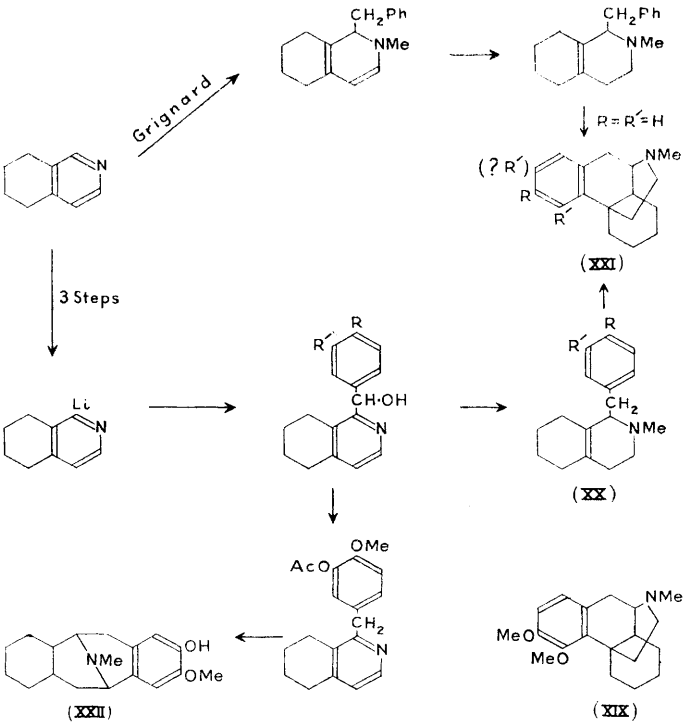
(XVIII)

Ginsburg's elegant two-stage synthesis [36] started from *m*-nitrophenylacetate, hydrogenation of which over Adams's catalyst gave *cis-m*-amino*cyclo*hexyl acetate directly; this gave the lactam spontaneously, and reduction with lithium aluminium hydride then completed the synthesis.

[34] Barltrop, *J.*, 1947, 399.
[35] *J. Org. Chem.*, 1949, **14**, 1013.
[36] *Ibid.*, 1950, **15**, 1003.

None of these syntheses of heterocyclic systems forming part of the morphine structure, however, approached very closely to morphine, and it was not until the results of Grewe and Mondon,[28] and of Grewe, Mondon, and Nolte [7] were published that a synthesis of morphine from pre-formed heterocyclic compounds appeared likely. The work of Grewe and his co-workers rested on the discovery, already briefly mentioned, that compounds of the 1-benzyloctahydro*iso*quinoline series cyclise under the influence of acid to a tetracyclic compound of type (XV), obviously closely related to morphine.

In the original synthesis [25] 5 : 6 : 7 : 8-tetrahydro-1 : 3-dihydroxy*iso*quinoline, obtained from the condensation product of ethyl *cyclo*hexanone-2-carboxylate and ethyl cyanoacetate by hydrolysis and reaction with ammonium carbonate, was converted through the 1 : 3-dichloro-compound into the immediate starting material, 5 : 6 : 7 : 8-tetrahydro*iso*quinoline. Reaction with methyl iodide and with benzylmagnesium chloride thence gave 1-benzyl-1 : 2 : 5 : 6 : 7 : 8-hexahydro-2-methyl*iso*quinoline, converted



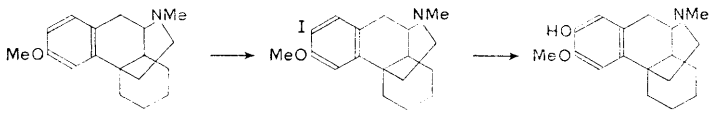
by hydrogenation into the desired octahydro-compound; this cyclised in phosphoric acid at 150° to *N*-methylmorphinan.

This remarkable cyclisation was then [7] applied to the preparation of

deoxytetrahydrocodeine (XIX). Because of the nuclear substituents, however, the Grignard reagent could not be used for introducing the benzyl group. The alternative procedure adopted involved amination of 5 : 6 : 7 : 8-tetrahydro*iso*quinoline with sodamide and replacement of the amino-group, under carefully controlled conditions, by bromine. The bromide with butyl-lithium in ether at — 35° gave the lithium compound which reacted with (substituted) benzaldehyde to give the carbinol. A variety of ways was found for the conversion of this into the corresponding benzyloctahydro-*iso*quinoline : the simplest was direct reduction with sodium in ethanol, but an alternative, of wider applicability to the substituted compounds, involved conversion of the carbinol into benzyltetrahydro*iso*quinoline, either through the bromide by zinc-dust reduction or through the ketone by Clemmensen reduction, and hydrogenation of benzyltetrahydro*iso*-quinoline methiodide over a platinum catalyst in presence of a trace of iodine. This hydrogenation, which appears to be without precedent, afforded 1-benzyl-Δ^9-octahydro-2-methyl*iso*quinoline directly in excellent yield.

Cyclisation of the octahydro-compounds carrying substituents again proceeded in strong acid at high temperatures, and the compound (XX; R = OMe, R′ = H) obtained from *p*-anisaldehyde afforded, in good yield, 3-hydroxy-*N*-methylmorphinan (XXI; R = OH, R′ = H), which had previously been prepared for pharmacological tests by Schnider and Grüsser [37] from tetrahydro*iso*quinoline, methyl bromide, and *p*-methoxybenzylmagnesium bromide by the method of Grewe and Mondon [25] and has since been shown to have strong morphine-like analgesic action.

In an attempt [7] to prepare deoxytetrahydrocodeine (XIX) directly from 3-hydroxy-*N*-methylmorphinan, this was brominated by pyridine hydrobromide perbromide, but hydrolysis of the resulting mixture of mono- and di-bromo-derivatives proved troublesome. 3-Methoxy-*N*-methylmorphinan could, however, be titrated with iodine in alkaline solution, and the mono-iodo-compound so obtained was converted by butyl-lithium in ether into the lithium compound; this, when oxygen was passed through its solution, furnished a hydroxy-3-methoxy-*N*-methylmorphinan which was soluble in alkali, readily methylated, and negative to Gibbs's reagent (*p*-position blocked). It was concluded that this compound was the 2- and not the desired 4-hydroxy-compound.



Since these reactions failed to give deoxytetrahydrocodeine (XIX), Grewe, Mondon, and Nolte [7] condensed the 1-lithium derivative of 5 : 6 : 7 : 8-tetrahydro*iso*quinoline with benzyl*iso*vanillin (3-benzyloxy-4-methoxybenzaldehyde). Conversion of the resultant carbinol into the bromide, by

[37] Grewe, Pohlmann, and Schnoor, *Ber.*, 1951, **84**, 527; cf. B.P. Appl. 20,349/50.

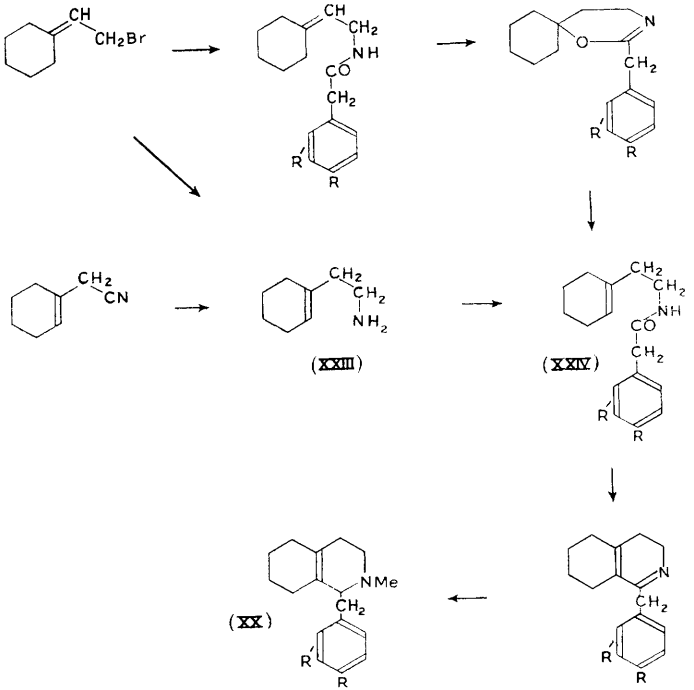
concentrated hydrobromic acid, and zinc-dust reduction gave the substituted 1-benzyltetrahydro*iso*quinoline carrying a free phenolic hydroxyl group, methylation of which with methyl iodide proved difficult. Moreover, the acetyl derivative could not be converted into the octahydro*iso*quinoline, because the methiodide only absorbed one mol. of hydrogen on hydrogenation and cyclised, probably to (XXII). Finally, therefore, diazomethane was used for the methylation of the phenolic group. Rapid hydrogenation of the resulting benzyltetrahydrodimethoxy*iso*quinoline over platinum in presence of methyl iodide and of a trace of iodine gave smoothly the desired octahydro-compound, but on slow hydrogenation some decahydro-compound was also produced. Slow cyclisation of the benzyloctahydro*iso*quinoline with concentrated hydrochloric acid at 120° gave (±)-deoxytetrahydrocodeine (XIX) directly, though in small yield. This product proved to be identical with racemic material obtained by mixing the deoxytetrahydrocodeines from natural dehydrothebainone and sinomenine, and this identity established for the first time the attachment of the ethanamine chain at $C_{(13)}$ of the phenanthrene nucleus.

The direct comparison of the *N*-methylmorphinan obtained by Grewe and Mondon [25] with the material of Gates and his co-workers [22, 23, 24] left no doubt that the substances were epimers at $C_{(14)}$, and the latter material is, in fact, identical with a by-product of the cyclisation reaction of Grewe and Mondon.[25] There are, therefore, at present, two synthetic methods by which a tetracyclic morphinan system, closely related to that of the morphine alkaloids, may be built up; the only major feature of the morphine skeleton missing in the morphinans is the oxygen bridge. Both methods are, on paper, capable of furnishing ultimately synthetic morphine or codeine (or isomers thereof), and it is curious and unexpected that both epimeric main products, *N*-methylmorphinan and its isomer, have strong analgesic properties.

For the synthesis of morphine by Grewe's method, substituted octahydro-*iso*quinolines are required as starting materials. This class of compound is not well known, but has recently received considerable attention both by Grewe and his co-workers [37] and by Schnider and his co-workers [38, 39] at Hoffmann-La Roche.[40] Schnider and Hellerbach [38] have described an elegant synthesis of 1-benzyloctahydro*iso*quinolines from amides of 2-*cyclo*hex-1′-enylethylamine and substituted phenylacetic acids (cf. Schlittler and Müller [41]). 1-Cyanomethyl*cyclo*hexene, prepared from *cyclo*hexanone and cyanoacetic acid, was converted into the desired unsaturated amine by hydrogenation over Raney cobalt or by reduction with lithium aluminium hydride. These methods of reduction left the required olefinic linking intact. The amide obtained from this amine with phenylacetic acid, readily cyclised over phosphorus pentachloride to the hexahydro*iso*quinoline, the methobromide of which on hydrogenation in alkaline solution furnished the

[38] *Helv. Chim. Acta*, 1949, **32**, 821; cf. also B.P. 620,258.
[39] Schnider and Hellerbach, *Helv. Chim. Acta*, 1950, **33**, 1437.
[40] Hoffmann-La Roche, B.P. 633,266; B.P. Appl. 26,912/50.
[41] *Helv. Chim. Acta*, 1948, **31**, 914.

desired octahydro*iso*quinoline. This, then, was one method by which a wide range of octahydro*iso*quinolines were available as starting materials for possible morphine synthesis.



Grewe's latest synthesis [37] of the octahydro*iso*quinoline system starts from *cyclo*hexylidene-ethyl bromide; reaction [42] of this with hexamethylenetetramine and then with acid, proceeds with shift of the olefinic linking and gives the amine (XXIII), identical with that of Schnider and Hellerbach.[38] On reaction of the bromide with (substituted) phenylacetamide, however, the olefinic link remains, and acid treatment then gives a dihydro-oxazine spiran in quantitative yield; this on heating rearranges, again quantitatively, to the *cyclo*hexenylethylamide (XXIV), which is cyclised by phosphorus oxychloride in the usual manner. This synthesis proceeds in high yield at all stages and provides an advantageous alternative route, of wide applicability, to the octahydro*iso*quinolines.

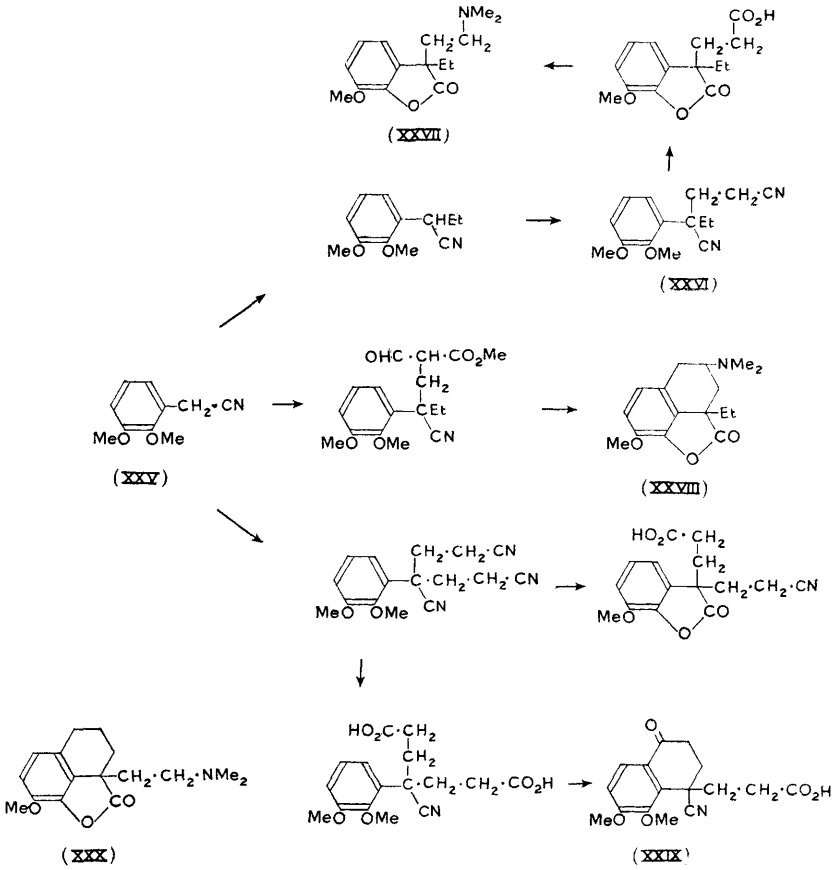
Syntheses from Phenyl*cyclo*hexanones

A third approach which promises to lead to polycyclic compounds closely related to morphine is that of Horning and his co-workers.[43] The starting material for these syntheses, which so far have produced a number of "model" compounds, was 2 : 3-dimethoxybenzyl cyanide (XXV), contain-

[42] Hahn and Walter, *Ber.*, 1921, **54**, 1531; Delépine, *Compt. rend.*, 1895, **120**, 501.
[43] Horning and Schock, *J. Amer. Chem. Soc.*, 1948, **70**, 2941, 2945; 1949, **71**, 1359.

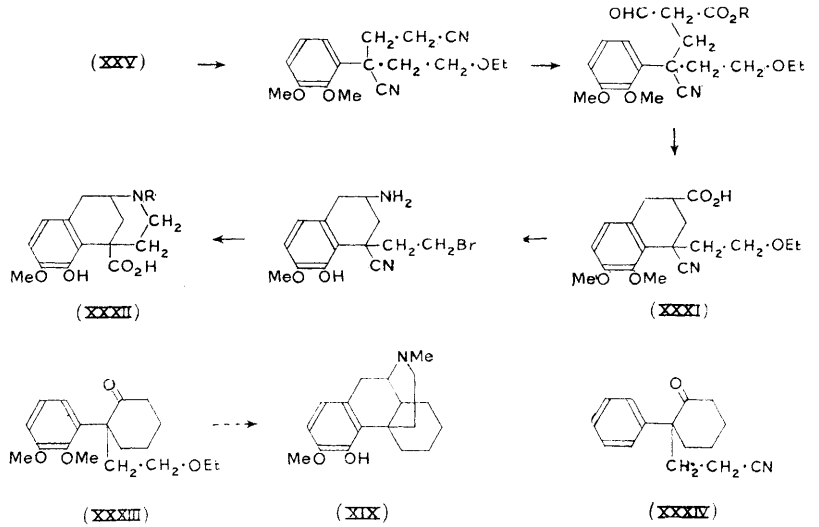
ing a methylene group reactive towards sodium and thus readily alkylated, and towards acrylonitrile which causes cyanoethylation in the usual manner. Ethylation and subsequent cyanoethylation of the cyanide (XXV) thus gave a dicyanide (XXVI), converted by hydrolysis with concentrated hydrobromic acid into an acid lactone, the carboxylic acid group of which was submitted to Curtius degradation. Methylation, by formaldehyde and formic acid, of the amine produced gave the model substance (XXVII).

By an analogous series of reactions, including the introduction of a formyl group, a labile tricyclic tetrahydronaphthalene lactone (XXVIII) was prepared; but cyclisation of another analogue (XXIX) to the lactone (XXX) could not be effected, apparently owing to the steric configuration.



The most promising of these fragmentary syntheses, however, involved reaction of the cyanide (XXV) with 2-ethoxyethyl sulphite and addition of acrylonitrile to the product; the hydrolysed adduct was formylated with ethyl formate and sodium methoxide, cyclised with sulphuric–phosphoric

acid, and hydrogenated to give a tetrahydronaphthalene derivative (XXXI), the acid group of which was converted into the amino-group by Curtius degradation. Finally, refluxing with hydrobromic acid and quaternisation of the product at pH 5 gave the fused piperidinotetrahydronaphthalene compound (XXXII). A synthesis of (±)-deoxytetrahydrocodeine (XIX) may be envisaged, by use of these transformations and the recently synthesised 2-(2 : 3-dimethoxyphenyl)-2-2′-ethoxyethyl*cyclo*hexanone (XXXIII)[43a] as starting material instead of the cyanide (XXV).



This reaction scheme is in some ways reminiscent of that projected by Koelsch [44] who unsuccessfully attempted to cause 2-phenyl*cyclo*hex-2-enone (cf. Bachmann and Wick [45]) to react with butadiene or acrylonitrile. Oxidation of the expected adduct with butadiene or Reformatzky reaction of that (XXXIV) with acrylonitrile would have given substances of considerable interest for further morphine syntheses. Reaction of 2-phenyl-*cyclo*hex-2-enone with ethyl malonate was successful,[45] however, and may, in due course, provide an interesting variation to Horning's reaction scheme.[43]

Conclusion

At the present time, therefore, three promising approaches towards the synthesis of morphine are being pursued by different routes. Although two of these have now proved Robinson's generally accepted formula for morphine as correct, it is difficult to hazard a guess as to which of the routes is

[43a] Horning, Horning, and Platt, *J. Amer. Chem. Soc.*, 1948, **70**, 2072.
[44] *Ibid.*, 1951, **73**, 2951.
[45] Bachmann and Wick, *ibid.*, 1950, **72**, 3388; cf. Bachmann and Fornefald, *ibid.* p. 5529.

the most likely to lead to the ultimate synthesis, particularly since none has as yet successfully overcome the difficulties in the way of forming the oxygen bridge.

Moreover, one of the routes [8] produces the epimer of natural morphine, and another [7, 28] requires, for one cyclisation step, strongly acid conditions under which a deep-seated rearrangement of the morphine–apomorphine type might be expected to take place. On the assumptions that this cyclisation may proceed under milder conditions and that epimerisation at $C_{(14)}$ is possible, it is probably safe to predict that within the next few years the synthesis of morphine, and with it a most interesting and difficult chapter of alkaloid chemistry, will be brought to a successful conclusion.

The author is indebted to the Directors of J. F. Macfarlan and Co. Ltd. for permission to publish this Review.