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Benzomorphans: Synthesis, Stereochemistry Reactions, and Spectroscopic Characterizations

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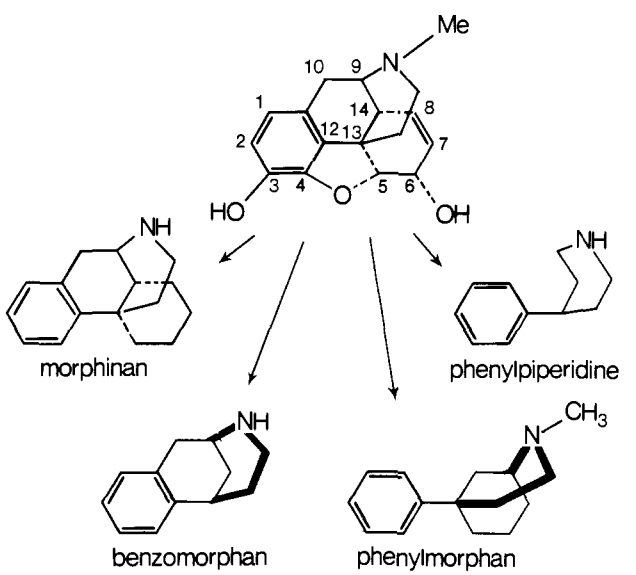
I. Introduction

A. Purpose and Scope

The problems of prolonged physical pain and mental anguish, the efficacy of opiates in ameliorating these experiences, and the consequent difficulties of physical dependence and addiction associated with opiate use have been the subject of extensive study by chemists, biochemists, pharmacologists, and physicians for many decades. The problems of opiate addiction in the United States and the associated social trauma have served, in part, to intensify efforts directed toward understanding the basic mechanisms of the action of these drugs and to intensify the search for a better analgesic[1] which has no harmful side effects and does not induce physical dependence. The detailed mechanisms of action are still in large part unknown and the ideal analgesic has not yet been found, but substantial progress is being made.[1-10]

From a chemical point of view, determination of the total structure of morphine by Robinson in 1925 was a landmark.[11] Morphine is the prototype of analgesic compounds and is still in many cases a preferred drug for pain relief, primarily because of confidence and experience gained during many years of use.[5] This will undoubtedly change as clinical experience with newer synthetic compounds increases. Of primary importance in the development of new synthetic analgesics was the observation that simpler morphine-like compounds could be prepared which contain only a portion of the parent structure, but which are as effective as or more effective than morphine as analgesics. Unfortunately, many of these compounds also have dependence-producing and other undesirable side effects of morphine. There are a significant number of appropriately substituted derivatives which do not, however. Examples of several simplified morphine-like derivatives are shown in Scheme I. Each of these

SCHEME I. Morphine and Simpler Analogues



represents a class of compounds which has, or is presently undergoing, intensive scrutiny. The synthesis of hundreds of analogues of varying structure, detailed studies of their pharmacological activity, and the introduction of some of these into clinical medicine are clear indications of the progress being made. Compounds containing the benzomorphan ring structure, Scheme I, have proven to be particularly interesting in this regard and are an important class of analgesics. When appropriately substituted, certain benzomorphans have useful narcotic antagonist activity. Two analgesic benzomorphans are now in clinical use. One of these, pentazocine, is an analgesic with weak antagonist activity and the other, phenazocine, is a strong analgesic with no antagonist activity. One other, cyclazocine, is a strong analgesic-antagonist with investigational status.

There are several structural features which seem to be consistently associated with the presence or absence of strong analgesic activity. These have been critically reviewed by Mellett and Woods.[5] Although there are numerous exceptions, many strong analgesics contain an aromatic ring bonded to a saturated two- or three-carbon chain terminating with an amino nitrogen. Other more restrictive generalizations have been made.[12] In the case of morphine analogues the presence of an appropriately positioned phenolic hydroxyl, tertiary amino functionality, and quaternary benzylic carbon (no bonds to hydrogen) all appear to enhance analgesic activity, and selective benzomorphan syntheses reflect these observations (vide infra). Profound and consistent changes in activity ranging from narcotic agonist to antagonist, brought about merely by changing *N*-methyl to *N*-allyl in morphine and many of its simplified derivatives, provides startling evidence of the dramatic and structurally reproducible changes in activity which can occur.

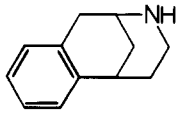
6,7-Benzomorphans are one of the most extensively investigated morphine analogues (see section I.B on nomenclature), first prepared and studied in detail by May and Eddy at the National Institutes of Health. Useful synthetic routes to this ring system have been developed, and chemical modifications have provided valuable new narcotic analgesics and narcotic antagonists of practical and theoretical importance. The practical development of effective, strong analgesics which antagonize the dependence-producing, respiratory-depressant, and other undesirable effects of morphine, heroin, and related compounds now seems a reasonable possibility. Some very useful analgesics which approach this ideal are benzomorphan derivatives.

There have been several short reviews of benzomorphan chemistry,[2,13] and numerous reviews of analgesic structure–reactivity relationships which include benzomorphans.[2-5] The only comprehensive review of benzomorphan chemistry is now ten years old,[13a] and the newer summaries are very short[2,13b] or have mainly emphasized pharmacology.[3] It is our purpose here to present a comprehensive review of interesting and important chemical aspects of this interesting class of compounds up through December 1975. We should note at the outset that there is a large volume of material published in the patent literature. Much of this involves very straightforward modification of substituents on the benzomorphan ring by classical reactions (alkylations, acylations, etc.). Unless some interesting or pertinent chemistry is involved, such reports are not included. In addition, thousands of different benzomorphans containing varying functionality have been prepared by various pharmaceutical firms for screening purposes using similar chemical methods for constructing the ring system. If we felt that the chemistry involved was not sufficiently unique or important, these reports also were not included.

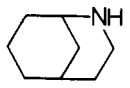
Wehave decided to include homologous modifications of the ring system and positional variation of nitrogen. Although such compounds are not truly benzomorphans, their pharmacological properties and chemistry are sufficiently similar so that their inclusion is considered worthwhile.

B. Nomenclature

Preparation of the first compound containing the benzomorphan ring system, **2**, was reported by Barltrop in 1947.[14] The



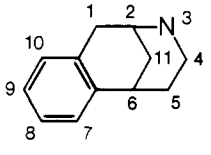
2
benzomorphan



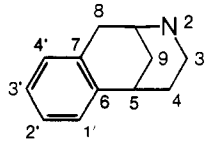
1
morphan

name is derived from the trivial name "morphan", initially suggested to Barltrop by Sir Robert Robinson, for the simple azabicyclo[3.3.1]nonane **1.**

There are two common benzomorphan numbering systems, **3** and **4,** now in use. We will use **3,** the numbering system



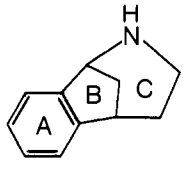
3



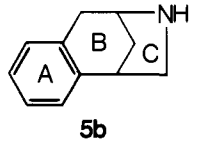
4

presently listed in *Chemical Abstracts*, rather than **4.** The latter system is still in use by many research groups, however, and the common name "6,7-benzomorphan" is the title of the last major review of benzomorphan chemistry. Although the name benzomorphan in most instances implies the 6,7 prefix and thus the numbering system *not* used by *Chemical Abstracts*, we will use the trivial name as it is used predominantly in the literature. The correct name as listed in the "Ring Index" and *Chemical Abstracts* (always associated with the numbering system shown in **3**) is *1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine.*

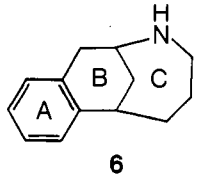
Since we will also be dealing with homologous modifications of the basic benzomorphan ring system and positional variation of nitrogen, brief mention of nomenclature involving these systems is appropriate. The major homologous modifications which have been made involve expansion or contraction of the two saturated six-membered rings to give benzazepines (*B*-norbenzomorphans) (**5a**),[15] correctly named 1,5-methano-



5a
B-norbenzomorphan



5b
C-norbenzomorphan

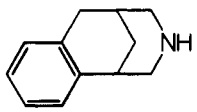


6
C-homobenzomorphan

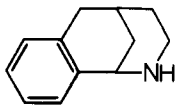
2,3,4,5-tetrahydro-1*H*-2-benzazepines: (*C*-norbenzomorphans) (**5b**),[18] correctly named 1,4-methano-2,3,4,5-tetrahydro-1*H*-3-benzazepines: and benzazonines (*C*-homobenzomorphans) (**6**),[16,17] correctly named 2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonines.

Positional variation of nitrogen has been carried out, and the isomers **7–11** or derivatives of these have been synthesized.[18]

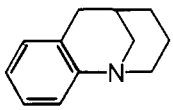
In addition, heteroatoms other than nitrogen have been substituted in the basic benzomorphan ring system, and the aromatic



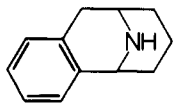
7
1,2,3,4,5,6-hexahydro-
1,5-methano-3-benzazocine



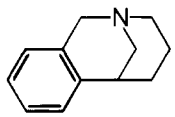
8
1,2,3,4,5,6-hexahydro-
1,5-methano-2-benzazocine



9
3,4,5,6-tetrahydro-2*H*-
1,5-methano-1-benzazocine



10
1,2,3,4,5,6-hexahydro-
1,5-iminobenzocyclooctene

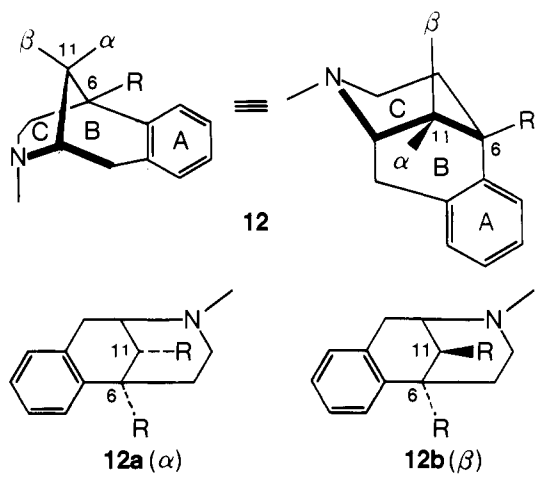


11
3,4,5,6-tetrahydro-1*H*-
2,6-methano-2-benzazocine

ring has been made heteroaromatic, as well as fused to other aromatic rings. These variations are discussed in section VI. There are so few examples that a detailed discussion of nomenclature is not necessary in these instances.

C. Stereochemical Conventions

A convention has been established regarding the stereochemical nomenclature of benzomorphans. Structure **12** represents the general benzomorphan framework. The stereochemistry at C-11 has been designated as α when the C-11



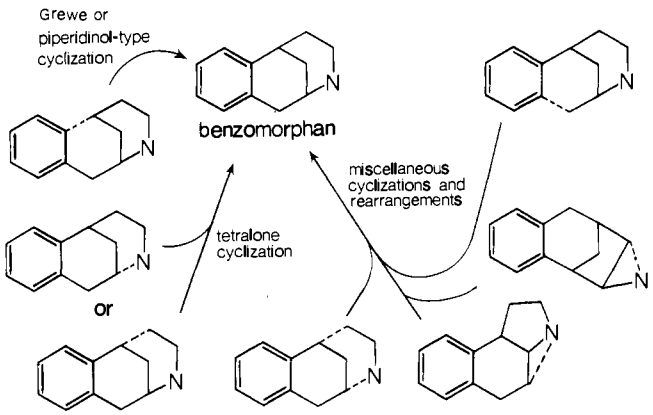
12a (α) **12b** (β)

substituent and C-6 substituent are *cis with respect to the B ring.*[13] It is designated as β when the C-6 and C-11 substituents are *trans with respect to the B ring.* We emphasize this point here as many papers show only two dimensional structures where this convention is not clear or is used incorrectly. When discussing important stereochemical features of a reaction we will show three-dimensional structures so that the spatial relationships will be unequivocally clear.

II. Synthetic Routes to the Benzomorphan Ring Systems

Three approaches seem reasonable in discussing the synthesis of benzomorphans. A discussion based on the types of substituents present and their position (e.g., mono-, di-, or trialkyl)

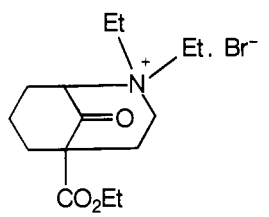
SCHEME II. Approaches to the Benzomorphan Ring System



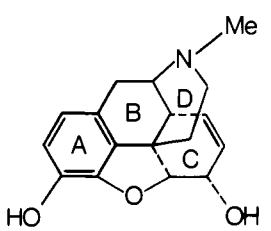
would be based primarily on product structures. An alternative would be to consider general synthetic routes used to construct the ring skeleton regardless of the substituents present. Lastly, a historical approach could be employed, outlining the major developments in the synthesis of benzomorphans regardless of the substituents or the synthetic method. For comparative purposes and critical review, a combination of the latter two approaches seems most appropriate. As noted previously, the patent literature lists hundreds of derivatives prepared either from straightforward modifications of known benzomorphans, or by classical synthetic methods (e.g., Grewe cyclization of tetrahydropyridines). These patents have not been included unless they represent new or novel approaches to the benzomorphan ring system. Four different ways of constructing benzomorphans are outlined schematically in Scheme II. The Grewe and tetralone routes, as well as modifications of these methods, are by far the most important synthetic approaches, and these will be discussed in some detail. The other routes are of interest for preparing structures with specific substitution and have not yet been developed into generally useful methods.

A. The Tetralone Route

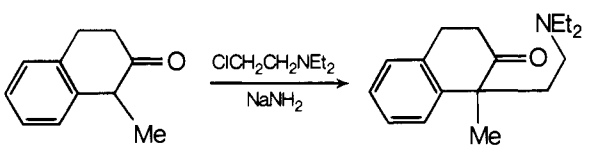
In 1947, Barltrop prepared the 2-azabicyclo[3.3.1]nonane **13** as a model compound for the B and D rings of morphine[14] (**14**). As an extension of this work using the tetralone **15**, he



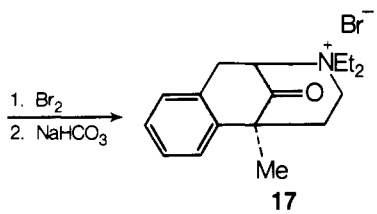
13



14



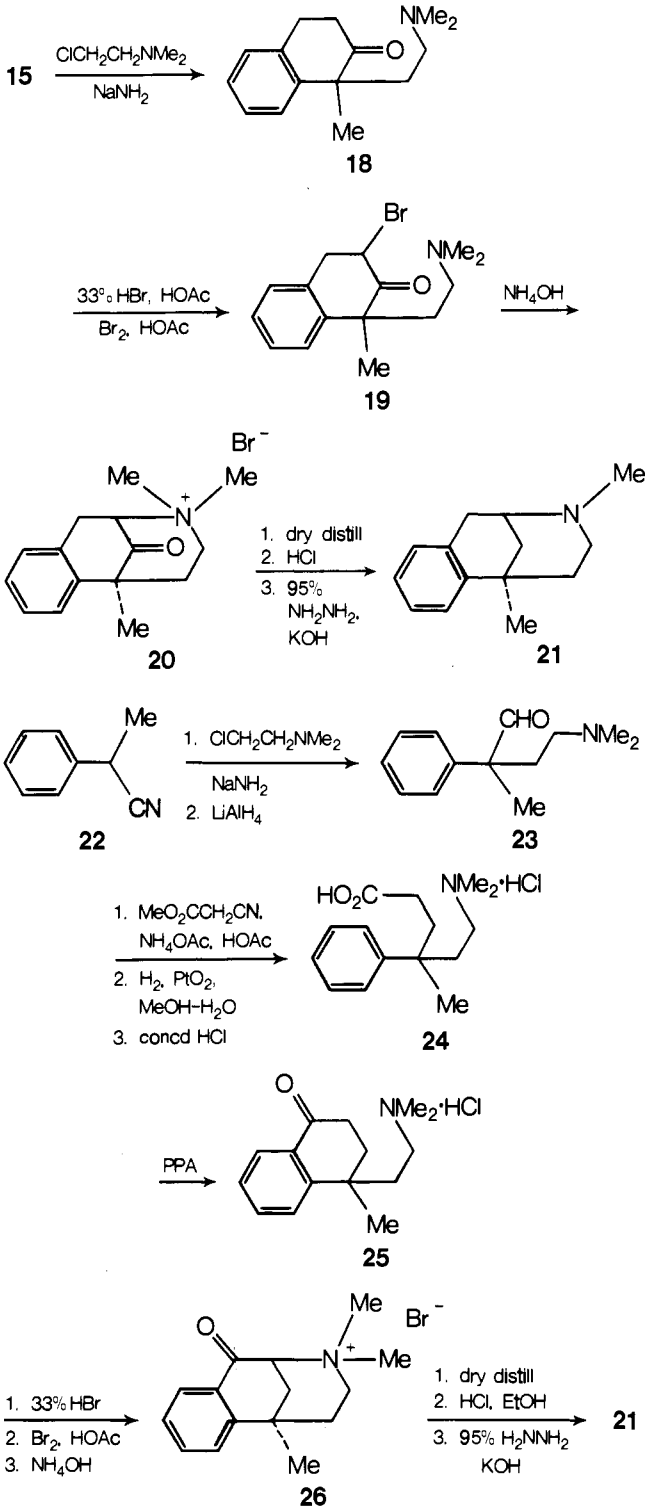
15 **16**

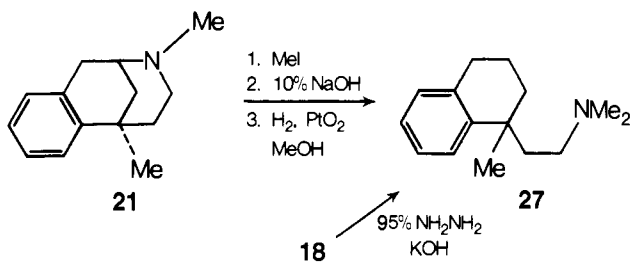


17

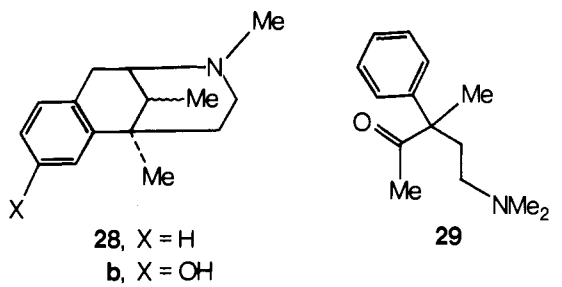
prepared **17** as a model for the A, B, and D rings of morphine (**14**). Although this latter synthesis suffers from low yield, it represents the first preparation of the benzomorphan ring skeleton.

Following Barltrop's initial work, May reported the synthesis of 3,6-dimethylbenzomorphan (**21**), initiating his extensive investigations into the synthesis and pharmacology of these compounds.[19] His first approach to **21** was analogous to Barltrop's synthesis of **17.** Owing to low yields (e.g., **15** → **18** (20–30%); **20** → **21** (30%)), this method was abandoned in favor of a longer synthesis beginning with hydratropanitrile (**22**) which afforded **21** in 5% overall yield. Alkylation of **22** with β-dimethylaminoethyl chloride followed by lithium aluminum hydride reduction afforded amino aldehyde **23** which was converted in four steps to the tetralone **25** in 61% overall yield. Subsequent bromination and cyclization afforded **26** which was dry distilled, converted to the hydrochloride salt, and subjected to Wolff–Kishner reduction (Huang-Minlon modification) to **21.** Degradation of **21** was accomplished in three steps and furnished the tetrahydronaphthalene **27,** identical with that prepared by Wolff–Kishner reduction of **18** which provided definitive evidence for the benzomorphan ring skeleton.



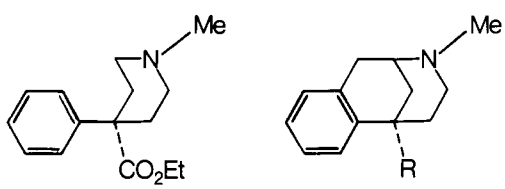


An unsuccessful attempt was made to extend this route to the 3,6,11-trimethylbenzomorphan derivatives **28a** and **28b.**[20] It was found that the key intermediate, amino ketone **29,** was unreactive under Knoevenagel conditions with either malononitrile or methyl



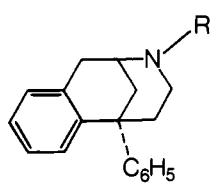
cyanoacetate.[21] The trimethyl derivatives were prepared by Grewe cyclization of the corresponding tetrahydropyridines (vide infra).[20] Although not applicable for the direct preparation of compounds like **28,** the tetralone synthesis has been a useful route to 6-substituted benzomorphans.[22-25]

As a hybrid of both the benzomorphan and meperidine ring systems, 3-methyl-6-carboethoxybenzomorphan (**31a**) was prepared in eight steps from phenylacetonitrile in a manner analogous to that used for **21.**[26] Although **31a** and **31b** show

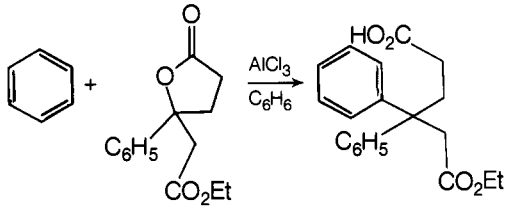


significant analgetic activity, it is interesting that the dimethylamino methyl derivative **31c** is essentially inactive.

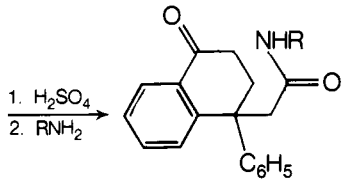
A modification of the normal tetralone synthesis was used to prepare 6-arylbenzomorphans (**32**), an interesting class of compounds which embody structural features of both benzo-



morphan and normethadone.[27] This approach involved the base-catalyzed cyclization of amido tetralones as *outlined below.* Alkylation of benzene with γ-carboethoxy-γ-phenylbutyrolactone (**33**) afforded **34** which was converted in two steps to the keto amide **35.** Bromination afforded an isomeric mixture of **36a** and **36b.** Reaction of the trans compound **36a** with sodium



33 **34**



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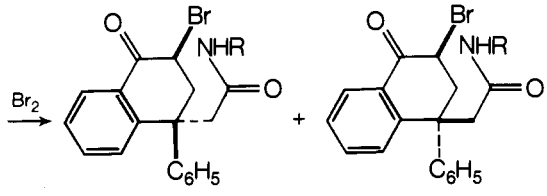
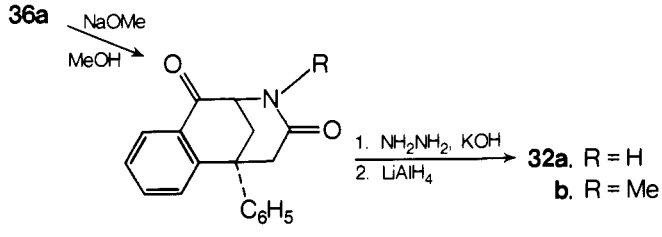


36a **36b**



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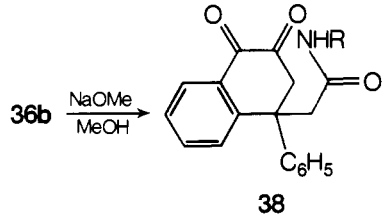
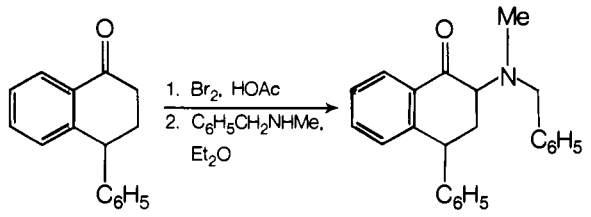


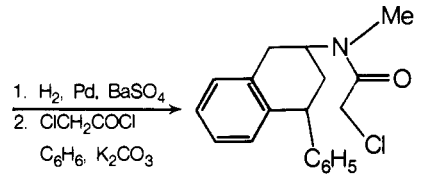
38

methoxide led to the benzomorphan **37** which was reduced in two steps to the 6-arylbenzomorphan **32.** Treatment of the cis isomer in a similar manner afforded the α-diketone **38** which was presumed to arise via solvolysis and air oxidation in the basic medium. Additional examples of 6-arylbenzomorphans prepared by the normal tetralone route as well as the Grewe cyclization of appropriately substituted tetrahydropyridines (vide infra) can be found in the patent literature.[28-32] A novel approach to 6-arylbenzomorphans has been reported which involves carbon–carbon bond formation rather than carbon–nitrogen bond formation in the cyclization step.[33] Bromination of 4-phenyl-1-tetralone (**39**), followed by reaction with *N*-benzylmethylamine afforded amino ketone **40** which was debenzylated, reduced, and acylated with chloroacetyl chloride to yield the amide **41.** Cyclization with sodium hydride followed by reduction led to 3-methyl-6-phenylbenzomorphan (**32b**).

In their extensive work on benzomorphans, norbenzomorphans, and related ring systems, Mitsuhashi and co-workers



39 **40**



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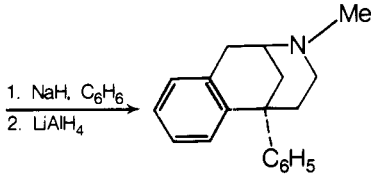
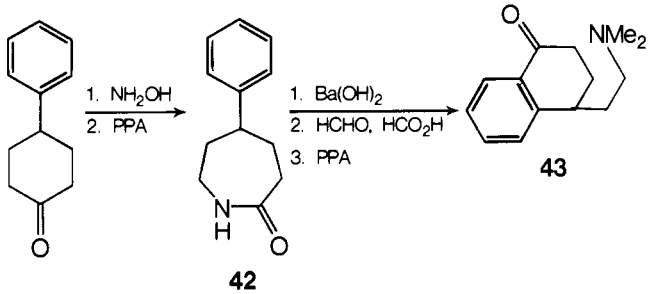
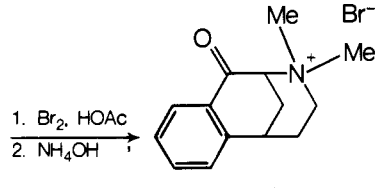


32b

employed the tetralone synthesis to prepare 3-methylbenzomorphan (**45**).[18] Their approach to the preparation of the tetralone precursor **43** involves conversion of 4-phenylcyclo-



42 **43**



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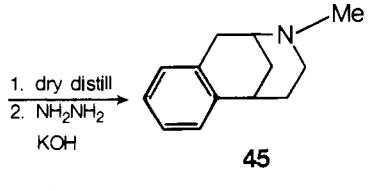
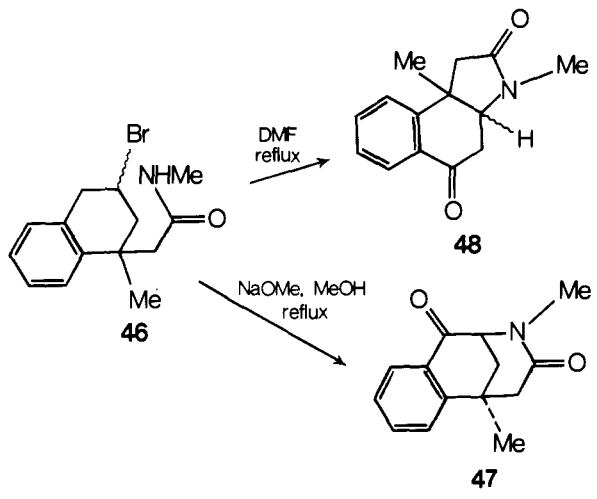


45

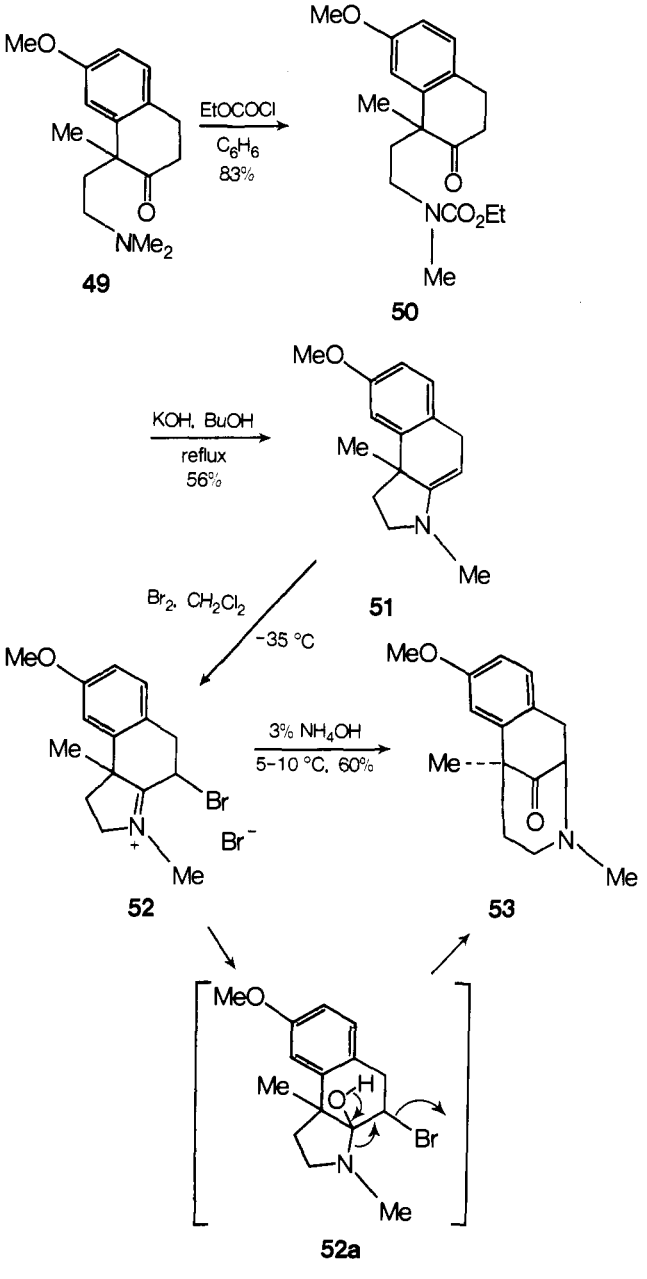
hexanone to the oxime followed by Beckmann rearrangement to 5-phenylcaprolactam (**42**). Hydrolysis with barium hydroxide afforded the amino acid which was subjected to Clark–Eschweiler methylation and cyclization with polyphosphoric acid to yield **43.** This was converted in the usual manner to **45.**

An intramolecular displacement with keto amide **46** was carried out in an attempt to prepare the 1-oxobenzomorphan **47.**[34] The only product isolated in 60% yield after refluxing **46** in DMF was the keto amide **48,** presumed to arise from loss of HBr followed by conjugate addition of the amide nitrogen. When **46** was treated with sodium methoxide, the desired 1-oxobenzomorphan **47** was obtained in 67% yield.

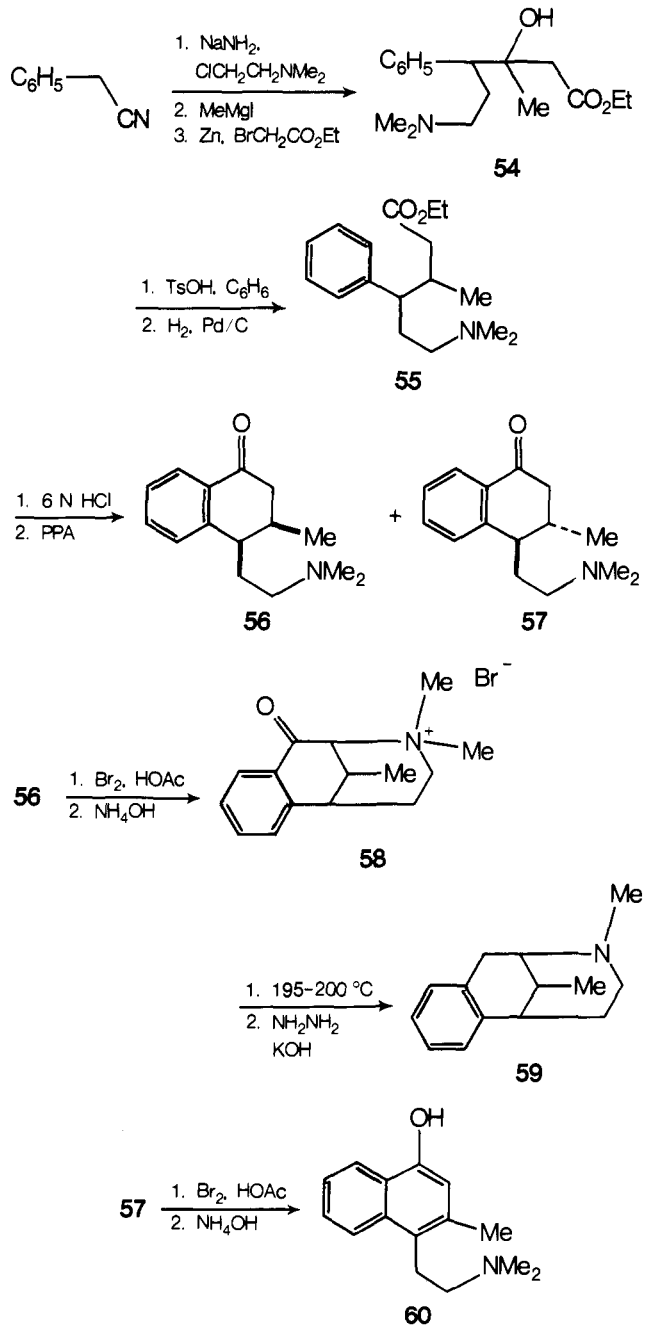
A novel synthesis of benzomorphan and related ring systems was recently reported involving bromination and rearrangement



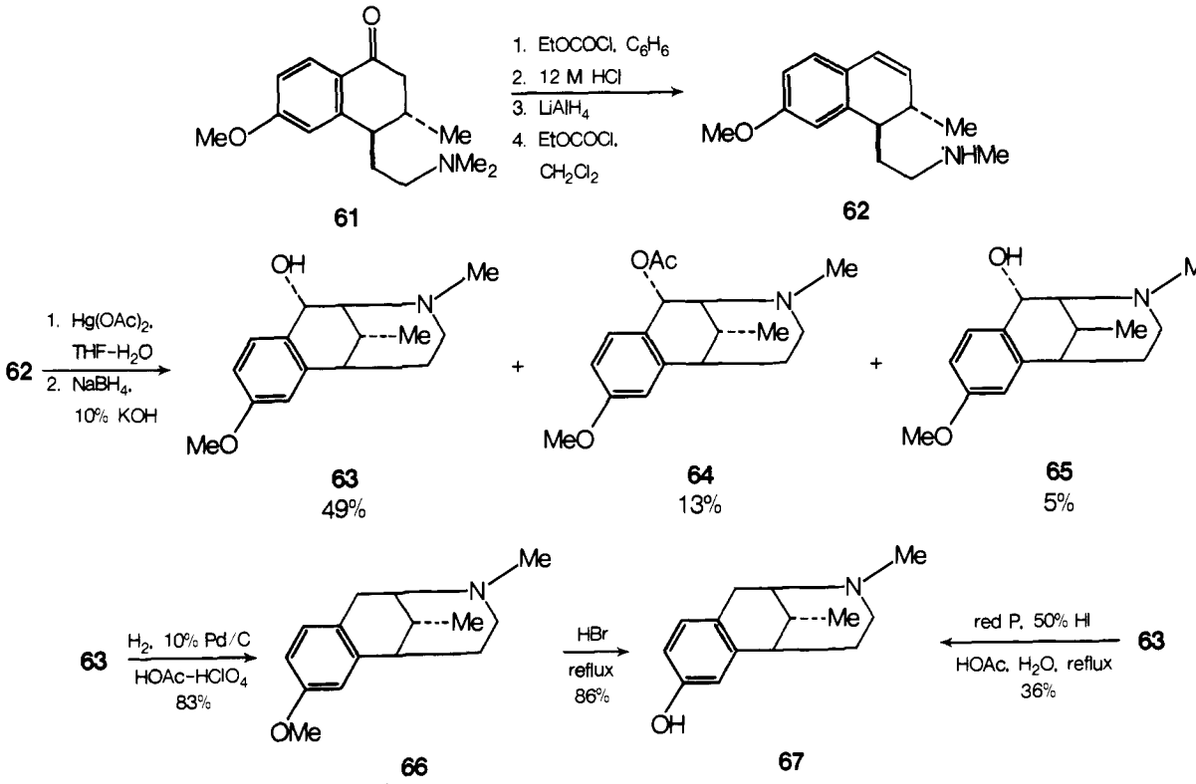
of a heterocyclic enamine.[35] Thus, reaction of the tetralone **49** with ethyl chloroformate afforded the carbamate **50** which was cyclized to the enamine **51.** Bromination followed by aqueous ammonia afforded the benzomorphan **53.** A mechanism for the conversion of the bromo iminium bromide to **53** involving intermediate **52a** has been proposed. This method had also been used successfully to prepare the homobenzomorphan analogues[35] (section III).



The preparation of 3,11β-dimethylbenzomorphan (**59**), unattainable by the usual Grewe cyclization methods, has been achieved utilizing the tetralone method.[36] The Reformatsky product **54,** obtained in 50% overall yield from phenylacetonitrile, was hydrated and hydrogenated to afford amino ester **55** as a mixture of diastereomers. Hydrolysis followed by cyclization led to the isomeric tetralones **56** and **57,** isolated in 71% yield in a 4:1 ratio. The major cis isomer was converted to benzomorphan **59** in the usual manner. Similar treatment of the minor trans isomer afforded the naphthol **60.** This method has also been applied successfully to the synthesis of 8-hydroxy-3,11β-dimethylbenzomorphan.[37]



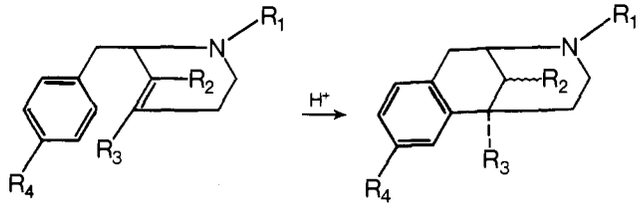
A new modification of this synthesis has been reported in which cyclization is effected by mercuric acetate oxidation.[38] Noteworthy is the observation that this modification can be used to prepare the 11α-alkylbenzomorphans from the corresponding trans-3,4-disubstituted tetralone which undergoes aromatization



rather than cyclization upon treatment with bromine and acetic acid.[36,37] Thus **61,** obtained in a manner analogous to that used for **57,** was converted in 41% overall yield to the key intermediate **62.** Oxidation of **62** with mercuric acetate in aqueous tetrahydrofuran afforded a mixture of **63, 64,** and **65.** The major product, **63,** could be converted in one or two steps to 3,11α-dimethyl-8-hydroxybenzomorphan (**67**). The formation of the 3,11β-dimethyl derivative **65** was postulated to arise from inversion (by allylic rearrangement) at C-2 of **62.** This inversion could be inhibited by base since addition of triethylamine to the cyclization medium afforded a mixture of only **63** and **64.**

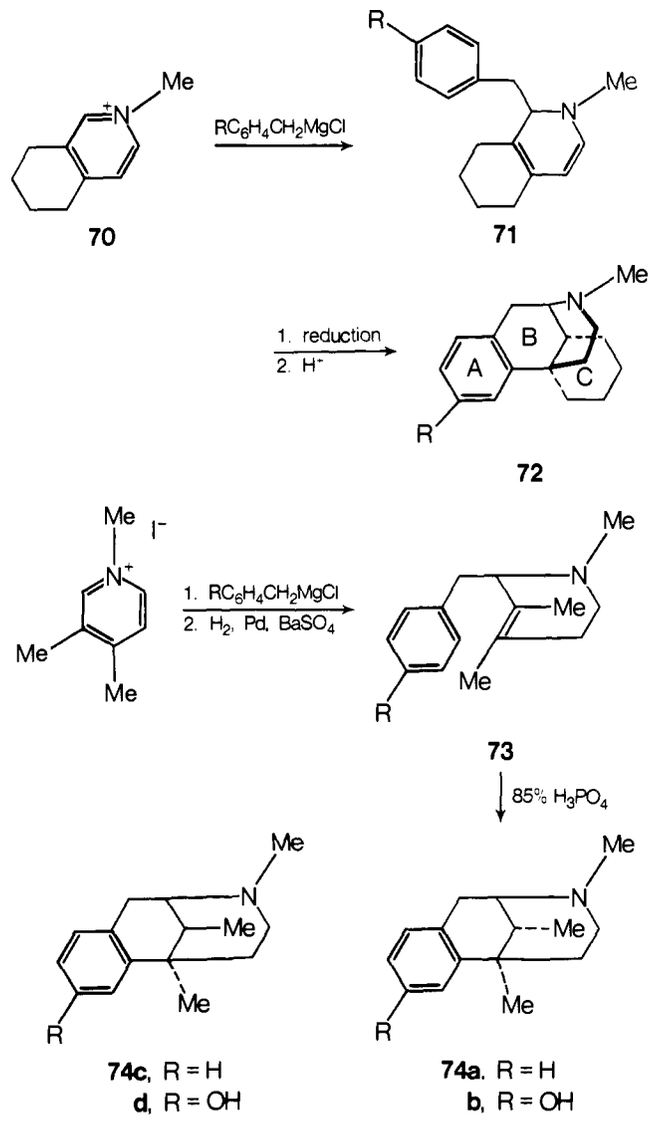
B. Grewe Cyclization

The most widely used approach to benzomorphan synthesis is based on the acid-catalyzed cyclization of appropriately substituted tetrahydropyridines (e.g., **68** → **69**). This method is



68 **69**

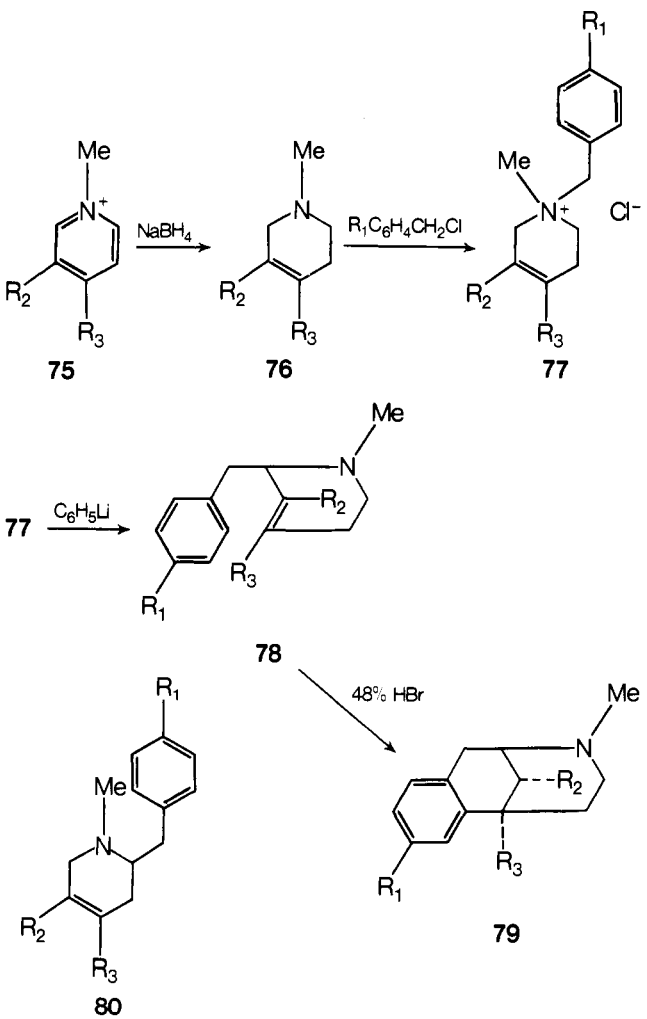
analogous to Grewe's synthesis of morphinans **72,** from appropriately substituted tetrahydroisoquinolines.[39,40] It is an especially useful route since the 3,6,11-trialkylbenzomorphans (which are structurally analogous to morphinans and are more effective analgesics) cannot be prepared directly via the tetralone route (vide supra).[20,21] The first examples of benzomorphans prepared by Grewe cyclization were the 3,6,11-trimethyl derivatives **74a** and **74b.**[20] Addition of an appropriately substituted Grignard reagent to 3,4-lutidine methiodide, followed immediately by reduction of the unstable dihydropyridine, afforded **73** which was cyclized with 85% H_3PO_4 to yield **74a** in 20% overall yield. Employing *p*-methoxybenzylmagnesium chloride in an analogous sequence afforded **74b** in 14% yield.



In this latter case, either 85% H_3PO_4 or 48% HBr could be used to effect cyclization with simultaneous cleavage of the methyl ether. The C-6 and C-11 methyl groups in the products **74a** and **74b** are cis with respect to the *B ring*, not trans as in **74c** and **74d.** Neither of the latter compounds could be detected.

The report of a Grewe-type cyclization of tetrahydropyridines opened a new approach to the synthesis of benzomorphans. As a result, hundreds of compounds have been prepared by variation of R_1–R_4 in **68.**

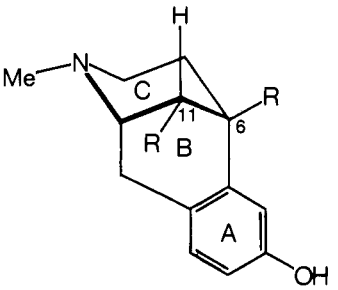
Shortly after this initial work, it was reported that the tetrahydropyridine precursors, e.g., **68,** could be obtained via Stevens rearrangement of the corresponding benzyl alkyl tetrahydropyridinium salts.[41] Thus sodium borohydride reduction of a 1,3,4-trialkylpyridinium salt (**75**) afforded the tetrahydropyridine **76** which was quaternized with the appropriate benzyl halide to yield the benzyl alkyl tetrahydropyridinium salt **77.** Rearrangement was effected by treating **77** with ethereal phenyllithium to afford the tetrahydropyridine **78.** It was noted



that **78** is formed in the Stevens rearrangement rather than the isomeric **80** since the ylide intermediate leading to **78** is stabilized by conjugation with the double bond.

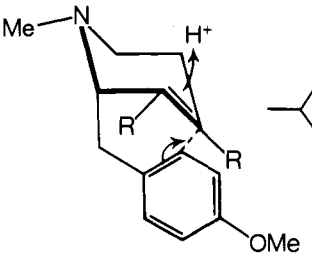
Subsequent cyclization of **78** was effected with 48% HBr. Numerous later reports of the synthesis of a wide variety of substituted benzomorphans have appeared which utilize the synthetic methods discussed above.[42-55]

The stereochemistry of **74a** and **74b** is analogous to the cis B and C ring fusion of the morphinan **72.** The result is that of trans addition to the double bond of the tetrahydropyridine. Interestingly, this mode of reaction is quite general as when a variety of related tetrahydropyridines, **73a,** are cyclized under acidic conditions,[44,46,47] the major product is always that in which the alkyl groups are cis with respect to the B ring. As noted in section I.C, May and Eddy have called this isomer α.[13] Small quantities of the trans (with respect to ring B) or β isomer can also be isolated in certain instances. Grewe has previously shown the B and C rings of morphinans like **72** to be cis fused,[39] and the



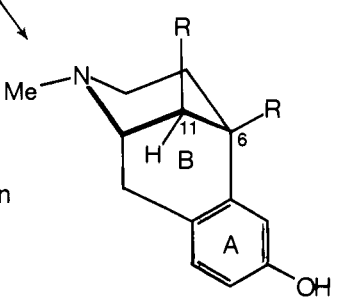
(±) cis, α

major product, only one enantiomorph shown



73a (±)

only one enantiomorph shown



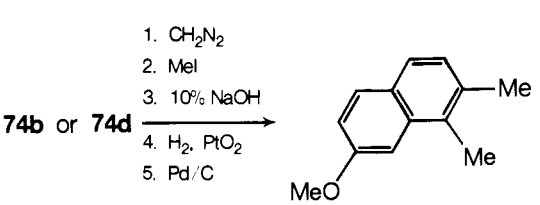
(±) trans, β

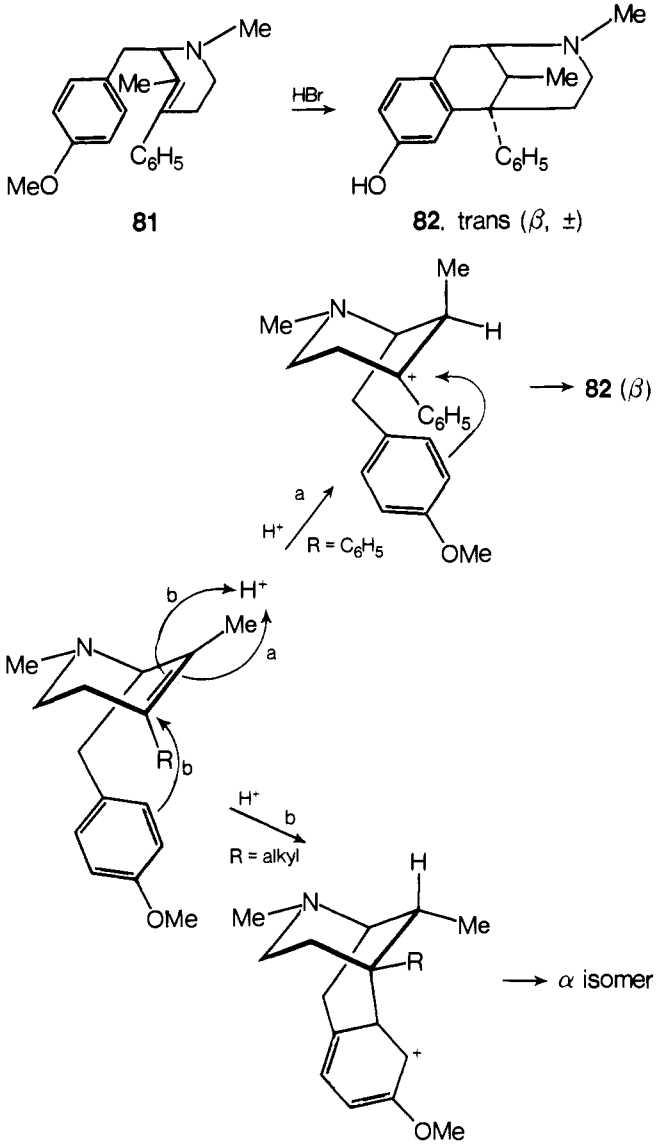
minor product, only one enantiomorph shown

C-6 and C-11 methyls in analogously prepared benzomorphans were also presumed to be cis. If cyclization can be viewed as a trans addition to a double bond, then this is not unexpected since protonation should occur from the less hindered β side.

A surprisingly different stereochemical pathway is observed when the 3-alkyl-4-phenyltetrahydropyridine **81** is cyclized in acid.[56] In this instance, *only*, the β isomer **82** is formed. This latter compound was resolved into its *d* and *l* antipodes by fractional crystallization of the *d*-mandelate salts, and the absolute configuration of the *l* isomer has been shown to correspond with that of morphine. The formation of only the β isomer upon cyclization of **81** is in striking contrast to cyclizations of 3,4-dialkyltetrahydropyridines **73a** where the α-benzomorphan predominates. This result has been rationalized[56] by assuming that the phenyl group stabilizes a predominate trans benzylcarbonium ion intermediate, which should be more stable than the cis. Cyclization of this intermediate can then only yield the benzomorphan **82.** In the case of 3,4-dialkyltetrahydropyridines, the reaction may occur in a more concerted fashion to yield the predominant α isomer.

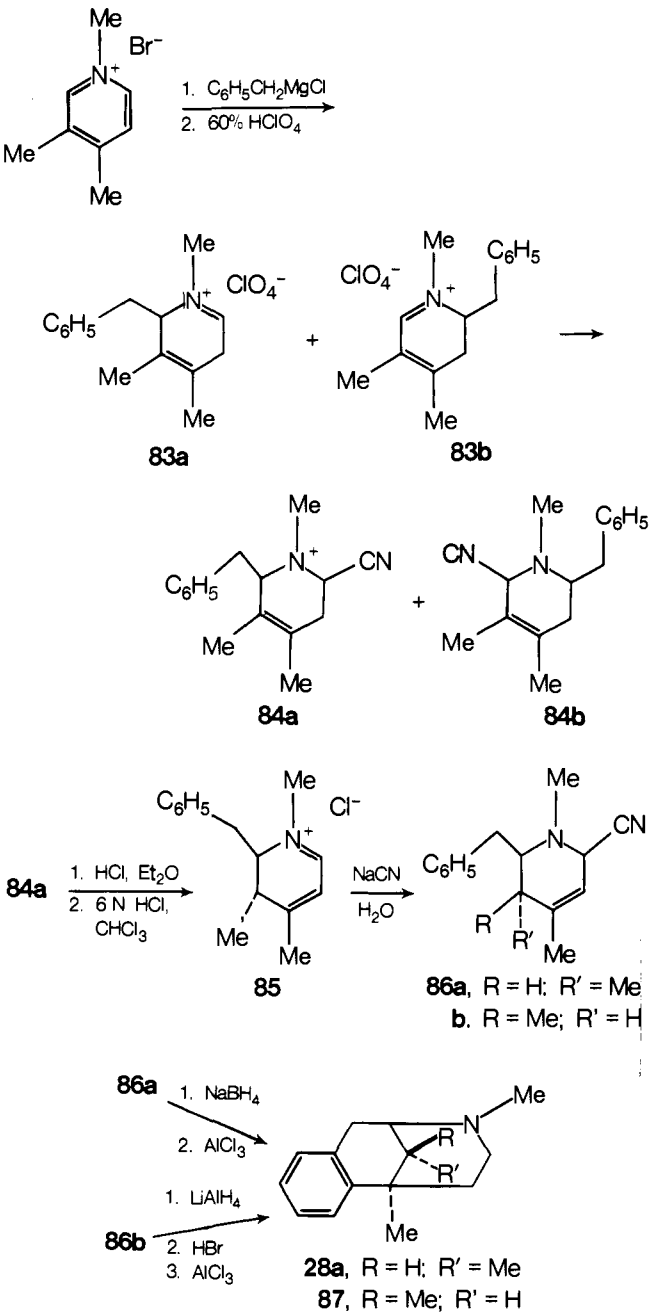
Isomerism at C-11 in benzomorphans has been studied in some detail because of important pharmacological differences between the diastereomers. Degradation of both **74d** and **74b**



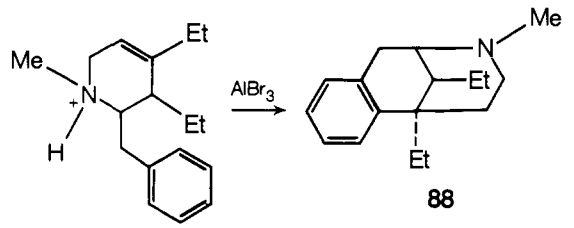


leads to the same 1,2-disubstituted naphthalene, indicative of the diastereomeric origin at C-11.[44,57] Supporting evidence was obtained by the rate of formation of methiodides and NMR studies on a series of α and β isomers.[58] It was found that the α isomers, where the C-11 alkyl substituent is oriented away from nitrogen, quaternized five to ten times as fast as the β isomers where approach to nitrogen is hindered. In addition, the rate of quaternization of the latter decreased with increase in size of the alkyl groups at C-6 or C-11. This method has been used by many workers to assign configurations at C-11. Also, the C-11 methyl group ^{1}H NMR absorption for **74a** is at 25 Hz higher field than for the β isomer **74c**, presumably because of the diamagnetic effect of the aromatic ring. This point is considered in more detail in section IX.

It has been shown that the α-benzomorphans are comparable in stereochemistry to morphine and also that levorotatory are in most cases more effective analgesics than dextrorotatory isomers.[58] Interestingly, the β isomers are lower melting, more soluble, and, as noted previously, many times more potent analgesics than their α diastereomers.[58] After this latter fact was well established, modifications of the Grewe synthesis to increase the amount of the 11β compound were undertaken (previously these compounds could be obtained selectively by hydrogenation of the corresponding 11-methylene benzomorphans: see section VIII). Although a small amount of the 11β-alkyl isomer was isolated from a Grewe synthesis of 3,6,11-trimethyl-8-hydroxybenzomorphan (**28b**),[57] it was several years before Fry demonstrated the utility of this method to prepare 11β-alkyl benzomorphans.[59] He found that reaction of benzylmagnesium chloride with *N*-methyl-3,4-lutidinium bromide afforded a mixture of the iminium dienes **83a** and **83b** which could be separated by reaction with NaCN. Reaction of the hydrochloride salt of **84a** with 6 N HCl in boiling $CHCl_3$ resulted in loss of HCN and formation of the rearranged dihydropyridine **85** which upon addition of aqueous sodium cyanide afforded *trans*-2-benzyl-1,3,4-trimethyl-6-cyano-1,2,3,6-tetrahydropyridine (**86a**) in 70.5% yield. Removal of the cyano group was effected in 81% yield with sodium borohydride followed by cyclization with aluminum chloride in carbon disulfide to afford 3,6,11β-trimethylbenzomorphan (**87**). Similarly, reaction of the hydrochloride salt of **84a** successively with 2.2 N HCl, aqueous NaCN, 8.8 N HBr, and aqueous NaCN resulted in a 33% yield of **86b**. After conversion to the perchlorate, the cyano group was eliminated with $LiAlH_4$ followed by cyclization of the hydrobromide salt to afford 3,6,11α-trimethylbenzomorphan (**28a**), identical with that obtained earlier by May and Fry.[20] The use of $AlCl_3/CS_2$ to effect the cyclization was the result of work done to improve the yields of 11β-alkyl isomers from cyclization of



the 2-benzyl-1,3,4-trialkyl-1,2,5,6-tetrahydropyridine precursors, i.e., **68**.[60,61] Ratios of α/β were found to range from 0.3 to 15 depending on the particular substrate, cyclizing medium, and reaction temperature. Fry's elegant work has also been used as the basis for the preparation of 3-methyl-6,11β-diethylbenzomorphan (**88**),[62] which is surprisingly almost identical in toxicity and analgesic potency with the α counterpart **89**, prepared by HBr cyclization of the 1,2,5,6-tetrahydropyridine.



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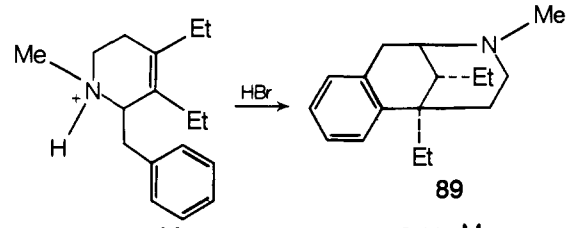

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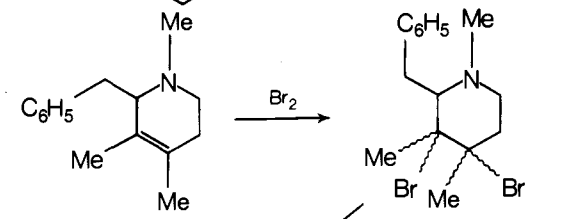

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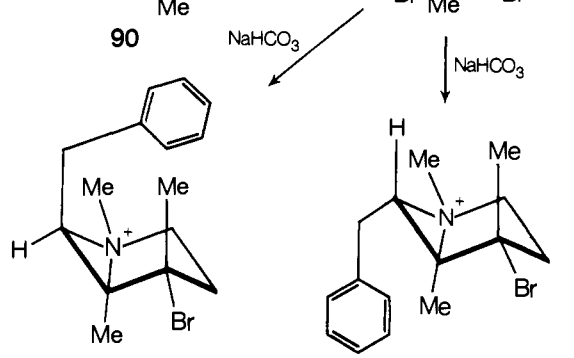

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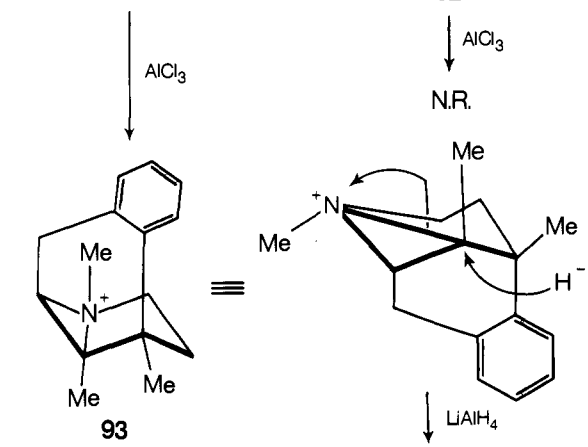
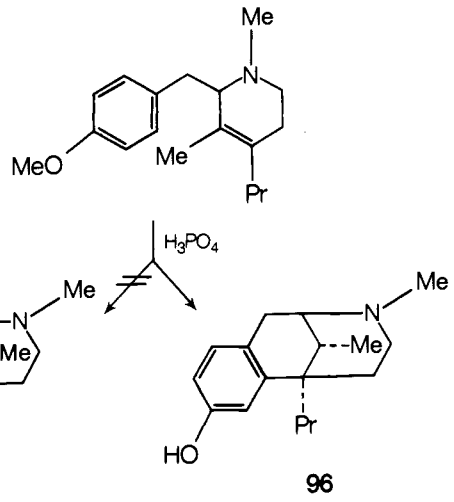


93 94

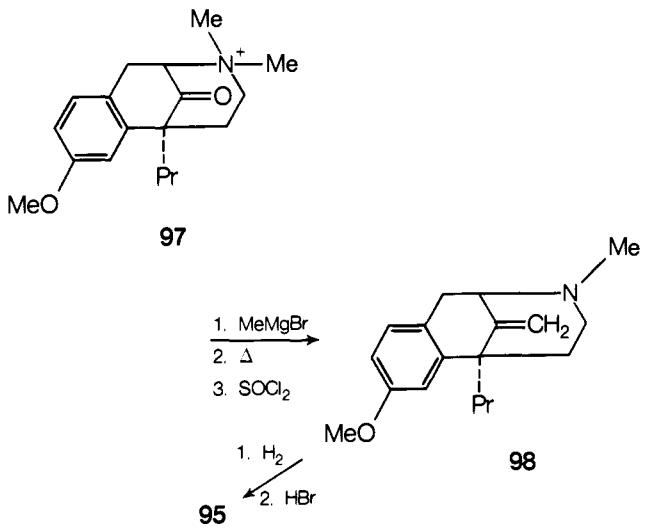
Another interesting route which leads stereospecifically to β-benzomorphans involves an aziridinium perchlorate intermediate.[63] Addition of bromine to the 1,2,5,6-tetrahydropyridine **90** and subsequent base treatment yields the isomeric aziridines **91** and **92**. Only in **91** is the benzene ring in position to cyclize, and **93** results on treatment of **91** with $AlCl_3$. Reduction of **93** with $LiAlH_4$ yields the β-benzomorphan **94**.

The β-benzomorphan **95** was not formed even in small amounts upon cyclization of the corresponding 2-benzyl-1,3-dimethyl-4-propyl1,2,5,6-tetrahydropyridine. Only the α isomer **96** was obtained.[24]



95 96

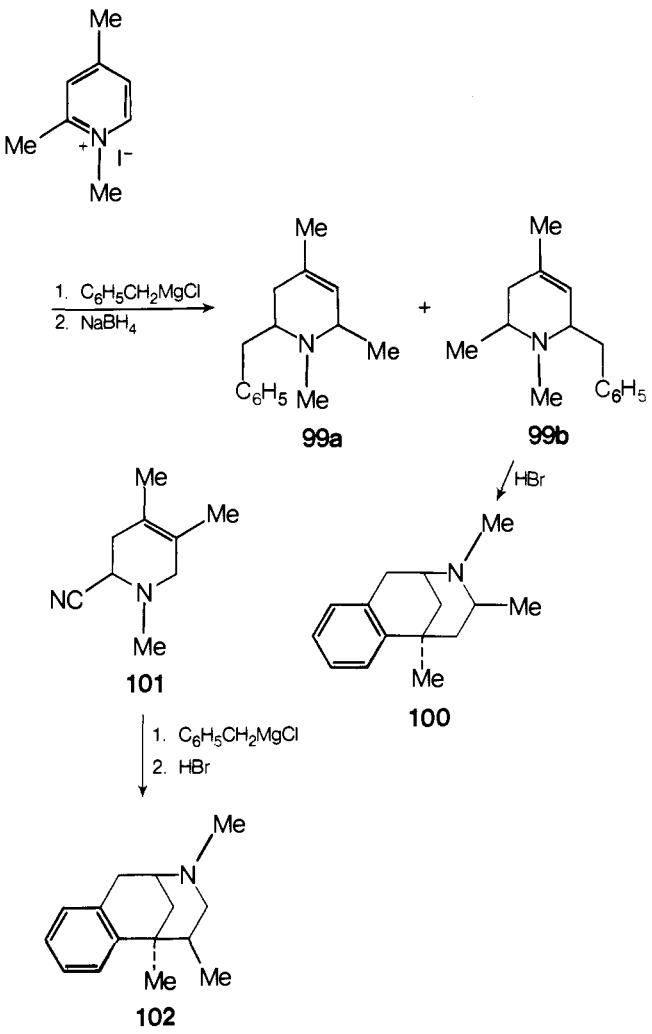
In order to prepare the β isomer in this instance, the 9-oxo compound **97**, prepared via the tetralone route, was converted to the C-11 methylene derivative **98**, which could be stereoselectively hydrogenated to **95** (see section VIII). A mixture of the deoxy analogues of **95** and **96** does result from $AlBr_3$-catalyzed cyclization of the corresponding benzyltetrahydropyridine, however.[49]



97 98 95

In their extensive investigations into the preparation of 6-phenylbenzomorphans, Block and Clarke have used the Grewe cyclization repeatedly.[2,29-32,56,64] They found that the Stevens rearrangement leading to the Δ^3-tetrahydropyridine precursor **81** could be effected in better yield using powdered KOH/C_6H_6 rather than ethereal phenyllithium.

A series of *N*-alkyl-4,6-dimethyl- and *N*-alkyl-5,6-dimethylbenzomorphans not easily accessible from the corresponding tetralones has been prepared via Grewe cyclization.[65] Reaction

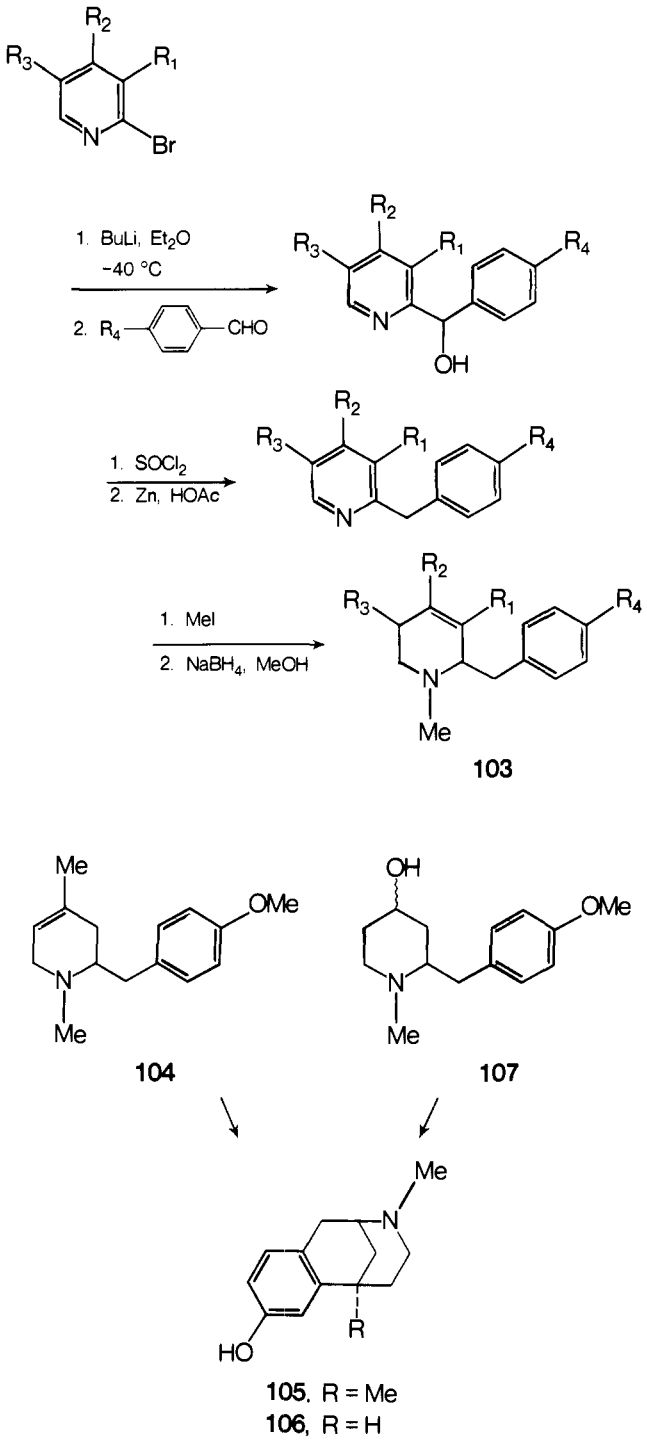


of 1,2,4-trimethylpyridinium iodide with benzylmagnesium chloride followed by alkaline sodium borohydride reduction affords a mixture of tetrahydropyridines **99a** and **99b.** Upon cyclization, 3,4,6-trimethylbenzomorphan (**100**) was obtained in 73% yield. 3,5,6-Trimethylbenzomorphan (**102**) was isolated in about 55% yield from the cyanotrimethyl compound **101** which had been obtained from *N*-methyl-3,4-lutidinium iodide via Fry's method.[66] Both **100** and **102** were subsequently converted to nor compounds with CNBr and subsequent hydrolysis of the *N*-nitrile. The corresponding *N*-alkyl derivatives were prepared in the usual manner (see section VIII).

A method for the direct synthesis of 2-benzyl-1,2,5,6-tetrahydropyridines **103**[67] which avoids the side products sometimes encountered in the Stevens rearrangement and the unstable or unpredicted products from the Grignard reaction[20,68-70] has been reported. It is based on the alkylation of the corresponding 2-bromopyridine with either benzaldehyde or anisaldehyde followed by conversion to the chloride and reductive dehalogenation. After quaternization with methyl iodide, $NaBH_4$ reduction in methanol affords the desired Δ^3-tetrahydropyridine in good yield.

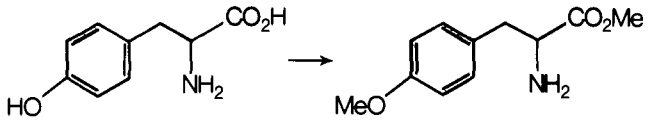
C. Piperidinol and Related Cyclizations

As part of a study done on side reactions from both Grignard reagents and the Stevens rearrangement, it was found that 3,6-dimethyl-8-hydroxybenzomorphan (**105**) could be prepared by cyclization of the tetrahydropyridine **104** while 3-methyl-8-hydroxybenzomorphan (**106**) could be obtained from the corresponding piperidinol **107.**[50,70] The conversion of substituted piperidinols to benzomorphans has been utilized by Kametani



on numerous occasions.[55,71-73] As an example, the synthesis of pentazocine (**116**) from tyrosine is outlined below. Tyrosine is converted to amino ester **108** which is condensed with benzaldehyde. The resulting Schiff base is immediately reduced to afford amino ester **109** in 87% yield. Condensation with methyl 3-chloroformylpropionate followed by Dieckmann cyclization of the resulting keto amide yields the keto ester **110** in 81% yield. This is alkylated and decarboxylated to **111** (82%), followed by conversion to the piperidinol **112** (75%) by reaction with methylmagnesium iodide. Subsequent cyclization and reduction afforded the nor compound **115** (67%) which had been previously converted to pentazocine **116.**[40] Additional examples of the use of substituted piperidinols as precursors to 11,11-dialkylbenzomorphans have been reported by Janssen.[2]

The synthesis of the parent ring system, 3-methylbenzomorphan (**45**), proved to be difficult. It was first prepared[74-76]



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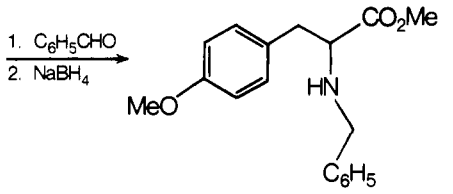

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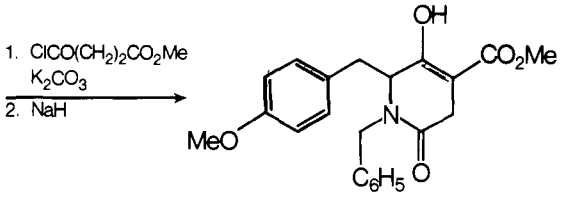

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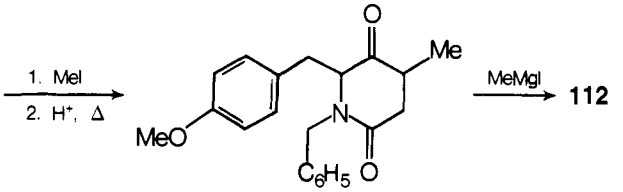

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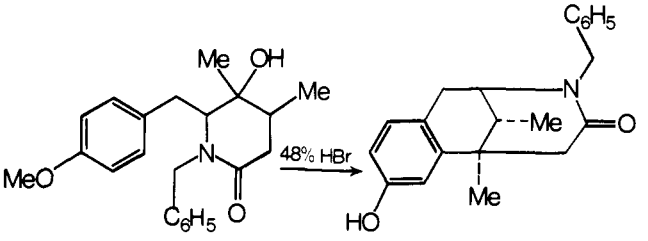

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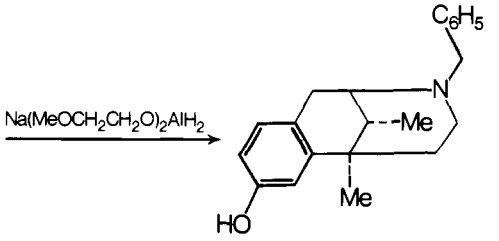

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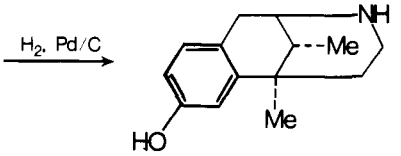

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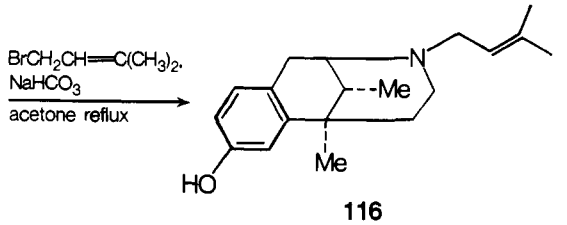
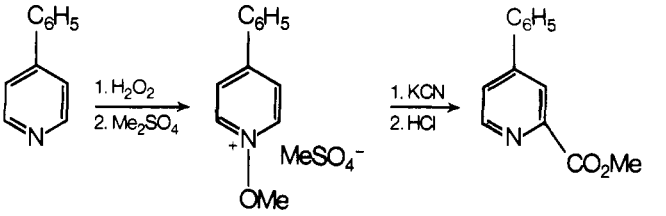
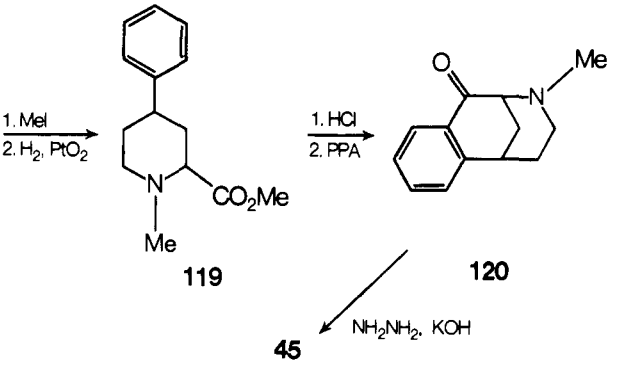


116

by oxidation of 4-phenylpyridine with 35% H_2O_2 followed by alkylation with dimethyl sulfate to give **117** which was converted to 2-carbomethoxy-4-phenylpyridine (**118**). Quaternization with methyl iodide and complete reduction yielded 1-methyl-2-carbomethoxy-4-phenylpiperidine (**119**). Attempted cyclization of



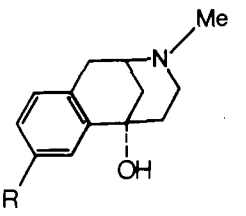
117 118



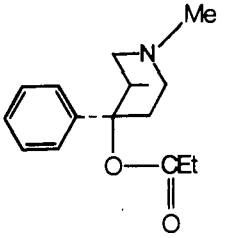
119 120 45

119 to **45** with polyphosphoric acid failed presumably since the most stable conformation (2,4-diequatorial) is the least favorable for cyclization. Conversion of **119** to the acid followed by treatment with hot polyphosphoric acid and Wolff–Kishner reduction afforded **45.** Since this acid could be reconverted to **119** with HCl/MeOH, the stereochemistry of the acid was also 2,4-diequatorial. With the acid, however, some inversion to the 2,4-diaxial conformer (favorable for cyclization) might have occurred in the presence of hot polyphosphoric acid. Grewe cyclization of 1-methyl-2-benzyl-1,2,5,6-tetrahydropyridine also yields **45.** As noted earlier, **45** has also been prepared via the tetralone route.[18]

The availability of 4-pyridones from 4-methoxypyridine[70,77] provided precursors for the preparation of 6-hydroxybenzomorphans **121** which were acylated to afford "hybrids" of the 6-alkylbenzomorphans and the "prodines" (**122**).[78]



121, R = H, OH



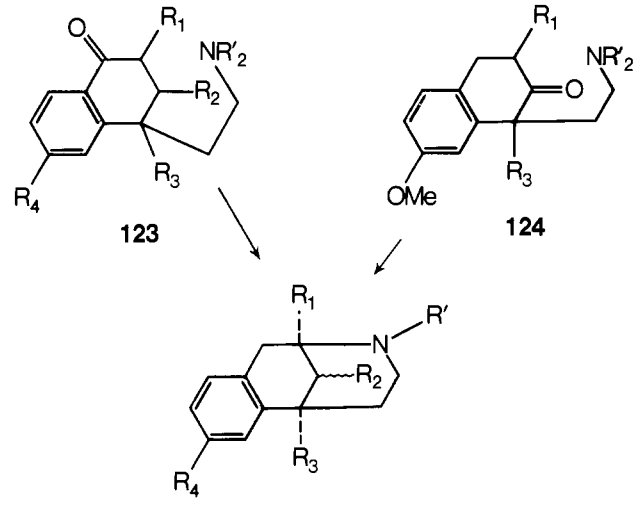
122, α-prodine

Although the Grewe synthesis is extremely useful, it suffers in certain instances from difficulties in preparing the required alkyl pyridines. One example is the preparation of 3,6-dimethyl-11-propylbenzomorphan which had not been previously prepared because of the unavailability of 4-methyl-3-propylpyridine. In this case, however, May's group has recently reported the synthesis of both compounds. The piperidine precursor was prepared in about 35% overall yield in four steps from cyanoacetamide and ethyl 2-propylacetoacetate. This was converted to a mixture of the 3,6-dimethyl-11-propyl isomers using the Steven's rearrangement and Grewe cyclization.[79]

D. Miscellaneous Syntheses

1. Beckmann Rearrangement

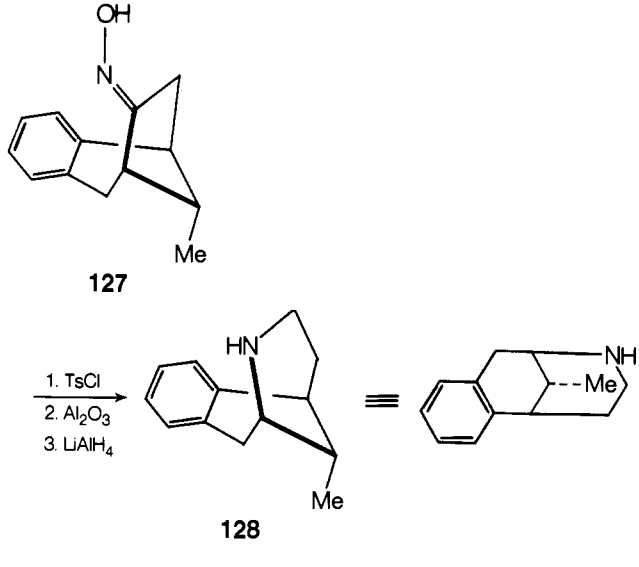
The 2,6,11-trialkylbenzomorphans are another class of compounds difficult to prepare owing to lack of the requisite starting materials **126.** These would presumably require precursors such as the tetralones **123** and **124** or the tetrahydropyridine **125.** In addition, there are no reports of functionalization of the bridgehead of any benzomorphan with an alkyl substituent after the basic ring skeleton has been constructed. This relatively inaccessible class of compounds has recently been prepared in an elegant synthesis by Sallay.[80] It should be noted that the key step in this synthesis, the Beckmann rearrangement, has been reported previously by Kotera et al., who obtained 11-methylnorbenzomorphan (**128**) in low yield from the tricyclic oxime **127.**[81]



123 **124**

126, $R' = R_1 = R_2 = R_3$ = alkyl; R_4 = H, OH

125



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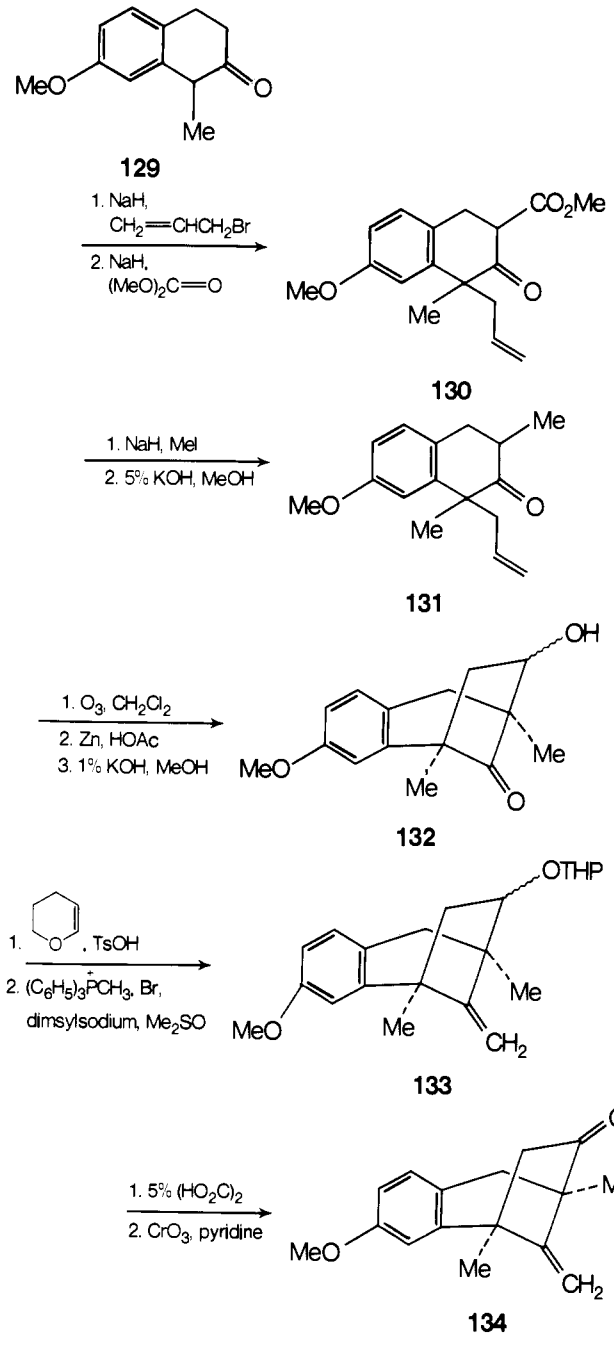
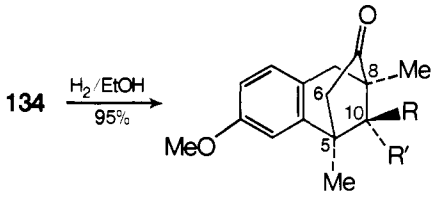
128



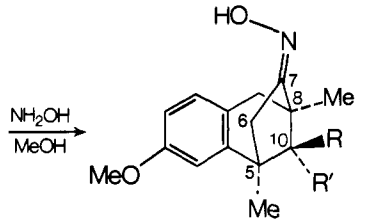
129 **130** **131** **132** **133** **134**

1-Methyl-7-methoxy-2-tetralone (**129**)[82] was alkylated with an allyl halide followed by carbomethoxylation to give the 1,1-dialkyl-β-keto ester **130.** Subsequent alkylation with methyl iodide followed by decarboxylation afforded the trialkyl tetralone **131.** Attempts to alkylate the 1,1-dialkyl-2-tetralone directly resulted in formation of the 1,1,3,3-tetraalkyl-2-tetralone. Ozonolysis of the allyl group followed by aldol condensation resulted in the tricyclic keto alcohol **132** which, protected as the tetrahydropyranyl ether, was converted to the methylene derivative **133.** The ether was removed with oxalic acid and the alcohol oxidized to give the methylene ketone **134.** The overall yield for these ten steps was 45%.

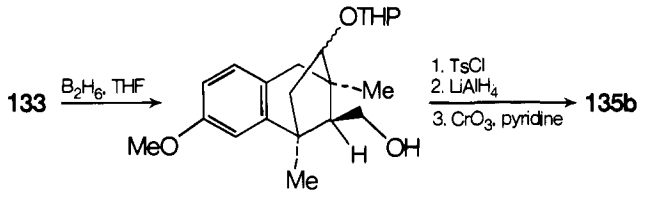
At this point two different sequences were employed for reduction and oxime formation. Catalytic reduction of **134** afforded a mixture of diastereomers at C-10. Use of Pd/C as the catalyst gave a ratio of cis/trans (**135a/135b**) of 3:2, whereas with PtO_2 this ratio was increased to 4:1. The pure trans isomer **135b** could be prepared stereoselectively in good yield by hydroboration–oxidation of **133** to **137.** The resulting equatorially oriented hydroxymethyl group was tosylated and reductively cleaved. Re-



135a, R = H; R' = Me
b, R = Me; R' = H



136a, R = H; R' = Me
b, R = Me; R' = H



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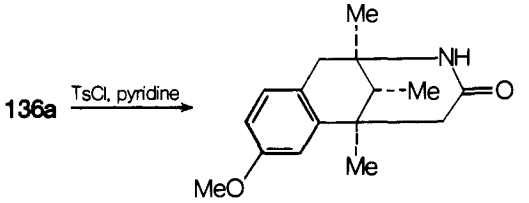
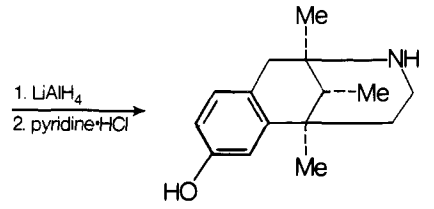
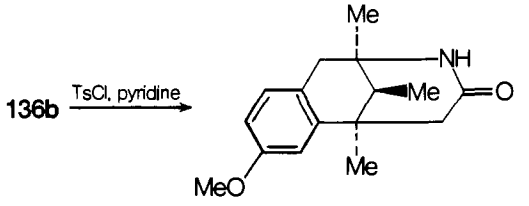


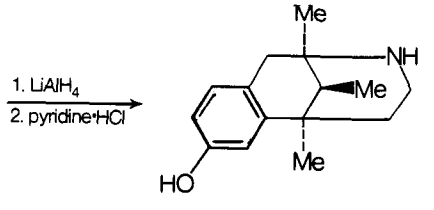
138a



139a



138b

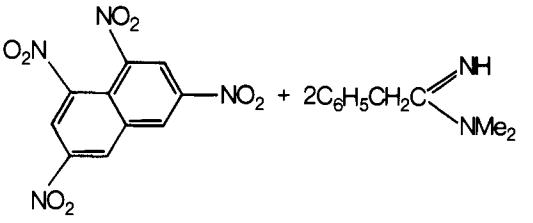


139b

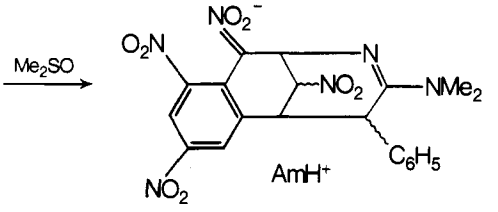
oxidation of the 7-hydroxy group gave **135b** uncontaminated with the cis isomer. Reaction of **135a** or **135b** with hydroxylamine produced the corresponding oximes **136a** and **136b.** Only the anti isomer was formed in each case. (Presumably, the syn and anti designations refer to the oximes with OH directed toward and away from C-10. The syn and anti designations have been used before to indicate the stereochemistry of similar oximes but with the 6-methylene group as a reference point.[81]) The absence of the syn isomer was attributed to steric hindrance of the C-8 methyl group. Exclusive formation of the anti isomer is significant when the mechanism of a Beckmann rearrangement is considered. Usually the migrating group occupies a trans (anti) orientation with respect to the leaving group. In the case of **136a** or **136b** the migrating group would then be the C-7–C-8 bond which would lead directly to the benzomorphan ring system. Subsequent rearrangement of the oxime tosylates afforded the lactams **138a** and **138b** in 40 and 45% yield, respectively. Reduction followed by ether cleavage with pyridinium chloride completed the synthesis of 2,6,11α-trimethyl- and 2,6,11β-trimethyl-8-hydroxybenzomorphans **139a** and **139b.** Other 2,6-dialkyl homologues were prepared in an analogous fashion. Not surprisingly, the nor compounds, e.g., **139a** or **139b,** did not show significant pharmacological activity. However, various *N*-alkyl derivatives were prepared and found to possess significant and interesting analgetic and/or antagonist activity.

2. *Meta Bridging*

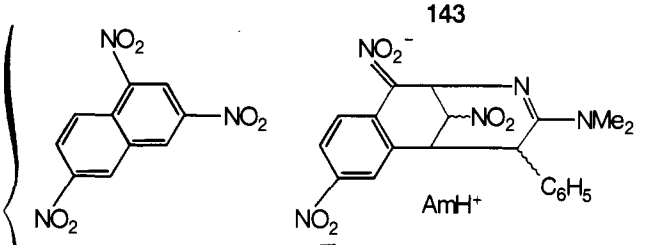
Perhaps the most straightforward route to the benzomorphan ring system is the recently described meta bridging of nitronaphthanes **140** and **141** with α-phenyl-*N,N*-dimethylacetamidine.[83,84] The obvious drawback to this preparation is the unusual functionality present in the products. This results from the necessity of activating the precursor aromatics as electrophilic substrates in the bridging reaction. It is interesting to note that with **140** in Me_2SO and **141** in ethanol the benzomorphan ring structure is formed, whereas with **141** and **142** in Me_2SO the isomeric **145** and **146** are formed. These structural assignments



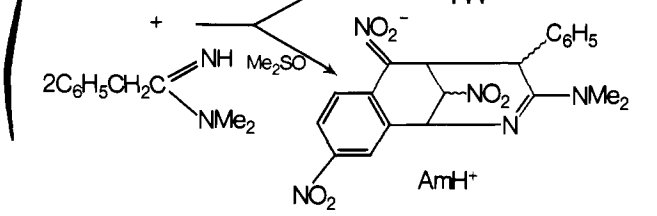
140



143



141 **144**



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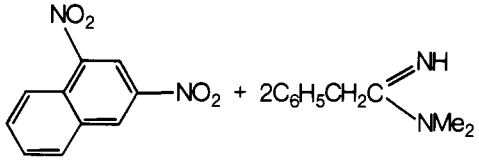

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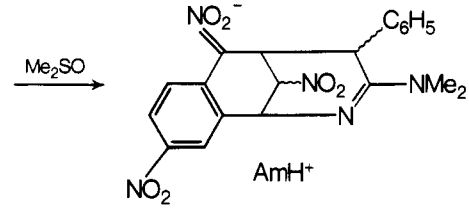
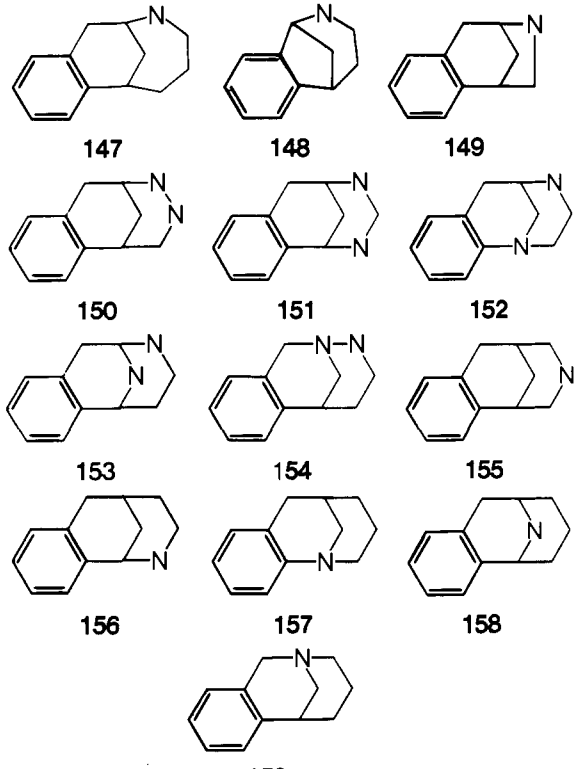


146

have been confirmed by NMR characterization of products obtained from C-1 deuterium-labeled **140** and **142.** The initial report[83] of a benzomorphan resulting from the reaction of **142** and α-phenyl-*N,N*-dimethylacetamidine was in error,[84] as the isomeric **146** was actually formed. If proper modification of nitro and nitronate functionality in structures like **144** can be achieved, and if the reaction can be extended to other amidines, meta bridging might be of considerable utility. It is interesting to note that **143** and **144** have significant long-lasting narcotic antagonist activity.[85,86]

III. Synthetic Routes to Homobenzomorphans and Norbenzomorphans

Various skeletal modifications of the benzomorphan ring have been reported in studies directed toward determining the effect on pharmacological activity. These include C-ring expansion to form the homobenzomorphans **147;** B-ring and C-ring contraction to form the *B*- and *C*-norbenzomorphans **148** and **149,** respectively; introduction of a second nitrogen to form the azabenzomorphans **150–154;** and synthesis of the basic skeleton with nitrogen in different positions, i.e., the N isomers **155–159.**

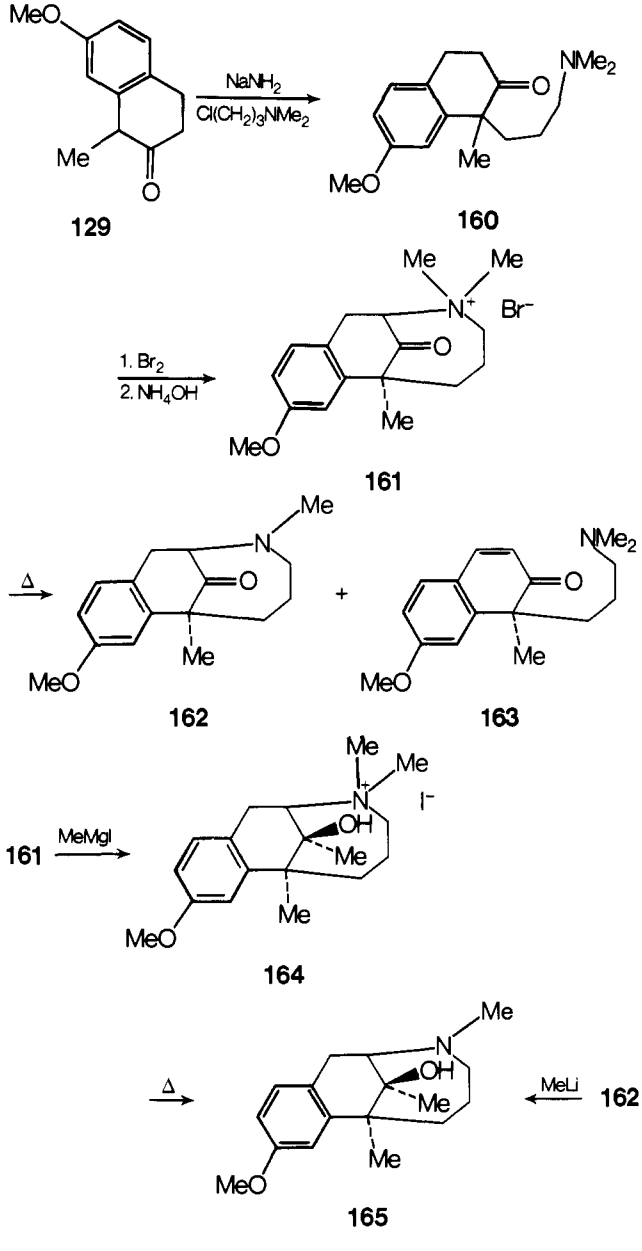


Benzomorphan Analogues

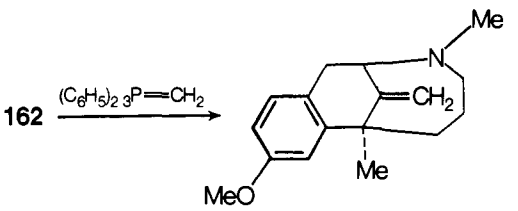
For nomenclature of several of these ring systems see section I.B. The methods used to prepare these related ring systems as well as other miscellaneous compounds related to benzomorphans are now considered.

A. Homobenzomorphans

The C-ring-expanded or homobenzomorphans attracted attention in 1970 when Takeda and Kugita synthesized the first members of this class using a route analogous to the tetralone synthesis for benzomorphans.[17] Analogous to benzomorphan synthesis discussed in section II.A, alkylation of **129** with 3-dimethylaminopropyl chloride afforded **160.** Bromination and cyclization of **160** afforded the quaternary salt **161** in yields of up to 40%. Pyrolysis of **161** led to a mixture of **162** and the elimination product **163.** Separation of similar products was a problem which also confronted May's group during the preparation of benzomorphans.[22,23] Brief comments regarding the reactivity of **161** and **162** should be made. Treatment of **161** with methylmagnesium iodide followed by pyrolysis gave the expected 12β-hydroxy-12α-methyl compound **165** in 48% yield, analogous to the results observed by May for Grignard additions in the benzomorphan series (section VIII). However, all attempts to prepare the 12-methylene derivatives **166** by dehydration of



129 160 161 162 163 164 165



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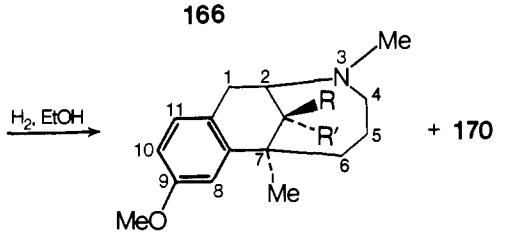
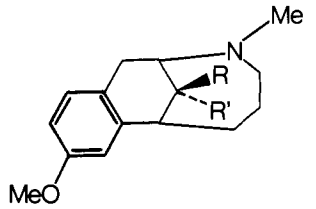
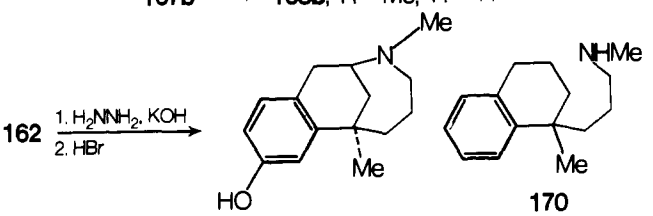


167a, R = H; R′ = Me
b, R = Me, R′ = H



167a $\xrightarrow{HBr}$ **168a**, R = H; R′ = Me
167b $\xrightarrow{HBr}$ **168b**, R = Me; R′ = H



169 170

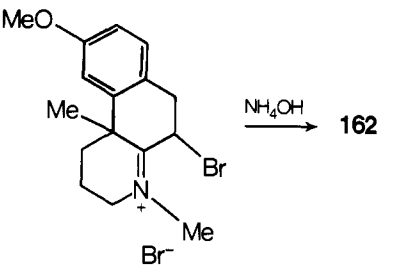
165 under a variety of conditions ($SOCl_2$, $POCl_3$, TsCl/pyridine) failed. This is in contrast to facile preparation of the 11-methylenebenzomorphan by dehydration of the corresponding 11β-hydroxy-11α-methylbenzomorphan.[87,88] Pyrolysis of the 12β-acetoxy compound afforded **166** only in low yields.

Surprisingly, attempts to prepare the 12α-hydroxy-12β-methyl derivative as a precursor to **166** were also unsuccessful. Addition of methyllithium to the free base **162** resulted in **165,** identical in all respects with **165** prepared from **161.** This is in contrast to the behavior of benzomorphans where alkyllithium additions to the free base produce the 11α-hydroxy-11β-alkyl isomer (section VIII). The 12-methlene compound was finally obtained in 98% yield by Wittig reaction of **162.**

Catalytic hydrogenation of **166** in the presence of PtO_2 gave the 12α-methyl and 12β-methyl derivatives **167a** and **167b** in 7 and 25% yields, respectively, accompanied by the secondary amine **170.** The predominance of 12β-alkyl isomer is noteworthy since it has been shown that under identical conditions the 11-methylenebenzomorphan afforded stereoselectively the 11α-methyl compound.[87] If the hydrogenation was conducted in the presence of 15% HCl/EtOH, then the expected 3,7,12β-trimethyl derivative was isolated in 85% yield together with 12% 3,7,12α-trimethyl-9-methoxyhomobenzomorphan. O-Demethylation of these with 48% HBr gave the corresponding phenols **168a** and **168b.** 3,7-Dimethyl-9-hydroxyhomobenzomorphan (**169**) was obtained in two steps from **162** in the usual manner.

The 12β-methyl isomer **168b** was found to be a more potent analgesic than the 12α-methyl isomer, analogous to results obtained with the 11α- and 11β-alkylbenzomorphans.

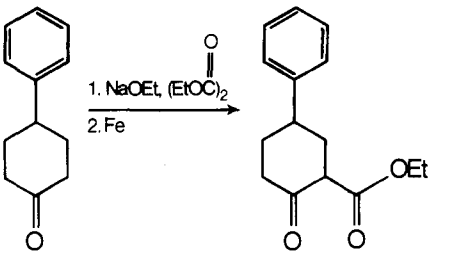
A more practical synthesis of **162** was reported in which re-



171

arrangement of the tricyclic bromoimmonium bromide **171** afforded **162** in 81% yield.[35] This method was also successfully applied to the benzomorphan analogue. This approach avoids the formation of ring-opened products such as **163.**

An interesting synthesis of 3-methylhomobenzomorphan (**179**) was developed which utilized a Beckmann rearrangement as the key step.[16] Condensation of 4-phenylcyclohexanone with



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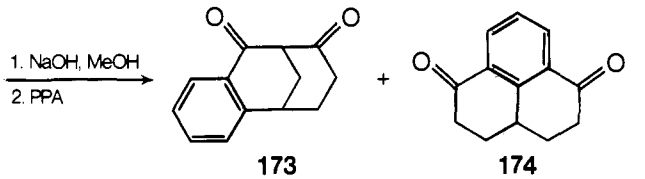
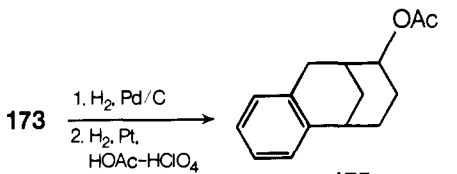


173 174



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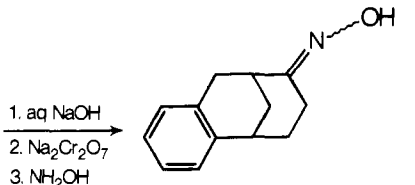

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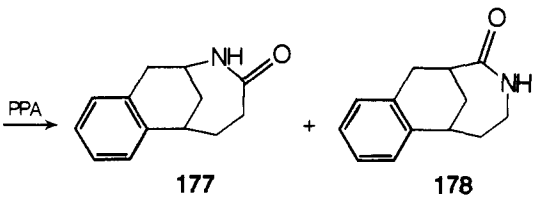
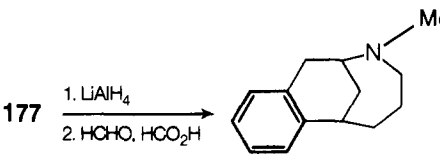
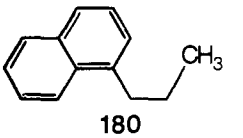


177 178



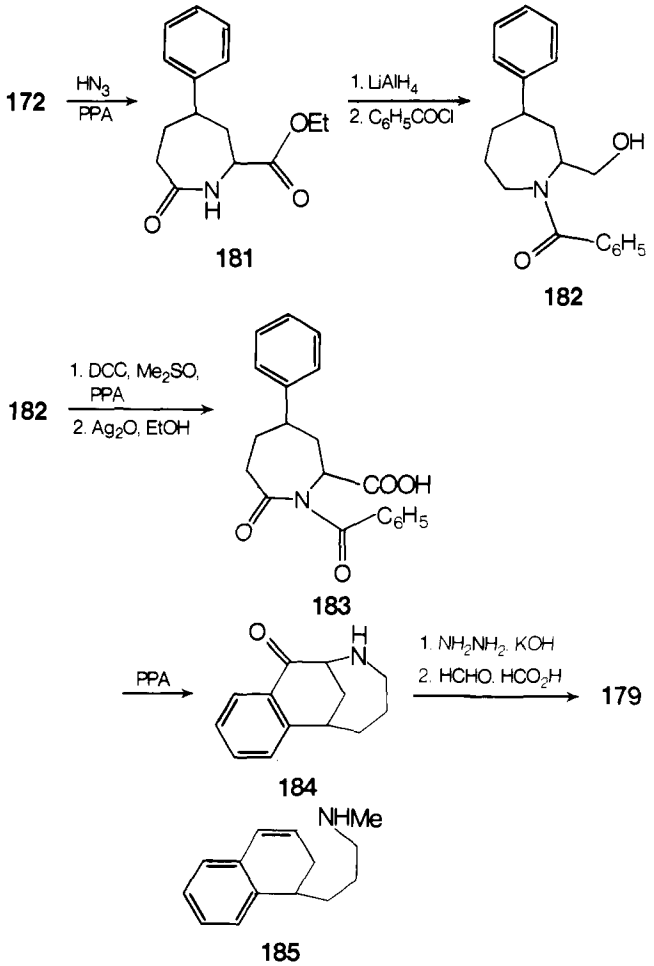
179



180

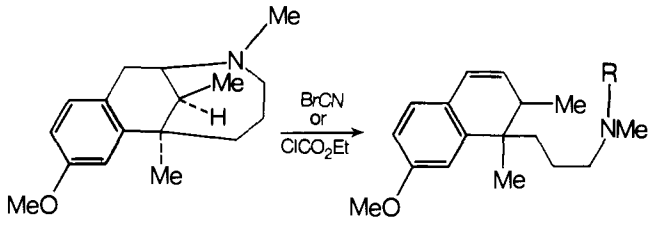
diethyl oxalate followed by decarbonylation gave the β-keto ester **172** which was hydrolyzed and cyclized with polyphosphoric acid to a 5:1 mixture of tricyclic diketones **173** and **174.** Catalytic reduction of **173** followed by hydrogenolysis of the benzylic hydroxyl group gave the acetate **175.** This was hydrolyzed and subjected to Jones oxidation, and the resulting ketone was converted to the oxime **176.** Beckmann rearrangement of **176** afforded the isomeric lactams **177** and **178** in a 10:1 ratio. Reduction of **177** with lithium aluminum hydride followed by Clarke–Eschweiler methylation completed the synthesis of **179.** To confirm the structure of **179,** degradation in the usual manner afforded the known 1-propylnaphthalene (**180**).

The above method which requires isolation of the mixture of lactams **177** and **178** was improved by a newer method which employed B-ring construction as the key step.[89] Schmidt reaction of ethyl 2-oxo-5-phenylcyclohexanecarboxylate (**172**) produced the lactam ester **181** which was reduced and benzylated by the Schotten–Baumann method to give the amide alcohol **182.** Two-step oxidation of **182** afforded **183** which was cyclized to 1-oxohomobenzomorphan (**184**). This somewhat circuitous route was necessary since attempts to cyclize **181** or the corresponding acid with PPA or concentrated sulfuric acid were unsuccessful. Wolff–Kishner reduction of **184** and subsequent reductive methylation gave **179.** Interestingly, if the reduction and methylation sequence was reversed, the only product isolated was the ring-opened amine **185.** This problem



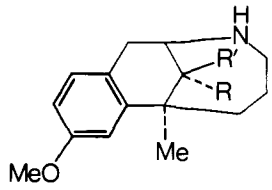
was circumvented by methylating **184,** reducing the ketone to the alcohol with $LiAlH_4$, followed by cleavage with 57% HI and red phosphorus.

The facile cleavage of the C-2–N bond in some homobenzomorphans, particularly those with a 12β-alkyl substituent, limits the previous method for the preparation of other *N*-alkyl derivatives via demethylated intermediates. For example, attempts to demethylate 3,7,12β-trimethyl-9-methoxyhomobenzomorphan (**167b**) resulted in the exclusive formation of the ring fission products **186a** or **186b.**[2] The use of diethyl azodicarboxylate did furnish **187** in low yields, however. This problem



167b

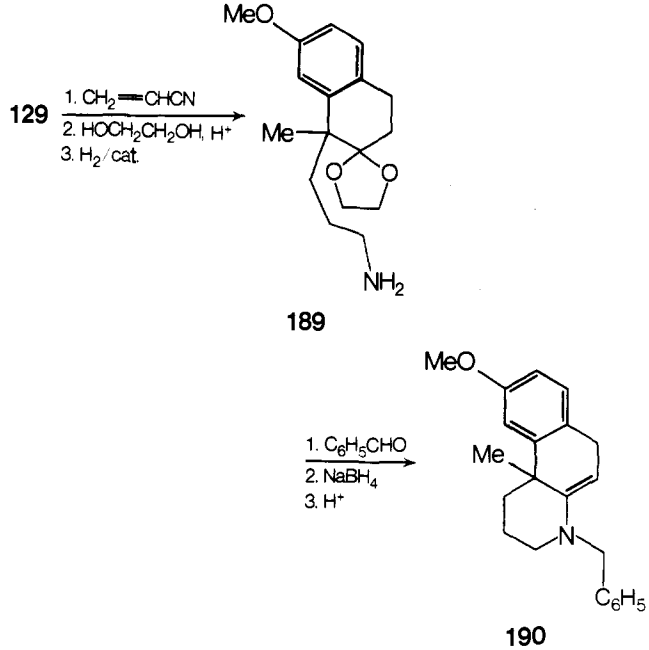
186a. R = CN
b, R = CO_2Et

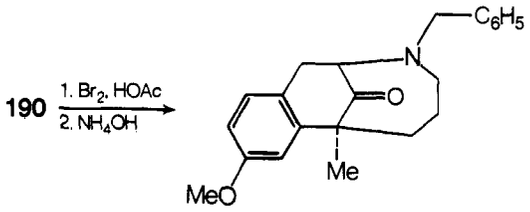


187. R = H; R' = Me
188. R = Me; R' = H

was not encountered with the corresponding 12α-methyl isomer which afforded the nor derivative **188** in good yield by treatment of **167a** with cyanogen bromide followed by lithium aluminum hydride reduction. Similar results were obtained with the diastereomeric benzomorphans. In the case of the 11β-methyl benzomorphan, however, the corresponding nor derivative was isolated together with some of the ring fission product in a 3:1 ratio.

This problem was overcome by modification of the previously reported synthesis based on the rearrangement of heterocyclic enamines (vide supra).[35] Thus, 1-methyl-7-methoxy-2-tetralone (**129**) was condensed with acrylonitrile followed by ketalization and reduction to the amino ketal **189.** This was converted in three steps to the enamine **190** which was rearranged to the *N*-benzyl-12-oxo compound **191** in 40% yield. The 12-methylene derivative **192** was obtained from **191** in 77% yield by a Wittig reaction. Hydrogenation of **192** resulted in both reduction and hydrogenolysis to afford the desired 3,12β-dimethyl-9-





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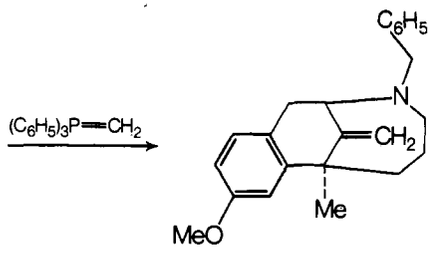
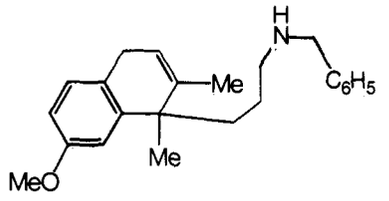


192

192 $\xrightarrow[EtOH,\ aq\ HCl]{H_2,\ Pd\ C}$ 187 + 188
64% 21%



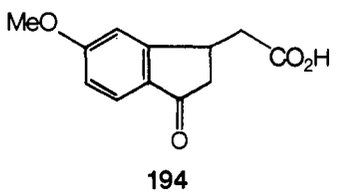
193

methoxynorhomobenzomorphan (**187**) in 64% yield together with the 3,12α-dimethyl isomer in 21% yield. Both **187** and **188** were then converted to the desired *N*-alkyl substituted compounds. Attempts to reduce **192** in the absence of acid resulted in formation primarily of the ring fission product **193.**[2]

B. Norbenzomorphans

The considerable analgetic activity of a 6,7-benzomorphan not containing quaternary carbon[75] prompted interest in the synthesis of *B*-norbenzomorphans. Although quite similar to 6,7-benzomorphans, superpositioning of the aromatic rings of Drieding models of each compound shows significant shortening of the distance from N-3 to C-8 oxygen functionality in the nor compound.

The synthesis of *B*-norbenzomorphan (**198**) was first achieved[15] starting with the previously prepared 5-methoxyindan-1-one-3-acetic acid (**194**). Esterification of **194** with methanol followed by reaction with hydroxylamine afforded the oxime **195** which was reduced and hydrolyzed to the amino acid **196.** Cyclization effected with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate yielded the



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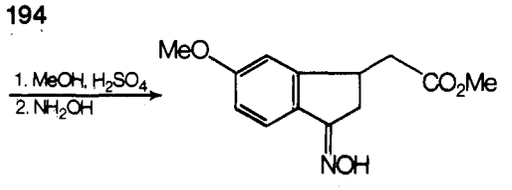

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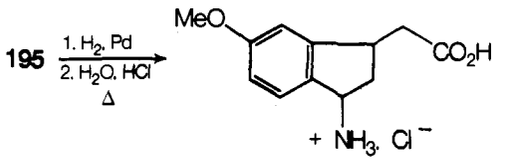

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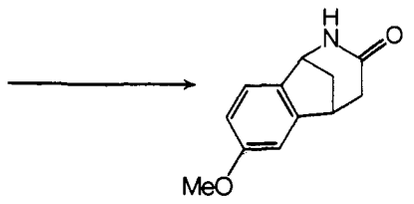

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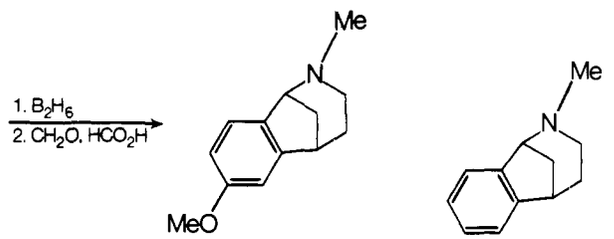
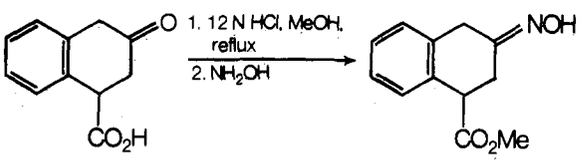


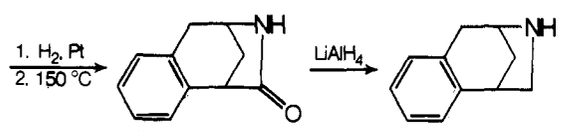
198 199

lactam **197** which was reduced with diborane and methylated to give **198.** A similar procedure was used to prepare the unsubstituted *B*-norbenzomorphan **199.**[90]

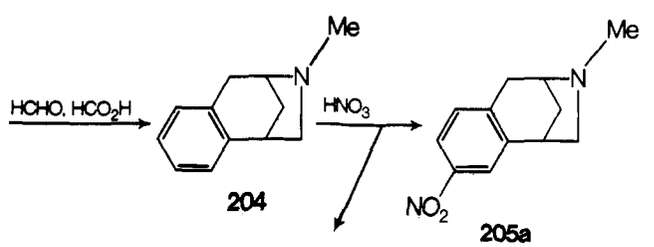
In an extensive study, Mitsuhashi and Shiotani, in addition to preparing a large series of azabenzomorphans, have reported the preparation of *C*-norbenzomorphans[18] and their aza an-



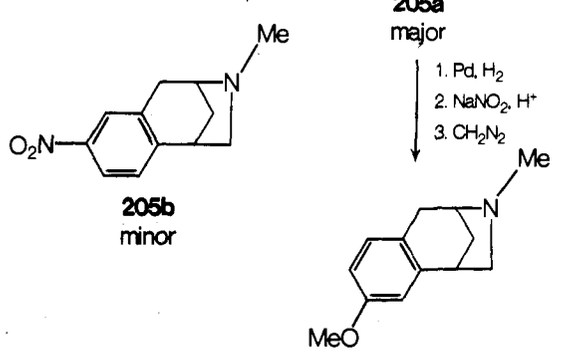
200 201



202 203



204 205a major



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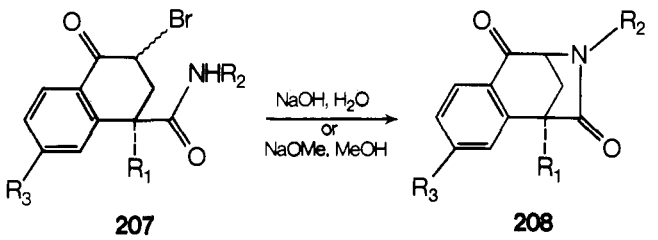
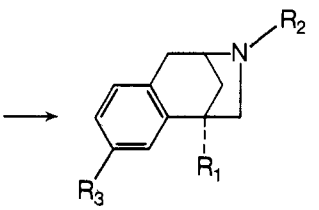
alogues. The *C*-norbenzomorphan **202** was prepared from the keto acid **200** in five steps. Esterification of **200** and conversion to oxime **201** was followed by reduction and cyclization to the lactam **202.** Further reduction with $LiAlH_4$ afforded the *C*-norbenzomorphan **203** which was methylated to yield **204.** The C-8 methoxyl was introduced by nitration, reduction, diazotization, and methylation.

Another preparation of *C*-norbenzomorphans has been reported in the patent literature.[91] Cyclization of the amide **207** in base, followed by reduction of the resulting lactam **208,** yields structures like **209.**



207 **208**



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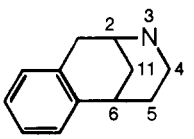
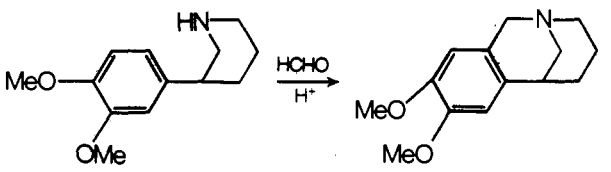
IV. Positional Variation of Nitrogen

A considerable effort has been made to prepare isomers of 6,7-benzomorphans in which nitrogen at position 3 is interchanged with carbon at positions 2, 4, 5, 6, and 11. All of these isomers have now been prepared. The correct name and numbering systems for these ring systems are summarized in section I.B.



The earliest report is the synthesis of the 2-benzazocine **211**[92] by Pictet–Spengler cyclization of phenylpiperidine **210.**

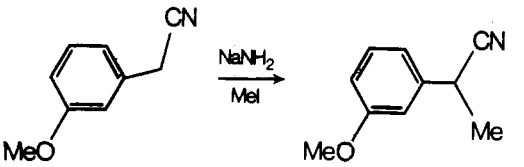


210 **211**

The same ring system was synthesized later with C-6 methyl and C-8 hydroxyl functionality from *m*-methoxyphenylacetonitrile.[93] Thus, alkylation of the phenylacetonitrile gave **212** which in a Michael addition with methyl acrylate afforded **213.** Catalytic reduction yielded the lactam **214** which was reduced with $LiAlH_4$ to **215.** Cyclization was then effected as with **210.** Compounds like **216** were not found to be useful analgesics.[93]

The α- and β-6,11-dimethyl isomers **219** and **220** in this ring system have been prepared by Pictet–Spengler cyclization of the diastereomeric phenylpiperidines **217** and **218.**[94]

Perhaps the most extensive effort in the preparation of N-3 positional isomers of 6,7-benzomorphans was carried out by Mitsuhashi and Shiotani.[18] Their approach to 2-benzazocines like **211** and **216** involves a Dieckmann cyclization as the key step. Thus the tetrahydroisoquinoline **221** was condensed with ethyl acrylate to give **222,** which was subjected to Dieckmann



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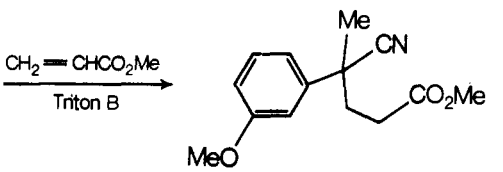

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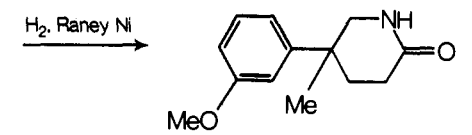

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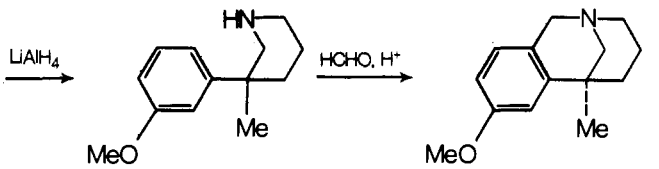
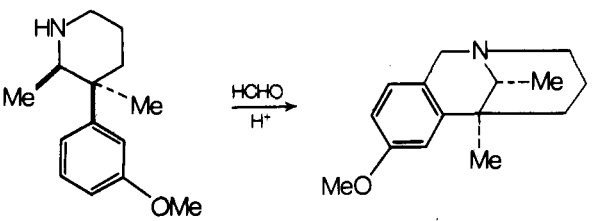
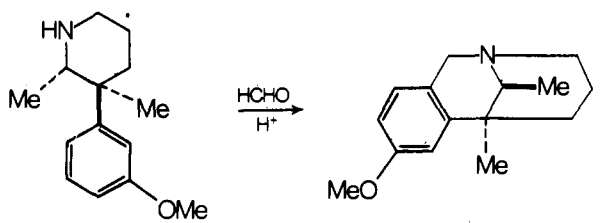


215 **216**

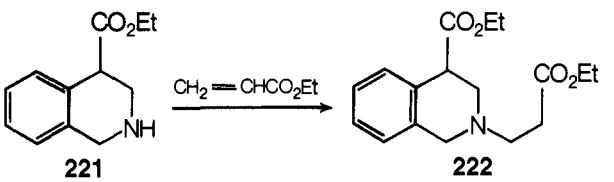


217 **219** (α)

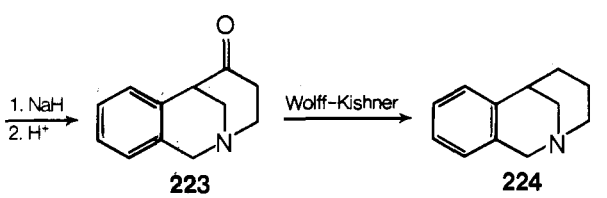


218 **220** (β)

cyclization and hydrolysis to **223.** Wolff–Kishner reduction of **223** afforded **224.** A rather novel preparation of this ring system

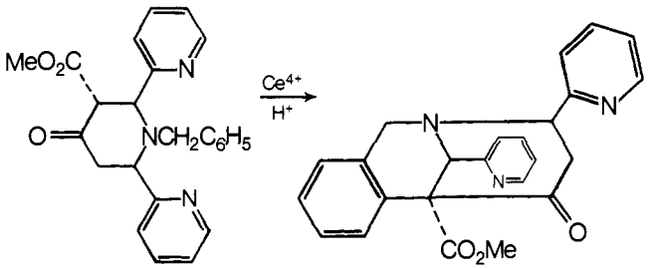


221 **222**



223 **224**

was recently reported which involves ceric sulfate mediated intramolecular bridging of the piperidone **225.**[95]



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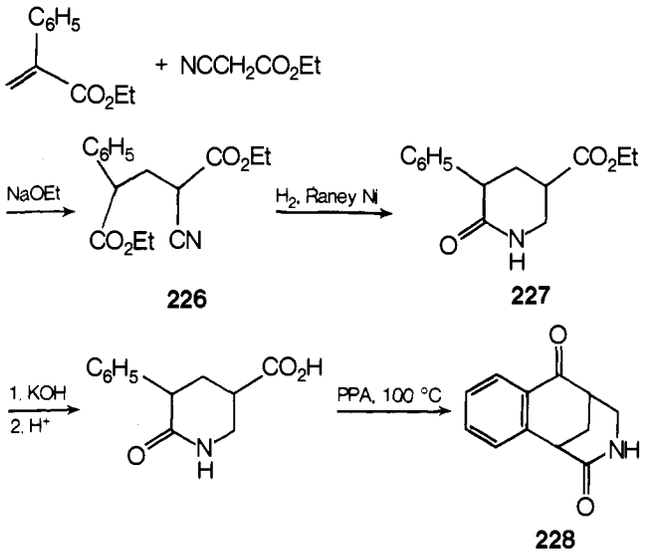
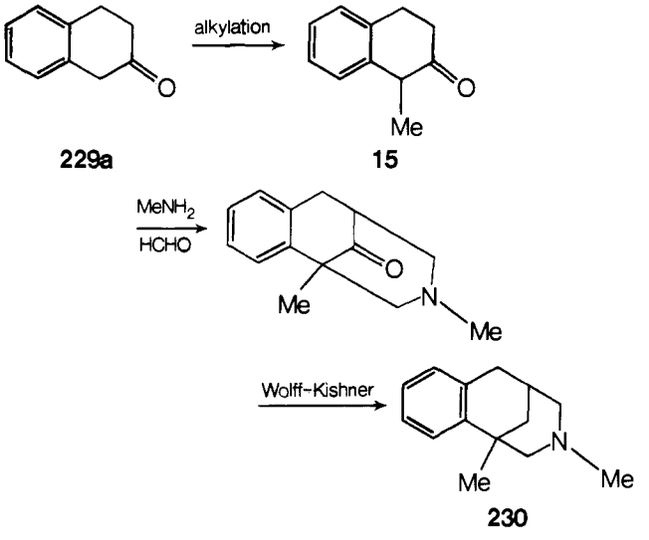
Preparation of the 3-benzazocine ring system **228** was first reported in 1959.[96] Condensation of ethyl phenylacrylate and ethyl cyanoacetate in base afforded **226** which upon reduction cyclized to give **227.** Basic hydrolysis of **227** followed by intramolecular cyclization in acid yielded **228.**



226 227 228

This ring system was also prepared in an elegant fashion from the tetralone **15** by a Mannich condensation with methylamine and formaldehyde.[18] Atempts to carry out the Mannich reaction starting with **229** failed owing to the considerably greater reactivity of the benzylic carbon which presumably added 2 equiv of formaldehyde.

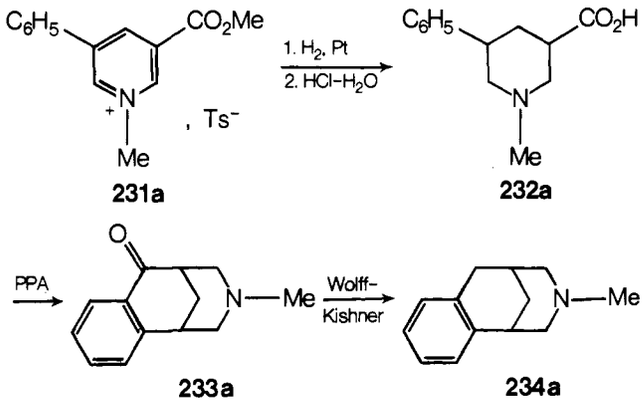


229a 15 230

A synthesis of this ring system similar to the earlier preparation[96] was recently reported.[97] Reduction of the nicotinate ester **231a** to **232a** followed by acid-catalyzed cyclization yielded **233a** which was reduced to **234a.** A variety of different C-6 functionalized derivatives of **234a** were prepared by reaction of **233a** with $LiAlH_4$, phenyllithium. or Grignard reagents. None of these compounds exhibited interesting analgesic or antagonist activity.[97]

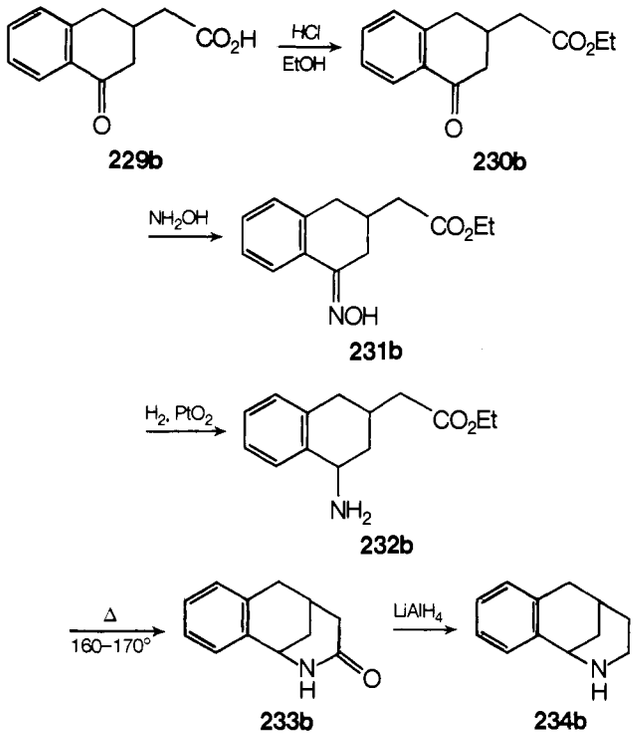
An additional example of a bridgehead-substituted derivative in this series, as well as a recent synthesis of a 1,3,6,-trialkyl-system have been reported.[97a,b]

Synthesis of the 2-benzazocine **234b** was achieved starting with the keto acid **229b.**[18] Esterification, reaction with hydroxylamine, and reduction afforded the amino ester **232b** as a mixture of cis and trans isomers with the former predominating. Pyrolysis of this mixture gave the lactam **233b** which was readily reduced with $LiAlH_4$ to **234b.**



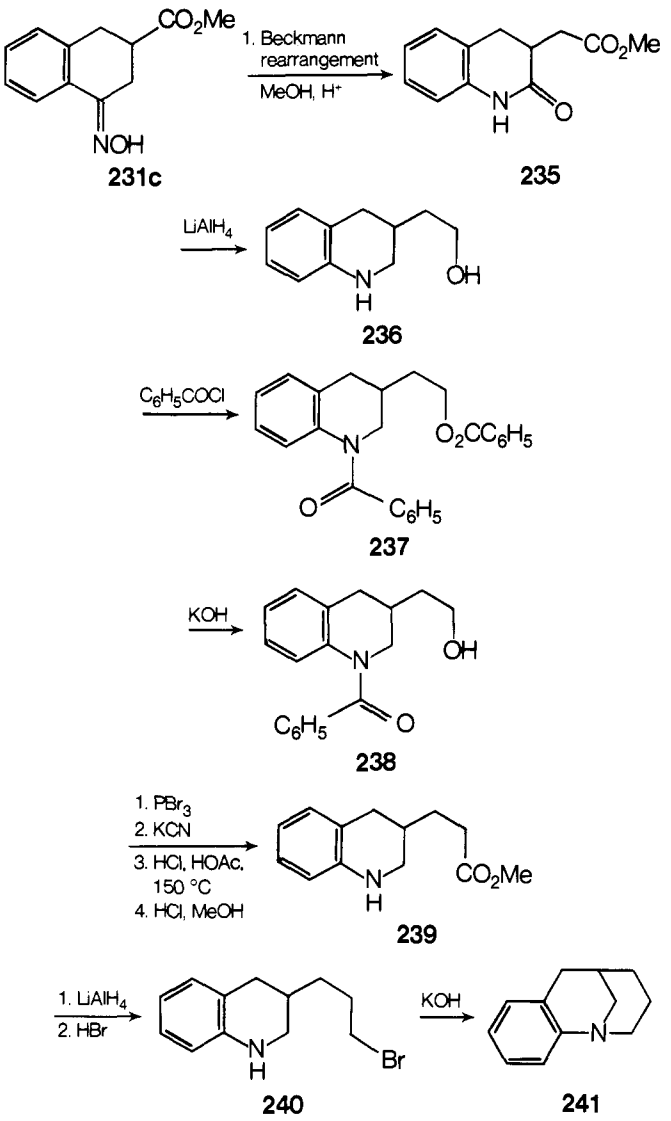
231a 232a 233a 234a

Meta bridging of 1,3,-dinitronaphthalene with α-phenyl-*N,N*-dimethylacetamidine yields **146,**[83] a highly functionalized derivative of **234b.**



229b 230b 231b 232b 233b 234b

Starting with an oxime ester analogous to **231b,** the 1-benzazocine **241** was prepared.[18] Thus, Beckmann rearrangement of **231c** leads to ring-expanded lactam. This was opened and underwent intramolecular interchange[98] in acidic methanol to give **235.** After reduction and reaction with benzoyl chloride, the amide ester **237** was hydrolyzed to the alcohol **238.** Bromination, reaction with cyanide, hydrolysis, and esterification yielded the amino ester **239** which was reduced and converted to the bromide **240.** Cyclization of **241** was effected with potassium hydroxide in refluxing aqueous ethanol.



The final benzazocine in this series of isomers, **242**, was synthesized from the ethyl ester of 3,4-dimethoxyphenylalanine in seven steps,[99] as outlined in Scheme III. Further reduction and debenzylation of **242** has been reported.[18]

A series of N-3 positional isomers of *B*-norbenzomorphans have also been reported.[18] Discussion of such ring systems will not be presented here.

V. Azabenzomorphans

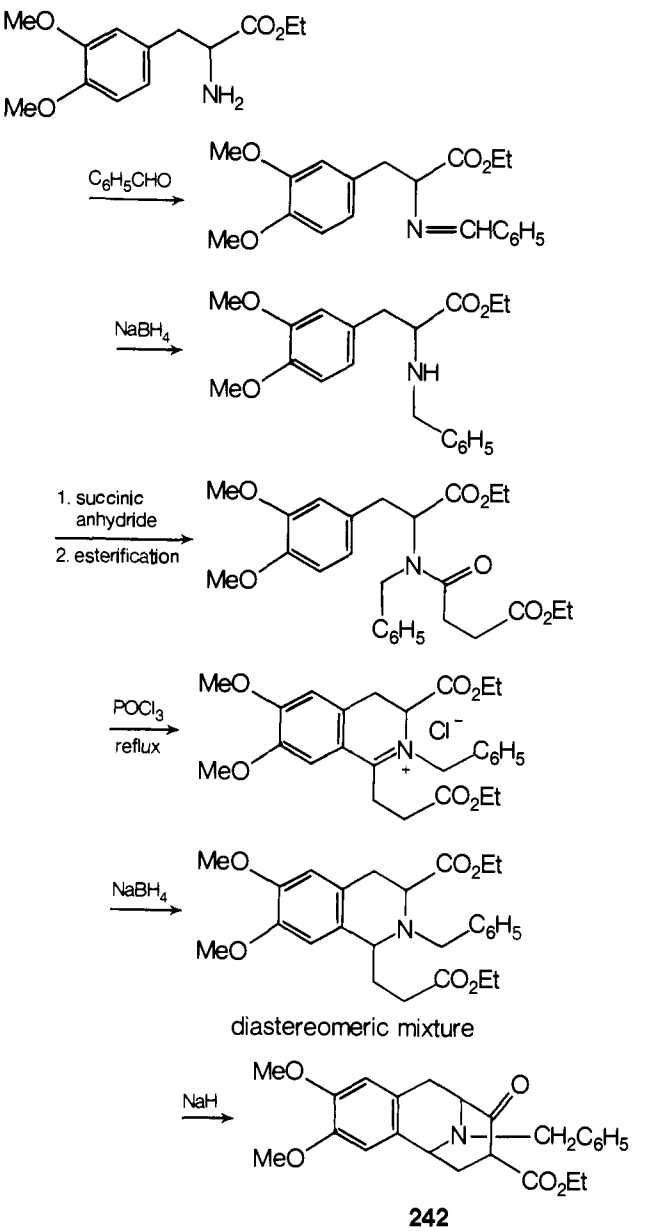
An extensive review of the synthetic work done on azabenzomorphans (benzodiazocines) has been published very recently by Kametani and co-workers.[100] This account is quite comprehensive and further discussion here is not appropriate. It is important to note, however, that introduction of an additional nitrogen atom into the benzazocine ring system has an unfavorable effect on analgesic activity.[100]

VI. Miscellaneous Compounds

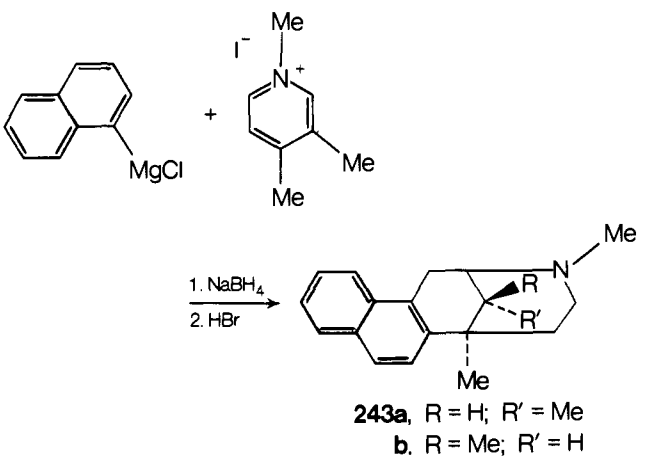
Although not considered benzomorphans, a variety of compounds structurally similar to the basic ring system will be discussed briefly.

A synthesis of naphthazocines which utilizes Grignard reagents derived from naphthyl halides has been reported.[101,102] Reaction of α-naphthylmagnesium chloride with 1,3,4-trimethylpyridinium iodide followed by reduction and cyclization afforded a mixture of the naphthazocines **243a** and **243b** in a 4:1 ratio. The β isomer, **243b**, could be obtained in good yield

SCHEME III



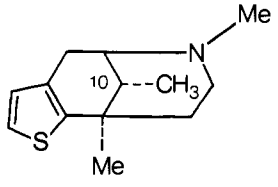
as the major product using Fry's method (vide supra).[59] The nor bases and *N*-alkyl derivatives were prepared in the usual manner.



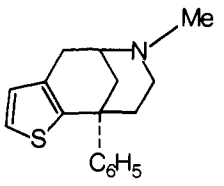
243a, R = H; R′ = Me
b, R = Me; R′ = H

The synthesis of analogues with a heterocyclic ring substituted for the benzo fusion has also been achieved.[103] Thus, the thiophene derivatives **244** and **245** were prepared by Grewe cycli-

zation of the corresponding tetrahydropyridines. For **244** it is interesting to note that none of the 3,6,10β-trimethyl isomer was isolated. All attempts to prepare the 8-hydroxy or 8-amino derivatives of **244** or **245** were unsuccessful. This was attributed to the known instability of 2-amino- and 2-hydroxythiophenes. However, *N*-alkyl derivatives of both **244** and **245** were obtained from the corresponding nor bases without difficulty. The thiophene ring did not favorably influence analgetic activity.

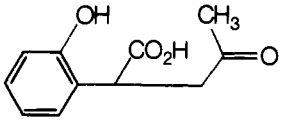


244 (α)



245

Although the substitution of nitrogen for carbon to form azabenzomorphans is well documented, similar substitution for carbon by oxygen is less frequently encountered. An example of this benzoxazocine ring system **249** has recently been reported.[104] The keto acid **246** was treated with benzyl bromide and K_2CO_3 followed by ketalization to give **247** which was converted to the amide and reduced to the amine **248.** Heating



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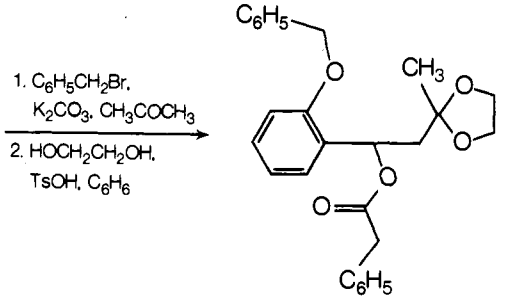

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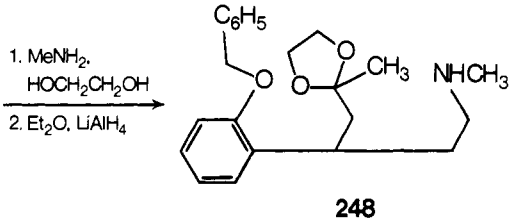

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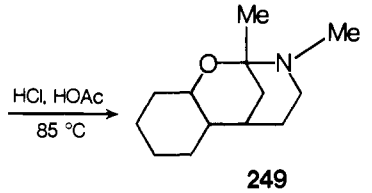
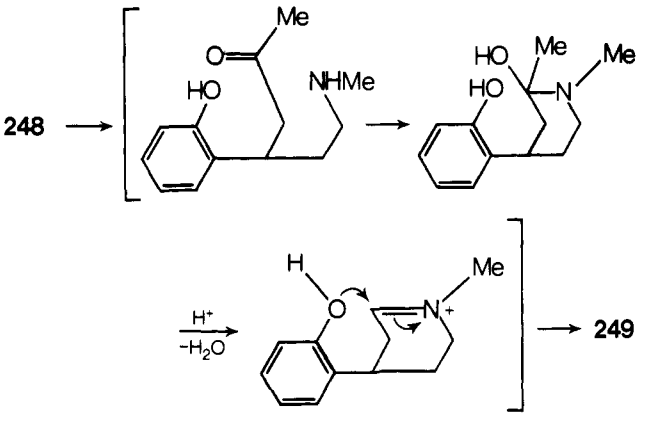


249

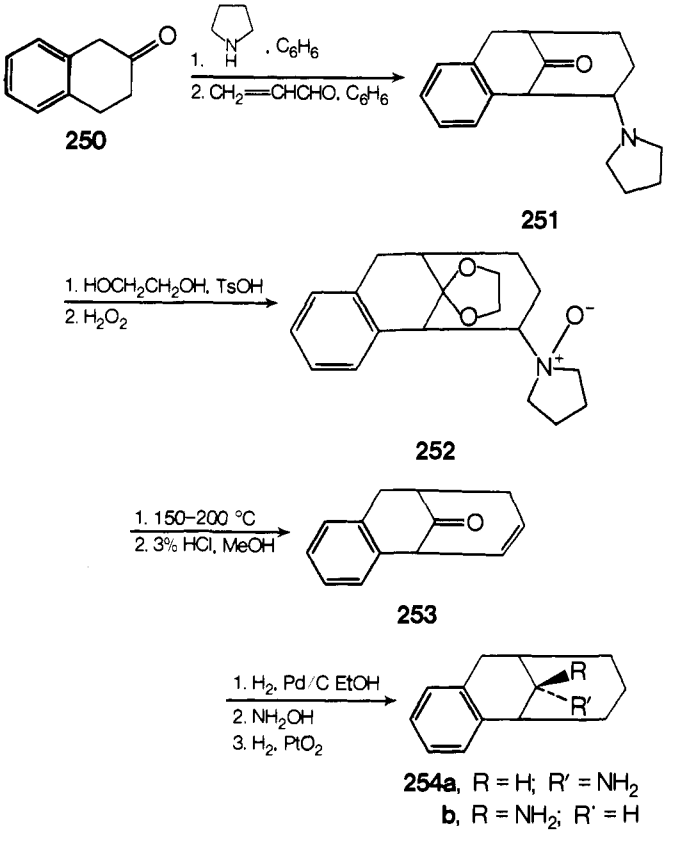
248 with a mixture of concentrated HCl and HOAc (1:2) afforded the benzoxazocine **249** in 80% yield. A proposed mechanism is outlined in Scheme IV. Additional examples of oxygen as well as aza analogues of nitrogen isomers of benzomorphans and homobenzomorphans have been reported.[105-111]

The bridged amino tetralins are an interesting class of compounds in which the spatial arrangement of the nitrogen atom and the aromatic ring is similar to that in morphine. This ring system, 11-substituted-2,3-benzobicyclo[3.3.1]nonane (**254**), is comparable to the basic skeleton of the benzomorphans. The

SCHEME IV



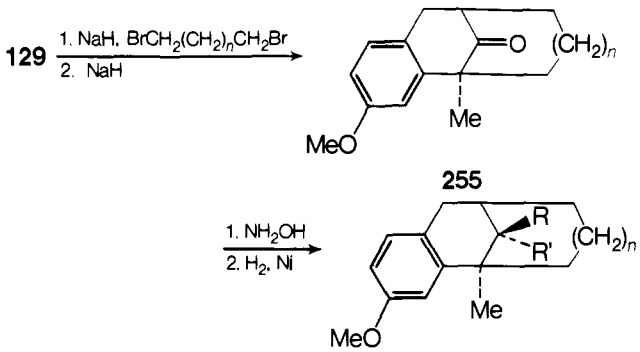
SCHEME V



initial synthesis is shown in Scheme V.[112] Condensation of the pyrrolidine enamine of **250** with acrolein gave the tricyclic ketone **251** which was ketalized and oxidized to **252.** Pyrolysis followed by ketal hydrolysis yielded the unsaturated ketone **253** which was converted in three steps to a mixture of the epimeric 11-amino-2,3-benzobicyclo[3.3.1]nonanes **254a** and **254b.**

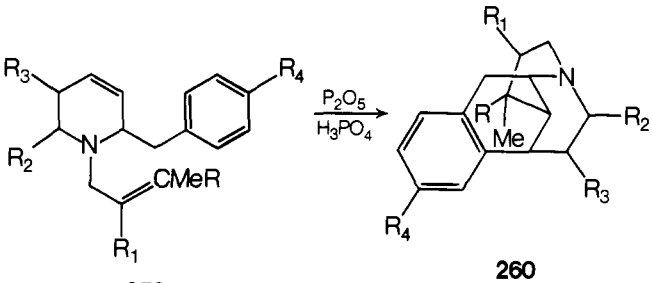
A later synthesis has furnished bridged amino tetralins possessing both a quaternary carbon and an aromatic substituent (OH, OCH_3) characteristic of many potent benzomorphan analgesics.[113] In this approach 7-methoxy-1-methyl-2-tetralone (**129**) was alkylated with an appropriately substituted dihalide to give tricyclic ketone **255** which, after conversion to the oxime, was catalytically reduced to afford a mixture of the 11α-amino and 11β-amino epimers **256a** and **256b.** These were separated as the hydrochloride salts.

Recent examples of novel tetracyclic benzomorphan derivatives have appeared in the patent literature. A series of 3,11-propano bridged compounds **260** have been obtained by Grewe cyclization of the tetrahydropyridine **259.**[114] Synthesis



256a, R = H; R' = NH_2; *n* = 1
256b, R = NH_2; R' = H; *n* = 1
257a, R = H; R' = NH_2; *n* = 2
257b, R = NH_2; R' = H; *n* = 2
258a, R = H; R' = NH_2; *n* = 3
259b, R = NH_2; R' = H; *n* = 3

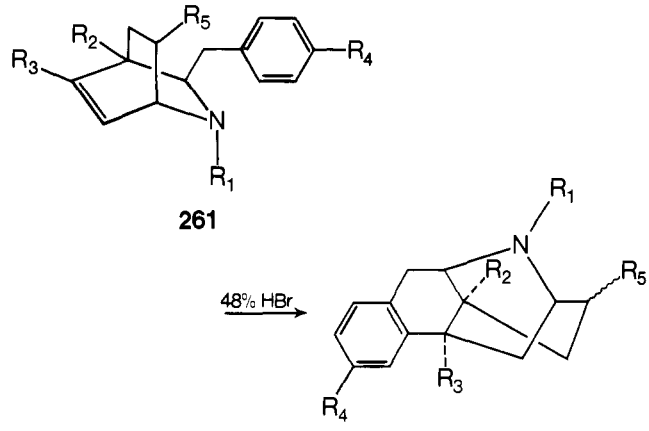
of the 4,11-ethano bridged benzomorphans **262** by Grewe cy-



259 **260**

R = Me, Et, Pr; R_1–R_4 = H, Me

clization of the corresponding substituted 5-azabicyclo[2.2.2]-oct-2-enes (**261**) is shown below.[115]



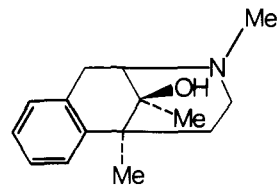
261 **262**

R_1 = alkyl
R_2 = H, alkyl
R_3 = alkoxy
R_4 = H, alkoxy, OH, acyloxy
R_5 = Me, CH_2NH_2

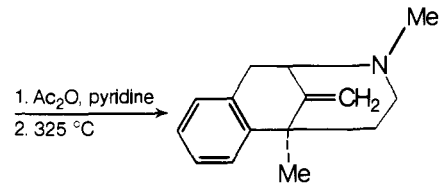
VII. Rearrangements

Reactions of benzomorphans at C-1, nitrogen or on the aromatic ring usually proceed in a straightforward manner without complications. At C-11, however, unusual and/or unexpected products have been observed as a result of rearrangements of the ring skeleton.

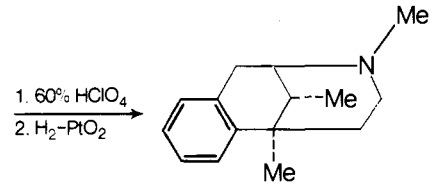
In an early attempt to prepare 3,6,11α-trimethylbenzomorphan (**74a**), the alcohol **263** was converted to the acetate, which



263

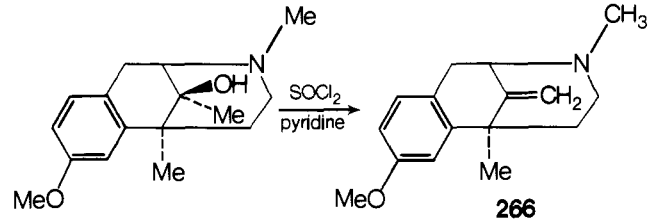


264



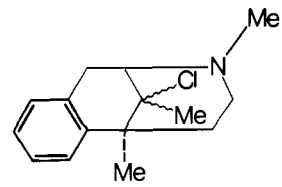
74a

was pyrolyzed in low yield to the 11-methylene derivative **264** which (as the perchlorate) was reduced to **74a**.[20] Later during a similar study with the 8-methoxy analogues, the previous procedure was abandoned in favor of a dehydration using a large excess of thionyl chloride and pyridine.[87] Thus **265** was converted to **266** in good yield employing this method. However, use of these new conditions to prepare **264** was not successful.



265 **266**

When **263** was treated with thionyl chloride and pyridine, two minor products, **267** and **268**, were isolated in addition to a 35% yield of **264**.[116] One of these, **267**, was shown to have the molecular formula $C_{15}H_{20}NCl$ and was tentatively identified as 11-chloro-3,6,11-trimethylbenzomorphan, although the possibility of skeletal rearrangement was not excluded. The other product, **268**, was a halogen-free base isomeric with **264**. Spectroscopic studies showed no evidence for either a terminal methylene group or a benzene ring conjugated with a double bond (typical of ring opened products). Reduction of **268** afforded two isomers which, coupled with spectroscopic data, provided evidence for a skeletal rearrangement involving phenyl migration. The proposed structure **268** is shown below. Additional examples of unknown rearrangement products isolated from reaction of **263**, **265**, or 6-alkyl homologues with thionyl chloride were reported.[24,25,88]



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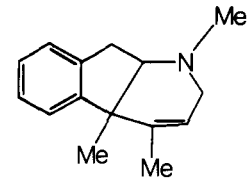
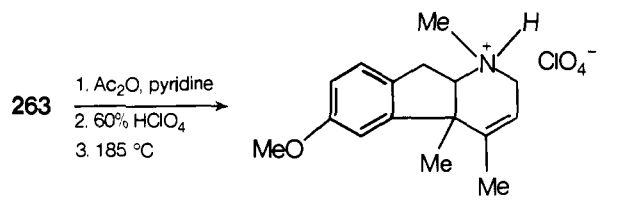


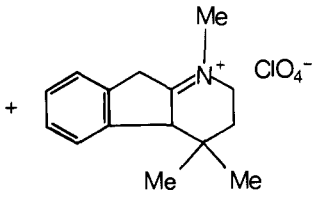
268

These reports prompted a reinvestigation of both the pyrolysis[117] and thionyl chloride reactions.[118] When **263** was converted to the acetate and pyrolyzed as the perchlorate, none of

the perchlorate of **264** was isolated. Instead, two new bases, 1,2,4a,9a-tetrahydro-1,4,4a-trimethyl-9*H*-indeno[2,1-*b*]pyridine perchlorate (**268a**) and 1,2,3,4-tetrahydro-1,4,4-trimethyl-9*H*-

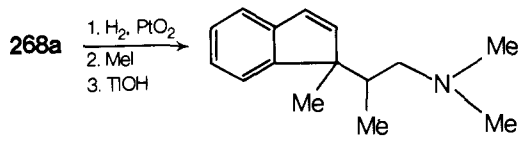


268a

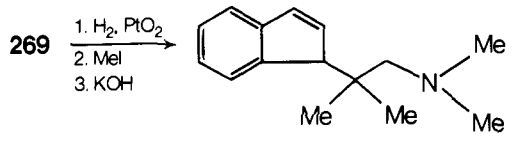


269

indeno[2,1-*b*]pyridine perchlorate (**269**) were isolated. After 5 min a mixture of 70% **268a** and 11% **269** was obtained whereas after 25 min **269** was the major product (70%) with 11% of **268a** isolated. Interestingly, **268a** could not be converted to **269** under any of the conditions used to simulate the pyrolysis experiment. The structures of **268a** and **269** were supported by spectro-



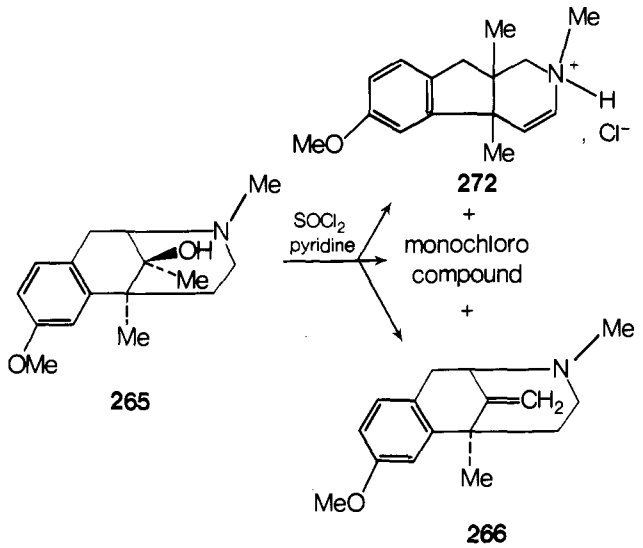
270



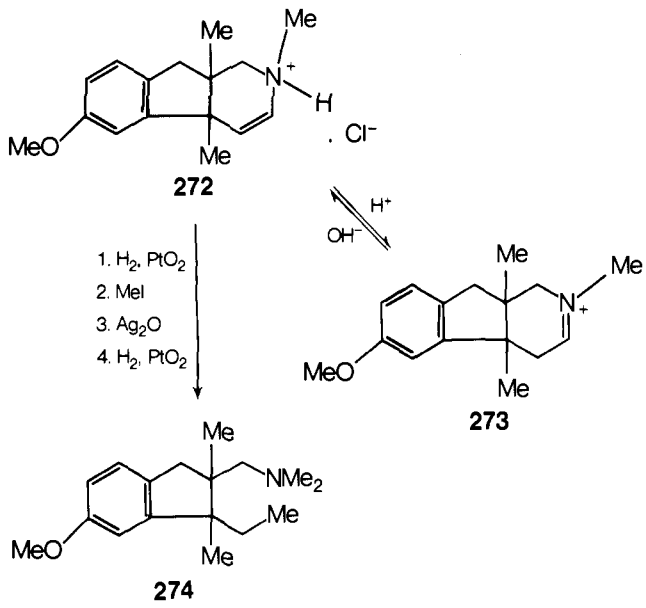
271

scopic and mass spectral data. In addition each compound was converted to the respective indene **270** and **271.** Separation of the mixture obtained from reaction of **263** with thionyl chloride, showed that the base, isolated in 4% yield and isomeric with **264,** was identical in all respects with **268.** This confirmed the earlier proposed structure of this compound.[116]

A later report established the identity of the rearrangement products obtained from the thionyl chloride reaction of **265.**[118]

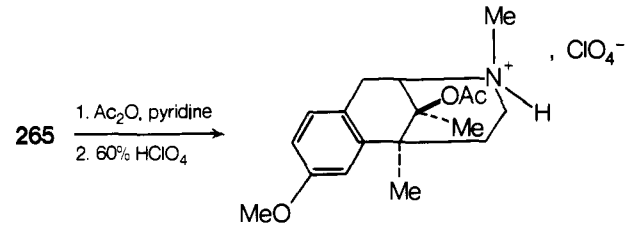


SCHEME VI

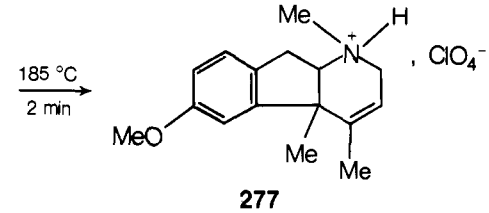


Previous work had indicated that this reaction afforded **266,** a monochloro derivative, and an unknown rearranged base isomeric with **266.**[88] This compound was identified as 6-methoxy-2,4a,4b-trimethyl-1,2,4a,4b-tetrahydro-1*H*-indeno[2,1-*c*]pyridine hydrochloride (**272**) on the basis of spectroscopic and mass spectral evidence. In acid solution, **272** was converted to the immonium salt **273.** The indane **274** was obtained from **272** in four steps (Scheme VI). To account for products like **268** and **272** the mechanism in Scheme VII was proposed.

A brief investigation of the product **265a** obtained from the carbinol **265** was also reported.[118] It was found that pyrolysis of **265a** afforded 6-methoxy-1,2,4a,9a-tetrahydro-1,4,4a-trimethyl-9*H*-indeno[2,1-*b*]pyridine perchlorate (**277**), in 58% yield.



265a



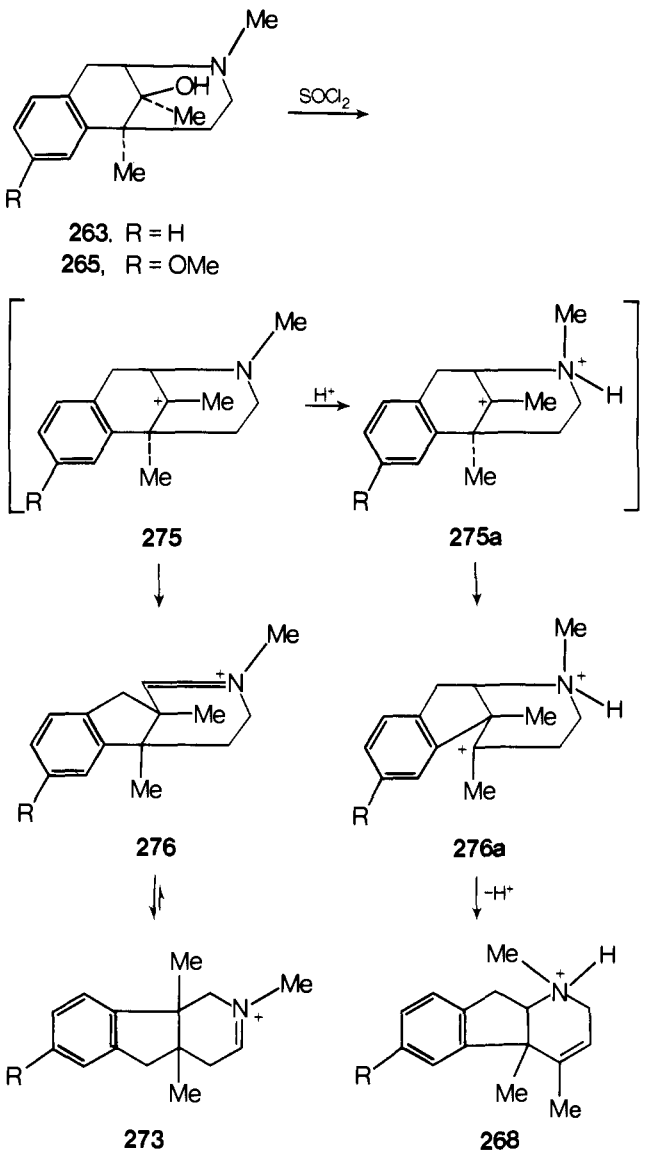
277

VIII. Reactions and Substitutions on the Benzomorphan Framework

A. Substitution on Nitrogen

As with other morphine-like analgesics the synthesis of various N-substituted derivatives has provided benzomorphans with profound differences in pharmacological activity (i.e., agonist to antagonist). It is therefore not surprising that thousands of different N-substituted compounds have been prepared for screening purposes. There are a variety of approaches to specific N-substituted compounds, and these are now considered.

SCHEME VII



1. Synthesis from N-Substituted Starting Materials

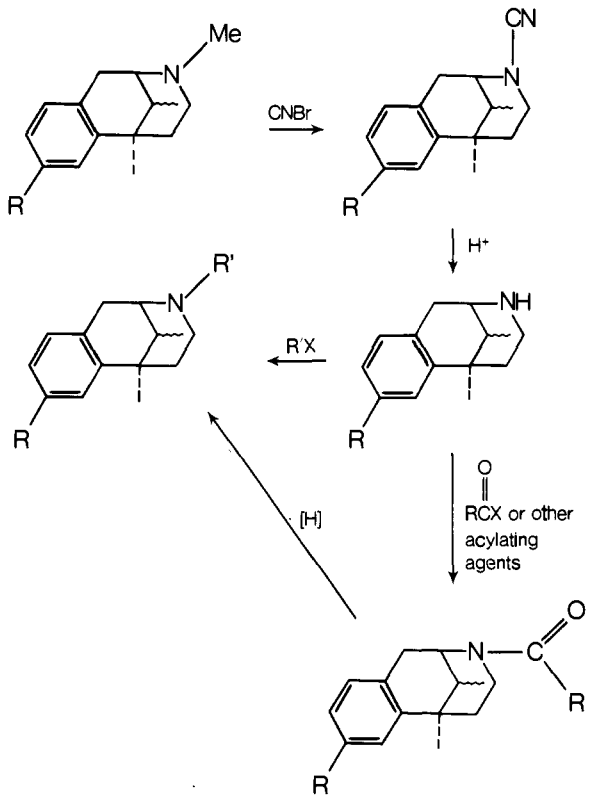
An obvious route to specific N-substituted benzomorphans is to employ appropriately substituted starting materials in the various synthetic procedures. The sequences involved and their limitations are summarized in section II. A series of *N*-alkylbenzomorphans of increasing chain length (C_4H_9, C_5H_{11}, and C_6H_{13}) have been prepared this way.[48]

2. Reactions with Benzomorphans Unsubstituted on Nitrogen

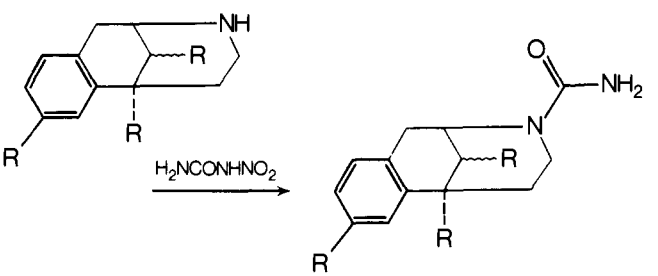
Demethylation of benzomorphans with cyanogen bromide followed by alkylation, acylation, arylation, or Mannich reactions provides good yields of a variety of N-substituted compounds (Scheme VIII).[43,118a]

There are hundreds of reports in the literature of such procedures, many of them in patents, and it would serve no purpose to summarize them here as no novel or unusual chemistry is involved. A recent summary of several methods of N-demethylation of benzomorphans along with a description of an improved procedure has recently been reported.[119] It is noted here that the von Braun cyanogen bromide demethylation procedure has been improved upon by the use of chloroformates,[120] since the intermediate carbamates are more easily hydrolyzed. One approach found particularly useful for demethylation of benzomorphans involves reaction with phenyl chloroformate to produce an intermediate carbamate which is easily cleaved with a 1:1 mixture of 64 and 95% hydrazine.[119]

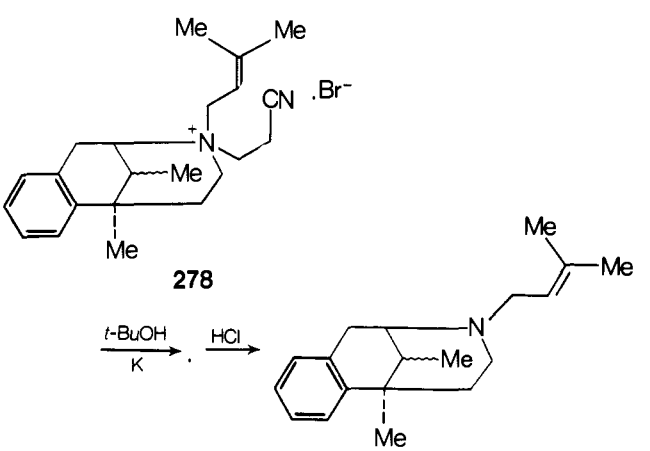
SCHEME VIII. Routes to N-Substituted Benzomorphans



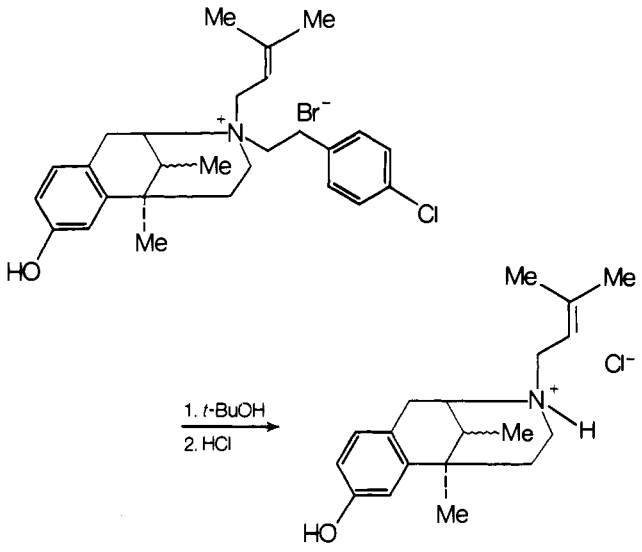
N-Carbamoylbenzomorphans have been prepared by reacting the nor bases with *N*-nitrourea.[121] A series of such compounds has been prepared. In a related procedure the *N*-carbamoyl derivatives were prepared by heating the nor compound in an aqeuous mixture of HCl, HOAc, and urea.[122]



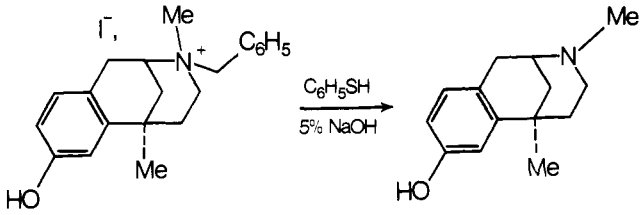
Quaternary benzomorphans are readily dealkylated by a variety of procedures and some of these are noted in section II. Preparation of *N*-dimethylallylbenzomorphans has been approached in this way by reaction of **278** with base.[123] In a similar



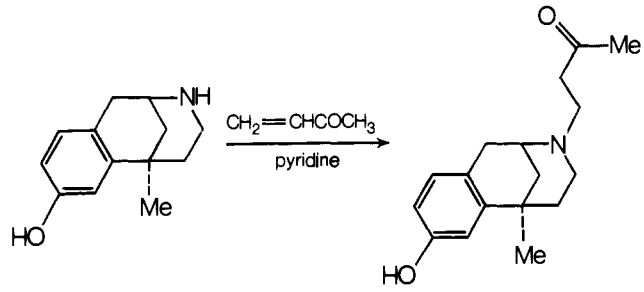
procedure, a related *N*-dimethylallylbenzomorphan has been



prepared.[124] Thiophenoxide has also been used to convert quaternary to tertiary compounds.[125,126]



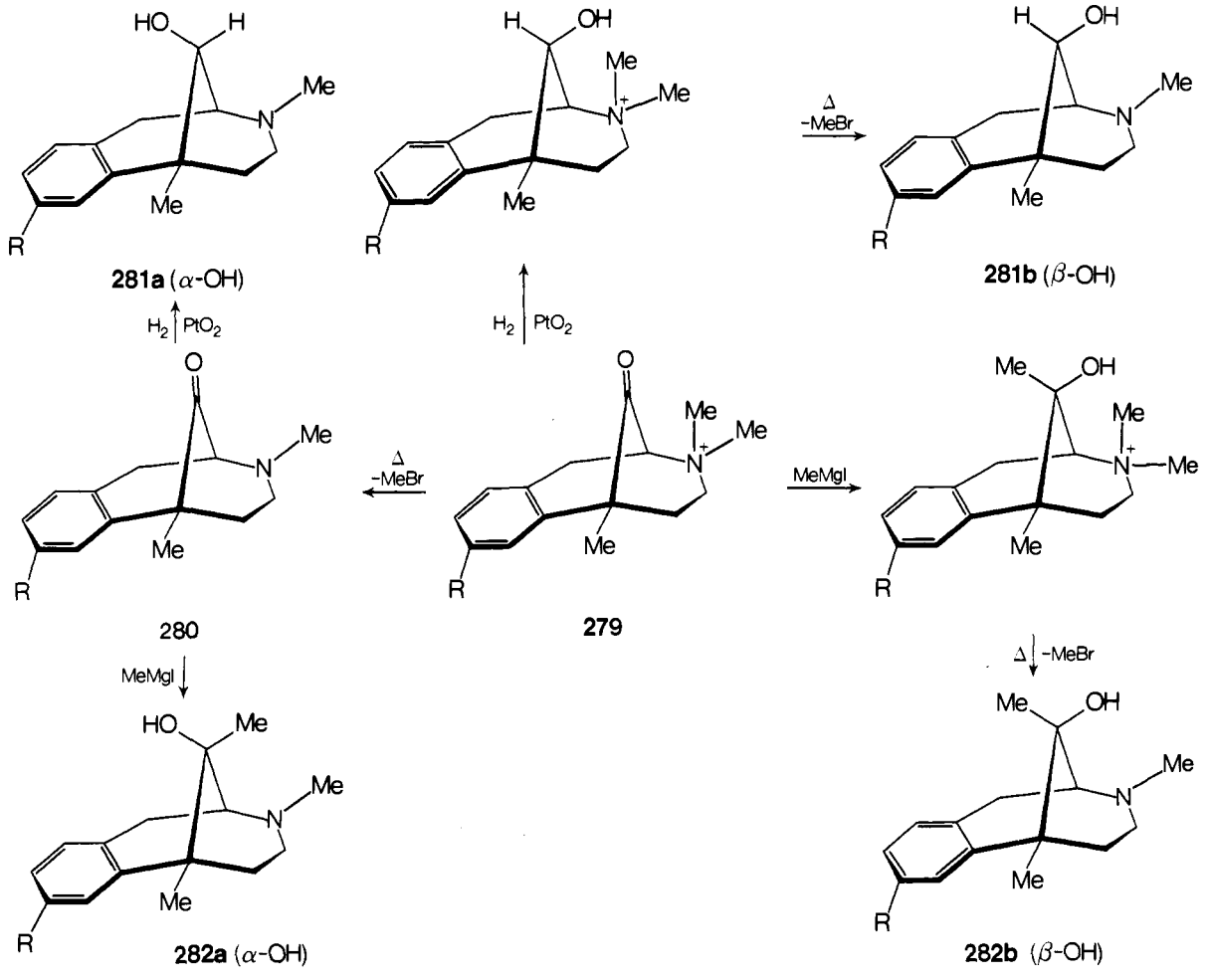
Norbenzomorphans have also been converted to tertiary bases by Michael addition of the nor base to methyl vinyl ketone.[127]



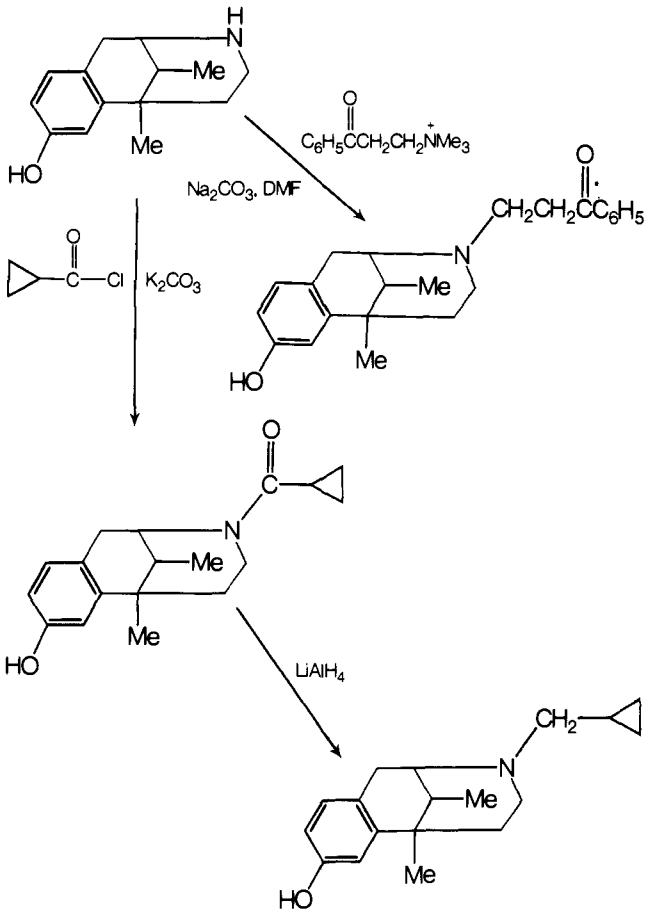
In a sequence related to the Mannich reaction, the 3-oxophenylbenzomorphan shown in Scheme IX has been prepared in one step from the unsubstituted compound.[127a] Acylation of this unsubstituted compound with cyclopropylcarbonyl chloride in the presence of potassium carbonate yields the amide.[127b] This can be reduced to the corresponding *N*-cyclopropylmethylbenzomorphan.

B. Substitution and Reactions at C-11

As noted earlier, significant differences in analgesic activity are associated with changes in configuration at C-11 in simple alkyl substituted benzomorphans. Both of the diastereomers **282a** and **282b** have been prepared by Grignard addition to the appropriate 11-oxobenzomorphans obtained via the tetralone route.[19,22] Addition of methylmagnesium iodide to the quaternary salt **279** gives, after pyrolytic extrusion of MeBr, the carbinol **282b** with hydroxyl anti to the benzofusion, whereas Grignard addition to the demethylated compound **280** yields the carbinol



SCHEME IX



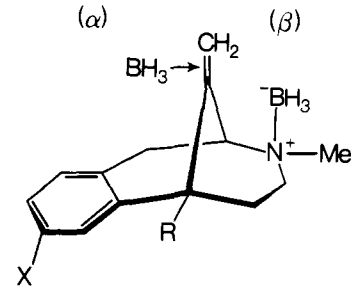
282a with hydroxyl syn to the benzofusion. These assignments were based on both infrared and degradation experiments.[128,129] The structures shown indicate one enantiomorph, but a racemic mixture is implied in our discussion as three-dimensional structures more effectively show stereochemical relationships. Similar modes of addition occur during catalytic reduction[128,130] resulting in **281a** and **281b.**

Changing the bridgehead methyl to ethyl in **279** does not change the stereochemical mode of Grignard addition, although the rate of reaction is slowed.[23] Neither EtMgI nor PrMgI adds to **279** whereas the less hindered **280** does react with EtMgI to yield the alcohol analogous to **282a.**[23]

May has summarized these observations by noting that when nitrogen is cationic, addition to the C-11 carbonyl occurs to yield alcohols with hydroxyl oriented toward nitrogen.[13] With neutral tertiary nitrogen, the C-11 epimeric alcohols are formed.[13]

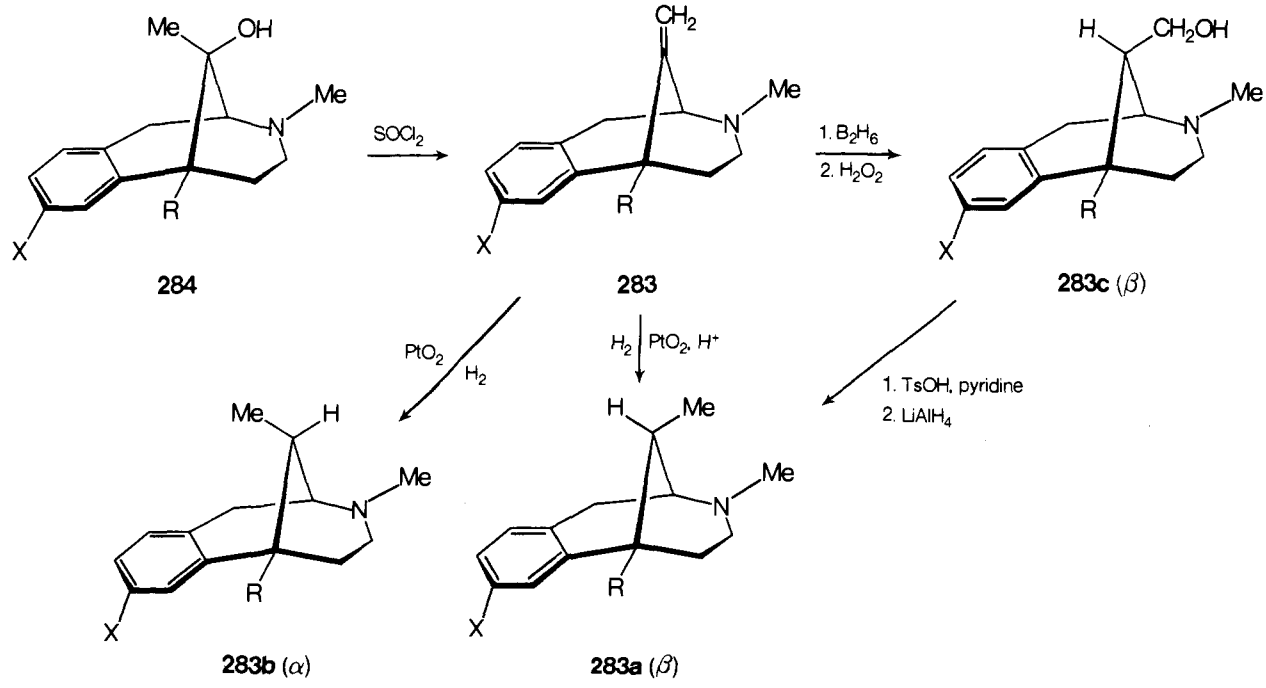
An interesting stereoselective hydrogenation of **283,** obtained from **284** via treatment with thionyl chloride, has been demonstrated (Scheme X). The mode of reaction in this case is also dependent on whether or not nitrogen is cationic.[25,87]

Hydroboration of **283** (X = H or OCH_3, R = CH_3) has also been carried out[116] to yield the alcohol **283c** which after conversion to the *p*-toluenesulfonate, followed by $LiAlH_4$ reduction, gave **283a.** This confirms β configuration for the hydroboration product **283c** and provides another route for the stereospecific preparation of β-benzomorphans. It has been proposed that β stereochemistry results from initial complexation of benzomorphan nitrogen with BH_3 followed by hydroboration of the exocyclic double bond from the least hindered side[88] as in **283d.** In fact, reaction of equivalent quantities of 11-methylene-3,6-dimethyl-8-methoxybenzomorphan and pyridine–borane gave the isolable complex **283e.** Heating **283e,** followed by peroxide and workup yielded a mixture of **283c** (X = OMe, R = Me) and its α isomer **283f** which provides evidence for concurrent intra- and intermolecular hydroboration. Since formation of the α



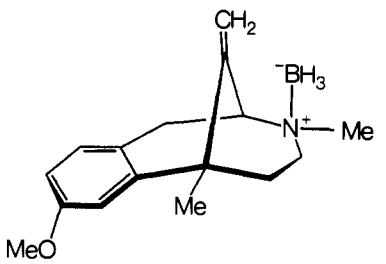
283d

SCHEME X



284 **283** **283c** (β)

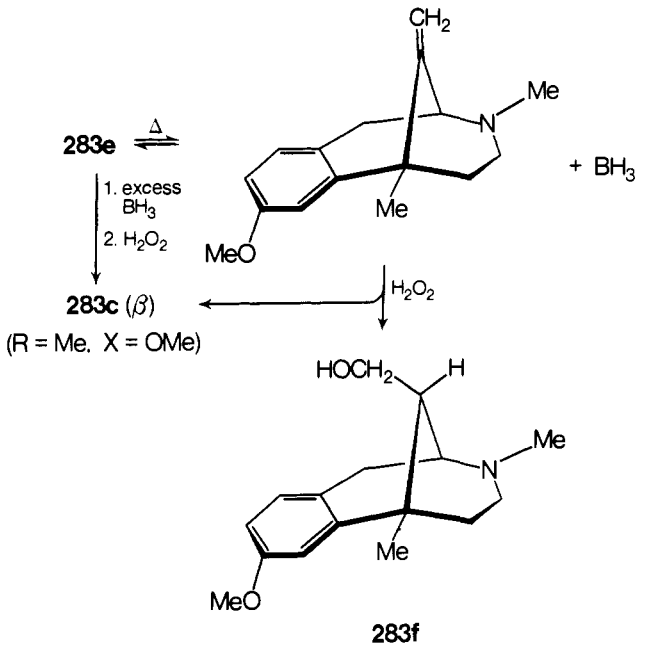
283b (α) **283a** (β)



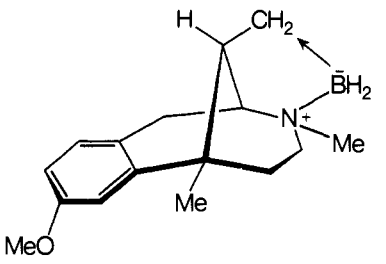
283e

isomer does not occur in excess diborane, Scheme XI best

SCHEME XI



summarizes the observed results.[131] Interestingly, the neutral intermediate **283g** was isolated from the hydroboration reaction mixture.

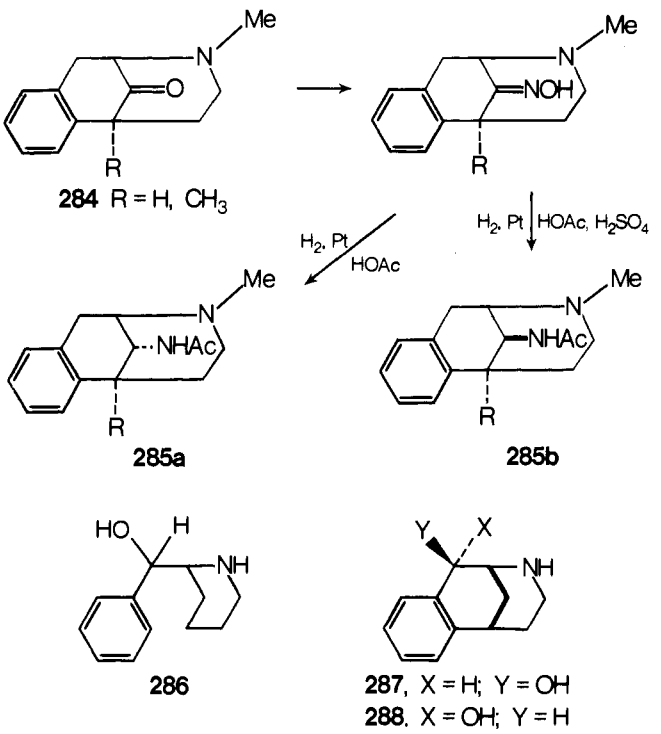


283g

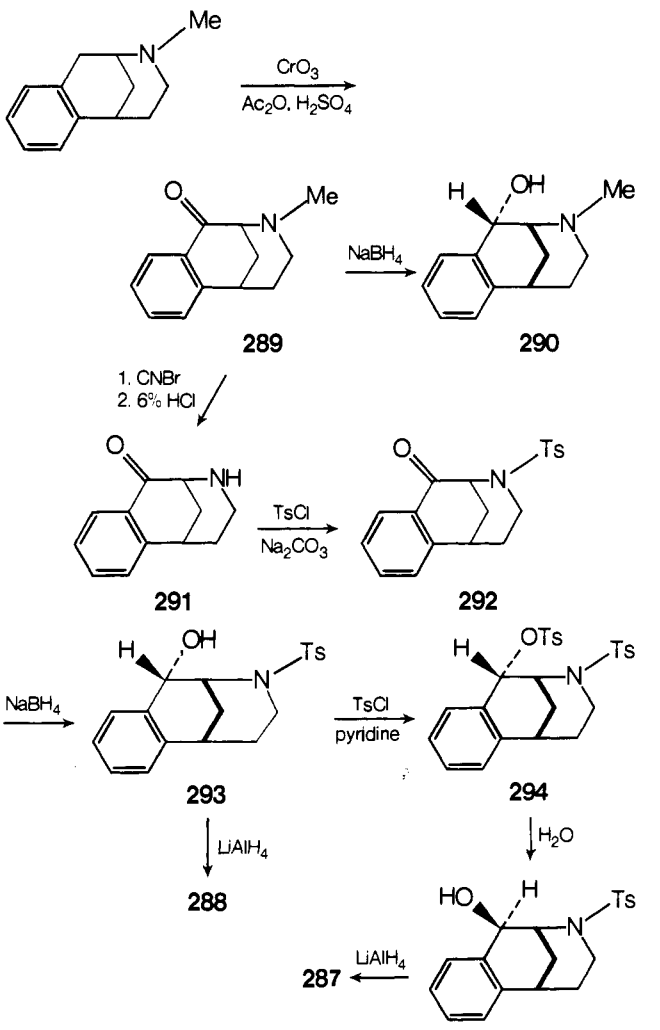
The 11-ketobenzomorphan **284** has been converted to the oxime and reduced to the diastereomeric acetamides **285a** and **285b.**[132]

C. Reactions at C-1

Interesting activity of **286** in modifying adrenergic activity and the utility of using conformationally rigid compounds as probes of the adrenergic receptor prompted the synthesis of diastereomeric benzomorphans **287** and **288.**[133] Oxidation of previously prepared *N*-methylbenzomorphan[75] with chromic oxide and sulfuric acid followed by reduction with sodium borohydride yielded the diastereomer **290** based on a $J_{1,2}$ coupling constant

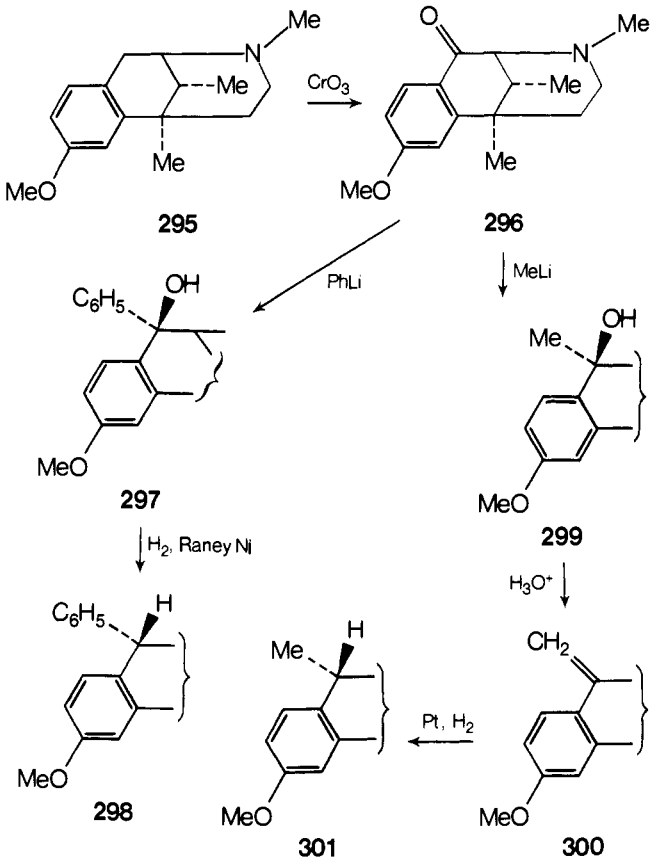


of 6.5 Hz. Demethylation of **289** yielded **291** which was converted to the tosyl derivative **292.** Reduction of **292** yielded **293** in which the one carbon bridge and C-1 hydroxyl are anti. Detosylation of **293** with $LiAlH_4$ afforded **288** ($J_{1,2}$ = 6.0 Hz).

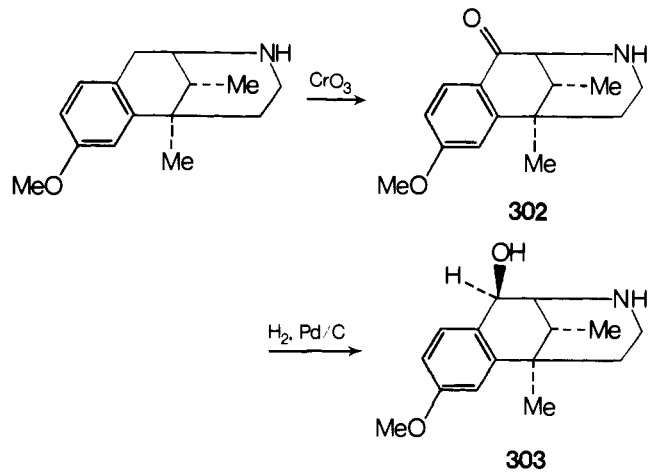


Conversion of **293** to **294** followed by aqueous solvolysis and reduction of the latter afforded **287** ($J_{1,2}$ = 1.0 Hz).

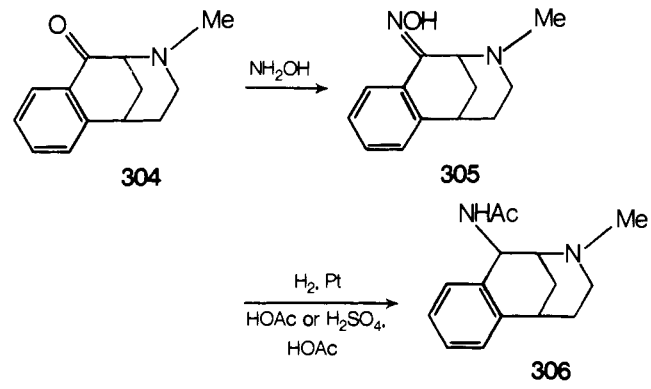
Oxidation of **295** provides a keto benzomorphan analogous to **289** which upon addition of alkyl- or aryllithium affords 1,1-difunctionalized benzomorphans.[134] Thus, reaction of phenyllithium with **296** afforded **297** which gave the C-1 phenyl derivative **298** upon hydrogenolysis with Raney Ni. Treatment of **296** with methyllithium afforded **299** which dehydrates on treatment with acid to the olefin **300.** Catalytic reduction of **300** afforded the C-1 methylbenzomorphan **301.**



The oxidized benzomorphan **302** has been prepared and was reduced to the C-1 alcohol **303** by catalytic hydrogenation.[135]



1-Oxobenzomorphan (**304**) was converted to the oxime **305** and was also catalytically reduced to the acetamide **306.**[135]

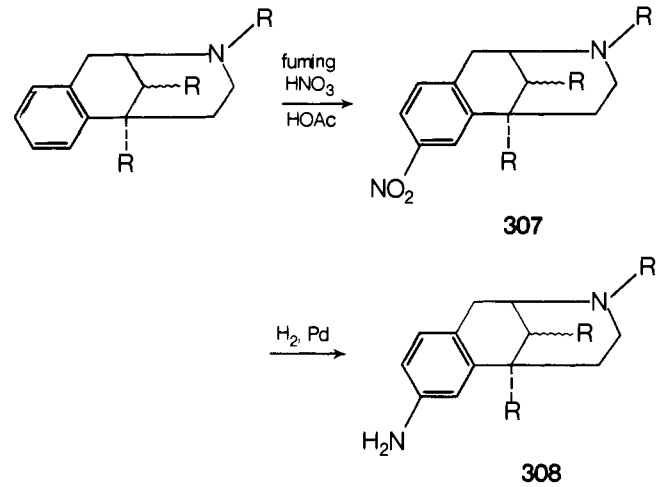


D. Substitution on the Aromatic Ring

The C-8 hydroxyl group in a variety of benzomorphans generally enhances analgesic potency and reduces toxicity compared to unsubstituted analogues. This observation is reflected in the fact that a vast majority of benzomorphan syntheses begin with substrates having functionality which places hydroxyl or methoxyl at C-8 in the final product (section II). Straightforward modification of this C-8 functionality by alkylation, acylation, esterification, etc., has been reported hundreds of times in the chemical and patent literature. Since no unusual or interesting chemistry is involved, these reports will not be considered here.

A series of benzomorphans containing chloro, fluoro, nitro, and amino functionality at C-8 has been reported.[136] All of these compounds are less potent analgetics and more toxic than the unsubstituted or C-8 hydroxyl analogues.

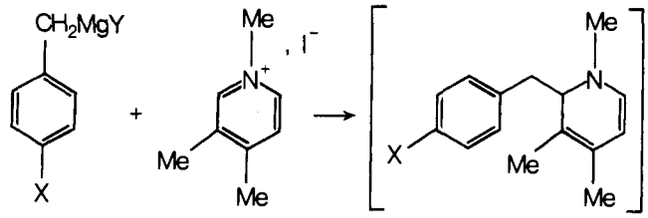
The C-8 nitro derivatives **307** were prepared by nitration of previously synthesized benzomorphans. The C-8 amino derivatives were obtained by reduction of **307** to **308.** The C-8 chloro



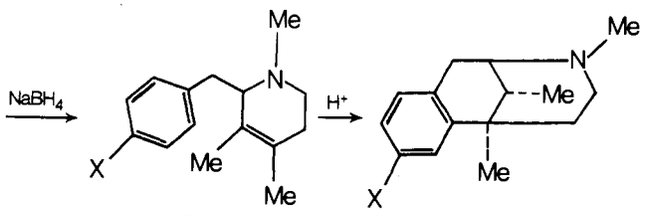
and fluoro derivatives were obtained by Grewe cyclization of the appropriate starting materials. Conversion of **309** to **313** was carried out as indicated in Scheme XII. The structures were confirmed by degradation to the corresponding dimethylnaphthalenes.

A series of C-9 substituted benzomorphans was prepared by amino alkylation of C-8 hydroxy derivatives followed by hydrogenolysis to **319.**[134] Dealkylation, acylation, and reduction of **319** provided a series of N-3 substituted derivatives. None of these compounds approached the analgesic activity of morphine. Some had significant antagonist activity but were not very potent.[134]

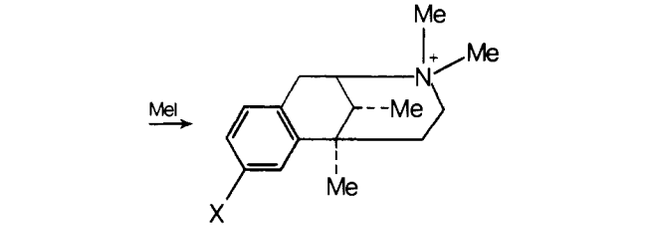
SCHEME XII



309, X = Y = Cl
310, X = F; Y = Br
311



312 313



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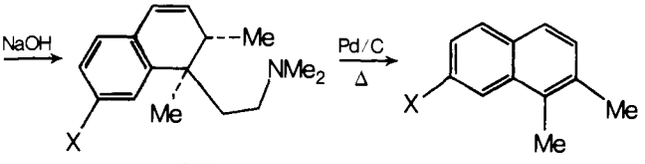
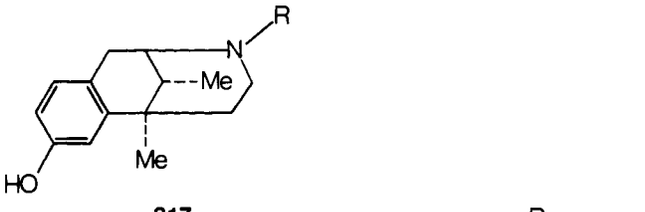


315 316



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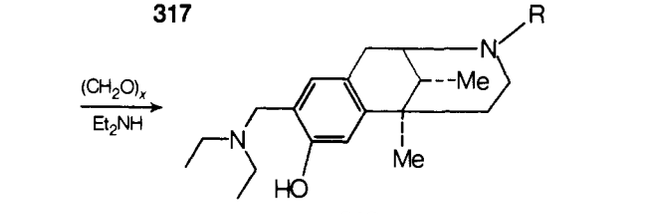

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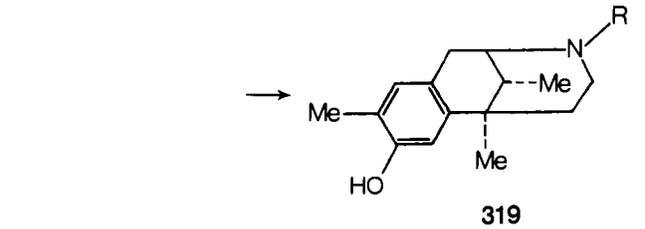


319

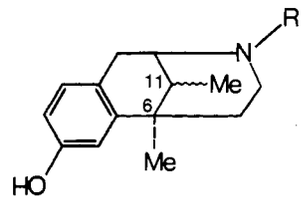
IX. X-Ray, Spectroscopic, and Conformational Studies

A. X-Ray Analyses

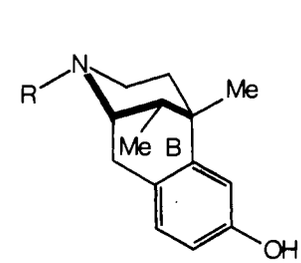
The detailed structural features of benzomorphans can best be studied by x-ray crystallographic analyses, and two such reports concerned with particularly important[137] analgesic–antagonist benzomorphan derivatives have been published.[138-140] The bond lengths and bond angles for both 2-allyl-[139] and 2-cyclopropylmethyl-6,11-dimethyl-8-hydroxybenzomorphans[140] are shown in Figure 1[138-140] (numbering system as in **4**). The former was determined as its hydrobromide salt. The racemates of both *N*-allyl- and *N*-cyclopropylmethylbenzomorphans as well as the biologically active (*l*) form of the latter were used in these studies. With the *N*-cyclopropyl compound, the absolute configuration was shown to be the same as *l*-morphine. Perspective views are shown in Figure 2. Both compounds are essentially three-ring segments of the morphine nucleus with stereochemical features the same as the corresponding part of morphine, and are thus the α isomers.[141] The four possible enantiomorphic pairs resulting from asymmetry at C-2, C-11, and C-6 are reduced to two due to the cis B–C ring fusion. These two pairs are the α and β diastereomers which differ in configuration at C-11. Ring C (piperidinium moiety) is approximately in a chair conformation, and the two methyl groups and N-substituent are in equatorial positions with respect to this ring. The free base of the *N*-cyclopropylmethyl derivative has a conformation very similar to that of the hydrobromide.[140] In both compounds the B ring has a slightly distorted half-chair conformation (intermediate between half-chair and half-boat), and thus the C-1–C-2 bond is intermediate between staggered and eclipsed.

B. NMR Studies

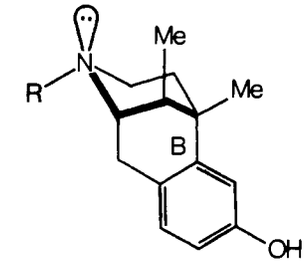
Conformational studies of benzomorphans have been carried out by ^{1}H NMR.[56,65,142,143] The ^{1}H NMR characteristics of a series of diastereomeric α and β 6,11-dimethyl-8-hydroxybenzomorphans **320** have been reported.[142] The free bases, hydrohalides, and methiodides were studied, and differences between isomers are interpreted in terms of different conformations of the piperidine moiety. The data are summarized in Table I.



320



320a, α (cis)



320b, β (trans)

The chemical shifts of the C-6 bridgehead methyl in both α and β isomers of **320** are similar ($\delta \sim 1.2$) in Me_2SO. The low-field position (usual 6-methyl at $\delta \sim 0.9$) is consistent with the expected geometry observed in Dreiding models in which the C-6 methyl lies close to and near the plane of the benzofusion, and is thus subject to anisotropic deshielding. The C-11 methyl in the α isomer is upfield over 20 cycles from that of the β. In the latter the C-11 resonance is almost identical with that of C-6. This result is similar to that noted earlier[58] by May for **74b** and **74d** in $CHCl_3$, and can again be interpreted in terms of a diamagnetic shielding of the α but not the β C-11 methyl by the fused benzene ring. It has also been pointed out[142] that the nitrogen lone pair may also in part determine the α/β C-11 methyl

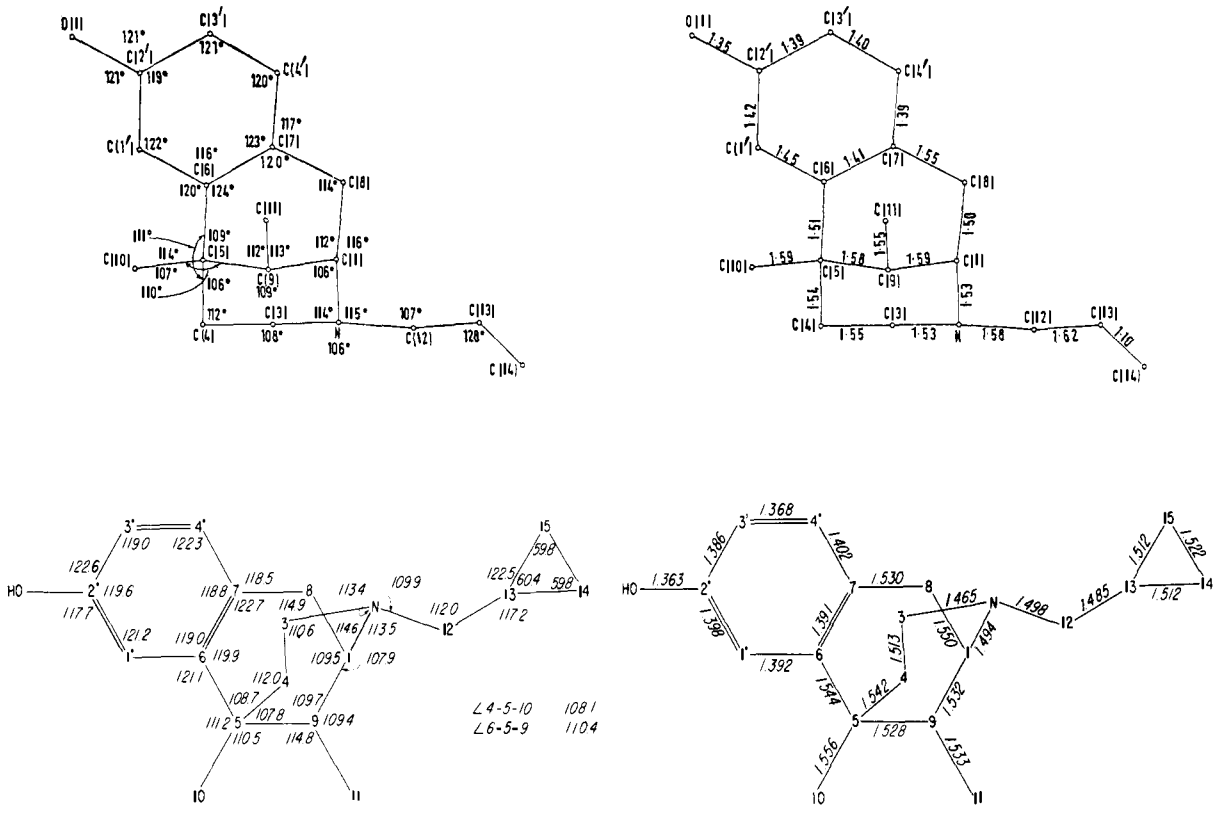
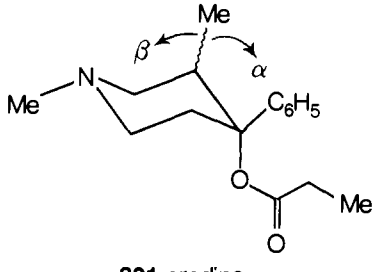


Figure 1. Bond angles and lengths for cyclopropylmethyl and *N*-allylbenzomorphans.[138-140]

chemical shift difference because of its proximity to the C-11 methyl in the β but not the α isomer.

In the salts of **320** (R = Me or H), both the α and β C-6 and C-11 methyl resonances move downfield. The shift is greater for the β isomers (7–11 cycles) than for the α (~5 cycles) in Me_2SO-d_6. Interestingly, in D_2O the C-11 methyl shifts of both α and β hydrohalides of **320** (R = Me) are about the same as the corresponding C-11 methyl resonances of the free bases in $CDCl_3$. Based on analogies to ^1H NMR spectra of the free base and protonated forms of α- and β-prodines (**321**), the differences



321 prodine

between the α and β downfield shifts of benzomorphan C-11 methyl groups induced in protonation are smaller than those expected on the basis of a true chair conformation of the piperidine ring moiety of the benzomorphan.[142] A skew boat conformation has been proposed to explain this result as the NH and C-11 methyl become further removed in such a conformation. The x-ray crystallographic studies discussed above[138-140] confirm this and provide much more definitive evidence for such conformations.

It has been pointed out that nonchair conformations of the piperidine ring moiety are even more likely in quaternized β-benzomorphan methiodides due to axial 1,3-dimethyl interactions in the chair conformation.[142] As supporting evidence it was shown that, in the 4-phenylpiperidine methiodides **322a** and **322b**, the difference in chemical shift ($CDCl_3$) between the two *N*-methyls is reduced from 12 to 3.5 cycles in going from **322a** to **322b**. This results from the smaller environmental difference between the *N*-methyls in **322b** which arises from more comparable populations of the chair and skew-boat conformations than in **322a**.

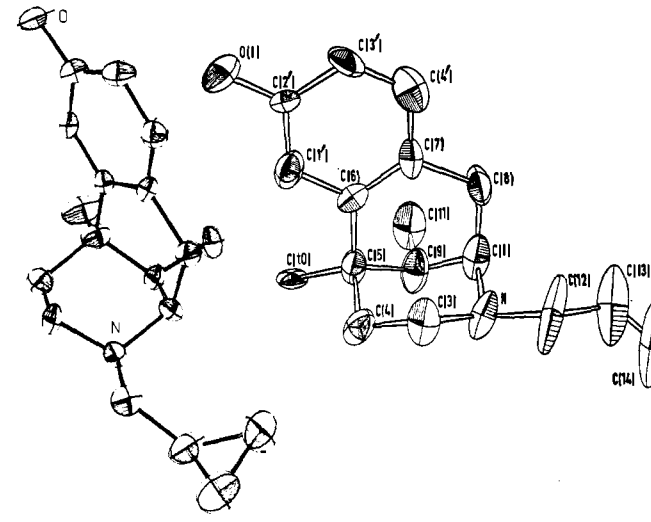
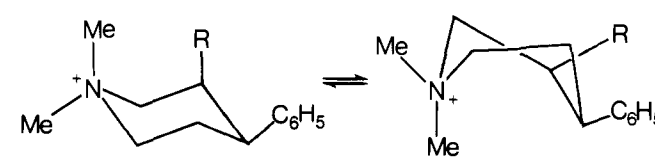


Figure 2. Perspective views of *N*-cyclopropylmethyl- and *N*-allylbenzomorphans.[138-140]



322a. R = H
b. R = Me

The ^1H NMR spectrum of the α-methiodide of **320** (R = CH_3) showed resonances at δ 3.37 and 3.24 whereas the β isomer showed resonances at δ 3.13 and 2.83. The larger separation

TABLE I. Proton Magnetic Resonance Characteristics of Some 6,11-Dimethylbenzomorphans (320)[142]

R	Isomer[a]	Form	Solvent	Chemical shift[b] N-Me[c]	6-Me[d]	11-Me[e]	Difference (salt − base)[f] 6-Me	11-Me
H	α	Base	Me_2SO-d_6		71	40	5.5	5
		HCl	Me_2SO-d_6		76.5	45		
H	β	Base	Me_2SO-d_6		69	65.5	6	7.5
		HCl	Me_2SO-d_6		75	73		
Me	α	Base	$CDCl_3$	145	78	48		
		Base	Me_2SO-d_6	131	71	42	7	5.5
		HCl	Me_2SO-d_6	163	78	47.5		
		HCl	D_2O	172	81	49.5		
		MeI	Me_2SO-d_6	202	83	50	12	8
				194.5				
		CD_3I	Me_2SO-d_6	192	82	49	11	7
CD_3	α	Me_2SO-d_6	Me_2SO-d_6		81	49	10	7
Me	β	Base	$CDCl_3$	141	78	74.5		
		Base	Me_2SO-d_6	128	67.5	64.5		
		HCl	Me_2SO-d_6	161	72.5	75.5	5	11
		HBr	D_2	173	81	77.5		
		MeI	Me_2SO-d_6	188	77	75.5	9.5	11
				170				
		CD_3I	Me_2SO-d_6	186.5	78.5	81	11	16.5
CD_3	β	CD_3I	Me_2SO-d_6		77	74.5	9.5	10

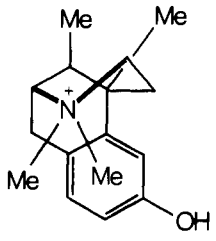
[a] α-cis and β-trans 6,11-dimethyl with respect to the hydroaromatic ring. [b] In Hz from TMS (internal with $CDCl_3$ and Me_2SO-d_6, external with D_2O as solvent), spectra being measured at 60 MHz. [c] Singlet except in some salts where spin–spin coupling with $^+$NH proton occurs to give a doublet ($J \simeq 5$ Hz). [d] Singlet. [e] Doublet (J = 6.5–7 Hz). [f] Me_2SO-d_6 solvent data.

TABLE II. ^{1}H NMR Absorptions (δ) of 324, 325, and 326 in Me_2SO-d_6 at 39 °C[56]

	324	325	326
11-αMe		0.83	
11-βMe	0.78		1.03
6-Me		1.23	1.20
7-H	5.77	6.60	6.69
9-H	6.48	6.48	6.48
10-H	6.89	6.87	6.85
N-Me	2.37	2.23	2.21

of the latter and the high-field resonance at δ 2.83 are consistent with a skew-boat conformation for the C ring of the β methiodide **323,** with one *N*-methyl group within the shielding region of the benzofusion.

A detailed ^{1}H NMR study of the quaternization of **320** (R = CH_3) with CD_3I has been made[56] which showed that reaction probably occurs via a pseudo-axial approach of CD_3I to the skew-boat conformation of **320** with direct formation of the favored quaternary conformation analogous to **323,** rather than

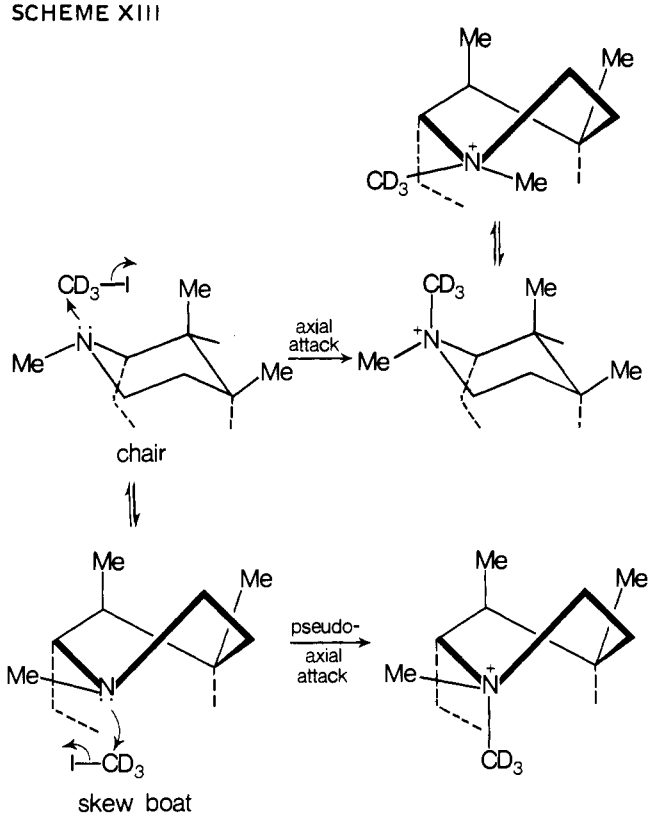


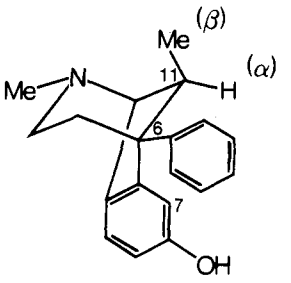
323

by axial attack on a chair conformation and subsequent conformational change to skew boat (see Scheme XIII).

The C-11 β-methyl and C-7 hydrogen absorptions are markedly different in benzomorphans containing a C-6 phenyl substituent.[143] The absorptions for the benzomorphans **324, 325,** and **326** are summarized in Table II. The C-11 β-methyl of **324** absorbs at the same position as that of the C-11 α-methyl of **325.** This is indicative of unusual shielding of the β-methyl of **324,** and is consistent with the observation, in Drieding models, that this methyl group has the same spatial relationship to the 6-phenyl ring in **324** as does the C-11 α-methyl to the fused benzene ring in **325.** From these observations and the construction of space-filling models, it has been proposed that the C-6 phenyl is approximately perpendicular to the fused benzene moiety in the benzomorphan skeleton. This idea is supported by x-ray crystallographic data. In addition the unusually high-field position of the aromatic C-7 hydrogen provides further evidence for such a preferred orientation for the C-6 phenyl ring. Interestingly, both the C-11 β-methyl and C-7 aromatic hydrogen absorptions in **324** move downfield at higher temperatures. This would be expected

SCHEME XIII





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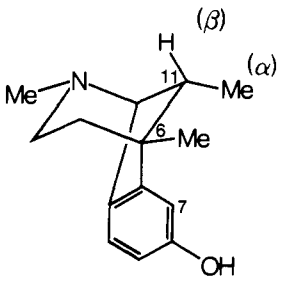
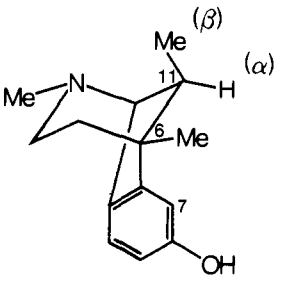


325

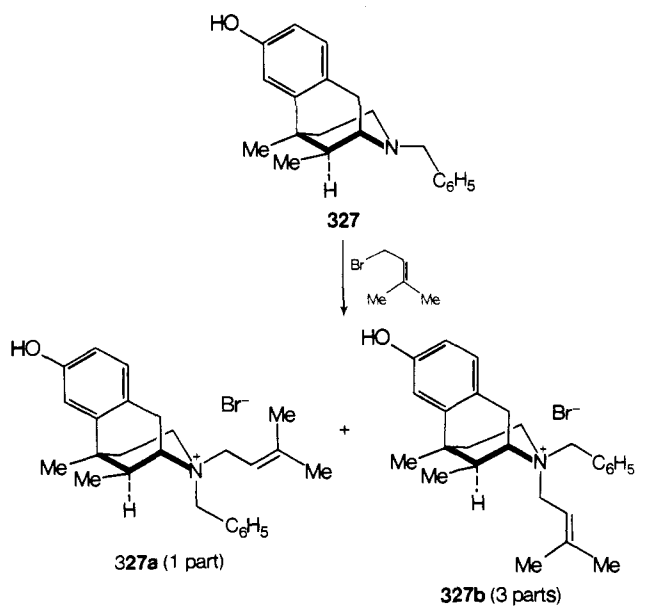


326

if the C-6 phenyl more freely rotates at elevated temperatures.[56]

There has been speculation about possible correlations between α- and β-benzomorphan conformational differences with variations in analgesic efficacy.[142] Such correlations could arise from conformational influences on drug-receptor interactions as well as on processes involved with transport and distribution of isomers. It has been proposed that skew-boat populations are probably high in β-derivatives when protonated in vivo and that such conformers favorably influence analgetic effectiveness by favorably influencing drug receptor interactions and/or transport and distribution.[142]

Conformational studies on quaternized derivatives of 6,11-dimethylbenzomorphans (**327a** and **327b**) have also been carried out by ^{1}H NMR.[143] The α isomer **327** was reacted with 1 equiv of 3-methyl-2-butenyl bromide to yield a mixture of the quaternary ammonium salts **327a** and **327b.** In cyclic amines like **327** with bulky N-substituents it is generally observed that axial attack to quaternized product occurs rather than equatorial attack when the N-substituent is larger than the electrophile.[144] As was noted earlier in this section, x-ray and ^{1}H NMR studies show quite definitively that the piperidine ring in compounds similar to **327** exists in a chair conformation and that the N-substituents are equatorial. The major product of quaternization of **327** is thus **327b.** This is further supported[143] by quaternization of pentazocine ($NCH_2CH{=}CMe_2$) with benzyl bromide. In this reaction the major product was **327a** rather than **327b.**

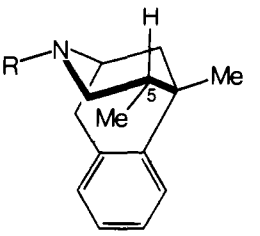


327a (1 part) **327b** (3 parts)

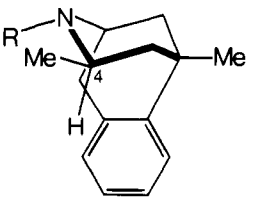
The benzylic protons in **327b** appear at δ 4.80, upfield from those of **327a** at δ 4.92.[143] This observation is consistent with ^{1}H NMR absorption and assignments for the methiodide and deuteriomethiodide of **320** (Table I). In that case the equatorial *N*-methyl is also upfield from the axial due to the effect of the fused benzene ring.

Further synthetic and ^{1}H NMR studies on related *N*-benzyl-*N*-methyl quaternized benzomorphans are consistent with the above observations, and confirm that the electrophile enters axially. This supports the work of Casy[142] and McKenna.[144]

In a study examining the effects of steric crowding of nitrogen on the analgesic activity of benzomorphans, the ^{1}H NMR characteristics of a series of 4- and 5-methyl-substituted benzomorphans were determined.[65] The results are summarized in Table III. Interestingly, in examining this series, the 5-methyl appears strongly shielded at δ 0.6 whereas the 4-methyl is not. The 6-methyl chemical shift is the same for both series of compounds. It is surprising that in the Grewe cyclization leading to **328** and **329** (precursors of the rest of the series via N-demethylation and further alkylation or acylation and reduction) that epimers at C-4 and C-5 in the respective series were not formed. Only a single isomer could be isolated in each case. Shielding in the 5-methyl series has been rationalized by noting that when the piperidine ring moiety is in the favorable chair conformation and the 5-methyl is equatorial, the latter lies in the shielding region of the fused benzene ring, i.e., **334.** It has also been hypothesized that since the 4-methyl has a normal field position at δ ~1.0, it also must be equatorial, **335.** If it were axial, it would also lie in a deshielding region.



334

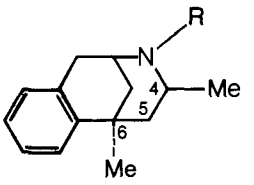


335

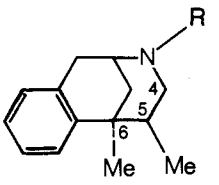
C. ORD–CD Studies

ORD characterization of trimethylbenzomorphans has proved of value in assigning absolute configurations, and an interesting study and interpretation of such spectra for metazocine (**336**) and levorphanol (**337**) has been reported.[145] The Cotten effects exhibited by these compounds are summarized in Table IV. They are attributed to the phenolic chromophore, as the midpoints between trough and peak are near the UV maxima of phenols. Since the sign of the Cotten effect is determined primarily by the local stereochemical environment around the phenolic moiety, it thus reflects the geometrical environment about C-6 rather than C-11, as the latter asymmetric function is further removed from the phenolic chromophore. Identical Cotten effect signs and similarities of peak and trough of α-**336** (−) and **337** provide evidence for the configurational identity of the corresponding C-6 and C-13 asymmetric centers. The identity of C-11 and C-14 centers has already been determined from previously established relative configurations (vide supra), as has the absolute configuration of **337.**[146] The absolute configuration of α-**336** (−) is thus 2*R*:6*R*:11*R*. The absolute configurations for all the isomers of metazocine (**336**) are shown below. The essentially mirror image α(−) and β(+) ORD absorptions substantiates the C-6 configurational identity of β-(−)- and α-(−)-**336** and demon-

TABLE III. Chemical Shifts (δ) of 4- and 5-Methyl Groups in $CDCl_3$[65]



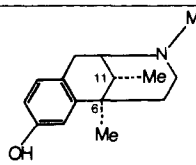
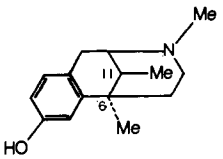
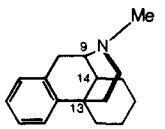
4-CH_3,d (J = 6.5 Hz)



5-CH_3,d (J = 6.5 Hz) | 6-CH_3, s

328, R = CH_3	0.92		1.37
		329, R = CH_3	0.60 1.36 1.38
330a, R = H	0.92		
		330b, R = H	0.61 1.35 1.36
331a, R = $CH_2CH{=}C(CH_3)_2$	0.96		
		331b, R = $CH_2CH{=}C(CH_3)_2$	0.60 1.35 1.38
332a, R = $CH_2C_6H_5$	0.98		
		332b, R = $CH_2C_6H_5$	0.62 1.36 1.37
333a, R = CH_2-c-Pr	0.92		
		333b, R = CH_2-c-Pr	0.60 1.35

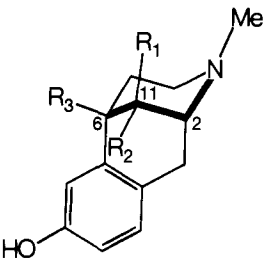
TABLE IV. ORD Characteristics of Isomeric Benzomorphans (336) and Levorphanol (337)[145]

	Form	λ_{max}, nm	Mol rotation [ϕ], deg
α-**336** (−) 	Base	293 trough	−40 425
		275 peak	+8 800
	HBr	289 trough	−31 225
		276 peak	+31 820
		247 trough	−7 175
β-**336** (−) 	Base	294 peak	+37 975
		272 trough	−3 675
		240 peak	+7 360
	HBr	294 peak	+34 500
		270 trough	−6 240
		245 peak	+6 240
337 	Base	290 trough	−40 460
		268 peak	+16 190
	HCl	291 trough	−45 320
		268 trough	+18 880

strates the negligible effect of C-11 geometry upon the ORD characteristics of this benzomorphan. A perspective view of the hydrobromide *N*-allyl analogue of α-(−)-**336** is shown in section IX.A.

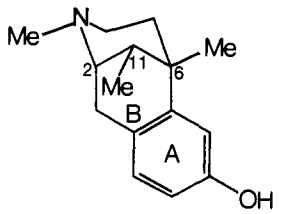
Although the β isomers are generally more active analgetics or analgetic-antagonists than their α counterparts, the configuration at C-11 is not the predominant determinant of such activity since the α-(−) and β-(−) isomers of a variety of N-substituted benzomorphans are markedly more active than the (+) enantiomers. Thus the 6*R* configurations of 6,11-dimethylbenzomorphans containing *N*-methyl, *N*-dimethylallyl, *N*-cyclopropylmethyl, and *N*-allyl substitution have been related to α-(−)-**336**.[145]

Circular dichroism curves of several C-6 substituted levorotatory benzomorphans (**337**) have been obtained and correlated with sterochemical features in a study similar to that for metazocine (**336**).[147] Significant changes in the far-ultraviolet were shown to occur with changes of configuration of C-11. The earlier study[147] did not include measurements in this region. As noted earlier, both **337b** and **337d** are known to have the same absolute configuration as (−)-morphine.[147]

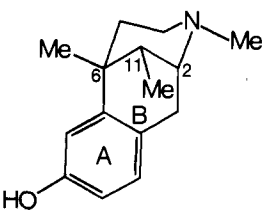


337 (−) cis

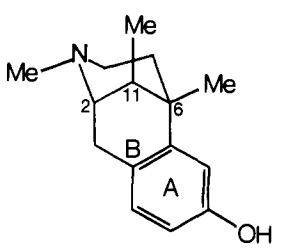
	R_1	R_2	R_3
337a	Et	H	Et
b	H	Et	Et
c	H	H	C_6H_5
d	Me	H	C_6H_5



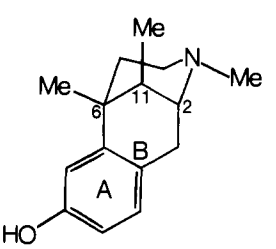
2*S*:11*S*:6*S*
cis, α(+)



2*R*:11*R*:6*R*
cis, α(−)



2*S*:11*R*:6*S*
trans, β(+)



2*R*:11*S*:6*R*
trans, β(−)

Both **337a** and **337c** have CD curves similar to those of **337b** and **337d** and are thus also assigned the same absolute configuration. As with the levorotatory metazocine, (−)-**336**, negative maxima appear in the 280–295-nm region associated with the phenolic chromophore of **337a–d**, presumably all resulting from the influence of an *R* configuration at C-6. Since **337a** and **337b** both have only the phenolic chromophore and since they only differ in configuration at C-11, remote from this chromophore, the similarity of their CD curves in the near-ultraviolet region is not surprising. Both have minima at about 285 nm. Interestingly, however, important differences are observed in the rotational strengths of Cotten effects in the far-ultraviolet. The β isomer **337a** shows a negative maximum at 204 nm ([θ] = −11 500) for the $^1A_{1g} \rightarrow {}^1E_{1u}$ benzene transition. The α isomer **337b** shows a stronger negative maximum at 199 nm for this transition ([θ] = −50 000). It is clear from these data that substantial differences in amplitude and rotational strength which

occur below 240 nm in the CD curves are indeed dependent on C-11 geometry.[147]

Compounds **337c** and **337d** which contain the C-6 phenyl substituent have more complex CD curves because of the additional chromophore. In addition to long-wavelength bands of the phenolic transitions, three negative Cotten effects appear in the 250–270-nm region from overlapping transitions of the phenyl substituent. The C-6 phenyl series also exhibits very intense Cotton effects at 191 nm with molecular ellipticities of approximately −300 000.[147]

X. Addendum

Benzomorphans: All Methods. An improved stereospecific synthesis of (*Z*)-1-cyano-2-methyl-2-butene, a key intermediate in earlier preparations of pentazocine,[54,71] has been reported.[148] The Stevens rearrangement has been used to prepare highly substituted 2-benzyl derivatives of 1,3,4-trimethyl-1,2,5,6-tetrahydropyridine. These compounds were also obtained by condensation of 2-lithio-3,4-dimethylpyridine with the appropriate benzaldehyde followed by conversion of the alcohol to the chloride, methylation, and reductive dechlorination.[149] Additional examples of the tetracyclic 3,11-propano bridged benzomorphans have been obtained by Grewe cyclization as previously described. Some of these compounds exhibited very high analgesic potency.[150] The use of pyrrolidone hydrotribomide to effect bromination under mild conditions in the presence of an allyl group was the key step in the synthesis of 3,6,11α-trialkyl-11β-hydroxybenzomorphans via the classical tetralone approach.[151,152] Phenylalanine has been converted, in ten steps, to 3,6,11-trimethylbenzomorphan, utilizing the displacement of bromide by nitrogen as the final step to form the N–C-4 bond in construction of the C ring.[153] Recently, a novel approach to benzomorphans involving a retro-Mannich reaction has been reported. When the reaction was conducted with excess formic acid, good yields of 11β-alkyl isomers were obtained. However, in the presence of $5HCO_2H$–$2NMe_3$, a rearranged product was the major material obtained. This is postulated to arise via a retro-Michael reaction followed by condensation, double-bond isomerization, and reduction.[154]

Homobenzomorphans. New homobenzomorphans with positional isomerization of nitrogen in the C ring have been prepared.[155,156] In certain cases, these compounds may represent a new class of potent analgesic.[156]

Positional Variation of Nitrogens. A new multistep preparation of **233a** from 5-phenyl-2-piperidone has appeared recently.[155] The product obtained from the 1,4-Stevens rearrangement of a tetrahydropyridinium precursor has been cyclized to afford a highly substituted member of 1,5-methano-2-benzazocine (**8**).[157]

Miscellaneous Compounds. Substitution of the benzo fusion by a heteroaromatic ring has been recently extended to include a pyridylbenzomorphan.[158] New derivatives of naphthazocine, benzonaphthomorphans, have been prepared by reaction of the appropriate quinolinium iodide with the Grignard reagent derived from α-(chloromethyl)naphthalene and subsequent cyclization of the dihydro compound in the usual manner.[159] A novel 3,6-dialkylbenzomorphan which contains a benzo fusion at C-4–C-5 has been obtained from reaction of benzylmagnesium chloride with the appropriate quinolinium iodide followed by cyclization.[160] New examples of bridged aminotetralins, wherein the synthesis was extended to include 1,4- and 1,5-bridged compounds, have appeared. Resolution of some of the analgetically potent β epimers has been achieved.[161,162]

Rearrangements. An unusual product obtained from the pyrolysis of 3-methyl-6-allyl-8-methoxy-11-oxobenzomorphan methobromide has been isolated and characterized. A radical mechanism has been proposed to account for this rearrangement.[163]

Substitution on Nitrogen. The use of sodium bis(2-methoxyethoxy)aluminum hydride for selective cleavage of aryl benzyl ethers and allyl aryl ethers has been used in a recent synthesis of pentazocine.[164]

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