SYNTHESIS OF 2-AZABICYCLO[3.3.1]NONANES.

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All methods for the synthesis of 2-azabicyclo[3.3.1]nonanes paying special attention to those which lead to functionalyzed systems are reviewed. This system, present in several alkaloids, is synthetically and theoretically interesting. The synthetic routes are classified according to the method used for the final cyclization to the morphan system.

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1. Introduction.

The 2-azabicyclo[3.3.1]nonane system is present in many compounds, both natural and synthetic ones. This grouping occurs in morphine, the main opium alka-
loid, as well as in a great number of heterogeneous indole alkaloids\(^3\), such as the strychnos alkaloids (strychnine, tubifoline, condyfoline), the picralime alkaloids (akuammine, akuammicine), the aspidospernum alkaloids (uleine, dasycarpidine), and the geissospernum alkaloids (geissoschizoline); it is also present in some calabash curare alkaloids as fluorocurarine.

\[\text{MORPHINE} \quad \text{ULEINE} \]

\[\text{PENTAZOCINE} \quad \text{THIENOMORPHAN} \]

Among the synthetic molecules containing the 2-azabicyclo[3.3.1]nonane nucleus, morphinans\(^4\) (e.g. levorphanol) and 6,7-benzomorphans\(^4,5\) (e.g. pentazocine) are specially interesting since they are strong synthetic analgesics. Heteromorphans\(^6\), bioisosters of 6,7-benzomorphans, in which the benzene ring is substituted by an heteroaromatic ring are also included. In the last years, some thieno-\(^6-9\), benzo[b]thieno-\(^10\), pyrido-\(^11-13\), indolo-\(^14,15\), furo-\(^16\), and pyrrolomorphans\(^17\) have been described.

Other compounds including the 2-azabicyclo[3.3.1]nonane system are the structurally interesting 2-azaadamantane\(^18\), some clohex[\(j\)](and[\(d\)]) indolo[2,3-\(f\)]morphans\(^19-21\), of interest in biogenetic type syntheses of indole analogues of morphine alkaloids, and some methanobenzo[furo[3,2-\(d\)]azocines prepared as transformation products of thebaine\(^22\).

The systems of 2-azabicyclo[3.3.1]nonane, especially the functionalized ones, are of great interest for the study of some structure-reactivity relationships and for being intermediates in the synthesis of more complex structures.
In the field of structural chemistry, 2-azabicyclo[3.3.1]nonanes allow to extend the studies, now in rapid developing, which are carried out with their carbocyclic analogues, bicyclo[3.3.1]nonanes. Thus, through these type of bridged systems, the reach of the Bredt's rule was studied, the bicyclo[3.3.1]non-1-ene and its corresponding 2-aza analogue were synthesized and their unusual reactivity was examined. The conformational analysis and the stability of nonenolizable 1,3-dicarbonyl derivatives of these systems are further aspects of their structural interest.

In the field of organic synthesis, functionalized 2-azabicyclo[3.3.1]nonanes have been used as intermediates in the preparation of model structures related to natural products, especially of indole alkaloids, and as precursors of complex polycyclic systems. They have also been used as intermediates in the preparation of potentially active systems from the pharmacological standpoint. In this aspect some 2-azabicyclo[3.3.1]nonanes are themselves interesting, just as it happens with 5-phenylmorphans, strong analgesics. Moreover, the study of the structure-activity relationships in synthetic analgesics has been enlarged through them.

In this review on the synthesis of 2-azabicyclo[3.3.1]nonanes we are not going to take into account those approaches which lead to systems in which this grouping is part of a more complex polycyclic structure.

2. First syntheses: cyclization by lactamization.

In 1947 Barltrop reported the first reference about 2-azabicyclo[3.3.1]nonanes, in the context of the synthesis of cyclic ring systems occurring in the morphine molecule. It describes an approach to this system by alkylation of ethyl 2-oxocyclohexanecarboxylate with 2-chloroethylidethylamine and further cyclization through the 6-bromo derivative, to give the ammonium salt in a yield lower than 1%.
The preparation of 2-azabicyclo[2.2.2]octane by copper chromite reduction of the lactam of cis-4-aminocyclohexanecarboxylic acid suggested to Cronyn that the unsubstituted 2-azabicyclo[3.3.1]nonane (5) could be similarly synthesized by lactamization of cis-3-aminocyclohexanecetic acid (2, R=H) or of that of its corresponding ester (2, R=Et) and subsequent reduction of the resulting lactam 4.

The synthesis was achieved from ethyl m-nitro-O-benzoylmandelate (3) using different procedures. The best one was the direct hydrogenation over Raney nickel in tert-butanol at 200°C, since in these conditions cyclization occurs and the lactam 4 was obtained in 35% of overall yield. Finally, the lactam 4 was hydrogenated to 2-azabicyclo[3.3.1]nonane (5) over copper chromite in tert-butanol (46% yield).

A parallel synthesis of Ginsburg introduced some variations in the experimental aspect. Thus, reduction of ethyl m-nitrophenylacetate in glacial acetic acid using Adam's catalyst gave the aminoester 2 (R=Et) in good yield, and subsequent lactamization by heating at 150°C afforded 4 in 84% yield. Final reduction to the morphan system 5 was carried out with lithium aluminum hydride. Later on, an analogous synthesis of 4 from m-nitrophenylacetic acid has been described. N-Methylation with sodium hydride and methyl iodide gave 2-methyl-2-azabicyclo[3.3.1]nonan-3-one, and this lactam was reduced to the N-methylmorphan 6 with lithium aluminum hydride.
In a study of 2-azabicyclo[3.3.1]non-1-ene systems as reaction intermediates with a bridgehead double bond a new synthesis of the lactam \( \text{4} \) and of some \( \text{C}_1 \)-substituted derivatives were reported. The aminoester \( \text{2} \) was obtained from methyl 3-oxocyclohexaneacetate through 0-methyloxime \( \text{7} \) and subsequent reduction and esterification. Heating of \( \text{2} \) in the presence of sodium methoxide afforded lactam \( \text{4} \) in 50-60% yield.

Treatment of \( \text{4} \) with lead tetraacetate gave 1-acetoxy-3-oxo-2-azabicyclo[3.3.1]nonane \( \text{9} \), being 2-azabicyclo[3.3.1]non-1-ene \( \text{8} \) the probable intermediate. From acetoxy lactam \( \text{9} \), some substitution reactions at \( \text{C}_1 \)-position were carried out, and 1-methoxy- and 1-cyanoderivatives were obtained, their formation involving again the presence of an imino intermediate of type \( \text{8} \).
Similarly, when the alkaloid methyl homosecodaphniphyllate, which contains the 2-azabicyclo[3.3.1]nonane system, was treated with lead tetraacetate the formation of an unusually anti-Bredt’s-rule imine containing the 2-azabicyclo[3.3.1]non-1-ene system was described.\textsuperscript{41}

The preparation of 9-hydroxy-2-azabicyclo[3.3.1]nonane\textsuperscript{42} is one of the few approaches to C\textsubscript{9}-functionalized morphans, and together with the precedent one are the only ways to morphan systems which involve the formation of an amide bond at the last step without using aromatic compounds as starting materials.

From 3-carbethoxy-2-oxocyclohexanecetic acid (10) piperidine ring was formed. Thus, the replacement of the carbethoxy group by the oximino group gave 11, which was catalytically hydrogenated affording the hydrochloride of the aminoester 12. Reduction of this hydrochloride with sodium borohydride yielded (36\%) the isolable crystalline isomer ethyl c-3-amino-\textdagger-2-hydroxycyclohexanecetate (13). On heating at 150-160°C and further reduction with lithium aluminum hydride of the resulting lactam, the 9-hydroxymorphan 14 was obtained. When reduction of 12 was carried out by catalytic hydrogenation in the presence of platinum oxide, the C\textsubscript{2}-epimer alcohol of 13 was obtained. However, its cyclization afforded the same lactam than that of 13, thus indicating that an epimerization is produced during the heating process.
3. Phenylmorphans.

Once the nucleus of 2-azabicyclo[3.3.1]nonane was synthesized, the interest was focused on the preparation of 2-methyl-5-phenyl-2-azabicyclo[3.3.1]nonanes, since this type of substances possess the three structural features necessary for a compound to have an analgesic activity similar to morphine. They are (a) a phenyl nucleus, (b) a quaternary carbon attached to this nucleus, and (c) a tertiary nitrogen two carbon atoms removed from the quaternary carbon.

The main problem of the first syntheses of morphans 18 (Ar=C₆H₅ and Ar= m-OH₆H₄) was the low yield (20%) in the formation of 2-dimethylaminoethyl-2-aryl cyclohexanones 16 owing to the competition of the O-alkylation process (60%) \(^{44,45}\). The predominance of this process is probably due to steric hindrance to C-alkylation and to stabilization of the enolate of 15 by the aromatic nucleus. However, after House's studies on the factors as favoring C-alkylation \(^{46}\), the synthesis was improved and 16b was formed from 15b in 40% yield using dimethylformamide, sodium hydride and 2-dimethylaminoethylchloride hydrochloride at room temperature. Since 15b could be regenerated from enol ether 17b, the process appears then to be more interesting.\(^{34}\).

\[\begin{align*}
15 & \quad 16 \\
\text{a. } \text{Ar} = \text{C}_6\text{H}_5 & \quad \text{b. } \text{Ar} = \text{m-OCH}_2\text{C}_6\text{H}_4 & \quad \text{c. } \text{Ar} = \text{m-OH}_6\text{H}_4 \\
\end{align*}\]

The synthesis goes on converting 16a and 16b into their corresponding 6-bromoderivatives, later cyclization in basic media at room temperature, and dry distillation of the resulting ammonium salts. Finally, Wolff-Kishner reduction of...
ketones 18a and 18b gave the phennylmorphan nucleus 19. Through the m-methoxyphenyl-derivative 19b, the corresponding phenol 19c and its acetylderivative were obtained44.

In an alternative synthesis of 19b34, alkylation of 15b with ethyl bromoacetate (sodium amide-ether) gave the C-alkyl product 20 in a 80% yield. Reduction of 20 with lithium aluminum hydride afforded (98%) a diol that, by oxidation under controlled conditions (chromic oxide, pyridine) gave (77%) the keto aldehyde 21. In tramolecular aldol condensation of 21 yielded (45%) a mixture of epimeric keto alcohols 22. Wolff-Kishner reduction of which (93%) followed by oxidation of the hydroxy function gave (73%) 1-m-methoxyphenylbicyclo[3.2.1]octan-6-one (23).

\[
\begin{align*}
\text{CO}_2\text{Et} & \xrightarrow{\text{Ar}} \text{CHO} \\
\text{20} & \xrightarrow{\text{OH}} \text{22} \\
\text{23} & \xrightarrow{\text{Me}} \text{24} \\
\text{Ar} &= \text{m-OC}_3\text{H}_7\text{C}_6\text{H}_4
\end{align*}
\]

Formation of its oxime (64%) and subsequent Beckmann rearrangement, critical step of this synthesis (84%), afforded the morphan nucleus 24. Methylation of 24 followed by reduction with diborane gave quantitatively phenylmorphan 19b.

Due to the strong pharmacologic action of (+)-5-(m-hydroxyphenyl)-2-methyl morphan 19c34, the activity of both enantiomers, previously resolved with d-mandelic acid34,47, was evaluated. They possess significant enantiomeric stereoselectivity in their biological actions. Thus, the levo isomer, an analgesic with morphine-like potency, exhibits a weak narcotic antagonist activity and only a very slight physical dependence capacity47. The dextro isomer, four times more potent analgesic than morphine, has no antagonist activity and has a high physical dependence capacity47,48. The N-propyl, allyl, and cyclopropylmethyl derivatives of (+)-19c and its racemate were also prepared and their analgesic and antagonist activities studied48. Later on, the absolute configuration of the analgesic agonist-antagonist (-)-19c was es-
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Established\textsuperscript{29} to be 1R, 5S by single-crystal X-ray analysis of its hydrobromide salt. Both rings of the 2-azabicyclo[3.3.1]nonane system exist in chair conformations with the phenyl and methyl substituents equatorial.

On the other hand, the enantiomer (+)-19c was stereochemically correlated\textsuperscript{49} with the normorphan (+)-(1R,5S,7R)-1-(m-hydroxyphenyl)-6,7-dimethyl-6-azabicyclo [3.2.1]octane (25c), compound of interest for its analgesic and antagonist properties. Thus, the methoxy derivative (-)-25b, a precursor of (+)-25c, gave the olefin (+)-26b as the sole product on Hofmann degradation. Hydroboration and subsequent oxidation of (+)-26b afforded the carbinol (+)-27b which through the respective chloride was turned into methochloride of morphan 19b. Dry distillation followed by 0-demethylation gave a product identical in all respects to an authentic sample of the dextro isomer of phenylmorphan 19c. As in the process the configuration of the carbon bonded to the aromatic ring was not modified, this series of reactions provides an additional proof for the absolute configuration of normorphan (+)-25c.

5-Phenylmorphans, with pharmacological interest on their own, have been used when functionalized as intermediates in the synthesis of more elaborated products. Thus, a Knoevenagel reaction on ketone 18 allowed obtention of tetracyclic compound 28\textsuperscript{43,50}, a position isomer with respect to nitrogen attachment of N-methyl morphinan.
Likewise, 9-cis-amino-5-(m-methoxyphenyl)-2-methyl-2-azabiclo[3.3.1]nonane (29), prepared\textsuperscript{32} from ketone 18b, leads by Pictet-Spengler cyclization to the tetracyclic system \textsuperscript{30}\textsuperscript{32} and by photolysis of its chloroacetamido derivative \textsuperscript{31} to 4,11b-propanopyrido[4,3-a][3]benzazepine systems of type 32\textsuperscript{51}.

The first synthesis of a C-8 functionalized 2-azabicyclo[3.3.1]nonane was described in 1970. It concerns the obtention of 2-methyl-8-hydroxy-2-azabicyclo[3.3.1]nonane (33)\textsuperscript{52}, based on the easiness of N-chloramines for intramolecular addition to olefinic double bonds\textsuperscript{53,54}. To explain such reactions, the formation of nitrenium ions\textsuperscript{55} via a heterolytic process in neutral protic media (methanol reflux or tetrahydrofuran-water in the presence of silver ion catalysis) was postulated. Functionalized 6-azabicyclo[3.2.1]octanes\textsuperscript{54} have been prepared in these conditions. The procedure was not applicable to the synthesis of morphan \textsuperscript{52} and it was necessary to resort to a solvolysis in 1 M sulfuric acid. The mechanism differs in the sense that chloronium ions formed by ionization of chloramine \textsuperscript{34} once protonated are now involved. Their addition to the double bond implies the formation of the cyclic chloronium cation \textsuperscript{35}, which when neutralizing the acidic aqueous reaction media would suffer a solvolysis with the formation of the diastereomeric epoxides \textsuperscript{36}.

\[
\begin{align*}
\text{34} & \rightarrow \text{Cl} & \text{H} & \text{N-Me} \\
\text{Cl} & \text{H} & \text{N-Me} & \text{35} \\
\text{36a} & \rightarrow \text{H} & \text{O} & \text{H} & \text{N-Me} & \text{36b} & \rightarrow \text{33}
\end{align*}
\]

Intramolecular opening of the epoxide ring of the \textit{trans} isomer \textsuperscript{36b} yielded (37%) 2-methyl-8-hydroxy-2-azabicyclo[3.3.1]nonane (33), which was converted into 2-methyl-2-azabicyclo[3.3.1]nonane (6) upon oxidation with Jones reagent, thioacetylation of the resulting ketone \textsuperscript{37}, and subsequent Raney nickel desulfurization.
Alternatively, ketone 37 has been synthesized\textsuperscript{56,57} by intramolecular reaction under acidic conditions of an N-chloramine with the activated double bond of an enol ether, this reaction being already used in similar cyclizations\textsuperscript{58}. The required enol ether 38 was prepared in six steps from p-hydroxyphenylacetic acid in 27\% overall yield. The corresponding N-chloramine was obtained by reaction of 38 with 1 M sodium hypochlorite solution, and by trifluoroacetic acid treatment it yielded a mixture (96\%) of 37 and 40 in 4:1 ratio. The process involved again a chloronium ion addition to an activated double bond. When cyclization was carried out in methanol instead of pure trifluoroacetic acid, the formation in high yields of epimeric chloro ketal 39 was described. These can be cyclized (73\%) by acidic hydrolysis followed by base treatment to a 4:1 mixture of the elimination-cyclization product 40 and the ketone 37. Acid hydrolysis of the enol ether 40 afforded almost quantitatively the same ketone 37. Finally, morphan 6 was obtained by hydrogenolysis\textsuperscript{56,57} of 37 in acidic conditions with platinum oxide, the procedure having been described for some azabicyclic ketones\textsuperscript{59}.

The synthesis of ketone 37 has also been reported by cyclization of the N-chloramine corresponding to 38 in the presence of Lewis acids. The best yields (40-50\%)\textsuperscript{60} were obtained with ZnX\textsubscript{2} type agents in methylene chloride at 0\°. The same ketone 37 was also obtained by cyclization of dioxolane 41 under acid solvolysis conditions (anhydrous trifluoroacetic acid-methanol solution) through an electrophilic
chlorination of the enol ether 42 formed from 41 and subsequent intramolecular displacement of the halide 43 by the amino group. Thus, ketone 37 was obtained in 50% yield, together with the enol ether 40 (10-30%)\(^5\).

As it can be deduced from the methods reviewed in this section, the N-chloramines route permits to obtain only C-8 functionalized 2-azabicyclo[3.3.1]nonanes. Contrary to what it occurs in the 2-azabicyclo[3.2.1]octane series\(^5\) where the bridged carbon can be functionalized by this procedure, the application of this type of reactions as potential way to C-9 functionalized systems has been unsuccessful\(^6\).

Thus, the silver nitrate catalyzed methanalysis of the N-chloramine 44 took place\(^6\) with formation of 7-substituted 1-methyl-cis-octahydroindole systems 45 and less than 1% of the desired 2-methyl-9-methoxy-2-azabicyclo[3.3.1]nonane (46). On the other hand, N-chloramine 47 failed to cyclize to the expected azabicyclic ketone 48, giving instead complex reaction mixtures\(^5\).
5. Intramolecular Michael-type cyclization.

The synthesis of C-7 functionalized 2-azabicyclo[3.3.1]nonanes can be achieved by means of an intramolecular Michael-type cyclization of an amine group upon an α,β-unsaturated ketone.

\[ \text{R} \]

![Diagram](image)

The synthesis of 6-azabicyclo[3.2.1]octan-3-ones through an 1,4 intramolecular addition suggested two independent but analogous syntheses of 2-methyl-2-azabicyclo[3.3.1]nonan-7-one (50, R=CH₃)₁²,₆₄.

From diethyl 3-oxoglutarate, 3,5-dihydroxyphenylacetic acid 51 was obtained, and hydrogenated (77% yield) to the dione 52 with rhodium on alumina in basic media at high temperature. The formation of amide 5₃ requires a laborious process.

Treatment of 52 with two equivalents of isobutyl chloroformate did not only activate the carboxyl group by forming a mixed anhydride but also protect the enolic hydroxyl as the carbonate ester. Subsequent treatment with benzylamine or methylamine, followed by hydrolysis of the intermediate carbonate and neutralization afforded the amides 5₃a and 5₃b, respectively, which were converted into enol ethers 5₄ with

\[ \text{R} \]

![Diagram](image)
methanol and p-toluenesulfonic acid. Reduction of 54 with lithium aluminum hydride in tetrahydrofuran gave the unisolated amino alcohols 55 which through acid hydrolysis followed by basic treatment yielded the desired 2-alkyl-2-azabicyclo[3.3.1]nonan-7-ones (50) through the conjugated ketones 49.

\[ \begin{align*}
51 & \xrightarrow{\text{CO}_2\text{H}} 56 \\
56 & \xrightarrow{\text{CONH}_2} 57 \\
57 & \xrightarrow{\text{CONH}_2} 58 \\
58 & \xrightarrow{\text{R}} 53 \\
\end{align*} \]

In the synthesis of Mitsuhashi and co-workers\(^\text{12}\) from the same acid 51 the key intermediate 53 was obtained by an alternative way which avoids the formation of the amide group in the presence of the conjugated enolic system of 52. Thus, 3,5-dimethoxyphenylacetamides 57b and 57c were prepared from 51 by methylation with dimethyl sulfate, subsequent conversion of the resulting carboxylic acid (56) into the corresponding acid chloride and treatment with ammonia or methylamine. Reduction of 57 with sodium in liquid ammonia gave the dihydro derivatives 58. Hydrolysis of 58 with diluted hydrochloric acid afforded quantitatively the intermediate 53, from which the C-7 functionalized morphans 50b and 50c were prepared.

Condensation\(^\text{12}\) of N-acetyl and N-formyl derivatives of 50 with 3-aminoacrolein gave the pyrido[3,2-e]morphans 59 (R=COCH₃, CHO), (systematic name: 8-acyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrido[2,3-d]azocine). This synthesis is the first approach to an heteromorphan system through a strategy which employed functionalized morphans. However, the carbonyl group at C-7 position confers ambiguity in the formation of the pyridine ring since the synthesis of 59 is accompanied by that of its structural isomer 60.

\[ \begin{align*}
59 & \\
60 &
\end{align*} \]
On the other hand, 2-methyl-2-azabicyclo[3.3.1]nonan-7-one (50b) was converted into a mixture of 2-methyl-2-azabicyclo[3.3.1]non-6-ene (62) and its position isomer (63) through the hydroxyderivative 61. Thus, reduction of 50b with sodium borohydride gave stereoselectively the endo amino alcohol 61 whose dehydration (methanesulfonyl chloride in pyridine) afforded the olefins 62 and 63, both of which upon catalytic hydrogenation were converted into 2-methyl-2-azabicyclo[3.3.1]nonane (6). The 6,7 double bond in 62 is postulated to provide the π-electron density that is usually imparted by the aromatic ring in 6,7-benzomorphans. However, this replacement of an aromatic ring by a single unsaturation does not result in compounds with significant analgesic activity.

6. Other syntheses with formation of piperidine ring in the last stage.
The unexpected formation of the azabicyclic system 67 when 3-methyl-2-cyclohexen-1-one (64) is treated with ethyl cyanoacetate and ammonia in alcohol, suggested the synthesis of 4-cyano-1-hydroxy-5-methyl-3-oxo-2-azabicyclo[3.3.1]nonane (70) which is the first approach to 2-azabicyclo[3.3.1]nonane systems with an alkyl substituent at C-5 position.

The lactam 67 probably results from an initial Knoevenagel condensation followed by Michael addition, ammonolysis of the resulting diester 65 and final cyclization by conjugated addition. Its hydrolysis and decarboxylation afforded 68 which later on was reduced with lithium aluminum hydride to give 5-methyl-2-azabicyclo[3.3.1]nonane-1-ethanol (69). Likewise, when α,β-unsaturated ketone 64 was treated with cyanoacetamide in the presence of piperidine-water, the azabicyclo 70 was obtained in 77% yield.

Another approach to C-8 functionalized 2-azabicyclo[3.3.1]nonanes involves a series of reactions different from the previously mentioned even through based on the same disconnections. This method consists in the formation of C1-N bond by intramolecular nucleophilic attack of an amide upon an epoxide in the presence of potassium tert-butoxide.
Thus, in model studies of the synthesis of the alkaloid echitamine, 2-benzoyl-2-azabicyclo[3.3.1]nonan-8-one (74) was prepared and converted into the tetracyclic system 75 by Fischer indole synthesis\textsuperscript{31}. Formation of alcohol 73 took place in 87\% yield when the cyclization was achieved with the trans amido epoxide 72, and in 45\% yield when the crude epoxide mixture resulting from epoxidation of the double bond of 71 was directly used. Oxidation to the ketone 74 took place in moderate yield (29\%) with chromic acid in aqueous acetic acid.

A similar strategy was used to synthesize N-benzyl-2-azaadamantan-4-ol (76)\textsuperscript{18} which could be formally considered as a rigid 2-azabicyclo[3.3.1]nonane due to an additional carbon bridge between the 3 and 7 positions of the morphan nucleus.

\[
\begin{align*}
\text{NHCOCH}_3\text{H}_5 & \quad \text{MCPBA} \quad \text{HO} & \quad \text{NCOCH}_3\text{H}_5 \quad \text{B}_2\text{H}_6 \quad \text{THF} & \quad 76
\end{align*}
\]

Photolysis of $\Delta^5,6$-alkenyl nitrosamines\textsuperscript{66} in acidified methanol afforded satisfactorily azabicyclic nucleus of 6-azabicyclo[3.2.1]octan-4-one type, either directly or through the respective oximes by a mechanism which involved aminium radicals\textsuperscript{67}. Their addition reactions to internal olefinic bonds are highly regiospecific, and the procedure was extended, but with moderate yield, to the synthesis of the C-8 functionalized 2-azabicyclo[3.3.1]nonane 37. In this case cyclization was carried out with the crude $\Delta^6,7$-alkenyl nitrosamine 78 prepared from the secondary amine 77 previously used in the synthesis of these systems via chloramines. From the crude photolysate a 6\% yield of morphan 37 together with a mixture of its E (16\% yield) and Z (9\% yield) oximes were isolated.

\[
\begin{align*}
\text{H} & \quad \text{Me} \quad \text{NaO}_4 \quad 43\% \quad \text{Me} & \quad \text{H}^+ \quad \text{H}_2\text{O} & \quad 37
\end{align*}
\]

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The picrate prepared from ketone 37 revealed hydroxyl absorptions at 3615 and 3345 cm\(^{-1}\) but not carbonyl absorption in its IR spectrum. This suggested that protonation occurred at the carbonyl oxygen but not at the amine group as in 37a.

7. Formation of carbocyclic ring in the last step: Dieckmann cyclization.

A new strategy in the synthesis of 2-azabicyclo[3.3.1]nonan-8-ones was the formation of the carbocyclic ring from a well substituted piperidine via a Dieckmann cyclization followed by decarboxylation. This way was adopted to prepare 5,6,7,8,9,10-hexahydro-6,10-methanopyrido[2,3-c]azocines (79), since the presence of a \(\beta\)-keto ester moiety in the azabicyclo 83 was suitable for the subsequent elaboration of a pyridine ring.
The requisite piperidine 82 was prepared from 4-pyridineacrylic acid by esterification and hydrogenation to give ethyl 4-pyridinepropionate (80). Through the corresponding N-oxide and formation of a methoxy pyridinium salt, a cyano group was introduced, and in the same reaction media was hydrolyzed and esterified to ethyl 2-carbethoxy-4-pyridinepropionate (81). Catalytic hydrogenation over platinum oxide in acetic acid afforded the piperidine derivative 82 (R=H). Acylation of the secondary amine 82 with formic acetic anhydride or benzoyl chloride and subsequent Dieckmann cyclization (sodium hydride-toluene) of the resulting acyl derivatives gave beta-keto esters 83a and 83b respectively. Although the compound 83b reacted with hydrazine to give a pyrazolone derivative, the enolic character of the ketone group present in 83 prevented this system to react in Knoevenagel and Michael condensations or in the Reformatsky reaction. However, on hydrolysis with methanolic potassium hydroxide 83b afforded in 78% yield 2-benzoyl-2-azabicyclo[3.3.1]nonan-8-one (74). Spectroscopic data of compound 74, specially the multiplicity of N-benzoyl signal in the nmr spectrum (δ7.4, singlet) differs from those reported by Dolby31 (67.1-7.8, multiplet) for the same compound. The first agree with the observed magnetic equivalence of aromatic protons in dialkylbenzamides68.

Treatment of ketone 74 with ethyl formate in the presence of sodium hydride gave the beta-keto aldehyde 84 which was subjected to a condensation with guanidine to yield the amino pyrimidine derivative 85. Finally, pyridoazocine 79 (R=COC₆H₅) was prepared (57%) by treatment of 74 with 3-aminoacrolein in triethylamine in the presence of catalytic amount of ammonium acetate at 100-110°C, and from it, N-benzyl, N-formyl, N-H and N-methyl derivatives of 79 were described.
Through a Dieckmann cyclization of a suitably polysubstituted piperidine, a 2-azabicyclo[3.3.1]nonan-6-one which possesses a quaternary carbon in C-5 was obtained for the first time. Thus, monoalkylation of diethyl glutamate (86) with ethyl 4-bromobutyrate followed by benzylation gave diethyl N-benzy1-N-(3-carbethoxypropyl)glutamate (88). Ring closure of this triester was accomplished by the Dieckmann reaction with sodium ethoxide-benzene as cyclizing agent. The alkylation of β-keto ester 89 (methyl iodide, potassium carbonate, acetone) led to a diastereomeric mixture 90 which, after conversion into the ethylenedithioketal 91 (boron trifluoride etherate, 80°C) and subsequent desulfurization (Raney nickel), was converted into the diester 92, also in the form of diastereoisomeric mixture (1:1, 96). On standing, the trans isomer was obtained, and the resulting cis-enriched mixture was subjected to Dieckmann cyclization (sodium hydride, toluene) to give the desired functionalized 2-azabicyclo[3.3.1]nonane system 93, which was decarbalkoxylated to 94 by treatment with sodium chloride in wet dimethylsulfoxide (155°C, 3 h).
These functionalized morphans are versatile intermediates for the elaboration of condensed heterocyclic systems, and provide a new approach to the synthesis of heteromorphans. From \( \beta \)-keto ester 93, the pyrazolo[3,4-f]morphan 95 was prepared. From ketone 94, the pyrido[2,3-f]morphan 96 by reaction with 3-aminoacrolein and indolo[2,3-f]morphan 97 by Fischer indole synthesis were prepared. In this heterocondensed morphans the heteroaromatic ring is fused unambiguously between the 6 and 7 position of the 2-azabicyclo[3.3.1]nonane system, and they possess a methyl substituent on the carbon atom attached to the aromatic ring.

![Chemical structures](image)

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