Synthesis of analogues of Batrachotoxinin A

PRELIMINARY STUDIES FOR THE SYNTHESIS OF ANALOGUES OF BATRACHOTOXININ A

by

Guy Yang-Chung

Ingénieur chimiste (1967),

ENSC de Montpellier .

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science .

Department of Chemistry,

McGill University

Montreal, Quebec . July, 1973 .

M.Sc. Chemistry

ABSTRACT

The use of various Diels-Alder reactions in possible routes for the synthesis of batrachotoxinin A analogues has been studied . Model studies involving 3-vinyl-2-cyclohexen-1-ol and 3-vinyl-2-cyclohexen-1--one have been done .

A study of relevant derivatives of 1,3-diones has been carried out .

The Mannich reaction of an enamino ketone and an unusual cyclisation are reported .

M.Sc. Chimie

RESUME

La possibilité d'utiliser diverses réactions de Diels-Alder dans la synthèse d'analogues de la batrachotoxinin A a été étudiée . Des réactions de Diels-Alder, avec comme diènes les composés modèles : vinyl-3-cyclohexen-2-ol-1 et vinyl-3-cyclohexen-2-ol-1 et avec comme diénophiles divers diénophiles, symétriques et dissymétriques ont été faites, et les résultats obtenus interprétés .

Une étude de dérivés de diones-1,3 a été faite .

La réaction de Mannich d'une énamino cétone et une cyclisation inhabituelle sont décrites .

ACKNOWLEDGEMENTS

The author would like to express his sincere gratitude and appreciation to Dr. G.Just, for his helpful advice and guidance throughout this work .

Special acknowledgement is extended to A.Martel, P.A. Rossy and B.McDonald, who contributed with valuable discussions .

Thanks are also due to Miss M.Lambert for typing the manuscript .

TABLE OF CONTENTS

To L.D.V.

INTRODUCTION

Studies conducted by Witkop and coworkers (1,2), in 1963-65, on the potent venom from the columbian arrow poison frog "Phyllobates bicolor" (3), have shown the presence of three major alkaloids :

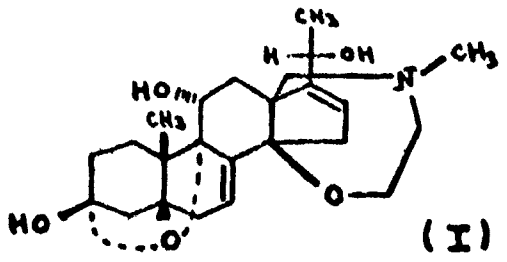
batrachotoxin

batrachotoxinin A

batrachotoxinin B

Batrachotoxin, the major alkaloid isolated is the strongest cardiotoxin known.

The structure of batrachotoxinin A was determined by Witkop and coworkers in 1968 by x-ray diffraction (4) using an O-p-bromobenzoate derivative and was found to be 3α,9α- epoxy- 14β,18β[epoxyethano-N-methylamino]-5β-pregna-7,16-diene-3β,11α,20α- triol (I)



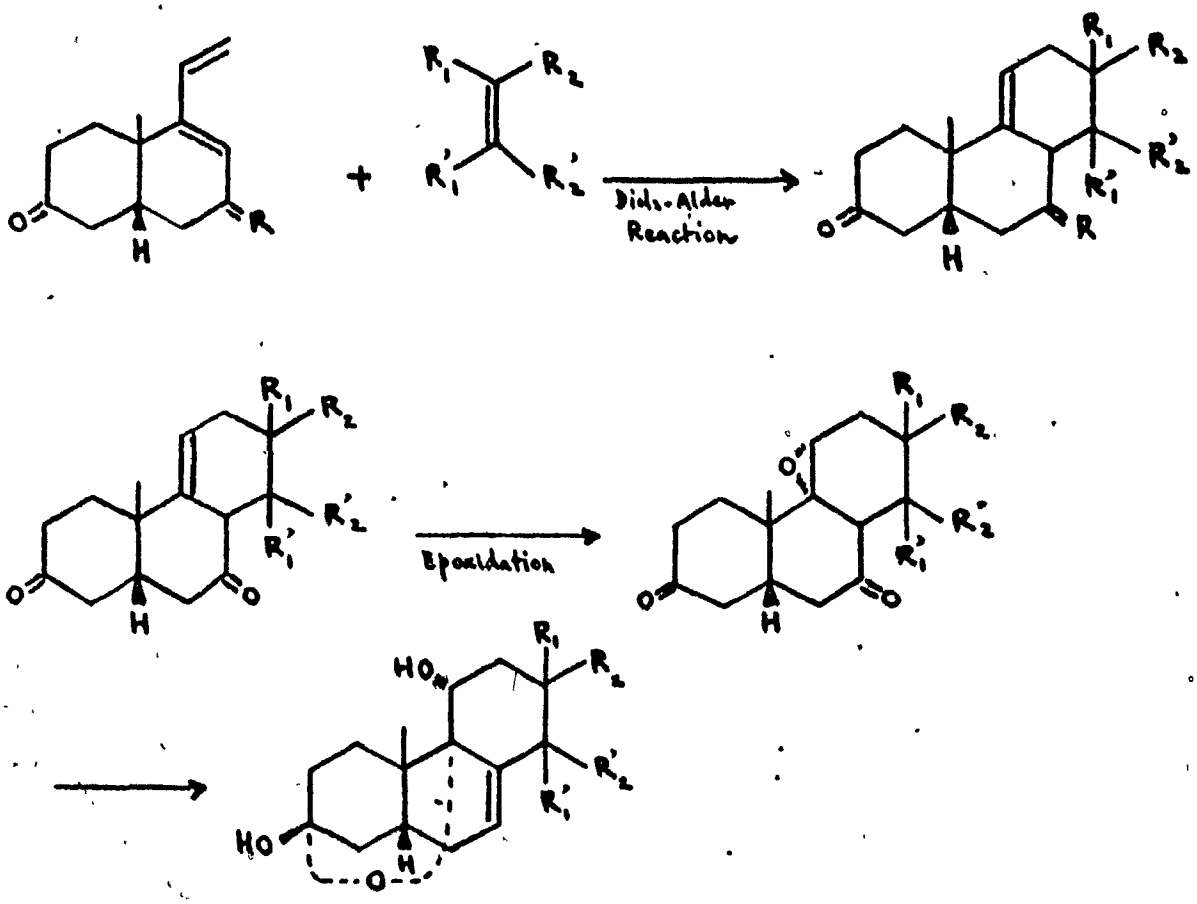
(I)

Along with its biological activity, batrachotoxinin A exhibits unusual features: It is not only an alkaloid derived from an animal source, but it is also a precursor of choline.

The following work deals with a study of Diels-Alder reactions possibly applicable to the synthesis of batrachotoxinin A analogues.

The general scheme is shown below.

Scheme I

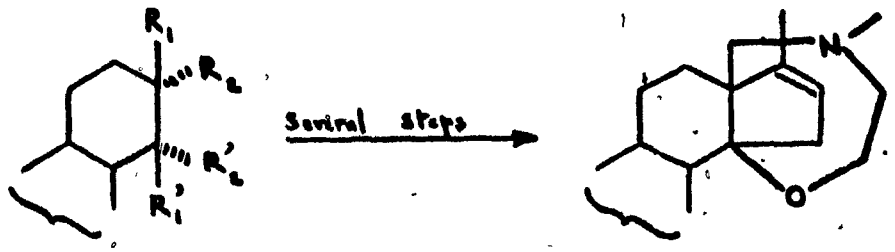


The keto group in position 7 could be used at this stage to introduce the $\Delta^{7,8}$ double bond (cf reference 5 for this particular point).

CHAPTER I

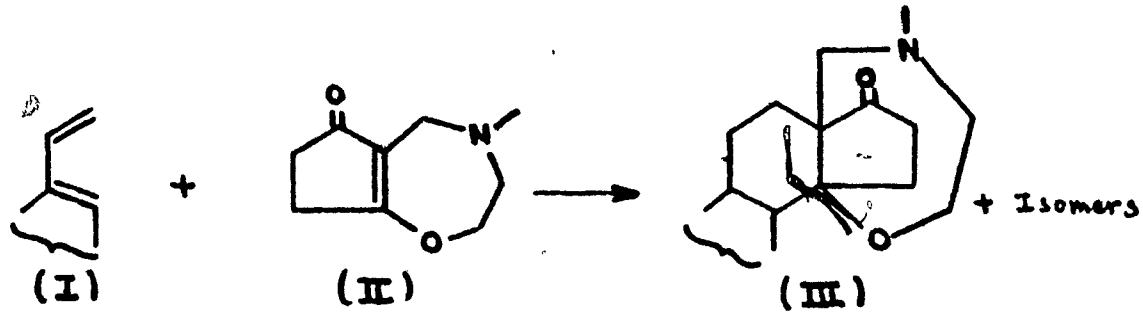
Study of some derivatives of 1,3-diones.

In the above scheme, R_1, R_1', R_2, R_2' groups are suitable precursors of the propellane part of the desired analogues of batrachotoxinin A :

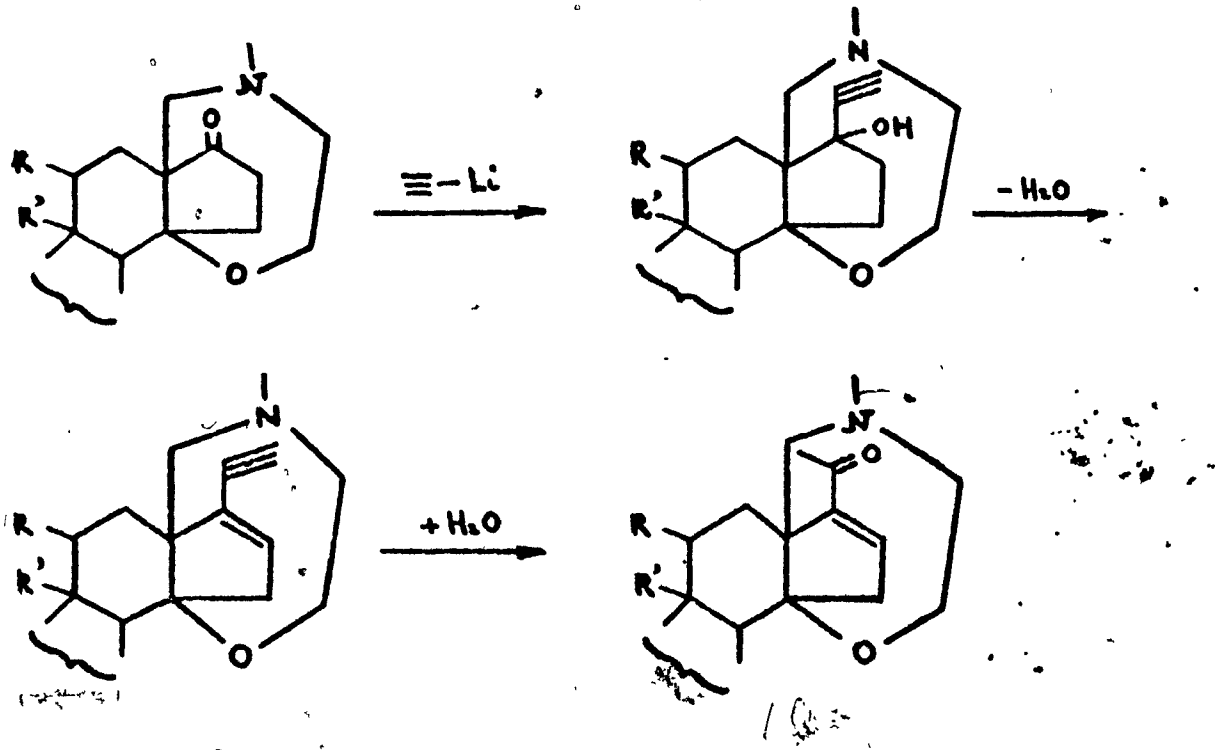


In this chapter, a first route, using derivatives of 1,3-diones was investigated. The scheme involving the Diels-Alder reaction of the bicyclic compound (II) with the suitable diene (I), to give the adduct (III), was considered .

Scheme a

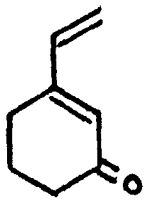


Subsequent modifications of the double bond and carbonyl group of (III) (6,7) would then permit the synthesis of compounds related to batrachotoxinin A.

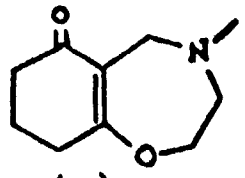


Though this route was giving rise to many problems, its main advantage was to give the propellane structure directly.

A model study was then undertaken, involving a Diels-Alder reaction between 3-vinyl-2-cyclohexen-1-one and the bicyclic compound (V).



(IV)

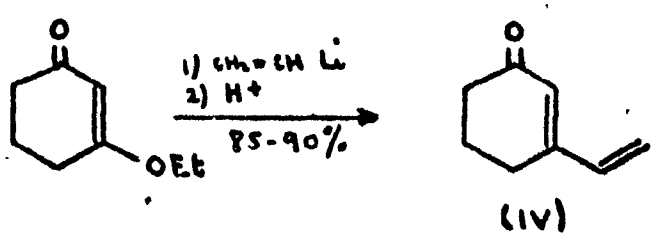


(V)

(V) was chosen as a model compound because of the availability of the starting compound cyclohexane-1,3-dione, compared to cyclopentane-1,3-dione.

Synthesis of 3-vinyl-2-cyclohexen-1-one (IV)

(IV) was easily obtained by reaction of vinyl lithium on 3-ethoxy-2-cyclohexen-1-one, in anhydrous conditions, followed by dehydration in acidic medium.



(IV)

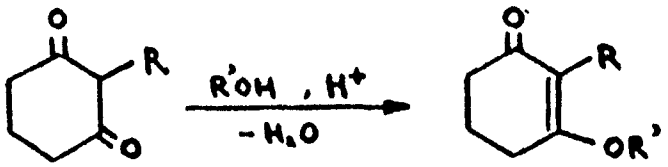
5-Alkoxy-2-cyclohexen-1-one derivatives are known to react with aluminium hydride (8) and lithium acetylide (9,10) in particular.

The diene was obtained as a colorless liquid, in good yield, and the separation (column chromatography or thin layer chromatography) was easy.

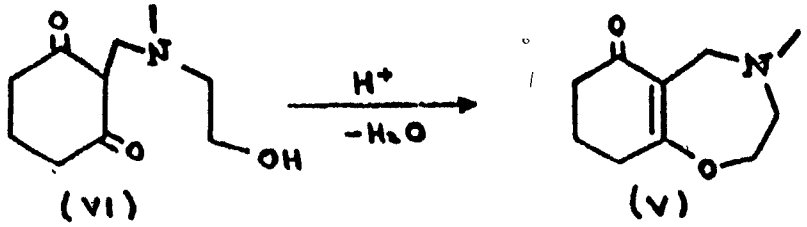
Attempted synthesis of the bicyclic enol ether (V)

i) Preliminary considerations

The enol ether part of (V) could be theoretically conceived as deriving from the corresponding 1,3-dione (11).

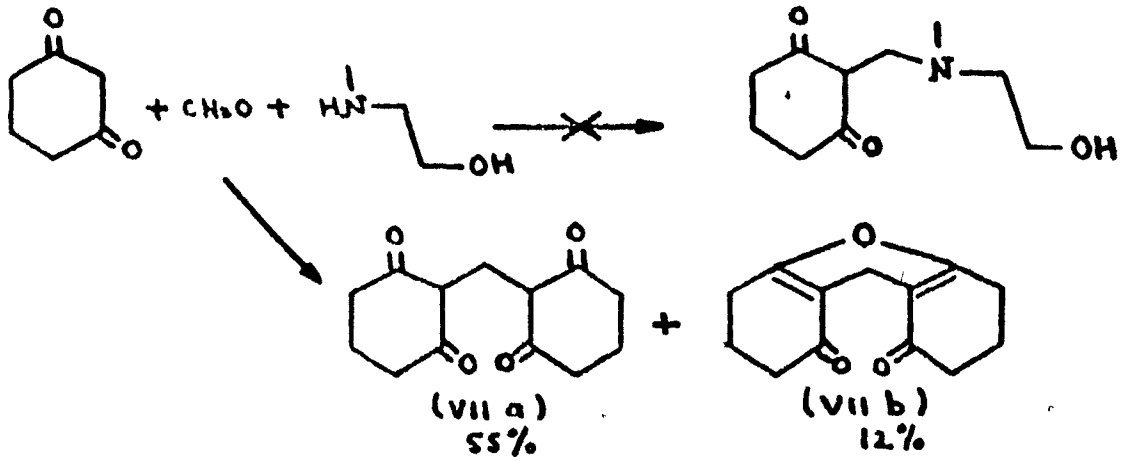


The γ-amino ketone part is usually obtained (12) from the corresponding ketone, using the Mannich reaction. If the Mannich base (VI) could be obtained, the formation of (V) could possibly be reached by subsequent internal reaction of the alcohol function on the dione system.



(VI) (V)

However, some 1,3-diones are known to give very unstable Mannich bases (13). The Mannich reaction with cyclohexane-1,3-dione and N-methylethanolamine was tried, and a crystalline compound, identified as the cyclohexane-1,3-dione-formaldehyde adduct (VII a) was obtained along with a small amount of another crystalline compound, the physical data of which are consistent with the structure (VII b).

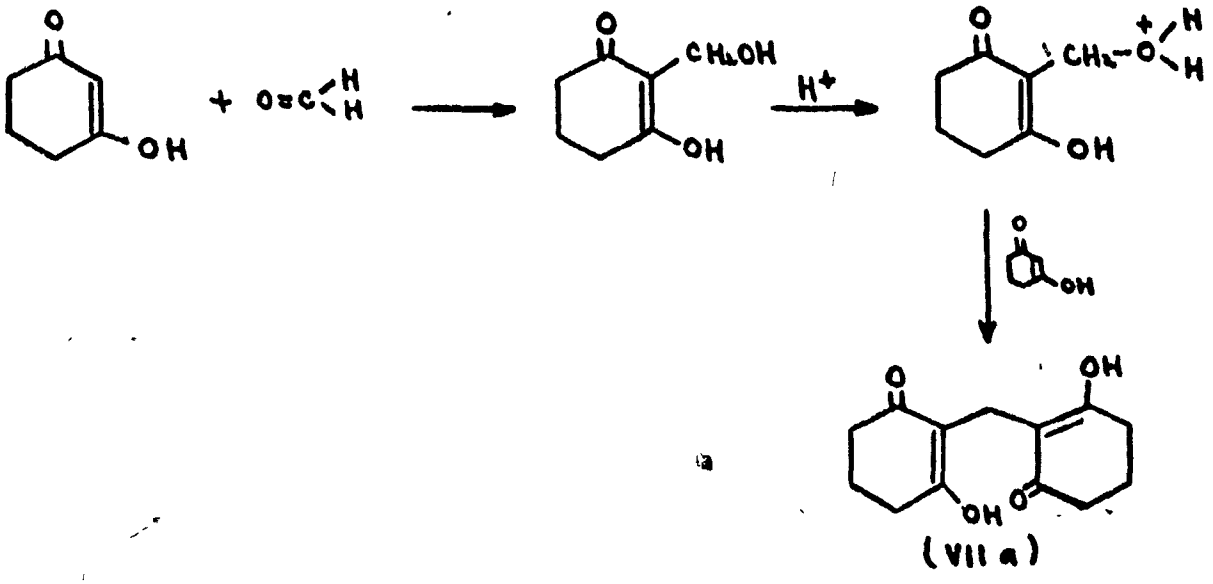


(VII a) 55% (VII b) 12%

(VII a) is known to result from the interaction of cyclohexane-1,3-dione and formaldehyde (14).

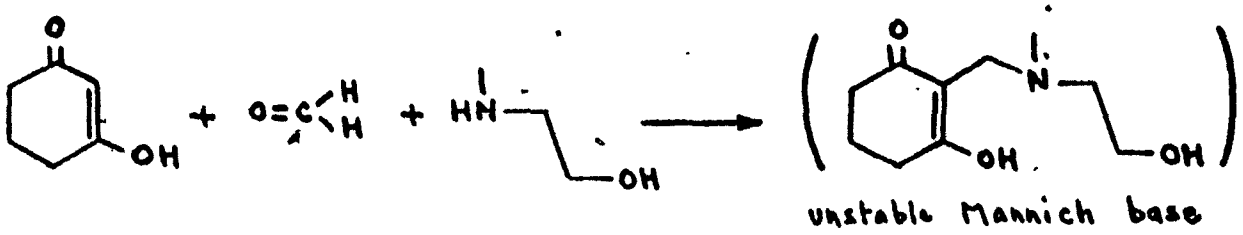
In the case of the attempted Mannich reaction, two types of mechanisms can be thought of to explain the formation of the adduct (VII a).

(1)

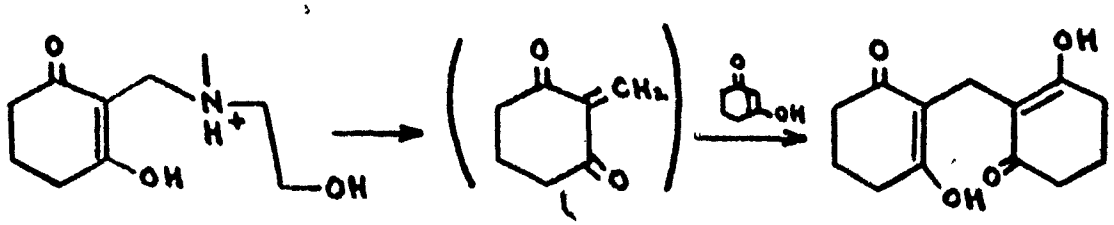


(VII a)

(2)



unstable Mannich base



The mechanism (2) involves the formation of an unstable Mannich base; the mechanism (1) implies only interaction of cyclohexane-1,3-dione and formaldehyde .

Two points may be noticed here :

i) The adduct (VIIa) may be possibly be stabilized by hydrogen bonds, as seen from IR spectrum (15) .

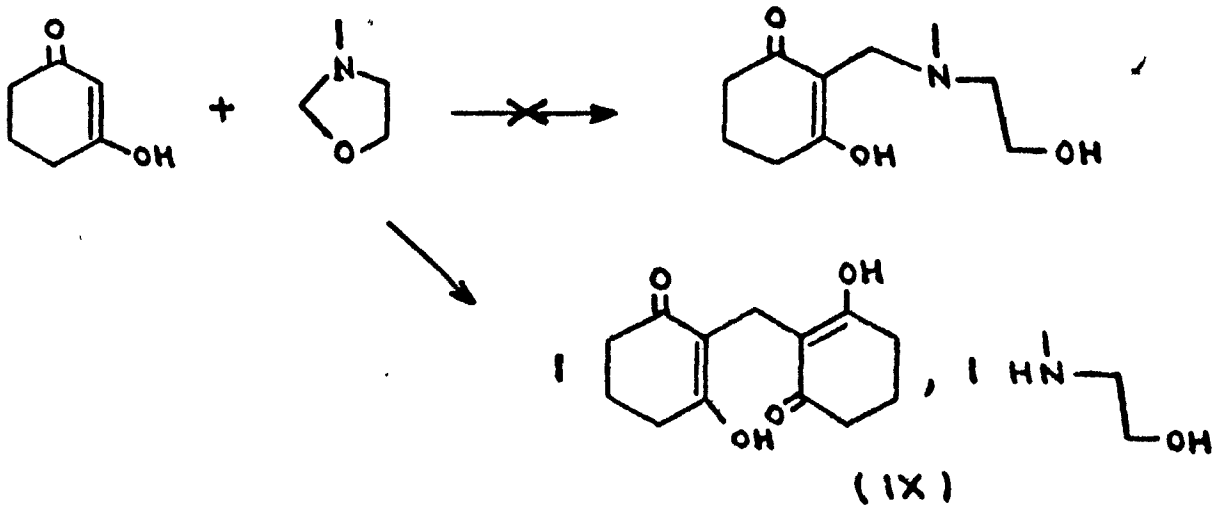
ii) Cyclohexane-1,3-dione is well known to be a good nucleophile (16) .

With these considerations in mind, a modification involving the reaction, in anhydrous conditions of cyclohexane-1,3-dione and 3-methyl oxazolidine (VIII) was tried. 3-Methyl oxazolidine was easily obtained by interaction of N-methylethanolamine and formaldehyde, followed by distillation .

It was hoped that if the reaction between cyclohexane-1,3-dione and (VIII) was more rapid than the attack of cyclohexane-1,3-dione on the unstable base (VI), (VI) could be isolated .

The reaction between cyclohexane-1,3-dione and 3-methyl oxazolidine afforded a solid compound, which could be purified by several reprecipitations in benzene . The physical data of this compound (IX) agreed with the mentioned structure, that is a (I:I) adduct of (VIIa) and N-methylethanolamine . This was further confirmed by washing carefully

a solution of (IX) with an aqueous acidic solution and isolating (VII a) .

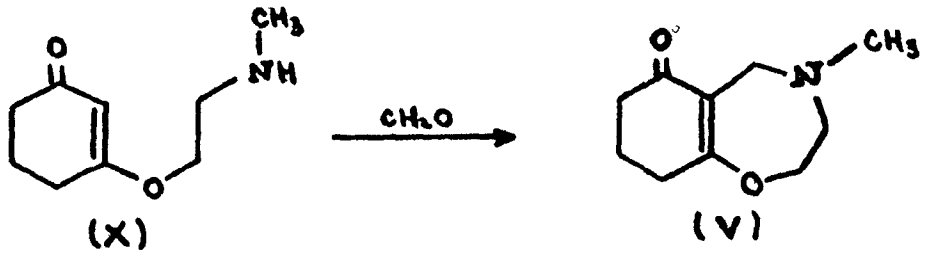


(IX)

ii) Attempts of internal Mannich reactions

As seen previously the desired Mannich base (VI) of cyclohexane-1,3-dione could not be isolated; the results obtained then suggested that a derivative of the 1,3-dione, and not the dione itself, should be used.

The study of the possibility of an internal Mannich reaction on the enol ether (X), 3-(N-methyl-(β-amino)ethoxy)--2-cyclohexen-1-one, was undertaken.



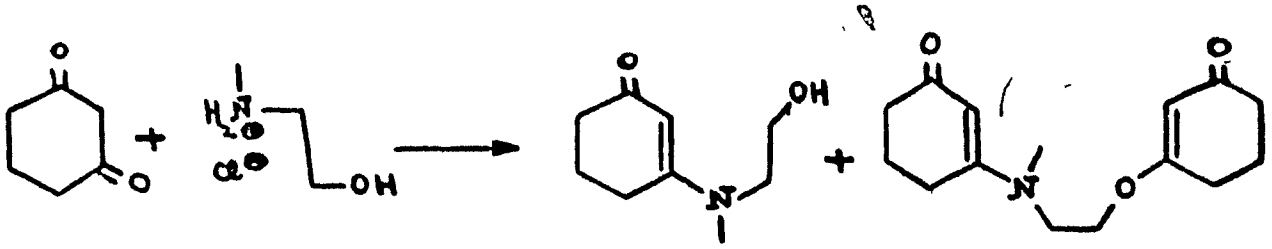
(X) (V)

However, difficulties were experienced in the attempted synthesis of (X) .

iii) Attempted synthesis of 3-(N-methyl-(β-amino)ethoxy)--2-cyclohexen-1-one (X)

Cyclohexane-1,3-dione analogues are known to react readily with alcohols (11) to give the corresponding 3-alkoxy-2-cyclohexen-1-one. However, they have been reported too to react readily with amines (17,18,19) .

The reaction of cyclohexane-1,3-dione with the hydrochloride salt of N-methylethanolamine, with removal of the water formed by azeotropic distillation, gave a compound identified as N-methyl, N-(β-ethanol) 3-amino 2-cyclohexen-1-one (XI) along with a small quantity of a compound identified as (XII) .



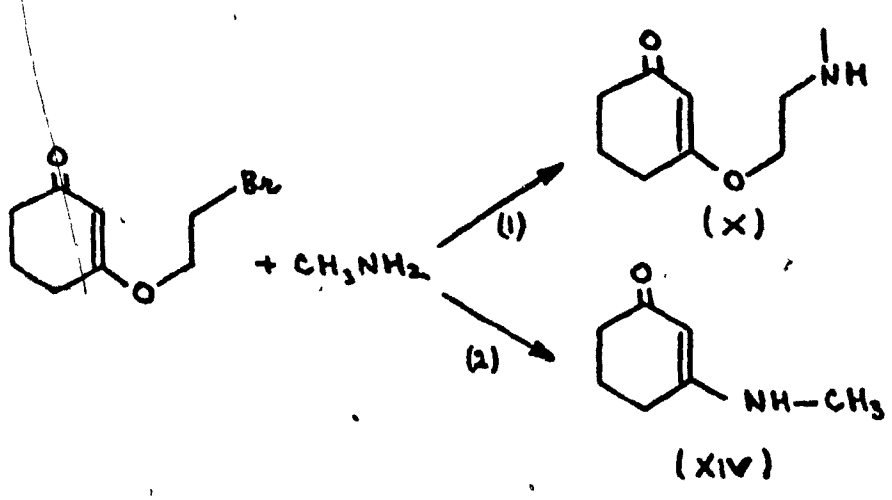
(XI) (XII)

(XII) may possibly be formed by further reaction of (XI) and cyclohexane-1,3-dione.

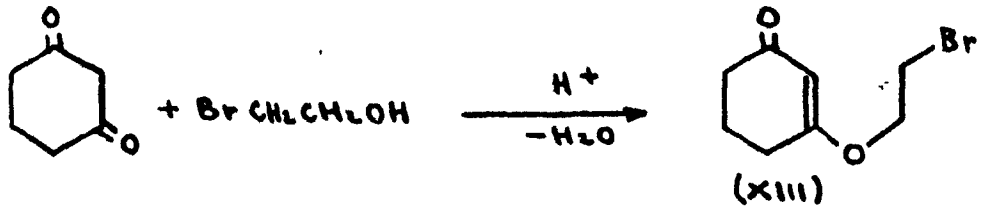
So, apparently, the nucleophilicity of the amino group, even with the amine in the salt form, prevented the formation of the desired enol ether in appreciable amount.

Another route to get (X) was tried; this route involved the attack of N-methylamine on the bromo derivative (XIII), 3-(β-bromoethoxy)-2-cyclohexen-1-one . However, enol ethers derivatives of cyclohexane-1,3-dione have been reported to undergo easily displacement reactions when reacted with nucleophiles (8,10).

So, two products might be obtained here, depending upon the relative ease of the displacement of the alkoxy part compared to the displacement of the bromine, in the reaction with N-methylamine .



The bromo derivative (XIII), was easily obtained by reaction of cyclohexane-1,3-dione and 2-bromoethanol .



When (XIII) was treated with methylamine, only 3-(N-methylamino)-2-cyclohexen-1-one (XIV) was obtained .

The study of the reaction by UV spectroscopy was done too, showing a progressive decrease of the UV absorption at 249 mμ (enol ether system) and increase at the same time of the UV absorption at 290 mμ (enamine system).

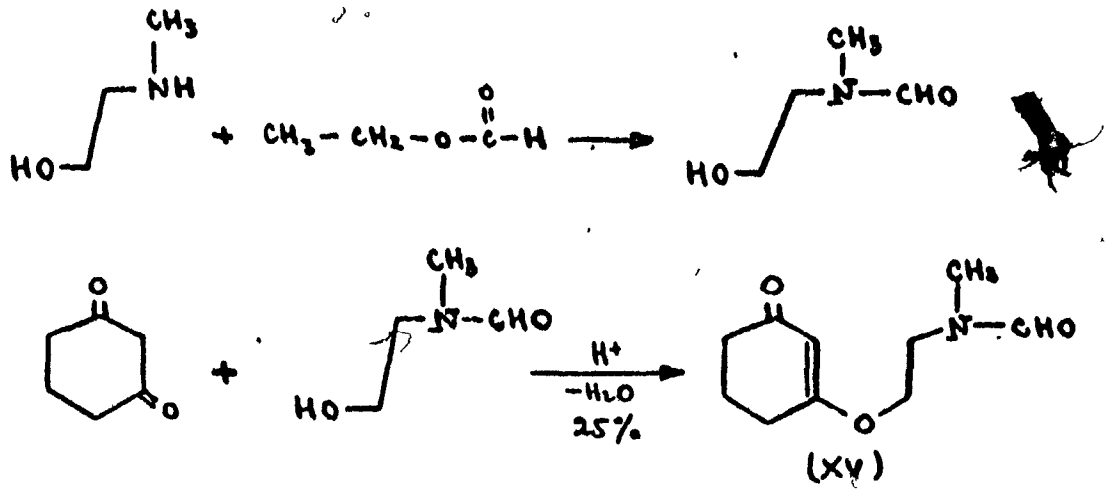
This was an indication that either no amino derivative (X) is formed at all or that it reacts rapidly once formed and cannot be isolated .

Other studies of some derivatives of 1,3-diones

These studies have been done in relation with schemes not mentioned here.

(i) Synthesis of 3-(N-methyl, N-formyl-(β-amino)ethoxy)--2-cyclohexen-1-one (XV)

The compound (XV) was obtained by the following route.

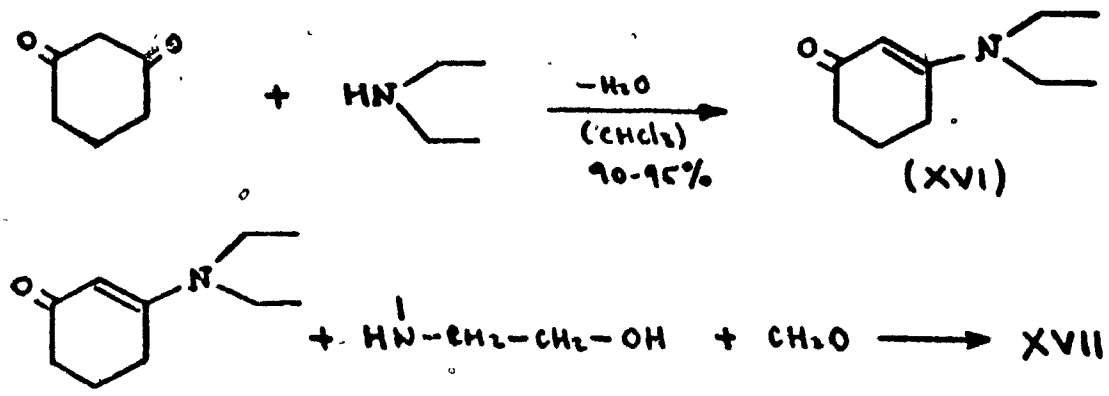


(XV) was purified by preparative thin layer chromatography. The low yield of (XV), compared to the formation of other 3-alkoxy-2-cyclohexen-1-ones, may be due to the high polarity of (XV). An appreciable amount of (XV) may be in effect lost during the work-up.

ii) Study of the Mannich reaction of an enamino ketone

We were interested to know if compounds such 3-(N,N-diethylamino)-2-cyclohexen-1-one (XVI) could react in a Mannich reaction and what would be the resulting

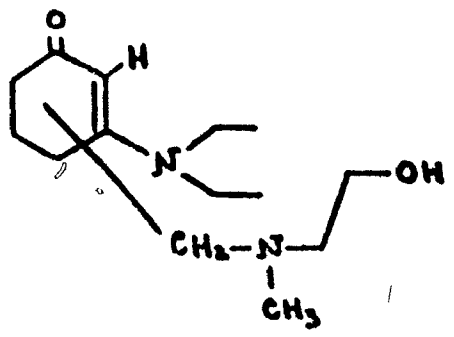
product. More precisely, we were interested to know if the substitution would be in position 2 or not, in the case where the Mannich reaction would be possible.



(XVI) was obtained in good yield by reaction of cyclohexane--1,3-dione and diethylamine in chloroform .

A product (XVII) was isolated in the Mannich reaction mentionned above, and could be separated easily by thin layer chromatography. Its spectral properties indicated that (XVII) was a Mannich base resulting from the reaction of (XVI), but that the substitution had not been effected in position 2 .

(XVII) =



Conclusion of the study of the derivatives of 1,3-diones

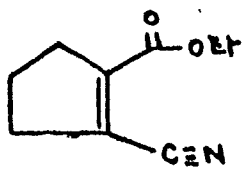
The reactivity of some enol ether derivatives of cyclohexane-1,3-dione in a Diels-Alder reaction, under the usual conditions, was tested. It was found that these derivatives reacted poorly and afforded mixtures not easily separated. The study of this Diels-Alder reaction under other reaction conditions (solvent, catalyst) was not undertaken because of the difficulty in getting the desired dienophile, as seen previously in the attempt to obtain the bicyclic enol ether (V) starting with cyclohexane-1,3-dione, and as deduced from what is reported in the literature concerning the chemistry of the derivatives of cyclopentane-1,3-dione.

The work described in the following chapters takes account of these results, in the selection of possible routes for the synthesis of analogues of batrachotoxinin A.

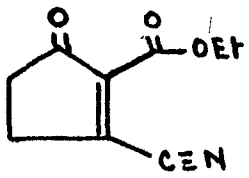
CHAPTER II

Study of the Diels-Alder reaction with 2-cyano-1-cyclopentene-1-carboxylic acid ethyl ester.

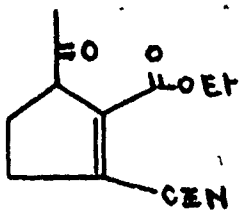
Preliminary considerations



(XVIII a)



(XVIII b)



(XVIII c)

The use of the dienophiles (XVIIIa,b,c) gives a means to avoid two difficulties met previously:

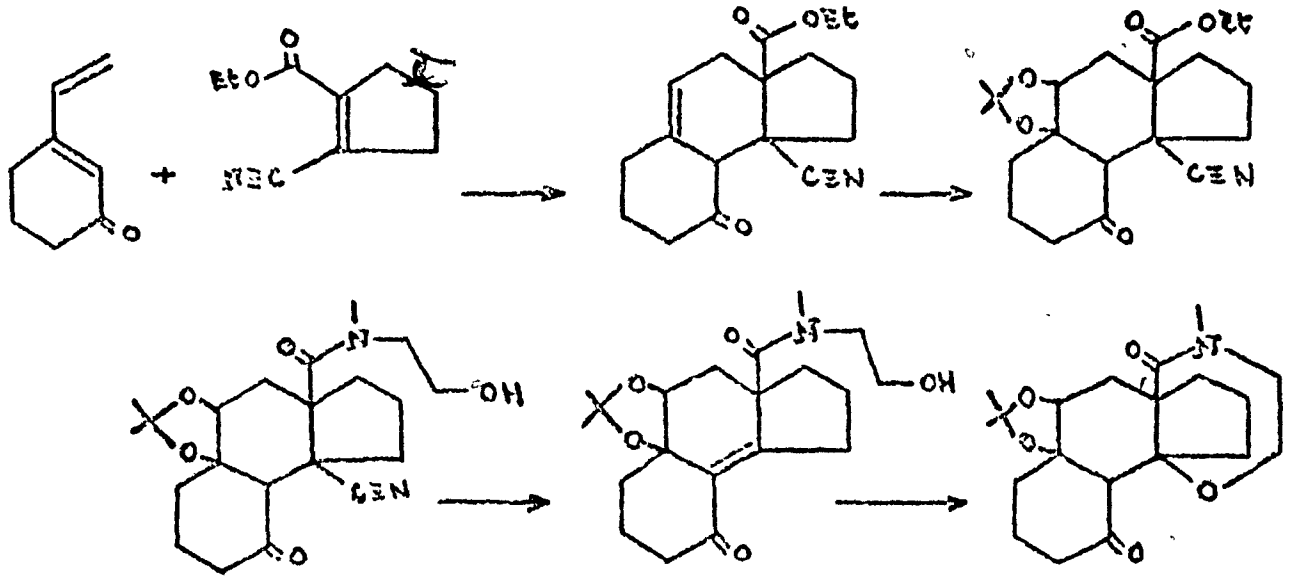
1) difficulty of the synthesis of the desired derivatives of 1,3-diones.

2) poor reactivity of the derivatives in Diels-Alder reactions.

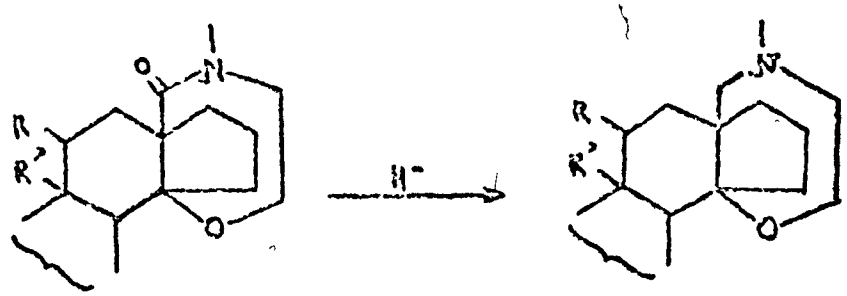
As shown in the following scheme, the ester group in the compounds (XVIII) could allow the introduction of an amide moiety, precursor of the amine part.

The cyano group could possibly be used after the Diels-Alder addition, for the introduction of a double bond conjugated with the ketone group of the Diels-Alder adduct (20).

The formation of the ether link of the propellane structure (26,27) is based on a Michael addition (21).

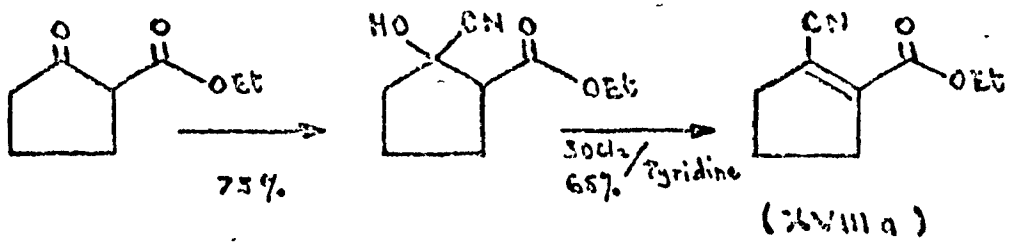


The amide part, obtained by attack of ester group by N-methylethanolamine is a convenient precursor of the amine group (22). This amide group permits to avoid the possible side-reactions due to the nucleophilicity of the amine group, for several critical steps.

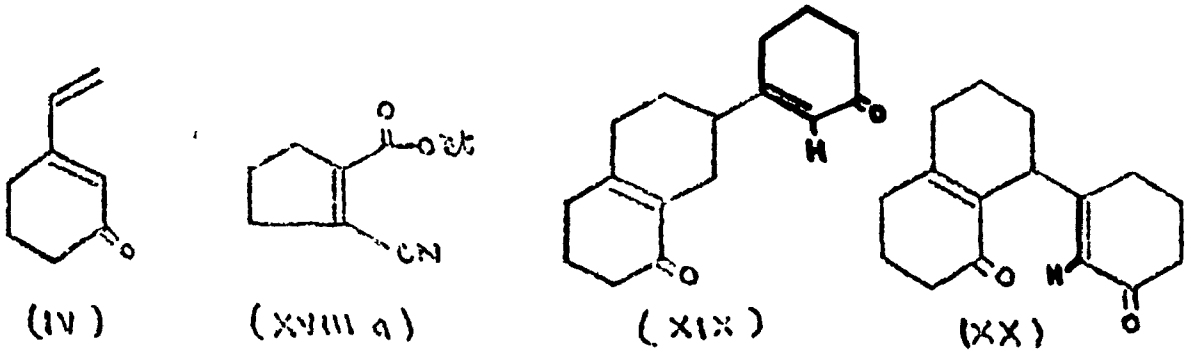


Preparation of 2-cyano-1-cyclopentene-1-carboxylic acid ethyl ester (XVIIIa)

(XVIIIa) was prepared by dehydration of the cyanohydrin of ethyl 2-oxocyclopentane-carboxylate. Several dehydration reactions were studied, taking account of the particular unstability of the considered cyanohydrin. The most convenient reaction found was the reaction with $SOCl_2$-pyridine (25). The cyanohydrin was prepared according to the procedure given in reference (24). The overall yield for the preparation of 2-cyano-1-cyclopentene-1-carboxylic acid ethyl ester was 50 %.



Reaction of (XVIIIa) and 3-vinyl-2-cyclohexen-1-one



3-Vinyl-2-cyclohexen-1-one (IV) and 2-cyano-1-cyclopentene-

-1-carboxylic acid ethyl ester were heated in a sealed tube, in a ratio (1:1.3), at 160-175°C for 20 hours. The thin layer chromatography of the reaction mixture showed only one spot besides the spot due to the starting material (XVIIIa). The compound that was obtained gave a positive test with 2,4-dinitrophenyl hydrazine on thin layer chromatography. It could be easily isolated by thin layer chromatography on silica gel.

The physical data (NMR: singlet at δ: 5.6(1H); singlet at δ: 3.4(1H); multiplet at δ: 1.5-2.6(17H), UV: λ_{max}^{EtOH}: 242 mμ, $\varepsilon \sim 12{,}500$) suggest for this compound the formula (XIX) or (XX), that is to say a dimer of 3-vinyl-2-cyclohexen-1-one produced in a Diels-Alder condensation. (XVIIIa) was recovered quantitatively. The yield for the dimerisation was 32%, after isolation on silica gel.

The Diels-Alder reactions with compounds (XVIII) were not investigated further.

CHAPTER III

Diels-Alder reactions with dimethyl acetylenedicarboxylate.

Preliminary considerations

Acyclic dienes and acetylenic compounds undergo cycloaddition to give 1,4-dihydroaromatic derivatives with varying ease; these 1,4-dihydroaromatic derivatives may in turn be used as dienophiles themselves. The Diels-Alder reactions of acetylenes have been reviewed adequately (28).

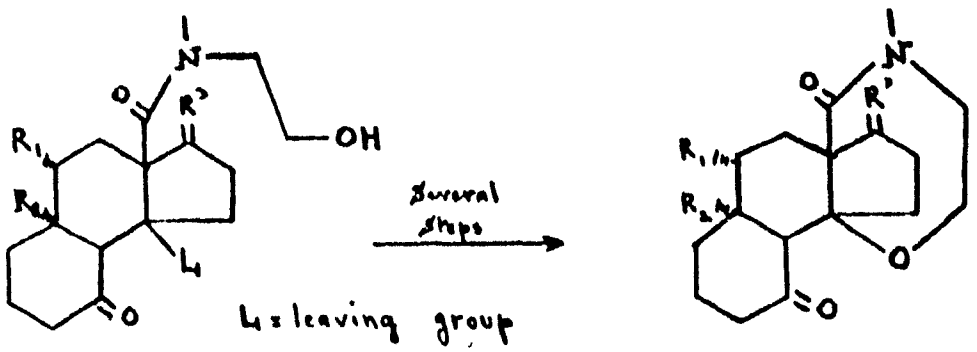
In this chapter, the possibility of using Diels-Alder reactions with dimethyl acetylenedicarboxylate has been studied .

Two points, more particularly, seemed worth to be considered :

a) first, the possibility of obtaining the desired 1,4-dihydroaromatic derivatives in good yield,

b) secondly, the possibility of differentiating between the two ester groups in the adduct .

If one could answer positively to these two points, one could then devise a series of reactions leading to a compound (XXI), with a chain terminated by an alcohol function and having a leaving group in the proper places; in other words, one would have a way to obtain some attractive intermediates analogous to those the synthesis of which has been attempted in the preceding chapter .



(XXI)

The two dienes chosen for a model study were 3-vinyl-2-cyclohexen-1-one (IV) and 3-vinyl-2-cyclohexen-1-ol (XXII).

Diels-Alder reaction with 3-vinyl-2-cyclohexen-1-ol

(i) Synthesis of 3-vinyl-2-cyclohexen-1-ol

Aluminium hydride has been used (29,30) to convert various unsaturated carbonyl groups to the corresponding unsaturated alcohols. Thus, cinnamaldehyde and ethyl cinnamate could be reduced smoothly (29), in excellent yield. Methyl phenylpropiolate was converted to phenylpropargyl alcohol.

A useful comparative study of different hydrides has been done (30); it has been found that aluminium hydride, lithium tri-t-butoxyaluminium hydride and sodium borohydride reduce specifically the carbonyl group, the double bond, and both the

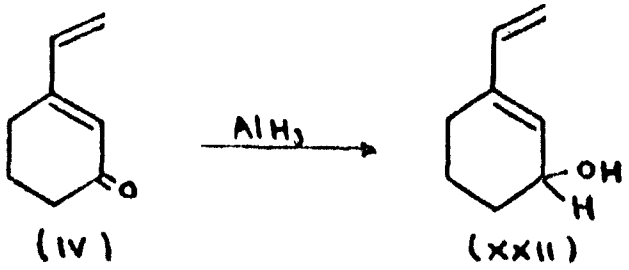
carbonyl group and the double bond respectively, of a conjugated cyclopentenone .

We found that AlH_3 was convenient to convert 3-vinyl-2-cyclohexen-1-one into 3-vinyl-2-cyclohexen-1-ol. Apparently, only one major product was obtained (1 spot on the thin layer chromatography on silica gel of the reaction mixture).

Aluminium hydride was employed as generated in situ, from lithium aluminium hydride following the stoichiometry:

$$3\ LiAlH_4 + AlCl_3 \rightarrow 4AlH_3 + 3LiCl\ .$$

The conjugated alcohol (XXII) could be easily purified by preparative thin layer chromatography on silica gel .

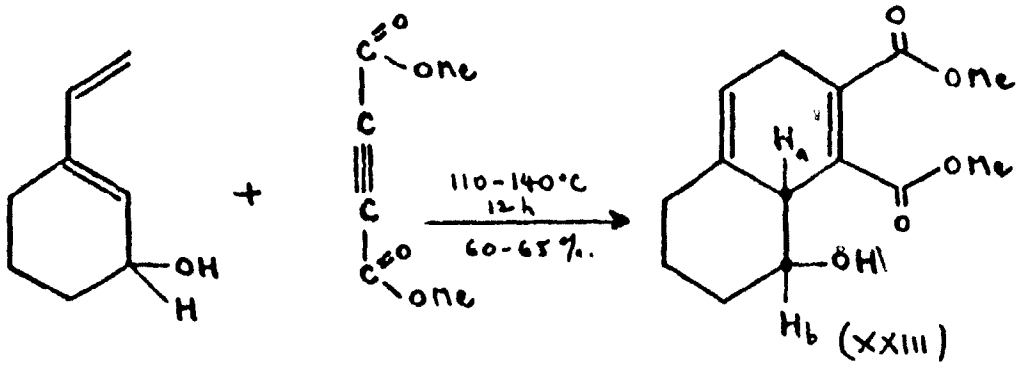


(IV) (XXII)

(ii) Diels-Alder reaction of 3-vinyl-2-cyclohexen-1-ol and dimethyl acetylenedicarboxylate

The Diels-Alder adduct (XXIII) of 3-vinyl-2-cyclohexen-1-ol (XXII) and dimethyl acetylenedicarboxylate was obtained by heating the two reagents, in a ratio 1:2, in a sealed tube, for 12 hours at 110°-140°C. Thin layer

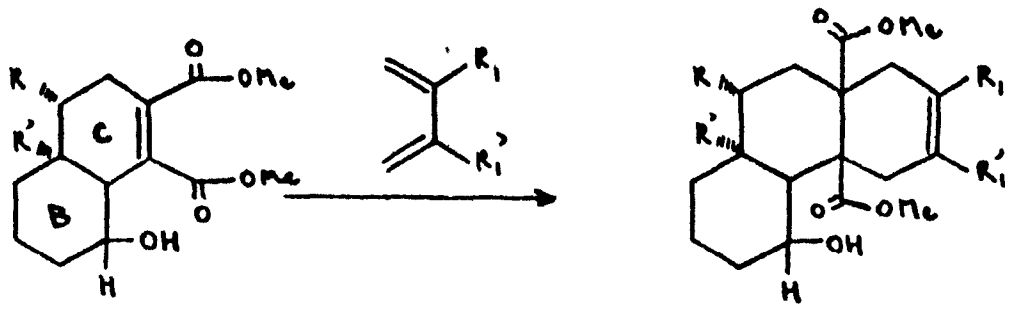
chromatography on silica gel of the reaction mixture showed only one spot besides the spots corresponding to the starting materials. The yield of isolated adduct was 60-65%. The reaction conditions were not fully investigated at this stage and it is possibly that milder conditions, lower temperature and shorter time, could be found. Such a study of the reaction conditions might be useful in the case of the synthesis of a closely related analogue of batrachotoxinin A, starting with a diene more fragile than 3-vinyl-2-cyclohexen-1-ol.



(XXIII)

The determination of the stereochemistry of the two hydrogen atoms H_a and H_b, in the adduct (XXIII), was attempted without success.

It was felt that the knowledge of this configuration might be useful, at the stage of a second Diels-Alder reaction using (XXIII) as dienophile, for the building of the D ring.



(a) R = R' = OH (b) RR' = —O—

(a') $R_1 = R_1' = H$ (b') $R_1 = Me$, $R_1' = H$

The attempt of determination of the relative positions of these two hydrogen atoms consisted basically in:

(i) building the molecular models of the possible isomers, calculating the angle H_a-C-C-H_b and studying the NMR spectrum of the obtained compound.

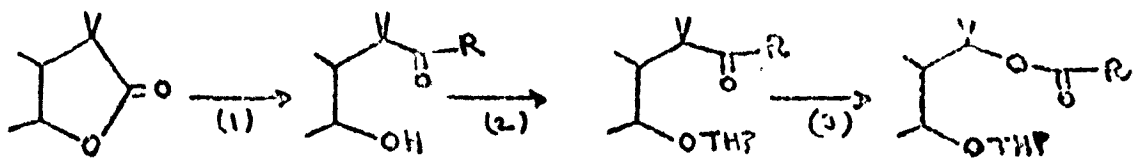
(ii) preparing a derivative of (XXII) such as the acetate, doing the Diels-Alder reaction with this derivative and dimethyl acetylenedicarboxylate, and comparing the adduct obtained with the corresponding derivative of (XXIII). This study would have given an indication of the factors affecting the stereochemistry of the reaction. Unfortunately, the attempts to prepare various suitable derivatives of 3-vinyl-2-cyclohexen-1-ol were not successful.

(iii) comparing by vapor phase chromatography the silyl derivative of the adduct (XXIII), and the reaction

mixture of the Diels-Alder reaction of the corresponding volatile derivative of the dienic alcohol (XXII) and dimethyl acetylenedicarboxylate. This study by VPC was not conclusive and the results obtained seem to indicate that the volatile derivative of (XXIII) undergoes a retro Diels-Alder reaction under the conditions used .

(iii) Study of the lactonisation reaction of the Diels-Alder adduct (XXIII)

The formation of a five-membered lactone from the Diels-Alder adduct (XXIII) seemed to be an attractive possibility. It was felt, in effect, that if an appreciable difference in reactivity between the five-membered lactone and the remaining ester group could be shown, one could use a series of reactions to transform this lactone ring into a leaving group and an alcohol function in the proper places; such a series of reactions is described in the following scheme.

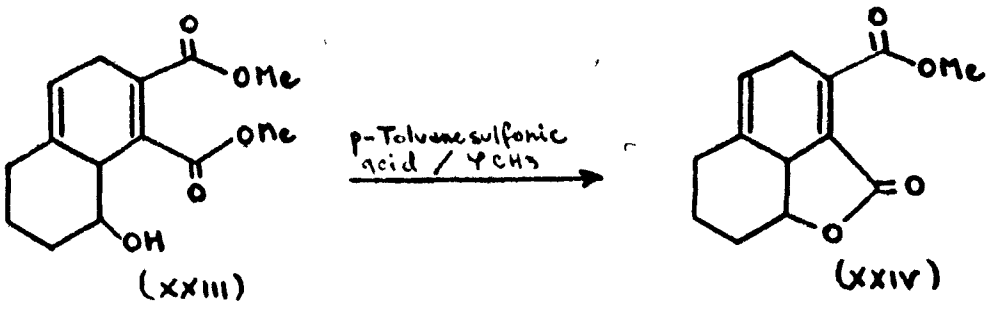


In this scheme, the first step, the opening of the five-membered lactone to give the corresponding keto alcohol might be done using a suitable Grignard reaction (32). The use of other organometallic reagents could be also considered (33).

The cyclisation of hydroxy esters leading to the formation of five membered lactones is known to occur under acidic conditions. The lactonisation of the Diels-Alder adduct (XXIII) was tried under various reaction conditions. In particular, the azeotropic distillation with toluene, with p-toluenesulfonic acid as catalyst , seemed promising, and the lactone formation with these conditions was followed by thin layer chromatography on silica gel and infra-red spectroscopy. After 8 hours, the thin layer chromatography of the reaction mixture showed the presence of only one new spot, the R_f of which was greater than the R_f of the starting material (XXIII). The infra-red spectrum of this reaction mixture showed the presence of a new band corresponding to the expected lactone band along with the ester band present in the infra-red spectrum of the hydroxy ester (XXIII). The intensities of these two bands were approximatively in the ratio 3:5, respectively.

These data strongly support the formation of the

lactone (XXIV); (XXIV) however was not separated at this stage.

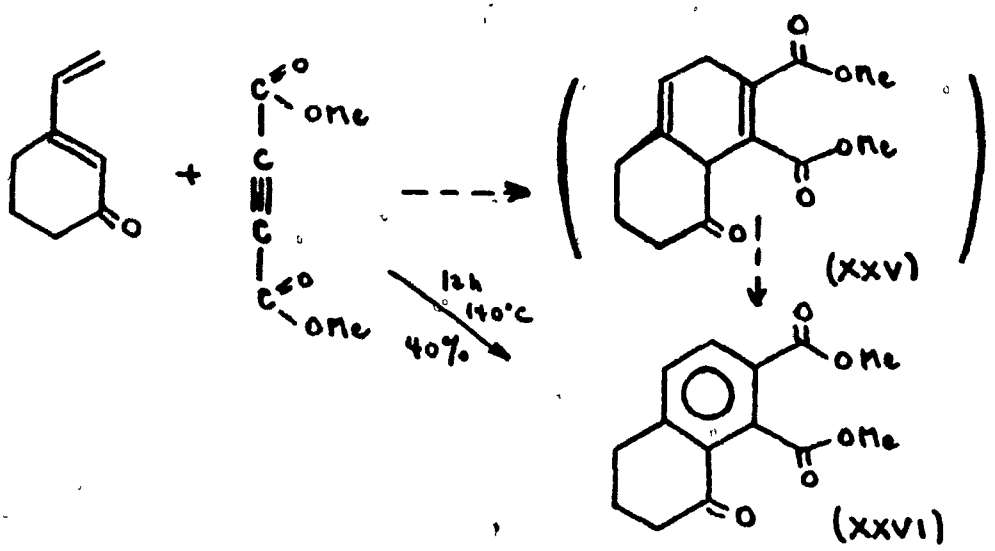


(XXIII) (XXIV)

Diels-Alder reaction with 3-vinyl-2-cyclohexen-1-one

The Diels-Alder reaction with 3-vinyl-2-cyclohexen--1-one and dimethyl acetylenedicarboxylate was undertaken in order to get the corresponding 1,4-dihydroaromatic adduct (XXV). This adduct is attractive since it could be used in modifications of the preceding scheme; one would condense the ester function and a group derived from the keto group, for example oxime or amine, to lead to a five or a six-membered cycle. This would greatly increase the possibility of distinguishing between the two ester groups in the Diels-Alder adduct obtained; in effect, this would mean to compare the reactivities of the five or six-membered cycle and the remaining ester group towards reagents such as Grignard reagents in the case where the opening of the

cycle is relatively easier, or reagents such as secondary amines in the other case .



However, the Diels-Alder reaction of 3-vinyl-2-cyclohexen-1-one (IV) and dimethyl acetylenedicarboxylate led to the aromatic compound (XXVI), the formation of which can be explained by aromatisation of the cycloadduct (XXV). (XXVI) was isolated on thin layer chromatography on silica gel; the yield was 40%, after separation

CHAPTER IV

Other studies

Reactions with dimethyl maleic anhydride

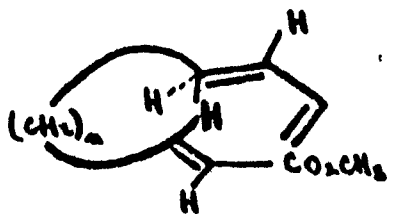
The possibility of intramolecular Diels-Alder reactions applicable to the synthesis of analogues of batrachotoxinin A was considered. Intramolecular Diels-Alder reactions could be very attractive. The suitable choice of the number and type of atoms bridging the diene and dienophile moieties could give a means to control the stereochemistry of the reaction, and obtaining only the desired adduct. The favorable entropy factor offered by intramolecular processes could facilitate the reaction; in effect, the low activation entropy values observed for Diels-Alder reactions support a transition state in which the diene and dienophile are rather rigidly oriented with respect to one another (35, 36, 37).

Several cases of intramolecular Diels-Alder reactions have been reported (38-42). An interesting study has been done by H.O. House and T.H. Cronin (43), who studied the thermal cyclisation of trans, trans and cis, trans isomers of methyl 2,6,8-nonatrienoate and of methyl 2,7,9-decatrienoate (Scheme I,a).

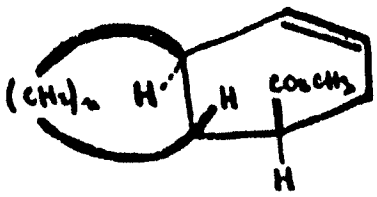
Another interesting case has been reported by D. Bilovic (44). By mixing maleic anhydride and (2-furfuryl) aniline at room temperature, a precipitate of N,N-furfurylmaleamic acid was obtained which by further heating or by solution in ethanol

Scheme 1

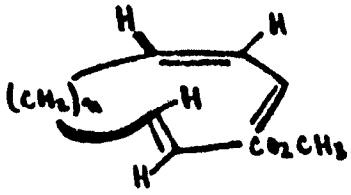
(a)

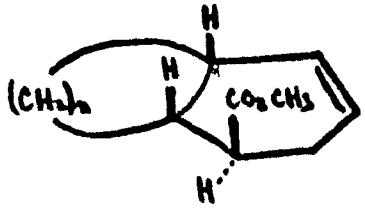


4a, n : 2
b, n : 3

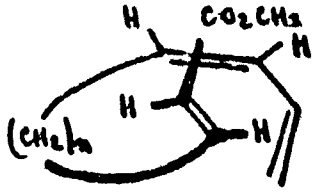


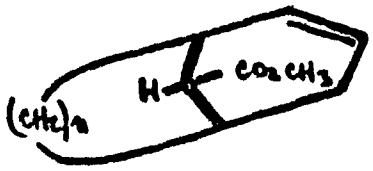
9, n : 2
6, n : 3





10, n : 2
7, n : 3

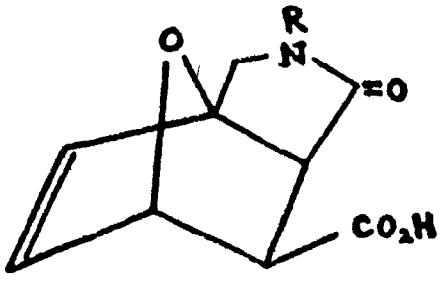




3a, n : 2
b, n : 3

11, n : 2
8, n : 3

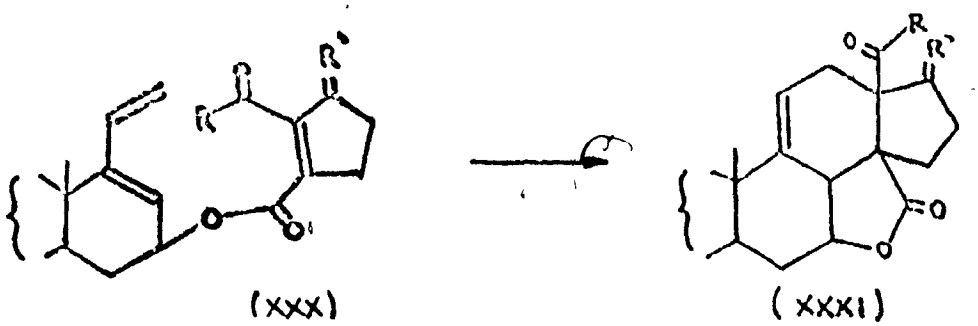
(b)



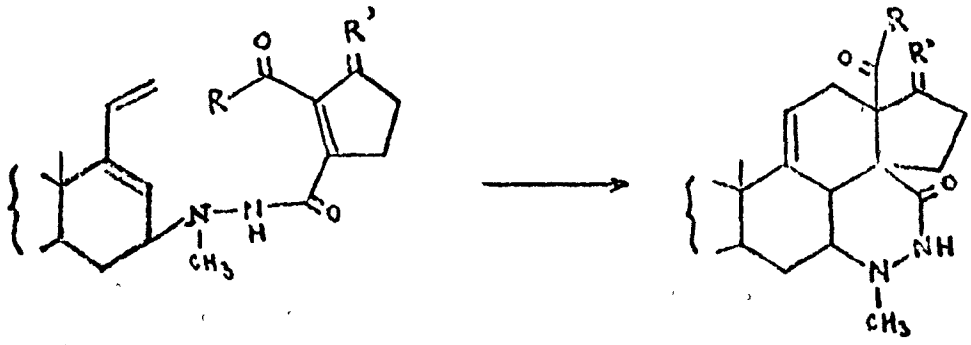
underwent an intramolecular reaction to give the Diels-Alder adduct (Scheme I,b).

Examples of reactions possibly applicable to the synthesis of analogues of batrachotoxinin A are described below.

It must be noticed that the choice of the bridge between the diene and the dienophile parts must be conditioned not only by the stereochemistry of the Diels-Alder reaction, but also by the feasibility of further cleavage of this bridge leading to compounds analogous of (XXI) of Chapter III.

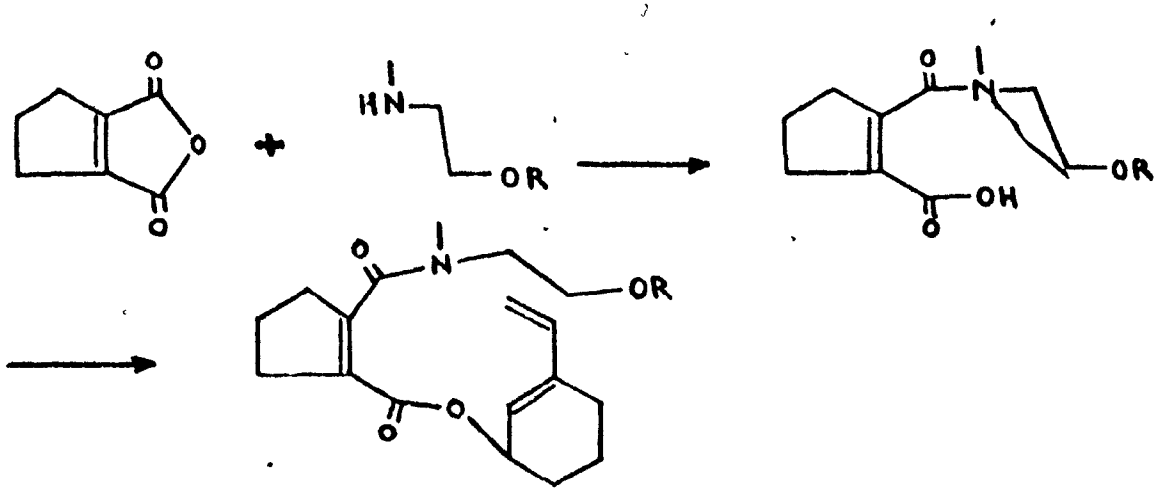


(XXX) (XXXI)



(i) Study of the opening of dimethyl maleic anhydride by N-methylethanolamine

To prepare the compound (XXX), one can use a sequence of reactions such as the one below.



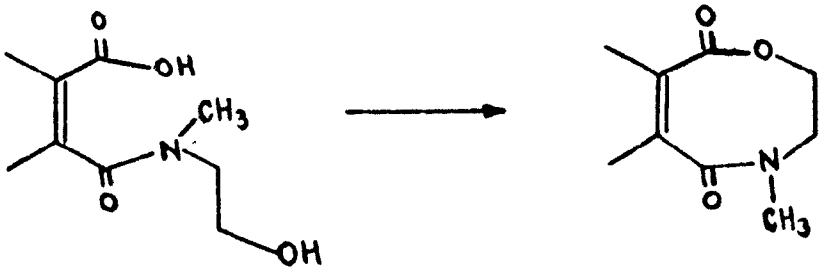
The first step involves the opening of the anhydride group by N-methylethanolamine. This reaction was thought, for various theoretical reasons, to be possibly more difficult than the corresponding opening of maleic anhydride.

A model study to determine the conditions of this first step was thus undertaken, using dimethyl maleic anhydride.

Dimethyl maleic anhydride was heated, usually for 12 hours, in various solvents, with an excess (4 to 6 fold) of N-methylethanolamine . After removal of the amine, a solid compound, which precipitated upon addition of anhy-

drous ether to the reaction mixture, was obtained in relatively low yield (10-15%). This compound was hygroscopic. Its physical data agreed with those of the monoacid (XXXIV).

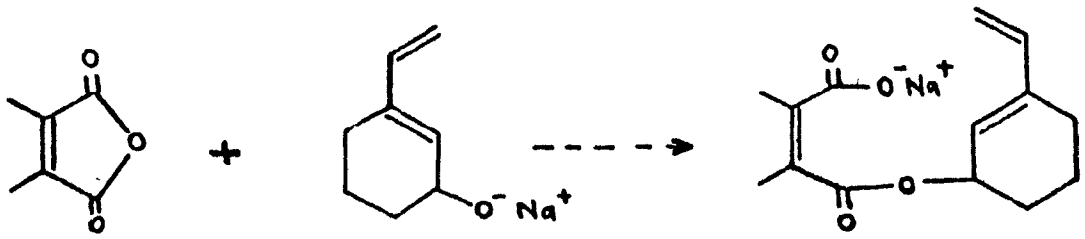
For further identification, (XXXIV) was treated with acetic anhydride in pyridine, at room temperature, for 15 hours. The resulting compound, identified (NMR, mass spectrometry, IR) as the cyclic compound (XXXV), was obtained in good yield (70-80%).



(XXXIV) (XXXV)

The yield and the mild conditions for the formation of this eight-membered cycle were somehow surprising.

(ii) Study of the opening of dimethyl maleic anhydride by the sodium salt of 3-vinyl-2-cyclohexen-1-ol



The opening of dimethyl maleic anhydride by the sodium salt of 3-vinyl-2-cyclohexen-1-ol was attempted. After work-up, no monoacid could be isolated. The poor results of this reaction may be explained by the possibility for the monoacid to give back dimethyl maleic anhydride during the work-up.

Heating the reaction mixture, after addition of the sodium salt of 3-vinyl-2-cyclohexen-1-ol, overnight failed to give the expected adduct.

EXPERIMENTAL

The melting points were taken on a Gallenkamp melting point apparatus in open end capillary tubes and were uncorrected. The analysis were carried out by Dr. Daessle, Montreal, and C.Beller, Gottingen, Germany. Infrared spectra were taken on a Perkin-Elmer 337, 257 and Infracord spectrometers using 1 millimeter sodium chloride cells . Ultraviolet spectra were measured in ethanol and pentane on a Beckman DK-1 recording spectrophotometer and on a Unicam SP-800 spectrophotometer . Proton magnetic resonance spectra were recorded on a Varian A-60 and A-60A instrument at 60 megacycles using carbone tetrachloride, chloroform-d_1,as solvents . Thin layer plates (20x20 cm) for preparative separations were made from Merck silica gel G, HF 254, and were 0.75 mm thick. Qualitative t.l.c. was usually carried out on microscope slides coated to a thickness of 0.50 mm .

The following abbreviations have been used in the description of the spectra : w.: weak ; m.: medium ; str.: strong ; sh.: sharp ; br.: broad .

Cyclohexane-1,3-dione: The product from Aldrich company (stabilized with 3% sodium chloride, 97%), was dissolved in benzene; the solution was filtered and concentrated. Cyclohexane-1,3-dione precipitated readily and was recrystallized from benzehe. It was sublimed when necessary giving a white solid.

3-Ethoxy-2-cyclohexen-1-one:From Aldrich company (99%), and distilled before use,
or : Prepared according to the procedure given in reference (8), with similar results (yield: 65-75%, b.p. : 115-121°/ 11 mm). The obtained product was compared by NMR and IR with an authentic sample.

3-Vinyl-2-cyclohexen-1-one (IV): To 8 ml of a solution 2.9 M vinyl lithium in tetrahydrofuran, 2.74 g of 3-ethoxy-2-cyclohexen-1-one in 5 ml anhydrous ether was added, dropwise, with vigorous stirring at 0°C, under nitrogen. After standing at room temperature 20h., the mixture was refluxed for 2 1/2 h.. The flask was then cooled with ice-salt and 7 ml distilled water was added dropwise; then at 0°C-10°C, 5 ml of an aqueous solution of sulfuric acid (1 volume concentrated sulfuric acid-2 volumes water) was added dropwise. The two phases were mixed vigorously for 2 h.. The aqueous phase was

separated and extracted once with 15 ml of ether. The combined ether phases were washed three times with 7 ml 5% aqueous sodium carbonate, four times with 7 ml distilled water. Ether was evaporated under vacuum, giving 3.7 g of a yellow liquid.

The product was separated on column chromatography (alumina activity II) or on preparative t.l.c. for smaller quantities (silica gel, solvent : $CHCl_3$-Et_2O 70:30). 3-Vinyl-2-cyclohexen-1-one was obtained as a colorless liquid (yield : 85-90%); it had to be kept in an etheral solution, under 0°C, protected from direct light. Otherwise, it decomposed, giving a yellow solid.

NMR : ($CDCl_3$) two quartets: δ: 6.6 (1 H), δ : 5.7 (3 H) (olefinic H), and a multiplet at δ: 1.8-2.7 (6 H).

UV : λ_{max}: 205 mμ , $\varepsilon \sim 16\,000$.

IR (liquid film) ν : 2930, 2880, 1670 (sh. at 1675 cm^{-1}), 1620, 1605, 1120 cm^{-1}.

Attempted Mannich reaction with cyclohexane-1,3-dione and N-methylethanolamine; obtention of (VII a) and (VII b):

To a solution of 261 mg of formalin in 15 ml 95% ethanol, was added a mixture of 753 mg of N-methylethanolamine and 2.5 ml of hydrochloric acid , and then 1.05 g of cyclohexane-1,3-dione . After standing at room temperature for 14 h., the mixture was refluxed for 2 ½h.. The flask was then cooled and kept under 0°C

overnight; 275 mg of white cristals (55%) (VII a) were collected. The solution was washed with ether, neutralized to $p_H 8$, with an aqueous 15% ammonium hydroxide solution. The solution was extracted with chloroform. By concentrating the solution, 56 mg of white cristals (VII b) were obtained, which could be cristallized from ether (12%).

(VII a); m.p.: 123-128°C (m.p. for the adduct cyclohexane-1,3-dione-formaldehyde reported to be: 132°C (14).)

NMR ($CDCl_3$): δ :2.8 (2 H), singlet.

:2.6-1.8 (12 H), multiplet.

IR : ν : 1600 (C=O), 1575 cm^{-1}(C=C).

mass spectrometry: m/e: 236 (M^+), 124 (possibly ).

(VII b): m.p.: 146-150°C, after two recristallizations from ether, m.p.: 160-162°C.

NMR ($CDCl_3$) : δ: 3.0 (2H), singlet.

: 2.6-1.8 (12 H), multiplet.

IR : ν : 1600 (C=O), 1625 cm^{-1}(C=C).

m/e : 218 (M^+) .

These data suggest that (VII b) is 1,8-dioxo octahydroxanthene; (VII b) was then compared (mixed m.p.: 160-2°C) with an authentic sample prepared according to the procedure given in reference (68) .

3-Methyl oxazolidine (VIII) : was prepared according to the procedure given in reference (69), by interaction of N-methylethanolamine and formaldehyde .
The purity of the liquid (b.p.:100-4°C, litt. b.p.:100°C) was confirmed by NMR (δ:4.3 (2H), singlet, N-$\underline{CH_2}$-O; δ:3.87 (2H), triplet, -O-$\underline{CH_2}$-CH_2-N ; δ:2.97 (2H), triplet, -N-$\underline{CH_2}$-CH_2-; δ:2.5 (3H), N-$\underline{CH_3}$) and by VPC .

(IX) from cyclohexane-1,3-dione and 3-methyl oxazolidine :
To 872 mg of 3-methyl oxazolidine (10^{-2} mole), distilled before use, in 30 ml anhydrous benzene, was added in several portions, with stirring, 835 mg (7.5×10^{-3} mole) of sublimed cyclohexane-1,3-dione. The mixture was refluxed for about 1 h., and became golden yellow. The solution was evaporated. A solid (1.3 g) was obtained which was washed with 10 ml petroleum ether. The solid was purified by several precipitations from benzene; 614 mg of a white yellow solid (IX) was obtained (80%).

(IX): NMR ($CDCl_3$) : δ : 3.8 (2H), triplet .
δ : 3.15, singlet; δ : 3.0, multiplet (total :5H)
δ: 2.16, singlet, δ : 2.5, multiplet (total :16 H).

UV : λ_{EtOH}^{max}: 258 mμ , $\varepsilon \sim 31\,000$.

IR : ν : 3350 (broad), 1600 cm^{-1} (sharp) .

mass spectrometry : m/e : 236 ($C_{13}H_{16}O_4^+$).

Analysis: Calculated for $C_{16}H_{23}O_8N$: C, 61.71; H, 8.09; N, 4.50.

found: C, 61.71; H, 7.98; N, 4.35.

Confirmation of the structure of (IX) : A solution was made by dissolving 168 mg of (IX) in 15 ml chloroform. This solution was washed with 1 ml 0.1 N hydrochloric acid solution, then with distilled water. The organic solution was dried over sodium sulfate and evaporated ; white cristals (98mg) of (VII a) were obtained (yield of the operation: 77%).

NMR : δ : 15 (2 H), broad singlet

: 2.9 (2 H), singlet

: 2.6-1.8 (12 H), multiplet.

N-methyl,N-(β-ethanol) 3-amino 2-cyclohexen-1-one (XI) and N,O-Bis (2-cyclohexen-1-one-3-yl)-N-methylethanolamine (XII) from cyclohexane-1,3-dione and N-methylethanolamine hydrochloride: Cyclohexane-1,3-dione (750 mg, 6.7 mmoles) and N-methylethanolamine hydrochloride (1.5 g, 14 mmoles) were refluxed in 30 ml anhydrous chloroform for 20 h. with removal of the water formed. Another 30 ml chloroform was added and the solution was washed several times with a 2N aqueous sodium bicarbonate solution, then with distilled water. The organic solution was dried over magnesium sulfate and

evaporated, and 1.02 g of residue was obtained. One part of this residue (300 mg) was separated by thin layer chromatography (silica gel HF 254+366, solvent: $CHCl_3$-MeOH 15:2), and (XI) (198 mg, 70%) was obtained as a colorless liquid, along with a small quantity of (XII) (34 mg, 15%) which was obtained as a colorless glass .

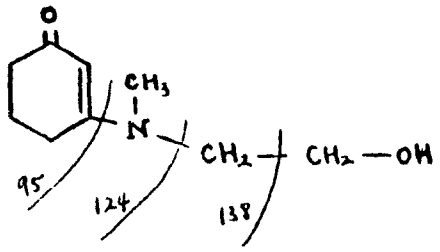
(XI): NMR ($CDCl_3$) δ : 5.2 (1H), singlet (olefinic proton)
: 4.4 (1H), broad signal (-O<u>H</u>)
: 3.65 (4H), quartet ($>N-CH_2-CH_2-O$)
: 3.05 (3H), singlet ($N-CH_3$)
: 2.8-1.8 (6H), multiplet (CH_2's of the ring)

UV : λ_{max}^{EtOH} : 297 mμ , ε_m 2.1 x 10^4 .

IR : ν : 3300 (br.), 1540 cm^{-1} (with shoulder at 1580 cm^{-1}, str., sh., enaminoketone system).

m/e : 169 (M^+), 138, 125, 124, 95 .

A possible breakage is suggested below :



Analysis: Calculated for $C_9H_{15}O_2N$: C, 63.88; H, 8.94; N, 8.28 .
Found : C, 63.29; H, 8.98; N, 8.10 .

(XII): NMR ($CDCl_3$): δ: 5.4 (1H), singlet, and 5.25 (1H), singlet (olefinic protons).
: 3.9 (4H), quartet (= N-CH_2-CH_2-O)
: 3.06 (3H), singlet (N-CH_3).
: 2.8-1.8 (12H), multiplet (CH_2's of the ring).

UV : λ^{max}_{EtOH}: 249 mμ ε: $1.69 \cdot 10^4$ (enol ether system)

and λ^{max}_{EtOH}: 296 mμ ε: $2.92 \cdot 10^4$ (enamine system)

IR : ν: 3300 (br.), 1620 (str., sh., with shoulder), 1550, 1130 cm^{-1}.

Preparation of 3-(β-bromoethoxy)-2-cyclohexen-1-one (XIII):

Cyclohexane-1,3-dione and 2-bromoethanol, in a ratio 1:1.1, were refluxed in benzene with a catalytic amount of p-toluenesulfonic acid, for 20 h., with removal of the water formed. The solution was washed with a sodium bicarbonate solution, then with distilled water. The organic phase was dried over magnesium sulfate and concentrated. After purification by thin layer chromatography on silica gel, 3-(β-bromoethoxy)-2-cyclohexen-1-one (XIII) was obtained as a colorless liquid (yield: 82%).

NMR ($CDCl_3$) : δ: 5.4 (1H), singlet (olefinic proton)
: 4.27 (2H), triplet
: 3.67 (2H), triplet
: 2.7 - 1.9 (6H), multiplet.

UV : λ_{EtOH}^{max}: 248 mμ , ε: 2.4×10^4

IR : ν: 3350, 2865, 1710 (str., sh., with shoulder at 1650), 1075 cm^{-1}.

Analysis : Calculated for $C_8H_{11}O_2Br$: C, 43.88; H, 5.06 ; Br, 36.48.

Found : C, 44.01; H, 5.11; Br, 36.12.

3-(Methylamino)-2-cyclohexen-1-one (XIV) from 3-(β-bromoethoxy)-2-cyclohexen-1-one and methylamine :

Methylamine hydrochloride (540 mg. 8 mmoles) was added to 3-(β-bromoethoxy)-2-cyclohexen-1-one (307 mg. 1.4 mmoles) in 20 ml absolute ethanol. A saturated sodium bicarbonate solution was added at room temperature to make the solution basic, and the mixture was kept at room temperature, with stirring, overnight. The mixture was concentrated and extracted with chloroform. The organic phase was dried over anhydrous magnesium sulfate and evaporated.

The residue was separated by thin layer chromatography (silica gel HF 254+ 366, solvent: $CHCl_3$-MeOH 70:10), and (XIV) (114 mg, 65%) was obtained as a colorless liquid and compared (tlc, NMR) with a sample prepared according to the procedure given in reference (71) .

NMR ($CDCl_3$) :

δ: 5.22 (1H), singlet (olefinic H)

: 3.08 (3H), singlet ($N-CH_3$)

: 2.8 - 1.8 (6H), multiplet (CH_2's of the ring.)

UV: λ_{EtOH}^{max}: 290 mμ ε: 2.01×10^4.

N-Formyl, N-methylethanolamine: In a flask protected from moisture, were placed 15.4g of N-methylethanolamine (0.2 mole) and 20.6g (0.28 mole) of ethyl formate was added dropwise. The mixture was allowed to warm up to room temperature, refluxed for 30 min. and kept at room temperature overnight. The reaction mixture was concentrated, and the residue distilled under reduced pressure (b.p.$_{30\ mm\ Hg}$: 130-135°C) and 14.4g of liquid (70%) were obtained.

NMR ($CDCl_3$) : δ : 8.2 (1H)

: 4.75 (1H), broad signal -(-O-H).

: 3.65 (4H), multiplet ($=N-CH_2-CH_2-O$)

: 3.05 and 3.01, (total 3H), 2 singlets, ($-N-CH_3$).

IR : ν : 3200 (str., sh.), 2900 (str., sh.), 1660 (str.,sh., carbonyl stretching vibration), 1090 cm^{-1}.

The purity of the liquid so obtained was checked by VPC (carbowax 20M column, t: 230°C).

Preparation of 3-(N-methyl, N-formyl-(β -amino)ethoxy)--2-cyclohexen-1-one (XV) :

In a flask protected from moisture, were placed 1.03 g (9.18 mmoles) of cyclohexane-1,3-dione, 930 mg (9.03 mmoles) of N-formyl, N-methylethanolamine and 150 mg of p-toluenesulfonic acid monohydrate in 40 ml anhydrous benzene. The mixture was refluxed for 12 hours with removal of the water formed. The mixture was allowed to cool to room temperature and was washed twice with 8 ml 2 N sodium carbonate solution, then with distilled water. The organic phase was dried over magnesium sulfate, evaporated, and 1.78 g of residue were obtained. After separation by thin layer chromatography (silica gel HF 254 + 366, solvent: $CHCl_3$-MeOH 80:10), 452 mg (25%) of (XV) were obtained as a colorless liquid .

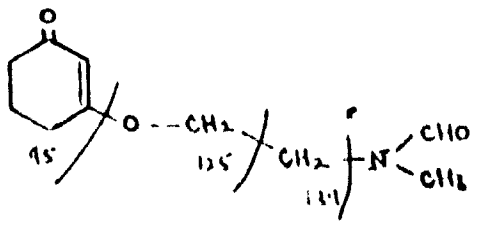
NMR ($CDCl_3$) : δ : 8.23 (1H), singlet ($-C\overset{H}{\leq O}$)
: 5.47 (1H), singlet (olefinic proton)
: 3.80 (4H), multiplet ($O-CH_2-CH_2-N<$)
: 3.05 and 3.15 (total: 3H), 2 singlets ($N-CH_3$)
: 2.85-1.65 (6H), multiplet (CH_2's of the ring)

UV : λ^{max}_{EtOH} : 247 mμ , ε: 2.5×10^4

IR : ν: 3350, 2870, 1715 (str., sh., with shoulder at 1650), 1660 cm^{-1} (str., sh.)

m/e = 197 (M^+), 149, 139, 126, 125, 96, 95.

A possible breakage pattern is suggested below =



Preparation of 3-(N,N-diethylamino)-2-cyclohexen-1-one (XVI)(75):

In flask protected from moisture were placed 4.48 g (4.10^{-2}mole) of cyclohexane-1,3-dione and 50 ml anhydrous chloroform. Diethylamine (14.6 g, 0.2 mole) was slowly added at room temperature; the mixture was refluxed for 8 h. and slowly concentrated. The residue obtained after evaporation under vacuum was dissolved in 100 ml chloroform. The solution was washed twice with 30 ml water and dried over magnesium sulfate. After evaporation under vacuum, 6.70 g of residue was obtained. A part (2 g) of this residue was purified by column chromatography (alumina activity III, solvents : chloroform-methanol) and 1.81 g (91%) of (XVI) was obtained as a colorless liquid, homogeneous on thin layer chromatography plate.

NMR ($CDCl_3$): δ : 5.03 (1H), singlet (olefinic H)

: 3.33 (4H), quartet ($N-\underline{CH_2}-CH_3$)

: 2.05-1.75 (6H), multiplet ($\underline{CH_2}$'s of the ring)

: 1.03 (6H), triplet (J: 8 Hz), ($N-CH_2-CH_3$)

UV : $\lambda^{max}_{dioxane}$: 270 mμ, ε: 2.0×10^4

IR : ν: 3310 (br.), 1545 (with shoulder at 1580), 1135 cm^{-1}.

(XVII) from the Mannich reaction of 3-(N,N-diethylamino)--2-cyclohexen-1-one and N-methanolamine :

In a 100 ml flask protected from moisture and fitted with a condenser and a magnetic stirrer, 486 mg (6.5 mmoles) of N-methylethanolamine and 484 mg (5.8 mmoles) of 40% formaldehyde solution, in 5 ml absolute ethanol were added to 935 mg (5.6 mmoles) of 3-(N,N-diethylamino)-2-cyclohexen-1--one in 10 ml absolute ethanol. The mixture was refluxed for two days, the reaction being followed by thin layer chromatography. The mixture was evaporated under vacuum and 1.63 g of residue (liquid) were obtained. This residue was dissolved into 60 ml of chloroform; this solution was washed with 15 ml distilled water. The aqueous phase was extracted with the same volume of chloroform. The organic phases were combined, dried over anhydrous magnesium sulfate and evaporated, giving 1.3 g of residue . A part(650 mg) of this residue was separated by thin layer chromatography (silica gel HF 254 + 366, solvent :

$CHCl_3$-MeOH 30:15), and 533 mg of (XVII) were obtained as a colorless liquid (75%).

NMR ($CDCl_3$): δ : 5.22 (1H), singlet (olefinic H)

: 3.68 (2H), quartet (J= 5.5 Hz),($-CH_2-O-$)

: 3.50 (1H), broad signal

: 3.33 (2H), quartet (J= 5.6 Hz),($>N-CH_2-$)

: 2.9-2 (total: 15H), multiplet with singlet at 2.4 ppm.

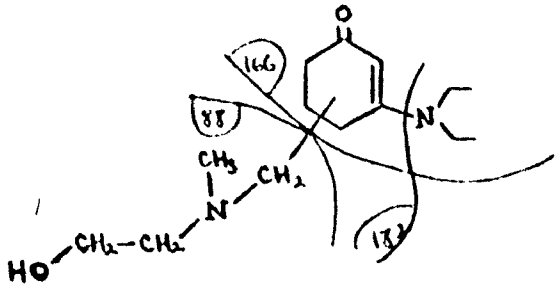
: 1.27 (6H), triplet (J= 5.6 Hz), triplet ($N-CH_2-CH_3$).

UV : λ^{max}_{EtOH}: 304 mμ ε : 1.98×10^4

IR : ν : 3300 (br., OH stretching), 2920 (sh.,m.), 2900 (m.,sh.), 1590 (str., sh.) and 1540 (str., sh.),(enaminoketone system), 1135 cm^{-1} (m., sh.).

m/e : 254 (M^+), 181, 125, 110, 108, 107, 88 .

A possible breakage pattern is described below :



Analysis : Calculated for $C_{14}H_{26}O_2N_2$: C, 66.10 H, 10.30

Found : C, 66.03 H, 10.14 .

Preparation of the cyanohydrin of ethyl 2-oxocyclopentane-carboxylate: The cyanohydrin of ethyl 2-oxocyclopentane-carboxylate was prepared according to the procedure given in reference (24). ($b.p._{15\ mm}$: 105-110°C).

Analysis : Calculated for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65.

Found: C, 59.00; H, 7.14; N, 7.51.

Preparation of 2-cyano-1-cyclopentene-1-carboxylic acid ethyl ester (XVIIIa) : In a dry flask protected from moisture, was placed 8 g of the cyanohydrin of ethyl 2-oxocyclopentane-carboxylate, freshly distilled, in 200 ml of dry pyridine. The mixture was cooled with an ice-salt bath and thionyl chloride (10 ml) was added dropwise. The mixture was then kept at room temperature overnight. After evaporation of the pyridine, the residue was distilled under vacuum, and (XVIII a) was obtained as a colorless liquid (4.7 g, 65%), ($b.p._{10mm}$:108-111°C).

NMR ($CDCl_3$) : δ: 4.14 (2H), quartet ($\dot{J}$: 7Hz)
: 2.88 (2H), triplet
: 2.35 (4H), triplet
: 1.43 (3H), triplet ($\dot{J}$: 6Hz)

UV : λ^{max}_{EtOH} 242 mμ ε : 6.2 x 10^3.

IR (liquid film) : ν : 2680 (m.), 2325 (w., sh., C≡N), 1700 (str., sh., with shoulder at 1605, C=O), 1245, 1110 cm^{-1}.

Analysis : Calculated for $C_9H_{11}O_2N$: C, 65.43; H, 6.71; N, 8.48 .

Found : C, 65.47; H, 6.69; N, 8.52 .

Attempted Diels-Alder reaction of 2-cyano-1-cyclopentene--1-carboxylic acid ethyl ester and 3-vinyl-2-cyclohexen--1-one: 3-Vinyl-2-cyclohexen-1-one and 2-cyano-1-cyclopentene-1-carboxylic acid ethyl ester (XVIIIa) (in a ratio 1:1.3) were heated in a sealed tube, at 160-175°C for 20 hours. The residue that was obtained was separated by thin layer chromatography on silica gel (yield: 32%, after separation), and a colorless glass was obtained.

NMR : δ : 5.6 (1H), singlet
: 3.4 (1H), singlet
: 1.5-2.6 (17H), multiplet.

UV : λ^{max}_{EtOH}: 242 mμ, $\varepsilon \sim 12500$.

IR : ν : 2930, 2830, 1670 (shoulder at 1675), 1620, 1120 cm^{-1}.

Analysis : Calculated for $C_{16}H_{20}O_2$: C, 78.62; H, 8.25 .

Found : C, 77.96; H, 8.35 .

3-Vinyl-2-cyclohexen-1-ol (XXII): In a dry 500 ml round-bottom flask fitted with a magnetic stirrer, was placed, under nitrogen, 532 mg of lithium aluminium hydride in 120 ml of dry ether. The flask was cooled in an ice bath and 540 mg of aluminium chloride was added slowly. The mixture was warmed to room temperature, and 1.2 g of 3-vinyl-2-cyclohexen-1-one in 25 ml of dry ether was then added. The reaction was allowed to proceed at room temperature for 30 min. The mixture was then cooled and water (or methanol) was added slowly. The organic phase was filtered and dried over sodium sulfate. After evaporation of the solvent, 456 mg of residue was obtained. The residue was separated by thin layer chromatography on silica gel, and 297 mg (25%) of (XXIII) was obtained.

NMR : ($CDCl_3$) two quartets: δ: 6.2 and δ: 5.5 (total: 4 H), (olefinic H).

: 3.95 (2H), multiplet.

: 1.8-2.7 (6H).

IR : $\nu_{cm^{-1}}$: 3320, 2930, 2825, 1610 (with shoulder at 1650); 1605, 1120 .

m/e : 124, 106 .

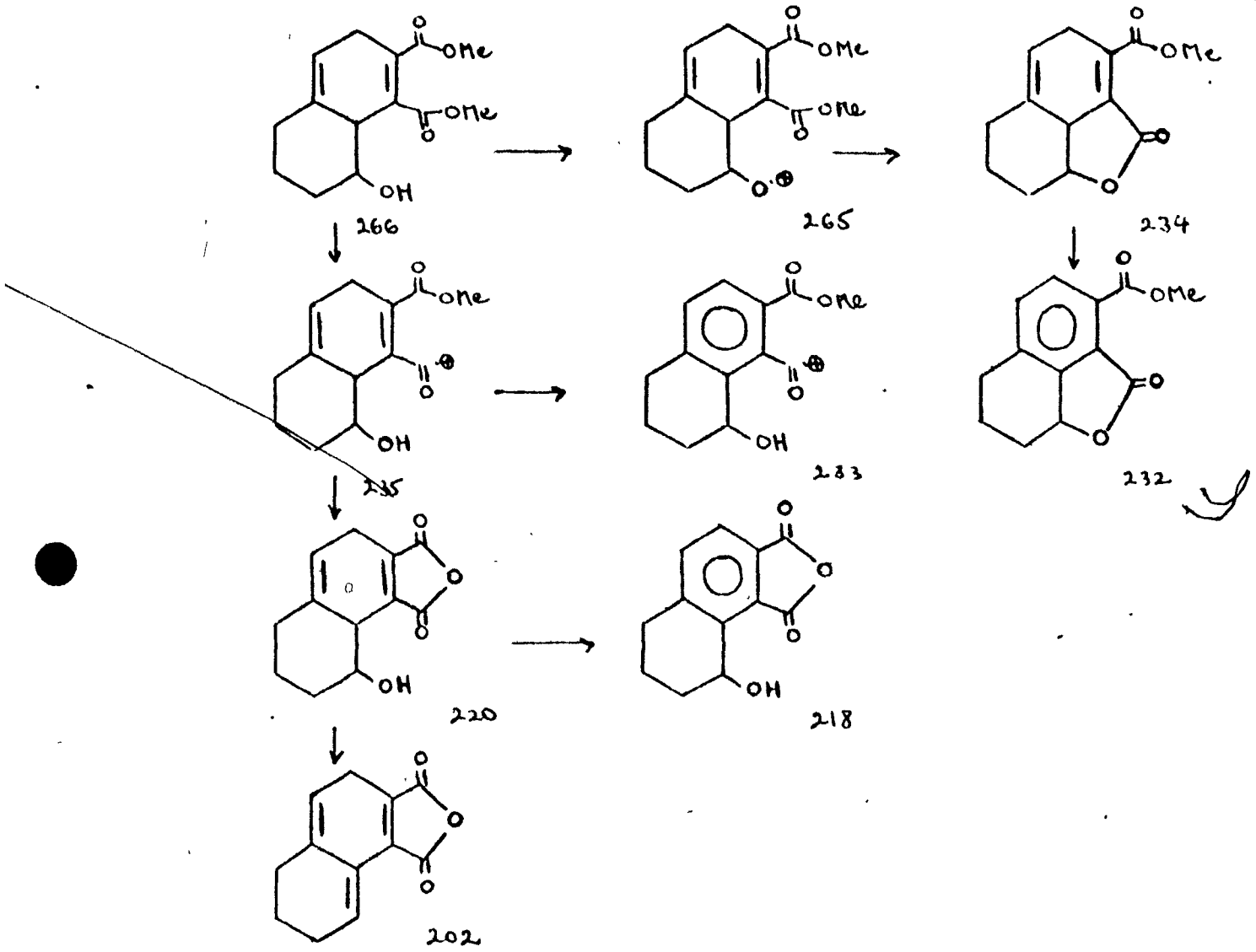
(XXIII) from 3-vinyl-2-cyclohexen-1-ol and dimethyl acetylenedicarboxylate: A mixture of 3-vinyl 2-cyclohexen-1-ol (125 mg) and dimethyl acetylenedicarboxylate (282 mg) was heated, in a sealed tube, for 12 hours at 110°-140°C. The residue obtained was dissolved in chloroform. The solution was washed with distilled water, and dried over magnesium sulfate. After evaporation of the solvent, 358 mg of residue was obtained. After separation by thin layer chromatography on silica gel, the Diels-Alder adduct (XXIII) (175 mg, 38%), was obtained as a colorless liquid.

NMR ($CDCl_3$) : δ : 5.6 (1H), singlet (olefinic proton).
: 3.9 (1H), multiplet ($-\underset{H}{\overset{OH}{C}}<$)
: 3.85 (6H), singlet ($-CH_3$)
: 3.10 (2H), singlet
: 2.65 (1H), broad signal
: 2.4-1.35 (6H), multiplet.

IR : ν : 3470 (br., m.), 2930, 2830, 1725 (str., sh., , shoulder at 1650 cm^{-1}), 1440, 1110 cm^{-1}.

m/e : 266 (M^+, weak), 265, 264, 263, 234, 232, 218, 175, 174, 173, 162 .

Possible breakage patterns are described below =



Lactonisation of the Diels-Alder adduct (XXIII) of 3-vinyl-2-cyclohexen-1-ol and dimethyl acetylenedicarboxylate: The Diels-Alder adduct (XXIII) (32 mg) was dissolved in anhydrous toluene (30 ml) containing a small amount (~3 mg) of p-toluenesulfonic acid, and the solution was submitted to azeotropic distillation till the volume was about 10 ml; toluene was added, and the previous operation was repeated four times. The solution was then refluxed, with removal of the water formed, for 8 hours. As explained p.28-29, the formation of the expected lactone was indicated by thin layer chromatography and by the IR spectrum of the reaction mixture (1725 and 1738 cm^{-1}); however, the lactone was not separated .

(XXVI) from 3-vinyl-2-cyclohexen-1-one and dimethyl acetylenedicarboxylate: A mixture of 3-vinyl-2-cyclohexen-1-one (130 mg) and dimethyl acetylenedicarboxylate (278 mg) was heated, in a sealed tube, for 13 hours at 130°-140°C. The residue was separated by thin layer chromatography on silica gel, and (XXVI) (103 mg, 40 %), was obtained as a colorless liquid .

NMR ($CDCl_3$): δ : 8.30-7.33 (2H), multiplet (aromatic protons).

: 3.83 (6H), singlet ($-O-CH_3$)

: 3.13 (2H), triplet (- $\underline{CH}_2$ -C-)

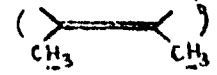
: 2.73-2.15, (4H) multiplet.

IR (liquid film) : ν : 2970, 1715 (str., br.), 1685 (str., br.); 1275 cm^{-1}.

m/e : 262, 231, 217, 215, 122.

Attempted opening of dimethyl maleic anhydride by the sodium salt of 3-vinyl-2-cyclohexen-1-ol. In a dry 100 ml round-bottom flask, fitted with a magnetic stirrer, was placed, under nitrogen, 62 mg of sodium hydride, which was washed three times with dry pentane. Then, 30 ml of dry toluene, and 130 mg of 3-vinyl-2-cyclohexen-1-ol in 2 ml of dry toluene, were added. The mixture was kept at room temperature for one hour. A solution of 250 mg of dimethyl maleic anhydride in 6 ml of dry toluene was then added slowly, and the mixture was refluxed for 12 hours. The reaction was followed by thin layer chromatography; no new product could be detected. Water (2 ml) was added to the mixture, in small portions. The organic phase was dried over sodium sulfate. The solvent was evaporated and 240 mg of dimethyl maleic anhydride was recovered.

Preparation of N-methyl, N-(β-hydroxyethyl)-pyrocinchonamic acid (XXXIV) = To 400 mg (3.2 mmoles) of dry dimethyl maleic anhydride in 12 ml anhydrous chloroform, was added 1.02 g (13.6 mmoles) of N-methylethanolamine. The mixture, protected from moisture (calcium chloride tube, nitrogen atmosphere), was refluxed overnight. The reaction mixture was allowed to cool down to room temperature, and 80 ml of chloroform was added. The solution was washed twice with 20 ml 1.0 N aqueous hydrochloric acid solution, then with distilled water, dried over magnesium sulfate and filtered. Upon addition of dry ether, 400 mg of N-methyl, N-(β-hydroxy-ethyl)-pyrocinchonamic acid (XXXIV) (62%) was obtained, as a white, hygroscopic precipitate, (m.p.= 58-62°C).

NMR ($CDCl_3$) : δ : 4.3 (2H), multiplet (CH_2-O-H)
: 3.70 (1H), broad signal
: 3.62 (2H), multiplet (CH_2-N<)
: 2.70, broad signal and 2.33, singlet, (total: 3H) (N-CH_3).
: 1.95 (6H), singlet ()

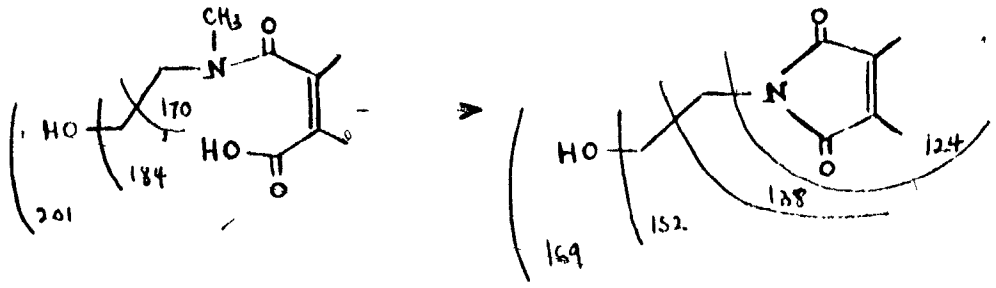
IR : ν : 3380 (str., br.), 2970, 2900, 1580 (str., br., with shoulder at 1630), 1300 cm^{-1}.

Analysis: Calculated for $C_9H_{15}NO_4$: C, 53.72 ; H, 7.51 .

Found : C, 53.21; H, 7.60 .

m/e : 201 (M^+), 199, 183, 182, 181, 164, 162, 152, 137, 136, 124, 117 .

A possible breakage is suggested below :



(XXXV) from the cyclisation of N-methyl, N-(β-hydroxyethyl)--pyrocinchonamic acid (XXXIV) : Acetic anhydride (1.42g, 13.9 mmoles) was added dropwise to 381 mg (1.9 mmoles) of N-methyl,N-(β-hydroxyethyl)-pyrocinchonamic acid (XXXIV) in 6 ml anhydrous pyridine, at 0-5°C, in a flask protected from moisture . The mixture was stirred at room temperature overnight. After evaporation of the pyridine, the residue was washed with dry ether and separated by thin layer chromatography (silica gel HF 254 + 366, solvent : $CHCl_3$-MeOH 70:10); (XXXV) was obtained as a colorless liquid (265 mg, 76%) .

NMR ($CDCl_3$) : δ : 4.27 (2 H), multiplet ($-CH_2-O-$)

: 3.35 (2H), multiplet ($-CH_2-N<$)

δ : 2.9, multiplet, and δ: 2.33 , singlet
(total: 3 H) ($N-CH_3$)
: 2.16, singlet, and δ: 1.93, singlet
(total: 6 H) ().

IR : ν : 2960, 1720 (str., sh., ester), 1680 (str., sh., amide), 1580, 1280 .

m/e : 183 (M^+), 182, 153, 140, 139, 138, 124 .

BIBLIOGRAPHY

(1) F.Märki and B.Witkop, Experientia 19, 239 (1963).

(2) J.W.Daly, B.Witkop, P.Bommer and K.Biemann, J. Am. Chem. Soc. 87, 124 (1965).

(3) J.W.Daly and C.W.Myers, Science 156, 970 (1967).

(4) T.Tokuyama, J.W.Daly, B.Witkop, I.L.Karle, J.Karle, J. Am. Chem. Soc. 90, 1977 (1968).

(5) O.Wintersteiner and M.Moore, J. Am. Chem. Soc. 65, 1507, 1507 (1943).

(6) J.H.Saunders, Org. Syn. 40, 14 (1960).

(7) M.S.Newman, J. Am. Chem. Soc. 75, 4740 (1953).

(8) W.F.Gannon and H.O.House, Org. Syn. 40, 14 (1960).

(9) A.Eschenmoser, J.Schreiber and S.A.Julia, Helv. 36, 482 (1953).

(10) C.F.Woods and I.W.Tucker, J. Am. Chem. Soc., 70, 2174 (1948)

(11) W.F.Gannon and H.O.House, Org. Syn. 40, 41 (1960).

(12) C.Mannich and W.Krosche, Arch. Pharm., 250, 647 (1912).

(13) K.Alder and K.Heimbach, Chem. Ber., 86, 1312 (1953).

(14) Beilstein, 7, 554; 7, 887 .

(15) R.S.Rasmussen and R.R.Brattain, J. Am. Chem. Soc., 71, 1068 (1949).

(16) H.Stetter and R.Lauterbach, Ann. 652, 40 (1962) .

(17) J.Reisch, Pharmazie 21, 770 (1966) .

(18) B.Halpern, L.B.James, Nature 202, 592 (1964) .

(19) J.K.Stille and R.Ertz, J. Am. Chem. Soc. 86(4), 661 (1964).

(20) H.O.House, "Modern Synthetic Reactions", Second Edition, p. 625; W.A.Benjamin, Menlo Park, California (1972).

(21) E.Winterfeld and H.Preuss, Chem. Ber. 99, 450 (1966).

(22) G.Büchi, P.Kulsa, K.Ogasawara and R.L.Rosati, J. Am. Chem. Soc., 92(4), 999 (1970).

(23) E.E.Smissman, J.T.Suh, M.Oxman and R.Daniels, J. Am. Chem. Soc. 84, 1040 (1962).

(24) S.C. Sen Gupta, J. Ind. Chem. Soc. 17, 183 (1940).

(25) W.R.Vaughan, C.T.Goetschel and C.L.Warren, J. Am. Chem. Soc. 85, 8282 (1963).

(26) D.Ginsburg, J.Altman and E.Babad, Tetrahedron 24, 975 (1968).

(27) D.Ginsburg, J.Altman and D.Becker, Tetrahedron Letters, 757, (1967).

(28) H.G.Viehe, "Chemistry of acetylenes", p.477; Marcel Dekker, New York (1969).

(29) W.T.Dilling and R.A.Plepys, Chem. Comm., 1969, 417 .

(30) H.C.Brown and H.M.Hess, J. Org. Chem. 34, 2206 (1969).

(31) F.J.Jorgenson, Tetrahedron Letters, 559, (1962).

(32) H.Ogura and F.Takahashi, J. Org. Chem., 37, 72 (1972).

(33) J.Schmidlin and A.Wettstein, Helv. 46, 2799 (1963).

(34) W.S.Johnson, R.G.Christiansen and R.E.Ireland, J. Am. Chem. Soc. 79, 1995 (1957).

(35) R.B.Woodward and T.J.Katz, Tetrahedron 5, 70 (1959).

(36) J.A.Berson and A.Remanick, J. Am. Chem. Soc. 83, 4947 (1961).

(37) C.Walling and H.J.Schugar, J. Am. Chem. Soc. 85, 607 (1963).

(38) K.Alder and K.Heimback, Chem. Ber. 86, 1312 (1953).

(39) E.T.McBee, J.O.Stoffer and H.P.Braendlin, J. Am. Chem. Soc. 84, 4540 (1962).

(40) H.H.Wasserman and A.R.Dourmaux Jr, J. Am. Chem. Soc. 84, 4611 (1962).

(41) G.Eglinton, R.A.Raphael, R.G.Willis and J.A.Zabkiewicz, J. Chem. Soc.,2597 (1964).

(42) D.Devaprabhakara, C.G.Cardenas and P.D.Gardner, J. Am. Chem. Soc. 85, 1553 (1963) .

(43) H.O.House and T.H.Cronin, J. Org. Chem. 30(4), 1061 (1965).

(44) D.Bilovic, Croat. Chem. Acta 40, 15-22 (1968); CA 69: 86 751 e .

(45) C.D.Wels , J. Org. Chem. 28, 74 (1963) .

(46) K.Alder and K.H.Backendorf, Chem. Ber. 71, 2199 (1938).

(47) N.P.Sopov and V.S.Viklashevskaya, Zhur. Obshchei Khim. 16, 1914 (1956); CA 51: 4968 a .

(48) O.Diels and K.Alder, Ann. 478, 137 (1930); 490, 236 (1931).

(49) J.Sauer, Angew. Chem. Inter. Ed. 5, 211 (1966).

(50) J.Sauer, Angew. Chem. Inter. Ed. 6, 16 (1967).

(51) H.G.Viehe, "Chemistry of acetylenes", p.515; Marcel Dekker, New York (1969).

(52) Yu A.Titov, Russ. Chem. Rev. Engl. Transl. 31, 267 (1962).

(53) E.G.Kataev, M.E.Kat'kova, Uchenye Zapiski Kazan. Gosudarst. Univ. im. V.I. Ul'yanovaLenina, Khim. 115, (3), 21 (1955); CA: 52: 1967 b .

(54) J.S.Meek, B.T.Poon, R.T.Merrow and S.J.Cristol, J. Am. Chem. Soc. 74, 2069 (1952).

(55) S.Murahashi, J.Suto and K.Kawasak , Chem. Zentr.,1957, 10167 .

(56) H.C. Barrett and G. Büchi, J. Am. Chem. Soc. 89, 5665 (1967).

(57) J.A.Marshall and M.T.Pike, J. Org. Chem. 33, 434 (1968).

(58) C.H.Heathcock and T.R.Kelly, Tetrahedron 24, 3753 (1968).

(59) D.J.Dunham and R.G.Lawton, J. Am. Chem. Soc. 93, 2075 (1971).

(60) J.A.Marshall and T.K. Warne,Jr., J.Org.Chem. 36, 178 (1971).

(61) K.C.Ling and C.Djerassi, J. Am. Chem. Soc. 92, 6019 (1970).

(62) H.Wieland and K.Hoecher, Helv. Chim. Acta 33, 2215 (1950).

(63) C.R.C.Boyce and J.S.Whitehurst, J. Chem. Soc., 2680 (1960).

(64) S.P.Pathak and G.V. Ulkarni, Chem. Ind., 913 (1968).

(65) R.F.Borch, Tetrahedron Letters, 61 (1968).

(66) G.W.K. Cavill and D.H.Solomon , J. Chem. Soc., 4426 (1955).

(67) G.Büchi, P.D. Erickson and M.Wakabayashi, J. Am. Chem. Soc. 83, 927 (1961).

(68) D.Vorländer and F.Kalkow, Ann. 309, 359 (1899) .

(69) L.Knorr and H.Matthes, Chem. Ber., 34, 3488 (1901)

(70) D.Vorländer and F.Kalkow, Chem. Ber., 30, 1802 (1897).

(71) F.Zymalkowski and J.Rimek, Naturwissenschaften 47, 83 (1960); CA: 54: 15/385 g.

(72) S.Danishefsky and R.Cunningham, J. Org. Chem. 30, 3676 (1965) .

(73) F.Bohlmann and O.Schmidt, Chem. Ber. 90, 1652 (1966).

(74) S.Hünig and H.Kahanek, Chem. Ber. 90, 238 (1957) .

(75) F.Hoffmann-La Roche & Co, A-G. Ger. 614,195 June 1935; CA: 29: P 59953 .