A STUDY OF THE INITIAL STEPS IN THE SYNTHESIS OF "CONGRESSANE 63"

Research Report for Ch 80

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ABSTRACT

Preliminary steps in the synthesis of "congressane 63" (pentacyclotetradecane) have been studied. Methods have been investigated to prepare the starting material, 1,4-cyclohexadione, its ethylene glycol- monoketal, and the initial products of the synthesis. The latter include the eneamine, bicyclo acrolein adduct, and the pyrolysis elimination of the amine group. The acrolein addition and the pyrolysis have yet to be satisfactorily performed.

A conformational analysis[1] to determine the most stable conformation of cyclodecane has yielded the following structure:

Fig. 1

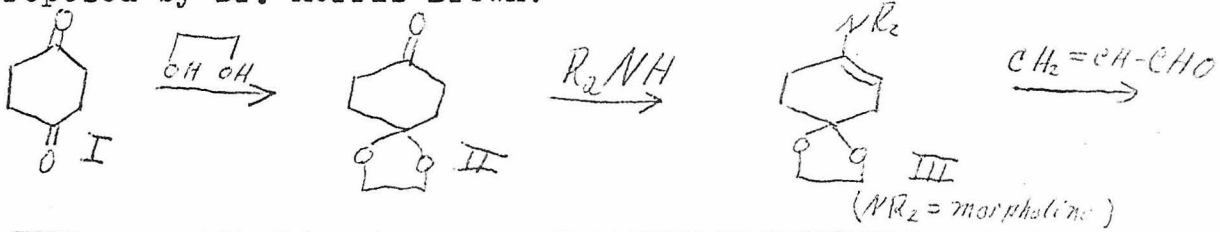
This stable form is derived from the diamond lattice; and the picture is a fairly faithful representation, if one disregards slight differences in the bond and torsion angles.

By replacing the six intra-annular hydrogen atoms one obtains pentacyclotetradecane:

Fig. 2

It appeared as the emblem of the I.U. P. A. C. Congress held in London in 1963 and has been given the provisional name of "congressane 63".

The unusual stability of cyclodecane and its relationship to the diamond lattice make the synthesis and study of "congressane 63" desirable. A scheme for its synthesis has been proposed by Dr. Morris Brown:



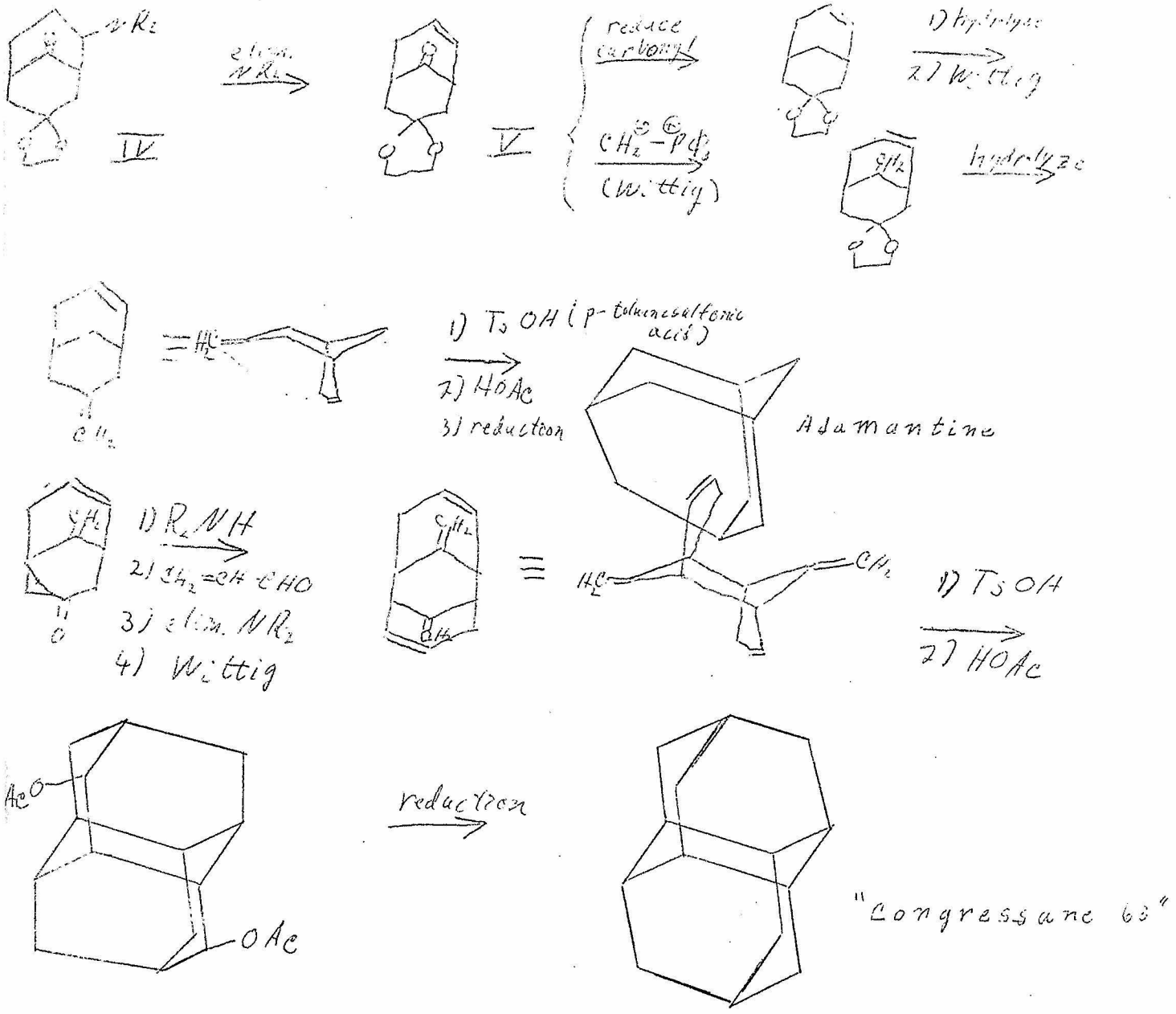


Fig. 3.

This report describes some work performed on the first steps of the synthesis.

The first part of the work was the investigation of the initial reactions and preparation of the starting material, 1,4 - cyclohexadione. At the beginning of the project none was available, so 1,4-cyclohexadiol was used as starting material. It was to have been step-wise oxidized to 1, 4 - cyclohexadione -ethyleneglycol-monoketal (II) by this route:

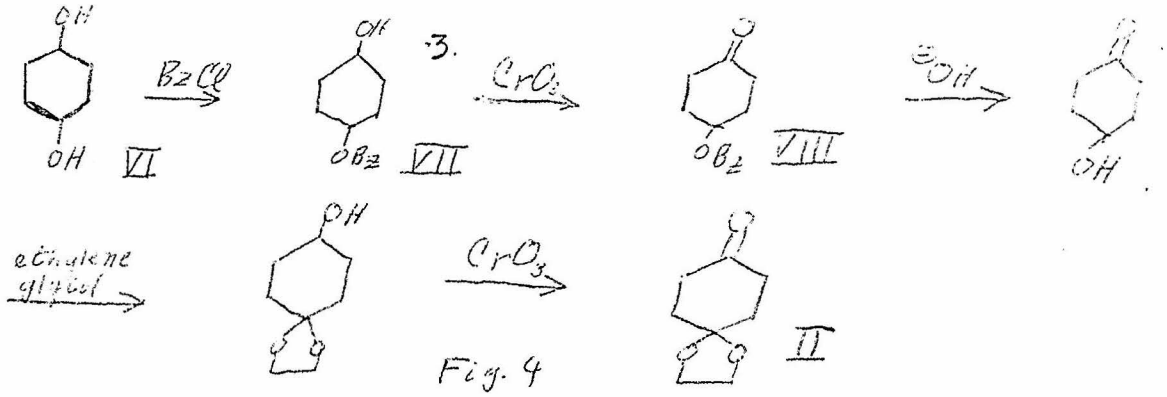


Fig. 4

By the time compound VIII was prepared, a supply of 1,4-cyclohexadione was secured, so this project was suspended.

In the investigation of the initial reactions cyclohexanone was used as starting material. The pyrrolidine eneamine was prepared, as was the acrolein adduct to the eneamine, but the elimination of the amine by the Hofmann method was not successful.

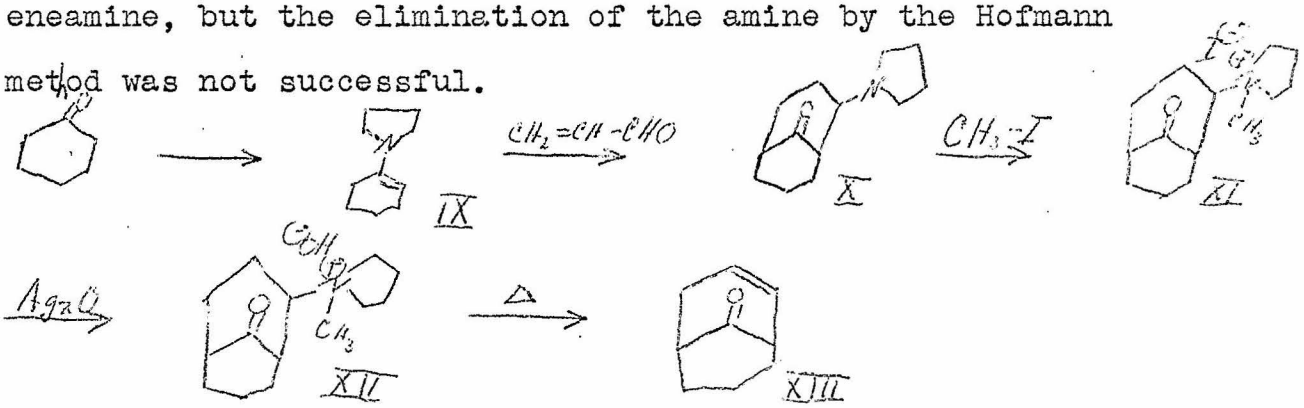


Fig. 5

Somewhat ~~more~~ successful was the exchange of dimethyl amine for pyrrolidine and subsequent pyrolysis of the N-oxide:

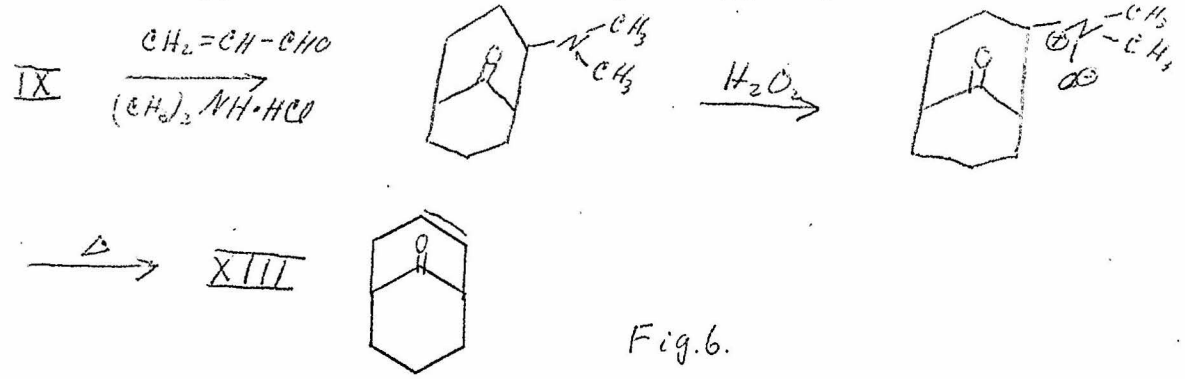


Fig.6.

When a supply of 1,4-cyclohexadine was obtained, a method was sought to convert it to its ethylene glycol-monoketal.

Ketalization of 1,4- cyclohexadione was found not to be a clean reaction; a large amount of the diketal is formed. A study of the kinetic course of the ketalization showed that the second ketalization occurs more rapidly than the first. The best equilibrium , 60% diketal, 40% monoketal, and negligible diketone, was found to occure when 1.5 equivalents of ethylene-glycol are used.

Separation of the mixture was not simple. High-vacuum distillation was complicated by sublimation of both compounds simultaneously and only slight differences in boiling points. A more tedious yet more effective method was used by co-worker S. Murayama; the monoketone was converted to bisulfite salt by reaction with potassium bisulfite. The diketal was partially hydrolyzed to yield a mixture about 2:1 of monoketal to diketal, which was then separated.

The initial reactions of the synthesis previously investigated were carried out with the 1,4-cyclohexadione-ethylene glycol-monoketal. The eneamine formation is clean and in good yield(80%), the amine used beeing morpholine. The acrolein addition and cyclization is not so smooth;it does not seem to go to completion even at reflux temparatures (in benzene or toluene). Infrared peaks characteristic of the eneamine remain. Murayama has succeeded in isolating an intermediate. The main problem is the purification of the crude

product mixture in good yield; the bicyclic product is a high-boiling oil that decomposes at distillation temperatures. At present no satisfactory method has been found.

Also no satisfactory technique has been developed for the pyrolysis to eliminate the amine. It is hoped that morpholine will eliminate in the desired manner, but the first trial was not successful - decomposition of the N-oxide occurred during heating. Perhaps a more suitable amine must be found or the present technique modified.

Experimental Part

Quinitol monobenzoate (VII):[2] 60g. quinitol (1,4-cyclohexadiol) was dissolved 130 ml. dry chloroform (freed from alcohol by shaking with sulfuric acid) and dry pyridine (130 ml.). A solution of benzoyl chloride (71 g.) in chloroform (150 ml.) was slowly added overnight with stirring in an ice bath. The pyridine was then thoroughly extracted with water and dilute sulfuric acid. The solution was dried and the solvent removed before vacuum distillation. B. p. of the viscous liquid, 145-150° C. (0.10 mm.). Yield 50%.

4-Benzoyloxycyclohexanone (VIII):[2] Chromium trioxide (13 g.) was dissolved in glacial acetic acid (30 ml.) and water (8 ml.). Dissolved in 50 ml. acetic acid was 30g. quinitol monobenzoate. The chromium trioxide was added slowly to the latter solution, stirred in an ice bath, and allowed to sit overnight. Ether (200 ml.) was then added; the acetic acid was removed by washing with water and sodium bicarbonate ($NaHCO_3$) solution. The dried solution was evaporated, then the residue crystallized from ether and pentane. M. p. 59-61° C.,

(Reported 62-64°).

Eneamines [3] (III, IX): One equivalent of the ketone was refluxed with 1.5 - 2.0 equivalents of the amine in benzene solvent under water separator until water stopped separating out. The reaction vessel was kept flushed with nitrogen. Vacuum distillation was performed on the residue after removal of solvent. Compound IX: B. p. 128-131°C (25 mm). III: B. p. 111 - 113°(0.04 mm) The products are colorless, viscous fluids, stable under dry nitrogen and refrigation.

Bicylic Acrolein Adduct to Eneamines (IV, X):

To one equivalent of eneamine in dry benzene or methanol was added one equivalent of freshly distilled acrolein slowly initially in ice bath. Apparatus was flushed with dry nitrogen. Reaction was completed by refluxing in benzene or toluene for up to six hours. Compound (X) distilled: B. p. 123 - 127°C (0.5 mm). Compound (IV) polymerized in distillation vessel. Satisfactory method of purification not yet found.

1 - pyrrolidino bicylo [3.3.1] nonan - 9- one - N - methyl iodide [5] (XI):

Ether solution of 100% excess methyl iodide was added slowly to solution of the amine (X) and refluxed. The salt was crystallized from ether: M. p. (impure) 159-170°. No yield measured.

1 - pyrrolidino bicyclo [3.3.1] nonan - 9 - one - N - methyl hydroxide: [5] (XII) To 3.5 g. of the methiodide salt were added 4.0 g. silver oxide & 20 ml. water. No silver iodide precipitate was noticed after three hours of stirring in an ice bath. A thin-plate

chromatograph showed a mixture of products, so the reaction was not clean. The reaction was not studied further.

1 - N, N - dimethyl-amino-bicyclo-[3.3.1]-nonan- 9 - one (XIV): To cyclohexanone - pyrrolidine eneamine (10g. in 100 ml. methanol) was added 56g. dimethylamine hydrochloride (10 equivalents). 4g (one equivalent) of acrolein was slowly added dropwise prior to reflux. After the reaction mixture cooled it was neutralized with crystalline potassium carbonate (140g.) and stirred for three hours. Addition of ether made the salt precipitate better before filtration through a scintered glass filter. The filtrate was evaporated to an oily residue which was distilled. B. p. 68 - 71°C (.0. 10 mm.) Yield 47%. Some pyrrolidine product was also obtained.

1 - N, N - dimethyl amine - N- oxide bicyclo [3.3.1] nonan - 9 - one (XIV):

The amine (XIV) (4.1g.) was dissolved in 10 ml. Methanol at 0°, to which was added a two- fold excess of 30% hydrogen peroxide slowly over a half hour. After 24 hours of stirring the solution was given a phenolphthalein spot test; it was negative, indicating that all the amine had reacted. The excess hydrogen peroxide was decomposed by adding a drop of catalase enzyme and stirring several hours. The absence of hydrogen peroxide was then tested with lead sulfide paper. The solvent was removed, but the oily product was not purified.

Bicyclo-[3.3.1]-non-Δ^1-ene-9-one (XIII): Two grams of the N-oxide (XV) was placed at the closed end of a horizontally mounted test tube and sponged up with a

piece of glass wool. The tube, which had two constrictions on its lower side, was oven heated at the closed end and attached to a vacuum pump. A small amount of yellow oil collected between the constrictions. After neutralization with dilute HCl, the ether solution of this oil was dried, then cooled on dry ice. White crystals formed in ether-pentane. Wet crystals melted over the range of 45-60 . Yield 0.2 g.

Cyclohexadione-ethylene glycol monoketal (II):

A. Kinetic study —

Into benzene solution of the diketone (I) (1 g) was stirred ten equivalents of ethylene glycol (6.3 g). A trace of para-toluenesulfonic acid (p-TSA) was added as catalyst. At intervals of a few minutes small portions of the reaction mixture were quenched by shaking with $NaHCO_3$. The samples were run through the vapor-phase chromatograph to determine the product ratios.

B. Varrying the conditions of ketalization —

Equilibrium in each case was established by 15 - 30 minutes of refluxing after adding a certain amount of ethylene glycol. One, two, and three equivalents were added, and product ratios were determined on the VPC.

C. Ketalization on a larger scale —

Ten grams or more diketone (I) was refluxed with 1.5 equivalents ethylene glycol and a trace p-TSA in benzene under water separator. When the reaction was complete the mixture was quenched with $NaHCO_3$, washed with

brine and water, and dried over Na_2SO_4. The wash solutions were promptly and repeatedly extracted with benzene or ether, the extracts being dried and added to the main solution. After removal of solvent the residue was crystallized from ether-pentane. Vacuum distillation to separate the two ketals was unsuccessful because both sublimed at the same temperatures and boiled close together. Yield up to 90%.

D. Separation by Bisulfite Method —

The ketal mixture (30 g) was dissolved in ether and ethanol (about 1:1); two-fold excess $NaHSO_3$ (40 g) in adequate water to dissolve it was slowly added with swirling. The fine precipitate was filtered with a scintered glass filter, then washed with benzene. The water solution of the salt was extracted with benzene, prior to decomposition of the salt by addition of excess solid K_2CO_3. The resulting monoketal was extracted repeatedly with benzene. Removal of solvents and crystallization from ether-pentane yielded the separated ketals. Yield: 90% (Murayama).

E. Conversion of the Diketal to the Monoketal by Partial Hydrolysis —

The diketal was dissolved in acetone (30 g. in 120 ml.) with 0.5 g. p-TSA as catalyst and 12 ml. water. Refluxing for two hours converted it to 60-70% monoketal (as shown on the VPC). The reaction was quenched with $NaHCO_3$, and the solvent removed. Redissolved in ether, the residue

was washed with brine and water, and dried. The wash portions were extracted with ether, the extracts being dried and added to the main ether solution.

References:

1. Prelog, Pure and Appl. Chem., 6. 545 (1963).
2. Jones and Sondheimer, J. Chem. Soc., 1949, 615.
3. Stork, J. Am. Chem. Soc., 85, 207, (1963).
4. Stork, ibid., 78, 5130, (1956).
5. Cope, ibid., 79, 4720, (1957).