An Alternative Mechanism to the Stork Ring Enlargement[1]

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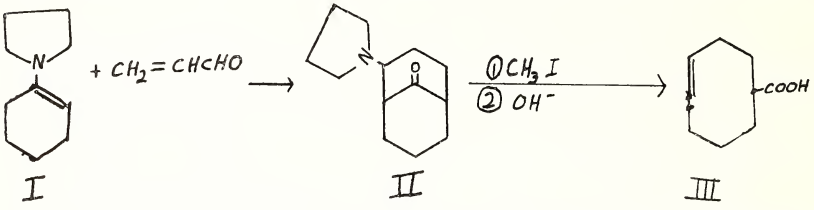
Several years ago a unique ring enlargement sequence was reported by Stork and Landesman.[1] It was found that when the pyrrolidine enamine of cyclohexanone (I) was allowed to react with acrolein, 2-N-pyrrolidylbicyclo [3.3.1] nonan-9-one (II) was formed in a 75% yield. Upon heating the methiodide of II with aqueous base, 4-cycloöctene-

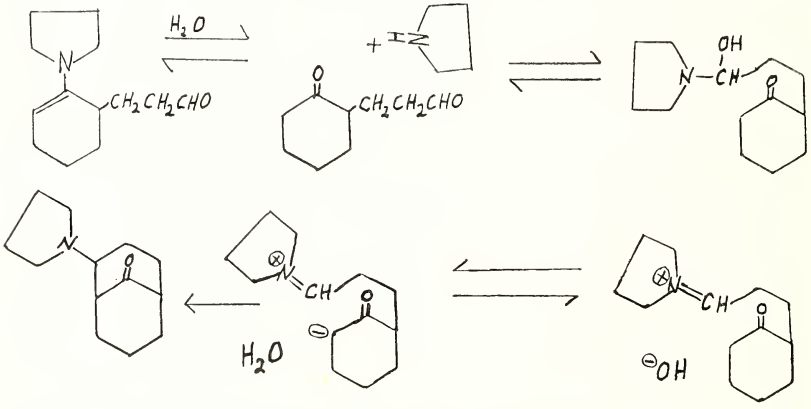


I II III

carboxylic acid (III) was formed. The structure of III was proven by consideration of the reactions involved in its formation along with a comparison of its hydrogenation product with an authentic sample of cycloöctanecarboxylic acid. This reaction has been found to be quite general for enamines prepared from a variety of secondary amines and substituted or unsubstituted cyclic ketones.[2] Likewise crotonaldehyde and methacrylaldehyde were successfully used in place of acrolein to produce the corresponding methyl substituted rings.

The mechanism of the initial reaction has been a subject of considerable speculation during the ensuing years. Any proposed mechanism will have to account for the apparent exchange of positions of the pyrrolidyl group and the oxygen atom.

It has been suggested by Untch[2] that, despite the attempt to make all the conditions of the reaction anhydrous, some moisture must have

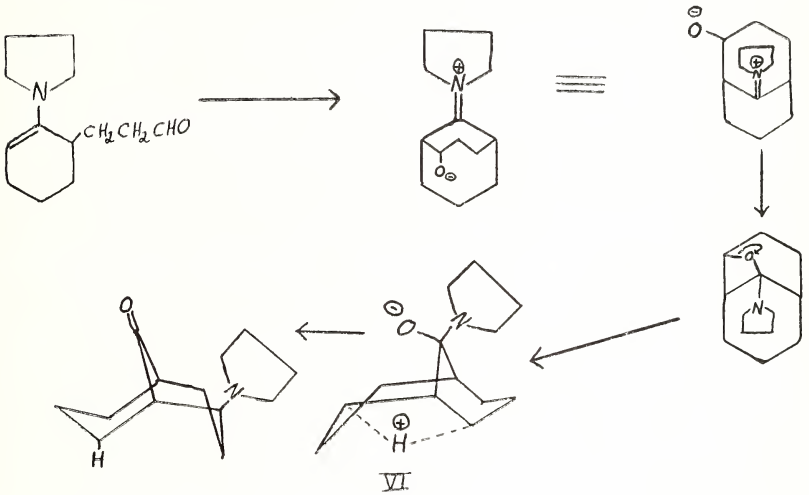


1. Work supported by the Research Corporation under a Gardner Fredrick Cottrell Grant.

crept in causing the following mechanistic sequence to take place following the initial addition of the acrolein to N-pyrrolidino-l-cyclohexene (I):

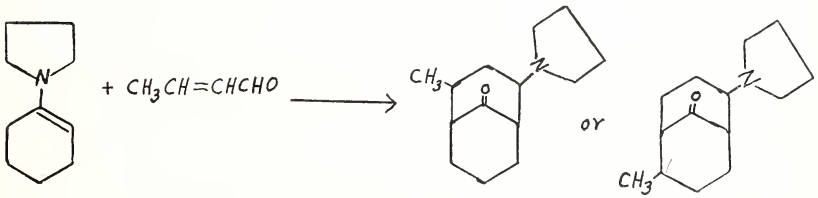
As substantiating evidence for this mechanism it was reported that when a mixture of N-pyrrolidino-l-cyclohexene (I) and N-piperidino-4-*t*-butyl-l-cyclohexene (IV) was allowed to react with acrolein, all four bicyclic products possible from such a mixture reacting according to the above mechanism (that is, with intermolecular exchange of amines) were observed. This observation was pointed to as substantiating evidence for this mechanism. However, this does not appear to be conclusive evidence for this mechanism since this same mixing can be explained merely from hydrolysis followed by reformation of the enamines possibly under the influence of the acrolein.

An alternative mechanism for this reaction involving a non-classical carbonium ion (VI)[3,4] is shown in the following sequence:



VI

In the reactions of crotonaldehyde or methacrylaldehyde the position of the methyl groups were assigned on the basis of I. R. analysis and analogy alone.[2] Therefore, they may be equally well assigned to other positions on the ring. The same uncertainty is present with the question as to which ring the pyrrolidyl group is attached to. For example, when



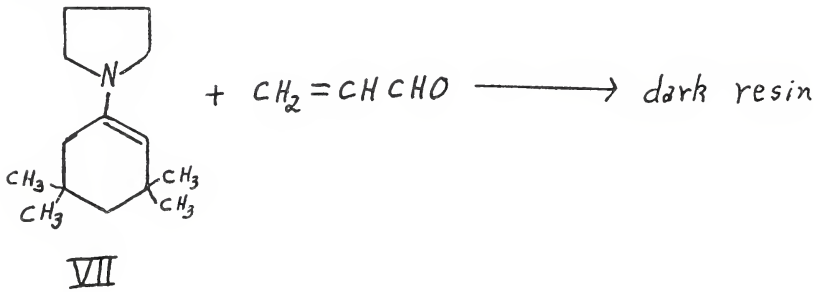
I

V

crotonaldehyde is allowed to react with N-pyrrolidino-l-cyclohexene (I), the bicyclic product, V, is produced. But the relative positions of the pyrrolidyl and methyl groups has not been unequivocally proven.[2] The unequivocal locating of these groups on the ring would certainly disprove one of the two mechanisms.

In the second alternative mechanism, if the 3 and 5 positions of the original cyclohexanone were blocked the reaction could not go to completion. With this in mind N-pyrrolidyl-3,3,5,5-tetramethyl-1-cyclohexene (VII) was synthesized in the usual manner starting with 3,3,5,5-tetramethyl-1-cyclohexene[5] and pyrrolidine in a 65% yield. The substitution of methyl groups at these fairly remote positions should not greatly influence the course of the reaction if the first proposed mechanism is in effect. This statement is further reinforced by the fact that N-pyrrolidyl-2-methyl-1-cyclohexene (in which the methyl group is in closer proximity to the reaction site) undergoes the normal reaction to give the usual bicyclic product.[2]

When N-pyrrolidyl-3,3,5,5-tetramethyl-1-cyclohexene (VII) was allowed to react with acrolein in dioxane solvent under the usual conditions, only a dark, undistillable resin remained upon removal of the solvent. Although this is not conclusive proof of the second alternative mechanism, it seems to give a strong indication that this may be the true reaction pathway.



VII

N-Pyrrolidyl-3,3,5,5-tetramethyl-1-cyclohexene. A stirred solution of 300 ml. of dry benzene, 25.1 ml. (0.30 mole) of pyrrolidine and 22.9 gms. (0.15 mole) of 3,3,5,5-tetramethylcyclohexane along with a catalytic amount of *p*-toluenesulfonic acid was refluxed under nitrogen in a one-liter flask equipped with a Dean-Stark trap for 18 hours. The solvent was removed and the residual oil was distilled through a good column. A total of 19.3 gms. (62%) of a colorless liquid product was obtained, b.p. 70° (0.2 mm.) n_D^{24} 1.4998. Anal. Calcd. for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76.

Found: C, 81.22; H, 12.09; N, 6.88.

Reaction of N-Pyrrolidyl-3,3,5,5-tetramethyl-1-cyclohexene with Acrolein. To a stirred, ice-cold solution of 3.36 gms. (0.06 mole) of acrolein in 50 ml. of dioxane was added all at once 12.22 gms. (0.06 mole) of *N*-pyrrolidyl-3,3,5,5-tetramethyl-1-cyclohexene in 20 ml. of dioxane. The reaction mixture was stirred under nitrogen at room temperature for 17

hours. The solvent was removed and only a dark, undistillable resin remained.

Literature Cited

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