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A STEREOELECTRONIC REQUIREMENT FOR THE CYCLIZATION OF CIS- AND TRANS-N-ACRYLYLOCTAHYDRO-7(1H)-QUINOLONES TO DECAHYDRO-3H,10H-BENZO[i,j]QUINOLIZINE-3,10-DIONES

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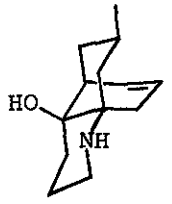
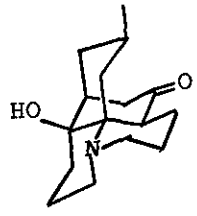
Cyclization of N-acrylyl-cis- and -trans-octahydro-7(1H)-quinolones to decahydro-3H,10H-benzo[i,j]quinolizine-3,10-diones is described. Possible stereoelectronic control in the intramolecular Michael addition step of cyclization, or a requirement for the successful ring closure, was discussed on the basis of experiments using stereoisomers of the model compounds.

We have recently reported[1] preparation of the tricyclic amino alcohol (I) which would serve as a key intermediate for lycodoline[2] (II), one of the Lycopodium alkaloids. Now, in this communication, we wish to describe the synthesis of the amido ketone (III), its attempted cyclization to the tetracyclic

lactam (IV), and also stereoelectronic aspects of the cyclization of the cis- and trans-amido ketones (V and VI).



I



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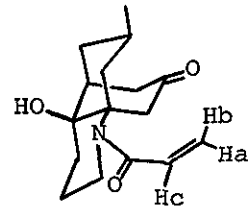
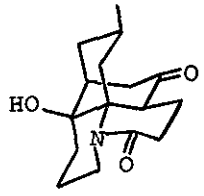


III



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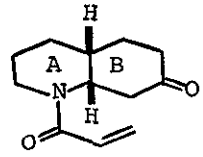
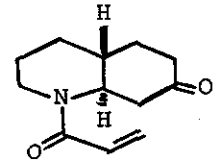


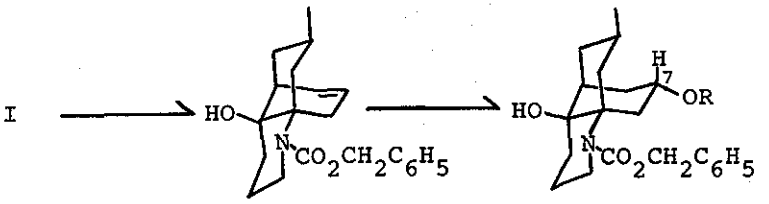
V



VI

Hydroboration-oxidation of the benzyl carbamate (VII) prepared from I afforded the diol (VIII) in 70% yield.[3] The ^{1}H-NMR (PMR) spectrum of its acetate (IX) displayed a multiplet ($W_{1/2}$ = 28Hz) due to the C-7 axial proton. Jones oxidation of VIII gave the ketol (X) in 82% yield, which was hydrogenolyzed to afford the amino ketol (XI) in good yield. Reaction of XI with acrylyl chloride in chloroform containing triethylamine furnished the amide (III) [mp 201-202°. IR ν($CHCl_3$): 3300(OH), 1700(C=O), 1640(amide), 1610(C=C). PMR δ(DMSO-d_6): 5.50(1H, d-d, J = 10, 3Hz, Ha), 5.87(1H, d-d, J = 18, 3Hz, Hb), 6.60(1H, d-d, J = 18, 10Hz, Hc)]. In spite of several attempts to cyclize III to IV under various acidic or basic conditions, the desired tetracyclic lactam ketone (IV) could not be obtained: the base-catalyzed reactions recovered the starting material, and the acid-catalyzed ones gave complex products.[4] The amido ketone (XII) having a trans-octahydro-7(1H)-quinolone

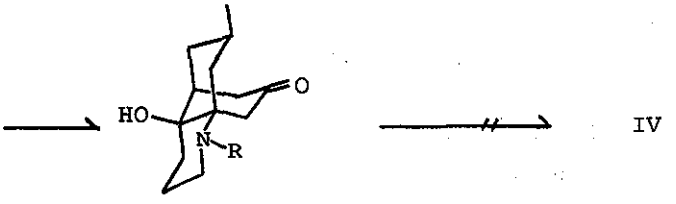
system, however, has been reported[5] to be smoothly cyclized to XIII under an acidic condition. The different results for cyclization, we assumed, were possibly attributable to the difference in ring junction of octahydro-7(1H)-quinolone moieties: the former is of cis, and the latter is of trans. In order to confirm our assumption, we examined the cyclization of model compounds available from cis- and trans-octahydro-7(1H)-quinolone[6] (XIVa and XIVb).



VII

VIII: R=H

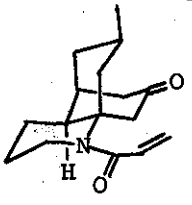
IX: R=$COCH_3$



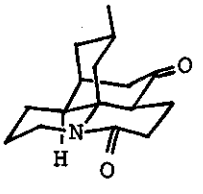
X: R=$CO_2CH_2C_6H_5$

XI: R=H

III: R=COCH=CH_2

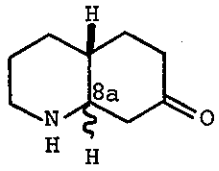


XII



XIII

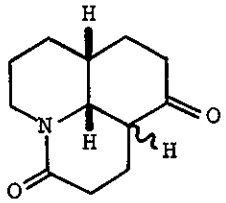
Treatments of XIVa and XIVb with acrylyl chloride gave the corresponding amides, V[oil. PMR $\delta(CDCl_3)$: 3.60-5.19(2H, m, C_2-equatorial H and C_{8a}-H)] and VI[oil. PMR $\delta(CDCl_3)$: 3.11-3.98(3H, m)], respectively. As expected, cyclization reaction of the trans-isomer (VI) with potassium tert-butoxide in tert-butanol at room temperature proceeded smoothly to give two isomeric decahydro-3H,10H-benzo[i,j]quinolizine-3,10-diones, XV[53% yield, mp 135.5-137°. IR $\nu(CHCl_3)$: 1720(C=O), 1625 (amide). PMR $\delta(CDCl_3)$: 4.76(1H, d-d-t, J = 13, 4, 2Hz, C_5-equatorial H)] and XVI[28% yield, mp 119-121°. IR $\nu(CHCl_3)$: 1720 (C=O), 1625(amide). PMR $\delta(CDCl_3)$: 4.79(1H, d-d-t, J = 13, 4, 2Hz, C_5-equatorial H), 3.28(1H, d-d, J = 11, 6Hz, C_{10b}-H)]. These lactam ketones were isomeric at the C-10a configuration, because the latter isomerized readily to the former during chromatography on basic alumina. Final and direct proof of stereochemistry of the main product (XV) was obtained by leading XV to a known perhydrojulolidine of all-trans backbone[7] (XVII). The same products (XV and XVI) were obtained on treatment of VI with p-toluenesulfonic acid in benzene at room temperature in 43% and 10% yields, respectively, along with the cis-amido ketone (V; 9% yield).[8] On the other hand, attempts to cyclize the cis-amido ketone (V) under the same conditions as above were unsuccessful, resulting in recovery of the starting material. A prolonged treatment under the basic condition gave complex products. These Michael-type cyclization should proceed under the severe stereoelectronic control, that is, via a perpendicular attack of the electrophilic center on the



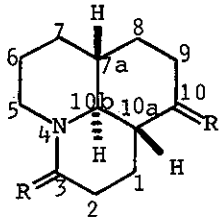
XIVa: β-H_{8a}

XIVb: α-H_{8a}

V , VI

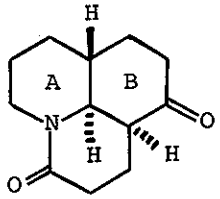


XIX

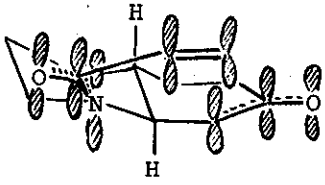


XV: R=O

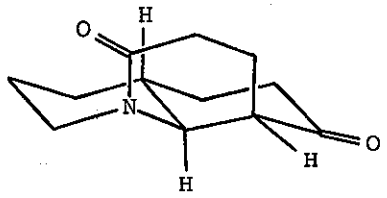
XVII: $R=H_2$



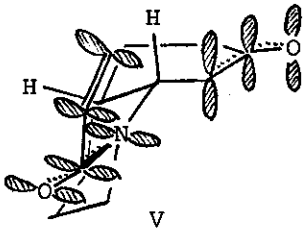
XVI



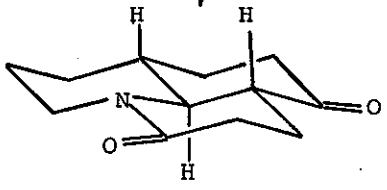
VI



XVI



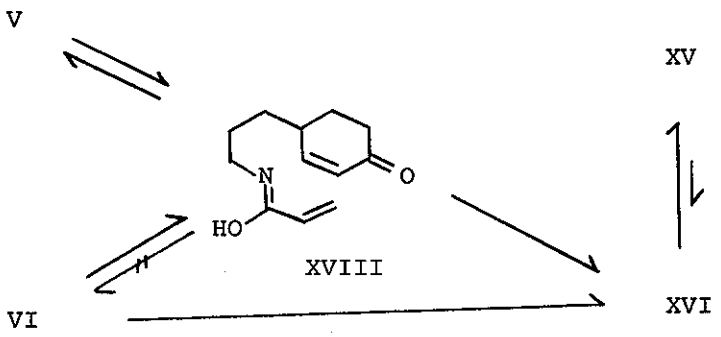
V



XV

enolate, which enables the π-electrons of both reaction centers to come into the maximum overlap.[9] Inspection of the Dreiding model indicates easy fulfilment of the requirement with the trans-isomer, while not with the cis-isomer.[10] Such a requirement on the cis-isomer can be satisfied only in the conformation which forces its A-ring to deform into a strained boat form.[11]

Treatment of V or VI with p-toluenesulfonic acid in boiling toluene gave the same products, XV(47% from V or 60% from VI) and XVI(11% from V or 9% from VI). The result is well interpreted by assuming formation of the same intermediate (XVIII)[12] from both V and VI followed by a thermal Diels-Alder cyclization to the endo-adduct (XVI) accompanying a subsequent isomerisation to the all-trans-isomer (XV). It is of great interest that the amido enone (XVIII) afforded only the A/B trans-tricyclic lactams (XV and XVI) rather than the A/B cis-isomers (XIX).[13]



Here, we have confirmed the importance of a stereoelectronic requirement in the cyclization of N-acrylyl-cis- and -trans-octahydro-7(1H)-quinolones.

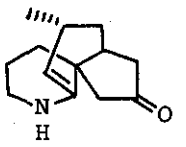
REFERENCES AND FOOTNOTES

1 Z. Horii, S. Kim, T. Imanishi, and T. Momose, Chem. Pharm. Bull. (Tokyo), 1970, 18, 2235.

2 D.B. MacLean, "The Alkaloids," Vol. XIV, ed. by R.H.F. Manske, Academic Press, New York, 1973, pp 347-405.

3 Structure of the hydroboration products from the N-ethoxycarbonyl analog has been described in our previous paper; ref. 1

4 Reaction of the N-ethoxycarbonyl derivative of III has afforded the rearranged product (A) in a moderate yield under an acidic condition: see ref. 1.



A

5 H. Dugas, M.E. Hazenberg, E. Valenta, and K. Wiesner, Tetrahedron Letters, 1967, 4931.

6 T. Momose, S. Uchida, N. Yamaashi, and T. Imanishi, Heterocycles, 1975, 3, 713.

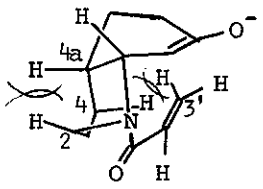
7 F. Bohlmann and C. Arndt, Chem. Ber., 1958, 91, 2167.

8 In N-benzoyl analogs, the trans-isomer is known to isomerize exclusively to the cis-isomer: see ref. 6.

9 Stereoelectronic requirements for the conjugate addition to enone systems have been discussed: see, for example, E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," John Wiley & Sons. Inc., New York, 1965, pp 314-316; N.L. Allinger and C.K. Riew, Tetrahedron Letters, 1966, 1269.

10 Only a favorable conformation was depicted for the cis-isomer (V): see footnote 4 in ref. 6.

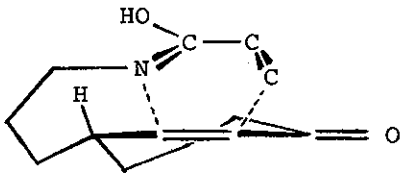
11 Although a boat conformation (V') could satisfy this requirement, the non-bonded interaction between C_2-H and C_{4a}-H and between C_4-H and $C_{3'}$-H in such a conformation would exclude its contribution in cyclization.



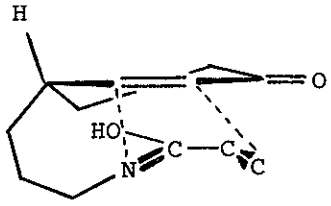
V'

12 A small amount of XVIII was isolated from both V and VI on treatment with p-toluenesulfonic acid in boiling benzene.

13 Inspection of the Dreiding model suggested that the transition state for the A/B cis-isomer (B) would be less favorable than that for the A/B trans-isomer (C) for the maximum overlap of the π-electron systems in the Diels-Alder type cyclization step.



C



B

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