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MECHANISTIC AND SYNTHETIC ASPECTS OF THE ACID-CATALYZED AMINO-CLAISEN REARRANGEMENT OF N-(β-KETOVINYL)ISOQUINUCLIDENES

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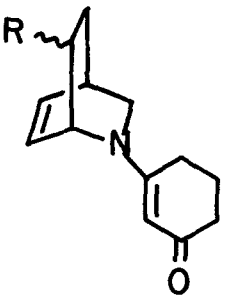
Summary. Studies of the acid-catalyzed, amino-Claisen rearrangement of N-(β-cyclohexenonyl)isoquinuclidenes have provided results which pertain to the mechanism of the process and to synthetic applications for construction of the lycorane tetracyclic skeleton.

In earlier studies,[2,3] we demonstrated that amino-Claisen rearrangements[4] of N-vinylisoquinuclidenium salts, generated *in situ* by reaction of the corresponding tertiary amines with 1-chlorobut-1-en-3-one, serves a mild and efficient method for preparation of cis-fused hydroisoquinolines. An alternate approach which we developed[2,3] involved the use of an acid-catalyzed version of the amino-Claisen rearrangement in which N-(β-ketovinyl)isoquinuclidenes are converted to hydroisoquinolines, as exemplified by the conversions $\underset{\sim}{1} \rightarrow \underset{\sim}{2}$. Activation of the systems for rearrangement was proposed to involve O-protonation of the β-enaminone function in $\underset{\sim}{1}$ followed by a stepwise sequence for C-N bond cleavage and C_2-C_5 bond formation. Qualitative evidence was provided[3] for an interesting substituent effect found in the increasing ease and efficiency for rearrangement of the isoquinuclidenes $\underset{\sim}{1}$ for the series of C-7 substituents R=H, $CH_3\overline{C\text{-}O\text{-}CH_2CH_2O}$, acetyl. In continuing studies, we have pointed out how the acid-catalyzed amino-Claisen rearrangement might be used in construction of substances possessing the tetracyclic structure found in the lycorane natural product series.[5] In this communication we report an example of this application along with results which pertain to the detailed mechanism of the reaction.

Previously, we had observed that γ-enolate anions of β-enaminones could be regioselectively generated by using stoichiometric quantities of the thermodynamic base, lithium hexamethyldisilazide (LHDS), and alkylated with a variety of alkyl halides.[5] We envisaged that a sequence

involving two carbon γ-alkylation of the isoquinuclidene 1a (R=methyldioxolane) followed by amino-Claisen rearrangement and lactamization might be useful for generation of the tetracyclic enamidoketone 5, a possible intermediate in a lycorane synthesis. Indeed, the esters 3a and 3b are formed as diastereomeric mixtures by reaction of 1a with LHDS (1eq, -78°C, THF) followed by quenching with either ethyl or t-butyl α-bromoacetate.[6] Interestingly, reaction of the ethyl esters 3a under the normal rearrangement conditions (p-TsOH, 1:30 H_2O-C_6H_6, 80°C) for 24h provided a 1:1 mixture of the tetracyclic enamidoketone 5 and dienone lactam 4[7] (50%). Reaction for longer time periods (48h) leads to exclusive production (40%) of 5[6], suggesting that the lactam 4 serves as a precursor to 5. This was confirmed by investigation of the time and temperature dependence of t-butyl ester 3b rearrangements. Accordingly, treatment of 3b under the rearrangement conditions for 2h at either 80°C or 130°C gave 5, 4 and the acetyl isoquinuclidene 3d in respective ratios of 4:2:3 and 7:1.5:1. The tetracyclic product can be obtained exclusively in 70% yield by reaction of 3b at 80°C for 24h.

These observations demonstrate the unique application of acid catalyzed, amino-Claisen rearrangements of N-(β-ketovinyl)isoquinuclidenes in routes for preparation of functionalized, polycyclic substances containing the hydroisoquinoline unit. Additionally, the results provide insight into the mechanistic intricacies of these reactions. Ketal hydrolysis precedes rearrangement under the reaction conditions as attested to by isolation of 1 (R=acetyl), 3c and 3b by brief treatment of the blocked ketones with pTsOH in wet benzene at room temperature. In the ethyl ester series, the O-protonated intermediate 6 (R=Et) undergoes eliminative C-N bond cleavage to produce the dienone ester 7 (R=Et) which can partition to the lactam 4 by amide bond formation or to the hydrophenanthridine 8 (R=Et) by acid catalyzed, cationic cyclization.[8] Both substances 4 and 8 serve as precursors for the tetracyclic enamidoketone 5. The slower rate of conversions of 3a to 5 can be rationalized by postulating that lactam formation from 7 (R=Et) is faster than cationic cyclization and that conversion of 4 to 5 is slow due to the low nucleophilicity of enamidoketone function. The greater rate and selectivity for reaction of the t-butyl ester 3b can be understood on this basis; t-butyl ester hydrolysis must occur prior to acid catalyzed ring opening under the acidic reaction conditions.[9] Cationic cyclization of the formed dienone acid 7 (R=H) to generate the hydrophenanthridine 8 (R=H) should now effectively compete with amide bond formation between the amine and acid functions. Conversion of 8 (R=H) to the tetracyclic product would then complete the overall transformation



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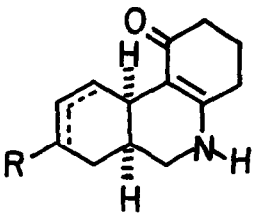

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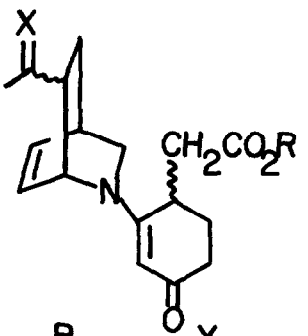
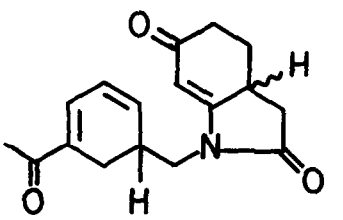


	R	X
3a	Et	OCH_2CH_2O
3b	t-Bu	OCH_2CH_2O
3c	Et	O
3d	t-Bu	O



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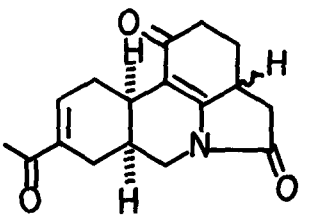

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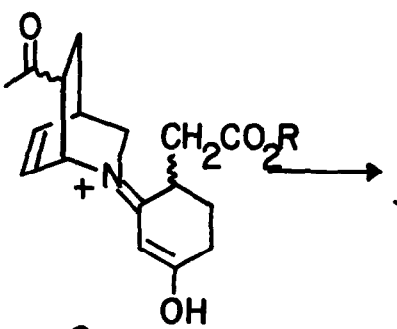

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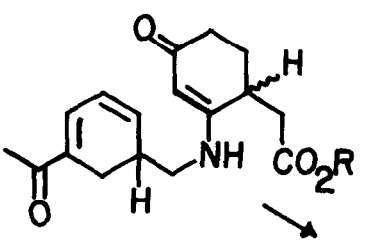

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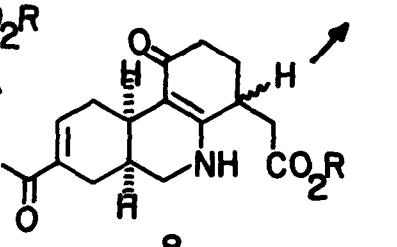

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of 3b to 5.

Although the postulates presented above are based on qualitative evidence only, they appear to provide a working hypothesis for understanding the acid catalyzed, amino-Claisen rearrangements of N-(β-ketovinyl)isoquinuclidenes. Moreover, the reaction appears to possess unusual synthetic potential. These and other aspects of this process are being subjected to continued investigation.

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REFERENCES AND NOTES

1. A portion of the initial phase of this study was conducted by PLH at Texas A&M University.
2. Mariano, P.S.; Dunaway-Mariano, D.; Huesmann, P.L.; Beamer, R., Tetrahedron Lett., 1977, 4299.
3. Mariano, P.S.; Dunaway-Mariano, D.; Huesmann, P.L., J. Org. Chem., 1979, 44, 124.
4. Rhoads, S.J.; Raulins, N.R.; Org. React., 1975,22, 1; Ziegler, F.E., Acc. Chem. Res., 1977, 10, 227.
5. Chen., Y.L.; Mariano, P.S.; Little, G.M.; O'Brien, D.; Huesmann, P.L., J. Org. Chem., 1981, 46, 4643.
6. All new compounds reported in this paper possess spectroscopic and analytical data consistent with the assigned structure.
7. Separation of 4 from mixtures containing 5 was not possible by use of a variety of techniques. Thus, product (4:5) ratios were obtained by ^{1}H-NMR analysis. The structure of 4 was assigned by comparison of its ^{1}H-NMR and ^{13}C-NMR spectra with those of closely related substances (ref. 3).
8. Johnson, W.S.; Angew. Chem. Int. Ed. Engl., 1976, 15, 9; Johnson, W.S.; Harding, K.E., J. Org. Chem., 1967, 32, 478; Johnson, W.S.; Lunn, W.H., Fitzi, K., J. Am. Chem. Soc., 1964, 86, 1972.
9. Schwyzer, R.; Kappeler, H., Helv. Chim. Acta., 1961, 44, 1991; Fonken, G.S.; Johnson, W.S., J. Am. Chem. Soc., 1952, 74, 831.

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