INTRAMOLECULAR MICHAEL ADDITIONS IN THE PELLETIERINE-BENZALDEHYDE CONDENSATION[1]

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All of the successful syntheses of the Lythraceae alkaloids (e.g., 1, vertaline)[2] have utilized the base catalyzed condensation of a substituted benzaldehyde with pelletierine (2) to form a quinolizidinone 3.[3] Despite the demonstrated utility of this reaction, there has been only speculation as to its mechanism.[4]

Hanaoka, et. al., have suggested the Mannich reaction outlined in Scheme 1 (path a) as the route for this condensation. Since the condensation occurs at high pH (> 10), the formation of the iminium ion appears unlikely. Direct nucleophilic displacements on the carbinolamine, 4, or on the β-hydroxyketone, 6, have also been suggested,[4] but are unlikely because of the steric hindrance involved, and because the stereochemical predictions (initial formation of trans-adduct) are not borne out experimentally (vida infra). We suggest an alternate pathway (b) which involves a base-catalyzed Claisen-Schmidt condensation followed by an intramolecular Michael addition. The evidence presented in this communication favors this latter pathway.

Two diastereomers of 3, defined by the relative stereochemistry of C-4 and C-10, may be produced in the condensation. Thus, in the cis-quinolizidinone, 8,[5] the C-4 aryl group is cis to the C-10 hydrogen. In the trans-quinolizidinone, 9,[5] they are trans to each other. Experimentally 8 and 9 may be differentiated by the presence of Bohlmann bands (2791, 2752 cm^{-1}) in the IR of 9 and by the NMR chemical shift of the benzylic (C-4) proton, δ4.27 in 8 and δ3.27 in 9.[6]

The condensation of 2 with benzaldehyde was the model chosen for our study of this condensa-

SCHEME I
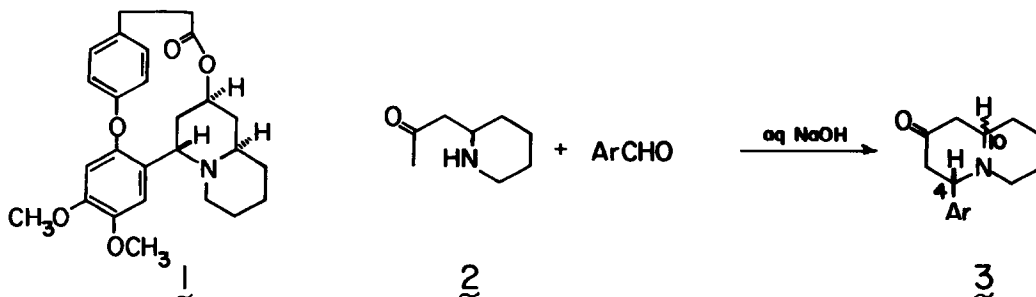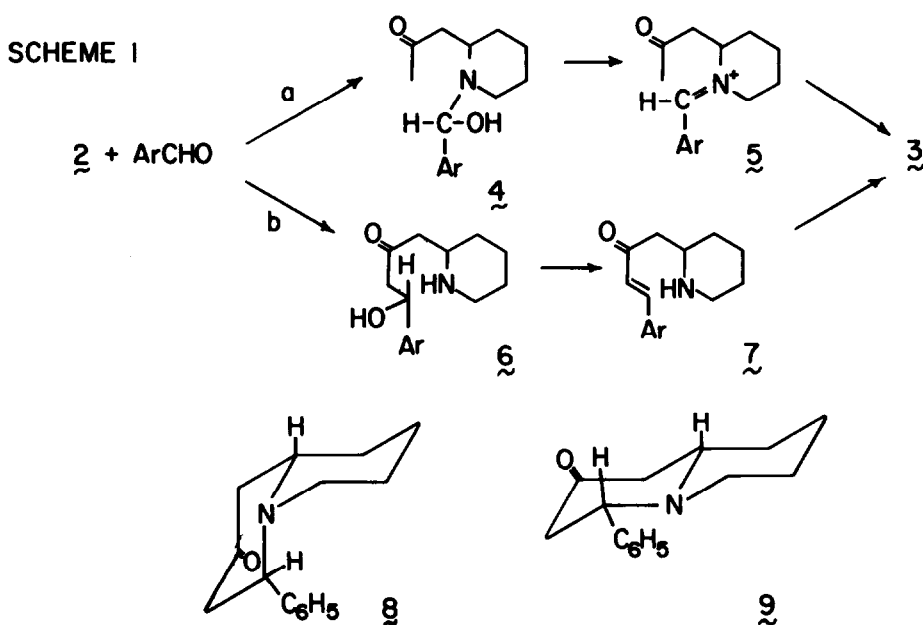
tion. Very limited information was available on this example. Matsunaga, et. al., obtained a
2:1 mixture of 8 and 9 from the condensation in aqueous NaOH at 50°.[3] Wrobel and Golebiewski
report a 50% yield of the trans isomer, 9, in aqueous NaOH.[4b] Since the condensations of substi-
tuted benzaldehydes had shown striking variations with solvent and time, the effects of these
variables on the yield and isomer ratio in the condensation of 2 with benzaldehyde were investi-
gated.

The results of these experiments are given in Table I. The condensations were run at 55°C
using molar equivalents of 2,[7] benzaldehyde, and aqueous NaOH. The reaction mixtures were analyzed
by preparative TLC on silica gel. The diastereomers 8[8] and 9[8] were identified as described above.

In water, where not all of the reaction mixture was soluble, the 8:9 ratio decreased more
slowly than in the methanol reactions which were homogeneous. However, even in methanol, at
short reaction times there was more 8 than 9. The cis isomer could be converted to a 1:5 mixture
of 8 and 9 by heating it with methanolic-aqueous NaOH. These results are in good agreement with

Table I. Condensation of Pelletierine with Benzaldehyde

Solvent	Time	% yield (8 + 9)	8:9
Water	1 hr	58	5/2
	14 hr	82	3/4
methanol[a]	1 hr	20	5/2
	14 hr	56	1/6

[a] Contained about 10% water from the NaOH solution.

those obtained with substituted benzaldehydes.[4a] These combined results have led to speculation that the cis-quinolizidinones are formed more rapidly in these condensation, but that they are readily isomerized to the thermodynamically more stable trans-quinolizidinones.[4]

Examination of Dreiding models of the proposed intermediates leads to some predictions concerning the relative ease of forming 8 and 9. The assumption is made that the ring in 5 and 7 would be a chair or pseudo-chair and that the side chain would be equatorial or pseudo-equatorial. On this basis it is predicted that the formation of 8 from 5 should be less favorable than the formation of 9, because continuous overlap of the involved orbitals is much more difficult in the former case. From 7, 8 would be predicted to be slightly more favored than 9. Thus, even this admittedly crude evaluation of stereoelectronic factors favors 7 as the intermediate.

Since both of these routes would be expected to be affected in the same manner by variation of electronic and steric factors, little information would be gained by a study of substituent effects. Furthermore, there is little to distinguish these mechanisms kinetically. However, synthesis of the proposed intermediates and the observation of their cyclization under the conditions of the benzaldehyde condensation would provide positive information on the mode of the condensation.

Intermediate 13 was prepared as described in Scheme 2. Grisar and Claxton had previously prepared 12 (X = Cl) by a non-related route.[9] The salt, 12, did not cyclize at an appreciable rate at 55°. However, cyclization of 13 occurred in $CDCl_3$ at room temperature. Monitoring by NMR or TLC demonstrated that within three days 13 has been completely converted to 8. After treatment of 12 with aqueous NaOH for 30 min, its vinyl protons could no longer be detected in the NMR whereas the C-4 proton of 8 was observed.

The results of the treatment of 12 with excess aqueous NaOH under various conditions are given in Table II. The trend in the 8:9 ratios is similar to the trend in the data in Table I. Since the total yields of the quinolizidinones do not vary significantly with time, it is likely that 13 is cyclizing rather than first forming another intermediate (i.e., 5). Thus, it has been demonstrated that the required Claisen-Schmidt reaction occurs readily under the conditions of the condensation and that the intermediate, 13, cyclizes very efficiently to yield quinolizi-
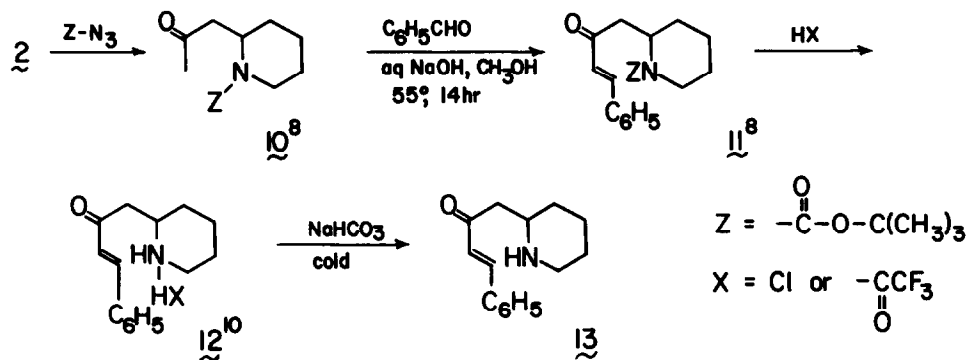
Table II. Treatment of 12 with excess aqueous NaOH (55°)

Solvent	Time (hr)	% yield (8 + 9)	8:9
Water[a]	1	70	4:1
	14	69	2:3
	90	64	1:20
methanol[b]	1	62	7:2
	6	67	6:7
	11	61	1:2
	16	79	1:5

[a] The reaction mixture was not homogeneous.

[b] Contained about 10% water from the NaOH solution.

SCHEME 2

dinones mixtures of similar composition to those formed by the direct condensation.

In our opinion the available data greatly favors the proposed intramolecular Michael addition route (path b) for the pelletierine-benzaldehyde condensation. The Mannich route is disfavored by the data. We are presently attempting to prepare 5 in order to obtain more information on the likelyhood of this latter route.

References and Notes

1. J. Quick, R. Oterson, and C. Mondello, presented in part at 172nd National Meeting of the American Chemical Society, San Francisco, Aug., 1976, Abstr. 78.

2. M. Hanaoka, N. Ogawa, and Y. Arata, Chem. Pharm. Bull. (Tokyo), 24, 1045 (1976); I. Lantos and B. Loev, Tetrahedron Letters, 2011 (1975); J. Wrobel and W. Golebiewski, Bull. Acad. Pol. Sci., 7, 601 (1975).

3. T. Matsunaga, I. Kawasaki, and T. Kaneko, Tetrahedron Letters, 2471 (1967).

4. a) M. Hanaoka, N. Ogawa, K. Shimizu, and Y. Arata, Chem. Pharm. Bull (Tokyo), 23, 1573 (1975); b) J. Wrobel and W. Golebiewski, Bull. Acad. Pol. Sci., 7, 593 (1975).

5. This is presumably the most stable chair conformation of this diastereomer.[4b] A flexible conformation of 8 may be of lower energy.[4]

6. See ref. 4 for a discussion of these spectrometric criteria.

7. J. Quick and R. Oterson, Synthesis, in press.

8. Satisfactory spectral and analytical data has been obtained on this compound and/or a derivative.

9. J. Grisar and G. Claxton, U.S. Pat. 3,853,855 (1974); cf. J. Grisar, G. Claxton, and K. Stewart, Synthesis, 284 (1974).

10. Salt 12 (X = Cl)[8] had the same melting point as that previously reported.[9]