The Pelletierine Condensation. Mechanistic Studies[1a]

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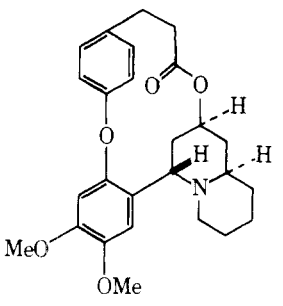
Evidence is presented to show that the pelletierine condensation proceeds via a Claisen–Schmidt condensation to the enone 8, which cyclizes to the 4-aryl-2-quinolizidinones by an intramolecular Michael-type addition. In aprotic solvents, 8 afforded the less stable *cis*-quinolizidinone (3) with relatively high selectivity. The implications of this finding for the mechanism of the isomerization of the *cis*- to the *trans*-quinolizidinones are discussed. In protic solvents the isomerization occurred without added base. The pelletierine condensation was also found to proceed in low yield under acidic conditions. An unusual carbonyl-assisted hydrolysis of a trifluoroacetamide was observed. An efficient procedure for the large-scale preparation of pelletierine is described in the Experimental Section.

The type I[2] alkaloids from the *Lythraceae* family have been found to possess sedative, antiinflammatory, and diuretic activities.[3] These properties, along with the unique structures of the alkaloids [e.g., vertaline (1)], have encouraged several



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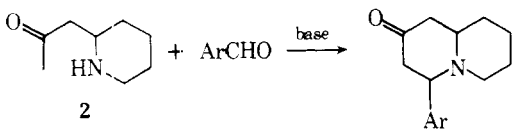
syntheses.[4,5] All of these syntheses have utilized the pelletierine condensation (eq 1) to establish the 4-aryl-2-quinolizidinone portion of the molecule. This condensation was originally described by Matsunaga et al. in 1967.[6] Recently Hanaoka and his co-workers[7] and Wrobel and Golebiewski[8] have reported on their extensive studies of the condensation of pelletierine with substituted benzaldehydes under various conditions. Both groups concluded that the *cis*-quinolizidinones (e.g., 3) were the major products of a kinetically controlled reaction but that these then isomerized to the *trans*-quinolizidinones (e.g., 4) under the reaction conditions. Hanaoka considered the condensation to proceed as a Mannich reaction (eq 2) via the carbinolamine 5 and/or the iminium ion 6. However, Wrobel favored a Claisen–Schmidt condensation in which 7 cyclized via displacement of the hydroxyl group by the nitrogen (eq 3a). No direct experimental evidence was presented to support either proposal.



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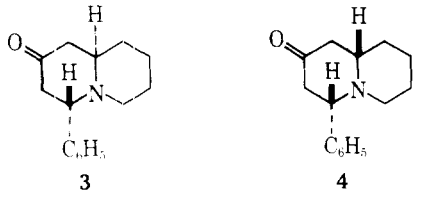
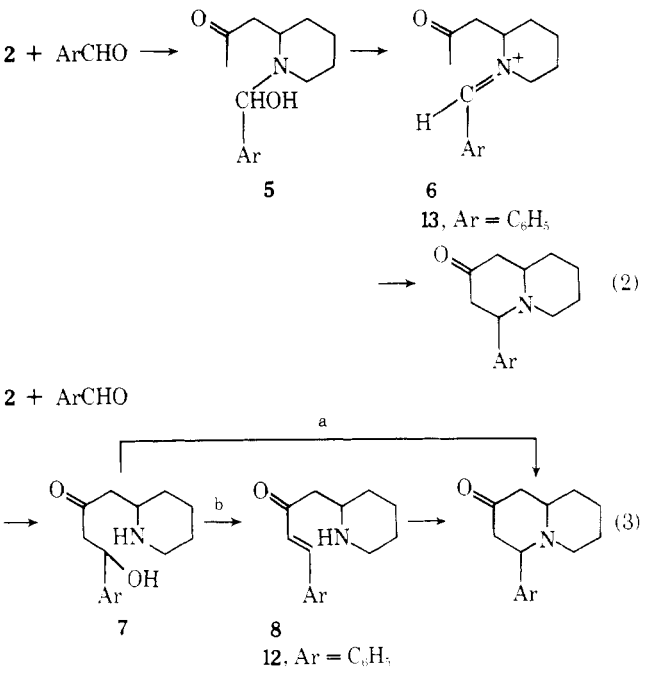


3 4

Our interest in establishing the nature of the pelletierine condensation stemmed from the hope that an understanding of the mechanism would allow for better stereochemical control of the condensation and thus enhance its utility for the synthesis of the *Lythraceae* alkaloids. This interest was also piqued by the omission of any discussion of what appeared to us to be the most reasonable mechanism, eq 3b, an intramolecular Michael-type reaction of 8 (a more likely intermediate than 7).[10] Detailed kinetic and substituent studies would be of little value in deciding between the mechanisms described in eq 2 and 3b, since these are expected to be affected in the same manner by the electronic and steric influences of aryl substituents. However, preparation of the proposed intermediates and observation of their cyclization under the conditions of the pelletierine condensation would provide a method for distinguishing between these mechanisms.



5 6

13, Ar = C_6H_5

(2)

7 8

12, Ar = C_6H_5

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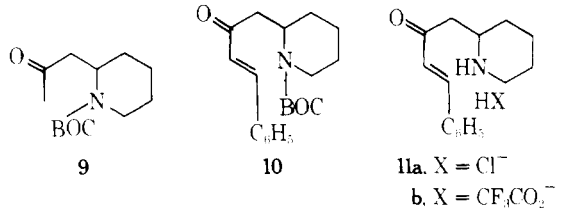

9 10

11a, X = Cl^-

b, X = $CF_3CO_2^-$

In this paper we discuss the preparation and cyclization of the Claisen–Schmidt intermediate, 8, and our attempts to prepare the Mannich intermediate (5 or 6) as well as our studies on the pelletierine condensation with benzaldehyde and on the isomerization of the product quinolizidinones.

Results and Discussion

The Pelletierine Condensation with Benzaldehyde. In order to avoid complication by substituent effects, benzaldehyde itself was chosen as the aldehyde component for these

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Table I. Formation of *cis*- and *trans*-4-Phenyl-2-quinolizidinone

expt[a]	solvent	base (equiv)	T, °C	t[b]	% yield	3:4
1	water	NaOH (6)	55	1	62	3.6
2	water	NaOH (6)	55	3	63	2.4
3	water	NaOH (6)	55	6	64	1.6
4	water	NaOH (6)	55	16	66	1.1
5	water	NaOH (1.5)	55	6	49	2.2
6	aq methanol[c]	NaOH (6)	55	1	61	2.9
7	aq methanol[c]	NaOH (6)	55	3	60	1.3
8	aq methanol[c]	NaOH (6)	55	6	57	0.40
9	aq methanol[c]	NaOH (6)	55	17	62	0.14
10	aq methanol[c]	NaOH (1)	55	1	20	2.4
11	aq methanol[c]	NaOH (1)	55	14	57	0.15
12	methanol	NaOH (1.5)	55	16	64	0.45
13	water	NaOH (1.5)	RT	15	45	6.6
14	ethanol	NaOEt (11)	RT	21	38	2.8
15	THF	Et_3N (4)	55	16	0	
16	water	NaOH (9)	55	1	70	3.8
17	water	NaOH (9)	55	14	69	0.67
18	water	NaOH (9)	55	90	64	0.04
19	aq methanol[c]	NaOH (9)	55	1	62	3.4
20	aq methanol[c]	NaOH (9)	55	6	67	0.82
21	aq methanol[c]	NaOH (9)	55	11	61	0.44
22	aq methanol[c]	NaOH (9)	55	16	79[d]	0.20
23	THF	Et_3N (2)	55	16	66	7.5

[a] In experiments 1–15 pelletierine was condensed with benzaldehyde. In experiments 16–23 intermediate **12** obtained in situ from **11a** was cyclized. See the text for a discussion of the analysis. [b] In hours. [c] Contains 10% water by volume. [d] Salt **11b** was used in this experiment.

studies. However, before considering the preparation and cyclization of the intermediates some knowledge of the effect of solvent, temperature, and time on the pelletierine condensation with benzaldehyde was required. The condensation was carried out with pelletierine and a slight excess of benzaldehyde under the conditions listed in Table I (experiments 1–15). The reaction mixtures were analyzed by preparative layer chromatography.

The structures of **3** and **4** were assigned from their NMR and IR spectra.[11] The *trans*-quinolizidinone (**4**) exhibits Bohlmann bands (2791, 2752 cm^{-1}) in its IR spectrum. These are absent in the cis isomer, **3**. The position of the NMR signal due to the benzylic (C-4) proton is also diagnostic. It is at δ 4.27 in **3**, but at δ 3.27 in **4**.

The results given in Table I show that the condensation was very rapid even under heterogeneous conditions, i.e., water. The yields did not vary significantly with time as long as an excess of the base was utilized (experiments 1–4 and 6–9). However, when approximately 1 equiv of base was utilized the reaction was slowed sufficiently to allow observation of a variation in yield with time (experiments 5, 10, and 11). Similar results have been noted with substituted benzaldehydes.[7] Changing from one protic solvent to another did not affect the yield. However, the condensation failed when tetrahydrofuran (THF) was utilized (experiment 15) although aqueous THF has been utilized.[4c] Triethylamine was used as the base in experiment 15 so as to avoid having a hydroxyl moiety in the reaction medium.

The **3:4** ratio showed a more interesting variation. The ratio decreased significantly with time at 55 °C. This change was less rapid in the heterogeneous reaction mixtures (experiments 1–4) than in the homogeneous mixtures (experiments 6–9). Similar trends have been noted with substituted benzaldehydes.[7] This decrease is due to the isomerization of the initially formed cis isomer to the more stable trans isomer (vide infra). Variation of the base concentration appears to have only a slight affect on the ratio (compare experiments 5, 10, and 11 with 3, 6, and 9, respectively) whereas changes in the reaction temperature significantly affected the **3:4** ratio. The isomerization was much slower at room temperature (experiments 13 and 14) than at the higher temperatures.[5] Unfortunately the rate of the condensation was also significantly depressed by the lower temperature.[8]

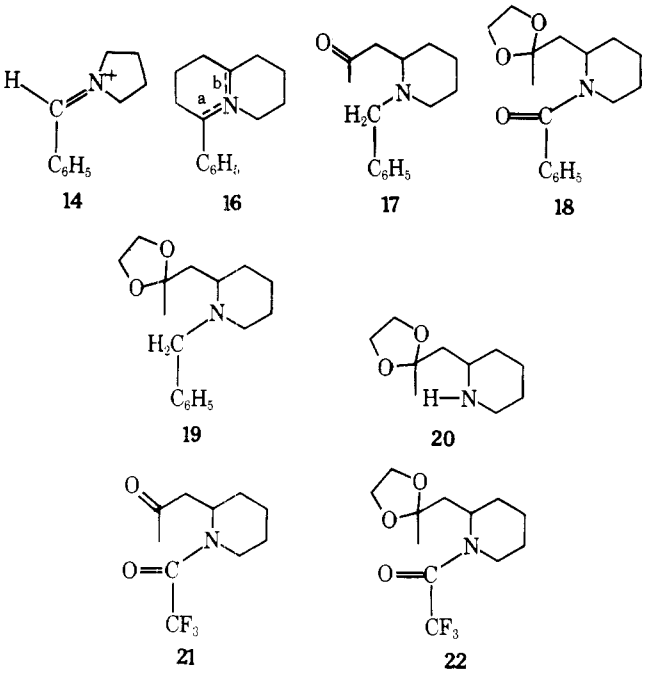
Preparation and Cyclization of the Claisen–Schmidt Intermediate. With the above data for comparison, the proposed intermediates could be studied. The intermediate in the Claisen–Schmidt route (eq 3b), **12** (**8**, Ar = C_6H_5), was prepared by the condensation of benzaldehyde with an N-blocked pelletierine followed by deblocking under controlled conditions. The *tert*-butoxycarbonyl (BOC) group was chosen as the blocking group since it is stable to base but easily removed under acidic conditions.[12] Thus, BOC pelletierine (**9**) was readily prepared from pelletierine and BOC-N_3 in 97% yield.[13] Condensation of **9** with benzaldehyde under the conditions of the pelletierine condensation afforded the enone, **10**, in 90% yield. The expected trans stereochemistry about the double bond was confirmed by the NMR signal due to the proton α to the carbonyl, δ 6.73 (doublet, J = 16 Hz). The analogous proton in *trans*-benzalacetone appears as a doublet at 6.70 (J = 16 Hz).[14]

Removal of the protecting group was readily accomplished by treatment with either hydrogen chloride in nitromethane or trifluoroacetic acid in methylene chloride.[12] The former method was normally utilized since it commonly afforded a crystaline product upon removal of the solvent. This hydrochloride salt, **11a**, has been purified and characterized by comparison with an authentic sample.[15] The required intermediate, **12**, could be prepared by treatment of **11** with cold, aqueous sodium bicarbonate followed by immediate extraction into chloroform. The NMR spectra of freshly prepared samples of **12** contained the signals of **3** as well as the signal expected for **12**. The cyclization of **12** in $CDCl_3$ was slow enough at room temperature to be monitored by NMR. The increase in the δ 4.27 signal of **3** was accompanied by a decrease in the δ 6.65 doublet of **12**. After 3 days **12** could no longer be detected and the spectrum was that of **3**. None of the trans isomer, **4**, was detected even after 2 weeks.

The results obtained when **11a** was treated with base are reported in Table I (experiments 16–23). From these it is apparent that the yields and **3:4** ratios are comparable to those obtained for the pelletierine condensation. This is compatible with **12** being an intermediate in the condensation. In the absence of a hydroxylic or protic solvent **12** cyclizes readily (experiment 23) yet the pelletierine condensation does not occur (experiment 15). Thus, it is unlikely that **12** is reverting to pelletierine and then cyclizing via the Mannich pathway (eq 2) in this case. This experiment also rules out the possibility that the cyclization of **12** occurs via **3** obtained by addition of water to the enone.

The Mannich Pathway. Our efforts were next directed toward demonstrating the possibility of the Mannich pathway (eq 2). Thus, several attempts were made to prepare the Mannich intermediate, **13** (**6**, Ar = C_6H_6). The related iminium ion, **14**, has been prepared in high yield by the condensation of pyrrolidine perchlorate and benzaldehyde.[16] When pelletierine perchlorate (**15**) was treated with benzaldehyde in refluxing benzene for 2 days, no signals other than those of **15** and benzaldehyde were observed in the NMR spectrum. The proton of **13** is expected to resonate at about δ 9.[16] Basification of the reaction mixture afforded a mixture of pelletierine and benzaldehyde. In contrast to this result we have found that the pelletierine condensation occurs in 0.12 N HCl to afford **3** and **4** (38%, 2.5:1) and with a catalytic amount of *p*-toluenesulfonic acid to give 19% (1:2) of the products.

Iminium ions have also been prepared from the corresponding tertiary amines by oxidation with mercuric acetate.[17]



A previous oxidation of a tertiary benzylamine did not afford the aryl iminium ion **16a** but rather ion **16b**.[18] However, since in **17** the proper orientation for the removal of the benzylic proton should be attainable, the conjugated ion, **13**, may be the major product. Benzylamine **17** was prepared from *N*-benzoylpelletierine[19] via the ketal, **18**. Reduction of **18** with $LiAlH_4$ afforded the benzylamine ketal, **19**, which gave **17**[20] upon deketalization. An aqueous acetic acid solution of **17** was treated with mercuric acetate as described by Leonard et al.[17] The NMR spectrum of this solution exhibited no peak at δ 9. Treatment of this solution under acidic or basic conditions analogous to those utilized in the pelletierine condensation yielded mixtures which did not contain the quinolizidinones, **3** or **4**, in amounts detectable by TLC or NMR. Similar treatment of **19** afforded no evidence of quinolizidinone or iminium ion formation.

Since functional group blocking had been effective in the synthesis of the Claisen–Schmidt intermediate, its application to the preparation of **13** was attempted. In this case the ketone reactivity of pelletierine was to be blocked by ketalization. Direct ketalization of pelletierine was unsuccessful, presumably because of competing Knovenagel condensations resulting in the formation of a red tar. To prevent this the nitrogen of pelletierine was blocked prior to ketalization. Thus, *N*-trifluoroacetylpelletierine (**21**) was ketalized in the usual manner to afford **22**. Treatment of **22** with base afforded **20**.[21] The condensation of **20** with benzaldehyde was attempted under several sets of conditions analogous to those of the pelletierine condensation. No evidence for either **5** (Ar = C_6H_5) or **13** was found. Since these products may have been hydrolyzed during the workup, an attempt was made to detect them in situ. Thus, a solution of **20**, benzaldehyde, and sodium hydroxide in methanol-d_4 was heated in a sealed NMR tube. After 3 days at 55 °C the only observable change in the NMR spectrum was a decrease in the benzaldehyde signal at δ 9.9 and the appearance of a signal at δ 4.5. The intermediate **5** would be expected to exhibit a signal at δ 6.4[23] while **13** would have a signal at δ 9.[16] The δ 4.5 signal was due to benzyl alcohol formed by Cannizzaro reduction of the benzaldehyde.

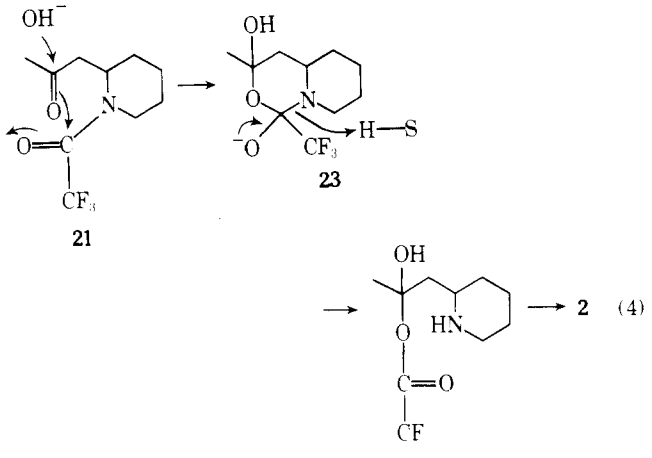
We have been unable to prepare or otherwise find evidence for the existence of either of the possible intermediates in the Mannich pathway. Although the path taken by the acid-catalyzed pelletierine condensation[24] is not known, the observation that the pelletierine perchlorate could not be condensed with benzaldehyde suggests that the condensation may not proceed via the Mannich pathway, even in acid. Models of **13** indicate that there is a substantial steric interaction ($A^{1,3}$ strain)[26] between the iminium hydrogen and the acetonyl when that group is equatorial. There are also unfavorable interactions between the hydrogens α to the nitrogen and the aryl hydrogens when that ring attempts to be coplanar with iminium ion. These interactions may be sufficient to discourage the formation of **13** and, thus, the Mannich route.

Table II. Isomerization of *cis*-4-Phenyl-2-quinolizidinone (3)

expt[a]	solvent	catalyst (equiv)	*T*, °C	*t*[b]	3:4
24	aq methanol[c]	NaOH (4)	55	22	0.11
25	aq methanol[c]	none	55	22	0.20
26	methanol	none	55	17	0.43
27	aq methanol[c]	HCl (10)	55	25	*d*, *e*
28	THF	Et_3N (2)	55	17	*d*

[a] Samples of **3** (50–150 mg) were treated under the described conditions. The products were analyzed as described in the text. [b] In hours. [c] Contains 10% water by volume. [d] No **4** was isolated. [e] There was some loss of quinolizidinone by decomposition.

The hydrolysis of the trifluoroacetyl group in **22** deserves some comment. Previous reports had indicated that trifluoroacetamides were very sensitive to base.[27] However, after 2 weeks of treatment with potassium carbonate in aqueous methanol at 55 °C the amide group absorption was still observable in the IR spectrum. Aqueous sodium hydroxide and other combinations of base and solvent were no more effective. *N*-Trifluoroactylpiperidine[28] behaved in the same manner as **22** whereas the hydrolysis of **21** to **2** was complete in less than 7 h under the same conditions. Thus, it appears that the hydrolysis of *N*-trifluoroacetylpiperidines is slower than that of other trifluoroacetamides and that some characteristic of **21** causes it to be more susceptible to attack. We may speculate that the hydrolysis of **21** is assisted by the ketone carbonyl, perhaps as depicted in eq 4. Attack by a nucleophile on the



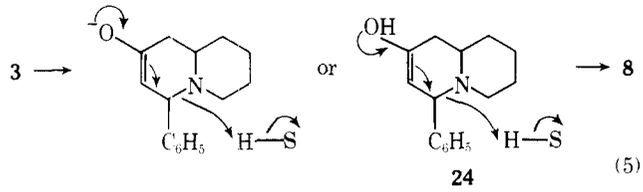
presumably more reactive ketone carbonyl would produce a hydrate which could add to the amide carbonyl affording the hemiketal alkoxide, **23**. Recently a diol intermediate related to **23** has been detected in the hydrolysis of *N*-trifluoroacetylpyrrole.[29]

Isomerization of *cis*-4-Phenyl-2-quinolizidinone. In order to learn more about the changes in the 3:4 ratio, **3** was subjected to a variety of conditions. The results of this study are given in Table II. The ratios were determined as above. The total recovery of **3** and **4** was usually better than 80% except in experiment 27 where there was some decomposition of the quinolizidinone. Isomerization occurred readily under the conditions of the condensation (experiment 24) as well as

in the absence of added base (experiments 25 and 26). Isomerization does not occur in strong acid (experiment 27); however, it has been observed by others in dilute acid.[5,30] This difference, which has been discussed by Lantos et al.,[5] may explain the different ratios observed in the acid-catalyzed condensations (vide supra).

The most reasonable mechanism for the isomerization involves a retro-Michael reaction to reform intermediate **8** (eq 5);[7] recyclization will eventually form the more stable[8] *trans*-quinolizidinone. A compound **8** has been isolated as its hydrochloride salt during an acid-catalyzed isomerization of a *cis*-quinolizidinone.[5] This analogue of **12** cyclized in refluxing aqueous methanol to afford the *trans*-quinolizidinone. On the assumption that isomerization does not occur under these conditions, Lantos et al. discounted the intermediacy of **8** in the pelletierine condensation. Experiments 25 and 26 demonstrate that this assumption is invalid at least for **3** and probably for most 4-aryl-2-quinolizidinones.[31] Under these neutral conditions, the enol, **24**, may be involved in the retro-Michael reaction.

Experiment 28 and the previously described NMR study of the cyclization of **12** in $CDCl_3$ demonstrate that the isomerization does not occur readily in the absence of a protic solvent. A protic solvent may assist in the retro-Michael reaction by protonating the nitrogen as it is being eliminated (eq 5). This protonation would be more difficult with the bulky, protonated triethylamine, the only proton source available in the nonprotic medium of experiment 28.



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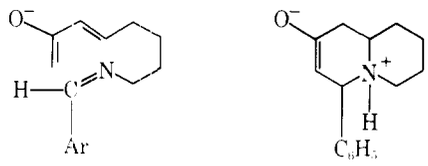

25 **26**

Conclusion

The data presented above conclusively demonstrate that the Claisen–Schmidt route (eq 3b) can occur under the conditions of the reaction. On the other hand, several methods of preparing or detecting the intermediates in the Mannich route (eq 2) have all met with failure. Thus, the mechanism presented in eq 3b must be favored for the pelletierine condensation.

The question still remains as to why the *cis*-quinolizidinones are the kinetic products. Lantos et al. have postulated that the penultimate intermediate is **25** which is formed by a retro-Michael reaction of **6** followed by enolate formation.[5] This diene imine might be expected to cyclize in a Diels-Alder fashion affording the *cis*-quinolizidinone. If it occurs at all it cannot be the *only* route to **3**, since **12** cyclized, under conditions which do not allow for the formation of **6** (experiment 23), to afford a high yield of the *cis*-quinolizidinone (**3**). The **3**:**4** ratio of 7.5:1 observed in experiment 23 suggests that the activation energy for the formation of **3** is at least 1.3 kcal/mol less than that for the formation of **4**. An examination of models of **12** and of **26**, the presumed intermediate in the Michael addition, suggests that the transition states for the two isomers should have similar energies. However, in such a complex system there may be subtle, unnoticed interactions which may account for the 1.3 kcal/mol. Thus, until a more sophisticated analysis of the transition states can be made the question of why the *cis*-quinolizidinones are the kinetic products remains unanswered.

Use is being made of the techniques suggested by experiments 13 and 23 for the preparation of *cis*-quinolizidinones for use in the synthesis of *Lythraceae* alkaloids. Thus, our objectives for undertaking this study have been reached. Our mechanistic analysis of the pelletierine condensation has been verified and some synthetically useful information has been obtained.

Experimental Section[32]

1. 2-Piperidylpropanone (Pelletierine) (2).[33] Into a 3 L, three-neck flask, equipped with a mechanical stirrer, thermometer, and 250-mL addition funnel, is placed 133.5 g (1 mol) of *N*-chlorosuccinimide and 1 L of ether. The vigorously stirred slurry is cooled to −4 °C (salt–ice bath) and 99 mL (1 mol, 85 g) of piperidine is added dropwise via the addition funnel. The rate of addition is controlled so that the temperature of the mixture does not exceed 4 °C. Upon completion of the addition, the cooling bath is removed and the reaction mixture is stirred at room temperature for 2 h. It is then filtered and the precipitate is washed with four 25-mL portions of ether. The filtrate and the ether washes are combined and washed with three 500-mL portions of water. The ether layer is dried (Na_2SO_4) and filtered. The solution is concentrated in vacuo to approximately 150 mL.[35]

In a 2 L, three-neck flask, equipped as above, is placed a solution of 85 g (1.29 mol) of 85% potassium hydroxide in 550 mL of absolute ethanol. After cooling this alkali solution to −4 °C, the *N*-chloropiperidine solution (from above) is slowly added. The rate of addition is controlled so that the internal temperature does not exceed 0 °C. After the addition is complete, the mixture is stirred for 1 h, then the cooling bath is removed and the mixture is stirred at room temperature for an additional 3 h. The reaction mixture is then filtered into a 3 L, three-neck flask containing a solution of sodium acetoacetate.[37] The precipitate is washed with six 25-mL portions of absolute ethanol, which is added to the above solution. The flask is fitted with a thermometer, gas inlet, and a mechanical stirrer. The mixture is gently warmed, with stirring, and a stream of nitrogen is passed over it in order to remove the residual ether. After 1 h the nitrogen stream is stopped, the gas inlet is replaced by a reflux condensor, and the mixture is slowly brought to reflux. The refluxing and stirring is maintained for 4 h. After cooling, the reaction mixture is concentrated in vacuo to a volume of 850 mL. The brown, two-phase solution is then extracted with six 300-mL portions of dichloromethane. The organic extracts are combined, dried (Na_2SO_4), filtered, and concentrated in vacuo to a weight of approximately 115 g. The resulting dark oil is distilled through a 20-cm Hempel type, unpacked column at 5 torr (76–79 °C) and the product is redistilled through a 20-cm fractionating column, 1–2 torr (62–64 °C). The condensor and receiving flasks should be ice–water cooled. A 68–72 g (48–51%) yield of pelletierine (**2**)[34] is routinely obtained.

2. *cis*- and *trans*-4-Phenyl-2-quinolizidinone (3 and 4). The experiments 1–15 in Table I were performed according to the following general procedure. To a solution of 143 mg (1.35 mmol) of distilled benzaldehyde and 146 mg (1.03 mmol) of pelletierine in 10 mL of methanol was added 1 mL of 6 N aqueous NaOH. This solution was stirred at 55 °C for 3 h then concentrated in vacuo. The residue was diluted with brine and extracted with chloroform. The extracts were combined, dried (Na_2SO_4), and concentrated. The resulting oil was purified by preparative layer chromatography (2.0 mm of silica gel; benzene–ether 5:1). Removal of the lower band (R_f 0.2 on analytical TLC) and two extractions with benzene–ethyl acetate (1:1) for 2 h afforded 81 mg (34% yield) of **3** as an oil: IR (film) 3020, 2940, 2860, 2820, 1725, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.6 (br s, ~6 H), 2.0–3.2 (m ~7 H), 4.27 (d of d, J_1 = 4 Hz, J_2 = 6 Hz, 1 H), 7.3 (m, 5 H).

Picrate: mp 188–9 °C. Anal. Calcd for $C_{21}H_{22}N_4O_8$: C, 55.02; H, 4.84; N, 12.22. Found: C, 55.13; H, 5.00; N, 12.16.

Extraction of the upper band (R_f 0.5 an analytical TLC) as above afforded 61 mg (26% yield) of a slowly crystalizing solid. Recrystalization from hexane afforded an analytical sample of **4**: mp 64–6 °C; IR (film) 3030, 2930, 2880, 2791, 2752, 1725, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.6 (br s, 6 H), 2.1–3.0 (m, 7 H), 3.27 (d of d, J_1 = 5 Hz, J_2 = 10 Hz, 1 H), 7.37 (s, 5 H). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.79; H, 8.32; N, 5.97.

Picrate: mp 167–8 °C (lit. mp 167–8 °C).[8] Anal. Calcd for

$C_{21}H_{22}N_{48}O$: C, 55.02; H, 4.84; N, 12.22. Found: C, 54.93; H, 4.85; N, 12.10.

3. *N*-*tert*-Butoxycarbonylpelletierine (9). To 759 mg (5.39 mmol) of pelletierine in 5 mL of dioxane was added 2.074 g (20.5 mmol) of triethylamine followed by 1.323 g (9.25 mmol) of *tert*-butyl azidoformate in 4 mL of water.[13] The mixture was heated at 50 °C for 18 h. Dilution with water and concentration in vacuo removed the dioxane. The aqueous solution was extracted with ether, dried (Na_2SO_4), and concentrated in vacuo to yield 1.269 g (97%) of **9**. Bulb-to-bulb distillation (0.6 torr, 100 °C) afforded an analytical sample: IR (film) 1710, 1685 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (s, ≃9 H), 1.6 (br s, ≃6 H), 2.17 (s, 3 H), 2.65 (d, J = 7 Hz, and m, 3 H), 3.95 (br d, $J \simeq$ 9 Hz, 1 H), 4.7 (br t, $J \simeq$ 7 Hz, 1 H). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.66; H, 9.77; N, 5.90.

4. (*E*)-1-(*N*-*tert*-Butoxycarbonyl-2-piperidyl)-4-phenyl-3-buten-2-one (10). To a solution of 661 mg (2.7 mmol) of **9** and 505 mg (4.8 mmol) of distilled benzaldehyde in 40 mL of methanol was added 1 mL of 6 N aqueous sodium hydroxide. After stirring at 55 °C for 15 h the solution was concentrated in vacuo, diluted with water, and extracted with methylene chloride. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to a solid which could not be purified by recrystalization. Chromatography on silica gel (10% ether–benzene) afforded 818 mg (90% yield) of **10** which could now be recrystallized from hexane: mp 86–8 °C; IR (film) 1690, 1613 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (s, ~9), 1.6 (br s, 6 H), 2.88 (d, J = 7 Hz, and m, 3 H), 4.0 (br d, J = 13 Hz, 1 H), 4.8 (br t, $J \simeq$ 6 Hz, 1 H), 6.73 (d, J = 16 Hz, 1 H), 7.4 (m, 6 H). Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.05; H, 8.13; N, 4.07.

5. (*E*)-1-(2-Piperidyl)-4-phenyl-3-buten-2-one (12). A nitromethane solution of **10** was saturated with hydrogen chloride and allowed to stand for 2 h. The solvent was then evaporated in vacuo to afford a waxy solid, mp 174–8 °C. Recrystallization from 2-propanol afforded the crystalline hydrochloride, **11a**: mp 184–5.5 °C dec (lit. mp 183–5 °C);[15] NMR ($CDCl_3$) δ 1.8 (br s, 6 H), 2.8–3.8 (m, 5 H), 6.70 (d, J = 17 Hz, 1 H), 7.4 (m, 6 H), 9.5 (br s, ~2 H).[38] Anal. Calcd for $C_{15}H_{20}NOCl$: C, 67.80; H, 7.53; N, 5.27; Cl, 13.37. Found: C, 67.67; H, 7.64, N, 5.23; Cl. 13.49.

The crude hydrochloride prepared as above was dissolved in methylene chloride and washed with cold, saturated $NaHCO_3$ solution. The organic layer was quickly dried (Na_2SO_4) and concentrated in vacuo at a low temperature (0–20 °C). An NMR spectrum taken immediately showed a small triplet at δ 4.27 (H-4 of **3**) and δ 1.5 (br s), 2.63 (d, J = 5 Hz), 2.4–3.2 (m, 6.65 (d, J = 16 Hz), 7.4 (m).[38]

6. Cyclization of 12. The experiments 16–23 in Table I were performed according to the following general procedure. Crude **11a** obtained from the treatment of 173 mg (0.53 mmol) of **10** as in procedure 5 was dissolved in 10 mL of methanol and 1 mL of 6 N aqueous sodium hydroxide. This solution was heated at 55 °C for 6 h. The quinolizidinones were isolated and separated as described in procedure 2. A 30% yield (37 mg) of **3** and a 37% yield (45 mg) of **4** were obtained.

7. Condensation of Pelletierine and Benzaldehyde in Acid. A mixture of 189 mg (1.3 mmol) of pelletierine, 137 mg (1.3 mmol) of distilled benzaldehyde, and 10 mL of 0.12 N hydrochloric acid was heated at 55 °C for 16 h. The cooled mixture was basified with saturated $NaHCO_3$ solution and extracted with chloroform. Isolation of the quinolizidinones as in procedure 2 afforded 80 mg (27% yield) of **3** and 32 mg (11% yield) of **4**.

8. Preparation of Pelletierine Perchlorate (15) and Its Treatment with Benzaldehyde. To 10 g (70 mmol) of pelletierine in 175 mL of ether was added a mixture of 70% aqueous perchloric acid and ethanol (1:1) until the solution was acidic (pH 3).[16] A few drops of pelletierine was added to the vigorously stirred two-phase mixture to bring the pH to 5. After 0.5 h the solvent was removed (in vacuo) to afford a yellow oil. After several days the oil partially crystallized. After removal of the remaining oil and two recrystallizations from ethyl acetate a 40% yield of crystalline **15** was obtained: mp 60–1 °C; NMR ($CDCl_3$) δ 1.8 (br s, 6 H), 2.23 (s, 3 H), 3.02 (d, J = 6 Hz, 2 H), 2.9–3.9 (m, ≈3 H), 7.0 (br s, 2 H).

Basification of an aqueous solution of **15** with aqueous sodium hydroxide and extraction with methylene chloride followed by drying (Na_2SO_4) and concentration of the organic layer afforded an oil which had an NMR spectrum identical to pelletierine.

A two-phase mixture of 3.0 g (12.4 mmol) of the perchlorate, **15**, 1.32 g (12.4 mmol) of distilled benzladehyde, and two drops of pelletierine in 30 mL of benzene was refluxed under a Dean-Stark trap for 2 days.[16] After this time no water was noted in the trap. The mixture was cooled and concentrated (in vacuo). The NMR spectrum of the resulting oil was superimposable with the combined spectra of **15** and benzaldehyde.

9. *N*-Benzoyl-2-(2,2-ethylenedioxypropyl)piperidine (18). A solution of 1.08 g (4.4 mol) of *N*-benzoylpelletierine,[19] 0.6 g (9.7 mmol) of ethylene glycol, and a catalytic amount of *p*-toluenesulfonic acid monohydrate in 40 mL of benzene was refluxed in a flasked fitted with a Dean-Stark trap. After 1 day the cooled mixture was washed with a saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated to yield 1.19 g of a brown oil. Bulb-to-bulb distillation at 170 °C (0.5 torr) afforded 0.8 g (67% yield) of **18**: IR (film) 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.67 (br s, 6 H), 1.9–2.5 (br m, 2 H), 3.0–3.8 (br m, 3 H), 3.94 (s, 4 H), 7.40 (s, 5 H). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 69.98; H, 7.97; N, 5.18.

10. *N*-Benzyl-2-(2,2-ethylenedioxypropyl)piperidine (19). To a stirred slurry of excess $LiAlH_4$ in 10 mL of dry tetrahydrofuran (THF) was added dropwise 734 mg (2.7 mmol) of **18** in 7 mL of THF. The solution was refluxed for 15 h. To the cooled solution was added, slowly and in order 1 mL of water, 3 mL of 6 N sodium hydroxide, and 1 mL of water. The mixture was filtered and extracted with ether. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Bulb-to-bulb distillation of the crude oil afforded 564 mg (81% yield) of pure **19**: IR (film) 3030, 2930, 1600 (w) cm^{-1}; NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.5 (br s, ≈6 H), 1.85 (br d, J = Hz, ≈2 H), 2.0–2.9 (br m, ≈3 H), 3.32, 3.80 (AB quartet, J = 14 Hz, 2 H), 3.94 (s, 4 H), 7.25 (s, 5 H). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 71.14; H, 9.15; N, 5.09. Found: C, 73.88; H, 8.90; N, 4.89.

11. *N*-Benzylpelletierine (17). A solution of 169 mg (0.6 mmol) of ketal **19** in 3 mL of 2 N sulfuric acid and 0.5 mL of methanol was allowed to stand at room temperature for 16 h. After basification with saturated $NaHCO_3$ the solution was extracted with chloroform. After drying (Na_2SO_4) the organic layers were concentrated in vacuo to afford 135 mg (96% yield) of **11**: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (br s, 6 H), 2.01 (s, 3 H), 2.1–3.0 (m, 5 H), 3.20, 3.67 (AB quartet, J = 14 Hz, 2 H), 7.16 (s, 5 H). Picrate: mp 143–144 °C (lit.[20] mp 141–2 °C).

12. *N*-Trifluoroacetylpelletierine (21). To a cooled (ice bath) and rapidly stirred solution of 14.7 g (0.11 mol) of pelletierine and 17 g (0.17 mol) of triethylamine in 100 mL of ether was slowly added 20 mL (0.14 mol) of trifluoracetic anhydride. After the addition was complete the mixture was stirred at room temperature for 5 h and then cooled again. To the mixture 100 mL of methylene chloride was slowly added followed by the slow addition of 100 mL of water. The aqueous layer was separated and extracted with methylene chloride. The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude oil was distilled, 158–160 °C (15 torr), to afford 23.9 g (95% yield) of **21**. An analytical sample was obtained by TLC (silica gel; acetone–benzene 2:35): IR (film) 1715, 1685, 1140 cm^{-1}; NMR ($CDCl_3$) δ 1.7 (br s, 6 H), 2.33 (s, 3 H), 2.75 (d, J = 8 Hz, 2 H), 3.0–5.5 (m, 3 H). Anal. Calcd for $C_{10}H_{14}O_2NF_3$: C, 50.62; H, 5.91; N, 5.91; F, 24.05. Found: C, 50.44; H, 6.04; N, 5.85; F, 23.90.

13. *N*-Trifluoracetylpelletierine Ethylene Ketal (22). A solution of 23.0 g (0.10 mol) of **21**, 13.0 g (0.21 mol) of ethylene glycol, and 2.5 g (0.013 mol) of *p*-toluenesulfonic acid monohydrate in 130 mL of dry benzene was refluxed in a flask fitted with a Dean-Stark trap for 28 h. The cooled mixture was washed with 5% aqueous sodium hydroxide. The organic layer was dried ($MgSO_4$) and concentrated in vacuo and the resulting oil was distilled, 145–157 °C (10 torr), to afford 23.3 g (82% yield) of ketal **22** which crystallized at −5 °C. Recrystallization from hexane afforded analytically pure **22**: mp 21–23 °C; IR (film) 1685 cm^{-1}; NMR (CCl_4) δ 1.3 (s, 3 H), 1.7 (br s, 6 H), 1.8–2.3 (m, 3 H), 3.0–3.7 (m, 1 H), 3.8 (s, 4 H), 4.0–5.1 (m, 1 H). Anal. Calcd for $C_{12}H_{18}O_3NF_3$: C, 51.25; H, 6.41; N. 4.98; F, 20.28. Found: C, 51.22; H, 6.45; N, 4.91; F, 20.49.

14. 2-(2,2-Ethylenedioxypropyl)piperidine (20). To 10 mL of a saturated solution of potassium carbonate in 40% aqueous methanol was added 203 mg (0.7 mmol) of **22** and the solution was stirred for 2 weeks at 55 °C. The solution was then concentrated in vacuo and the aqueous residue extracted with chloroform. The organic layers were dried (Na_2SO_4) and concentrated in vacuo and the resulting oil was subjected to bulb-to-bulb distillation (40 °C, 0.5 torr). Thus, 68.2 mg (53% yield) of analytically pure ketal **20** was obtained:[22] IR (film) 3360 cm^{-1}; NMR (CCl_4) δ 1.3 (s, 3 H), 1.35–1.9 (m, 7 H), 2.0 (br s, 1 H, disappears on addition of D_2O), 2.2–3.1 (m, 4 H), 3.80 (s, 4 H). Anal. Calcd for $C_{10}H_{19}O_2N$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.69; H, 10.40; N, 7.46.

15. NMR Study of the Attempted Condensation of 20 and Benzaldehyde. A solution of 40 mg (0.2 mmol) of **20**, 24 mg (0.2 mmol) of distilled benzaldehyde, and 9 mg (0.22 mmol) of sodium hydroxide in 0.5 mL of methanol-d_4 was sealed into an NMR tube. The tube was heated at 55 °C for 72 h. Periodically during this time the tube was cooled and the NMR spectrum recorded. The results are discussed in the text.

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Registry No.—**2,** 4396-01-4; **3,** 63459-11-0; **3** picrate, 68423-27-8; **4,** 57934-06-2; **4** picrate, 57934-07-3; **9,** 63459-12-1; **10,** 68423-28-9; **11a,** 55047-44-4; **12,** 68423-29-0; **15,** 68423-30-3; **17,** 68423-31-4; **18,** 68423-32-5; **19,** 68423-33-6; **20,** 68423-34-7; **21,** 68423-14-3; **22,** 68423-15-4; piperidine, 110-89-4; *N*-chloropiperidine, 2156-71-0; 2,3,4,5-tetrahydropyridine, 505-18-0; sodium acetoacetate, 623-58-5; benzaldehyde, 100-52-7; *tert*-butyl azidoformate, 1070-19-5; *N*-benzoylpelletierine, 68423-16-5; ethylene glycol, 107-21-1.

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(38) A sample of **11a** obtained from Dr. Grisar exhibited the same NMR spectra. It also behaved in the same manner as our sample upon neutralization.

Aminohaloborane in Organic Synthesis. 2.[1] Simple Synthesis of Indoles and 1-Acyl-3-indolinones Using Specific Ortho α-Chloroacetylation of Anilines[2]

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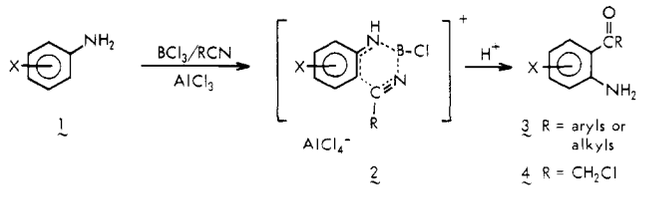
A general simple synthesis of 2,3-unsubstituted indoles (**5**) and 1-acyl-3-indolinones (**9** and **10**) was performed from anilines in two steps. The general procedure involved (a) specific ortho chloroacetylation of anilines to give 2-amino-α-chloroacetophenones (**4**), and (b) reductive cyclization of **4** to produce **5** and dehydrochlorination of 2-(acylamino)-α-chloroacetophenones (**7** and **8**) to yield **9** and **10**.

The search for an efficient synthesis of indoles has been a problem for nearly a century in organic synthesis. Beginning with the classical Fischer[3] and Reissert[4] methods, many reports[5] have appeared from practical and/or academic points of view. Among these, only the Leimgruber method[6] is a general one for synthesizing indoles which are substituted in the benzene ring but not in the heterocyclic nucleus.

We present here a new, efficient method for synthesizing such substituted indoles in two steps from anilines. In the preceding paper,[1] we reported the regiospecific synthesis of 2-amino phenyl ketone (**3**) from anilines (**1**) and nitriles using boron trichloride in the presence of aluminum trichloride, presumably via a cyclic transition state involving a boronium cationic species stabilized by tetrachloroaluminate (**2**).



1 **2** **3** R = aryls or alkyls **4** R = CH_2Cl

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