Formation of D-Nor Aspidosperma Alkaloids by Condensation of N^b-Benzylindoloazepine with Aldehydes

Martin E. Kuehne* and Stephen E. Kuehne

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

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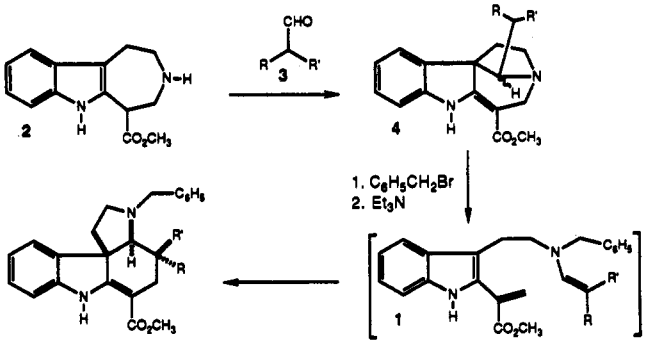
In a series of papers, from 1978 to 1992,[1,2] we described the total syntheses of aspidosperma alkaloids and binary alkaloids, such as vinblastine, based on the generation and biomimetic cyclization of indoloacrylate–enamine intermediates **1**. A major route (Scheme I) to these highly reactive key intermediates **1** was through condensation of the N^b-H-indoloazepine **2** with aldehydes **3**, followed by N^b-benzylation of the resulting bridged indoloazepines **4**. Treatment of the quaternary salt products with base led to fragmentation, with formation of the transient indoloacrylates **1**, and their spontaneous cyclization to the tetracyclic ring system **5a**.

As an alternative to this sequence of steps, we found in 1980 that the N^b-benzylindoloazepine **6a**,[3,4] on heating with aldehydes in refluxing toluene, also provided the same tetracyclic products **5a** (Scheme II). While this inverted reaction sequence might be valuable in instances where the aldehyde component contains functionality that is incompatible with the above N^b-quaternization step, its main interest was in providing a model for the reactions of indoloazepines **6b,c** with a chiral N^b-substituent. These would then lead to chiral indoloacrylate enamines **7b,c** and their enantioselective cyclization to predominantly one enantiomer of the tetracyclic products (**5b,c**). We described such results for the enantioselective syntheses of vinblastine,[5] but have been tardy in giving separate emphasis to the underlying condensations of the N^b-benzylazepine **6a** with aldehydes and now correct this delay for the benefit of others interested in routes to the indoloacrylate enamines **1**.[6]

While the reaction steps of Scheme I could be carried out below 50 °C, the N^b-benzylindoloazepine **6a** does not undergo reaction with aldehydes at a significant rate in refluxing benzene. In refluxing toluene it presumably cleaves to an indoloacrylate secondary amine **8a**, which can condense with aldehydes to form the required enamine intermediates **1**. In the absence of an aldehyde, the indoloazepine is recovered unchanged after several days in refluxing toluene.

Condensations with acetaldehyde, *n*-butyraldehyde, and isobutyraldehyde provided the tetracyclic products **5d–f**, previously obtained by condensation of these aldehydes with the N^b-H-indoloazepine **2** and N-benzylation.[7] While the condensation with acetaldehyde was essentially complete in 1 h, other aldehydes required longer heating in toluene. The rate of reaction decreased with α-substitution of the aldehyde. Some yields of tetracyclic products derived from low molecular weight aldehydes were lower than those found with the N^b-H-indoloazepine condensations at lower temperatures (Table I), perhaps because of competing aldol condensations. The products were accompanied by tars when a large excess of the aldehydes was used. Several other α-unsubstituted aldehydes have given us tetracyclic products **5a** in 85–98% yields on condensation with the N^b-benzylindoloazepine **6a**. Those results will be described in connection with total syntheses of alkaloids.

Scheme I



5a (racemic, for R' = H only this diastereomer)
5d R' = R = H
5e R' = H, R = CH_2CH_3
5f R' = R = CH_3
5g R' = H, R = $CH_2CH_2CH_2OH$
5h R' = $CH_2CH_2CO_2CH_3$, R = CH_2CH_3
5i R' = CH_2CH_3, R = $CH_2CH_2CO_2CH_3$

For a reaction with the cyclic hemiacetal 2-hydroxytetrahydropyran, 2 equiv of this masked aldehyde had to be used because of extensive formation of a tetrahydropyran derivative of the alcohol product **5g**. The latter was then obtained by hydrolysis.

Yields of tetracyclic products derived from α-substituted aldehydes were lowered because of the need for prolonged reflux in toluene. However, for generation of the tetracyclic diesters **5h,i**, obtained from 2-ethyl-4-(methoxycarbonyl)-butanal as a 1.1:1 mixture of epimers, the yield was comparable to that obtained by the earlier reaction sequence. These products had then been converted to 3-oxovincadifformine.[7]

In conclusion, this study shows that the highly productive, transient enamine acrylates **1** can be obtained not only by fragmentation of bridged indoloazepines **4**, but also by *in situ* formation of tryptamine acrylates **8a–c** and their condensations with aldehydes.

Experimental Section

Condensation of N^b-Benzylindoloazepine 6a with Acetaldehyde, *n*-Butyraldehyde, and Isobutyraldehyde. A solution of 100 mg (0.300 mmol) of the N^b-benzylindoloazepine and 70 mg (1.58 mmol) of acetaldehyde in 3 mL of toluene, or 100 mg (1.39 mmol) of *n*-butyraldehyde in 5 mL of toluene, was heated at reflux, under nitrogen, for 1 and 2 h, respectively. TLC (SiO_2, 10:1 benzene/triethylamine) then showed complete consumption of the indoloazepine **6a** and formation of the tetracyclic products **5d,e** (CAS spray blue). Concentration under vacuum and crystallization from methanol provided 70 mg (65% yield) of **5d**, mp 58–60 °C, and 64 mg (55% yield) of **5e**, mp 92–94 °C.

Analogously, 100 mg (0.300 mmol) of the indoloazepine **6a** and 100 mg (1.39 mmol) of isobutyraldehyde, in 4 mL of toluene, were heated at reflux for 20 h to produce 85 mg (72% yield) of

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Scheme II

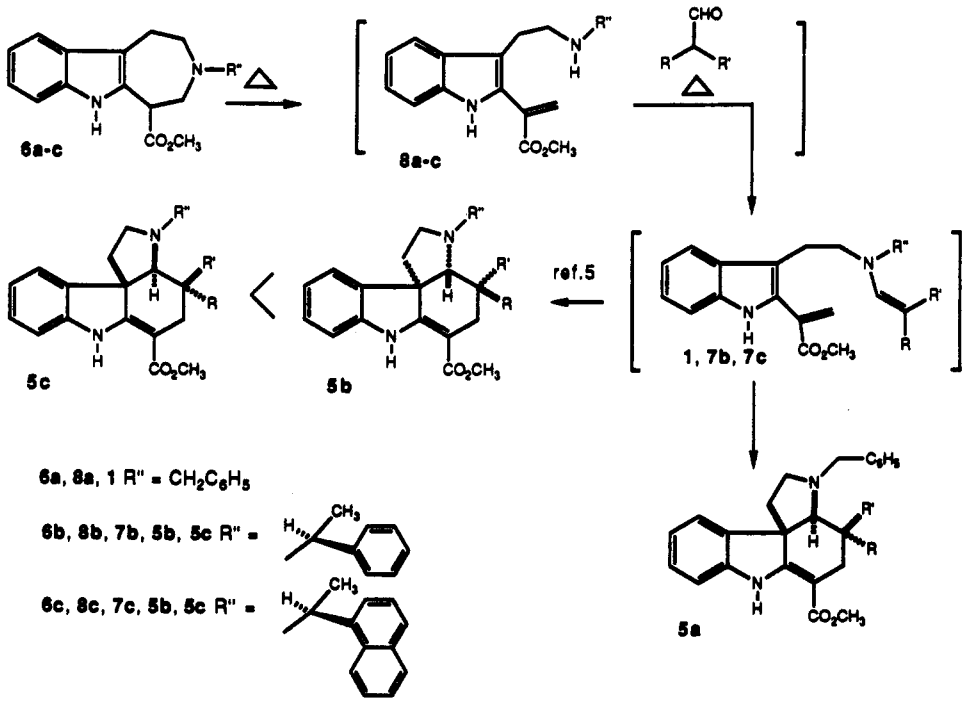

Table I. Yield Comparison of Products 5 Derived from 6a (Scheme II) and 2 (Scheme I)

	6a, %	2, %
5d	65	49[7]
5e	55	75[7]
5f	72	48[7]
5g	88	67[8]
5h + 5i	46 (1.1:1)	48 (1:1)[7]

the tetracyclic product **5f**, mp 96–97 °C, after crystallization from methanol. The compounds **5d–f** matched authentic samples in TLC, spectroscopic data, and mixture mp.[7]

Condensation of N^b-Benzylindoloazepine 6a with 2-Hydroxytetrahydropyran. To a solution of 334 mg (1.00 mmol) of the indoloazepine **6a** and 225 mg (2.20 mmol) of 2-hydroxytetrahydropyran, in 10 mL of toluene, was added 5 drops of ether saturated with HCl gas. The mixture was heated at reflux for 5 h, when TLC showed absence of the indoloazepine **6a** in the solution and formation of the tetracyclic product **5g**, as well as a higher R_f (acetal) component. After addition of 10 mL of methanol and 5 drops of concd HCl, the acidic mixture was stirred for 14 h at 20 °C, resulting in hydrolysis of the acetal component. Basification with ammonium hydroxide and extraction with 3 × 15 mL of dichloromethane, followed by washing of the combined organic extracts with 7 × 50 mL of water and concentration of the dried ($MgSO_4$) organic solution, provided 367 mg (88% yield) of the tetracyclic alcohol **5g**, TLC R_f 0.65 (SiO_2, 1:1 ether/hexane), which matched an authentic sample in spectroscopic data.[8] A reaction with tosyl anhydride provided a tosylate with mp and mixture mp 162–163 °C.[8]

Condensation of N^b-Benzylindoloazepine 6a with 2-Ethyl-4-(Methoxycarbonyl)butanal. A solution of 167 mg (0.500 mmol) of the indoloazepine **6a** and 115 mg (0.730 mmol) of 2-ethyl-4-(methoxycarbonyl)butanal in 10 mL of toluene was heated at reflux for 48 h. Concentration under vaccum and thick-layer plate chromatography (SiO_2, 1:1 ether/hexane, R_f 0.6) provided 110 mg (46% yield) of the epimeric esters **5h** and **5i** in a ratio of 1.1:1, as seen by integration of the saturated ester methyl signals at δ 3.62 and 3.60 vs the vinylogous urethane methyl group at δ 3.78 as well as the methine doublets at δ 4.10 and δ 4.13. These products have been separated by chromatography, fully characterized, and converted to 3-oxovincadifformine.[7]

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