Regioselectivity of the Amino-Claisen Rearrangement. The Rearrangements of *N*-Allyl-9-methoxy-1-oxajulolidinium Bromide and *N*-Allyl-8-methoxylilolidinium Bromide

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High regioselectivity was observed in the title rearrangements and the reactions were rationalized as occurring *via* a transition state which closely resembles the lowest energy valence-bond resonance form.

In general, *N*-(amino)-Claisen rearrangements are considered less facile than those of their oxygen counterparts.[1] However, if the lone pair on the nitrogen atom is trapped by protonation or quaternization, the rearrangement is accelerated considerably. We have investigated these charge-assisted *N*-Claisen rearrangements,[2a] especially in *N*-Claisen rearrangements of quaternary salts[2b] and reported the rearrangement of *N*-allyl-9-methoxyjulolidinium bromide (**1**) which gave the novel *meta*-rearrangement product (**2**).[3] We now report the rearrangement of *N*-allyl-9-methoxy-1-oxajulolidinium bromide (**5**) and *N*-allyl-8-methoxylilolidinium bromide (**9**) which have unsymmetrical substituents, so can give rise to regioisomers. Rearrangements of (**5**) and (**9**) give *meta*-rearranged products with high regioselectivity.†

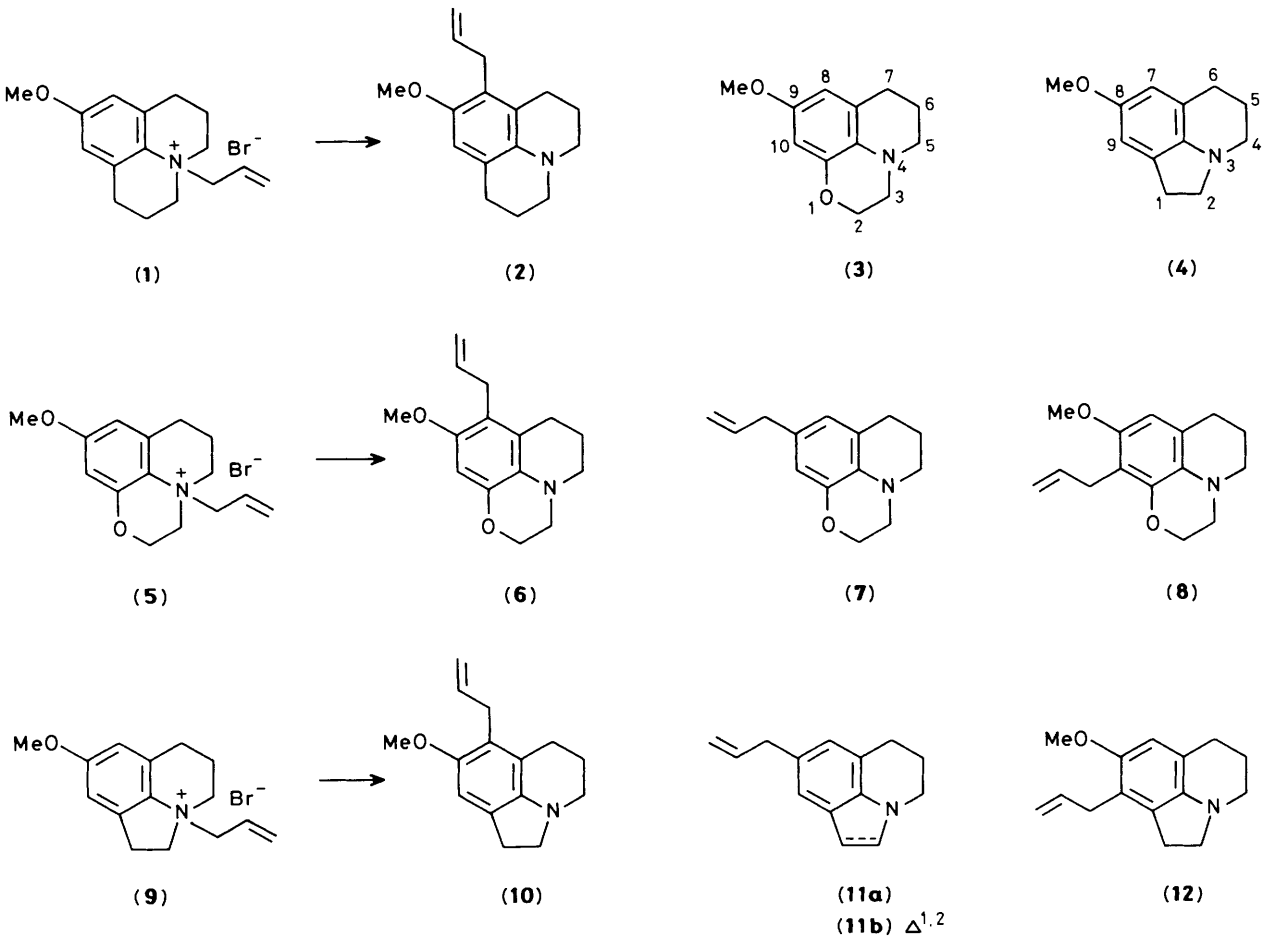
† Quaternary salts (**5**) (m.p. 148—150 °C) and (**9**) (m.p. 161—162.5 °C) were prepared by the allylation of 9-methoxy-1-oxajulolidine (**3**), hydrobromide m.p. 194—196 °C and 8-methoxylilolidine (**4**), hydrobromide m.p. 216—221 °C (W. A. Ayer, W. R. Brown, G. A. Cooke, and A. C. Sper, *Tetrahedron Lett.*, 1966, 2021) with allyl bromide respectively. 9-Methoxy-1-oxajulolidine (**3**) was derived from 1-oxojulolidine by (i) bromination with *N*-bromosuccinimide (R. H. Mitchell, Y-H. Lai, and R. V. Williams, *J. Org. Chem.*, 1979, **44**, 4733), and (ii) substitution reaction using sodium methoxide in the presence of copper(I) iodide (Y. Kikugawa, Y. Miyake, and M. Kawase, *Chem. Pharm. Bull.*, 1981, **29**, 1231).

Table 1.

Starting material	Reaction conditions[a]	Crude yield (%)	Products (%)[b]
(**5**)	A (2 h)	98	(**6**) 89[61], (**3**) 6[3]
(**5**)	B (2 h)	83	(**6**) 95[65], (**3**) 4
(**9**)	A (8 h)	77	(**10**) 68[34], (**4**) 27[9], (**11a**) <1
(**9**)	B (8 h)	97	(**10**) 11, (**4**) 13[8], (**11a**) 20 (**11a**) 20 (**11b**) 36 [29]

[a] Reaction conditions: A: a solution of quaternary salt (2 mmol) in glycerol–water (2:1, 6 ml) was heated at 140 °C (bath temperature) for the time indicated, in the absence (A) or in the presence (B) of sodium hydrogen carbonate (2.2 mmol). [b] The crude product was analysed by g.l.c. (10% SE-30, 3 mm × 2 m, 170—250 °C, 10 °C min^{-1}; N_2 30 ml min^{-1}). The values in [ ] are the isolated yields after column chromatography.

Rearrangements were carried out under two different sets of conditions and the results are summarized in Table 1. The products were analysed by g.l.c., separated by flash column



chromatography, and their structures determined from chemical and spectral characterization. The rearrangement of (**5**) was accompanied by some deallylation, but the *meta*-rearrangement product (**6**) was the dominant product (89% for reaction conditions A and 95% for B, Table 1).‡ The regioisomer (**8**) was not detected in the reaction products. The *para*-allyl compound (**7**) was not observed either, although it was obtained in the rearrangement of (**1**) under reaction conditions B.[3b]

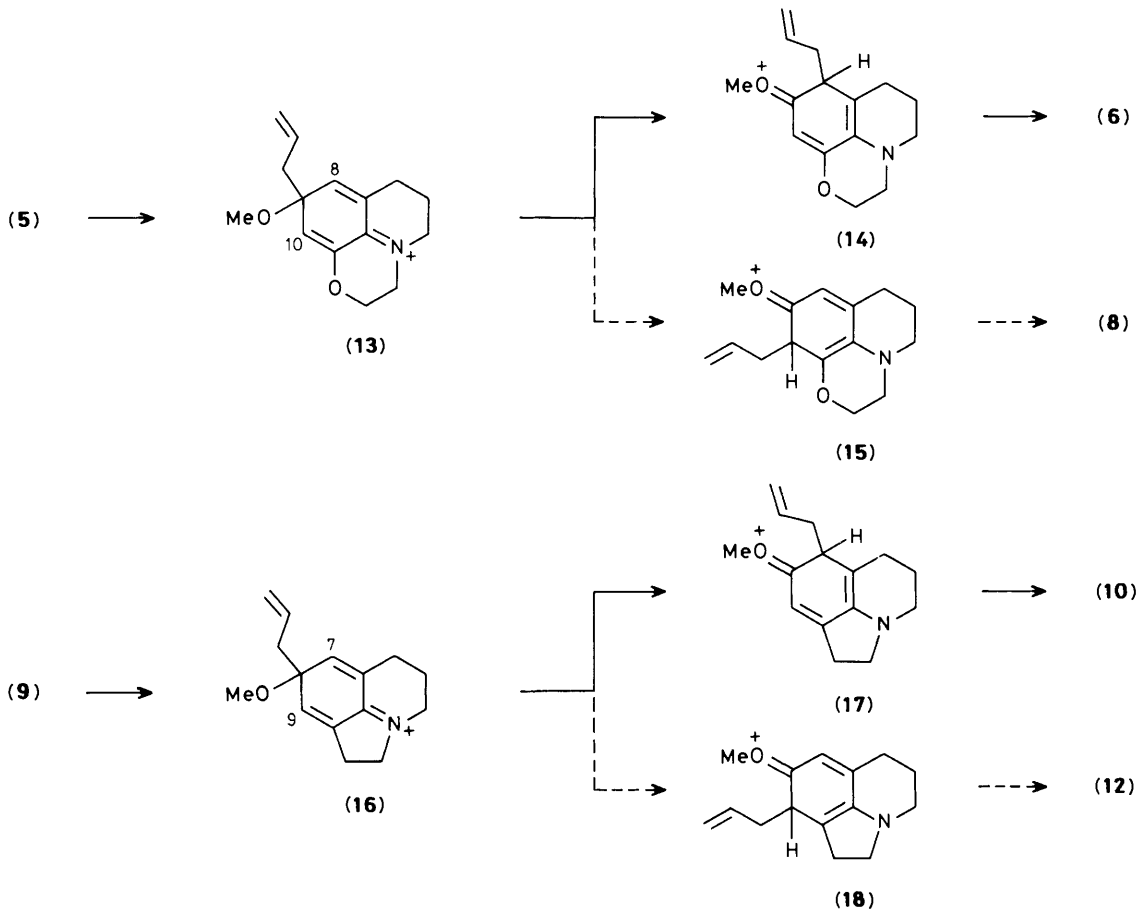
The rearrangement of (**9**) was dependent upon the reaction conditions and gave somewhat different results from that of (**5**). In the rearrangement of (**9**) under reaction conditions A, considerable deallylation occurred (27%) but the *meta*-rearrangement product (**10**) was obtained as a major product (68%).‡ The formation of the regioisomer (**12**) was not observed in the reaction products and the rearrangement occurred with high regioselectivity. The formation of *para*-allyl compound (**11a**) was detectable only by g.l.c.–mass spectroscopy of the crude product. Under reaction conditions B, (**9**) reacts differently and the *meta*-rearrangement product was no longer a major product of the reaction (11%). Instead of (**10**) the major components of this reaction were (**11a**) (20%) and (**11b**) (36%); the allyl group rearranged to the *para* position, substituting the methoxy group. These products could not be separated by column chromatography. In the n.m.r. spectrum of this mixture, AB type signals appeared at δ 6.36 and 7.03 (*J* 2.9 Hz) which supports the structure (**11b**). The mixture was then converted into a single compound (**11a**) by reduction with sodium cyanoborohydride in acidic media. The structure of (**11a**) was confirmed by the identification with an authentic specimen.§ Indolization of the lilolidine skeleton during *N*-Claisen rearrangement has not been observed previously.

The mechanism for *meta*-rearrangement of (**5**) and (**9**) is assumed to follow the reaction pathways proposed for (**1**),[3] *i.e.*, two [3,3] sigmatropic rearrangements into (**13**) and (**16**), and subsequent [1,2] sigmatropic rearrangement into (**6**) and

‡ *Selected spectroscopic data:* (**6**) M^+ *m/z* 245; $\nu_{max.}$ ($CHCl_3$) 1630, 910 cm^{-1}; ^1H n.m.r. δ 3.27 (2H, d, *J* 6.1 Hz), 4.85—4.95 (2H, m), 5.85 (1H, tdd, *J* 5.8, 9.0, 18.0 Hz), 6.29 (s, Ar). Irradiation at 7-H [δ 2.69 (t, *J* 6.7 Hz)] induced a 7.5% nuclear Overhauser effect (n.O.e) at the allylic methylene signals (δ 3.27) but not at the aromatic proton.

(**10**) M^+ *m/z* 229; $\nu_{max.}$ ($CHCl_3$) 1635, 910 cm^{-1}; ^1H n.m.r. δ 3.25 (2H, d, *J* 8 Hz), 4.89—5.00 (2H, m), 5.86 (1H, m), 6.65 (1H, s, Ar). Irradiation at 1-H (δ 2.85, m) induced a 12.5% n.O.e. at the aromatic proton, but no n.O.e. was observed on irradiation at 6-H [δ 2.63, (t, *J* 6.7 Hz)].

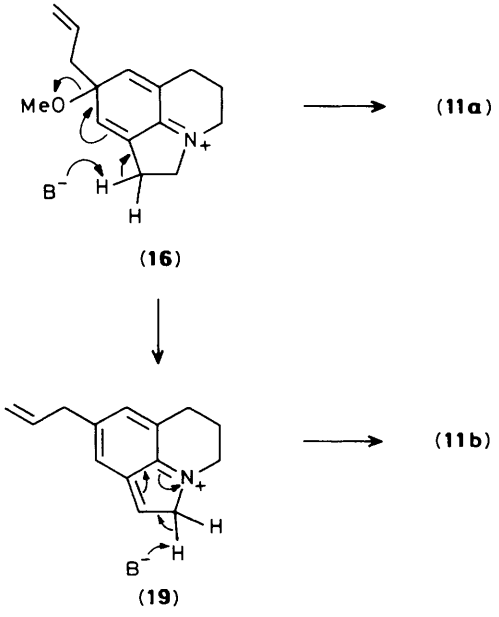
§ 8-Allyl-lilolidine (**11a**) was also obtained by *N*-Claisen rearrangement of *N*-allyl-lilolidinium bromide in good yield. The product (**11a**) was catalytically hydrogenated into 8-propyl-lilolidine and identified by comparison with an authentic sample prepared from lilolidine in three steps: (i) Vilsmeyer reaction, (ii) Wittig reaction, and (iii) catalytic hydrogenation.



Scheme 1

(**10**) respectively (Scheme 1).¶ The observed high regioselectivity suggests that the rate-determining step is the [1,2] sigmatropic shift. Recently Kruse and Cha proposed that, in the absence of overwhelming steric constraints, aromatic substitution will occur *via* the transition state which most closely resembles the valence-bond resonance form of lowest energy.[4] According to their interpretation, the relative stabilities of (**14**) and (**15**) determine the final product from the reaction of (**5**) and likewise the relative stabilities of (**17**) and (**18**) determine the product from (**9**). The valence-bond form (**14**) is more stable than (**15**), since the oxygen atom in (**14**) can pump its lone pair electrons directly into the positive centre and stabilize the structure (**14**) by a resonance effect, and this effect is not possible in (**15**). The exclusive formation of (**6**) occurs *via* a transition state which closely resembles (**14**). A similar argument can be applied to the rearrangement of (**9**) under reaction conditions A. The Baker–Nathan effect where a methylene group stabilizes carbocation formation is more effective when the methylene unit is in a five-membered rather than in a six-membered ring.[5] Thus intermediate (**17**) is more effectively stabilized by hyperconjugation than (**18**), so that the rearrangement of (**9**) into (**10**) *via* (**17**) proceeds with high regioselectivity.[6]

The reaction of (**9**) under reaction conditions B gave *para*-allyl compounds (**11a**) and (**11b**) as the major reaction products. A similar *para*-allyl compound was observed in the reaction of (**1**) under reaction conditions B.[3b] The reaction



Scheme 2

mechanism for the formation of (**11a**) is unclear at present. The treatment of (**11a**) under reaction conditions B did not provide (**11b**) and (**11a**) was recovered completely. The indole derivative (**11b**) was thus assumed to be derived from the reaction intermediate and one of the possible reaction

¶ Reaction pathways *via* [3,3] and [1,2] sigmatropic rearrangements are also feasible[3b] but give the same reaction intermediates.

pathways is shown in Scheme 2. The methylene proton on the five-membered ring in (**16**) is attacked by weak base, with subsequent elimination of methanol, leading to the formation of (**19**), which is readily deprotonated by base to (**11b**). The formation of a stable indole ring probably provides the driving force for these transformations.

In conclusion, we have shown that the introduction of oxygen or ring strain onto an aromatic ring can control the regiochemistry of *meta* *N*-Claisen rearrangements and high regioselectivity can be achieved by looking at the relative stabilities of the reaction intermediates close to the transition state.

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