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ALKYLATION OF DIENAMINES. MECHANISM OF N TO C ALKYL GROUP TRANSFER

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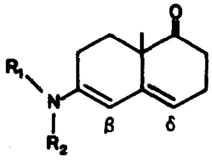
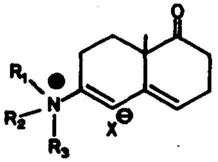
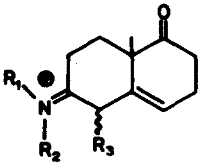
Dienamines possess three potential sites of electrophilic attack; the nitrogen atom and the β- and δ- carbon atoms. This communication describes the reaction of dienamine 1a with methyl iodide which illustrates the reactivity pattern of dienamines with a simple electrophile.



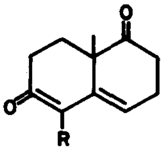
	R_1	R_2
1a	CH_3	CH_3
1b	$CH_2\phi$	CH_3
1c	CD_3	CH_3



	R_1	R_2	R_3	X
2a	CH_3	CH_3	CH_3	I
2b	CH_3	CH_3	CH_3	ClO_4
2c	CH_3	CH_3	$CH_2\phi$	Br
2d	CD_3	CH_3	CH_3	I



	R_1	R_2	R_3
3a	CH_3	CH_3	CH_3
3b	CH_3	CH_3	CD_3
3c	CD_3	CH_3	CH_3

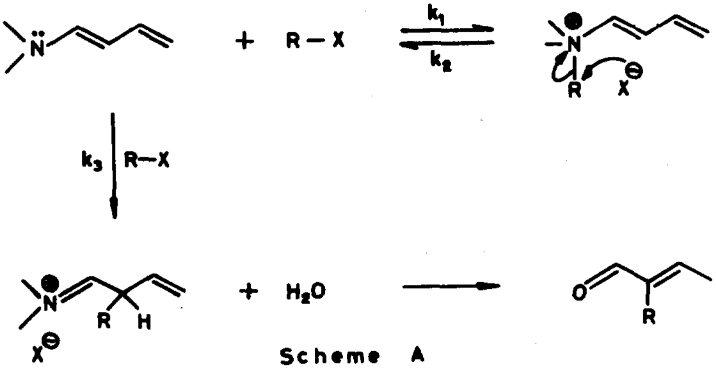


	R
4a	CH_3
4b	CD_3
4c	$CH_2\phi$

Reaction of 1 a with methyl iodide in DMF (0°, 90h) yielded the crystalline salt 2a, m.p. 195-196°, in 92% yield. Under similar reaction conditions little or no product formation was observed in benzene or diethyl ether. When, however, a 1:1 mixture of 1a and methyl iodide or salt 2a was heated in DMF at 160° (sealed tube, 70h), the only product isolated in each case, after hydrolysis, was the alkylated diketone 4a. In order to determine the path(s) by which the C-alkylation product is formed during the high temperature reaction (between 1a and methyl iodide), the dienamine was subjected to reaction with

CD_3I under identical conditions. Hydrolysis of the reaction products yielded a mixture of ketones 4a and 4b, the ratio of which was determined mass spectroscopically. From the value of this ratio, 4a/4b = 56/44, it can be calculated[1] that under the aforementioned reaction conditions direct C-alkylation proceeds to the extent of 16%. The remaining substitution obviously occurs via an initial N-alkylation step.

The question of the manner in which N-alkylated intermediates 2a and 2d rearrange to the C-alkylated products 3a-c, which constitute the precursors of 4a,b, is of considerable interest. In principle, three mechanisms are possible for this rearrangement: (a) a direct intramolecular N → C transfer; (b) partial dissociation of 2a into dienamine 1a and alkyl halide, followed by a reaction between 1a and the ammonium salt (2a), the latter acting as an electrophilic alkylating agent[2]; and (c) reversal of N-alkylation with a subsequent C-alkylation step leading to products[3] (Scheme A).



Scheme A

Mechanism (a) was tested by conversion of 2a to the corresponding perchlorate salt 2b and heating the latter in DMF (160°, sealed tube, 70h). In contrast to the behaviour of 2a the perchlorate 2b was completely inert, no alkylated ketone being observed in the hydrolysate of the reaction mixture. Since there is no apparent reason why an intramolecular N → C shift should be prohibited upon changing the anion from iodide to perchloride, the result excludes a direct alkyl group transfer as visualized in mechanism a. This experiment also emphasizes the important role of the nature of the anion in reversion of the N-alkylated ion-pair to the starting components. Information concerning mechanism (b) was derived from a comparison of the reaction - under similar conditions - of 1-N-(pyrrolidino)cyclohexene with N-benzyl salt 2c (prepared by treatment of 1b with CH_3I), with a reaction in which the enamine of cyclohexanone and dienamine 1a were allowed to compete for alkylation by benzyl bromide. In both cases, hydrolysis of the reaction mixtures resulted in the same two alkylated products, namely, 2-benzylcyclohexanone and 4c, in almost identical ratio (7:3). That the same ratio of the last mentioned alkylated products is formed in both cases indicates the congruency of the reacting species in the two reactions. The results thus argue against an intermolecular transfer of an alkyl group from the ene-ammonium salt 2c to the enamine or dienamine (mechanism b) and strongly suggest a dissociation and subsequent C-alkylation mechanism (c, Scheme A). Further support for the latter mechanism was obtained from studies with deuterated salt 2d, m.p. 197-199°, which was readily prepared by reaction of 1a with CD_3I. When 2d was heated with 10 eq. of CH_3I (DMF, 70h, 160°) in a sealed tube, a mixture of ketones 4a and 4b, in the ratio 95:5, was obtained upon quenching the reaction mixture. The predicted ratio for a situation where 2d is in equilibrium with the pool of CH_3I + CD_3I and 1a + 1c prior to C-alkylation, is 4a/4b = 92/8. The latter case would correspond to a relatively slow k_3 in comparison with k_1 and k_2 (Scheme A). Under conditions where $k_3 >> k_2$ the deuterated ketone 4b would be expected to be formed to the extent of 3%. That actually 5% of 4b is formed is indicative of a circumstance where the relative values of k_3 and k_1/k_2 lie in-between the aforementioned extreme cases. It should be noted that a higher than 8% value for 4b would have implied an intramolecular N → C process. The observed result is therefore consistent with the rejection of mechanism a.

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* To whom all enquiries may be addressed.

** Structure of all new compounds is supported by analytical and/or spectral data.

1. % of direct C-alkylation = (1.5 x % of deuterated product) - 50.
2. Such a mechanism has recently been suggested, though not substantiated, to explain the alkylation of certain ketone enamines; M.E. Kuehne and T. Garbacik, J.Org.Chem. 35, 155 (1970).
3. E. Elkik, Bull.Soc.Chim.Fr., 903 (1969).