

QUATERNIZATION REACTIONS WITH THE AID OF ETHYLENE OXIDE

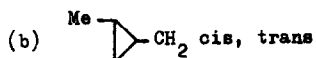
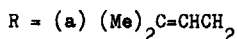
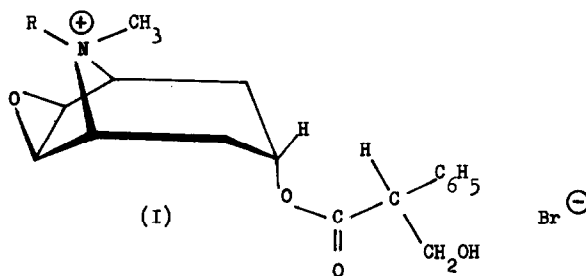
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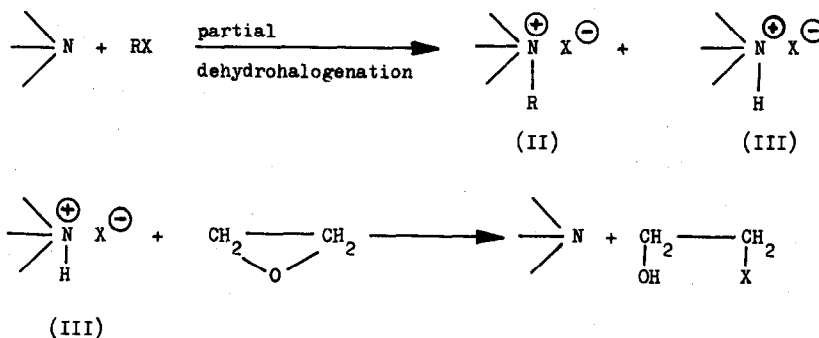
The quaternization of tertiary amines is an ordinary reaction which may present unexpected difficulties. Especially in the reaction of active halides with sterically hindered tertiary amines dehydrohalogenation may occur, this leading to formation of the corresponding amine salts in addition to the expected quaternary salts. Because of this, for instance, the 3,3-dimethylallyl ammonium salts that are key intermediates in the preparation of N-(3,3-dimethylallyl) adenosine¹, triacanthine², and pentazocine³, were isolated in rather low yields or after subsequent manipulations.

We encountered the same difficulty during the preparation of some quaternary 3,3-dimethylallyl and small-ring alicyclicalkyl ammonium salts of (-)-scopolamine (hyoscyine) (I a-d).



In this case, however, all the efforts to obtain pure compounds resulted in failure. Since the difficulty was to be ascribed to the concomitant formation of the quaternary (II)

and the tertiary amine salt (III), we felt that the use of ethylene oxide would alleviate this difficulty as it would either prevent the formation of (III) during the reaction or allow a facile isolation of the quaternary salt. In effect, in our experiments ethylene oxide behaved as a base, with the advantage that it could be easily removed from the reaction mixture along with its product of transformation, the halohydrine.



The method used to synthesize (-)-scopolamine-N-(3,3-dimethylallylbromide) (Ia, Table I) illustrates the procedure (Method A) which may be followed for quaternization reactions at room temperature. To a solution of 40 mmoles of (-)-scopolamine in 400 ml of anhydrous ether was added 120 mmoles of ethylene oxide and 80 mmoles of 3,3-dimethylallyl bromide⁴, and the solution was allowed to stand in a stoppered vessel for 10 days at room temperature. The product which crystallized was filtered and purified by triturating with anhydrous ether. In some experiments an additional crop of the quaternary salt could be obtained by adding a further quantity of ethylene oxide and 3,3-dimethylallyl bromide to the crystallization mother liquors and allowing to stand the reaction mixture for further 10 days.

For less reactive halides, such as small-ring alicyclical alkyl halides, the procedure for the quaternization was as follows (Method B). To a solution of 35 mmoles of (-)-scopolamine in 100 ml of acetonitrile was added 70 mmoles of the halide and the solution was refluxed for 3 days. The solution was then evaporated to dryness and the residue was dissolved in 100 ml of fresh acetonitrile. To this solution 0.105 mole of ethylene oxide was added and the mixture was allowed to stand in a stoppered vessel for 3 days. The solution was then evaporated to dryness and the residue was dissolved in water and washed thoroughly with ether. The aqueous solution was then filtered to remove any insoluble material, and lyophilized to give the quaternary salt as a colourless solid (Table I).

Table I^a

Quaternary salt (I)	Method	Yield, % ^b	$[\alpha]_D^{20}$ ^c	M.p., °C
a	A	66	- 12°	108
b	B	48	- 13°	78
c	B	51	- 30°	75
d	B	61	- 31°	76

^aSatisfactory spectral and elemental analytical data were obtained for all the new substances reported here. The purity of the compounds as well as the progress of the reactions were checked by TLC on Al₂O₃ plates using *n*-BuOH-H₂O-NH₄OH (8:10:2), and detecting the spots by spraying with Dragendorff's reagent. ^bNo systematic attempts were made to maximize the yields. ^cH₂O (C,3).

Note should be made that the basic behaviour of epoxides had been observed previously in isolated experiments carried out in dehydrohalogenation of β-haloalcohols by epoxide in the presence of halide ions⁵. Lately, Buddrus⁶ rediscovered the basic behaviour of the halide ion/epoxide system and demonstrated that the species that functions as the proton acceptor is neither the epoxide ion nor the halide ion, but the 2-haloethoxide ion. In his experiments he used a quaternary ammonium halide as catalyst in several deprotonation reactions in which ethylene oxide was found to be a base. In our conditions the initially formed quaternary salt is likely to function as catalyst in the regeneration of the free amine from its salt.

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