Reactions of Alicyclic Epoxy Compounds with Nitrogen-Containing Nucleophiles

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Abstract—The review considers reactions of alicyclic epoxy compounds and their analogs with nitrogen-containing nucleophilic reagents, such as amines, azides, hydrazines, etc., biological aspects of these reactions, and properties of amino alcohols which are practically important organic products and synths. Reaction mechanisms, including radical and radical ion reaction paths, the results of quantum-chemical studies, stereo- and regioselectivity aspects, and activation of epoxy substrates with achiral and chiral catalysts are discussed. The formation of nitrogen-containing heterocyclic systems via opening of the oxirane ring is described.

I. INTRODUCTION

Reactions of epoxy derivatives with amines were studied since 1860 when Wurtz reported on the reaction of oxirane (1) with ammonia [1]. Aminolysis of alicyclic (2) and other epoxy compounds was later described in some more general reviews [2–7], specifically in those dealing with reactions of substituted epoxynorbornanes 3 [8] and spirooxiranes 4 [9]. Reactions of epoxy derivatives with amines are important, for they provide one of the most convenient methods for the synthesis of vicinal amino alcohols which are used as building blocks in the preparation of natural and biologically active organic compounds [10–24]. In the recent review, Bergmeier reported numerous examples of isolation of natural compounds and synthesis of pharmacologically active compounds having amino alcohol structural fragments [10]. Various vicinal amino alcohols and their derivatives at the hydroxy group and the nitrogen atom exhibit diverse biological activity and are now used in medical practice [25–27].

II. SOME BIOLOGICAL ASPECTS OF THE CHEMISTRY OF ALICYCLIC VICINAL AMINO ALCOHOLS

Reactions of alicyclic epoxy compounds with nitrogen-containing nucleophiles are included in the metabolism of polycyclic aromatics and other carcinogenic and mutagenic substances containing an oxirane fragment. Some examples of aminolysis of biologically active epoxy compounds are given below. “Bay-region” epoxy diols which are formed by joint action of cytochrome
P450 and epoxyhydrolase on polyaromatic hydrocarbons suffer from attack by amino groups and other nucleophilic moieties in living cell molecules at the last stage of metabolism. 9,10-Epoxide-7,8-diols based on benzo[a]pyrene [(+)- and (-)-5] react with purine bases of nucleic acids through alkylation of exocyclic amino groups in the latter [28]. Enantiomeric epoxy diols (specifically, those diastereoisomers in which the 7-hydroxy group is oriented cis with respect to the oxirane ring) undergo mainly cis-opening of the three-membered fragment (Scheme 1). Aminolysis and azidolysis of various polycyclic epoxides derived from carbon- and nitrogen-containing polycyclic aromatic systems were studied in detail in [29–31]. In some cases, the amine component was also a polycyclic system, e.g., 5,10-dihydro-7,8,10-trimethylbenzopteridine-2,4(1H,3H)-dione, etc. [31].

The second example is concerned with activation and binding of aflatoxin B1 (AFB1), which is one of the strongest carcinogenic and mutagenic compounds and environmental pollutants. Baertschi et al. [32] reported on a successful metabolic activation of the toxin via epoxidation with dimethylformamide and subsequent transformation of epoxy derivative 6 by the action of DNA. The reaction occurs in a regio- and stereoselective fashion at the N7 atom of deoxyguanosine. The structure of the isolated product (7) was rigorously proved (Scheme 2).

One more example of practically important aminolysis is the reaction of stereoisomeric epoxy derivatives of thymidine with amines and b-amino acid ethyl esters [33]. The reaction of (+)-1,3-dimethylthymidine epoxy derivative with amines and b-amino acids was examined as a model of cross-coupling between nucleic acids and proteins. The epoxy derivatives were prepared from optically active bromohydrins. Their absolute configuration was determined by X-ray analysis and by the configuration correlation method [33]. The stereoisomers behave differently in this reaction: Isomer 8 with the amine component forms only the cis-adduct, while from isomer 9 both cis- and trans-adducts are obtained (Scheme 3). The steric structure of the adducts was established on the basis of the known cis-trans isomerization by the action of boron trifluoride–ether complex [34]. The reasons for the different reaction stereochemistry were not studied. It was only found that acylation of the d-hydroxy group has no effect on the process [33].

Among biologically active cyclopentanoid analog of nucleosides, there are compounds having an amino alcohol structure, e.g., neplanocin A (10), aristeromycin (11),...