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REAGENT DEPENDENCE OF THE STERIC COURSE OF BROMOHYDRIN AND ACETOXYBROMIDE FORMATION. A CASE OF FACILE 1,2-INTERCHANGE IN A COUPLE OF DIASTEREOISOMERIC BROMOHYDRINS.

G.Bellucci, M.Ferretti, G.Ingrosso, F.Marioni, A.Marsili and I.Morelli
Istituti di Chimica Organica e di Chimica Farmaceutica dell'Università
di Pisa. 56100 PISA, Italy

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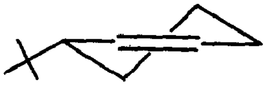
The steric course of electrophilic additions to 3-t-butylcyclohexene (1) is directly controlled by the steric effect of the t-butyl group.[1] In the case of the bromination of 1, the product distribution is also affected by the solvent and the brominating agent employed.[2] In order to get further information about the direction of the electrophilic attack and the influence of the reagent used, a study of the steric course of the addition of hypobromous acid and acetyl hypobromite to 1 under different conditions was undertaken.

G.l.c. analyses of the crude reaction products gave the results reported in Table 1. Since bromonium ion intermediates are expected to be involved in these additions, the results of the opening with HBr of the epoxides 2a and 3a, the protonated forms of which can be considered as models for the bromonium ions 2b and 3b, are also reported.



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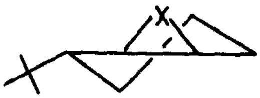
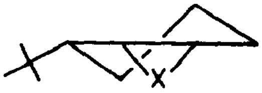


2 a, X = O
b, X = Br$^+$



3 a, X = O
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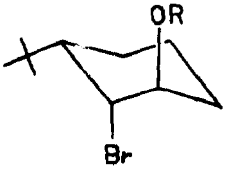
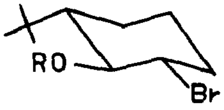
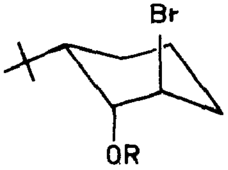


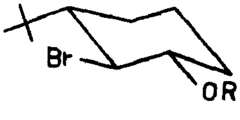
4, R = H
5, R = COCH$_3$



6, R = H
7, R = COCH$_3$



8, R = H
9, R = COCH$_3$



10, R = H
11, R = COCH$_3$

TABLE 1. The Formation of Bromohydrins and Acetoxybromides from 1, 2a and 3a.[a]

Run	Reagent	Solvent	Products (%) 4	5	6	7	8	9	10	11
1	1+NBS	DMSO-H_2O (95:5)	78		4		3		15	
2	1+NBA	Dioxane-H_2O (7:3)	81		3		4		12	
3	1+NBA	Dioxane-$HClO_4$ 0.2N (7:3)	76		4		5		15	
4	1+HOBr aq	Dioxane							b	
5	1+NBA-AcOLi[c]	Acetic acid		30		1		11		58
6	1+AcOBr[d]	CCl_4		19		2		12		67
7	2a+HBr[e]	$CHCl_3$	22		78					
8	3a+HBr[e]	$CHCl_3$					100			

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a. All the addition reactions were carried out at room temp with a 10% excess of the brominating agent; all the products were stable under the reaction conditions as well as under the glc analytical conditions. b. Main product. c. 20 mole excess of AcOLi. d. Prepared from Br_2 and AcOAg in CCl_4.[3] e. Dry HBr.

It was not possible to carefully analyse the crude product from run 4, owing to the presence of some side-products (such as dibromo derivatives and others); however column chromatography allowed separation of the main product 10 (oil, *p*-nitrobenzoate mp 116-118°). Furthermore treatment of the crude reaction mixture with ethanolic KOH gave the two epoxides 2a and 3a in the ratio 20:80. Very little or no dibromo derivatives, nor rearranged products were formed in all the other additions. Bromohydrins 4 (mp 70°), 6 (oil, phenyluretane mp 127-128°) and 8 (mp 74-76°) were separated from runs 1 and 2. Pure 8 was also obtained by HBr-opening of the *cis*-epoxide 3a, while the same opening of 2a was the best route to 6. The acetoxybromide 11 (mp 55°) was isolated by column chromatography from runs 5 and 6; pure 5 (oil), 7 (mp 34°) and 9 (oil) were preparated by acetylation of the respective bromohydrins. The configurations of the products were deduced both by conversion into 2a and 3a and from ir/nmr spectra.[4]

All the additions examined are expected to proceed through ionic mechanisms,[5,6] but the wide range of stereoselectivities observed imply an involvement of different pathways, according to the reagent employed as the source of positive bromine. The steric course of the addition of HOBr and AcOBr, as compared with that of the epoxidation of 1, followed by opening of 2a and 3a with HBr and other acids,[7] strongly suggest the irreversible formation of the bromonium ion intermediates 2b and 3b (analogous to the protonated forms of 2a and 3a) in the electrophilic steps of both these additions, the overall process being thus controlled first by the relative rates of attack *cis* and *trans* to the *t*-butyl group by positive bromine and then by that of nucleophilic attack on C-1 and C-2 of 2b and 3b. As the steric effect of the *t*-butyl group hinders a *cis* electrophilic attack on 1 to give 3b as well as a nucleophilic attack on C-2 of 2b, bromohydrin 10 or acetoxybromide 11 are the main product of these additions.

It has been pointed out[5a] that the exact nature of the brominating agent in the reactions of N-bromoamides with olefins remains undetermined. The product distribution from runs 1-3, while again suggesting the formation of bridged intermediates, allows to exclude that HOBr is the actual reactant in the reactions of 1 with NBA in dioxane-H_2O or with NBS in DMSO-H_2O, and speaks in favour of a direct transfer of Br^+ from the N-bromoamide to the olefin.[5b,8] However in these cases the steric course of the addition does not seem to depend on the rates of the electrophilic steps, but mostly on that of the nucleophilic ones. Indeed antiparallel opening of the *cis* bridged intermediate to give 4 is expected to be a faster process than either the antiparallel opening of the *trans* one involving an attack on C-2 *syn* to the *t*-butyl group, to give 8, or its parallel opening at C-1 through a twist-boat transition state to give 10. We therefore suggest that the reaction of 1 with NBA in dioxane-H_2O or with NBS in DMSO-H_2O proceeds through a fast pre-rate-determining step leading to the reversible formation of bridged intermediates followed by a slow nucleophilic attack leading to the products. Similar pathways have been invoked to rationalize the steric course of additions involving mercurinium and iodonium ion intermediates.[9,10]

On the other hand, since the product distribution of run 5 is very different from that obtained in runs 1-3 and approaches that of run 6, this shows a strong influence of the solvent and/or the added nucleophile on the overall steric course of the reaction with NBA.

Heating of both 8 and 10 at 80° led to equilibrium mixtures of the two bromohydrins in the ratio of 93·5:6·5. On the contrary 6 was stable when heated at 120°, while 4 under the same conditions gave some 6 besides extensive decomposition. The thermal equilibration between the acetyl derivatives 9 and 11 was slower and less clean than that of the corresponding bromohydrins and gave an about 9:1 ratio of 9 to 11 after heating at 90°. Although the diaxial ⟶ diequatorial rearrangement of vicinal steroid acetoxybromides has been widely investigated,[11] this is the first case to our knowledge of an 1,2-interchange between diastereoisomeric bromohydrins. The greater stability of compounds 8 and 9 with respect to their partners 10 and 11 provides a further evidence for the strong gauche interation between equatorial *t*-butyl and bromine, already observed in the thermal isomerization of the corresponding dibromo derivatives.[12]

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