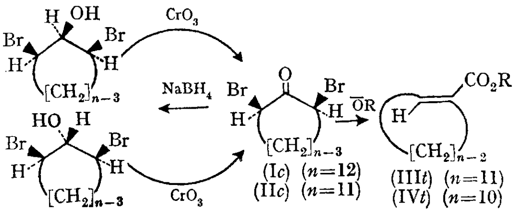
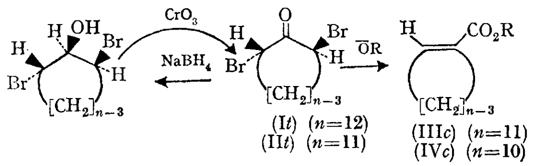
Stereospecific Favorskii Rearrangements of Diastereomeric αα'-Dibromo-ketones

By EDGAR W. GARBISCH, JUN.,* and JÜRGEN WOHLLEBE

(*Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455*)

FAVORSKII rearrangements of αα- and αα'-dihalogenoketones to give αβ-unsaturated acids or their derivatives have been shown in numerous instances to be stereoselective.[1] However, it is unknown whether these rearrangements are stereoconvergent or stereospecific in general. We have studied the Favorskii rearrangements of two pairs of diastereomeric αα'-dibromo-ketones under varying conditions and found in all cases substantial degrees of stereospecificity.





Bromination of cyclododecanone in ether or chloroform gave a 7 : 3 mixture of *cis*- and *trans*-2,12-dibromocyclododecanone [(I_c) and (I_t)] from which pure (I_c), m.p. 126°, and (I_t), m.p. 48°, were obtained by fractional crystallization. Similarly, *cis*- and *trans*-2,11-dibromocycloundecanone [(II_c), m.p. 80°; and (II_t), m.p. 56°] were synthesized in an 8 : 2 ratio. At thermodynamic equilibrium (ether–HBr, 25 to 30°), the ratios $I_c : I_t$ and $II_c : II_t$ were 79 : 21 and 62 : 38, respectively.

Structure assignments for the dibromo-ketones were based on their n.m.r. spectra, which showed quartets between τ 5·0 and 5·4 corresponding to two α-bromomethine protons. Configurations of the *cis*- and *trans*-αα'-dibromo-ketones were determined by the number of diastereomeric dibromohydrins obtained on reduction of the carbonyl group with sodium borohydride. (I_c) and (II_c) each yielded two chromatographically separable *meso*-dibromohydrins,† while (I_t) and (II_t) each

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† M.p. 49° and 40° in 51 and 38% yields, respectively from (I_c), and both melting at 65° in 84 and 2·1% yields from (II_c).

TABLE

Results of Favorskii rearrangements

Exp.	Compound	Method	Relative product composition[a] $\%(\text{III}_c)$	$\%(\text{III}_t)$
1	(I_c)	A and B	0	100
2	(I_c)	B (D_2O–LiOD)	No deuterium incorporation	
3	(I_t)	A and B	86	14
			$\%(\text{IV}_c)$	$\%(\text{IV}_t)$
4	(II_c)	A and B	0	100
5	(II_t)	A (at 10° only)	97	3
6	(II_t)	B	93	7

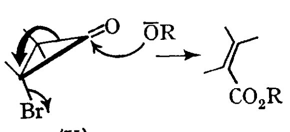
[a] Analyses were performed by g.l.c. and/or n.m.r. and are considered reproduceable to ±2%. Yields of esters were essentially quantitative and yields of acids were uniformly high (~85%).

gave a single (±)-dibromohydrin.‡ Oxidation of each dibromohydrin with chromium trioxide in pyridine regenerated the respective parent dibromo-ketone diastereomer.

Favorskii rearrangements were carried out by adding solutions of the dibromo-ketones in benzene to suspensions of sodium methoxide in benzene at both 10° and 80° (method A) or by adding solutions of the dibromo-ketones in dioxan to *ca.* 10% aqueous potassium hydroxide whilst maintaining the reaction temperature between 10 and 25° (method B).

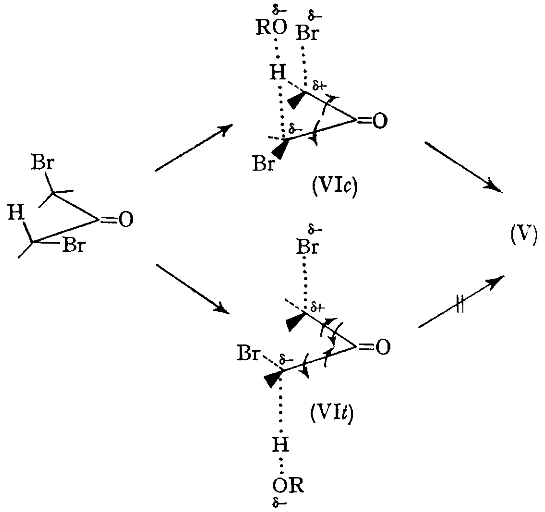
The configurations of the Favorskii rearrangement products (III) and (IV), were assigned after sodium methoxide-catalysed equilibration of the methyl esters in refluxing benzene. The geometric isomer that predominated at equilibrium was assigned the *cis*-configuration.§ Also, the n.m.r. spectra of the *cis*-isomers showed vinyl proton resonances approximately 0·6 p.p.m. to lower field than those of the *trans*-isomers. This is in agreement with empirical observations.[2]

The results of the Favorskii rearrangements are collected in the Table. They show these reactions to be largely stereospecific. However, we have found that the Favorskii rearrangements of other diastereomeric αα′-dihalogenoketones do not generally proceed stereospecifically.[3] Consequently, the detailed mechanism of these reactions may vary. The stereospecific reactions discussed here, if proceeding through cyclopropanone intermediate,[4] (V), which might be expected to react with base as shown, are most economically, although not uniquely, explained by considering a largely concerted elimination of hydrobromic acid to form (V). Rationale of questionable merit is required to account successfully for the results in the Table by invoking a two-step dehydrobromination in which (V) derives directly from the enolate ions of the dibromo-ketones.



(V)

For the dehydrohalogenation, a transition-state model [*e.g.* (VI)] that resembles a dipolar ion[5] accounts for the stereospecificity of these rearrangements, providing the departing hydrogen and halogen atoms both are partially bonded to the substrate. Dis-rotatory rather than con-rotatory



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‡ M.p. 79° (93% yield) from (I_t) and a chromatographically homogeneous oil (82% yield) from (II_t).

§ $K(\text{III}_c/\text{III}_t) = 27$ and $K(\text{IV}_c/\text{IV}_t) \simeq 100$. The melting points of (III_c), (III_t), (IV_c), (IV_t) (R = H) are 120°, 142·5°, 89·5°, and 132°, respectively.

cyclizations, as shown in (VI) for the *cis*- and *trans*-eliminations to form (V), are expected[6] to be preferred. However, both dis-rotatory cyclizations for *trans*-elimination [see (VI_t)] generate a departing atom, together with associated species, in the space of developing σ-bond occupation and therefore are unfavoured compared to the dis-rotatory *cis*-elimination shown in (VI_c). The model predicts a loss of stereospecificity, but not necessarily stereoselectivity, should the Favorskii rearrangements proceed through enolate or free dipolar ion intermediates.

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