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EFFECTS OF NEIGHBORING FUNCTIONAL GROUPS ON 1,2-ASYMMETRIC INDUCTION IN THE REDUCTION OF KETONES WITH SODIUM BOROHYDRIDE

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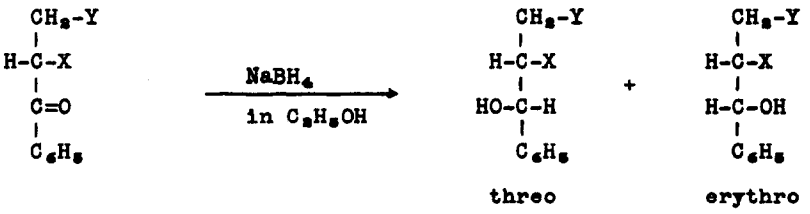
In relation to the previous report (1) on the stereoselective synthesis of l-norephedrine hydrochloride, the present authors examined the direction and the degree of 1,2-asymmetric induction in the sodium borohydride reduction of propiophenone derivatives (I～XVI) having functional groups such as amino, hydroxy, etc at α and/or β positions and an asymmetric center at α position to the carbonyl group (Table 1). The reduction of ketones (1 mmol.) was carried out with sodium borohydride (3 mmol. in the case of III, IV, VII, XII, XIII, XIV, XV, XVI, 4 mmol. in the case of I, II, V, VIII, IX, X, XI, and 5 mmol. in the case of VI) in ethanol (20 ml.) under reflux. Diastereoisomeric ratios (2) in the reduction products were determined either with n.m.r. spectroscopy (by making use of the considerable differences in the positions of signals between the produced diastereoisomers) or with gas chromatography.

From the results in Table 1, the following conclusions were drawn.

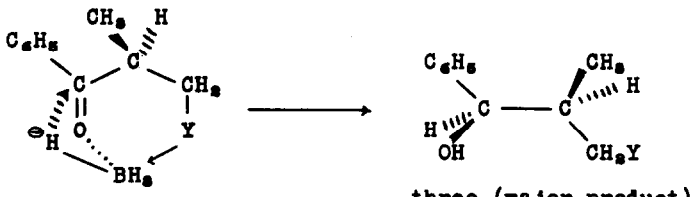
a) The direction of 1,2-asymmetric induction in the reduction of I and III is in accordance with that of the prediction by a five-membered cyclic model (3), with the participation of a functional group (NH_2 or OCH_3) at α position to the carbonyl group. In the case of II and IV, the reduction products are

TABLE I



No. of Ketone	X	Y	Method	threo : erythro
(I)	$NH_2 \cdot HCl$	H	n.m.r.(7)	8 : 92
(II)	CH_3	$NH_2 \cdot HCl$	n.m.r.(7)	90 : 10
(III)	OCH_3	H	n.m.r.(7)	27 : 73
(IV)	CH_3	OH	n.m.r.(7)	71 : 29
(V)	$NH_2 \cdot HCl$	OH	n.m.r.(7)	44 : 56
(VI)	$NH_2 \cdot HCl$	$NH_2 \cdot HCl$	n.m.r.(7)	36 : 64
(VII)	OCH_3	OH	v.p.c.(8)	41 : 59
(VIII)	OCH_3	$NH_2 \cdot HCl$	n.m.r.(7)	3 : 2
(IX)	$NHCH_2C_6H_5$ HCl	H	n.m.r.(9)	1 : 7~8
(X)	$N(CH_3)_2$ HCl	H	n.m.r.(9)	1.1~1.3 : 1
(XI)	$N(CH_3)CH_2C_6H_5$ HCl	H	n.m.r.(9)	3 : 1
(XII)	$NHCOCF_3$	H	n.m.r.(9)	3 : 10
(XIII)	$NHCOCH_3$	H	n.m.r.(9)	3 : 10
(XIV)	$NHCOC_6H_5$	H	n.m.r.(9)	3 : 10
(XV)	$N(CH_3)CH_2C_6H_5$	H	n.m.r.(9)	7 ~ 8 : 1
(XVI)	$N(COC_6H_5)CH_2C_6H_5$	H	n.m.r.(9)	7 ~ 8 : 1

rich in threo-isomer. This result is rationalized by supposing a six-membered cyclic model (XVII), with the participation of a functional group (NH_2 or OH) at β position to the carbonyl group (4). The six-membered cyclic model is, therefore, applicable for the prediction of the stereochemical course in the reduction of ketones having a functional group at β position to the carbonyl group as the transition state of the lowest energy (Fig. 1).



(XVII) Y = NH_2, OH

threo (major product)

FIG. I

b) The stereoselectivity is decreased in the reduction of ketones having functional groups both at α and β positions to the carbonyl group (4). This phenomenon is reasonable because the effect of a functional group at α position on the direction of 1,2-asymmetric induction is opposite to that at β position, resulting in cancelling these effects with each other.

c) It is already known that the stereoselectivity of the reduction is different among the ketones having various substituents on the amino group in I (5). The results of the present study show that the ketones having a di-substituted amino group at α position to the carbonyl group afford threo-rich products, contrary to the prediction by a five-membered cyclic model. This change in stereoselectivity may be attributable mainly to the bulkiness, not to the basicity, of the di-substituted amino group. In these cases, therefore, the model in which the bulky di-substituted amino group and the carbonyl oxygen are oriented anti to each other owing to their steric repulsion (similar to the so-called dipolar model (6)) may be considered for the explanation of the results.

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7) Analyzed with a Varian A-100 Spectrometer (100 Mc.).

8) Analyzed with a Shimadzu Gas Chromatograph GC-1B equipped with a hydrogen flame ionization detector. Column : 5% PEGA on Diasolid L. Sample : Diacetate of the reduction product.

9) Analyzed with a Japan Electron Co. JNN-C60 Spectrometer (60 Mc.).