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STERIC CONTROL OF ASYMMETRIC INDUCTION IN MEERWEIN-PONNDORF REDUCTION OF α-PHTHALIMIDO-β-SUBSTITUTED PROPIOPHENONES*

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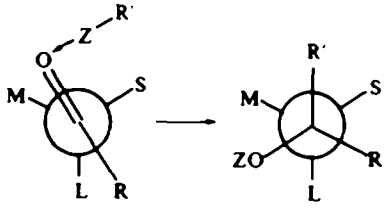
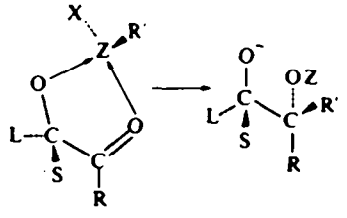
Abstract—Reduction of RCH_2—CH(N = Phthaloyl)-CO—Ph (R = H, Me, OMe, SMe) with aluminum isopropoxide gives predominantly the *threo* isomer. The results were interpreted on the bases of "Rule of Steric Control of Asymmetric Induction" postulated by Cram and it has been suggested that the "open chain model" significantly contributes to the steric course of the described reactions.

A NUMBER of papers have been published in which aluminum isopropoxide was used for the reduction of substituted propiophenones containing an asymmetric C atom adjacent to the CO group. In many of these examples the steric course of reduction could be predicted on the bases of Cram's rule of steric control of asymmetric induction.[1] Two mechanisms have been proposed to rationalize data pertaining to the steric direction of asymmetric induction. One is represented by open chain model I, in which the groups attached to the asymmetric center, S, M and L†,[2] do not complex with the reagent used for reduction of CO, while the second mechanism proceeds *via* the rigid cyclic model II in which one of the groups attached to the asymmetric C atom can form complexes with the reagent.



I (open chain model)



II (rigid model)

Cram and Green[3] found that the reduction of 3-cyclohexyl-2-butanone with aluminum isopropoxide gave results incompatible with the open chain model. The cyclic model however can be used to predict the correct steric results. Sicher *et al.*[4] studied the reduction of α-acylamino-β-substituted *p*-nitropropiophenones (III) with the same reagent and postulated that the Cram's rule can predict the correct diastereoisomer if R″ is H, Cl, OAc, SBz, Ph_3CO, but if R″ is OH the open chain model

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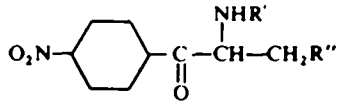
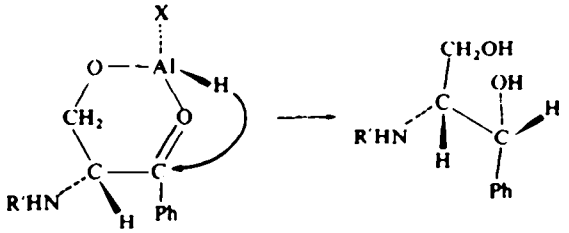
† S, M and L denotes small, medium and large groups according to the "effective bulk".

predicts the diastereoisomer opposite to that obtained experimentally. If however the rigid 6-membered ring system (IV) is applied, the correct diastereoisomer can be predicted in the reduction with aluminum isopropoxide. In previous studies on



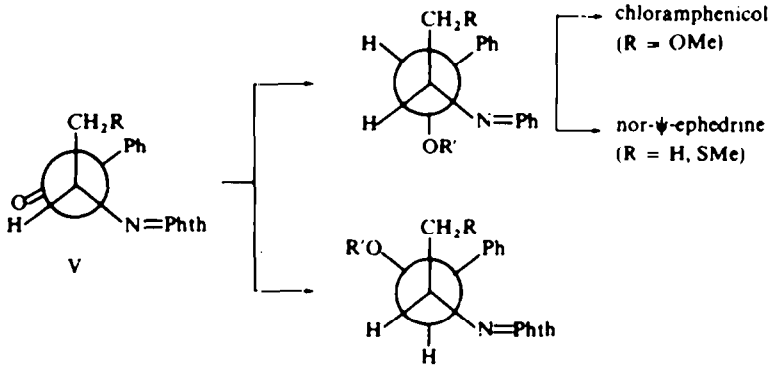
III

R' = $COCHCl_2$,
R'' = H, Cl, OAc, SBz, Ph_3CO, OH



IV

the configuration of nor-ψ-ephedrine[5] and chloramphenicol and derivatives[6,7] we reduced α-phthalimido-β-substituted-propiophenones (V) with aluminum isopropoxide under normal conditions of the Meerwein–Ponndorf–Verley reaction. In the papers,[5–7] the steric course of reduction was not specifically controlled, although in all cases the *threo* isomers were isolated as predominant products of the reaction.



V

VI-*erythro*

R = H, Me, OMe, SMe
R' = H, Ac

The configuration of the predominant diastereoisomers was determined by conversion to compounds of known configuration.

The major function of the present paper is to report the results of recent studies on the steric course of reduction of propiophenones (V) with aluminum isopropoxide. Propiophenones (V) were prepared from the corresponding acid chlorides via the

Friedel-Crafts synthesis and the ketones were then reduced to the diastereomeric carbinols (VI). The crude mixture of carbinols was acetylated and the ratio of *threo* to *erythro* isomer determined by means of NMR spectra.

The spectra of pure *threo* and *erythro* acetoxy derivatives were first recorded for VI (R = H, SMe, and OMe) and the chemical shifts of the Me group of β-substituent and of acetoxy groups determined. The configuration of the carbinol VI (R = Me) was assigned on the basis of analogy to the first three compounds. The ratio of *threo* to *erythro* epimer was determined from the integrals of the NMR signals of the Me groups from the β-substituent or from the acetoxy group (Table 1).

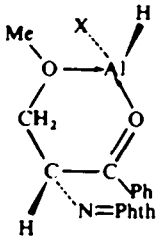
TABLE 1. CHEMICAL SHIFTS (PPM) OF CHARACTERISTIC GROUPS OF RCH_2 –CH(N = PHTHALOYL)-CH(OAc)–Ph AND THE RATIO OF *Threo* TO *Erythro* EPIMER

R	*Threo*	*Erythro*	*Threo/Erythro*
H	1·83 (Ac)	2·10 (Ac)	2·8 ± 0·1
	1·28 (Me)	1·60 (Me)	
OMe	1·89 (Ac)	2·10 (Ac)	2·7 ± 0·1
	3·18 (OMe)	3·32 (OMe)	
Me	1·62 (Ac)	1·9 (Ac)	2·4 ± 0·1
SMe	1·86 (Ac)	2·10 (Ac)	
	1·91 (SMe)	2·12 (SMe)	2·7 ± 0·1

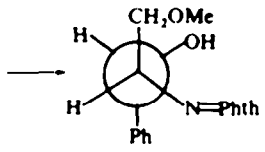
As evident from the Table 1, the *threo* isomer was in all cases the predominant product of reduction, the ratio of *threo* isomer to *erythro* being of the order of 2·7 : 1. It was further found that within the range of experimental error the same ratio of *threo* to *erythro* isomer was obtained when the reduction of ketone was stopped after 20 minutes, when a relatively low degree of conversion of ketone to carbinol was achieved. The ratio of both diastereoisomers did not change when the reaction mixture was heated for 24 hr under the normal condition of Meerwein–Ponndorf–Verley reduction. The pure *threo* and *erythro* isomers did not isomerize when heated for 24 hr with aluminum isopropoxide in isopropanol, which indicates the stability of both isomers under the conditions of experiment.

The predominant formation of one epimer in the reduction of ketone V, is an example of asymmetric induction which was extensively studied by Cram *et al.* and formulated as "Rule of Steric Control of Asymmetric Induction". By applying this rule to the steric course of reduction of ketone V (R = H and Me) with aluminum isopropoxide, the results indicate that the open chain model (I) best explains the course of the reduction, since there is no group capable of complexing with the reagent. The electron pair on the N of the phthalimido group is highly delocalized and is relatively unavailable for coordination. Since phthalimido > Me > H, the Cram's rule predicts the predominant formation of the *threo* epimer which is in agreement with the experimental findings. The reduction of ketone V (R = OMe and SMe) can proceed by both open chain model and by rigid 6-membered ring as proposed by Sicher[4] and Felkin[8] since OMe and SMe can form the complexes with the reagent. It is however unlikely that the mechanism of reduction of V (R = H or Me) differs from the one involved in the reduction of V (R = OMe or SMe) since

the ratio of *threo* to *erythro* isomer is practically the same in all four cases. We therefore propose that open chain model I contributes significantly in the reduction of ketones V with aluminum isopropoxide.



V



VI

EXPERIMENTAL

The preparation of carbinols VI (R = H, OMe, SMe) has been described.[6-8] NMR spectra were recorded with a Varian A-60 spectrometer at room temp in $CDCl_3$ or benzene-d solns (100 mg/ml).

2-Phthalimidobutyric acid.[9] A finely powdered mixture of 1 g (0·01 mole) 2-aminobutyric acid and 1·48 g (0·01 mole) phthalic anhydride was placed in a round bottomed flask and heated in an oil bath with a thermometer immersed in the reaction mixture. A vigorous evolution of wavter started between 130–140° and the reaction mixture melted. Heating was continued for 1 hr at the temp of 130–140°. After cooling the mixture was dissolved in 5 ml benzene. The benzene was partly evaporated, yielding 2·1 g (93%) of white crystals m.p. 101–102°.[9] (Found: C, 61·48; H, 4·56; N, 6·35. $C_{12}H_{11}NO_4$ requires: C, 61·79; H, 4·75; N, 6·01%).

2-Phthalimidobutyril chloride. 2-Phthalimodobutyric acid (22·02 g) was refluxed for 2 hr with 40 ml $SOCl_2$. The excess $SOCl_2$ was removed *in vacuo*, the residue repeatedly treated with benzene and distilled; b.p. 204° (20 mm); m.p. 53–55°; yield 18·8 g (80%). (Found: C, 57·61; H, 3·55; N, 5·40. $C_{12}H_{10}ClNO_3$ requires: C, 57·14; H, 3·99; N, 5·55%).

2-Phthalimidobutyrophenone. A mixture of 40 ml benzene and 10 g (0·075 mole) anhyd $AlCl_3$ was placed in a 500 ml 3-necked flask, equipped with a mechanical stirrer, a dropping funnel and a reflux condenser. The reaction mixture was heated to 70° and with rapid stirring, 6·3 g (0·025 mole) α-phthalimidobutyril chloride dissolved in 20 ml benzene was added. The mixture was refluxed for an additional 3 hr, cooled and hydrolysed with 25 g ice and 2 ml conc HCl. The water layer was separated and extracted with two 50-ml portions benzene. The combined benzene solns were washed with two 20-ml portions of satd $NaHCO_3$ aq followed by water and finally dried over Na_2SO_4. The benzene was removed *in vacuo*, and the residue (4·9 g, 62%, m.p. 110–113°) was recrystallized from abs EtOH, m.p. 114–116°. (Found: C, 73·72; H, 5·06; N, 4·65. $C_{18}H_{15}NO_3$ requires: C, 73·69; H, 5·27; N, 4·77%).

Reduction of 2-phthalimidobutyrophenone with aluminum isopropoxide. In a 100-ml round-bottomed flask fitted with a Hahn partial condenser, 3·36 g (0·012 mole) of V (R = Me), 7·34 g (0·036 mole) distilled aluminum isopropoxide and 70 ml dry isopropanol were heated at such rate as to maintain the slow distillation of acetone. After heating the mixture for 10 hr, the isopropanol was removed *in vacuo*, and the residue hydrolysed with a soln of 10 g tartaric acid in 50 ml water in the presence of 30 ml benzene. The water layer was removed and extracted with three 10-ml portions benzene. The combined benzene soln was dried, the benzene removed *in vacuo*, and the residue (3·5 g; 95·5%) acetylated without further purification.

Acetylation of mixture of threo *and* erythro-*1-phenyl-1-hydroxy-2-phthalimidobutane.* The crude mixture of carbinols VI (R = Me) (3·5 g) was dissolved in 18·1 g Ac_2O and 16 ml pyridine. The reaction mixture was cooled in ice for ½ hr, then left at room temp overnight, and the solvent evaporated to dryness. The crude mixture of acetylated isomers was used for NMR measurements.

threo-*1-Phenyl-1-hydroxy-2-phthalimodobutane.* The *threo*-isomer was obtained as the less soluble product in EtOH from the mixture of *threo* and *erythro* carbinols; m.p. 124–125°. (Found: C, 73·14; H, 5·65; N, 5·02. $C_{18}H_{17}NO_3$ requires: C, 73·20; H, 5·80; N, 4·74%).

[9] The preparation of the same compound by saponification of the corresponding ethyl ester has been reported m.p. 94–95°.[9]

threo-1-*Phenyl*-1-acetoxy-2-*phthalimidobutane*. *threo*-Carbinol VI (R = Me; 1 g) was acetylated with 6·7 g Ac_2O in 6 ml pyridine as previously described; m.p. 120–122°. (Found: C, 71·02; H, 5·82; N, 4·45. $C_{20}H_{19}NO_4$ requires: C, 71·20; H, 5·67; N, 4·15%).

threo-1-*Phenyl*-1-*acetoxy*-2-*phthalimidopropane*. *threo* Carbinol VI (R = H; 2 g) was acetylated with 8·6 ml Ac_2O in 17 ml pyridine, yield 1·56 g (68%), m.p. 117–118° from EtOH. (Found: C, 70·92; H, 5·55; N, 4·55. $C_{19}H_{17}NO_4$ requires: C, 70·57; H, 5·30; N, 4·38%).

erythro-1-*Phenyl*-1-*acetoxy*-2-*phthalimidopropane*. Acetylation of the mother liquor from which the *threo* carbinol was removed gave 16% of an oily product. (Found: C, 70·76; H, 5·53; N, 4·66. $C_{19}H_{17}NO_4$ requires: C, 70·57; H, 5·35; N, 4·33%).

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