# THE STEREOSELECTIVE REDUCTION OF α-AMINOPROPIOPHENONE DERIVATIVES WITH SODIUM BOROHYDRIDE

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Abstract —— The ratio of erythro and threo products from the sodium borohydride reduction of the hydrochlorides, and other acid salts, of α-aminopropiophenone derivatives was determined. It was found that this procedure resulted in stereoselective formation of erythro-2-amino-1-phenylpropanols in contrast to sodium borohydride reduction of the corresponding free bases. The method was successfully applied to the synthesis of dl-erythro-2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)propanol which has been used as a vasodilator.

We wish to report here the stereoselective reduction of α-aminopropiophenone derivatives with sodium borohydride. Although there are already many reports[1] concerning the sodium borohydride reduction of α-aminopropiophenone derivatives, the products have generally been mixtures of erythro and threo isomers with the predominant isomer being predictable to some extent from application of Cram's model[2] or Karabatsos's method.[3] The general method for the preparation of erythro-2-amino-1-phenylpropanols has therefore been catalytic hydrogenation of the corresponding α-aminopropiophenones.[1c,4]

We were interested in the reduction of α-aminopropiophenone hydrochlorides with sodium borohydride for the reason that amine salts with sodium borohydride produce aminoborines.[5] Accordingly, sodium borohydride reduction of the hydrochlorides of (1a, b, and c) was carried out with the result that erythro isomers (2) were

obtained with high selectivity, in contrast to reduction of the free bases, as shown in Table I. It was also observed that reaction temperature influenced the erythro/threo ratio of products. The low yields (Table I) of those products are due to losses incurred on silica gel column chromatography.

Table (I). Reduction of α-Aminopropiophenones(1) with $NaBH_4$

(1) (2)

| | Starting Material $R_1$ | $R_2$ | | Reduction Conditions | Yield (%) threo-(2) | erythro-(2) |
|---|---|---|---|---|---|---|
| 1a | Et | Et | free base | below 25° | 27.4 | 37.9 |
| | Et | Et | B:HCl | below 25° | trace | 85.3 |
| 1b | $-(CH_2)_5-$ | | free base | below 25° | 14.8 | 53.4 |
| | $-(CH_2)_5-$ | | B:HCl | below 25° | 4.1 | 64.8 |
| | $-(CH_2)_5-$ | | B:HCl | reflux(MeOH) | 10[a] | 90[a] |
| 1c | Me | By | free base | below 25° | 27.3 | 36.7 |
| | Me | By | B:HCl | below 25° | 2.0 | 65.8 |
| | Me | By | B:HCl | reflux(MeOH) | 60[a] | 40[a] |

a) Analysis by NMR spectroscopy (relative ratio). By=benzyl

From these results we speculate that the high degree of stereoselectivity observed is due to the initial formation of the aminoborine followed by the formation of Cram's five-membered cyclic transition state.[2]

The method was then applied to the reduction of various salts of α-piperidino-propiophenone derivatives (3a) and (3b). As shown in Table II, erythro (4a) and erythro(4b), which has been used as a vasodilator, were obtained with high selectivity. It was observed that the erythro/threo product ratio was virtually the same for reduction of the free base (3b) as for reduction of its acid salts, i.e. that utilisation of an acid salt in this reaction did not improve on the already highly stereoselective reduction of the free base. This anomalous stereoselective reduction

of the free base (3b) is attributed to formation of the amine salt, by virtue of the presence of a phenolic hydroxyl group, as suggested by the appearance of absorption bands at 2300 - 2700 $cm^{-1}$ in its infrared spectrum. This was readily proven by two simple experiments as follows. When (3b) was reduced with sodium borohydride in the presence of sodium hydroxide the aforementioned stereoselectivity was lost, and, when the non-phenolic free base (3a) was reduced in the presence of phenol, erythro (4a) was produced selectively.

Table (II). Reduction of α-Piperidinopropiophenones (3a and b)

(3) (4)

| | Starting Material | Reducing Agent | Solvent | Temperature | Yield (%) threo-(4) | erythro-(4) |
|---|---|---|---|---|---|---|
| 3a(R=By) | free base | $NaBH_4$ | MeOH | below 25° | 27.4 | 52.2 |
| | B:HCl | $NaBH_4$ | MeOH | below 25° | 0.2 | 96.6 |
| | oxalate | $NaBH_4$ | MeOH | below 25° | trace | 92.8 |
| | B:$H_2SO_4$ | $NaBH_4$ | MeOH | below 25° | 0.9 | 83.3 |
| | free base +phenol(x1.1) | $NaBH_4$ | MeOH | below 25° | 5.5 | 88.3 |
| | B:HCl | $NaBH_4$ | MeOH | reflux | 12[a] | 88[a] |
| | free base | RDB | benzene | room temp. | 46.2 | 24.3 |
| | B:HCl | RDB | benzene | room temp. | 55.4 | 24.1 |
| 3b(R=H)[b] | free base | $NaBH_4$ | MeOH | below 25° | 6 | 94 |
| | B:HCl | $NaBH_4$ | MeOH | below 25° | 5 | 95 |
| | B:$H_2SO_4$ | $NaBH_4$ | MeOH | below 25° | 6 | 94 |
| | oxalate | $NaBH_4$ | MeOH | below 25° | 7 | 93 |
| | free base +NaOH | $NaBH_4$ | MeOH | below 25° | 18 | 82 |
| | B:HCl | RDB | benzene | room temp. | 57 | 43 |

a) Analysis by NMR spectroscopy (relative ratio).

b) The yield was determined using a Chromatoscanner (relative ratio).

RDB=$NaAl(OCH_2CH_2OCH_3)_2H_2$ By=benzyl

Thus it has been shown that sodium borohydride reduction of the salts of α-amino-propiophenone derivatives, or of the free bases in the presence of acid, proceeds stereoselectively to give the corresponding erythro-2-amino-1-phenylpropanols.

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