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THE ROLE OF THIOUREA SS-DIOXIDE IN THE REDUCTION OF STEROIDAL KETONES

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Thiourea SS-dioxide[1] (TDO), long known to be a powerful reducing agent for metallic ions, has been also reported[2] to be a reducing agent of aromatic nitro, azoxy, azo and hydrazo compounds as well as of quinones, but not capable of reducing ketones. However, recently Nakagawa and Minami reported[3] that aromatic, aliphatic and alicyclic ketones were easily converted into the corresponding secondary alcohols, when treated with TDO in aqueous ethanolic solutions of caustic alkali, via a one-electron transfer process. Subsequently, Herz and de Márquez reported[4] that steroidal ketones were only partially reduced under such conditions, whereas the reductions became quantitative by using TDO in the presence of a stronger base such as sodium n-propoxide in anhydrous n-propanol.

On the other hand, we had found[5] that steroidal ketones undergo very fast and quantitative conversion into the corresponding secondary alcohols when simply refluxed with ethanolic or isopropanolic potassium hydroxide, according to a Meerwein-Ponndorf type mechanism. These results and the fact that TDO was reported to be ineffective in the reduction of ketones, when pyridine or dimethylformamide were used as solvents,[2] suggested that the mentioned reductions of ketones by TDO in the presence of strong bases could be more or less completely operated by the alkoxide present in the solution.[6]

In this view, we performed the reduction of some of the substrates used by the above authors under their same experimental conditions only with exclusion of TDO. Thus for instance, cyclohexanone, which was reported to undergo reduction in 81% yield in the presence of TDO, was found to be reduced to a comparable degree (GLC) in the absence of TDO.

In order to determine the actual role of TDO in the reduction of ketones in the presence of strong bases, we carried out the reduction of cholestan-3-one under reflux (2 hr) with potassium hydroxide in 2-deuteropropan-2-ol, respectively in the absence and in the presence of TDO (2:1 moles KOH:TDO). Both the reactions were quantitative. In the first case, the epimeric cholestanols were obtained in a 6.0:4.0 β-equatorial to α-axial ratio and were shown to be, as could be predicted, completely deuterated at C-3 (MS,NMR). In the second case, they were obtained in a slightly different ratio (6.3:3.7)[7] but, most significantly, the β-equatorial epimer was shown to contain

16% of C-3 non-deuterated product (corresponding to 10% of the overall yield of alcohols) and the α-axial form to contain about 3% of the C-3 non-deuterated compound (corresponding to 1% of the overall yield of alcohols). Therefore, the actual ratio between the C-3 deuterated cholestan-3-ols is the same as found in the absence of TDO.

However, these data would be meaningless if deuterium exchange at C-3 occurs through alkaline equilibration of the epimeric 3-ols. Accordingly, the ratio between 3α- and 3β-cholestanol was checkedthroughout all the reduction time and found to be constant; in addition, when cholestan-3α-ol (1 mmole) was refluxed (2 hr) in isopropanolic potassium hydroxide with cholestan-3-one (2 mmoles added, 1.8 mmole of the α-axial epimer and 1.2 mmole of the β-equatorial epimer were isolated, thus providing evidence that no equilibration occurs during the reduction.

Apparently, either acetone formed and/or cholestan-3-one still present in the reaction mixture is ineffective in the stereochemical equilibration of the epimeric alcohols,[8] the former being rapidly converted into higher molecular weight products, the latter probably because of steric reasons. Accordingly, when refluxed for 100 hr with isopropanolic potassium hydroxide in the presence of 5% moles of cyclohexanone (acetone was ineffective), pure 3α- and 3β-cholestanols afforded a mixture of both the epimers.

In conclusion the C-3 deuterated cholestan-3-ols, representing 89% of the overall yield of alcohols, originate from hydride (deuteride) attack by the alkoxide ion whereas only 11% of the total alcohols come from TDO reduction. Furthermore, it is noteworthy that the ratio between the C-3 non-deuterated epimers is 10:1, thus being in much better agreement with a one-electron transfer reduction mechanism as postulated for TDO.

In the light of these results, thiourea SS-dioxide does not seem to play a major role in the reaction and, therefore, cannot be considered an useful reducing agent for ketones.

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