Regiospecific Oxidation of Cyclic Amino-compounds with Ruthenium Tetroxide

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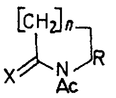
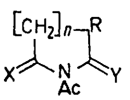
Summary Regiospecific oxidation of 2-substituted-*N*-acetyl pyrrolidines and piperidines to the corresponding lactams can be carried out, with retention of the absolute configuration, using ruthenium tetroxide.

FOR work on the chiroptical behaviour of amino compounds, we needed cyclic substituted amines of known absolute configuration.[1] The chirality and optical purity of some alkyl substituted piperidines have already been determined.[2] A suitable reaction for determining the absolute configuration of aryl substituted pyrrolidines and piperidines seemed to be the oxidation of the phenyl substituent to a carboxyl group since the configurations of the corresponding carboxylic acids are well known. Since ozone[3] was unsuccessful as the oxidising agent (using the *N*-acetyl derivatives of the amines) ruthenium tetroxide was used. It has previously been used in preparing imides,[4] a reaction which could constitute a convenient step in converting 3-substituted piperidines and pyrrolidines to the corresponding glutaric and succinic acids which have known configurations.[5]



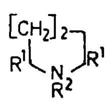
(I); *n* = 1, R = Ph

(II); *n* = 2, R = Me



(III); *n* = 1, R = Ph

(IV); *n* = 2, R = Me



(V) R^1 = Me (cis), R^2 = Bz

(VI) R^1 = H, R^2 = Bz

(VII) R^1 = H, R^2 = Ac

(a) $X = H_2$, (b) $X = O$, (c) $X = Y = H_2$; (d) $X = O, Y = H_2$, (e) $X = H_2$, $Y = O$

Sheehan and Tulis have worked on ruthenium tetroxide oxidation of unsubstituted cyclic amines,[6] and we now report results for *N*-acetyl-2- and 3-substituted pyrrolidines and piperidines.

The reaction of *R*-(+)-*N*-acetyl-2-phenylpyrrolidine[7] (Ia) with ruthenium dioxide hydrate and sodium metaperiodate in a two-phase system of water–carbon tetrachloride, gave *R*-(+)-*N*-acetyl-5-phenyl-2-pyrrolidinone (Ib), identical to a sample prepared from optically pure *R*-(−)-4-amino-4-phenylbutyric acid hydrochloride.[7] Similar results were obtained from *N*-acetyl-2-methylpiperidine (IIa) which gave the piperidone (IIb). The *N*-acetyl lactams (Ib) and (IIb) were the only products of the two reactions, no compound arising from the oxidation of the tertiary carbon atom was found. Moreover, *N*-benzoyl-*cis*-2,6-dimethylpiperidine (V) was quantitatively recovered from a reaction similar to those described for the compounds (Ia) and (IIa).

In the 3-substituted *N*-acylamines (IIIc) and (IVc), the reagent oxidises one of the methylene groups linked to the nitrogen atom; they are never both oxidised since no imides could be detected in the reaction mixture which contains only the *N*-acetyl lactams [(IIId), (IIIe)] and [(IVd,) (IVe)] respectively in a 1 : 1 ratio (n.m.r. integral of benzylic–H and CH–Me signals respectively); no racemization was observed in the oxidation of (IIIc) obtained from *S*-(+)-3-phenylpyrrolidine.[8]

In all of these reactions, as well as in the oxidation of *N*-benzoyl (VI) and *N*-acetylpiperidine (VII), the yields are *ca.* 60%. Satisfactory analyses and spectral data were obtained for all new compounds.

The results suggest that ruthenium tetroxide oxidation of *N*-acetyl 2-substituted cyclic amines is regiospecific and that this property cannot be ascribed only to steric factors since they are completely inoperative in the oxidation of 3-substituted compounds.

The preferential oxidation of the methylene groups next to the nitrogen atom of the ring and the retention of the absolute configuration make ruthenium tetroxide a promising synthetic and degradative tool in nitrogen chemistry.

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