A Convenient Alternative to the Beckmann Rearrangement

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Summary Alkyl nitrones from ketones are smoothly transformed by treatment with toluene-*p*-sulphonyl chloride in pyridine into *N*-alkylamides, a reaction sequence which provides a convenient alternative to the Beckmann rearrangement.

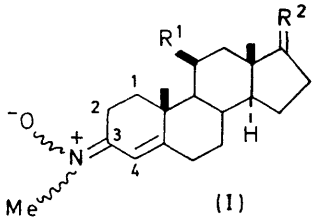
THE rearrangement of aldo-nitrones to amides is a well known process (reaction 1).[1] We now report that the

$$R^1CH{=}\overset{O^-}{\underset{|}{\overset{|}{\underset{+}{N}}}}{-}R^2 \rightarrow R^1CONHR^2 \qquad (1)$$

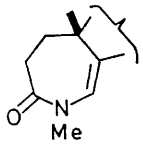
methyl (and, by implication, other) nitrones derived from Δ^4-3-keto-steroids (*e.g.* Ia) undergo a smooth rearrangement on treatment with toluene-*p*-sulphonyl chloride in pyridine to afford A-aza-A-homo-steroid analogues (*e.g.* IIa). We have also observed a comparable rearrangement for nitrones derived from saturated ketones. An analogous rearrangement of benzimidazole *N*-oxides has been recently reported.[2] The rearrangement products from Δ^4-3-keto-steroids were identified by analysis and by spectral methods. In particular, one may reject the isomeric formulation (III) on the basis of n.m.r. and u.v. spectra [λ_{max} 239—242 nm; *cf.* the isomeric azapenones (IV) and (V)[3]]. The direction of rearrangement of a keto-nitrone to an amide does not appear to depend on the stereochemistry of the nitrone (contrast with the Beckmann rearrangement[4]) for mixtures of isomeric nitrones afforded essentially a single amide product (Table). Indeed, the two isomeric forms of nitrones (Ib) when resolved were found to rearrange to the same product (IIb).

The rearrangement is initiated by toluene-*p*-sulphonylation of the nitrone followed presumably by capture of a

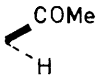
nucleophile (pyridine) at C-3 (reaction 2). The resulting hydroxylamine *O*-tosylate would be expected to rearrange

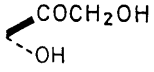


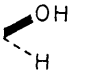
(I)

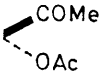


(II)

a; $R^1 = H$, $R^2 =$  9(11)-dehydro

b; $R^1 = OH$, $R^2 =$ 

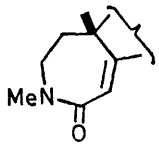
c, $R^1 = H$, $R^2 =$ 

d, $R^1 = H$, $R^2 =$ 

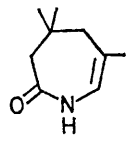
e; $R^1 = H$, $R^2 = O$

readily as shown. We favour the rearrangement of an intermediate hydroxylamine rather than the direct reorganization of the corresponding nitrone for several reasons, among them the lack of steric control and the preference for *vinyl* migration. Thus, the analogous oxime (VI) which is disposed for vinyl migration is quite resistant to Beckmann rearrangement.[5]

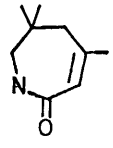
The nitrone–amide rearrangement provides entry to a class of aza-steroids not accessible *via* the Beckmann rearrangement. This is by virtue of the presence of an *N*-substituent, and more significantly, the location of the double bond. Oximes derived from steroidal Δ^1- or Δ^4-3-ketones which undergo the Beckmann rearrangement afford amides of type (III) rather than type (II).[5] It is clear that where a ketone can be conveniently converted into a nitrone, the rearrangement of the latter provides an



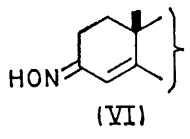
(III)



(IV)

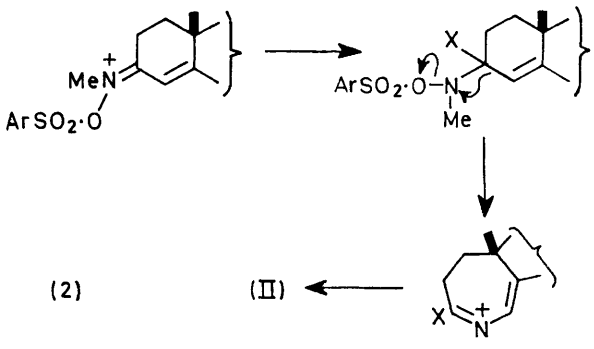


(V)



(VI)

alternative to the Beckmann rearrangement. In addition it provides directly *N*-substituted amides.



(2)

Nitrone	Ratio of nitrones	Amide produced	M.p. (°C)	Yield (%)
(Ia)	85:15*	(IIa)	146—147	45
(Ib)	1:1*	(IIb)	226—228	Form A, 63 Form B, 71
(Ic)	3:2†	(IIc)	217—218	52
(Id)	3:1*	(IId)	208—209	43
(Ie)	Not determined	(IIe)	169—170	52

* The isomer ratio of nitrones was determined by n.m.r. analysis of the 4-vinyl proton and represents high field : low field protons.
† The isomer ratio of nitrones is approximate (t.l.c.) and represents more polar : less polar compounds.

We thank Dr. V. A. Moss for help in the preparation of several of the nitrones used by us. All new compounds showed the expected spectral data and gave correct analyses.

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