Tetrahedron Letters No. 33, pp 3393 - 3396, 1972. Pergamon Press. Printed in Great Britain.

CYCLIZATION OF β-KETOSULFOXIDE

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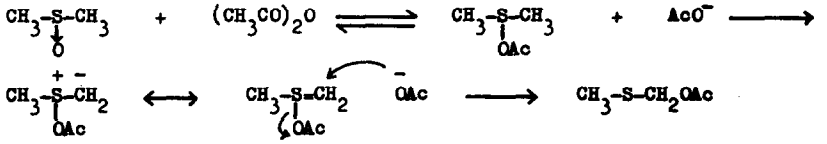
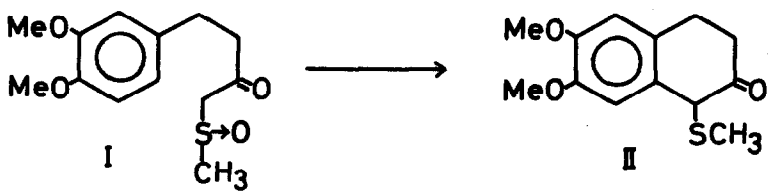
(Received in Japan 14 June 1972; received in UK for publication 10 July 1972)

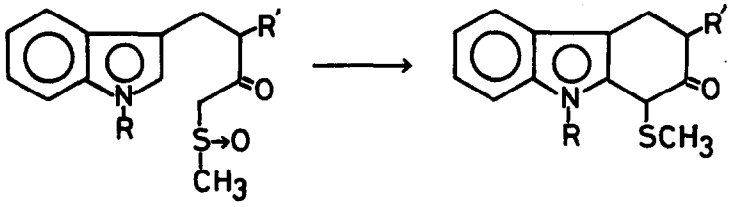
It is most probable that the Pummerer reaction[1] of dimethylsulfoxide with acetic anhydride proceeds through an intermolecular nucleophilic attack[2] of acetoxy group on the methylene carbon of the ylide-ylene intermediate.[3] If this is the mechanism, taking the place of acetoxy anion, a nucleophile existing at the suitable position in a sulfoxide molecule may attack intramolecularly the methylene carbon of a ylene intermediate. In order to prove the possibility, we have now examined a cyclization reaction of β-ketosulfoxide having an aromatic nucleus as a nucleophile.



When 3,4-dimethoxyphenethyl methylsulfinylmethyl ketone (I) was heated under reflux with 2 equivalent of trifluoroacetic acid in benzene for 1 hr, 2,3-dimethyoxy-5-methyl-mercapto-6-oxo-5,6,7,8-tetrahydronaphthalene (II, mp 99-102°), was isolated in 70 % yield. The structural assignment of II rests mainly on its spectral data. On the basis of the mass spectrum and the elemental analysis, II has the composition $C_{13}H_{16}O_3S$ (mol wt 252). A carbonyl group appears at 1700 cm^{-1} in the ir spectrum. The nmr spectrum showed the S-methyl group at δ 2.16 ppm (3H, s), the methyne proton ($-\underline{C}HSCH_3$) at δ 4.04 (1H, s) and the aromatic protons at δ 6.68 (1H, s) and δ 6.80 (1H, s).



Indole derivatives IIIa and IIIb were similarly subjected to the reaction. The treatment of IIIa with 0.5 equivalent of trichloroacetic acid in boiling dichloroethane yielded IVa (46 %), and IIIb gave IVb (60 %) when heated with 2 equivalent of the same acid in boiling benzene. Tryptophan derivative V also gave the same type of product VI in 66 % yield under similar conditions without any detectable formation of a dihydroisoquinoline by the Bischler-Napieralski reaction.

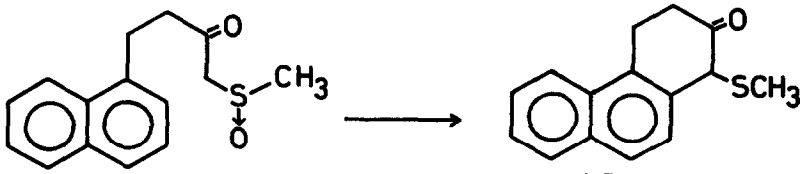


IIIa R=H, R'=H IVa

IIIb R=CH_3, R'=H IVb

V R=CH_3, R'=$NHCOCH_3$ VI

On the other hand, β-(α-naphthyl)ethyl methylsulfinylmethyl ketone (VII) and phenethyl methylsulfinylmethyl ketone (IX) failed to cyclize with trichloroacetic acid or trifluoroacetic acid, which may be well explained by the less nucleophilicity of the aromatic nuclei in VII and IX. Instead of just protonation, acylation of the sulfinyl group, however, may assist this cyclization reaction, because a O-acyl group will act much more effectively as a leaving group than a hydroxy group. In fact, when VII was heated with 2 equivalent of trifluoroacetic anhydride, a cyclization product (VIII) was easily isolated in 41 % yield. However, even such conditions, IX was not converted to a cyclization product (X), but to a methylmercaptal (XI) in 42 % yield, whose structure was easily confirmed by its mass and nmr spectra. The formation of this type of compounds have been previously observed in the reaction with hydrochloric acid.[4]



VII VIII

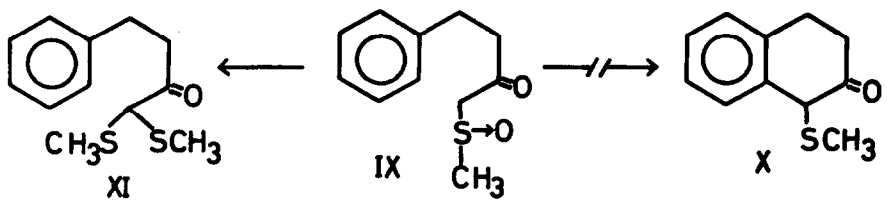
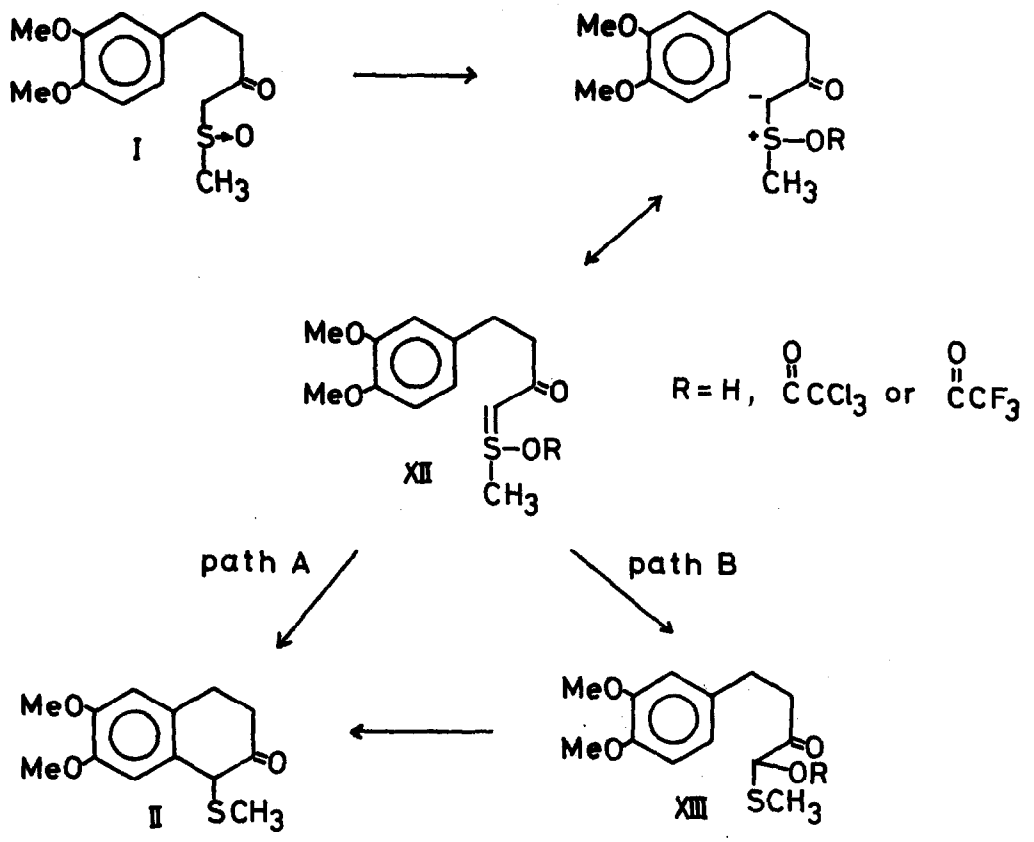


Table Nmr spectra of compounds IVa, IVb, VI, VIII and IX

compound	mp (°C)	nmr (δ ppm in $CDCl_3$)	
		$-\underline{CH}SCH_3$	$SC\underline{H}_3$
IVa	149-151	4.36	2.18
IVb	147-148	4.16	2.19
VI	162	4.32	2.16
VIII	109-112	4.18	2.22
XI	oil	4.25	1.95

Finally, two mechanisms of the cyclization of β-ketosulfoxide may be described as shown in the following scheme. The protonation or the acylation on a sulfinyl oxygen forms a ylene intermediate (XII), which can readily cyclized to afford II, accompanied by the simultaneous elimination of ROH (path A). Another pathway (B) involves the Pummerer rearrangement followed by the ring closure. The clear difference in the cyclization reactions dependent on the nucleophilicity of aromatic nuclei may indicate that the rate determing step lies in the final stage, If it is true and the reactions proceed via path B, the Pummerer rearrangement product (XIII) is expected to be detected in the course of the cyclization. However even a trace of XIII (R = $COCCl_3$) from I could not be observed by careful nmr measurements, though the cyclization of I with trichloroacetic acid at 80° was found to follow first-order kinetics (in benzene, $k = 3.14 \times 10^{-4}$ sec^{-1}; in carbon tetrachloride, $k = 4.1 \times 10^{-4}$ sec^{-1}). Therefore the cyclization reaction may proceed predominatly through the concerted nucleophilic substitution of the ylene intermediate (path A). Detailed kintic studies and applications of this cyclization are now under investigation.



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