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REDUCTIVE CLEAVAGE OF 1,4-THIAZINES
THE GENERATION OF POWERFUL REACTIVE INTERMEDIATES FOR THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

S. Hoff*, A.P. Blok and Miss E. Zwanenburg
Koninklijke/Shell-Laboratorium, Amsterdam
(Shell Research N.V., Amsterdam-N., The Netherlands)

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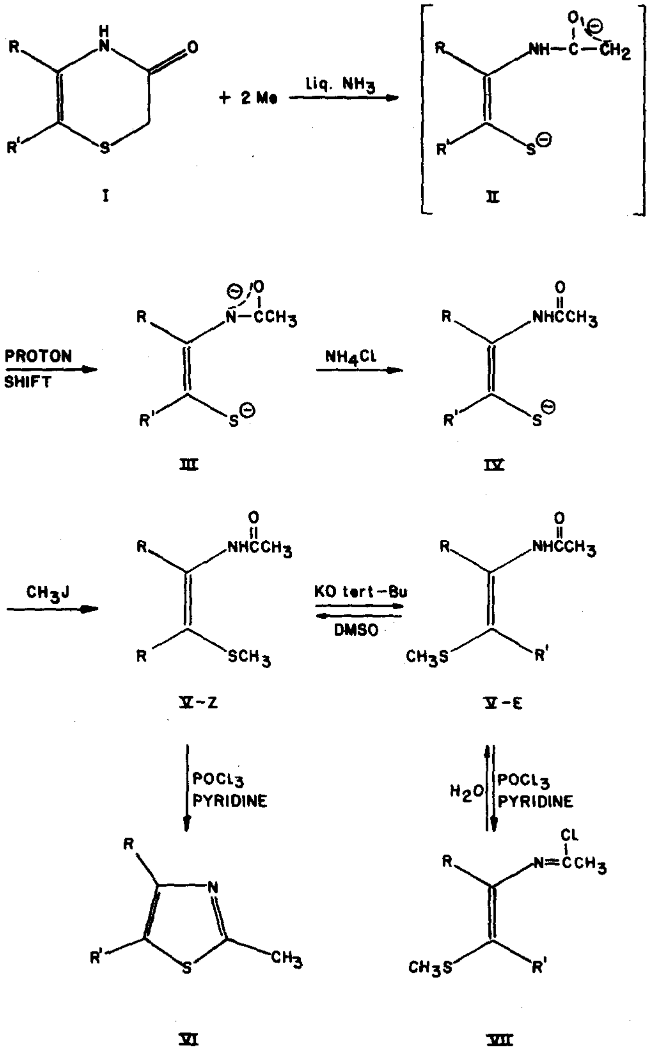
It has been recognized for some time that the reductive cleavage of sulphur-carbon bonds in organic molecules with alkali metals in liquid ammonia can be used for purposes of synthesis. However, little attention has been paid so far to sulphur-containing heterocycles. Knowles and Watt have studied to some extent the reaction of benzothiazole[1] and more recently Kaiser et al.[2] reported the successful fission of cyclic dithioketals with sodium in liquid ammonia.

We have concentrated on the cleavage of functionalized heterocyclic compounds with the intention to generate reactive ionic species which may serve as building blocks for the synthesis of new heterocyclic compounds. In this and the following communication we report the cleavage of the carbon-sulphur bond in substituted 2,3-dihydro-1,4-thiazin-2-ones, which we selected as model compounds[+], and discuss the applicability of the resulting dianionic species in heterocyclic synthesis.

When two equivalents of lithium or sodium were added to a solution of substituted 2,3-dihydro-1,4-thiazin-2-ones[3] (I) in liquid ammonia the sulphur-carbon sp^3 bond[4] was quantitatively cleaved in a fast reaction. The initially formed dianion II (see Scheme 1) rearranged to the more stable dianion III. Addition of one equivalent of ammonium chloride to the solution of III in liquid ammonia produced the 2-acetamido alkenethiolates IV. The alkali-metal salts of both the dianion and the monoanion were isolated in quantitative yields by simply evaporating the ammonia from the respective solutions. The two salts were surprisingly stable and could be stored for several months without noticeable decomposition; acidification with dilute hydrochloric acid, however, resulted in the formation of the corresponding thiazoles.

SCHEME 1

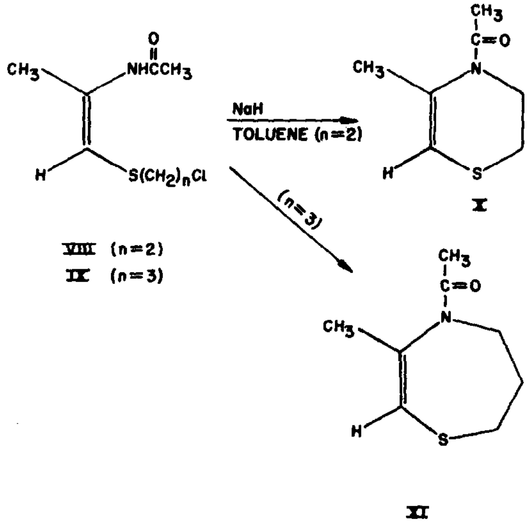


Me=Li OR Na
R =ALKYL, R'=H OR ALKYL

Alkylation of IV with methyl iodide either in liquid ammonia or in methanol as the solvent afforded the S-methylated compound V with the Z configuration. Apparently, the geometry of the double bond was not affected during the cleavage. Isomerization of V-Z into V-E was achieved with strong bases such as potassium tert-butoxide in dimethyl sulphoxide.

The structural assignments of the E and Z isomers are based on PMR-spectral and chemical evidence. The vinylic hydrogen in the V-E isomer with R = alkyl and R' = H is deshielded by the acetamido group and appears at a lower field than the corresponding hydrogen in the Z isomer. Moreover, the allylic coupling constant is expected to be larger in the Z isomers V with R = alkyl and R' = H, (J_{cisoid} = 1.2 Hz) than in the E isomers ($J_{transoid}$ = 0.9 Hz). Chemical evidence for the structures is provided by the reactions of V-Z and V-E with phosphorus oxychloride in pyridine: the Z isomer affords the thiazole VI in 70 % yield and the E isomer gives rise to exclusive formation of the corresponding imidoyl chloride VII. The geometry of VII prohibits subsequent intramolecular cyclization and starting material can be recovered upon hydrolysis.

When the monoanion IV was treated with 1-bromo-2-chloroethane or 1-chloro-3-bromopropane in methanol as the solvent the corresponding S-chloroalkylated compounds VIII and IX were isolated in high yields. Subsequent reaction with sodium hydride in boiling toluene gave intramolecular N-alkylation to N-acetyl-5-methyl-2,3-dihydro-4H-1,4-thiazine (X) and N-acetyl-3-methyl-4,5,6,7-tetrahydro-1,4-thiazepine (XI) in yields of 24 and 41 %, respectively[++].



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1. C.M. Knowles and G.W. Watt, J. Org. Chem. **7**, 60 (1942).
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3. Prepared according to: C.R. Johnson and C.B. Thanawalla, J. Heterocycl. Chem. **6**, 247 (1969).
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[+] In a forthcoming publication a detailed discussion of the scope of carbon-sulphur bond fission in heterocyclic compounds will be presented.

[++] The low yields are due to the occurrence of side-chain dehydrohalogenation, affording the corresponding vinyl or allyl thioethers.