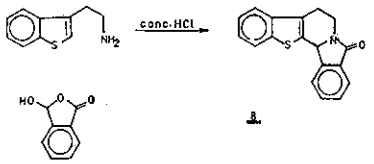

8

7

Comparison with the wellknown classical synthesis of the quinolizidine alkaloid ring systems **4**, **5** and **6** points out that preparation of these systems with the help of lactones uses to be the most convenient and sucessfull method, which can be recommended for the synthesis of labeled compounds.

The factor most limiting this synthetic method is the availability of the different substituted lactones. The problem is discussed in connection with a synthesis of emetine. To what extent stereoselective synthesis are possible has not been investigated up to now.

PL 5

SYNTHESIS AND STRUCTURE DETERMINATION OF THIAZOLINES AND RELATED COMPOUNDS

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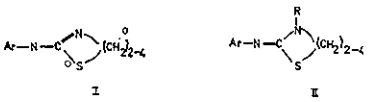
Several years ago we have started in our Institute a research project dealing with the synthesis and biological investigation of open-chain, as well as ring-closed thiourea derivatives. At first we studied those heterocyclic compounds which were obtained from 1-aryl-3-hydroxyalkyl-thioureas by known cyclisation methods.



I II

R = H, methyl, acetyl, carbethoxy, benzoyl, methanesulfonyl.

Among the spectroscopic methods the ^{1}H-n.m.r. seemed to be most suitable for determining the tautomeric or isomeric structures of these compounds, by using the corresponding N-methyl derivatives as model substances.

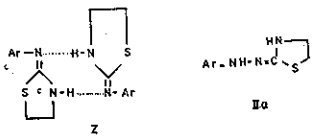
In some cases however, the proposed structures were in disagreement with the X-ray diffraction results. To avoid these discrepancies the ^{1}H-n.m.r. signals of the aromatic protons were studied in detail. The aromatic protons give a different pattern in the N-methyl-derivatives I and II, respectively according to the different electron distribution. This significant difference is independent from both, the size of the hetero ring as well as from the aromatic substituents. In the case of other derivatives, however, this difference was less characteristic, therefore the ^{13}C-n.m.r. spectra of these compounds were studied. In agreement with our expectotion the conjugation results in a higher electron density at the aromatic p-carbon atom in the case of structure II, causing an upfield chemical shift of the corresponding signal.

Similar results were obtained simultaneously by other authors who investigated different cyclic amidines, among them some 2-arylamino-thiazines too.

These ^{13}C-n.m.r. data proved, that not only the thiazines, but the 5 and 7 membered analogs possess the tautomeric structure II too. The same structure corresponds to the benzoyl derivatives, whereas the primarily formed mesyl-amides have structure I and are rearranged only by heating into II. During acetylation and carbethoxylation different structures or mixtures of the two possible isomers were obtained, but in the latter case the more stable isomer II predominoted.

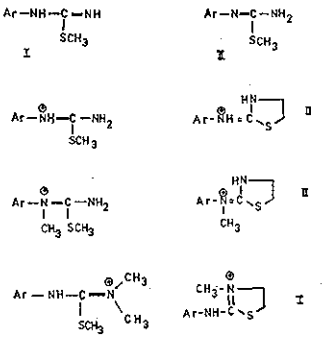
Further X-ray diffraction studies of the thiazolidines II proved the presence of dimeric Z isomers in solid state. The corresponding E isomers could be detected only in polor solvents at low temparature (below —50°) by n.m.r. $CDCl_3$:CD_3OD, 1 : 1 (Z : E = 30 : 70).

It should be mentioned that the X-ray diffraction of the related 2-aryl-hydrazino compounds revealed their 2-imino-structure IIa too.

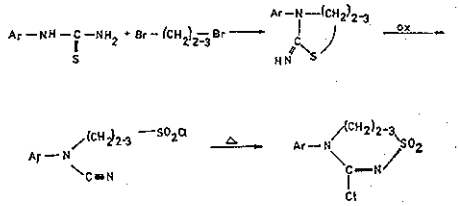


Z IIa

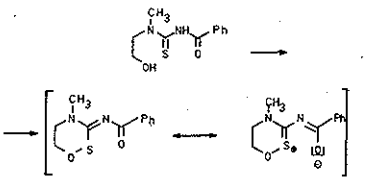
Investigating the salts of the heterocyclic compounds and their thiorea analogs we could show, that while structure I corresponds to the 1-aryl-S-methyl-isothioureas in solid state and structure II is formed only in solution, their salts possess the same structure as the corresponding salts of their heterocyclic analogs. In the case of the arylimino structures II the Z-E isomerism could be detected, but the rotation barrier, characterised by ΔG, is too small for preparative separation.



In our further experiments we established a generally applicable synthesis of III type 2-imino-heterocyclic compounds, reacting 1,2-, and 1,3-dihalogeno-alkanes with 1-aryl-thioureas. Oxidation of III led to several interesting results. E.g. a new formation of cyanamide derivatives was found which underwent an addition reaction with sulfochloride yielding a new type of cyclic sulfonyl-chloroformamidines.



The oxidation of some 1-benzoyl-3-(2-hydroxyethyl)-thioureas with bromine in pyridine led to substituted 1,2,4-oxathiazines which are new cyclic derivatives of the sulfenic acid ester type compounds. X-ray investigation of this compounds showed a strong S... O non bonded interaction, referring to a mesomeric system.



Some of the synthesized derivatives showed diuretic, hypotensive and CNS activities. The most biologically promising compounds were obtained by combining the oxathiazine structure with steroids. Reaction of steroido 17-spiro-oxiranes with methylamine led to aminoalcohols which were converted into thioureas. Oxidation of the latter with iodine gave new spiro-steroids, possessing moderate antialdosteron activity. The compounds can be converted by elimination of sulfur and hydrolysis into spirooxazolidinones, which can be synthesized via a different, more simple route too. The activity of some of these derivatives equalled that of spironolacton, and showed less pronounced side effects.