

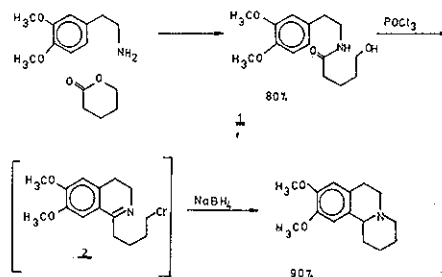
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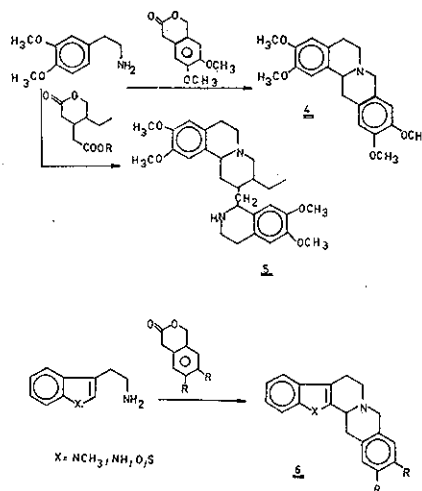
LACTONES AS BUILDING BLOCKS FOR THE SYNTHESIS OF ALKALOID LIKE HETEROCYCLES

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By reaction of γ -butyrolactone or δ -valerolactone with homoveratrylamine ω -hydroxyalkyl carboxamides **1** are obtained, which are cyclized by phosphorus oxychloride to give 1-(ω -chloroalkyl)-3,4-dihydroquinolines **2**. Immediate treatment of the not isolated rough product with sodium borohydride affords benzoquinolizines (**3**) or benzindolizines respectively in very good yields, for example:



This simple two step synthesis can be used with good success for the preparation of quinolizidine alkaloids of the types **4**, **5** and **6**:



Replacing tryptamine by benzofuranyl or thionaphthyl ethylamines as starting material allows the preparation of oxo or thio analogues of the yohimbine ring system. These compounds are significant in respect to their biological effects.

Some investigations about scope and limitation of this synthetic pathway are discussed. Using the lactone like phthalaldehydic acid **7** the Bischler-Napieralsky ring closure is displaced by the Pictet-Spengler reaction. For example by the influence of thionaphthyl ethylamine **7** is converted to the thionaphthylbenzindolizone **8**, the Pictet-Spengler reaction being combined with an intramolecular N-acylation:

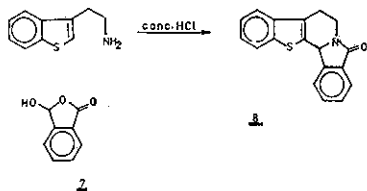
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 SYNTHESIS AND STRUCTURE DETERMINATION
 OF THIAZOLINES AND RELATED COMPOUNDS

L. G. Toldy

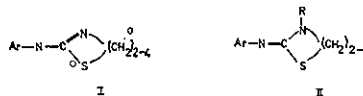
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Several years ago we have started in our Institute a research project dealing with the synthesis and biological investigation of open-chain, as well as ring-closed thiourea derivatives. At first we studied those heterocyclic compounds which were obtained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



Comparison with the wellknown classical synthesis of the quinoxaline 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 successful 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.



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

Among the spectroscopic methods the ^1H -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.

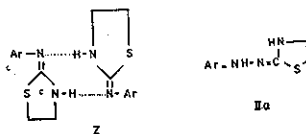
In some cases however, the proposed structures were in disagreement with the X-ray diffraction results. To avoid these discrepancies the ^1H -n.m.r. signals of the aromatic protons were studied in detail. The aromatic protons give a different pattern in the N-methyl-derivatives I and II, respectively 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 expectation 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 predominated.

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 polar solvents at low temperature (below -50°) by n.m.r. $\text{CDCl}_3:\text{CD}_3\text{OD}$, 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.



Investigating the salts of the heterocyclic compounds and their thiourea analogs we could show, that while structure I corresponds to the 1-aryl-S-methyl-isothiureas 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.