# SYNTHESIS OF DERIVATIVES OF 1-OXO-1H-2,3,4,5-TETRAHYDROAZEPINO[3,4-b]INDOLE AND ITS 9-AZA ANALOG FROM CAPROLACTAM

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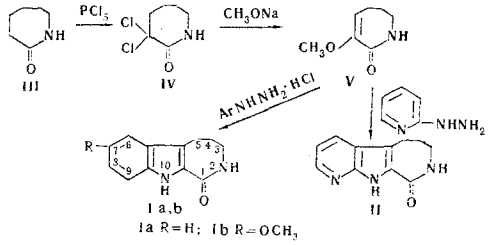
Derivatives of 1-oxo-1H-2,3,4,5-tetrahydroazepino[3,4-b]indole (**Ia, b**) [1] and 1-oxo-1*H*-2,3,4,5-tetrahydro-9-azaazepino[3,4-b]-indole (**II**) are of interest as key compounds for the synthesis of 1- and 2-substituted derivatives of **I** and **II** and also of various condensed heterocyclic systems including indole and azaindole rings. In addition, **I** and **II** may be the starting materials for the preparation of 3-(γ-aminopropyl) derivatives of the indoles [1] and 7-azaindoles.

The methods of obtaining **I** from indol-3-ylbutyric ester [2] and 1-oxo-1,2,3,4-tetrahydrocarbazole [3] published in the literature are complex and can hardly be used for the synthesis of **II**.

We have developed a method for obtaining **I** [1] and **II** from caprolactam (**III**) in the following way:




According to this scheme, **III** is converted via α, α-dichlorocaprolactam **IV** [4] into 3-methoxy-2-oxo-2H-1,5,6,7-tetrahydroazepine (**V**) [5]. When **V** is heated (4 hr) with a small excess of phenylhydrazine hydrochloride in ethanolic sulfuric acid solution, i.e., under the conditions generally used for the conversion of carbonyl compounds into indoles by the Fischer reaction [6], **Ia** is obtained. Found, %: C 71.87; H 5.97; N 13.90. Calculated for $C_{12}H_{12}N_2O$, %: C 72.00; H 6.00; N 14.00. Yield 75%, mp 225–227° C (from ethanol, 1:20). According to the literature [3], mp 224–227° C. The generality of this reaction for the synthesis of tetrahydroazepino[3,4-b]indoles substituted in the benzene ring and of tetrahydro-9-azaazepino[3,4-b]indoles has been shown by the condensation of **V** with p-methoxyphenylhydrazine hydrochloride (**VI**) and with pyrid-2-ylhydrazine (**VII**). Thus, in analogy with the production of **Ia**, the reaction of **V** and **VI** gives **Ib**. Found, %: C 67.81; H 5.90; N 12.01. Calculated for $C_{13}H_{14}N_2O_2$, %: C 67.82; H 6.08; N 12.17. Yield 60.9%, mp 190–191° C (from ethanol). When **V** was fused (230–240° C, 7 min) with a 10% excess of **VII** and 3 mole of zinc chloride, **II** was obtained. Found, %: C 65.94; H 5.50; N 20.88. Calculated for $C_{11}H_{11}N_3O$, %: C 65.65; H 5.51; N 20.89. Yield 66.9%, mp 300° C (decomp., from ethanol). The IR spectra of compounds **I–II** have absorption bands at 1630–1650 $cm^{-1}$ (amide carbonyl) and 3200–3290 $cm^{-1}$ (NH group). The UV spectrum of **II** (in ethanol) has three absorption maxima: $\lambda_{max}$, nm (log ε): 222 (4.15); 235 (4.07); 300 (4.11).

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# THE QUESTION OF THE MECHANISM OF CHLORINATION IN THE HERZ REACTION

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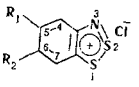
In agreement with statements by Weinberg [1,2], Huestis [3], by the action of thionyl chloride on o-aminothiophenol obtained benzo-1,3,2-thiazathionium chloride (**I**) which, according to their results, does not contain a chlorine atom in the benzene nucleus. The proof of the structure of the products obtained was based on an analysis of the derivatives obtained by the hydrolysis and further transformations of **I**. The results obtained were interpreted by the authors as a proof of the fact that chlorination in the Herz reaction takes place by an electrophilic mechanism with the formation of **I** according to the scheme proposed by Gompper [4]. We have established that the action of



| Compound | $R_1$ | $R_2$ | $\lambda_{max}$, nm (log ε) | Empirical formula | Found, % | | Calculated, % | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | S | Cl | S | Cl | |
| I | H | H | 425 (3.285) | $C_6H_4ClNS_2$ | 34.01 | 18.47 | 33.86 | 18.69 | 56 |
| II | H | Cl | 423 (3.595) | $C_6H_3Cl_2NS_2$ | 28.88 | 31.31 | 28.61 | 31.52 | 100 |
| III | $CH_3O$ | H | 420 (2.935) | $C_7H_6ClNOS_2$ | 29.31 | 16.25 | 29.12 | 16.15 | 79 |
| IV | $CH_3O$ | Cl | 450 (3.291) | $C_7H_5Cl_2NOS_2$ | 25.31 | 28.00 | 25.23 | 27.91 | 100 |
| V* | H | $C_6H_5NH$ | 520 (4.279) | $C_{12}H_9ClN_2S_2 \cdot ZnCl_2$ | 15.27 | 25.61 | 15.38 | 25.52 | 100 |
| VI* | $CH_3O$ | $C_6H_5NH$ | 512 (4.103) | $C_{13}H_{11}ClN_2OS_2 \cdot ZnCl_2$ | 14.58 | 23.65 | 14.33 | 23.79 | 100 |

*Double salts with zinc chloride: V · $ZnCl_2$; VI · $ZnCl_2$.

thionyl chloride on o-aminothiophenol gives compound **I** only when these substances are allowed to react briefly (1 min). The more prolonged interaction described by Huestis leads to the partial formation of the product of chlorination in position 6 (about 4% after 4 hr), the amount of which increases with an increase in the duration of the process (12% after 8 hr).

If compound I is treated with sulfur monochloride in thionyl chloride solution, chlorination in position 6 takes place quantitatively. These observations indicate that in the Herz reaction chlorination in the nucleus takes place, contrary to the statements of Huestis and Gompper [3 and 4], after the formation of **I**. Taking the high reactivity of benzothiazathionium salts to the action of nucleophiles and their incapacity for electrophilic reactions into account, it may be considered that chlorination in position 6 takes place by a nucleophilic mechanism, the sulfur monochloride or, more feebly, the thionyl chloride acting as hydride ion acceptor. Confirmation of this is the analogous reaction of 2-amino-4-methoxythiophenol which we have performed; under the action of thionyl chloride this gave 5-methoxybenzo-1,3,2-thiazathionium chloride (on brief reaction) and the product of its chlorination in position 6, which takes place considerably more easily than in the preceding case.

The content of products of chlorination in position 6 was determined by spectrophotometry of the products of the nucleophilic displacement of the chlorine atom by aniline, since the products unchlorinated in the nucleus do not react with aniline.

The table gives the analytical and spectral characteristics of the benzo-1,3,2-thiazathionium salts (**I–VI**) obtained.

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## HYDROLYTIC CLEAVAGE OF THE HETERO RING OF 6-PHENYLTETRAZIN-3-ONE

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In the study of the lactam-lactim tautomerism of tetrazinone, we have made an attempt to methylate a comparatively accessible tetrazinone derivative—6-phenyltetrazin-3-one (**I**)—in order to obtain a derivative with a fixed tautomeric form. Methylation was carried out with methyl iodide in an aqueous alkaline medium. Instead of the expected methylation product we obtained a yellow substance with the composition $C_{14}H_{12}N_2$, mp 92° C, which proved to be benzaldehyde azine (**V**). The same substance was formed by heating I with aqueous alkali in the absence of methyl iodide. It was also obtained under the same conditions from 3-bromo-*, 3-amino-*, and 3-dimethylamino-6-phenyltetrazines. Evidently, in an aqueous alkaline medium all these compounds are converted into I and then undergo cleavage and give **V**. Cleavage does not take place in ethanolic alkali.

The mechanism of this reaction can be deduced by taking into account the results of calculations that we have carried out by the MO LCAO method in Hückel's approximation using Pullman's parameters. For **I**, the charge on $C^3 = +0.2189$ and that on $C^6 = +0.0508$. For the tautomeric hydroxy form, 3-hydroxy-6-phenyl-s-tetrazine, the charge on $C^3 = +0.0812$ and that on $C^6 = +0.0002$. It is obvious from the results of calculation (with the question of tautomerism still remaining open*), that there is a considerable positive charge on $C_3$,

*Obtained according to Grakauskas et al. [1].

*A separate report will be made on the lactam-lactim tautomerism of the compound.