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THE SYNTHESIS OF ISOMERIC as-TRIAZINONES FROM α-KETO-ESTERS AND AMIDRAZONES, AND SOME REACTIONS OF THE PRODUCTS

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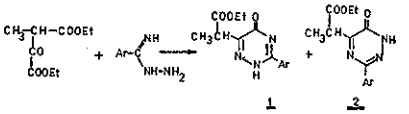
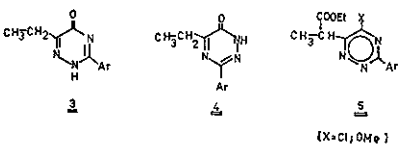
As a part of our attempts to prepare new antiinflammatory α-hetaryl-propionic acid derivatives, ethyl 2-methyl-3-oxo-succinate was condensed with a series of benzamidrazones to obtain type 1 and 2 as-triazinones.



Alkaline hydrolysis and decarboxylation of 1 and 2 furnished 3 and 4, respectively. Aromatic as-triazines of type 5 were obtained by allowing to react 1 with phosphoryl chloride and diazomethane. Further reactions of type 1 and 2 compound will be discussed:



LE II 20

SULPHUR ANALOGUES OF s-TRIAZINE-2,4(1H,3H)-dione (5-AZAURACIL)

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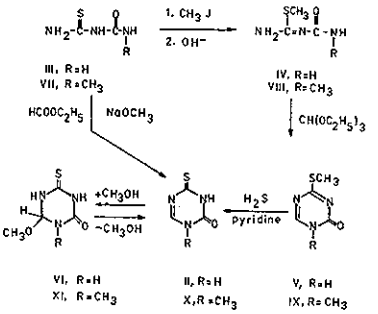
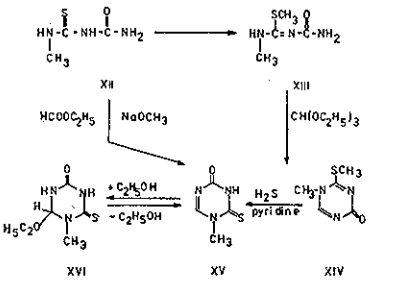
In connection with the study of 5-azapyrimidine nucleobases we also investigated the synthesis of sulphur analogues of s-triazine-2,4(1H,3H)-dione (5-azauracil; I). In this paper we describe the preparation of thio-5-azauracil (II) and its N-methyl derivatives.

We started the synthesis of thio-5-azauracil (II) from thiobiuret (III) which we converted to hydriodide of S-methylisothiobiuret on reaction with methyl iodide. We obtained the free base IV on treatment with a weakly basic ion exchanger in OH^- form. The free isothiobiuret IV was submitted to cyclocondensation with ethyl orthoformate, offording 4-methylthio-s-triazin-2(1H)-one (V) in high yield. The latter gave on thiohydrolysis with hydrogen sulphide in pyridine the required sulphur analogue of 5-azauracil II. The product was isolated in the form of a covalent adduct with methanol, VI. When heated at 130 °C in a vacuum the adduct lost methanol under regeneration of thio derivative II. When the covalent adduct is dissolved in dimethylsulphoxide an equilibrium between the substances II and VI is obtained, which is distinctly shifted in favour of the non-solvated product II.



Starting from 1-methyl-4-thiobiuret (VII) and using an analogous reaction sequence we synthetized 1-methyl-4-thio-5-azauracil (X) via the intermediates VIII and IX. Compound X also gives a covalent adduct, XI, with methanol. However, in this case, the equilibrium between substances X and XI in dimethylsulphoxide solutions is shifted in favour of the covalent solvate XI.

In a similar manner we also prepared the isomeric 1-methyl-2-thio-5-azauracil (XV) from 1-methyl-2-thiobiuret (XII) via the isothiobiuret XIII and methylthiotriazinone XIV. Compound XV was isolated in the form of a covalent solvate with ethanol, XVI. This substance behaves in dimethylsulphoxide solution similarly as solvate XI.



We also succeeded in the preparation of the sulphur analogues II, X and XV in lower yields by direct cyclocondensation of the corresponding thiobiurets III, VII, and XIII with ethyl formate, under catalysis with sodium methoxide in methanol.

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REACTIONS OF OCTAHYDROQUINAZOLINONES

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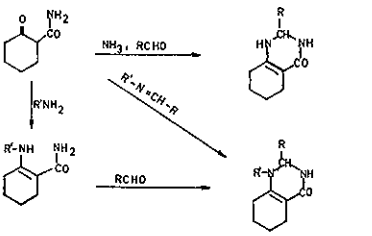
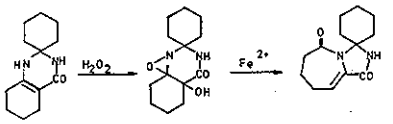
From cyclohexanone-2-carboxamide octahydroquinazolinones are formed by the following reactions:



Octahydroquinazolinone **1** reacts with H_2O_2 to the hydroxy--oxaziridino-quinazolinone **2**, which with ferrous sulphate forms compound **3**.



1 **2** **3**

LE II 22

SYNTHESIS OF ISOQUINOBENZODIAZEPINONES

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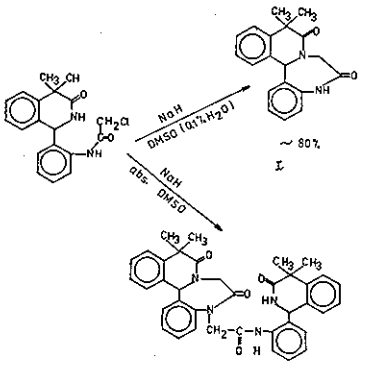
Based on former investigations in the field of 3(2H)-isoquinolinones, a method has been developed for the synthesis of new condensed ring systems, such as benzodiazepinones and benzoxazepinones with condensed isoquinolinone. According to the working hypothesis, the starting compound in the case of benzoxazepinones was 1,4-dihydro-1-(2'-hydrophenyl)-3(2H)-isoquinolinone, whereas the preparation of benzodiazepinones was planned to be done from 1,4-dihydro-1-(2'-aminophenyl)-3-(2H)--isoquinolinone. Both compounds were acylated with chloroacetyl chloride, followed by an attempt to bring about cyclization of the 2'-chloracetylated derivatives obtained. So far the preparation of the oxazepine derivative by this method has failed.



I

~50% + 20% I

As for the benzodiazepinones, by the suitable selection of the reaction conditions, the synthesis of the hitherto unknown 10,10--dimethyl-6,9,10,14b-pentahydro-5H-isoquino-[2,1-d] [1,4]-benzodiazepine-6,9-dione **I** has been successfully carried out.
Upon the cyclization of 1,4-dihydro-1-(2'-aminophenyl)-3(2H)--isoquinolinone a new compound wih unkown structure has been isolated, which proved to be identical with compound **II**. The ratio of compounds **I** and **II** depends on the water content of the solvent DMSO; an attempt is made at interpreting the two reaction paths.