PO 34

TAUTOMERIC FORMS OF THE BENZOTHIAZOLYL DERIVATIVES OF β-DICARBONYL COMPOUNDS

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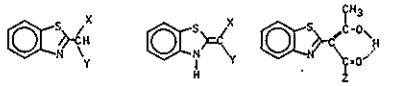
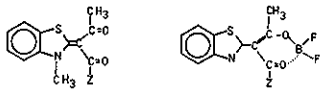
2-Benzothiazolyl derivatives of β-dicarbonyl compounds may exist in several tautomeric forms. Recently, on the basis of nmr spectra, the diketo form I was discarded and the thiazoline form II was suggested for ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate and malononitrile derivatives.



I II III

We have prepared the compounds quoted (extended by acetylacetone derivative) by the reaction of 2-fluorobenzothiazole with sodium salts of appropriate C-acids in ether or THF. For ethyl acetoacetate and acetylacetone derivatives we have also considered the enol form III (Z = CH_3, OC_2H_5). As comparative samples we have synthetised N-methyl derivatives IV and complexes V:



IV V

Spectroscopic and quantum chemical investigations has been performed to confirm or deny the thiazoline and enol forms.

PO 35

YLIDES OF MALONYL HETEROCYCLIC COMPOUNDS

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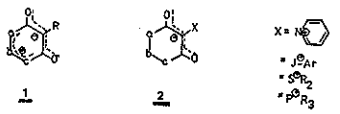
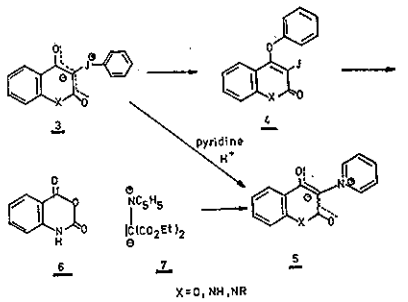
During the course of work on sixmembered mesoionic compounds of type 1, containing the negatively charged malonyl residue, we became interested in ylides of malonyl heterocyclic compounds (2) in which the positive charge is located outside of the heterocyclic ring system. For a comparative study a number of synthetic routes for the preparation of pyridinium-, iodonium-, sulfonium-, and phosphonium-ylides (2) have been developed.



1 2

We have already described the synthesis of pyridinium-ylides from dichloro-[1] and monochloro-malonyl derivatives[2]. We have now found, that iodonium-ylides, which are readily obtained from malonylheterocycles and aryliodonium diacetates, are converted to pyridinium ylides with pyridinine in the presence of acids. Without acidic catalysis rearrangement to arylethers takes place. These reactions are examplified with coumarin and carbostyril derivatives according to the following reaction scheme:



3 4 5 6 7

The iodonium-ylides **3** undergo a thermal rearrangement yielding the 3-iodo-4-arylethers **4**, which can be converted by photocyclization to benzofuran derivatives (f. i. **4**, X = O, — „coumestan"). However, with pyridine in acetic acid the pyridinium-ylides **5** are obtained. The reaction of isatoic anhydride (**6**) with the pyridinium betaine **7** yields the ylide **5** (X = NH), too.

The corresponding phosphonium- and sulfonium-ylides can be prepared by exchange reactions starting with iodonium-ylides, however, the latter are also obtained from the unsubstituted malonyl heterocycles and sulfoxides with acetic anhydride as dehydrating agent.

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2) G. Schindler, T. Kappe, Synthesis *1977*, 243.

PO 36

CONFORMATIONAL ANALYSIS OF MORPHINE-TYPE OPIATE AGONISTS AND ANTAGONISTS, RELATIONSHIP BETWEEN THE CONFORMATION OF THE PIPERIDINE RING IN THESE OPIATES AND THE TYPE OF THEIR ACTIVITY (AGONIST OR ANTAGONIST)

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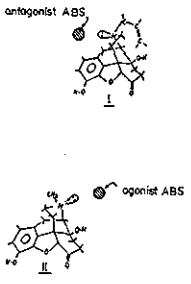
Qualitative conformational analysis of naloxone (I, an opiate antagonist) shows that the overall stability of naloxone is greater when the piperidine ring is in the skew boat conformation (N-allyl pseudo-equatorial) rather than the chair conformation (N-allyl equatorial) since in the latter conformation there are unfavorable interactions between the N-allyl group and the ring B. The most stable piperidine conformation of oxymorphone (II, an opiate agonist) is, however, a chair form (N-methyl equatorial). The results of this conformational analysis revealed a new aspect of the structure-activity relationship of morphine-type agonists and antagonists and led to a proposal of a new opiate-receptor model (V. M. Kolb, **J. Pharm. Sci.**, in press). The salient features of this new opiate-receptor model are: (1) Only one receptor conformation is necessary for the binding of opiate agonists and antagonists; (2) The receptor possesses two amine -binding sites (ABS) - agonist and antagonist; (3) Agonists and antagonists interact via their nitrogen lone-pair electrons with the respective ABS; (4) In naloxone (I), for example, the antagonist effect is derived indirectly through the N-allyl group which sterically forces the N-lone- pair lobe in the direction of the antagonist ABS. According to this model, the respective conformations of naloxone, an antagonist, and oxymorphone (II), an agonist, required for binding to the receptor, are illustrated:



PO 37

SYNTHESIS OF 1-ALKYL- and 1-ARYL-3-(2-PYRIDYL) ISOQUINOLINES

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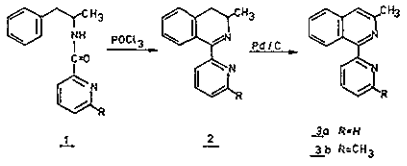
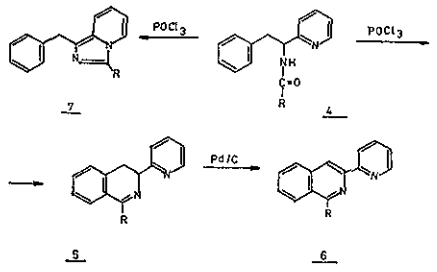
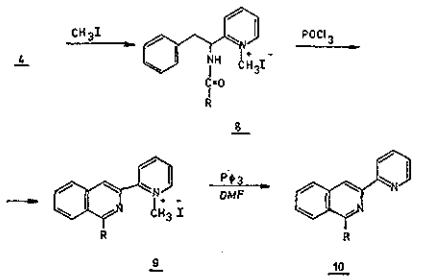
In an investigation concerning the anti-Mycoplasma activity of compounds possessing the 2,2'-bipyridyl skeleton it was found that ortho substitution has a pronounced positive effect[1]. To study the influence of substitution on the anti-Mycoplasma activity in more detail a series of 1-alkyl- and 1-aryl-3-(2-pyridil)isoquinolines was prepared. For the synthesis of isoquinolines the Bischler-Napieralski reaction is often applicated. In this way the preparation of the 1-(2-pyridyl)isoquinolines 3a and 3b indeed could be accomplished.



This reaction fails, however, in the synthesis of 3-(2-pyridyl)isoquinolines 6. Instead of a 3,4-dihydroisoquinoline 5 an imidozo [1,5-a]pyridine 7 is formed.



To prevent this reaction the pyridine ring of the amide 4 was quaternized. Under Bischler-Napieralski conditions the ring-closure now could be effectuated, leading directly to the isoquinoline 9. After demethylation the desired product 10 could be isolated.



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PO 38

DEVELOPMENTS IN CHEMISTRY OF NITROGEN ANALOGUES OF FLUORENE

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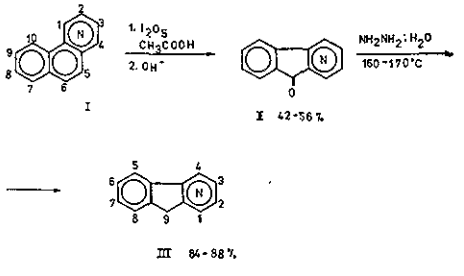
In connection with the considerable current interest in the chemistry and biological activity of some azafluorenone and azafluorene derivatives we report a convenient synthesis of this class of compounds and results of their N-alkylation and oxidation. Monoazaphenanthrenes (I) and phenanthrolines (IV) were used as starting materials. Treatment of 1- and 4-azophenanthrene with I_2O_5 in acetic acid afforded azaphenanthrene-5,6-diones which were converted to 4- and 1-azafluorenones (II) respectively, by rearrangement in alkaline medium. The next step was reduction of (II) with hydrazine to monoazafluorenes (III).



Phenanthrolines (IV) were oxidized directly by means of permanganate in alkaline medium to 1,5-, 2,5-, 4,5- and 1,8-diazafluorenones (V) which were reduced with hydrazine to give diazafluorenes (VI).