

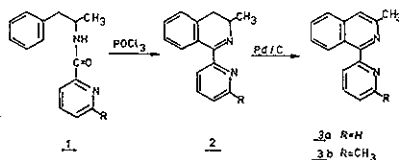
PO 37

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

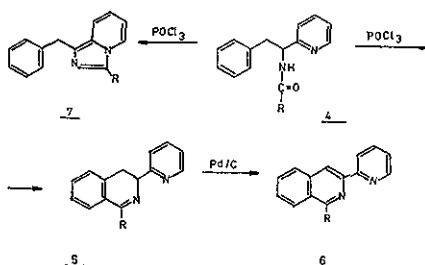
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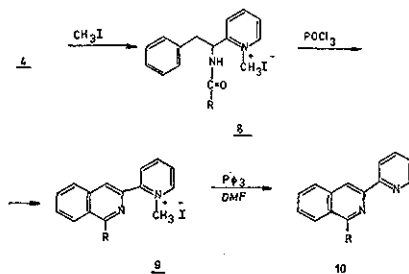
In an investigation concerning the anti-Mycoplasma activity of compounds possessing the 2,2'-bipyridyl skeleton it was found that ortho substitution has a pronounced positive effect¹. To study the influence of substitution on the anti-Mycoplasma activity in more detail a series of 1-alkyl- and 1-aryl-3-(2-pyridyl)isoquinolines was prepared. For the synthesis of isoquinolines the Bischler-Napieralski reaction is often applied. 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 on imidazo [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.



REFERENCES:

- 1) H. van der GOOT, J. G. OOSTENDORP and W. TH. NAUTA, Eur. J. Med. Chem. 10, 603-606 (1975).
- 2) B. M. ANTIC, H. van der GOOT, W. TH. NAUTA, S. BALT, M. W. G. de BOLSTER, A. H. STOUTHAMER, H. VERHEUL and R. D. VIS, Eur. J. Med. Chem. 12, 573-575 (1977).

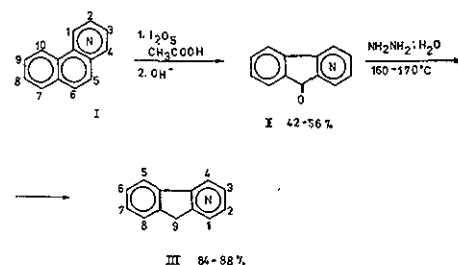
PO 38

DEVELOPMENTS IN CHEMISTRY OF NITROGEN ANALOGUES OF FLUORENE

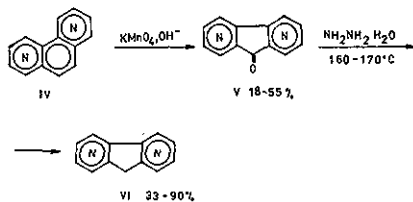
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In connection with the considerable current interest in the chemistry and biological activity of some azafluorenone and azafluorene derivatives we report a convenient synthesis of this class of compounds and results of their N-alkylation and oxidation. Monoazaphenanthrenes (I) and phenanthrolines (IV) were used as starting materials. Treatment of 1- and 4-azaphenanthrene with I₂O₅ in acetic acid afforded azaphenanthrene-5,6-diones which were converted to 4- and 1-azafluorenone (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).



Under the reduction conditions 4-aza-, 2,5- and 4,5-diazafluorenones yielded besides azaphenanthrenes also condensation products — 9,9'-bis- azaphenanthrenes.

It was established that azaphenanthrenes (III, VI) undergo N-methylation with methyl iodide to give only monomethyl iodides with 39 to 98% yield. The kinetic data give evidence that the nitrogen atoms of azaphenanthrenes are less active toward N-alkylation than those of azaphenanthrenes. This is due to the negative electromeric effect of the carbonyl group. We confirmed the lower susceptibility of the 4-N atoms to N-methylation than of the other N atoms; this fact can be explained by the shielding effect of the 5-H atoms.

The azaphenanthrenes were oxidized with hydrogen peroxide in an acetic acid — benzene mixture. Some of the diazafluorenones N-oxides were unstable in acidic media and oxidation had to be accomplished directly with hydrogen peroxide in the presence of Na_2WO_4 . The monoazaphenanthrenes under the same conditions were oxidized to azaphenanthrone N-oxides, but oxidation of diazafluorenones led first to diazafluorenones which then formed diazafluorenone N-oxides. Yields of N-oxides were 22 to 69%.

Bacteriological properties of most synthesized compounds were tested. The most interesting results have been obtained for the 2,5-diazafluorenone-di-N-oxide and 1-azaphenanthrene-N-methyl iodide.

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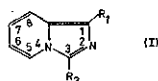
SYNTHESIS AND ANTIPARASITIC PROPERTIES OF IMIDAZO [1,5-a]-PYRIDINE DERIVATIVES

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A number of new imidazo[1,5-a]pyridine derivatives (I) were prepared by different methods:



- Cyclization of aminomethyl-2 pyridine derivatives to the fused ring system (I).
- Electrophilic substitution at C-1 of (I).
- Nucleophilic substitution at C-3 of (I).

The protozoocidal and anthelmintic activities of the imidazo[1,5-a]pyridine derivatives (I) are reported.

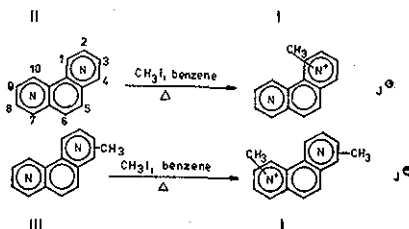
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ALKYL DERIVATIVES OF AZAPHENANTHRENES

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Since the N- and C-alkyl derivatives of polycyclic azines, and especially N-methyl iodides are receiving considerable attention as potential antineoplastic agents, we studied the synthesis and properties of the hitherto unknown alkyl azaphenanthrenes. N-methyl derivatives (I) were synthesized by direct alkylation of suitable azaphenanthrenes (II) or their methyl derivatives (III) in 77 to 98% yield.



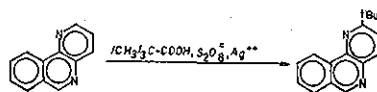
where N 1 or 4 as well as 1,5, 1,6, 1,7, 1,8, 1,10 4,6, 4,7 CH3 1,2,3,4,8 or 9

The nitrogen lone electron pairs are shielded less by methylated N atoms (for instance in the 1 position), except in the case of 1,10-diazafluorenene, whose unexpectedly high reactivity is due to the absence of boat protons, as well as to the high electron density of the neighbouring nitrogen atoms.

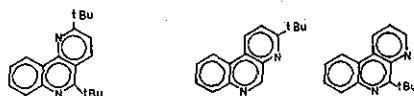
The nitrogen lone electron pairs are shielded less by methyl groups than by protons in the boat position.

t-Butylation was performed on azaphenanthrenes using t-butyl radicals generated from pivalic acid in the presence of $\text{S}_2\text{O}_8^{2-}$ and Ag^+ ions.

For 1,5-diazafluorenene:



1,6-Diazafluorenene gave 2,5-di-t-butyl derivative, and 4,6-diazafluorenene — a mixture of 3- and 5-mono-t-butyl derivatives (2 : 1). The yields were 26 to 42%.



It was found, that the substitution positions were those predicted by calculation of localization energy values for nucleophilic reactions; this result suggests nucleophilic character of t-butyl radicals. However, steric factors also had to be considered.

Some of N-methyl iodides, especially those derived from 1,10-diazafluorenene possess high antibacterial and antifungal activities.