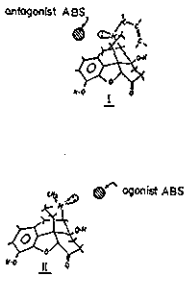


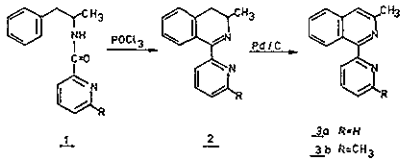
PO 37

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

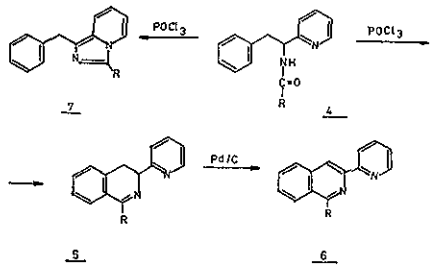
P. J. Pijper*, H. van der Goot and W. Th. Nauta,

Department of Medicinal Chemistry, Vrije Universiteit, De Boelelaan 1083, Amsterdam, The Netherlands

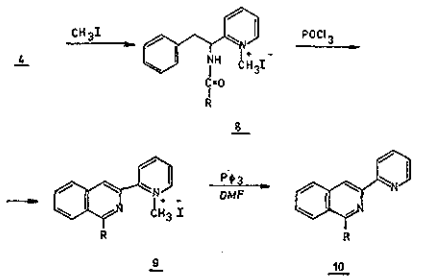
In an investigation concerning the anti-Mycoplasma activity of compounds possessing the 2,2'-bipyridyl skeleton it was found that ortho substitution has a pronounced positive effect[1]. To study the influence of substitution on the anti-Mycoplasma activity in more detail a series of 1-alkyl- and 1-aryl-3-(2-pyridil)isoquinolines 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.



REFERENCES:

1) H. van der GOOT, J. G. OOSTENDORP and W. TH. NAUTA, Eur. J. Med. Chem. 10, 603-606 (1975).
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).

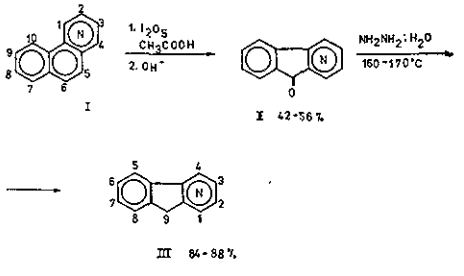
PO 38

DEVELOPMENTS IN CHEMISTRY OF NITROGEN ANALOGUES OF FLUORENE

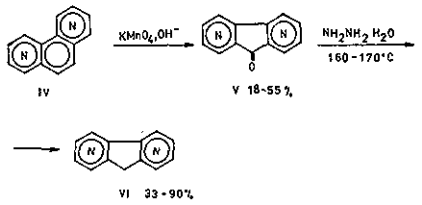
J. Młochowski*, K. Kloc, Z. Szulc

Institute of Organic and Physical Chemistry, Polytechnical University, 50—370 Wrocław, Poland

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).



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

It was established that azafluorenones (III, VI) undergo N-methylation with methyl iodine to give only monomethyliodines with 39 to 98% yield. The kinetic data give evidence that the nitrogen atoms of azafluorenones are less active toward N-alkylation than those of azafluorenes. 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 azafluorenones were oxidized with hydrogen peroxide in an acetic acid — benzene mixture. Some of the diazafluorenone 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 monoazafluorenones under the same conditions were oxidized to azafluorenone N-oxides, but oxidation of diazafluorenes 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 obtainel for the 2,5-diazafluorenone-di-N-oxide and 1-azafluorenone-N-methyl-iodide.

PO 39

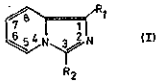
SYNTHESIS AND ANTIPARASITIC PROPERTIES OF IMIDAZO [1,5-a]-PYRIDINE DERIVATIVES

J. Bourdais*, A. Deberly*, P. Gayral** and A. Lorre*

*Laboratoire de Chimie Hétérocyclique et Organométallique. Centre d'Orsay, Université Paris-Sud, 91405 Orsay, France.

**Laboratoire de Parasitologie, Faculté de Pharmacie, Université Paris-Sud, 92290 Chatenay-Malabry, France.

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



(I)

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

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

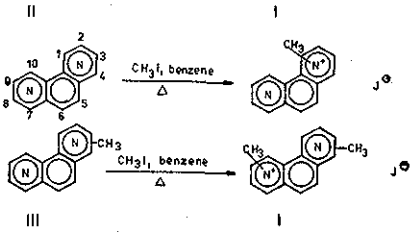
PO 40

ALKYL DERIVATIVES OF AZAPHENANTHRENES

W. Sliwa*, M. Jastrzębska-Glapa

Institute of Organic and Physical Chemistry, Polytechnical University, 50—370 Wroclav, Poland

Since the N- and C-alkyl derivatives of polycyclic azines, and especially N-methyl iodies 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 synthesides by direct alkylation of suitable azaphenanthrenes (II) or their methyl derivatives (III) in 77 to 98% yield.



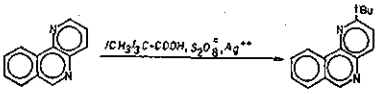
where N 1 or 4 as well as 1,5, 1,6, 1,7, 1,8, 1,10 4,6, 4,7 CH_3 1,2,3,4,8 or 9

The nitrogen ione electron pairs are shielded less by methyl dered N atoms (for instance in the 1 position), except in the case of 1,10-diazaphenanthrene, 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.

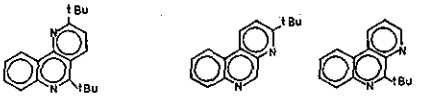
The nitrogen ione electron pairs are shielded less by methyl groups than by protons in the boat position.

t-Butylation was performed on azaphenanthrenes using t-butyl radicals generated from pivalic acid in the presence of $S_2O_8^{=}$ and Ag^{++}ions.

For 1,5-diazaphenantherene:



1,6-Diazaphenanthrene gave 2,5-di-t-butyl derivative, and 4,6-diazaphenanthrene — 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-diazaphenanthrene posses high antibacterial and antifungal activities.