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USE OF THE NUCLEAR OVERHAUSER EFFECT FOR THE DETERMINATION OF THE SUBSTITUTION SITES IN HETEROAROMATIC SYSTEMS*

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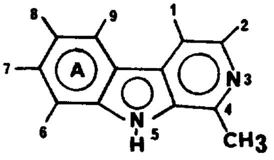
The tricyclic molecules resulting from the fusion of heterocyclic compound such as benzothiophene, benzofuran or indole and a five-membered (thiophene, pyrrole) or six-membered ring (pyridine, pyridazine, pyrimidine, etc) are presently extensively studied (1)(2)(3) because of their structural analogy with the alkaloids of the Harman group I showing psychomimetic properties (4).



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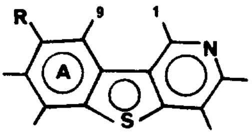
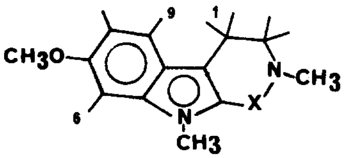


IIa R = H

IIb R = Cl



VIIa X = CH2

VIIb X = C=O

The synthesis of these systems often leads to uncertainty regarding either the structure of the cyclized product or the position of the substituent in the benzene ring. A similar

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***Address correspondence to this author* uncertainty arises in respect of the site of electrophilic substitution which usually occurs in ring A.

NMR has not yet been used for structure determination of these substituted tricyclic derivatives. This is due to certain difficulties : first order spectra, and inter-ring coupling constants are not obtained, lanthanide complexation is inefficient (5) and insufficient ^{13}C data are available. Therefore, structures are presently determined by time consuming, difficult and not always conclusive synthetic methods (2)(6)(7).

In the present communication, we propose a new application of the OVERHAUSER effect which is fast, easy and unambiguous (8)(9).

PRINCIPLE OF THE METHOD

In all the models studied, the protons in the 1 and 9 positions are spatially close together, and are shielded compared with the other protons in the molecule. This is particularly true for H_1 which belongs to a ring containing one or more electronegative heteroatoms. The signals of the pyridine ring are easily distinguished by their characteristic coupling constants. Under these conditions, and if the 9 position is not substituted, irradiation of H_1 leads to an increase of the H_9 signal and *vice versa*, due to the strong intramolecular relaxation between these protons. Examination of the coupling constants of the perturbed signal allows the unambiguous determination of the structure of the substituted compounds. For example, the chlorination of benzothieno [3,2-c] pyridine (II *a*) leads to a monochloro derivative. The irradiation of the easily assigned H_1 proton shows an increase of 20% on a specific signal in the spectrum. This perturbed signal has meta and para coupling constants, so it can be concluded that the chlorine atom is in position 8 (II *b*).

RESULTS

We have illustrated the proposed method by a large number of examples in the benzothienopyridine (II, III, IV), benzothienopyridazine (V) and benzothienothiophene (VI) series. The results of the observed NOE and the structural determinations are reported in the Table.

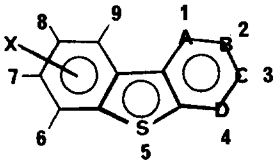
In the case of pyridines IV where A=N, a 1-proton is not present ; this difficulty is overcome by the synthesis of the methiodide and irradiation of the methyl group. The large observed NOE (37%) is due to the close proximity of CH_3 and H_9 (Fig.)

Many of the most important indole alkaloids (isolated from Apocynaceae) contain the β-carboline ring with a reduced or partially reduced pyridine ring. In these compounds, the signal of the strongly coupled methylene group in position 1 is broad. Consequently irradiation does not produce any OVERHAUSER effect on H_9. In this case, the method can still be applied after methylation of the pyrrole ring on the nitrogen. Thus the structures of VII *a* and VII *b* (alkaloids isolated from Phalaris arundinacea (4)) are established by irradiation on the pyrrole $N\text{-}CH_3$ group. The increased (30%) H_6 signal contains m and p coupling constants, showing that the methoxy group is at the 7 position. The position of the substituent in these molecules is in accordance with the structure proposed after a long and difficult synthesis (2).

The application of the method here described to other bicyclic and tetracyclic models and the discussion of very interesting results on coupling constants and conformational preference will be reported further.

Table

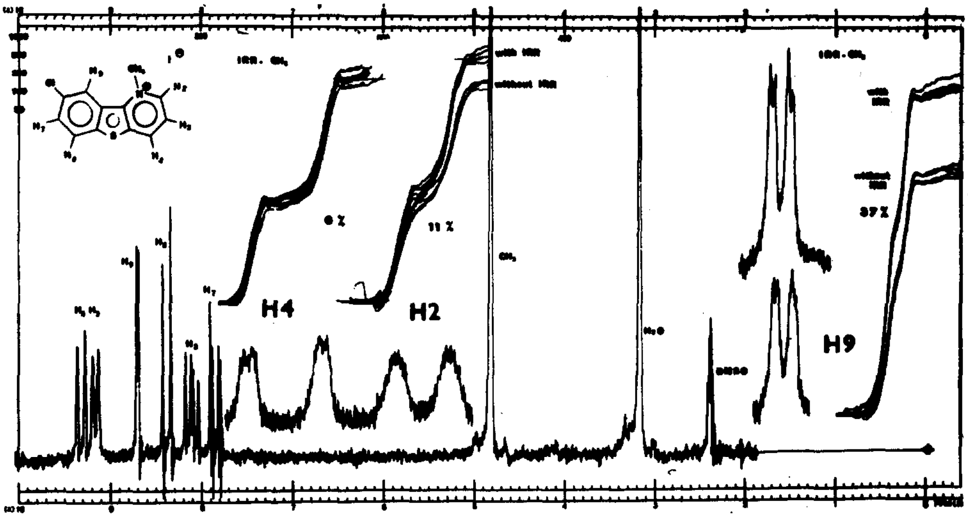
STRUCTURAL DETERMINATIONS BY NOE



	A	B	C	D	X	irr^{ted} proton	*coupling constants	NOE %	Substitution site
II *a*	CH	N	CH	CH	H	H_1	o,m,p	20	none
b	CH	N	CH	CH	Cl	H_1	m,p	27	8
III *a*	CH	CH	N	CH	H	H_1	o,m,p	12	none
b	"	"	"	"	Cl	"	m,p	16	8
c	"	"	"	"	Cl	"	o,p	15	7
d	"	"	"	"	Cl	"		0	9
IV *a*	$\overset{+}{N}-CH_3$	CH	CH	CH	H	$\overset{+}{N}-CH_3$	o,m,p	32	none
b	"	"	"	"	Cl	"	m,p	37	8
V *a*	CH	N	N	CH	H	H_1	o,m,p	20	none
b	"	"	"	"	Br	"	m,p	20	8
VI	$C-CH_3$	CH		S	Cl	$C-CH_3$	m,p	44	8

*coupling constants of the perturbed signal ; o=ortho, m=meta, p=para.

Fig.



NOE experiments on IV *b*

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