

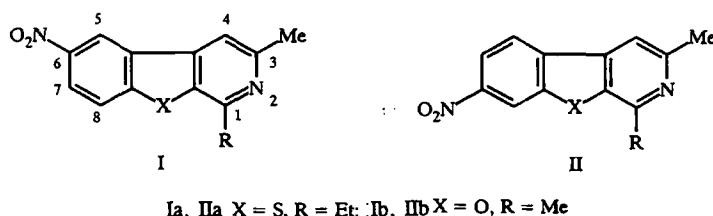
ELECTROPHILIC SUBSTITUTION IN BENZO[b]THIENO- AND BENZO[b]FURO[2,3-c]PYRIDINES.

USE OF THE NUCLEAR OVERHAUSER EFFECT FOR DETERMINATION OF SUBSTITUTION POSITION

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The site of electrophilic substitution in benzo[b]thieno- and benzo[b]furo[2,3-c]pyridines has been determined using the nuclear Overhauser effect and by a method based on the difference in reactivity of the isomeric products.

We have previously studied electrophilic substitution in benzo[b]thieno- and benzo[b]furo[2,3-c]pyridines [1-3]. The structure of the substitution products was determined from their ^1H NMR spectra. It was found that nitration in these pyridines occurs at position C_6 . However, in view of the similarity in the ^1H NMR spectra of the 6-nitro derivative I and its potential 7-isomer our assignment is, in fact, uncertain. Hence it became necessary to return to the question of the substitution position in benzo[b]thieno- and benzo[b]furo[2,3-c]pyridines



For the nitro derivative of 1-ethyl-3-methylbenzo[b]thieno[2,3-c]pyridine, the ^1H proton spectrum shows the following features (Fig. 1b): a triplet at 1.33 and quartet at 3.02 ppm for the C_1 ethyl group, a singlet at 2.59 ppm (3H) for the C_3 methyl group, and a singlet at 8.07 ppm (1H) (whose position and absence of any spin-spin coupling infer an assignment as the C_4 proton). The remaining signals fit a 1,2,4-system of aromatic protons: a doublet at 8.36 ppm ($J = 8.4$ Hz), a double doublet at 8.43 ppm (the larger coupling of 8.4 Hz being the ortho and the smaller ($^4J = 1.8$ Hz) the meta aromatic splittings respectively), and a doublet at 8.93 ppm with the same meta constant.

In a differential nuclear Overhauser experiment (NOE, Fig. 1a), irradiation of the proton absorption at C_4 (8.07 ppm) leads to signals at 2.59 and 8.93 ppm, i.e., closest to the proton at position 4 is the meta-para component of the three proton system and hence the nitro group is at position 6. In the other case, the NOE would be observed on the proton which showed an ortho coupled doublet ($J = 8.4$ Hz). A similar procedure has been used for similar systems in [4].

The ^1H NMR spectrum of the nitration product of 1,3-dimethylbenzo[b]furo[2,3-c]pyridine (Fig. 2b) has a system of bands in the aromatic region of the spectrum which is similar to that observed for the mono nitro benzothienopyridine Ia excepting a change of the triplet-quartet of the ethyl group for a three proton singlet at 2.65 ppm (3H) for C_1 . The pattern of bands in the aromatic region appears as follows: doublet at 7.91 ppm ($J = 12$ Hz), double doublet at 8.42 ppm ($J = 12$ and

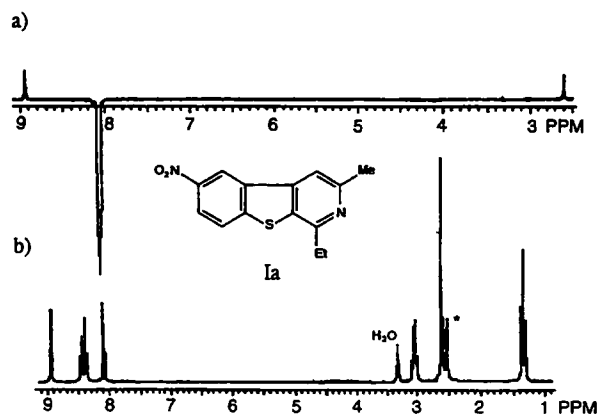


Fig. 1. ^1H NMR spectrum of 1-ethyl-3-methyl-6-nitrobenzo- $[b]$ thieno[2,3- c]pyridine Ia: a) differential NOE experiment; b) 1M spectrum (here and subsequently the stars indicate signals for the residual solvent).

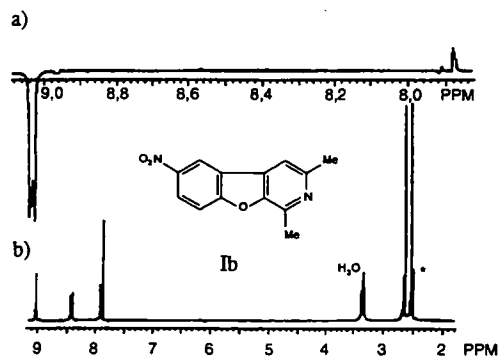
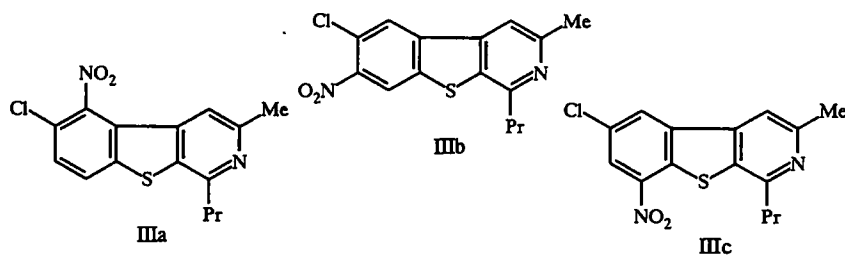


Fig. 2. ^1H NMR spectrum of 1,3-dimethyl-6-nitrobenzo $[b]$ furo[2,3- c]pyridine Ib: a) differential NOE spectrum; b) 1M spectrum.

$^4J = 2.4$ Hz), doublet at 9.03 ppm ($^4J = 2.4$ Hz), and singlet at 7.88 ppm. However, due to overlap of the singlet and doublet at 7.9 ppm, selective irradiation of the C_4 proton (as carried out for compound Ia) was technically difficult. Irradiation of doublet at 9.03 ppm led to an NOE signal at 7.88 ppm (Fig. 2a). Hence, following on from the results for the C_4 proton in Ia, the proton at C_5 in the condensed benzene ring does not show a single course of cross-relaxation (there being an interaction with the methyl group protons). This unambiguously shows that C_5 is the meta-para component of the three spin system [5], i.e. the nitro group occupies position 6 in the condensed benzene ring.

As has previously been reported, nitration of 1-propyl-3-methyl-6-chlorobenzo $[b]$ thieno[2,3- c]pyridine yields all three possible mono substituted products at C_5 (IIIa), C_7 (IIIb), and C_8 (IIIc) [1].

Interpretation of the structure of IIIa is without difficulty. The ^1H NMR spectra of the other nitration products IIIb, c show the following pattern of aromatic proton signals:



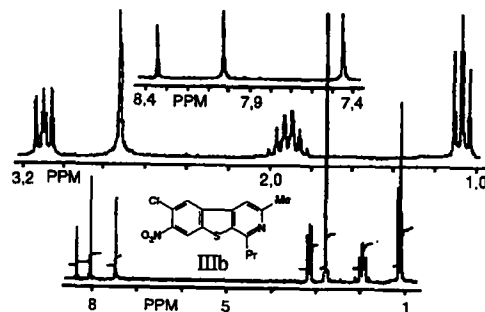


Fig. 3. ^1H NMR spectrum of 1-propyl-3-methyl-6-chloro-7-nitrobenzo[*b*]thieno[2,3-*c*]pyridine (IIIb) (CDCl_3 , TMS).

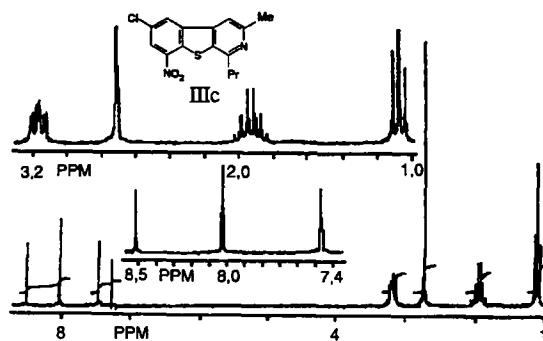
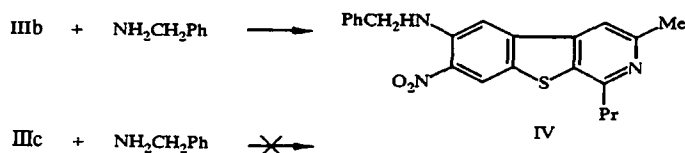


Fig. 4. ^1H NMR spectrum of 1-propyl-3-methyl-6-chloro-8-nitrobenzo[*b*]thieno[2,3-*c*]pyridine (IIIc) (CDCl_3 , TMS).

two singlet signals for the protons of both compounds with identical shifts at 7.47 and 8.03 ppm which are assigned to the protons at positions 4 and 5 respectively (Figs. 3 and 4). The signal of the third proton is, in one case, shifted to 8.35 ppm (Fig. 3) and in the other to lower field (8.52 ppm, Fig. 4). Hence, these two compounds are the mono nitration products at position 7 or 8.

Identification of both materials can be made in the following way: the individual isomers were treated with benzylamine in xylene. The reactive compound was identified as the 7-nitro isomer (IIIb) and the unreactive one the 8-nitro isomer (IIIc).



EXPERIMENTAL

^1H NMR spectra for Ia, b (solvent $\text{DMSO}-d_6$, internal standard TMS) were recorded on a Varian VXR-300 (300 MHz) and IIIb, c and IV (solvent CDCl_3 , internal standard TMS) on a Gemini-200 instrument (200 MHz).

1-Propyl-3-methyl-6-benzylamino-7-nitrobenzo[*b*]thieno[2,3-*c*]pyridine (IV). A mixture of IIIb (0.08 g, 0.25 mmole), benzylamine (0.14 g, 1.25 mmole), and *m*-xylene (10 ml) was refluxed for 8 h. At the end of the reaction the excess solvent was distilled off under reduced pressure, the residue treated with hexane (5 ml) and the precipitated pyridine IV was filtered, washed on the filter with hexane, and dried in air. Recrystallization from ethanol gave IV (0.08 g, 82%) with mp 262–263°C.

¹H NMR spectrum (CDCl₃): 1.08 (3H, t, 1-CH₃(Pr)); 1.94 (2H, m, 1-CH₂(Pr)); 2.72 (3H, s, 3-CH₃); 2.94 (2H, s, CH₂(PhCH₂)); 3.17 (2H, t, 1-CH₂(Pr)); 7.22 (2H, d, J = 9.3 Hz, Ph); 7.27 (1H, s, 4-H); 7.35-7.55 (5H, m, 5.8-H₂, Ph); 8.83 ppm (1H, s, NH). Found, %: C 67.54; H 5.42; N 10.70; S 8.23. C₂₂H₂₁N₃O₂S. Calculated, %: C 67.49; H 5.41; N 10.73; S 8.19.

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