ELECTROPHILIC SUBSTITUTION IN BENZO[*b*]THIENO[2,3-*c*]PYRIDINES. NITRATION

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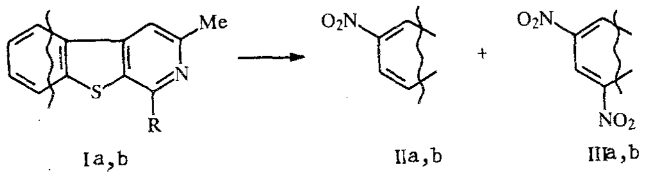
A study was carried out on the nitration of substituted benzo[b]thieno[2,3-c]pyridines. Depending on the conditions, either one nitro group is introduced at $C_{(6)}$ *or two nitro groups are introduced at* $C_{(6)}$ *and* $C_{(8)}$. *If* $C_{(6)}$ *is blocked, a mixture of products is formed.*

Although electrophilic substitution in the benzene part of the molecule has been extensively studied for β-carbolines, there is no information on the chemical behavior of benzo[*b*]thieno[2,3-*c*]pyridines, which are S-isosteres of β-carbolines. The nitration of β-carbolines by concentrated nitric acid at 80°C or by a mixture of concentrated nitric and glacial acetic acids at reflux gives a mixture of the 6- and 8-mononitro derivatives, while nitration by 86% nitric acid at 2-4°C leads only to 6-nitro derivatives [1-3]. The nitration of β-carbolines by a mixture of concentrated sulfuric and nitric acids gives 6,8-dinitro derivatives [4].

We have shown that the nitration of benzo[*b*]thieno[2,3-*c*]pyridines (I) by nitric acid leads predominantly to the formation of their 6-nitro derivatives (II), while the use of a mixture of concentrated sulfuric and nitric acids gives both mononitro and dinitro derivatives (III).

Thus, the nitration of 1,3-dimethylbenzo[*b*]thieno[2,3-*c*]pyridine Ia by 99% nitric acid at from −5 to 0°C gives a mixture of 1,3-dimethyl-6-nitrobenzo[*b*]thieno[2,3-*c*]pyridine IIa (97%) and 1,3-dimethyl-6,8-dinitrobenzo[*b*]thieno-[2,3-*c*]pyridine IIIa (3%). The nitration of Ia by 85% nitric acid at room temperature leads only to 6-nitro derivative IIa (89% yield). A further decrease in the nitric acid concentration lowers the yield of IIa with retention of selectivity. The yield of IIa when 78% nitric acid is used is reduced to 35%, while Ia is not nitrated when 56% nitric acid is used even when the reaction mixture is maintained at 80°C for 3 h. The nitration of Ia by a mixture of concentrated sulfuric and 99% nitric acids at from −5 to 0°C leads to a 55:45 mixture of IIa and IIIa. 1-Ethyl-3-methylbenzo[*b*]thieno[2,3-*c*]pyridine Ib behaves analogously under these conditions (Scheme 1).

Scheme 1



I—IIIa R = Me; b R = Et

We studied the direction of substitution in derivatives of benzo[*b*]thieno[2,3-*c*]pyridines when the ordinary nitration positions are blocked. For this purpose, 1,3,6-trimethylbenzo[*b*]thieno[2,3-*c*]pyridine Ic and 1,3,8-trimethylbenzo[*b*]thieno-[2,3-*c*]pyridine Id were subjected to nitration using a mixture of concentrated sulfuric acid and 99% nitric acid at from −5 to 0°C. In the case of Ic, 1,3,6-trimethyl-5-nitrobenzo[*b*]thieno[2,3-*c*]pyridine IIc (88%) is the predominant product with 8% 8-nitro derivative IIIc and 4% 5,7-dinitro derivative IVc. Upon nitration of Id, only 1,3,8-trimethyl-6-nitrobenzeno[b]thieno[2,3-*c*]pyridine IId is formed (Scheme 2).

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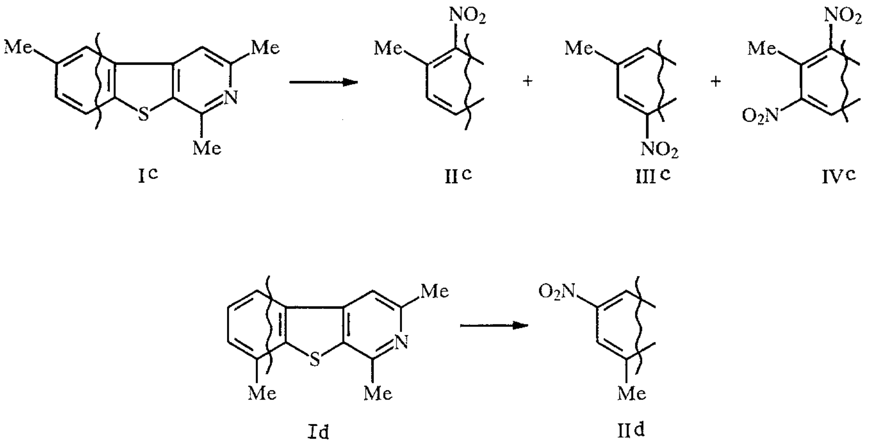
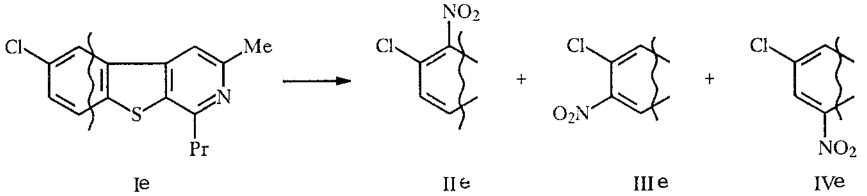
Scheme 2


Ic IIc IIIc IVc

Id IId

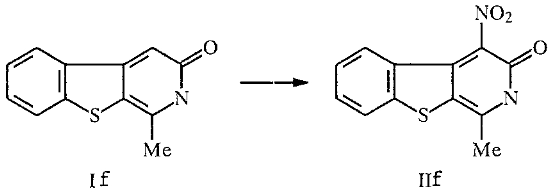
The product isomer distribution obtained in the nitration of 1-propyl-3-methyl-6-chlorobenzo[*b*]thieno[2,3-*c*]pyridine Ie differs from that in the nitration of Ic. In the case of Ie, all three products of the substitution at $C_{(5)}$ (IIe), and $C_{(7)}$ (IIIe), and $C_{(8)}$ (IVe) were isolated (Scheme 3). We should note that a satisfactory result in the nitration of Ie was obtained only upon heating the reaction mixture at 80°C.

Scheme 3


Ie IIe IIIe IVe

In contrast to Ia-Ie, 1-methyl-3(2H)benzo[*b*]thieno[2,3-*c*]pyridone If gives several products upon nitration by a mixture of concentrated sulfuric and 99% nitric acid at from −5 to 0°C. These products are the subject of further investigation. However, we have found that the nitration of If by 85% nitric acid in acetic acid at 10-15°C gives 4-nitro derivative IIf in 62% yield (Scheme 4).

Scheme 4


If IIf

The composition and structure of all the compounds synthesized were supported by elemental analysis and IR and PMR spectroscopy (Table 2).

The IR spectra of the nitro derivatives of benzo[*b*]thieno[2,3-*c*]pyridines show bands characteristic for the nitro group at 1340 and 1510 cm^{-1}. The band at 1510 cm^{-1} is superimposed on a band for the benzo[*b*]thiophene ring.

EXPERIMENTAL

The PMR spectra were taken on a Gemini-200 spectrometer at 200 MHz in $CDCl_3$ with TMS as the internal standard. The PMR spectral data for II-IV are given in Tables 1 and 2. The purity and isomer content of the products were checked by thin-layer chromatography on Alufol and Silufol UV-254 plates. The isomers were separated by chromatography on neutral alumina or silica gel columns (Table 1).

TABLE 1. Indices of II-IV

Compound	Chemical formula	mp, °C	R_f	Chromatography eluent	Content of isomer in mixture, %
IIa	$C_{13}H_{10}N_2O_2S$	228...229	0,13	Benzene—chloroform 27 : 8*	55
IIIa*	$C_{13}H_9N_3O_4S$	233...234	0,63		45
IIb	$C_{14}H_{12}N_3O_4S$	170...172	0,16	Benzene—chloroform 7 : 1*	60
IIIb	$C_{14}H_{11}N_3O_4S$	216...217	0,85		40
IIc	$C_{14}H_{12}N_2O_2S$	215...216	0,19	Benzene—chloroform 6 : 1*	88
IIIc	$C_{14}H_{12}N_2O_2S$	(223)	0,06		8
IVc	$C_{14}H_{11}N_3O_4S$	221...222	0,74		4
IId	$C_{14}H_{12}N_2O_2S$	228...229	0,23	Methylene chloride—ethanol 40 : 1**	71***
IIe	$C_{15}H_{13}ClN_2O_2S$	164...165	0,75	Benzene—chloroform 12 : 1*	48
IIIe	$C_{15}H_{13}ClN_2O_2S$	203...205	0,19		32
IVe	$C_{15}H_{13}ClN_2O_2S$	185...187	0,08		20
IIf	$C_{12}H_8N_2O_3S$	> 350	0,83	Benzene—ethanol 6 : 1**	62***

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*Neutral alumina.

**Silica gel.

***Yield of IIf given.

TABLE 2. Spectral Indices of II-IV

Compound	PMR spectrum, δ, ppm (coupling constant, J, Hz)
IIa	2,74 (3H, s, 3-CH_3); 2,91 (3H,s, 1-CH_3); 7,94 (1H,s, 4-H); 8,42 (1H, d, J = 8, 8-H); 8,56 (1H, d, J = 8, 7-H); 8,87 (1H,s, 5-H)
IIIa*	2,80 (3H,s., 3-CH_3); 3,15 (3H, s, 1-CH_3); 8,11 (1H,s, 4-H); 9,39 (1H, s., 5-H); 9,61 (1H, s, 7-H)
IIb*	1,55 (3H,t, 1-CH_3); 2,67 (3H, s, 3-CH_3); 3,34 (2H, q, 1-CH_2); 7,73 (1H,s., 4-H); 8,44 (1H,d, J = 8, 8-H); 8,51 (1H, d, J = 8, 7-H); 8,89 (1H, s, 5-H)
IIIb*	1,55 (3H,t, 1-CH_3); 2,67 (3H,s, 3-CH_3); 3,34 (2H,q, 1-CH_2); 8,11 (1H, s, 4-H); 9,39 (1H, s, 5-H); 9,61 (1H,s, 7-H)
IIc	2,48 (3H, s, 3-CH_3); 2,71 (3H, s, 1-CH_3); 2,95 (3H, s, 6-CH_3); 7,07 (1H, s, 4-H); 7,59 (1H,d, J = 8, 7-H); 8,05 (1H, d, J = 8, 8-H)
IIIc	2,48 (3H, s, 3-CH_3); 2,71 (3H,s, 1-CH_3); 2,92 (3H,s, 6-CH_3); 7,39 (1H,s, 4-H); 7,93 (1H,s, 5-H); 8,14 (1H, s, 7-H)
IVc	2,48 (3H,s, 3-CH_3); 2,71 (3H,s, 1-CH_3); 2,95 (3H,s., 6-CH_3); 7,35 (1H, s, 4-H); 8,59 (1H, s, 8-H)
IId	2,73 (3H, s, 3-CH_3); 2,89 (3H, s, 1-CH_3); 2,92 (3H, s, 8-CH_3); 7,52 (1H, s, 4-H); 8,23 (1H, s, 7-H); 8,49 (1H, s, 5-H)
IIe	1,08 (3H,t, 1-CH_3); 1,94 (2H,m, 1-CH_2); 2,72 (3H, s, 3-CH_3); 3,17 (2H, t, 1-CH_2); 7,47 (1H,s., 4-H); 8,03 (1H, s, 5-H); 8,52 (1H,s, 7-H)
IIIe	1,08 (3H, t, 1-CH_3); 1,94 (2H, m, 1-CH_2); 2,72 (3H, s, 3-CH_3); 3,17 (2H,t, 1-CH_2); 7,47 (1H,s, 4-H); 8,03 (1H, s, 5-H); 8,35 (1H, s, 8-H)
IVe	1,08 (3H, t, 1-CH_3); 1,94 (2H, m, 1-CH_2); 2,72 (3H, s, 3-CH_3); 3,17 (2H, t, 1-CH_2); 7,43 (1H, s, 4-H); 8,13 (1H, d, J = 2,4, 7-H); 8,33 (1H, d, J = 2,4, 8-H)
IIf**	3,12 (3H, s, 1-CH_3); 7,6...7,8 (3H, m, H_{arom}); 8,90 (1H, d, J = 3,0, 5-H)

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*Spectrum taken in C_5D_5N.

**Spectrum taken in CF_3CO_2H.

The elemental analysis data for C, N, S, H, and Cl in II-IV were in accord with the calculated values.

Products Ia-Ie were obtained according to our previous procedure [5].

1,3-Dimethyl-6-nitrobenzo[*b*]thieno[2,3-*c*]pyridine (IIa). A. A sample of 1.7 mmole Ia was added with stirring to 6 ml 78% nitric acid, maintained at 15-20°C. The reaction mixture was maintained at this temperature for 2 h and then a mixture of ice water and ammonia was added. The precipitate of IIa was filtered off, washed with water, and dried.

B. A sample of 1.7 mmole Ia was added in small portions with stirring to 4.5 ml 85% nitric acid, maintaining the reaction conditions and separation procedure decreased for method A.

General Method for the Nitration of Ia-Id. A sample of 5 ml nitric acid (d = 1.520) was added dropwise with stirring to a solution of 4.7 mmoles Ia-Id in 10 ml sulfuric acid (d = 1.832) at from −5 to 0°C. The reaction mixture was maintained at this temperature for 1 h and then treated as described above.

Nitration of Ie. A sample of 1.1 ml nitric acid (d = 1.520) was added dropwise with stirring to a solution of 1 mmole Ie in 2.2 ml sulfuric acid (d = 1.832) at 15-20°C. The reaction mixture was heated to 80-85°C and maintained at this temperature for 1 h. The product was separated as described above.

Nitration of If. A sample of 4.8 ml 85% nitric acid was added dropwise with stirring to a solution of 2.33 mmole If in 4.5 ml acetic acid maintained at 15°C. The reaction mixture was maintained at this temperature for 20 min. After ordinary work-up, the product was filtered off, washed with a small amount of cold ether, and dried.

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