Naphtho[1,2-*b*]thiophen. Part 2.[1] Substitution Reactions of Derivatives with One or More Substituents in the Thiophen Ring and of the 4,5-Dihydro-derivative

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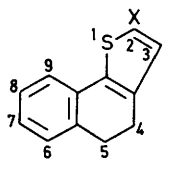
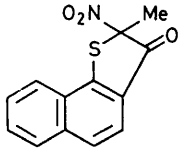
Acetylation, formylation, and bromination of 2- or 3-methylnaphtho[1.2-*b*]thiophen and bromination of naphtho-[1,2-*b*]thiophen-3-carbaldehyde take place in the free thiophen position. Nitration of the 2-methyl compound gives mainly the 5-nitro-derivative and 2-methyl-2-nitronaphtho[1.2-*b*]thiophen-3(2*H*)-one; nitration of the 3-methyl compound gives a mixture of the 2- and 5-nitro-derivatives. 2,3-Dimethylnaphtho[1,2-*b*]thiophen undergoes bromination and acetylation in the 5-position. 4,5-Dihydronaphtho[1.2-*b*]thiophen undergoes mono-substitution in the 2-position; attempted nitration of its 2-ethoxycarbonyl derivative gave mainly the aromatised ethyl naphtho[1,2-*b*]thiophen-2-carboxylate and its 7-nitro-derivative.

SUBSTITUTED naphtho[1,2-*b*]thiophens [2,3] and their 4,5-dihydro-derivatives [4,5] are being used increasingly as intermediates in the synthesis of biologically active molecules. However, apart from our study [1] of some substitution reactions of the parent molecule, the chemistry of naphtho[1,2-*b*]thiophen has not been examined systematically. We therefore now describe some electrophilic substitution reactions of naphtho[1,2-*b*]-thiophens containing one or more substituents in the thiophen ring, and of the 4,5-dihydro-derivatives (1) and (2).

Vilsmeier–Haack formylation, Friedel–Crafts acetylation, and monobromination of 3-methylnaphtho[1,2-*b*]-thiophen gave the appropriate 2-substituted derivative in each case, for which the n.m.r. spectrum lacked a



(1) X = H
(2) X = CO_2Et



(3)

quartet due to 2-H [the n.m.r. spectrum of a 2-unsubstituted 3-methylnaphtho[1,2-*b*]thiophen shows a characteristic quartet ($J_{2,3\text{-Me}}$ *ca.* 1 Hz)]. These results were not

[1] Part 1, K. Clarke, D. N. Gregory, and R. M. Scrowston, *J.C.S. Perkin I*, 1973, 2956.
[2] O. Dann, G. Volz, E. Demant, W. Pfeifer, G. Bergen, H. Fick, and E. Walkenhorst, *Annalen*, 1973, 1112.
[3] B. P. Das, R. T. Cunningham, and D. W. Boykin, *J. Medicin. Chem.*, 1973, **16**, 1361.
[4] A. Rosowsky, K. K. N. Chen, and M. Lin, *J. Medicin. Chem.*, 1973, **16**, 191.
[5] E. F. Elslager, P. Jacob, and L. M. Werbel, *J. Heterocyclic Chem.*, 1972, **9**, 775.

unexpected, since the parent compound also undergoes substitution in the 2-position.[1] The fact that formylation proceeded smoothly in the presence of phosphoryl chloride and dimethylformamide illustrates the enhanced reactivity of the 3-methyl compound; naphtho[1,2-*b*]-thiophen itself is formylated only in the presence of the more reactive *N*-methylformanilide.[1] Nitration of 3-methylnaphtho[1,2-*b*]thiophen in glacial acetic acid gave a mixture of the 2- (40%) and 5-nitro-isomers (60%). The 2-nitro-compound was too insoluble to allow a satisfactory n.m.r. spectrum to be obtained. However, it was successively reduced and acetylated, and the spectrum of the resulting acetamido-compound showed clearly the absence of a 2-H signal. As we have already indicated,[1] the 4- and 5-H signals in the n.m.r. spectra of naphtho[1,2-*b*]thiophen derivatives are often not well resolved, thus rendering it almost impossible to differentiate between a 4- or 5-substituent. However, advantage could be taken of the nuclear Overhauser effect to identify 5-substituted naphtho[1,2-*b*]thiophen derivatives. Thus, saturation of the 3-Me resonance from the major isomer from the nitration reaction gives a 20% enhancement of the signal at δ 8.48; from the stereochemistry of the system, this signal can only be due to 4-H. Chemical proof of the structure of the 5-nitro-compound came from its conversion by standard means into 5-bromo-3-methylnaphtho[1,2-*b*]thiophen; this could also be obtained unambiguously by cyclodehydration of (4-bromo-1-naphthylthio)acetone.

Dibromination of 3-methylnaphtho[1,2-*b*]thiophen gave the 2,5-dibromo-derivative. Its structure followed from the observation that it could also be obtained by bromination of either 5-bromo-3-methyl- or 2-bromo-3-methyl-naphtho[1,2-*b*]thiophen.

Next we prepared 2-methylnaphtho[1,2-*b*]thiophen, both by Huang-Minlon reduction of the corresponding aldehyde [1] and, preferably, by reductive silylation [6] of the readily available [1] 2-carboxylic acid in the presence of trichlorosilane and triethylamine, followed by alkaline hydrolysis of the resulting trichloro-(2-naphtho[1,2-*b*]-thienylmethyl)silane. Previously,[7] we had shown that the isomeric 2-methylnaphtho[2,1-*b*]thiophen undergoes substitution in the 5-position, rather than in the remaining free thiophen position. We suggested that this behaviour might be due to steric interaction between the 1-position (corresponding to the 3-position in the [1,2-*b*]-isomer) and the 9-position. Since a steric effect of this type is not possible for the [1,2-*b*]-isomer, we expected that the 3-position in 2-methylnaphtho[1,2-*b*]thiophen would be activated towards electrophiles by the methyl group (*cf.* the behaviour of 2-methylbenzo[*b*]thiophen [8]). Our predictions were confirmed: bromination, acetylation, and formylation of 2-methylnaphtho[1,2-*b*]thiophen each gave a 3-substituted derivative, which lacked a signal due to 3-H in its n.m.r. spectrum. When the 2-methyl compound was treated with bromine (2 mol. equiv.) the second bromine atom entered the methyl group. The resulting 3-bromo-2-bromomethylnaphtho-[1,2-*b*]thiophen could not be obtained pure, probably because of the lability of the bromine atom in the side-chain. It was converted into the corresponding ethoxymethyl compound merely by heating with ethanol. Nitration of 2-methylnaphtho[1,2-*b*]thiophen gave a mixture of seven components, from which 2-methyl-5-nitronaphtho[1,2-*b*]thiophen (16%) and 2-methyl-2-nitronaphtho[1,2-*b*]thiophen-3(2*H*)-one (3) (10%) were isolated; surprisingly, no 3-nitro-compound was detected. An *ipso*-nitration product analogous to the ketone (3) is also formed during the nitration of 2-bromo-3-methylbenzo[*b*]thiophen.[9] Spectroscopic evidence for structure (3) is cited in the Experimental section. The structure of the 5-nitro-compound did not follow immediately from its n.m.r. spectrum (*cf.* discussion above). However, by comparing the spectrum of 5-nitronaphtho-[1,2-*b*]thiophen [1] with that of naphtho[1,2-*b*]thiophen,[10] substituent chemical shifts for a 5-nitro-substituent in the naphtho[1,2-*b*]thiophen nucleus could be calculated. When these values were added to the chemical shift of each proton in 2-methylnaphtho[1,2-*b*]thiophen, the resulting calculated chemical shifts corresponded closely with those observed for the product from the nitration reaction. The structure was confirmed by converting the 5-nitro-compound into the corresponding 5-bromo-compound; this was identical with a sample of 5-bromo-2-methylnaphtho[1,2-*b*]thiophen prepared unambiguously from the corresponding 2-carboxylic acid.

We next prepared 2,3-dimethylnaphtho[1,2-*b*]thiophen by Huang-Minlon reduction of 3-methylnaphtho[1,2-*b*]-thiophen-2-carbaldehyde and established that it underwent bromination in the 5-position, by demonstrating that an identical product could be obtained by successive formylation and Huang-Minlon reduction of 5-bromo-3-methylnaphtho[1,2-*b*]thiophen. Earlier workers [11] believed that 2,3-dimethylnaphtho[1,2-*b*]thiophen underwent Friedel–Crafts acetylation in the 6-position. However, such a result would not fit in with the pattern which our work had indicated for the order of reactivity towards electrophiles of the various positions in substituted naphtho[1,2-*b*]thiophens (*i.e.* 2 > 3 > 5). We therefore obtained the 5-carbonitrile from the 5-bromo-compound, treated it with methylmagnesium iodide, and confirmed that the resulting ketone was indeed identical with the acetylation product.

We have already shown [1] that the presence of the electron-withdrawing 2-ethoxycarbonyl substituent in the naphtho[1,2-*b*]thiophen nucleus leads to electrophilic attack in the 5-position. We now wished to examine the effect of an electron-withdrawing group

[6] *Cf.* R. A. Benkeser, K. M. Foley, J. M. Gaul, and G. S. Li, *J. Amer. Chem. Soc.*, 1970, **92**, 3232.
[7] K. Clarke, G. Rawson, and R. M. Scrowston, *J. Chem. Soc.* (*C*), 1969, 1274.
[8] B. Iddon and R. M. Scrowston, *Adv. Heterocyclic Chem.*, 1970, **11**, 177.
[9] J. Cooper and R. M. Scrowston, *J. Chem. Soc.* (*C*), 1971, 3052.
[10] D. F. Ewing and R. M. Scrowston, *Org. Magnetic Resonance*, 1971, **3**, 405.
[11] P. Cagniant, D. Cagniant, and P. Faller, *Bull. Soc. chim. France*, 1964, 1756.

in the 3-position, and therefore brominated naphtho[1,2-*b*]thiophen-3-carbaldehyde. The aldehyde was conveniently obtained from the 3-bromomethyl compound *via* the Sommelet reaction. Bromination took place with difficulty in the 2-position, thus illustrating again the high reactivity of this position. The result was unexpected, because the corresponding aldehyde in the naphtho[2,1-*b*]thiophen series is brominated [7] in the 5-position. Further, benzo[*b*]thiophen-3-carbaldehyde resists bromination, even under forcing conditions,[12] and is nitrated entirely in the benzenoid ring.[13]

Finally, we obtained 4,5-dihydronaphtho[1,2-*b*]thiophen from the readily available [1] ester (2), in order to compare its substitution reactions with those [1] of naphtho[1,2-*b*]thiophen and those of 9,10-dihydrophenanthrene. It is believed [14] that the substitution patterns of fluorene, 9,10-dihydrophenanthrene, and related compounds are governed by the mesomeric interactions of the two benzene rings, and that the alkyl chain simply modifies these interactions by altering the angle between the planes of the two aromatic nuclei which it links. Models show that the 4,5-bridge in the dihydro-compound (1) causes the two aryl groups to have roughly the same spatial relationship as the two phenyl groups in 9,10-dihydrophenanthrene. It might be expected, therefore, that 4,5-dihydronaphtho[1,2-*b*]thiophen, like 9,10-dihydrophenanthrene,[14,15] would undergo substitution first in the 2-position, then in the 7-position. However, the possibility of the second substituent entering the remaining vacant position in the thiophen ring could not be discounted.

The results of bromination (bromine–acetic acid), formylation, and monoacetylation reactions confirmed our predictions. Each reaction gave the appropriate 2-substituted 4,5-dihydronaphtho[1,2-*b*]thiophen, which was converted (see Experimental section) into 4,5-dihydronaphtho[1,2-*b*]thiophen-2-carboxylic acid in order to confirm its structure. Treatment of the dihydro-compound (1) with *N*-bromosuccinimide gave mainly naphtho[1,2-*b*]thiophen (61%) [*cf.* the dehydrogenation (88%) of the ester (2) by *N*-bromosuccinimide [1]], together with starting material (15%), 2-bromo-4,5-dihydronaphtho[1,2-*b*]thiophen (14%), and an unidentified product (10%). The acetylation reaction with acetyl chloride (1 mol. equiv.) gave the 2-acetyl compound (83%) and a diacetyl derivative (16%). When acetyl chloride (2 mol. equiv.) was used the proportion of the latter increased to 40%; the n.m.r. spectrum showed clearly that the second acetyl group occupied either the 7- or the 8-position, but no firm distinction was possible. However, we shall show that the ester (2) undergoes substitution in the 7-position; by analogy, it seems likely that the second acetyl group of the diacetyl compound occupies the 7-position. Further, 2-phenylthiophen, which is structurally analogous to the dihydronaphthothiophen (1), undergoes substitution [16] first in the thiophen ring, then in the *para*-position of the benzenoid ring; the latter position corresponds to the 7-position in the dihydro-compound (1). In common with the nitration reactions already described, the nitration of 4,5-dihydronaphtho[1,2-*b*]thiophen did not proceed smoothly. Nitration with nitric acid under various conditions or with copper(II) nitrate in acetic anhydride gave a tar in each case, from which 4,5-dihydro-2-nitronaphtho[1,2-*b*]thiophen (*ca.* 10%) could be isolated. Its structure was not immediately evident because the relevant peaks in the n.m.r. spectrum were unresolved. It was therefore aromatised with *N*-bromosuccinimide, to give 2-nitronaphtho[1,2-*b*]thiophen which, because it was too insoluble for examination by n.m.r. spectroscopy, was converted by the route already described into the 2-acetamido-compound. An identical product was obtained from the Beckmann rearrangement of 2-acetylnaphtho[1,2-*b*]thiophen oxime.

We next attempted to acetylate ethyl 4,5-dihydronaphthothiophen-2-carboxylate (2) in the hope that the structure of the product could be related to that of the diacetyl compound already described. However, under mild conditions no reaction was observed; under more forcing conditions only intractable products were obtained. We therefore nitrated the ester (2) in order to observe how the presence of an electron-withdrawing group in the 2-position affected the substitution pattern of the dihydro-system (1). However, the major product (73%) was ethyl naphtho[1,2-*b*]thiophen-2-carboxylate, thus confirming our previous [1] observation that the ester (2) is readily dehydrogenated. The other products were ethyl 7-nitronaphtho[1,2-*b*]thiophen-2-carboxylate (9%) and ethyl 4,5-dihydro-7-nitronaphtho[1,2-*b*]thiophen-2-carboxylate (18%). Only the former was obtained pure, but the structural relationship between the two products was evident from a spectroscopic examination of the mixture and from the fact that the mixture was converted almost quantitatively into the former product by dehydrogenation. As before, the splitting pattern in the n.m.r. spectrum of ethyl 7-nitronaphtho[1,2-*b*]-thiophen-2-carboxylate was consistent with the presence of either a 7- or an 8-substituent. However, the substituent chemical shifts for the nitro-group in benzene are well authenticated; [17] knowing the chemical shifts for 6-, 7-, 8-, and 9-H in ethyl naphtho[1,2-*b*]thiophen-2-carboxylate (δ 7.88, 7.58, 7.51, and 8.11, respectively), it is possible to predict the chemical shifts of the ABX system for both a 7- and an 8-nitro-substituent. The calculated δ values for 6-, 8-, and 9-H in the 7-nitro-compound are 8.83 (8.85), 8.46 (8.38), and 8.28 (8.30), respectively; the observed values are quoted in parentheses. For the 8-nitro-compound, the calculated δ

[12] Y. Matsuki and T.-C. Lee, *J. Chem. Soc. Japan*, 1966, **87**, 186.

[13] G. C. Brophy, S. Sternhell, N. M. D. Brown, I. Brown, K. J. Armstrong, and M. Martin-Smith, *J. Chem. Soc.* (*C*), 1970, 933.

[14] P. B. D. de la Mare, E. A. Johnson, and J. S. Lomas, *J. Chem. Soc.*, 1963, 5973; 1964, 5317.

[15] *Cf.* J. W. Krueger and E. Mosettig, *J. Org. Chem.*, 1938, **3**, 340; N. P. Buu-Hoï, P. Mabille, and D.-C. Thang, *Bull. Soc. chim. France*, 1966, 1667.

[16] S. Gronowitz and N. Gjøs, *Acta Chem. Scand.*, 1967, **21**, 2823.

[17] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, p. 202.

values are 8.05 (6-H), 8.53 (7-H), and 9.06 (9-H). These data show that the nitro-compound is almost certainly the 7-nitro-isomer. Ethyl naphtho[1,2-*b*]thiophen-2-carboxylate is nitrated in the 5-position,[1] so the 7-nitro-derivative just described must have been formed by nitration of the dihydro-compound (2), followed by dehydrogenation.

We calculated electron densities and localisation energies (*cf.* ref. 1) for each of the naphtho[1,2-*b*]thiophens on which we had carried out substitution reactions; 3-methyl-2-(*o*-tolyl)thiophen was used as a model for our calculations on 4,5-dihydronaphtho[1,2-*b*]thiophen. Except for 2- and 3-methylnaphtho[1,2-*b*]thiophen, there was poor correlation between these values and the observed position of substitution, thus highlighting the inadequacies (*cf.* ref.1) of LCAO-MO Hückel calculations as applied to polycyclic thiophen derivatives.

EXPERIMENTAL

General experimental details and general procedures for substitution reactions are described in Part 1.[1]

(4-*Bromo*-1-*naphthylthio*)*acetone*.—Prepared (61%) from 4-bromonaphthalene-1-thiol[18] by the usual method (*cf.* ref. 19), this was obtained as an *oil*, b.p. 180—186° at 0.5 mmHg (Found: C, 52.7; H, 3.7%; M^+, 294/296. $C_{13}H_{11}BrOS$ requires C, 52.9; H, 3.75%; M^+, 294/296), $\nu_{max.}$ (film) 1 705 cm^{-1} (C=O).

3-*Methylnaphtho*[1,2-b]*thiophen*.—Treatment of (1-naphthylthio)acetone[19] with polyphosphoric acid at 80—90 °C for 4 h gave a mixture (8 : 1), b.p. 120—126° at 0.2 mmHg, m.p. 62—68° (lit.,[19] m.p. 60.5—61.5°), of 3-methylnaphtho-[1,2-*b*]thiophen and 3-methylnaphtho[1,8-*bc*]thiopyran. Fractional crystallisation from ethanol gave the former (39%) as prisms, m.p. 76—77° (lit.,[11] 77°), δ 2.46 (d, Me) and 7.08 (q, 2-H, *J* 1.0 Hz). Attempted purification of the latter *via* the picrate gave material of only 70% purity, δ 2.84 (Me).

Similar cyclisation of (4-bromo-1-naphthylthio)acetone gave a homogeneous product, from which 5-*bromo*-3-*methylnaphtho*[1,2-b]*thiophen* (65%) was obtained as needles, m.p. 115.5—117° [from ethanol (charcoal)] (Found: C, 56.6; H, 3.5%; M^+, 276/278. $C_{13}H_9BrS$ requires C, 56.35; H, 3.25%; M^+ 276/278), δ 2.33 (d, Me) and 7.02 (q, 2-H, *J* 0.8 Hz).

3-*Methylnaphtho*[1,2-b]*thiophen*-2-*carbaldehyde*.— 3-Methylnaphtho[1,2-*b*]thiophen was formylated with phosphoryl chloride and dimethylformamide, to give the *aldehyde* (75%), m.p. 209—210° (prisms from ethanol) (Found: C, 74.5; H, 4.6%; *M*, 226. $C_{14}H_{10}OS$ requires C, 74.3; H, 4.45%; *M*, 226), $\nu_{max.}$ 1 640 cm^{-1} (C=O), δ 10.34 (CHO) (no 2-H signal).

Obtained similarly from 5-bromo-3-methylnaphtho[1,2-*b*]-thiophen, 5-*bromo*-3-*methylnaphtho*[1,2-b]*thiophen*-2-*carbaldehyde* (31%) formed yellow prisms, m.p. 163—166° (from ethanol) (Found: C, 55.35; H, 3.0%; M^+, 304/306. $C_{14}H_9BrOS$ requires C, 55.1; H, 2.95%; M^+, 304/306), $\nu_{max.}$ 1 665 cm^{-1} (C=O), δ 2.77 (s, Me), 8.08 (s, 4-H), and 10.28 (s, CHO).

2-*Acetyl*-3-*methylnaphtho*[1,2-b]*thiophen*.— Friedel–Crafts acetylation of 3-methylnaphtho[1,2-*b*]thiophen with acetyl chloride in methylene chloride gave prisms (70%), m.p. 138—139° (lit.,[11] 141°) (from ethanol), $\nu_{max.}$ 1 640 cm^{-1} (C=O).

The acetyl group was reduced by the Huang-Minlon method, to give 2-*ethyl*-3-*methylnaphtho*[1,2-b]*thiophen* (55%), m.p. 42—44° (prisms from ethanol) (Found: C, 79.9; H, 6.4%; *M*, 226. $C_{15}H_{14}S$ requires C, 79.6; H, 6.25%; *M*, 226).

Bromination of 3-*Methylnaphtho*[1,2-b]*thiophen*.—Treatment with bromine (1 mol. equiv.) in carbon tetrachloride gave 2-*bromo*-3-*methylnaphtho*[1,2-b]*thiophen* (93%) as needles, m.p. 120—122° (from ethanol) (Found: C, 56.0; H, 3.4%; M^+, 276/278. $C_{13}H_9BrS$ requires C, 56.3; H, 3.25%; M^+, 276/278).

Use of bromine (2.01 mol. equiv.) in boiling glacial acetic acid gave the 2,5-*dibromo-compound* (78%), m.p. 133—136° (needles from ethanol) (Found: C, 43.8; H, 2.6%; M^+, 354/356/358. $C_{13}H_8Br_2S$ requires C, 43.85; H, 2.3%; M^+, 354/356/358), δ 2.35 (Me) and 7.87 (4-H). The same product was obtained (70 and 80%, respectively) by treatment of either 5-bromo-3-methyl- or 2-bromo-3-methyl-naphtho-[1,2-*b*]thiophen with bromine (1 mol. equiv.) in acetic acid.

Nitration of 3-*Methylnaphtho*[1,2-b]*thiophen*.—Nitration in acetic acid gave a mixture of two components [3 : 2 (g.l.c.)] from which 3-*methyl*-2-*nitronaphtho*[1,2-b]*thiophen* (the minor component) was obtained by several recrystallisations from ethanol. It formed yellow feathers, m.p. 245—248° (Found: C, 63.7; H, 3.95; N, 6.0%; *M*, 243. $C_{13}H_9NO_2S$ requires C, 64.15; H, 3.75; N, 5.75%; *M*, 243). The 5-*nitro-isomer* was obtained from the mother liquors as pale red needles, m.p. 154.5—155.5° (from light petroleum) (Found: C, 64.05; H, 3.6; N, 5.7%; *M*, 243), δ 2.51 (d, Me), 7.24 (q, 2-H, *J* 1.0 Hz), and 8.48 (s, 4-H).

The 2-nitro-compound was reduced with Raney nickel and hydrazine hydrate by the method used for 5-nitronaphtho-[1,2-*b*]thiophen.[1] The resulting amine was acetylated with acetic anhydride in pyridine, to give 2-*acetamido*-3-*methylnaphtho*[1,2-b]*thiophen* (87%), m.p. 222—223.5° (from ethanol) (Found: C, 70.6; H, 5.0; N, 5.25%; *M*, 255. $C_{15}H_{13}NOS$ requires C, 70.55; H, 5.15; N, 5.5%; *M*, 255).

Similar reduction of the 5-nitro-isomer gave the corresponding amine, the hydrochloride of which had m.p. 230—233° (from ethanol). The diazotised amine was treated with copper(I) bromide in hydrobromic acid,[20] to give 5-bromo-3-methylnaphtho[1,2-*b*]thiophen, m.p. and mixed m.p. 115—117°.

2-*Methylnaphtho*[1,2-b]*thiophen*.—A mixture of naphtho-[1,2-*b*]thiophen-2-carboxylic acid[1] (4.56 g, 0.02 mol), trichlorosilane (16.3 g, 0.12 mol), and dry acetonitrile (40 ml) was heated under reflux for 1 h. The cooled solution was then treated dropwise with triethylamine (5.75 g, 0.057 mol) at such a rate that the temperature did not exceed 15 °C, and heated under reflux overnight. Ether (150 ml) was added to the cooled solution to precipitate the amine hydrochloride, then the filtered solution was evaporated under reduced pressure. The residual oil was boiled with methanol (10 ml) for 1 h, then the mixture was heated under reflux overnight with potassium hydroxide (11 g) in methanol (20 ml) and water (5 ml), and poured into water. Extraction with ether gave the product as a pale yellow oil (3.15 g, 79%), b.p. 108—115° at 0.1 mmHg (lit.,[1] 110—118° at 0.1 mmHg).

[18] J. E. Banfield, W. Davies, N. W. Gamble, and S. Middleton, *J. Chem. Soc.*, 1956, 4791.

[19] W. Knapp, *Monatsh.*, 1932, **60**, 189.

[20] A. I. Vogel, 'A Text-book of Practical Organic Chemistry,' 3rd edn., Longmans, London, 1956, p. 602.

Obtained similarly, *5-bromo-2-methylnaphtho*[1,2-b]*thiophen* (48%) formed needles, m.p. 90—90.5° (from ethanol) (Found: C, 56.55; H, 3.7%; M^+, 276/278. $C_{13}H_9BrS$ requires C, 56.35; H, 3.25%; M^+, 276/278), δ 2.60 (d, Me) and 6.96 (q, 3-H, *J* 1.0 Hz).

Substitution Reactions of 2-*Methylnaphtho*[1,2-b]*thiophen.*—(a) *Formylation.* Use of phosphoryl chloride and *N*-methylformanilide gave *2-methylnaphtho*[1,2-b]*thiophen-3-carbaldehyde* (53%) as off-white needles, m.p. 133.5—135° (from ethanol) (Found: C, 74.4; H, 4.4%; *M*, 226), $\nu_{max.}$ 1 665 cm^{-1} (C=O), δ 10.01 (s, CHO).

(b) *Acetylation.* *3-Acetyl-2-methylnaphtho*[1,2-b]*thiophen* (83%) was obtained as prisms, m.p. 81—83° (from ethanol) (Found: C, 74.8; H, 4.9%; *M*, 240. $C_{15}H_{12}OS$ requires C, 74.95; H, 5.05%; *M*, 240), $\nu_{max.}$ 1 665 cm^{-1} (C=O).

(c) *Bromination.* Use of bromine (1 mol. equiv.) in carbon tetrachloride gave *3-bromo-2-methylnaphtho*[1,2-b]*thiophen* (72%) as needles, m.p. 98—100° (from ethanol) (Found: C, 56.0; H, 3.25%; M^+, 276/278).

Use of bromine (2 mol. equiv.) in boiling acetic acid gave 3-bromo-2-bromomethylnaphtho[1,2-*b*]thiophen as an oil (Found: M^+, 354/356/358), δ 4.68 (s, 2 H, CH_2Br). Boiling the crude product with ethanol gave *3-bromo-2-ethoxymethylnaphtho*[1,2-b]*thiophen* (31% overall) as needles, m.p. 65—67° (from ethanol) (Found: M^+, 319.9861. $C_{15}H_{13}{}^{79}BrOS$ requires *M*, 319.9870), δ 3.93 (q, $O{\cdot}CH_2Me$) and 4.37 (s, $ArCH_2{\cdot}O$).

(d) *Nitration* (with G. Rawson). The mixture obtained by carrying out the nitration reaction in acetic acid was chromatographed on silica gel. Elution with benzene gave *2-methyl-5-nitronaphtho*[1,2-b]*thiophen* (16%), m.p. 156—157° (yellow needles from ethanol) (Found: C, 64.5; H, 3.95; N, 5.7%; *M*, 243), δ 7.13 (7.16) (3-H), 7.61 (7.59) (7-H), 7.63 (7.67) (8-H), 8.05 (8.16) (6-H), 8.43 (8.43) (4-H), and 8.59 (8.56) (9-H); calculated chemical shifts (see text) are given in parentheses. The nitro-compound was converted as before into 5-bromo-2-methylnaphtho[1,2-*b*]thiophen, identical with authentic material.

Chromatography of the nitration product on alumina (grade II) and elution with benzene gave first a brown oil, then a yellow oil. The latter solidified on trituration with hexane–chloroform (1 : 1), to give *2-methyl-2-nitronaphtho*[1,2-b]*thiophen-3*(2H)*-one* (3) (10%) as yellow prisms, m.p. 139—141° (from ethanol) (Found: M^+, 259.0328. $C_{13}H_9NO_3S$ requires *M*, 259.0303), $\nu_{max.}$ 1702 (C=O), 1 335, and 1 465 cm^{-1} (NO_2), δ 2.26 (s, Me).

2,3-*Dimethylnaphtho*[1,2-b]*thiophen.*—Obtained (70%) by Huang-Minlon reduction (*cf.* ref. 1) of 3-methylnaphtho[1,2-*b*]thiophen-2-carbaldehyde, this had m.p. 100.5—102.5° (lit.,[11] 108.5—109.5°) (from ethanol), δ 2.44 and 2.51 (2 × Me).

5-Bromo-2,3-dimethylnaphtho[1,2-b]*thiophen,* obtained similarly by reduction of the appropriate 2-carbaldehyde formed prisms (68%), m.p. 98—99.5° (from ethanol) (Found: C, 57.9; H, 4.0%; M^+, 290/292. $C_{14}H_{11}BrS$ requires C, 57.75; H, 3.8%; *M*, 290/292), δ 2.25 and 2.47 (2 × Me) and 7.86 (4-H). The same bromo-compound was obtained (62%) by treatment of 2,3-dimethylnaphtho[1,2-*b*]thiophen with bromine (1 mol. equiv.) in carbon tetrachloride.

5-Acetyl-2,3-dimethylnaphtho[1,2-b]*thiophen.*—(*a*) A stirred mixture of the foregoing bromo-compound (0.25 g), copper(I) cyanide (0.1 g), and quinoline (10 ml) was heated under reflux for 2 h, then cooled and poured into an excess of dilute hydrochloric acid. Extraction with chloroform gave a green oil which was filtered in benzene through alumina, to give *2,3-dimethylnaphtho*[1,2-b]*thiophen-5-carbonitrile* (0.16 g, 78%) as needles, m.p. 140—142° (from benzene–light petroleum) (Found: C, 75.95; H, 4.5; N, 5.9%; *M*, 237. $C_{15}H_{11}NS$ requires C, 75.9; H, 4.65; N, 5.9%; *M*, 237), $\nu_{max.}$ 2 225 cm^{-1} (C≡N).

(*b*) A solution of the 5-carbonitrile (0.5 g) in ether (20 ml) was added dropwise during 15 min to a stirred solution of methylmagnesium iodide [from magnesium (0.1 g)] in ether (10 ml). The mixture was kept at 0 °C overnight, then poured into ice and concentrated hydrochloric acid. Extraction with ether gave the ketone (0.3 g, 56%), m.p. 117—119° (lit.,[11] 116—117°) (from ethanol), identical with the product obtained by Friedel–Crafts acetylation of 2,3-dimethylnaphtho[1,2-*b*]thiophen.

Naphtho[1,2-b]*thiophen-3-carbaldehyde.*—(*a*) Bromination of 3-methylnaphtho[1,2-*b*]thiophen with freshly recrystallised *N*-bromosuccinimide in the usual way gave 3-bromomethylnaphtho[1,2-*b*]thiophen (71%) as needles, m.p. 85—87° (from light petroleum), M^+ 276/278, δ 4.65 (CH_2Br).

(*b*) A solution of the bromomethyl compound (8.0 g) in dry chloroform (40 ml) was added slowly to a boiling solution of hexamethylenetetramine (4.0 g) in chloroform (30 ml). The mixture was heated under reflux for 3 h, then cooled and filtered. The hexamine salt was washed [light petroleum (b.p. 40—60°)] and dried, then heated under reflux for 3 h with aqueous 50% acetic acid (35 ml). Water (30 ml) and concentrated hydrochloric acid (7 ml) were added, then the mixture was boiled for 5 min and kept at 0 °C overnight. The precipitate was filtered off and crystallised from aqueous ethanol, to give yellow *prisms* (3.8 g, 62%), m.p. 81.5—83° (Found: C, 73.3; H, 3.8%; *M*, 212. $C_{13}H_8OS$ requires C, 73.55; H, 3.8%; *M*, 212), $\nu_{max.}$ 1 675 cm^{-1} (C=O), δ 10.15 (s, CHO).

2-Bromonaphtho[1,2-b]*thiophen-3-carbaldehyde.*—The foregoing aldehyde was brominated in chloroform for 9 h at 40 °C, to give *needles* (51%), m.p. 139—142° (from ethanol–water) (Found: C, 53.6; H, 2.5%; M^+, 290/292. $C_{13}H_7BrOS$ requires C, 53.6; H, 2.4%; *M*, 290/292), $\nu_{max.}$ 1 675 cm^{-1} (C=O), δ 7.87 (d, 5-H), 8.38 (d, 4-H, *J* 8.6 Hz), and 10.13 (s, CHO) (no 2-H signal).

4,5-Dihydronaphtho[1,2-b]*thiophen* (1).—Hydrolysis of the ester (2) with ethanolic sodium hydroxide gave *4,5-dihydronaphtho*[1,2-b]*thiophen-2-carboxylic acid* (99%) as prisms, m.p. 199—200° (from ethanol) (Found: C, 68.0; H, 4.5%; *M*, 230. $C_{13}H_{10}O_2S$ requires C, 67.8; H, 4.4%; *M*, 230), $\nu_{max.}$ 1 660 cm^{-1} (C=O). This was decarboxylated with copper in quinoline at 210 °C (*cf.* Part 1 [1]), to give an *oil* (87%), b.p. 97—106° at 0.1 mmHg (Found: C, 77.5; H, 5.4%; *M*, 186. $C_{12}H_{10}S$ requires C, 77.35; H, 5.4%; *M*, 186), δ 2.80 (m, $CH_2{\cdot}CH_2$).

Bromination of 4,5-*Dihydronaphtho*[1,2-b]*thiophen* (1).—(*a*) Use of *N*-bromosuccinimide under the conditions already described [1] gave the results indicated in the text.

(*b*) Use of bromine (1 mol. equiv.) in glacial acetic acid in the presence of an iron catalyst gave a dark residue which was distilled under nitrogen, to give the *2-bromo-compound* (81%) as an unstable, pale green oil, b.p. 114—116° at 0.1 mmHg (Found: M^+, 264/266. $C_{12}H_9BrS$ requires *M*, 264/266), δ 6.72 (s, 3-H).

The bromo-compound was heated with copper(I) cyanide in quinoline under the conditions already described, to give *4,5-dihydronaphtho*[1,2-b]*thiophen-2-carbonitrile* (75%) as a dark red oil, b.p. 176—178° at 1.0 mmHg (Found: C, 73.4; H, 4.35; N, 6.8%; *M*, 211. $C_{13}H_9NS$ requires C, 73.9; H, 4.3; N, 6.65%; *M*, 211), $\nu_{max.}$ 2 210 cm^{-1} (C≡N).

The nitrile was hydrolysed with sodium hydroxide in ethanol–water (1 : 1), to give 4,5-dihydronaphtho[1,2-*b*]-thiophen-2-carboxylic acid (73%), identical with authentic material.

4,5-*Dihydro*-2-*nitronaphtho*[1,2-b]*thiophen*.—Nitration of the dihydro-compound (1) in acetic acid gave an oily mixture (1 : 2) of starting material and the 2-nitro-compound (g.l.c.). Chromatography on silica gel and elution with benzene gave the nitro-compound as the slower running component. It formed yellow *prisms* (12%), m.p. 117—119° (from ethanol) (charcoal) (Found: C, 62.45; H, 3.65; N, 6.25%; *M*, 231. $C_{12}H_9NO_2S$ requires C, 62.3; H, 3.9; N, 6.05%; *M*, 231), δ 2.92—2.98 (m, $CH_2{\cdot}CH_2$).

Nitration with nitric acid in AcOH–Ac_2O at 0 °C or with copper(II) nitrate in Ac_2O at 40 °C gave similar mixtures of products, admixed with tarry material.

Identification of 4,5-*Dihydro*-2-*nitronaphtho*[1,2-b]*thiophen*. —(a) 2-*Acetamidonaphtho*[1,2-b]*thiophen*. Powdered phosphorus pentachloride (0.5 g) was added in portions to a stirred solution of 2-acetylnaphtho[1,2-*b*]thiophen oxime [1] (0.5 g) in dry ether (100 ml). The resulting solution was kept at room temperature for 3 h, then it was washed (H_2O and 2M-NaOH), dried, and evaporated. The residue formed white *needles* (0.3 g, 60%), m.p. 194—195.5° (from benzene) (charcoal) (Found: C, 69.6; H, 4.7; N, 5.8%; *M*, 241. $C_{14}H_{11}NOS$ requires C, 69.7; H, 4.6; N, 5.8%; *M*, 241), $\nu_{max.}$ 1 650 (C=O) and 3 240 (NH) cm^{-1}.

(b) 2-*Nitronaphtho*[1,2-b]*thiophen*. The 4,5-dihydro-2-nitro-compound was aromatised with *N*-bromosuccinimide by the method described in Part 1,[1] to give brown *needles* (61%), m.p. 161.5—163.5° (from ethanol) (Found: C, 62.5; H, 3.1; N, 5.9%; *M*, 229. $C_{12}H_7NO_2S$ requires C, 62.85; H, 3.1; N, 6.1%; *M*, 229), i.r. spectrum was identical with that of the minor product [1] from the nitration of naphtho[1,2-*b*]thiophen.

(c) *Reductive acetylation of* 2-*nitronaphtho*[1,2-b]*thiophen*. A solution of the nitro-compound (0.1 g) in glacial acetic acid (30 ml) and acetic anhydride (1 ml) was shaken overnight with hydrogen in the presence of Adams catalyst (30 mg), then filtered. The filtrate was poured into water and neutralised with sodium hydrogen carbonate. Extraction with ether gave the 2-acetamido-compound (0.04 g, 38%), m.p. 192—194°, identical with that obtained in (a).

Friedel–Crafts Acetylation of 4,5-*Dihydronaphtho*[1,2-b]-*thiophen*.—Use of acetyl chloride (1 mol. equiv.) gave a mixture of mono- and di-acetyl compounds (5 : 1) (g.l.c.), which was resolved by chromatography on silica gel and elution with chloroform. The 2-*acetyl compound*, eluted first, formed long yellow needles, m.p. 112—115° (from ethanol) (Found: C, 73.45; H, 5.4%; *M*, 228. $C_{14}H_{12}OS$ requires C, 73.65; H, 5.3%; *M*, 228), $\nu_{max.}$ 1 640 cm^{-1} (C=O), δ 2.54 (s, Ac) and 2.90 (m, $CH_2{\cdot}CH_2$).

Continued elution gave the 2,7-*diacetyl compound*, which crystallised from ethanol as pale yellow needles, m.p. 141—143.5° (Found: C, 70.8; H, 5.25%; *M*, 270. $C_{16}H_{14}O_2S$ requires C, 71.1; H, 5.2%; *M*, 270), $\nu_{max.}$ 1 650 and 1 670 cm^{-1} (C=O), δ(C_6D_6) 2.10 and 2.17 (s, 2 × Ac), 2.30—2.57 (m, $CH_2{\cdot}CH_2$), 7.01 (s, 3-H), 7.19 (dd, 9-H), 7.52 (dd, 8-H), and 7.66 (dd, 6-H) ($J_{8,9}$ 8.5, $J_{6,8}$ 1.5, $J_{6,9}$ 0.5 Hz). The diacetyl compound was obtained in 40% yield when acetyl chloride (2 mol. equiv.) was used for the acetylation.

Oxidation of the 2-acetyl compound with sodium hypoiodite in dioxan gave 4,5-dihydronaphtho[1,2-*b*]thiophen-2-carboxylic acid (68%), identical with authentic material.

4,5-*Dihydronaphtho*[1,2-b]*thiophen*-2-*carbaldehyde*.—Formylation of the dihydro-compound (1) with phosphoryl chloride and dimethylformamide gave a pale yellow *oil* (70%), b.p. 138—142° at 0.1 mmHg (Found: C, 72.7; H, 4.9%; *M*, 214. $C_{13}H_{10}OS$ requires C, 72.85; H, 4.7%; *M*, 214), $\nu_{max.}$ 1 660 cm^{-1} (C=O), δ 2.82—2.97 (m, $CH_2{\cdot}CH_2$) and 9.82 (s, CHO).

It was oxidised by silver oxide (*cf.* ref. 1) to the corresponding 2-carboxylic acid (70%), identical with authentic [1] material.

Nitration of Ethyl 4,5-*Dihydronaphtho*[1,2-b]*thiophen*-2-*carboxylate* (2) —Nitration of the ester (2) in boiling glacial acetic acid for 1 h gave a solid product which contained three components (8 : 2 : 1) (g.l.c.). Chromatography on silica gel and elution with benzene gave first the major component, ethyl naphtho[1,2-*b*]thiophen-2-carboxylate, m.p. and mixed m.p. 86—88° (lit.,[1] 87—88°) (from ethanol). Continued elution gave a crystalline mixture (1 : 2) of ethyl 7-nitronaphtho[1,2-*b*]thiophen-2-carboxylate and the corresponding 4,5-dihydro-compound. Recrystallisation from ethanol gave the former as yellow needles, m.p. 194—195.5° (from ethanol), M^+ 301, $\nu_{max.}$ 1 715 cm^{-1} (C=O); see Discussion for details of the n.m.r. spectrum. The mixture of the 7-nitro-compound and its 4,5-dihydro-derivative was converted entirely into the former by heating it with *N*-bromosuccinimide in carbon tetrachloride for 1 h.

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