Approaches to the Synthesis of 1*H*-[1]Benzothieno[2,3-*d*]imidazoles and Thieno[2,3-*d*]imidazoles

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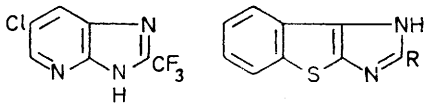
Photolysis of three *NN*-disubstituted 3-amino-2-nitrobenzo[*b*]thiophen derivatives gave mixtures of 2-nitrobenzo[*b*]thiophen-3-ol and benzo[*b*]thiophen-2,3-quinone 2-mono-oxime. 3-Benzylamino-2-nitrobenzo[*b*]thiophen was cyclised to an *N*-oxide under basic conditions. This *N*-oxide was converted into a benzoyloxy-derivative and was also deoxygenated to give 2-phenyl[1]benzothieno[2,3-*d*]imidazole. Reduction of 3-formamido-2-nitrobenzo[*b*]thiophen gave [1]benzothieno[2,3-*d*]imidazol-2(3*H*)-one in low yield. Efforts to extend these cyclisation processes to analogous thiophen derivatives did not succeed.

NUMEROUS benzimidazole derivatives [1] have been marketed commercially over the last decade in the fields of pharmaceuticals, veterinary and human anthelmintic agents, and fungicides, and it is therefore desirable to synthesise analogues of useful benzimidazoles in which the benzene ring is replaced by a heterocyclic ring [*cf.* the herbicide Nortran (1)]. We report our

[1] *Cf.* P. N. Preston, *Chem. Rev.*, 1974, **74**, 279.

attempts to synthesise compounds in the 1*H*-[1]benzothieno[2,3-*d*]imidazole [*cf.* (2)] and thieno[2,3-*d*]imidazole [*cf.* (3)] series.

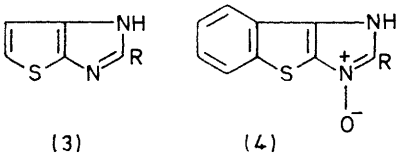
Only two reports [2,3] have appeared concerning the synthesis of 1*H*-[1]benzothieno[2,3-*d*]imidazoles [*cf.* (2)].



(1)

(2)

a; R = Me
b; R = Ph



(3)

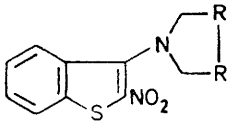
R = H, alkyl, or aryl

(4)

a; R = Ph
b; R = H

Scrowston *et al.*[2] failed to synthesise 7-halogeno-derivatives of (2), but the 2-methyl derivative (2a) was eventually prepared by two procedures.[2,3]

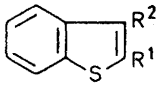
We approached the preparation of 1*H*-[1]benzothieno[2,3-*d*]imidazoles *via* hitherto unknown *N*-oxides [*cf.* (4)], using conventional benzimidazole *N*-oxide syntheses. Accordingly a series of 3-amino-2-nitrobenzo[*b*]thiophen derivatives (5a—c) was prepared and their photochemical behaviour was examined (*cf.* ref. 4). The materials (5a—c) were obtained in high yield by



(5)

RR

a; $[CH_2]_2$
b; $[CH_2]_3$
c; $CH_2O{\cdot}CH_2$



(6)

	R^1	R^2
a;	NO_2	OH
b†;	NO	OH
c;	NO_2	$NH{\cdot}CH_2Ph$
d;	NO_2	$NMe{\cdot}CH_2Ph$
e;	NO_2	NH·CHMePh
f;	NO_2	NH·CHO

† exists as the oxime tautomer

nucleophilic displacement of bromide ion from 3-bromo-2-nitrobenzo[*b*]thiophen [5,6] by secondary amines.

It was hoped (*cf.* ref. 4) that photolysis would give directly imidazoles of type (2) or imidazole *N*-oxides of type (4), but this was not the case. The photolysate from (5a) was a complex mixture, one component of which was 2-nitrobenzo[*b*]thiophen-3-ol (6a). A second compound isolated was identified as benzo[*b*]thiophen-2,3-quinone 2-mono-oxime (6b). The other amines (5b and c) behaved in similar fashion (see Table) and in each reaction mixture a trace of thioindigo (7) was found.

Products from photolysis of the nitro-derivatives (5a—c)

Starting material	Yield (%) (6a) *	(6b)
(5a)	48	10
(5b)	30	13
(5c)	30	9

* Isolated as the sodium salt.

Following these disappointing results an attempt was made to synthesise the *N*-oxides (4) by base-catalysed cyclisation of 3-(benzylamino)-2-nitrobenzo[*b*]thiophen derivatives (6c—e) (*cf.* the synthesis [7] of benzimidazole *N*-oxides from analogous arenes). The *N*-benzyl compound (6c) gave the desired *N*-oxide (4a) in 53% yield when treated with sodium hydroxide in dry methanol. The mass spectrum of this product (4a) shows ions at *m/e* 250 (100%) and 249 (17%) corresponding to losses of O and (O + H) from the molecular ion. Analogous ions have been observed in the spectra of other heteroaromatic *N*-oxides [8] including benzimidazole *N*-oxide. Unfortunately it was impossible to ascertain the tautomeric behaviour [9] of this *N*-oxide (4a) because of the unavailability of a 3-methyl analogue [*viz.* (4a; NMe for NH)]. Thus attempted cyclisation of the nitro-compounds (6d and e) gave only 2-nitrobenzo[*b*]thiophen-3-ol (6a).

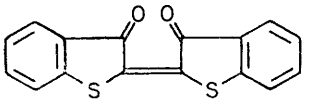
The *N*-oxide (4a) was converted into the imidazole derivative (2b) in moderate yield by heating with zinc dust; [10] it also formed a benzoyloxy-derivative (2b; N·OBz for NH) when treated with benzoyl chloride in pyridine at 90 °C.

Finally an approach was made on the basis of the reported [9] method of conversion of 2-formamido-1-nitrobenzene into a mixture of benzimidazole *N*-oxide and benzimidazol-2-one. Reduction of the appropriate formamido-derivative (6f) did not give the desired *N*-oxide (4b) but afforded a complex mixture from which only the imidazolone (8) was isolated (6% yield).

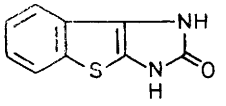
No success was attained in efforts to synthesise thieno[2,3-*d*]imidazoles: pure products could not be isolated from the photolysis of 3,5-dinitro-2-piperidinothiophen (9a) in acidic solution nor from reaction of the benzylamino-derivative (9b) with sodium hydroxide in methanol. Disappointing results were also obtained

[2] M. S. El Shanta, R. M. Scrowston, and M. V. Twigg, *J. Chem. Soc.* (*C*), 1967, 2364.
[3] P. I. Abramenko, *Khim. geterotsikl. Soedinenii*, 1970, 1473 (*Chem. Abs.*, **74**, 53653z).
[4] R. Fielden, O. Meth-Cohn, and H. Suschitzky, *Tetrahedron Letters*, 1970, 1229.
[5] E. B. Middleton and G. A. Dawson, U.S.P., 2,424,483, 1947, (*Chem. Abs.*, 1949, **42**, 1141).
[6] D. E. Boswell, J. A. Brenna, P. S. Landis, and P. G. Rodewald, *J. Heterocyclic Chem.*, 1968, **5**, 69.
[7] *Cf.* P. N. Preston and G. Tennant, *Chem. Rev.*, 1972, **72**, 627.
[8] A. Tatematsu, H. Yoshizumi, E. Hayashi, and H. Nakata, *Tetrahedron Letters*, 1967, 2985.
[9] *Cf.* S. Takahashi and H. Kano, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 1375.
[10] *Cf.* G. W. Stacy, B. V. Ettling, and A. J. Papa, *J. Org. Chem.*, 1964, **29**, 1537.

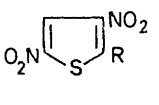
from the pyrolysis [11] and photolysis [12] of 2-(carboxymethylamino)-3,5-dinitrothiophen (9c): heating in nitrobenzene under reflux gave 2-amino-3,5-dinitrothiophen



(7)



(8)



(9)

R

a; piperidino

b; NH·CH_2Ph

c; NH·CH_2CO_2H

in low yield (*ca.* 5%), and u.v. irradiation in acidic aqueous methanol gave green solutions, probably indicating that 2-nitroso-3,5-dinitrothiophen is formed. No pure compounds were isolated.

EXPERIMENTAL

Analytical and spectroscopic data for new compounds are available in Supplementary Publication No. SUP 21591 (3 pp.).*

3-Amino-2-nitrobenzo[b]*thiophens* (5a—c).—These were prepared by heating 3-bromo-2-nitrobenzo[*b*]thiophen [6] with the appropriate amine in excess on a water-bath. They were purified by column chromatography (silica gel; benzene as eluant) (see Supplementary Publication, Table 1).

Photolysis of the 3-Amino-2-nitrobenzo[b]*thiophen Derivatives* (5).—A 100 W medium-pressure Hanovia mercury lamp with a Pyrex filter was employed. 0.002M-Solutions in 10% aqueous methanolic N-hydrochloric acid were irradiated. In each case the photolysate was evaporated under reduced pressure; t.l.c. indicated *ca.* seven components. The starting material and side products were removed by basifying the photolysate and extracting with chloroform. The aqueous layer was neutralised with dilute hydrochloric acid and extracted with chloroform. The yellow solid obtained after evaporation was finally purified by preparative t.l.c. with benzene as eluant. The product, m.p. 160—161° (lit.,[13] 168°) was benzo[*b*]thiophen-2,3-quinone 2-mono-oxime (6b).

The aqueous layer of the neutralised solution was evaporated and the product was recrystallised from water to give orange needles of the sodium salt of compound (6a),[14] m.p. 245° (decomp.). The relative amounts of (6a) and (6b) are shown in the Table; in addition, thioindigo (<5%) was isolated in each case.

3-Benzylamino-2-nitrobenzo[b]*thiophen Derivatives* (6c—e). These were prepared by treating 3-bromo-2-nitrobenzo[*b*]-thiophen [6] with the appropriate amine in excess at room temperature (see Supplementary Publication, Table 1).

Reaction of 3-Benzylamino-2-nitrobenzo[b]*thiophen* (6c) *with Methanolic Sodium Hydroxide.*—A mixture of the benzothiophen (2.84 g, 0.01 mol) and sodium hydroxide (2 g) in dry methanol (20 ml) was heated under reflux for 4 h. The mixture was neutralised with dilute hydrochloric acid and the product was filtered off; yield 1.6 g (60%); m.p. 145—150°. Brief treatment of this material with boiling water and recrystallisation from ethanol afforded needles of *2-phenyl*[1]*benzothieno*[2,3-d]*imidazole N-oxide* (4a) (1.4 g, 53%), m.p. 149—151° (see Supplementary Publication, Table 2).

1-Benzoyloxy-2-phenyl[1]*benzothieno*[2,3-d]*imidazole* (2b; N·OBz *for* NH).—A mixture of the imidazole derivative (4a) (100 mg, 0.3 mmol), benzoyl chloride (1.12 g), and pyridine (0.3 ml) was heated at *ca.* 90 °C for 0.5 h. After addition of water, the resultant oil was extracted with ether; the extract was washed with dilute sodium hydrogen carbonate solution, then dilute hydrochloric acid, and finally with water. Evaporation of the extract left a red solid (70 mg, 50%), which was recrystallised from ethyl acetate to provide red *needles* (40 mg, 30%), m.p. 174° (see Supplementary Publication, Table 2).

Reduction of 2-Phenyl[1]*benzothieno*[2,3-d]*imidazole N-Oxide* (4a).—A mixture of the *N*-oxide (200 mg, 0.6 mmol) and zinc dust (190 mg, 2.85 mg atom) was heated at 240 °C for 2 h, allowed to cool, and extracted with warm ethanol. The ethanol was decanted and the residue was washed with dilute hydrochloric acid; the remaining solid was dissolved in ethanol and the solution was evaporated. The product crystallised from ethanol–benzene to give *2-phenyl*[1]*benzothieno*[2,3-d]*imidazole* (2b) as a solid (60 mg, 30%), m.p. 189—190° (decomp.) (see Supplementary Publication, Table 2).

3-Formamido-2-nitrobenzo[b]*thiophen* (6f).—A mixture of acetic formic anhydride (30 ml) [prepared [9] by adding dropwise an equimolar quantity of formic acid (19 ml, 0.5 mol) to acetic anhydride (45.5 ml, 0.5 mol) at 45 °C] and 3-amino-2-nitrobenzo[*b*]thiophen [14] (1.8 g, 9.1 mmol) was heated on a water-bath until all the solid had dissolved. The mixture was left overnight at room temperature, then the yellow material which had separated was recrystallised from ethyl acetate to give the *product* (1.56 g, 78%), m.p. 196—197°, $\nu_{max.}$ 3 250m (NH str.), 2 920w (aldehydic C–H str.), and 1 680s cm^{-1} (C=O str.).

Reduction of 3-Formamido-2-nitrobenzo[b]*thiophen.*—Ammonium chloride (0.7 g) was added to a solution of the amide (1.4 g, 6.3 mmol) in aqueous ethanol (50%; 50 ml); zinc dust (3.5 g) was added to this mixture in portions with stirring. The mixture was heated under reflux for 3 h and was then filtered hot, and the solid was washed with hot ethanol. The filtrate was evaporated; t.l.c. (1.2 g) indicated that it contained eight components. The residue was triturated with acetone to leave an insoluble purple solid (70 mg, 6%), which was recrystallised from acetone to give [1]benzothieno[2,3-*d*]imidazol-2(3*H*)-one (8), m.p. 250° (decomp.) (see Supplementary Publication, Table 2). No other pure compounds were isolated.

Thiophen Derivatives (9a—c).—*2-Piperidino-* (9a) and *2-benzylamino-* 3,5-*dinitrothiophen* (9b) were prepared by

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue

[11] *Cf.* R. S. Goudie and P. N. Preston, *J. Chem. Soc.*, 1971, 1139.

[12] *Cf.* D. W. Russell, *J. Medicin. Chem.*, 1967, 984; D. J. Neadle and R. J. Pollitt, *J. Chem. Soc.* (*C*), 1969, 2127; R. S. Davidson, S. Korkut, and P. R. Steiner, *Chem. Comm.*, 1971, 1052.

[13] Badische Anilin and Soda Fabrik, Ger. P., 213,458, 1906; *cf.* B.P. 26,190, 1960 (*Chem. Abs.*, 1907, **1**, 2838).

[14] G. Van Zyl, C. J. Bredeweg, R. H. Rynbrandt, and D. C. Neckers, *Canad. J. Chem.*, 1966, **44**, 2283.

adding the appropriate amine dropwise to a cold solution of 2-bromo-3,5-dinitrothiophen [15] in chloroform. The 2-(*carboxymethylamino*)-*derivative* (9c) was prepared by the general procedure of Sanger [16] (see Supplementary Publication, Table 1). No pure products were obtained when (9a) was irradiated with u.v. light (as described earlier; both acidic and neutral solutions were employed).

Thermolysis and Photolysis of 2-(*Carboxymethylamino*)-3,5-*dinitrothiophen* (9c).—The amino-acid (9c) (0.8 g, 3.2 mmol) was heated under reflux in nitrobenzene (24 ml) for 5 h. The solution became black and a black solid separated, which was filtered off and extracted with hot acetone. Nitrobenzene was evaporated from the filtrate under reduced pressure, and the resultant syrup was extracted with acetone. The extracts were combined and evaporated under reduced pressure. The black solid (600 mg, 75% by weight) gave a yellow solution when extracted with hot water. The solid obtained by evaporation was further purified by preparative t.l.c. and recrystallised from benzene to give 2-*amino*-3,5-*dinitrothiophen* (30 mg, 5%), m.p. 165° (decomp.), $\nu_{max.}$ 3 350m (NH str.), 3 270m (NH str.), 3 190 and 3 110m, broad, 1 610s, 1 550s, 1 530s, 1 490s, 1 410s, 1 350m, 1 050s, 750m, and 730s cm^{-1} (Found: M^+, 188.9841. $C_4H_3N_3O_4S$ requires M, 188.9845).

When the acid (9c) was heated in admixture with acid-washed sand at 200 °C for 4 h a black tar was obtained from which no pure products were isolated. Neither did we isolate pure products from u.v. irradiation of the acid (9c) in either 11N-hydrochloric acid or aqueous 5% sodium hydrogen carbonate, despite the fact that colour changes from yellow to green and from violet to yellow, respectively, were observed.

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[15] *Cf.* C. D. Hurd and K. L. Kreuz, *J. Amer. Chem. Soc.*, 1952, **74**, 2965.
[16] F. Sanger, *Biochem. J.*, 1946, **39**, 507.