Synthesis of 2-Substituted Isothiazolopyridin-3-ones

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The synthesis of some 2-substituted derivatives **1-4** of all four isomeric isothiazolopyridin-3-ones is described. Several novel 1,2-dithiolopyridin-3-ones and 3-thiones were prepared as intermediates.

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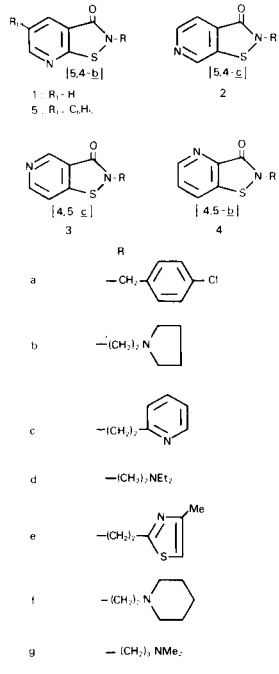
Although numerous 1,2-benzisothiazol-3-ones are known (1,2), examples of isothiazol-3-ones fused to heterocyclic rings are relatively scarce in the literature. All three thienoisothiazol-3-one 1,1-dioxides have recently been described (3,4), but the only pyrido analogues reported to date are some substituted isothiazolo[5,4-*b*]pyridin-3-ones, disclosed (5) whilst the present work was in progress.

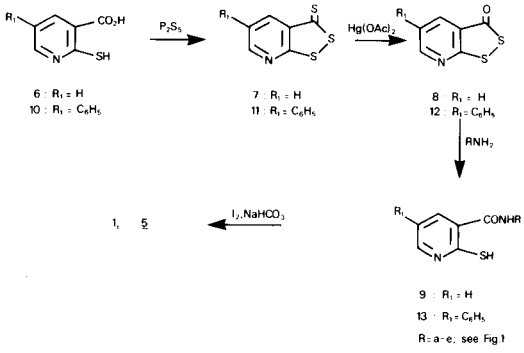
Fig 1
Substituted Isothiazolopyridin-3-ones



This paper details the synthesis of novel 2-substituted derivatives **1-4** of all four isomeric isothiazolopyridin-3-ones (Figure 1). In one series 5-phenyl derivatives **5** were also obtained. The general approach differs from the previously published work (5) on the [5,4-*b*] system in that 1,2-dithiolopyridin-3-ones and 3-thiones are employed as intermediates. Data for the compounds prepared are collected in Tables 1-4.

Our initial investigations were directed towards the preparation of **8** and its conversion into the isothiazolo[5,4-*b*]-pyridin-3-one **1a** (Scheme 1), an approach based on known reactions (6,7,8) of benzo analogues related to **8** and **9**.

Scheme 1



The starting material chosen was the readily accessible (9) 2-mercaptopyridin-3-carboxylic acid **6**, which on treatment with phosphorus pentasulphide gave 1,2-dithiolo[5,4-*b*]-pyridin-3-thione **7**. Reaction of this compound with mercuric acetate (10) yielded the oxo analogue **8** which gave the amide **9a** when heated with 4-chlorobenzylamine. Ring-closure of **9a** to **1a** was achieved by oxidation with iodine in the presence of sodium bicarbonate. Similarly, compounds **1b** and **1c** were prepared from **8** and the appropriate amine *via* the amides **9b** and **9c**. Aniline, however, would not react with **8**, even in high boiling solvents.

The route shown in Scheme 1 was also applied to the preparation of the 5-phenyl analogues **5d** and **5e** *via* intermediates **11** and **12**. Isolation of the 2-mercaptonicotinamides **13d** and **13e** was found to be unnecessary. 5-Phenyl-2-mercaptonicotinic acid (**10**) was synthesized by the method of Schmidt and Kubitzek (11).

A similar sequence of reactions yielded compounds in the isomeric series **2-4** (Table 1). The 1,2-dithiolopyridin-3-ones (**14-16**) were obtained from the corresponding 3-thiones (**17-19**) and converted in two steps into the required isothiazolopyridines (**2-4**) without isolation of the intermediate carboxamides. Compound **17** and the known (12) thione **19** were prepared from the appropriately substituted mercaptopyridine carboxylic acids and phosphorus pentasulphide. Compound **18** was synthesized from 4-hydroxypyridine-3-carboxylic acid (13) as previously described (14).

Table 1

Analytical and Spectral Data of 2-Substituted Isothiazolopyridin-3-ones

Compound	Mp °C Solvent (a)	Yield % (b)	Formula	Analysis % Found/(Calcd.) C	H	N	S	IR cm^{-1} (c)	PMR (δ) (d)
1a	160-162 A	35	$C_{13}H_9ClN_2OS$	56.20 (56.52	3.37 3.26	10.09 10.15	11.31 11.59)	1660	5.00 (s, 2H), 7.30 (s, on dd, 5H), 8.30 (dd, H, J = 8 and 2), 8.70 (dd, J = 6 and 2)
1b	67-69 A	67	$C_{12}H_{15}N_3OS$	57.85 (57.80	6.15 6.06	16.79 16.85	12.81 12.86)	1650	1.70 (m, 4H), 2.70 (m, 6H), 3.98 (t, 2H, J = 5), 7.48 (dd, H, J = 8 and 5), 8.30 (dd, H, J = 8 and 2), 8.85 (dd, H, J = 5 and 2)
1c	188-190 A	61	$C_{13}H_{13}N_3OS$	60.18 (60.20	5.16 5.05	16.11 16.20	12.19 12.36)	1655	3.20 (t, 2H, J = 6), 4.33 (t, 2H, J = 6), 7.30 (m, 4H), 8.50 (m, 3H)
5d	85-87 B	61	$C_{18}H_{21}N_3OS$	65.97 (66.02	6.57 6.46	12.84 12.83	9.74 9.97)	1650	1.05 (t, 6H, J = 7), 2.70 (m, 6H), 3.97 (t, 2H, J = 6), 7.50 (m, 5H), 8.36 (d, H, J = 2), 8.90 (d, H, J = 2)
5e	115-116 B + C	29	$C_{18}H_{15}N_3OS_2$	60.81 (61.16	4.67 4.78	11.77 11.89	18.27 18.14)	1670	2.45 (s, 3H), 3.40 (t, 2H, J = 7), 4.35 (t, 2H, J = 7), 6.72 (s, H), 7.50 (m, 5H), 8.40 (d, H, J = 2), 8.90 (d, H, J = 2)
2b	75-79 B	22	$C_{12}H_{15}N_3OS$	57.31 (57.86	6.28 6.06	16.99 16.85	12.81 12.86)	1640	1.82 (m, 4H), 2.70 (m, 6H), 4.07 (t, 2H, J = 6), 7.88 (d, H, J = 6), 8.62 (d, H, J = 6), 8.97 (s, H)
2f	101-103 B + C	29	$C_{13}H_{17}N_3OS$	59.49 (59.28	6.60 6.51	15.80 15.96	12.11 12.17)	1645	1.60 (m, 6H), 2.55 (m, 6H), 4.05 (t, 2H, J = 6), 7.90 (dd, H, J = 5 and 1), 8.60 (d, H, J = 5), 8.96 (s, H)
3b	84-85 B	32	$C_{12}H_{15}N_3OS$	57.71 (57.80	6.16 6.06	16.81 16.85	12.62 12.86)	1655	1.78 (m, 4H), 2.70 (m, 6H), 4.00 (t, 2H, J = 6), 7.52 (d, H, J = 6), 8.60 (d, H, J = 6), 9.14 (s, H)
3f	100-101 B	38	$C_{13}H_{17}N_3OS$	59.36 (59.28	6.70 6.51	15.93 15.96	12.46 12.17)	1655	1.58 (m, 6H), 2.55 (m, 6H), 4.00 (t, 2H, J = 6), 7.50 (d, H, J = 6), 8.60 (d, H, J = 6), 9.17 (s, H)
4b	105-107 B + C	85	$C_{12}H_{15}N_3OS$	57.64 (57.80	6.01 6.06	16.79 16.85	13.08 12.85)	1650	1.78 (m, 4H), 2.80 (m, 6H), 4.06 (t, 2H, J = 5), 7.40 (dd, H, J = 8 and 4), 8.00 (dd, H, J = 8 and 2), 8.65 (dd, H, J = 4 and 2)
4g	59-60 D	27	$C_{11}H_{15}N_3OS$	55.85 (55.67	6.39 6.37	17.45 17.70	13.47 13.51)	1660	2.25 (m, 10H), 4.00 (t, 2H, J = 7), 7.50 (dd, H, J = 8 and 4), 7.95 (dd, H, J = 8 and 2), 8.70 (dd, H, J = 4 and 2)

(a) Recrystallisation solvents were as follows: A = ethanol, B = diisopropyl ether, C = dichloromethane, D = diethyl ether, E = *n*-propanol. (b) Yields quoted are for recrystallized material and are based on the preceding, isolated intermediate. (c) Potassium bromide disc spectra. The carbonyl frequency is given. (d) Spectra were run in deuteriochloroform solution, with TMS as internal reference, 60 MHz unless otherwise indicated. Coupling constants are reported in Hz; chemical shifts quoted in the case of multiplets were measured from the approximate centre.

14 X = O
17 X = S

15 X = O
18 X = S

16 X = O
19 X = S

All the isothiazolopyridin-3-ones prepared, except those in the [4,5-*b*] series, were found to be potent inhibitors of collagen- and ADP-induced platelet aggregation in human platelet-rich plasma *in vitro* (15).

EXPERIMENTAL

Melting points were determined on a Reichert Thermopan apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Proton magnetic resonance spectra were determined on a Perkin-Elmer-Hitachi R24A spectrometer (60 MHz) or a Brücker WP 80S (80.13 MHz) instrument using tetramethylsilane as an internal standard. The mass spectra were obtained on an AEI MS6 spectrometer. Solutions of organic compounds were dried over anhydrous magnesium or sodium sulphate and solvents were evaporated under reduced pressure. No attempt was made to optimize yields in the reactions described.

Preparation of 1,2-dithiolopyridin-3-thiones (Table 4).

The following procedure for compound **7** exemplifies the method. 2-Mercaptopyridine-3-carboxylic acid (17.65 g, 0.11 mole) and phosphorus pentasulphide (15.0 g, 0.06 mole) were heated in pyridine (150 ml) under reflux for 2 hours. The reaction mixture was cooled, diluted with water, and the product was filtered off. Recrystallisation from ethanol yielded 1,2-dithiolo[5,4-*b*]pyridine-3-thione (**7**) (7.89 g, 37%) as red needles.

Preparation of 1,2-Dithiolopyridin-3-ones (Table 3).

The following procedure for compound **8** is representative.

To a stirred suspension of mercuric acetate (17.0 g, 0.053 mole) in

Table 2

Analytical and Spectral Data of *N*-Substituted 2-Mercaptonicotinamides (a)

Compound	Mp °C Solvent (b)	Yield % (c)	Formula	Analysis % Found/(Calcd.) C	H	N	S	IR cm^{-1} (d)	PMR (δ) (e)
9a	216-219 A	89	$C_{13}H_{11}ClN_2OS$	55.95 (56.00	3.99 3.98	10.11 10.05	11.78 11.50)	1640	(DMSO-d_6) 4.60 (d, 2H, J = 6), 7.01 (dd, H, J = 8 and 6), 7.40 (s, 4H), 7.98 (dd, H, J = 6 and 2), 8.53 (dd, H, J = 8 and 2), 11.22 (t, H, J = 6), 14.00 (broad s, H)
9b	202-205 A	67	$C_{12}H_{17}N_3OS$	57.22 (57.37	6.85 5.77	16.84 16.73	12.96 12.75)	1650	(DMSO-d_6) 1.66 (m, 4H), 2.58 (m, 6H), 3.38 (q, 2H, J = 6) [+ D_2O, t, J = 6], 7.00 (dd, H, J = 8 and 6), 8.00 (dd, H, J = 6 and 2), 8.50 (dd, H, J = 8 and 2), 10.86 (t, H, J = 6) [D_2O exchangeable], 11.36 (s, H) [D_2O exchangeable]
9c	188-190 A	61	$C_{13}H_{13}N_3OS$	60.18 (60.20	5.16 5.05	16.11 16.20	12.19 12.37)	1650	(DMSO-d_6) 3.03 (t, 2H, J = 6), 3.78 (q, 2H, J = 6), 7.20 (m, 3H), 7.65 (m, H), 7.95 (m, H), 8.50 (m, 2H), 10.86 (t, H, J = 6), 13.90 (broad s, H)

(a) Compounds **9a-c** probably exist in equilibrium with the corresponding 1*H*-1,2-dihydro-2-thione tautomer. (b) Recrystallisation solvents were as follows: A = ethanol, B = diisopropyl ether, C = dichloromethane, D = diethyl ether, E = *n*-propanol. (c) Yields quoted are for recrystallized material and are based on the preceding, isolated intermediate. (d) Potassium bromide disc spectra. The carbonyl frequency is given. (e) Spectra were run with TMS as internal reference, 60 MHz unless otherwise indicated. Coupling constants are reported in Hz; chemical shifts quoted in the case of multiplets were measured from the approximate centre.

Table 3

Analytical and Spectral Data of 1,2-Dithiolopyridin-3-ones

Compound	Mp °C Solvent (a)	Yield % (b)	Formula	Analysis % Found/(Calcd.) C	H	N	S	IR cm^{-1} (c)	PMR (δ) (d)
8	97-99 A	70	$C_6H_3NOS_2$	42.45 (42.59	1.85 1.79	8.32 8.28	37.70 37.89)	1670	7.37 (dd, H, J = 8 and 4), 8.23 (dd, H, J = 8 and 2), 8.83 (dd, H, J = 4 and 2)
12	149-150.5 E	80	$C_{12}H_7NOS_2$	59.18 (58.75	2.99 2.88	5.89 5.71	26.56 26.14)	1678	7.40 (m, 5H), 8.18 (d, H, J = 2), 8.90 (d, H, J = 2)
14	142-142.5 A	63	$C_6H_3NOS_2$	42.84 (42.59	1.78 1.79	8.31 8.28	37.89 37.89)	1640	(deuteriochloroform + DMSO-d_6) 7.75 (d, H, J = 6), 8.60 (d, H, J = 6), 9.05 (s, H)
15	175-176 A	93	$C_6H_3NOS_2$	42.52 (42.59	1.97 1.79	8.30 8.28	37.74 37.89)	1650	(DMSO-d_6) 8.44 (d, H, J = 6), 8.88 (d, H, J = 6), 9.30 (s, H)
16	133-135 A	69	$C_6H_3NOS_2$	42.64 (42.59	1.76 1.79	8.17 8.28	37.95 37.89)	1650	(deuteriochloroform + DMSO-d_6) 7.65 (dd, H, J = 8 and 4), 8.20 (dd, H, J = 8 and 2), 8.85 (dd, H, J = 4 and 2)

(a) Recrystallisation solvents were as follows: A = ethanol, B = diisopropyl ether, C = dichloromethane, D = diethyl ether, E = *n*-propanol. (b) Yields quoted are for recrystallized material and are based on the preceding, isolated intermediate. (c) Potassium bromide disc spectra. The carbonyl frequency is given. (d) Spectra were run in deuteriochloroform solution, with TMS as internal reference, 60 MHz unless otherwise indicated. Coupling constants are reported in Hz; chemical shifts quoted in the case of multiplets were measured from the approximate centre.

glacial acetic acid (200 ml) was added a solution of the thione **7** (5.0 g, 0.025 mole) in chloroform (100 ml) and the mixture was stirred at room temperature for 3 days. Celite (*ca.* 25 g) was added, the mixture was filtered, and the filtrate was evaporated. The residue was treated with dichloromethane (*ca.* 100 ml), undissolved solid was removed by filtration, and the filtrate was evaporated. The latter process was repeated several times. The residue was then taken up in dichloromethane (20 ml) and the solution was filtered through a short column of silica gel using dichloromethane as eluant. Subsequent recrystallisation of the product from ethanol yielded 1,2-dithiolo[5,4-*b*]pyridin-3-one (**8**) (3.21 g, 70%) as pale yellow needles.

Preparation of *N*-Substituted-2-mercaptonicotinamides (Table 2).

The procedure for compound **9a** is typical.

A solution of **8** (1.50 g, 0.009 mole) and *p*-chlorobenzylamine (1.30 g, 0.009 mole) in ethanol (50 ml) was heated under reflux for 4 hours and the reaction mixture was filtered while still hot. When cool, the filtrate afforded yellow crystals (2.2 g, 89%) of *N*-(*p*-chlorobenzyl)-2-mercaptonicotinamide (**9a**).

Preparation of Isothiazolopyridin-3-ones (Table 1).

The compounds **1a**, **1b** and **1c** were obtained from isolated

Table 4

Analytical and Spectral Data of 1,2-Dithiolopyridin-3-thiones

Compound	Mp °C Solvent (a)	Yield % (b)	Formula	Analysis % Found/(Calcd.) C	H	N	S	PMR (δ) (c)
7	185-186 A	37	$C_6H_3NS_3$	38.95 (38.70	1.64 1.63	7.54 7.56	51.91 51.91)	(DMSO-d_6, 80 MHz) 7.63 (dd, H, J = 8 and 4.5), 8.40 (dd, H, J = 8 and 2), 8.99 (d, H, J = 4.5 and 2)
11	135 A	47	$C_{12}H_7NS_3$	54.93 (55.14	2.68 2.70	5.22 5.36	36.64 36.80)	7.50 (m, 5H), 8.48 (d, H, J = 2), 9.03 (d, H, J = 2)
17	150-151 A	40	$C_6H_3NS_3$	38.90 (38.70	1.38 1.63	7.50 7.56	51.62 51.91)	(DMSO-d_6, 80 MHz) 7.86 (d, H, J = 5), 8.65 (d, H, J = 5), 9.48 (s, H)
18	201-203 A	20	$C_6H_3NS_3$					Known compound (Reference 14) (lit mp 206-208°)
19	174-176 A	61	$C_6H_3NS_3$					Known compound (Reference 12) (lit mp 178°)

(a) Recrystallisation solvents were as follows: A = ethanol, B = diisopropyl ether, C = dichloromethane, D = diethyl ether, E = *n*-propanol. (b) Yields quoted are for recrystallized material and are based on the preceding, isolated intermediate. (c) Spectra were run with TMS as internal reference. Coupling constants are reported in Hz; chemical shifts quoted in the case of multiplets were measured from the approximate centre.

N-substituted mercaptonicotinamides (Table 2), as exemplified by the preparation of **1a** (see below).

Other compounds in Table 1 were obtained directly from the appropriate amine and 1,2-dithiolopyridin-3-one (Table 3) *via* an intermediate *N*-substituted mercaptopyridine-carboxamide, prepared in the manner described for **9a** above but not isolated. The intermediate carboxamide was then cyclized *in situ* by the procedure described below for **1a**.

A stirred mixture of **9a** (1.50 g, 0.0056 mole) and sodium bicarbonate (1.0 g, 0.0094 mole) in ethanol (50 ml) was treated portionwise with iodine (1.27 g, 0.005 mole) over a period of 1.5 hours. The solvent was evaporated and the residue was partitioned between water and dichloromethane. The organic layer was washed with water, dried and evaporated to dryness. The residue was purified by column chromatography on alumina (*ca.* 30 g) using dichloromethane as eluant. Subsequent recrystallisation of the product from ethanol gave 2-(*p*-chlorobenzyl)isothiazolo[5,4-*b*]pyridin-3-one (**1a**) as colourless needles (0.52 g, 35%); ms: M^+ at 276.01249 (calcd. for $C_{13}H_9ClN_2OS$ is 276.012407).

3-Cyano-2-mercapto-5-phenylpyridine.

This compound was prepared from 2-phenylmalondialdehyde (16) and 2-cyanothioacetamide in 74% yield, using the method of Schmidt and Kubitzek (11), mp 205-209° (from acetone); ir (potassium bromide): 2230 cm^{-1}; nmr (DMSO-d_6): δ 7.5 (m, 5H), 8.2 (d, H, J = 2 Hz), 8.45 (d, H, J = 2 Hz), 15.5 (br s, H).

Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.89; H, 3.80; N, 13.30; S, 15.1. Found: C, 67.99; H, 3.58; N, 13.50; S, 15.02.

5-Phenyl-2-mercaptonicotinic Acid (**10**).

Hydrolysis of 3-cyano-2-mercapto-5-phenylpyridine with 48% hydrogen bromide (11) gave the acid **10** in 64% yield, mp 268-270°; ir (potassium bromide): 1680 cm^{-1}; nmr (DMSO-d_6): δ 7.5 (m, 5H), 8.43 (d, H, J = 2 Hz), 8.73 (d, H, J = 2 Hz), 14.7 (br s, H).

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