The Chemistry of *o*-Phenylene Di-isothiocyanate. Part 2.[1] Reactions with Enamines, an Ynamine, and Some Reactive Methylene Compounds

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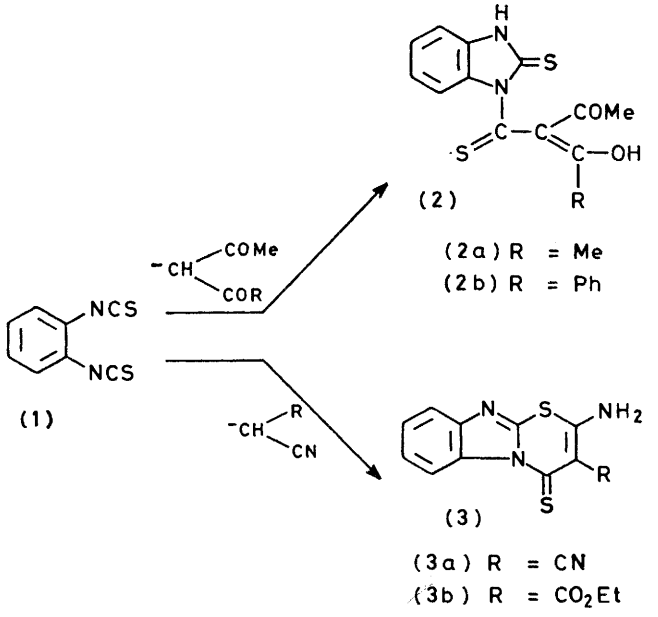
Reactions of *o*-phenylene di-isothiocyanate with activated methylene compounds have given, with acetylacetone and benzoylacetone, 1-substituted thiocarbonyl benzimidazoline-2-thiones and with malononitrile and ethyl cyanoacetate 3,4-dihydro-2*H*-benz[*d*]imidazol[2,1-*b*][1,3]thiazines. Enamines, as exemplified by 1-pyrrolidin-1-ylcyclohexene, react with the di-isothiocyanate and give benzimidazo[2,1-*b*][1,3]benzothiazine-11-thiones or substituted thiocarbonyl benzimidazoline-2-thiones. An ynamine, 1-diethylaminoprop-1-yne, reacted with *o*-phenylene di-isothiocyanate to give 2-diethylamino-3-methylbenzimidazo[2,1-*b*][1,3]thiazine-4-thione.

o-PHENYLENE DI-ISOTHIOCYANATE (1) was first reported by Billeter and Steiner in 1887.[2] It is now fairly readily available[3] and we report here some further aspects of its chemistry.

RESULTS AND DISCUSSION

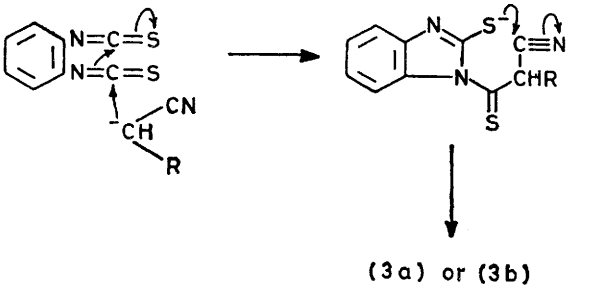
Reactions with Reactive Methylene Compounds (*Scheme* 1).—Michael, in 1887,[4] first demonstrated that thio-



SCHEME 1

anilides could be synthesised from the reaction of sodiomalonic ester upon mustard oils. Later investigators[5] have used a variety of activated methylene compounds.

We found that the carbanions produced from acetylacetone and benzoylacetone, when treated with the di-isothiocyanate (1) in equimolar amounts in dry ether, gave the substituted benzimidazoline-2-thiones, (2a) and (2b), respectively. When activated methylene compounds were used containing a cyano-group, *e.g.* malononitrile and ethyl cyanoacetate, we found that a further cyclisation step took place to yield the imidazothiazines, (3a) and (3b), respectively. The propensity of isothiocyanates to undergo nucleophilic additions together with the formation of a thiolate ion proximal to a nitrile suggest the following reaction path.



Reactions with Enamines and an Ynamine (*Scheme* 2).—Numerous examples of the reactions of isothiocyanates with enamines are known,[5,6] some showing their useful application, after a cyclisation reaction, to the synthesis of heterocycles,[7] but no work appears to have been done with 1,2-di-isothiocyanates.

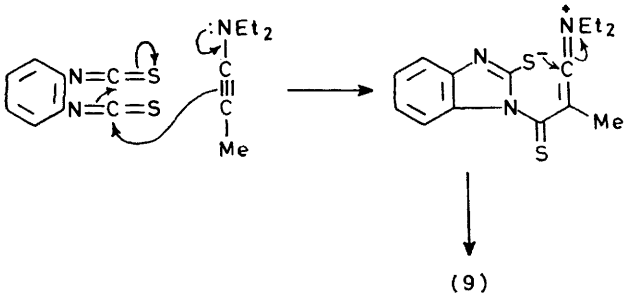
It was now expected that reaction of the di-isothiocyanate (1) with a suitable enamine would take place on a 1 : 1 basis. This was borne out in practice. With the di-isothiocyanate (1) and 1-pyrrolidin-1-ylcyclohexene in dry ether, reaction and ring closure took place and thus produced the hexahydrobenzimidazobenzothiazine (4). Methylation yielded the methylthiotetrahydrobenzothiazine (5), and acid treatment of (4) gave the parent tetrahydrobenzimidazobenzothiazine (6). The related cyclopentadienothiazine (10) was obtained under the same reaction conditions from the reaction of the di-isothiocyanate (1) and 1-morpholinocyclopentene, morpholine being lost during the course of the reaction.

Reinhoudt[8] has reported on the synthesis of certain heteroaromatic compounds substituted with a pyrrolidin-1-yl group and has shown, using 3-pyrrolidin-1-ylthiophens, that they can undergo the normal type of enamine reaction. We took 2-phenyl-4-pyrrolidin-1-ylthiophen as a typical example and found that on reaction with the di-isothiocyanate (1) in dry ether we obtained the benzimidazothienothiazine (7) in reasonable yield. 3-Pyrrolidin-1-ylbenzo[*b*]furan[9] reacted similarly with the di-isothiocyanate (1), to yield the thiazine (8).

Viehe and co-workers[10] have pioneered much of the chemistry of ynamines, but reactions with 1,2-di-isothiocyanates have not been reported.

1-Diethylaminoprop-1-yne, when treated with one equivalent of the di-isothiocyanate (1), gave the diethyl-

amino-methylbenzimidazothiazine (9) as orange needles presumably by the following mechanism.



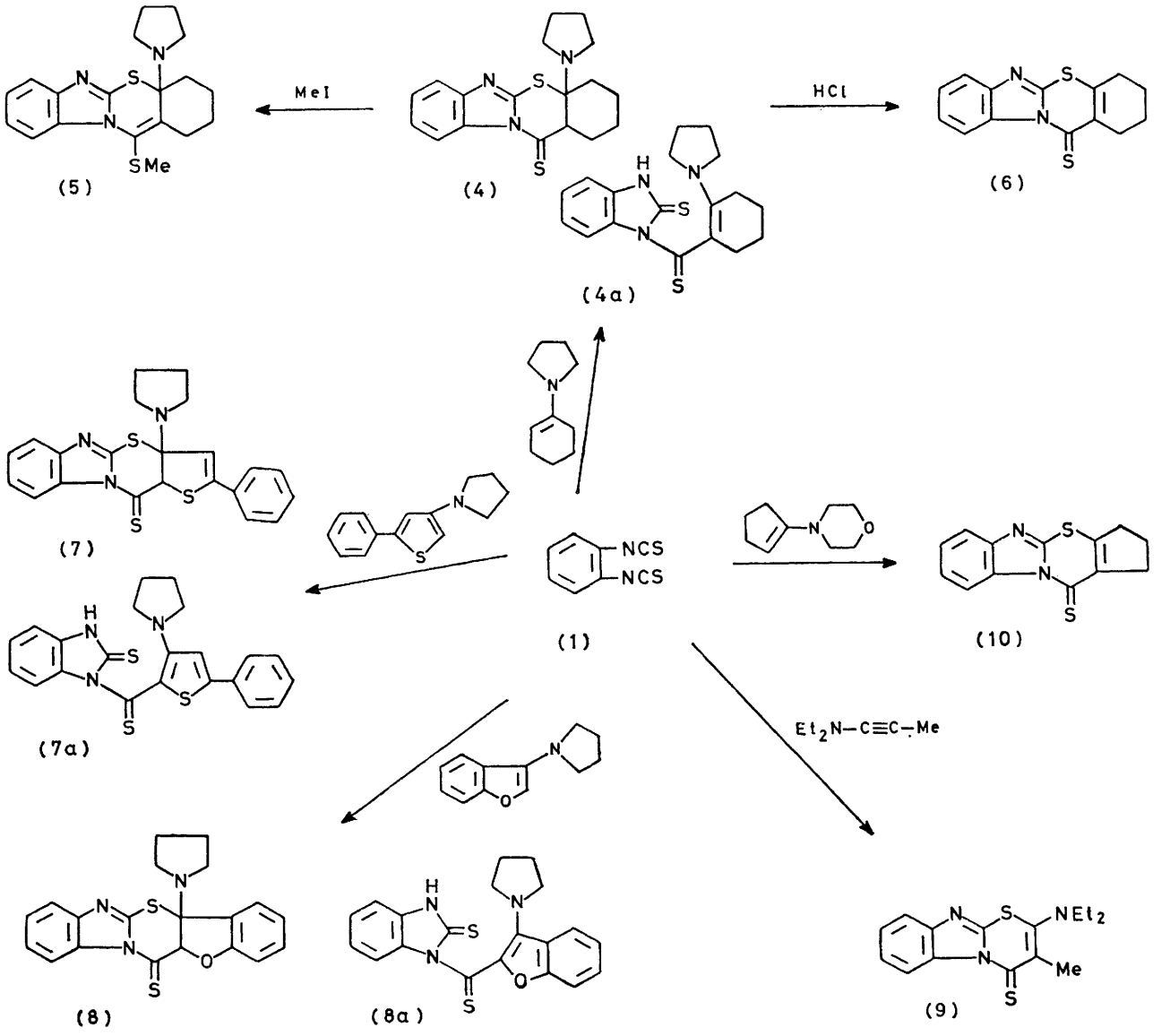
(9)

It will be noted (Experimental section) that whereas compounds (3a), (3b), (10), (6), and (9) show a low-field resonance in the aromatic n.m.r. region, compounds (4), (7), and (8) do not show any signal at such low field. We attribute the low-field resonance in the first five compounds to the deshielding by the proximal C=S group. Further studies on compound (8), chosen because of its greater solubility, show that the ^{13}C n.m.r. spectrum in dimethyl sulphoxide solution exhibits only two high-field (aliphatic like) carbons at δ 25.71 and 55.22 and 16 low field (aromatic and C=S) carbons from δ 109.27 to 167.33 which is consistent with structure (8a) but not for (8). If we are permitted to apply the same reasoning then the other compounds (4) and (7) would be better represented by (4a) and (7a).

Many of the derivatives obtained from the di-isothiocyanate are now available for extensive exploitation as intermediates to more complex heterocycles.

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian HA 100 spectrometer ($SiMe_4$ as internal standard). Mass spectra were measured with a Hitachi RMU 6E or A.E.I. MS9



SCHEME 2

spectrometer. M.p.s were determined with a Reichert hot-stage apparatus and were uncorrected.

4-Hydroxy-3-[(2-thioxo-2,3-dihydrobenzimidazol-1-yl)-thiocarbonyl]pent-3-en-2-one (2a).—50% Oil-dispersed sodium hydride (0.14 g, 0.003 mol) was added to a solution of acetyl acetone (0.3 ml, 0.003 mol) in dry ether (10 ml). The resultant suspension was stirred at ambient temperature for 2 h before the addition of a filtered solution of the di-isothiocyanate (1) (0.58 g, 0.003 mol) in dry ether (20 ml) and then stirred for a further 2 days. The precipitated solid was filtered off, washed with a little ether, then dissolved in water. The filtered aqueous solution was acidified with 2N hydrochloric acid and the precipitated red *product* was filtered off and dried (0.55 g, 63%), m.p. 143 °C; re-formed as needles, m.p. 330 °C (decomp.) (Found: C, 50.6; H, 4.0; N, 8.9; S, 20.6. $C_{13}H_{12}N_2O_2S_2 \cdot H_2O$ requires C, 50.3; H, 4.5; N, 9.0; S, 20.6%); δ[$CDCl_3$] 2.1 (6 H, s, Me), 7.2 (3 H, m, H-4—6), and 8.0 (1 H, m, H-7).

Similarly prepared was (2b) using benzoylacetone in 65% yield, m.p. 120 °C (Found: C, 61.2; H, 3.9; N, 7.8; S, 17.9. $C_{18}H_{14}N_2O_2S_2$ requires C, 61.0; H, 4.0; N, 7.9; S, 18.1%); *m/e* 336 ($M^+ - H_2O$); we were unable to obtain a satisfactory n.m.r. spectrum, since it decomposes in solution.

2-Amino-4-thioxo-3,4-dihydro-2H-benzimidazo[2,1-b]-[1,3]thiazine-3-carbonitrile (3a).—50% Oil-dispersed sodium hydride (0.28 g, 0.006 mol) was added to a solution of malononitrile (0.4 g, 0.006 mol) in dry ether (30 ml) and the suspension was stirred at ambient temperature for 24 h. A filtered solution of the di-isothiocyanate (1) (1.16 g, 0.006 mol) in dry ether (40 ml) was then added, and the mixture was stirred for a further 3 days. The precipitated yellow solid was filtered off, washed with ether, then partitioned between 2N sodium hydroxide and dichloromethane. The separated aqueous phase was acidified and the precipitated *product* was filtered off (0.6 g, 39%), m.p. 285 °C (Found: C, 50.1; H, 2.5; N, 21.0. $C_{11}H_6N_4S_2 \cdot 0.33H_2O$ requires C, 50.1; H, 2.5; N, 21.2%); *m/e* 258 (M^+); δ[$(CD_3)_2SO$] 7.2—7.7 (3 H, m, H-7, 8, and 9), and 9.3 (3 H, m, exchangeables + H-6).

Similarly prepared was (3b) using ethyl cyanoacetate except that the solid *product* was obtained in 14% yield from the extraction of the acidified aqueous phase with dichloromethane, removal of the solvent and trituration with ethyl acetate, m.p. 180 °C (decomp.) (Found: C, 50.8; H, 3.4; N, 13.5; S, 20.7. $C_{13}H_{11}N_3O_2S_2$ requires C, 51.1; H, 3.6; N, 13.8; S, 21.0%); *m/e* 305 (M^+); δ[$(CD_3)_2SO$] 1.3 (3 H, t, Me), 4.3 (2 H, q, CH_2) 7.3—7.7 (3 H, m, H-7—9), 8.4 (2 H, S, NH_3), and 9.3 (1 H, m, H-6).

Typical Procedure for Enamine/Ynamine Reactions.—*6a-Pyrrolidin-1-yl-6a,7,8,9,10,10a-hexahydrobenzimidazo-[2,1-b][1,3]benzo[1,3]thiazine-11-thione* (4).—A solution of 1-pyrrolidin-1-ylcyclohexene (1.1 g, 0.007 3 mol) in dry ether (10 ml) was added to a filtered solution of the di-isothiocyanate (1) (1.4 g, 0.007 3 mol) in dry ether (50 ml) and the mixture stirred for 4 h at ambient temperature. The precipitated *benzothiazine* was collected as yellow prisms (2.1 g, 84%), m.p. 133—134 °C (Found: C, 62.8; H, 6.4; N, 12.5; S, 18.5. $C_{18}H_{21}N_3S_2$ requires C, 63.0; H, 6.1; N, 12.25; S, 18.65%); *m/e* 343 (M^+) and 272 (M^+ — pyrrolidine); δ[$(CD_3)_2SO$] 1.1—2.85 (12 H, m, methylene H), 3.7 (4 H, m, NCH_2), 4.65 (1 H, br, H-10a), and 7.0—7.5 (4 H, m, aromatics).

In a similar manner were prepared: *2-phenyl-3a-pyrrolidin-1-yl-3a,11a-dihydrobenzimidazo[2,1-b]thieno[2,3-e][1,3]thiazine-11-thione* (7), in 61% yield from 2-phenyl-4-pyrrolidin-1-ylthiophen,[8] m.p. 196—202 °C (Found: C, 60.1; H, 4.5; N, 9.2; $C_{22}H_{19}N_3S_3 \cdot H_2O$ requires C, 60.1; H, 4.8; N, 9.5%; *m/e*, M^+ not seen, and 350 (M^+ — pyrrolidine); δ($CDCl_3$) 1.5—2.3 (4 H, m, methylene H), 3.3 (2 H, m, CH_2N), 6.2 (2 H, m, CH_2N), 6.9 (1 H, S, H-3), and 7.0—7.7 (9 H, m, aromatics): *4b-pyrrolidin-1-yl-4b,-12a-dihydrobenzofurano[2,3-e]benzimidazo[2,1-b][1,3]thiazine-12-thione* (8), in 76% yield as bright red prisms from 3-pyrrolidin-1-ylbenzo[*b*]furan,[9] m.p. 167—168 °C (Found: C, 62.8; H, 4.4; N, 10.8; S, 16.9. $C_{20}H_{17}N_3OS_2$ requires C, 63.3; H, 4.5; N, 11.1; S, 16.9%); *m/e* 379 (M^+) and 308 (M^+ — pyrrolidine); δ($CDCl_3$) 1.7—2.5 (4 H, m, pyrrolidine H), 3.4 (2 H, m, CH_2N), 4.1 (2 H, m, CH_2N), and 7.0—8.0 (8 H, m, aromatics): *2-diethylamino-3-methylbenzimidazo[2,1-b][1,3]thiazine-4-thione* (9), in 48% yield as orange needles from 1-diethylaminoprop-1-yne, m.p. 83—84 °C (Found: C, 59.4; H, 5.7; N, 13.7. $C_{15}H_{17}N_3S_2$ requires C, 59.4; H, 5.6; N, 13.9%); *m/e* 303 (M^+); δ($CDCl_3$) 1.3 (6 H, t, *J* 6 Hz, NCH_2Me), 2.55 (3 H, s, Me), 3.45 (4 H, q, *J* 6 Hz, NCH_2), 7.3—8.0 (3 H, m, aromatics), and 9.7 (1 H, m, H-1) : *2,3-dihydro-1H-benzimidazo[2,1-b]-cyclopentadieno[e][1,3]thiazine-10-thione* (10), in 33% yield as orange prisms from 1-morpholinocyclopentene, m.p. 218—220 °C (Found: C, 60.7; H, 4.0; N, 11.0; S, 24.6. $C_{13}H_{10}N_2S_2$ requires C, 60.5; H, 3.9; N, 10.85; S, 24.8%); δ(C_5D_5N) 1.5—1.9 (2 H, m, H-8), 2.65 (2 H, t, *J* 7 Hz, H-9), 2.85 (2 H, t, *J* 7 Hz, H-7), 7.1—7.7 (3 H, m, aromatics), and 9.4 (1 H, d, H-1).

11-Methylthio-6a-pyrrolidin-1-yl-7,8,9,10-tetrahydro-6aH-benzimidazo[2,1-b][1,3]benzothiazine Hydroiodide (5).—Iodomethane (0.95 ml, 0.015 mol) was added to a suspension of (4) (2.55 g, 0.007 5 mol) in dry acetone (70 ml) and the solution was then stirred for 16 h. The precipitated solid was filtered off, washed with acetone, and crystallised from ethanol to give the *benzothiazine* (2.6 g, 72%) as needles, m.p. 211—213 °C (Found: C, 46.7; H, 5.0; N, 8.4; S, 13.5. $C_{19}H_{23}N_3S_2 \cdot HI$ requires C, 47.0; H, 4.9; N, 8.65; S, 13.2%); δ[$(CD_3)_2SO$] 2.0 (3 H, s, SMe), 1.5—2.5 (10 H, br, pyrrolidine-H, and H-8—10), 3.15 (2 H, br, H-7), 4.1—4.8 (4 H, br, NCH_2), 7.1—7.7 (4 H, m, aromatics), and 13.2 (1 H, exchangeable).

7,8,9,10-Tetrahydrobenzimidazo[2,1-b][1,3]benzothiazine (6).—A suspension of (4) (1.6 g, 0.004 7 mol) in 2N hydrochloric acid (20 ml) was boiled for 5 h. After cooling to ambient temperature the crude product was filtered off, washed with water, and recrystallised from DMF (550 mg, 45%) as orange *needles*, m.p. 174—175 °C (Found: C, 61.8; H, 4.5; N, 10.2; S, 23.5. $C_{14}H_{12}N_2S_2$ requires C, 61.8; H, 4.4; N, 10.3; S, 23.5%); *m/e* 272 (M^+); δ($CD_3)_2SO$ + CF_3CO_2H] 1.95 (4 H, br, H-8 and -9), 2.8 (2 H, br, H-10), 2.95 (2 H, br, H-7), 7.5—8.0 (3 H, m, aromatics), and 9.6 (1 H, m, H-1).

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