The Preparation and Properties of Some 2,1-Benzisoxazole and 2,1-Benzisothiazole Derivatives

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A number of 2,1-benzisoxazole and 2,1-benzisothiazole compounds containing alkoxy or amino substituents in the 3-position and carboxy substituents in the 7-position, and potentially capable of valency tautomerism have been synthesized by reduction or oxidation, respectively, of suitable 2-nitro- or 2-aminoisophthalic acid derivatives. Thionation of 2-aminoisophthalic esters gave benzothiazaphosphorine derivatives. A temperature dependent n.m.r. study of the benzisoxazole and benzisothiazole derivatives indicates that in only one case, for methyl 3-methoxy-2,1-benzisothiazole-7-thionocarboxylate is there evidence for tautomerism at 200°.

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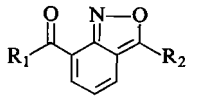
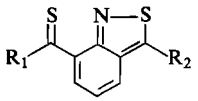
On a synthétisé un certain nombre de dérivés du benzisoxazole-2,1 et du benzisothiazole-2,1 contenant des substituants alkoxy et amino en position 3 et des substituants carboxy en position 7; ces composés qui sont susceptibles de présenter de la tautomérie de valence, ont été respectivement obtenus par réduction ou oxydation des dérivés appropriés des acides nitro-2 ou amino-2 isophtaliques. La thionation des esters de l'acide amino-2 isophtalique donne les dérivés benzothiaphosphorines. On a examiné les spectres r.m.n. des dérivés du benzisoxazole et du benzisothiazole à différentes températures; on n'a trouvé qu'un seul cas, celui du méthoxy-3 benzisothiazole-2,1 thiono-7 carboxylate de méthyle où de la tautomérie de valence existe à 200°. [Traduit par le journal]

2,1-Benzisoxazole (anthranil) derivatives, particularly certain 7-substituted compounds, are of interest in studies on valency tautomerism (1). The ease with which the process occurs, however, appears to depend in some measure on the solvent used (1, 2). To obtain more information on these compounds we have therefore attempted the synthesis of some other 2,1-benzisoxazoles and studied their properties. It was also of interest to compare the properties of such 7-acyl-2,1-benzisoxazoles (**1**) with the corresponding 7-thioacyl-2,1-benzisothiazoles (**2**) to determine the relative effects, if any, of the sulfur and oxygen atoms in the valency tautomerism of the compounds, since the compounds **2**, more so than **1**, parallel the structure of a benzo-1,2-dithiolium derivative (3) which demonstrates magnetic equivalence of substituents on the 3- and thioacyl positions. These comparisons were frustrated in an earlier study (1) by the lability of an aliphatic thione substituent. In this work therefore, studies were directed towards the synthesis of esters and amides possessing the required potential symmetry. The sulfur analogs of these would be expected to be sufficiently stable to provide an adequate comparison.



1

a $R_1 = OH; R_2 = OMe$
b $R_1 = R_2 = OMe$
c $R_1 = R_2 = Me$
d $R_1 = OH; R_2 = NMe_2$
e $R_1 = R_2 = NMe_2$
f $R_1 = OMe; R_2 = NMe_2$
g $R_1 = NMe_2; R_2 = \overset{+}{O}Me$
h $R_1 = O^-; R_2 = \overset{+}{N}HMe_2$

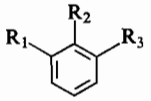


2

a $R_1 = R_2 = OMe$
b $R_1 = R_2 = NMe_2$

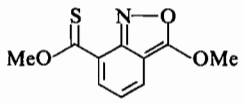
Syntheses were based on two methods, the reduction of *o*-nitrocarbonyl compounds or the oxidation of *o*-amino compounds. While both methods have been used for the conversion of suitable aldehydes and ketones to 2,1-benzisoxazoles (4) and are also applicable to the conversion of suitable thiocarbonyl compounds to 2,1-benzisothiazoles (5), they have not been used for the conversions of *o*-nitro- or *o*-aminoesters or thionoesters to 3-alkoxy-2,1-benzisoxazoles or 2,1-benzisothiazoles. Indeed such compounds appear to be unknown. 3-Amino-2,1-benzisoxazoles are available (6, 7) by reduction of suitable *o*-nitrobenzoic acid derivatives.

Methyl 2-nitroisophthalate (**3***a*) was reduced by stannous chloride in hydrochloric acid to methyl 2-aminoisophthalate (**3***b*). Treatment of this with hydrogen peroxide in acetic acid regenerated **3***a* but with Caro's acid 3-methoxy-2,1-benzisoxazole-7-carboxylic acid (**1***a*) was produced. Hydrolysis of an ester group had obviously accompanied the oxidative cyclization. We were unsuccessful in intercepting the required 2,1-benzisoxazole ester and other reductive methods were unsuccessful. The acid **1***a* treated with diazomethane afforded the desired ester **1***b* which has a structure of the required potential symmetry. The azide **3***c*, prepared from the amine **3***b*, failed to give **1***b* on either thermolysis or photolysis, although a similar reaction succeeded for 2,6-diacetylazidobenzene **3***d*, giving **1***c*.



3

a $R_1 = R_3 = CO_2Me$; $R = NO_2$
b $R_1 = R_3 = CO_2Me$; $R_2 = NH_2$
c $R_1 = R_3 = CO_2Me$; $R_2 = N_3$
d $R_1 = R_3 = COMe$; $R_2 = N_3$
e $R_1 = R_3 = CONMe_2$; $R_2 = NO_2$
f $R_1 = R_3 = CONMe_2$; $R_2 = NH_2$
g $R_1 = R_3 = CSNMe_2$; $R_2 = NO_2$
h $R_1 = R_3 = CSNMe_2$; $R_2 = NH_2$
i $R_1 = R_3 = COSMe$; $R_2 = NO_2$
j $R_1 = R_3 = COSMe$; $R_2 = NH_2$
k $R_1 = R_3 = CS_2Me$; $R_2 = NO_2$



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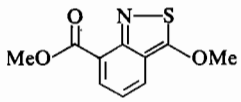
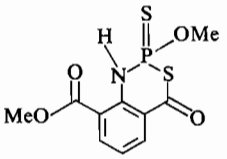


5

Thionation of **1***b* by phosphorus pentasulfide in toluene gave the 2,1-benzisothiazole **2***a* accompanied by the partially thionated compound **4** and the isomeric methyl 3-methoxy-2,1-benzisothiazole-7-carboxylate (**5**). The latter appears to be derived from **2***a* by hydrolysis of the thionoester function on the silica gel chromatogram used in separation but **2***a* appears to be otherwise stable. The ring sulfur in **2***a* is probably derived from the thionoester group in the initially thionated product **4** by valency tautomerism, similarly to a previously described example (1).

We also treated *N,N,N′,N′*-tetramethyl-2-nitroisophthalamide (**3***e*) with stannous chloride in hydrochloric acid. Two products were obtained, 3-dimethylamino-2,1-benzisoxazole-7-carboxylic acid (**1***d*) and the amine **3***f*. No 2,1-benzisoxazole **1***e* could be intercepted and other reductive methods failed to yield the desired product. The acid **1***d* was also converted by diazomethane into methyl 3-dimethylamino-2,1-benzisoxazole-7-carboxylate (**1***f*) but various attempts to form **1***e* from this by suitable chemical conversions were unsuccessful. The compound **1***f* is, however, suitable for study since it is potentially capable of valency tautomerism.

N,N,N′,N′-Tetramethyl-2-nitroisophthalamide (**3***e*) was smoothly thionated to the bisthioamide **3***g* which was reduced with stannous chloride to form a mixture of the desired *N,N*-dimethyl-3-dimethylamino-2,1-benzisothiazole-7-thiocarboxamide (**2***b*) and the amine **3***h* which were separated by fractional crystallization. The amine, as with many such structures (8), could be reoxidized to the benzisothiazole by peracetic acid.



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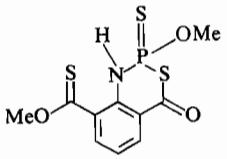

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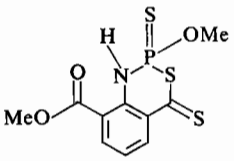

8

Methyl 2-nitroisothiolphthalate (**3***i*), prepared by treatment of 2-nitroisophthaloyl chloride with methanethiol, gave on stannous chloride reduction only methyl 2-aminoisothiolphthalate (**3***j*). No 2,1-benzisoxazole could be intercepted. The ester **3***j* could not be reoxidized to the desired 2,1-benzisoxazole by any method tried. The nitro compound **3***i* was slowly thionated by phosphorus pentasulfide in toluene to yield methyl 2-nitrotetrathioisophthalate **3***k* but this only gave what appears to be a hydrolysis product on attempted reduction. The failure to

effect suitable reduction of **3***k* in contrast to **3***i* or **3***a* is disappointing but it is probable that the nitro group is sterically hindered by the bulky sulfur functions. It is interesting that in contrast to the other compounds, which exhibit a low field displacement of aromatic protons *ortho* to the carbonyl or thiocarbonyl groups because of the electron withdrawing and anisotropic effects, the aromatic protons in **3***k* appear as a singlet.

The direct thionation of methyl 2-aminoisophthalate **3***b* with phosphorus pentasulfide gave two products, both of which contained phosphorus. The analysis, mass spectral data, and n.m.r. of one of these were in accord with the benzothiazaphosphorinethione structure **6**. This structure is analogous to some obtained by Legrand and Losac'h (9) by thionation of *N*-substituted anthranilic esters. The other compound, which was dark green, had one oxygen atom replaced by sulfur. Since a peak at 1700 cm^{-1} in **7**, due to the ester carbonyl frequency, was absent, we tentatively assign to this compound the thionoester structure **7** rather than the isomeric phosphorinedithione structure **8**.

Nuclear magnetic resonance spectra were performed in dimethyl sulfoxide. Earlier work (2) had indicated that this was a satisfactory solvent. Over the temperature range studied (40–200°) the methyl groups in **1***b* were nonequivalent, although some approach of τ values and line broadening was evident. The corresponding 2,1-benzisothiazole **2***a* exhibited coalescence at 200°. For the thioamide **2***b*, at 40° three methyl signals were observed due to the equivalent amine methyls and the nonequivalent thioamidic methyls. At 200° the latter had become equivalent but were still different from the former, two singlets being observed. These results are consistent with values for rotational barriers in thioamides (10). The net result of the alkoxy- or dimethylamino groups on the system appears to be to reduce the ease of tautomerism. The small enhancement by sulfur that is evident by comparison of the compounds **1***b* and **2***a* is expected (11) in view of the generally lower free energy of activation of reactions at sulfur atoms.

While methyl 3-dimethylamino-2,1-benzisoxazole-7-carboxylate (**1***f*) is potentially capable of tautomerism to *N*,*N*-dimethyl-3-methoxy-2,1-benzisoxazole-7-carboxamide (**1***g*), no evidence for this was obtained under the conditions studied. At 40° the amine methyl groups were nonequivalent but coalescence of their signals occurred on warming to 120°. At 200° only two signals, due to the amine and ester methyls, were apparent. It is interesting in that whereas the amine methyls in **1***f* were nonequivalent at room temperature, those in the 2,1-benzisothiazole **2***b* demonstrated equivalence in any solvent tried. The differences may be due to the greater electronegativity of the oxygen atom over sulfur in the heterocyclic ring affecting the amount of double bond character in the exocyclic carbon to nitrogen band. It is also likely that there is a significant effect of the carbonyl or thiocarbonyl group in the 7-position.

The amino methyl groups in the acid **1***d*, in contrast to the ester **1***f*, are equivalent due to its existence as the zwitterionic structure **1***h* akin to normal amino acids. The i.r. spectrum indicated a band at 2350 cm^{-1}, typical of protonated amines. When the compound was treated with sodium bicarbonate solution, to suppress protonation, the n.m.r. indicated nonequivalence of the methyl groups.

Experimental

The i.r. spectra were performed on a Perkin-Elmer model 337 spectrophotometer in liquid paraffin mulls. The n.m.r. spectra were obtained on a Varian model 56/60A spectrometer and, unless otherwise stated, in deuteriochloroform at 40°, using tetramethylsilane as an internal standard. Chromatography was performed using Camag silica gel, type D.S.F.5., supplied by Terochem Laboratories. Development of plates was carried out using benzene, with increasing proportions of chloroform, unless otherwise stated. Melting points were obtained on a precalibrated Thermopan apparatus.

Preparation of Methyl 2-Nitroisophthalate (3a)

A mixture of 2-nitroisophthaloyl chloride (9.92 g, 40 mmol) (1) and methanol (150 ml) was refluxed for 30 h. Excess methanol was removed by evaporation and the residue crystallized from a benzene – petroleum ether, 1:1 mixture, as colorless plates m.p. 133–134° (98%).

Anal. Calcd. for $C_{10}H_9NO_6$: C, 50.21; H, 3.76; N, 5.85. Found: C, 50.38; H, 3.86; N, 5.93.

The i.r. spectrum, 1735 cm^{-1} (C=O str). The n.m.r. spectrum, 6.49 (6H singlet, the methyl protons) 2.85–2.09 τ (3 H bands the aromatic protons). The mass spectrum, M^+ Calcd.: 239. Found: 239.

Preparation of 2,6-Diacetylazidobenzene (3d)

2,6-Diacetylaniline (1.77 g, 10 mmol) in 20% hydrochloric acid (20 ml) was diazotized at 0° with sodium nitrite (0.69 g). The mixture was filtered and added to sodium azide (1.5 g) in water (10 ml) and allowed to stand 16 h. The crystalline precipitate was collected,

washed, and recrystallized from petroleum ether. Colorless needles m.p. 48° were obtained (76%).

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.15; H, 4.44; N, 20.69. Found: C, 59.01; H, 4.52; N, 20.70.

The i.r. spectrum, 2151 cm^{-1} (N_3). The n.m.r. spectrum, 7.35 τ (6H singlet, the methyl protons), 2.13–2.84 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 203. Found: 203 (M^+), 175 ($M^+ - N_2$).

Preparation of 7-Acetyl-3-methyl-2,1-benzisoxazole (1c)

2,6-Diacetylazidobenzene (0.51 g, 2.5 mmol) in *o*-dichlorobenzene (5 ml) was refluxed 20 min. The solution slowly acquired a purple color. Evaporation and chromatography indicated a number of products but the yellow and orange bands on work-up gave a crude crystalline product which was recrystallized from petroleum ether – benzene, 1:1 mixture, as colorless needles m.p 103°, identical (mixture m.p. and i.r.) with an authentic sample (1).

Reduction of Methyl 2-Nitroisophthalate to form Methyl 2-Aminoisophthalate (3b)

Methyl 2-nitroisophthalate (2.86 g, 12 mmol) was slowly added over 10 min to a stirred solution of stannous chloride dihydrate (12 g) in concentrated hydrochloric acid (36 ml) at 25° under a nitrogen atmosphere. The mixture was stirred 1.5 h then diluted with water (100 ml). The precipitate was filtered and recrystallized from a mixture of benzene – petroleum ether, 1:1, to give the desired amine as colorless needles m.p. 102–103°. The yield was virtually quantitative.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.45; H, 5.26; N, 6.70. Found: C, 57.57; H, 5.41; N, 6.82.

The i.r. spectrum 1705 cm^{-1} (C=O str). The n.m.r. spectrum, 6.17 (6H singlet, the methyl protons), 3.45 and 1.92 τ (1H triplet and 3H doublet, the aromatic protons), and 1.89 τ (2H band, the amine protons, exchanged in D_2O). The mass spectrum M^+ Calcd.: 209. Found: 209.

Oxidation of Methyl 2-Aminoisophthalate

(a) With Caro's Acid

A mixture of the amine (313 mg, 15 mmol) and Caro's acid (prepared by stirring a mixture of potassium persulfate (10 g), concentrated sulfuric acid (7 ml), and ice (50 g)) was stirred at 30° for 5 h. The mixture was diluted with water, filtered, and the residue extracted with hexane (4 × 20 ml). The combined extracts on evaporation gave starting material. The residue was crystallized from a mixture of chloroform and petroleum ether to give 3-methoxy-2,1-benzisoxazole-7-carboxylic acid (43%) as colorless needles, m.p. 160–161°. Further small amounts of products were obtained by extraction of the aqueous filtrate with methylene chloride.

Anal. Calcd. for $C_9H_7NO_4$: C, 55.95; H, 3.63; N, 7.26. Found: C, 55.79; H, 3.63; N, 7.37.

The i.r. spectrum, 1751 cm^{-1} (C=O str). The n.m.r. spectrum 6.01 (3H singlet, the methyl protons), 2.95–1.75 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 193. Found: 193.

(b) With Hydrogen Peroxide

A mixture of the amine (170 mg, 8 mmol), glacial acetic acid (5 ml), and 50% aqueous hydrogen peroxide, 1.0 ml) was left at 30° for 70 h. Work-up afforded methyl 2-nitroisophthalate (63%).

Preparation of Methyl 3-Methoxy-2,1-benzisoxazole-7-carboxylate (1b)

To a solution of diazomethane (40 mg) in ether (30 ml) was added a solution of 3-methoxy-2,1-benzisoxazole-7-carboxylic acid (58 mg, 3 mmol) in ether (20 ml). Immediate evolution of gas was evident. After ½ h, the mixture was evaporated to yield the ester, which was recrystallized from hexane as colorless needles, m.p. 134–135° (96%). The compound exhibited a strong blue fluorescence in u.v. light.

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.95; H, 4.45; N, 6.77. Found: C, 57.89; H, 4.40; N, 6.78.

The i.r. spectrum, 1764 cm^{-1} (C=O str). The n.m.r. spectrum, 6.45 (3H singlet, the ester methyl), 6.02 (3H singlet, the methoxyl protons) 2.80–1.54 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 207. Found: 207.

Preparation of Methyl 2-Azidoisophthalate (3c)

To a stirred suspension of methyl 2-aminoisophthalate (1.67 g, 8 mmol) in 50% hydrochloric acid (10 ml) was added dropwise at 0° a solution of potassium nitrite (0.7 g) in water (10 ml). The solution was stirred a further 10 min and filtered. To the stirred filtrate was added a solution of sodium azide (2.0 g) in water (15 ml). A colorless precipitate was produced. The mixture was stirred a further 2 h then the precipitate collected and recrystallized from a benzene – petroleum ether, 1:1 mixture, as colorless plates m.p. 67° (88%).

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.10; H, 3.83; N, 17.85. Found: C, 51.13; H, 3.96; N, 17.81.

The i.r. spectrum, 1737 (C=O str) and 2163 cm^{-1} (N_3). The n.m.r. spectrum, 6.04 (6H singlet, the methyl protons), 2.84–1.92 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 235. Found: 235.

Attempted Conversion of Methyl 2-Azidoisophthalate to Methyl 3-Methoxy-2,1-benzisoxazole-7-carboxylate

Pyrolysis of the azide (156 mg, 0.65 mmol) in boiling *o*-dichlorobenzene or photolysis of the azide (235 mg, 1 mmol) dissolved in dry benzene (350 ml) under nitrogen with a medium pressure mercury lamp in a quartz reactor for 1 h yielded traces of methyl 2-aminoisophthalate and much polymeric material.

Thionation of Methyl 3-Methoxy-2,1-benzisoxazole-7-carboxylate

The ester (250 mg, 1.2 mmol) and phosphorus pentasulfide (420 mg) in dry toluene (20 ml) were refluxed 5 h. The solvent was removed under reduced pressure and the residue treated with 5% aqueous sodium bicarbonate solution. The mixture was extracted with ether (4 × 100 ml) and the extract washed, dried, and evaporated gave a crude product which was separated by chromatography using a 1% methanol solution in chloroform as an eluent to give methyl 3-methoxy-2,1-benzisothiazole-7-thionocarboxylate as yellow plates, m.p. 128–129°, from petroleum ether (7%).

Anal. Calcd. for $C_{10}H_9NO_2S_2$: C, 50.21; H, 3.77; N, 5.86; S, 26.75. Found: C, 50.35; H, 3.89; N, 5.93; S, 26.60.

The mass spectrum M^+ Calcd.: 239. Found: 239.

Methyl 3-methoxy-2,1-benzisoxazole-7-thionocarboxylate, yellow prisms, m.p. 123–124°, from petroleum ether (4%), was also separated by chromatography.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 53.81; H, 4.03; N.

6.27; S, 14.35. Found: C, 53.71; H, 4.18; N, 6.10; S, 14.49.

The n.m.r. spectrum, 4.22 and 4.00 (two 3H singlets, the methyl protons), 2.72–1.52 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 223. Found: 223.

A small quantity of pale yellow material tentatively methyl 3-methoxy-2,1-benzisothiazole-7-carboxylate (0.5%) was also isolated. The mass spectrum M^+ Calcd.: 223. Found: 223. The i.r. spectrum, 1765 cm^{-1} (C=O str).

Preparation of N,N,N′,N′-Tetramethyl-2-nitroisophthalamide (3e)

2-Nitroisophthaloyl chloride (24.8 g, 0.1 mol) was dissolved in dry benzene (200 ml) and 40% aqueous dimethylamine solution (20 ml) was added slowly. The mixture was stirred for 3 h at 50°. The benzene layer separated, washed with saturated sodium chloride solution, dried, and evaporated gave a pale yellow product which was recrystallized from a benzene – petroleum ether, 1:1 mixture, as colorless plates, m.p. 151–152° (83%). The product was stable but turned red on prolonged exposure to light.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.34; H, 5.65; N, 15.82. Found: C, 54.33; H, 5.70; N, 15.68.

The i.r. spectrum, 1640 cm^{-1} (C=O str). The n.m.r. spectrum 7.08 and 6.92 (two 6H singlets, the methyl protons), 2.72–2.14 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 265. Found: 265.

Reduction of N,N,N′,N′-Tetramethyl-2-nitroisophthalamide

The nitro compound (2.99 g, 12.5 mmol) was added to a stirred solution of stannous chloride (12.0 g) in concentrated hydrochloric acid (36 ml) under nitrogen. The solution was stirred 1½ h at 0°, saturated sodium chloride solution (150 ml) added, and the mixture extracted with chloroform (3 × 150 ml). Work-up of the combined chloroform extracts yielded a crystalline residue which was recrystallized from benzene to give 3-dimethylamino-2,1-benzisoxazole-7-carboxylic acid as colorless needles, m.p. 164–165° (70%).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.85; N, 13.59. Found: C, 58.32; H, 4.95; N, 13.74.

The i.r. spectrum, 1602 (tentatively asym. CO_2^- str) and 2350 cm^{-1} (N^+—H str). The n.m.r. spectrum in $CDCl_3$ 6.86 (6H singlet, the methyl protons), 2.94–2.22 (3H bands, the aromatic protons), −1.10 τ (broad 1H band, exchanged in D_2O (the acidic proton)). In D_2O saturated with $NaHCO_3$ the methyl protons were evident as two peaks at 6.94 and 7.08 τ.

Neutralization of the aqueous layer from above with sodium bicarbonate and chloroform extraction gave on evaporation a crystalline product which was recrystallized from benzene – petroleum ether, 1:1 mixture, to give *N,N,N′N′*-tetramethyl-2-aminoisophthalamide as colorless needles, m.p. 177–178° (15%).

Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.27; H, 7.23; N, 17.87. Found: C, 61.19; H, 7.48; N, 17.69.

The i.r. spectrum, 1661 cm^{-1} (C=O str). The n.m.r. spectrum, 6.95 (12H singlet, the methyl protons), 3.25–2.65 τ (3H bands, the aromatic protons).

Preparation of Methyl 3-Dimethylamino-2,1-benzisoxazole-7-carboxylate (1f)

3-Dimethylamino-2,1-benzisoxazole-7-carboxylic acid (248 mg, 1.2 mmol) in dry ether (300 ml) was added to the calculated amount of diazomethane in dry ether (50 ml). The solution was left at room temperature for 5 h then the ether was removed by evaporation. The residue was crystallized from a benzene – petroleum ether, 1:1 mixture, as colorless needles m.p. 105–106° (98%).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.45; N, 12.73. Found: C, 60.04; H, 5.43; N, 12.72.

The i.r. spectrum, 1761 cm^{-1} (C=O str). The n.m.r. spectrum 7.06 and 6.84 (two 3H singlets, the amine methyls), 6.73 (3H singlet, the ester methyl), 2.72–1.98 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 220. Found: 220.

Preparation of N,N,N′,N′-Tetramethyl-2-nitroisothiophthalamide

A mixture of *N,N,N′N′*-tetramethylisophthalamide (7.0 g, 2.66 mmol) and phosphorus pentasulfide (10.0 g) in toluene (50 ml) was refluxed for 3 h. The solvent was evaporated and the residue treated with 5% sodium bicarbonate solution and extracted with chloroform (3 × 100 ml). The combined extracts were washed with water and evaporated. The residue was crystallized from benzene to give the product as yellow plates m.p. 204–205° (88%).

Anal. Calcd. for $C_{12}H_{15}N_3O_2S_2$: C, 48.48; H, 5.05; N, 16.14; S, 21.55. Found: C, 48.64; H, 5.05; N, 14.11; S, 21.66.

The n.m.r. spectrum 6.73 and 6.43 (two 6H singlets, the methyl protons), 2.96–2.41 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 297. Found: 297.

Reduction of N,N,N′,N′-Tetramethyl-2-nitroisothiophthalamide

To a solution of stannous chloride (2.5 g) in concentrated hydrochloric acid (15 ml) was added the thioamide (1.435 g, 5 mmol) and the mixture stirred under nitrogen 3 h. The mixture was filtered and the residue washed with water then dissolved in benzene. The benzene solution was washed with 50% aqueous sodium hydroxide solution, washed with water, dried, and evaporated to give a crude product which was separated by chromatography using 1% methanol in chloroform as an eluant to give starting material and a mixture of *N,N,N′,N′*-tetramethyl-2-aminoisothiophthalamide (80%) and *N,N*-dimethyl-3-dimethylamino-2,1-benzisothiazole-7-thiocarboxamide (16%). These were separated by fractional crystallization from benzene, in which the isothiazole is more soluble, to give products m.p. 207–208 and 202°, respectively.

For the amine, Anal. Calcd. for $C_{12}H_{17}N_3S_2$: C, 53.93; H, 6.37; N, 15.71; S, 24.00. Found: C, 53.63; H, 6.28; N, 15.53; S, 24.02.

The n.m.r. spectrum 6.84 and 6.46 (two 6H singlets, the methyl protons), 5.90 (broad band, exchangeable in D_2O, the amine protons), 2.11–1.54 τ (3H bands, the aromatic protons). The mass spectrum, M^+ Calcd.: 267. Found: 267. Rigorous drying was necessary for proper analysis.

For the 2,1-benzisothiazole, Anal. Calcd. for $C_{12}H_{15}N_3S_2$: C, 54.2; H, 5.65; N, 15.85; S, 24.12. Found: C, 54.44; H, 5.65; N, 15.72; S, 24.12.

The n.m.r. spectrum, 6.84 and 6.27 (two 3H singlets, the amidic methyls), 6.66 (6H singlet, the amino protons),

2.19–2.04 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 265. Found: 265.

Oxidation of N,N,N′,N′-Tetramethyl-2-aminoisothiophthalamide with Hydrogen Peroxide in Acetic Acid

The thioamide (80 mg, 0.3 mmol) in acetic acid (5 ml) was treated with 30% hydrogen peroxide (0.03 ml) and the solution heated at 50° for 1 h. The solution was diluted with water, extracted with chloroform, and the chloroform layer washed with saturated sodium bicarbonate solution. Evaporation yielded a yellow oil which on examination by chromatography, using repeated development with chloroform, yielded three yellow bands. The second of these on elution gave *N,N*-dimethyl-3-dimethylamino-2,1-benzisothiazole-7-thiocarboxamide, identical (mixture m.p. and mass spectrum) to a sample prepared above (10%).

Preparation of Methyl 2-Nitroisothiolphthalate (3i)

A mixture of 2-nitroisophthaloyl chloride (12.4 g, 50 mmol), dry benzene (150 ml), and methanethiol (19.2 g) was treated with triethylamine (30 g), and the mixture stirred 3 h. The mixture was warmed to 60° to remove excess methanethiol, then poured into water. The benzene layer was extracted with dilute sodium hydroxide and dilute hydrochloric acid, dried, and evaporated under reduced pressure to give the crude ester, which was recrystallized from a mixture of benzene and petroleum ether as colorless plates m.p. 130–131°.

Anal. Calcd. for $C_{10}H_9NO_4S_2$: C, 44.28; H, 3.32; N, 5.16; S, 23.61. Found: C, 44.44, H, 3.35, N, 5.21; S, 23.79.

The i.r. spectrum, 1635 cm^{-1} (C=O str). The n.m.r. spectrum, 7.52 (6H singlet, the methyl protons), 2.46–1.82 τ (3H bands, the aromatic protons). The mass spectrum M^+ Calcd.: 271. Found: 271.

Reduction of Methyl 2-Nitroisothiolphthalate with Stannous Chloride

A mixture of methyl 2-nitroisothiolphthalate (4.06 g, 1.5 mmol), stannous chloride dihydrate (36 g), and concentrated hydrochloric acid (100 ml) was heated at 60° for 16 h under nitrogen. Water (300 ml) was added to the reaction mixture and the precipitate filtered. The residue was extracted with boiling petroleum ether which on concentration and cooling gave methyl 2-aminoisothiolphthalate. The product was recrystallized from petroleum ether as lemon yellow plates, m.p. 93–94°, (63%).

Anal. Calcd. for $C_{10}H_{11}NO_2S_2$: C, 49.79; H, 4.56; N, 5.81; S, 26.55. Found: C, 49.69; H, 4.63; N, 5.79; S, 26.74.

The i.r. spectrum, 3300 and 3405 (NH_2 str), 1655 cm^{-1} (C=O str). The n.m.r. spectrum, 7.63 (6H singlet, methyl protons), 3.56 and 1.80 (1H triplet, 2H doublet, the aromatic protons), and 1.80 τ (2H band, the amine protons). The mass spectrum M^+ Calcd.: 241. Found: 241.

Thionation of Methyl 2-Nitroisothiolphthalate to form 3k

A mixture of methyl 2-nitroisothiolphthalate (4.06 g, 15 mmol), phosphorus pentasulfide (12.0 g), and toluene (2.50 ml) was refluxed 3 days. The mixture was filtered, washed with sodium bicarbonate solution, and evaporated to yield a brown residue. Crystallization from a benzene, petroleum ether mixture gave the tetrathioester as orange plates, m.p. 138–139°, (71%).

Anal. Calcd. for $C_{10}H_9NO_2S_4$: C, 39.60; H, 2.97; N, 4.62; S, 42.24. Found: C, 39.67; H, 3.08; N, 4.69; S, 42.48.

The n.m.r. spectrum, 7.26 (6H singlet, the methyl protons) and 2.48 τ (3H singlet, the aromatic protons). This absorption remained a singlet when the compound was dissolved in hexadeuteriobenzene. The mass spectrum M^+ Calcd.: 303. Found: 303.

Attempted Reduction of Methyl 2-Nitroisotetrathiophthalate with Stannous Chloride

A mixture of the tetrathioester (1.0 g), stannous chloride (9.0 g), and concentrated hydrochloric acid (27 ml) was heated at 60–70° for 4 h. Work-up afforded mainly starting material and traces of hydrolyzed products.

Reaction of Methyl 2-Aminoisophthalate with Phosphorus Pentasulfide

A mixture of the ester (418 mg, 2 mmol), phosphorus pentasulfide (600 mg, 1.35 mmol), and toluene (25 ml) was refluxed for 8 h. The mixture was filtered and the residue washed with benzene and the benzene washings united with the toluene. The solvent was removed *in vacuo* and the residue treated with sodium bicarbonate solution. An ether extract was dried and evaporated to yield green material which was separated by chromatography in benzene to give **7** as dark green prisms m.p. 99–100° (58%) and **6** as greenish yellow prisms m.p. 150–152° (11%).

For **7**, Anal. Calcd. for $C_{10}H_{10}NO_3PS_3$: C, 37.61; H, 3.13; N, 4.39; P, 9.71; S, 30.09. Found: C, 37.79; H, 3.25; N, 4.50; P, 9.93; S, 30.06.

The i.r. spectrum, 1675 cm^{-1} (C=O str). The n.m.r. spectrum, 6.33 (3H doublet, $J = 16$ Hz, the methoxy protons, split by phosphorus) and 5.98 τ (3H singlet, the ester methyl). The mass spectrum M^+ Calcd.: 319. Found: 319.

For **6**, Anal. Calcd. for $C_{10}H_{10}NO_4PS_2$: C, 39.60; H, 3.30; N, 4.02; P, 10.23; S, 21.12. Found: C, 39.68; H, 3.22; N, 4.68; P, 10.03, S, 21.11.

The i.r. spectrum, 1695, 1660 cm^{-1} (C=O str). The n.m.r. spectrum, 6.33 (3H doublet, $J = 16$ Hz, the methoxy protons, split by phosphorus), 6.08 τ (3H singlet, the ester methyl). The mass spectrum M^+ Calcd.: 303. Found: 303.

Nuclear Magnetic Resonance Spectral Data

These were obtained on samples dissolved in hexadeuteriodimethyl sulfoxide in degassed sealed tubes and over the temperature range 40–200°.

Methyl 3-methoxy-2,1-benzisoxazole-7-carboxylate. At 40° two singlets at 6.70 and 6.21 τ were evident. At 200°, two singlets, separated by 0.52 τ were still observed, although some line broadening was evident.

Methyl 3-methoxy-2,1-benzisothiazole-7-thionocarboxylate. At 40° two singlets were observed at 6.54 and 6.20 τ. At 200° these had coalesced into a broad singlet at 6.30 τ.

Methyl 3-dimethylamino-2,1-benzisoxazole-7-carboxylate. At 40° this exhibited three methyl absorptions. Two at 7.28 and 7.10 τ were assigned to the amine methyl and one at 6.89 τ to the ester methyl. At 120° the former became equivalent but even at 200° there was no evidence for the valency isomerism.

N,N-Dimethyl-3-dimethylamino-2,1-benzisothiazole-7-thiocarboxamide. At 40°, this exhibited three methyl signals, at 7.07 and 6.54 τ, the amidic methyls, and at 6.72 τ, the equivalent amino methyls. At 180° the peaks were still discrete. At 200° the amidic methyl peaks had collapsed to a singlet but were still nonequivalent to the amine methyl. An attempt to study the temperature dependent rotational equivalence of the amine methyls in chloroform or acetone was unsuccessful as the compound was too insoluble in these solvents below −20°.

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