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Mechanism of formation of benzothiazole-2-thiol

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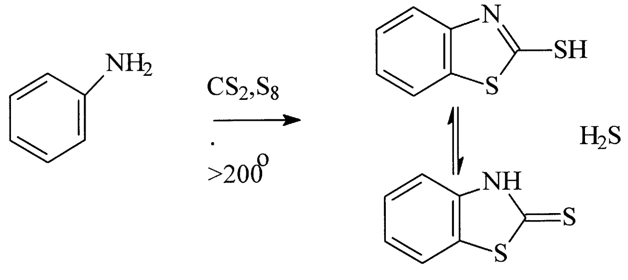
ABSTRACT: The formation of benzothiazole-2-thiol from aniline, carbon disulphide and sulphur at 230°C was shown to occur by a sequence of three principal steps. Labelling experiments confirmed that both sulphur atoms originate from carbon disulphide. An initial polar reaction to form thiocarbanilide via phenylcarbamic acid and a tetrahedral intermediate is followed by radical cyclization of these to benzothiazole-2-thiol and 2-phenylamino-benzothiazole; the latter is converted into the desired product by a polar displacement of aniline by H_2S. Mechanisms for the formation of minor byproducts are also considered. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: benzothiazole-2-thiol; formation mechanism

Benzothiazole-2-thiol (mercaptobenzthiazole; MBT) **1** is an important bulk chemical used as an accelerator in the vulcanization of rubbers.[1] It is prepared by a process originating in 1927 in which aniline, carbon disulphide and sulphur in equimolar amounts are heated together in a closed autoclave at 220–250°C over a period of about 4 h (the Kelly Process).[2] The stoichiometry of the reaction is as follows:



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The yield of the desired product can reach 90% but there are many minor byproducts; more than 50 can be separated by liquid chromatography and most have been identified (see Figure 1).

Several mechanistic schemes have been put forward to explain the formation of the principal product, some of which are indicated below and all of which are now shown to be incorrect.

1. The formation and sulphurization of phenyl isothiocyanate (Scheme 1):[3] Phenyl isothiocyanate is formed in only very minor amounts whereas, according to this hypothesis, it should be obtained as a major initial product. Furthermore, although the authors claimed that its reaction with sulphur leads to MBT, the present work does not substantiate this. No reaction appears to take place between phenyl isothiocyanate and sulphur at 230°C.

Thiocarbanilide forms readily and quantitatively from the reaction between aniline and carbon disulphide and the present work has shown that MBT results from heating this substance with sulphur (Scheme 2). The earlier workers assumed the role of sulphur was to supply the ring sulphur atom, now shown to be incorrect, and could not account for specific *ortho* attack if this were the mechanism.

2. The thiolation of phenylcarbamic acid (**3**[2–5] (Scheme 3): the initial product, **3**, formed from aniline and carbon disulphide was proposed to react with sulphur to form the 2-thiol, which then cyclizes. An alternative version proposes sulphurization of diphenyldithiobiuret (**4**), followed by cyclization.

3. The sulphurization of aniline and cyclization:[6] aniline and sulphur do indeed react together at temperatures well below those of the process to form a mixture of thiols and bis(anilino)polysulphides. The products are discussed below (see Figure 3). The present work can eliminate this as a major pathway although it is shown to account for 3–4% of the product. The argument against this reaction as a major route to MBT is that it would require specific attack in the *ortho* position, an unlikely situation and one which is demonstrably untrue. Thiolation of aniline by sulphur is shown by the present study to be random in its orientation.

Two key observations which must find an explanation in any mechanistic scheme are first, the formation of a carbon–sulphur bond exclusively in the *ortho* position of the aniline unit, for which an intramolecular attack of sulphur on carbon seems the only possibility, and second, the sudden incursion of reaction at 180 °C. Other uncertainties before the present work were the origin of

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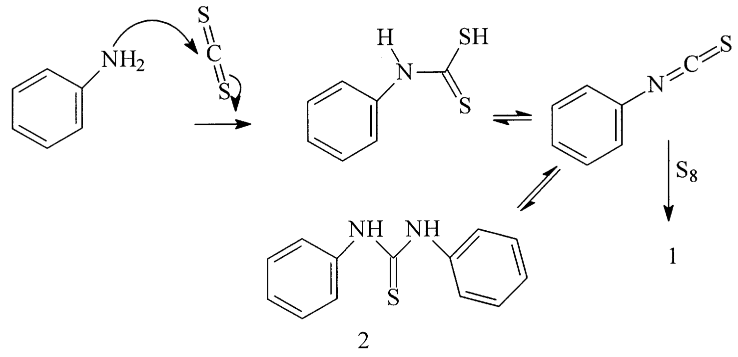
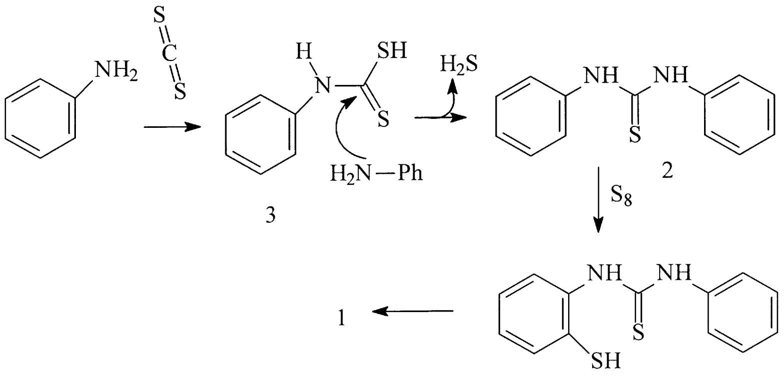


Scheme 1



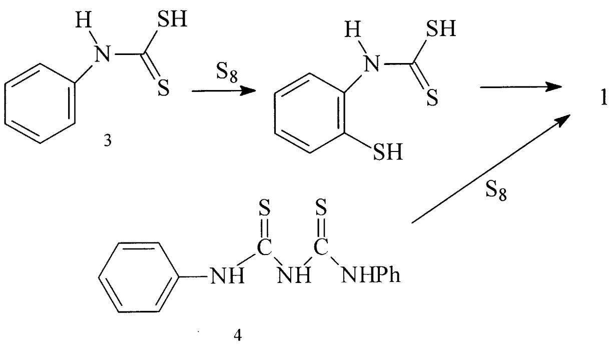
Scheme 2

each sulphur in MBT and the actual role of the sulphur in the reaction. These questions are answered below.

EXPERIMENTAL

Sealed tube experiments

Reactions were conducted in tubular vessels made of stainless steel (100 × 4 mm i.d. and 1 mm wall thickness) which could be filled to at least three quarters of their volume with reagents and sealed by means of a Swagelok cap. These tubes were able to withstand the considerable pressure of hydrogen sulphide developed during the reaction (about 30 bar) while at the same time the head-space was kept to a minimum. Heating was commenced very rapidly (final temperature reached in <1 min) by placing a series of such tubes into holes in an aluminium block in a thermostated oven, removing the tubes singly at suitable time intervals and quenching the reaction by cooling. The contents were removed and made up to a fixed volume with acetonitrile and the solution was analysed by liquid chromatography (Varian Star system fitted with multi-diode array detector, monitoring the eluent at 254 nm). In this way, kinetic information on the disappearance of starting materials and the build-up and decay of intermediates and products was obtained. What is referred to below as the 'standard' reaction used aniline (0.0500 g, 537 mmol), carbon disulphide (0.0409 g, 537 mmol) and sulphur (0.0173 g, 540 mmol) at 230 °C. The chromatogram of the mixture of products is given in Figure 1 and curves for the progress of the reaction for several products in Figure 2.



Scheme 3

The analytical conditions were as follows: Ultrasphere OD 5 µm column at 35 °C; solvent A, acetonitrile–water (20:80) buffered with acetic acid (0.3 g l^{-1}); solvent B,

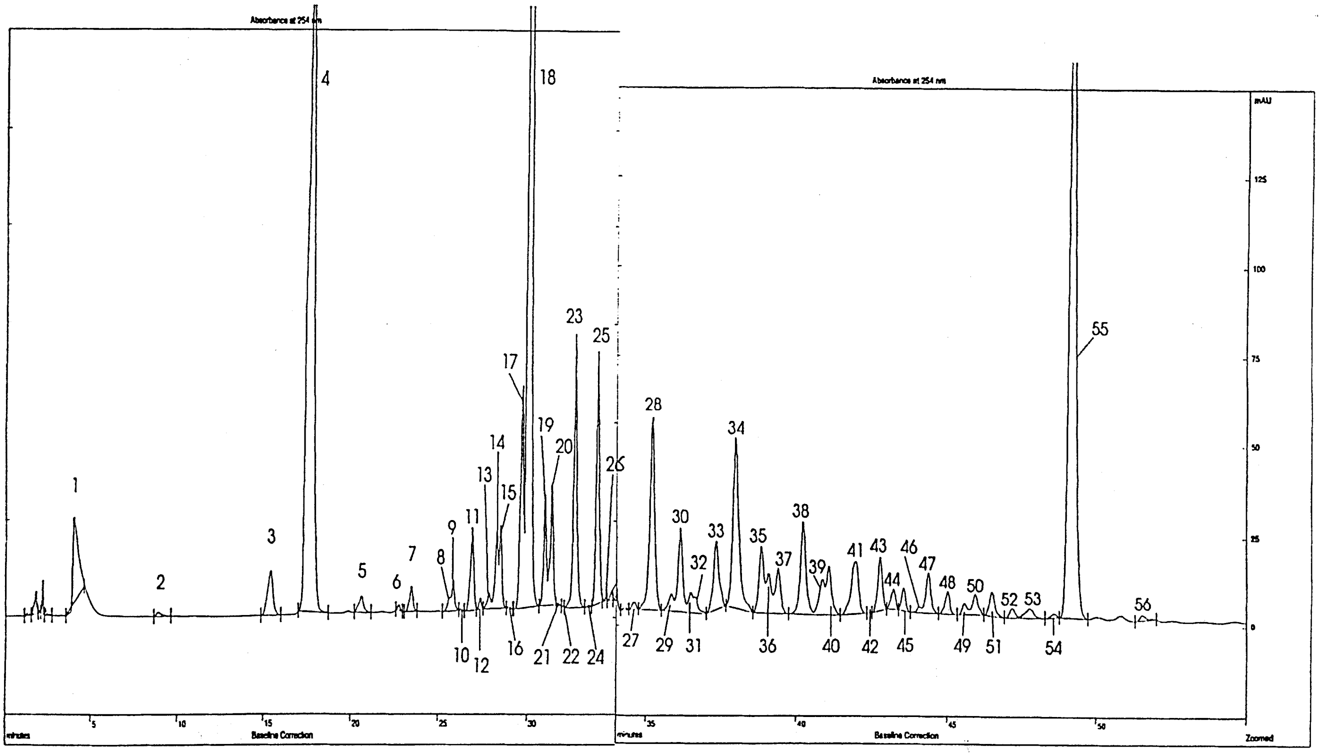


Figure 1. Liquid chromatogram of products from the standard reaction between aniline, carbon disulphide and sulphur at 230°C. Peaks: 1, aniline; 3, benzothiazole; 4, benzothiazole-2-thiol (MBT); 6, thiocarbanilide; 18, 2-*N*-anilinobenzothiazole (AnBTh); 21, phenyl isothiocyanate; 29, 3-(2-benzothiazolyl)-2-benzothiazolinethione; 30, 2,2′-dibenzothiazolyl sulphide; 32, 2,2′-dibenzothiazole; 37, 2,2′-dibenzothiazolyl disulphide; 55, sulphur. Compounds 5, 8, 11, 17, 20, 24, 28, 33, 35, 39, 41, 43, 44, 47 and 51 are products of the reaction between aniline and sulphur (see Figure 3). Note: the peaks were numbered for convenience and not all are referred to specifically in the text

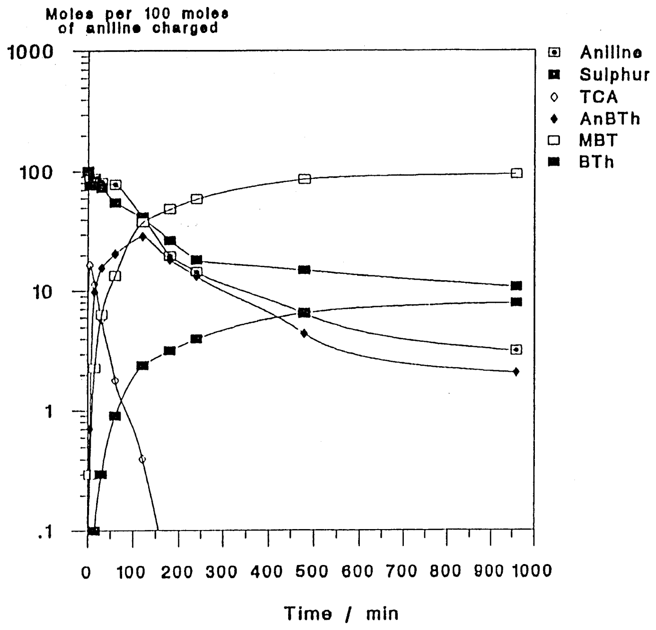


Figure 2. Reaction progress curves for reagents and products in the standard reaction between aniline, carbon disulphide and sulphur at 230°C

acetonitrile; gradient elution from A–B (95:5) at the start to pure B at 60 min at a flow rate of 1.6 ml min^{-1}; multi-diode array detector, monitoring wavelength 254 nm.

Sulphur labelling experiments

Preparation of C^{35}S. To a solution of sodium sulphide, $Na_2S{\cdot}9H_2O$ (5 g, 20 mmol) in water (25 ml) was added labelled sodium sulphide, $Na_2{}^{35}S{\cdot}9H_2O$ (1.2 mg, 1 mCi) (Amersham). The solution was placed in a tubular glass vessel fitted with stopcocks at either end. Carbon disulphide (5.0 g, 65 mmol) was added and the mixture shaken for 15 min, during which it developed an orange–red colour due to the formation of trithiocarbonate, an intermediate in the sulphur interchange reaction. After standing for a few minutes, the lower carbon disulphide layer was separated and dried over anhydrous calcium chloride. The radioactivity was determined by scintillation counting.

Elemental sulphur, $^{35}S_8$ (1 mCi), was purchased from Amersham.

Table 1. Results of labelling reactions

Active material	Specific activity (counts min^{-1} $mmol^{-1}$) From ^{35}S	Specific activity (counts min^{-1} $mmol^{-1}$) From $C^{35}S_2$
^{35}S reagent	2239×10^5	
$C^{35}S_2$ reagent		6059×10^3
MBT product	184×10^5	5538×10^3
BABT product	100×10^5	2780×10^3
Incorporation of label (%):		
Into ring	4.5	46
Into thiol	3.5	45

Degradation of MBT. In order to separate the two sulphur atoms present in MBT, the following conversion was made. A sample of MBT (2.43 g, 15 mmol) was dissolved in benzylamine (15 g, 140 mmol) in a closed stainless-steel vessel (a Whitey cylinder) at 200 °C for 1 h. The cylinder was cooled and the contents were removed, dissolved in 20% hydrochloric acid and extracted with chloroform (2 × 25 ml). The chloroform layers were separated, combined and dried. On evaporation of the solvent, 2-*N*-benzylaminobenzothiazole (BABT) was obtained as a white crystalline solid of 99% purity (by HPLC).

Using the sealed tube method for the standard reaction described above, samples of MBT were prepared by reaction of equimolar mixtures of aniline, $C^{35}S_2$ and sulphur (S_8) and of aniline, CS_2 and $^{35}S_8$, that is, with each of the two sources of sulphur separately labelled. The determination of the extent of incorporation of the radiolabel into each of the two sulphur positions in benzothiazole-2-thiol was carried out as follows. From each experiment a pure sample of MBT was isolated by extraction of the crude product into aqueous sodium hydroxide, precipitation by acid and sublimation, and its specific activity was determined by scintillation counting. A sample of the labelled MBT was converted into 2-*N*-benzylaminobenzothiazole and its specific activity determined. Each experiment was performed in duplicate. The results given in Table 1 were obtained.

DISCUSSION

Origin of sulphur in MBT

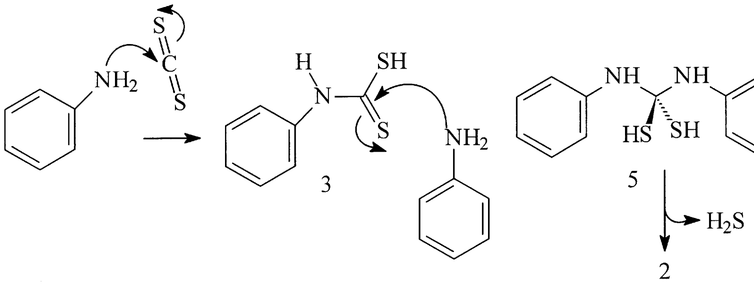
The ratiolabelling experiments show conclusively that both sulphur atoms of MBT originate from carbon disulphide. The very small amount of incorporation of labelled sulphur and the small loss of activity from the carbon disulphide can be accounted for by a small amount of exchange of MBT with H_2S in minor pathways discussed below.

Formation of the benzothiazole ring

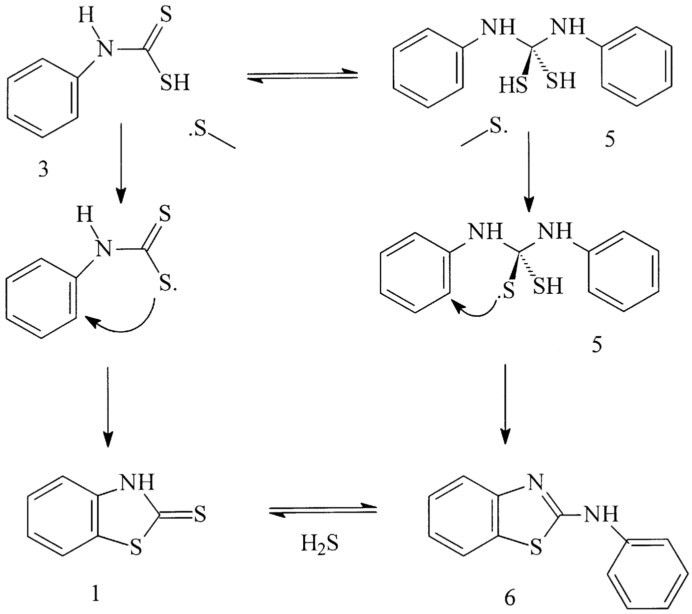
When the reaction between aniline, carbon disulphide and sulphur is carried out in a sealed tube at 230° conditions similar to those used commercially, around 50 products can be detected and separated by HPLC (Figure 1), MBT being in greatest abundance and which eventually reaches >90% conversion. The identification of the majority of these products has been made by comparison with the characteristics of authentic samples both by retention times and by UV spectra. By carrying out reactions over periods of time up to 960 min, progress of reaction curves were drawn for the products of major interest (Figure 2).

Clearly, the first-formed product is thiocarbanilide (**2**), which peaks within a few minutes and is undetectable after 3 h. However, separate experiments on the reaction between aniline and carbon disulphide show that an equilibrium is set up; at 50 °C this is reached after 3 h with 58% conversion to thiocarbanilide. It is therefore not a requirement that thiocarbanilide lies on the reaction pathway to MBT. This reaction must be a normal polar process of nucleophilic addition to carbon disulphide, in support of which it is noted that *p*-toluidine reacts very much faster than does aniline; a yellow precipitate of *p,p*-dimethylthiocarbanilide forms at room temperature within 30 s of mixing. This mechanism would require the intermediate formation of phenylcarbamic acid (**3**) and a tetrahedral intermediate (**5**) (Scheme 4).

Attempts were made to observe these species by NMR spectroscopy. Aniline and carbon disulphide were sealed into a thick-walled NMR tube and allowed to come to equilibrium. A series of weak additional carbon resonances in the aromatic region but not attributable to the principal ingredients was observed, which might have been due to low concentrations of **3** and **5**. An observation which does not apparently accord with the polar formation of thiocarbanilide was that the reaction appeared to be accelerated by the presence of sulphur. At 50 °C, for example, conversion to thiocarbanilide had reached 11% after 30 min in the absence of sulphur but 30% in its presence.



Scheme 4

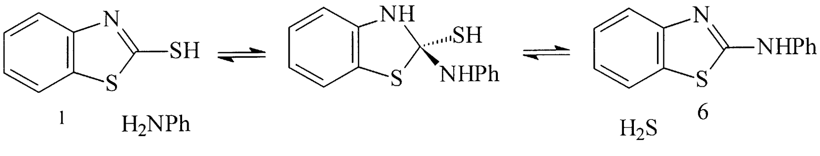


Scheme 5

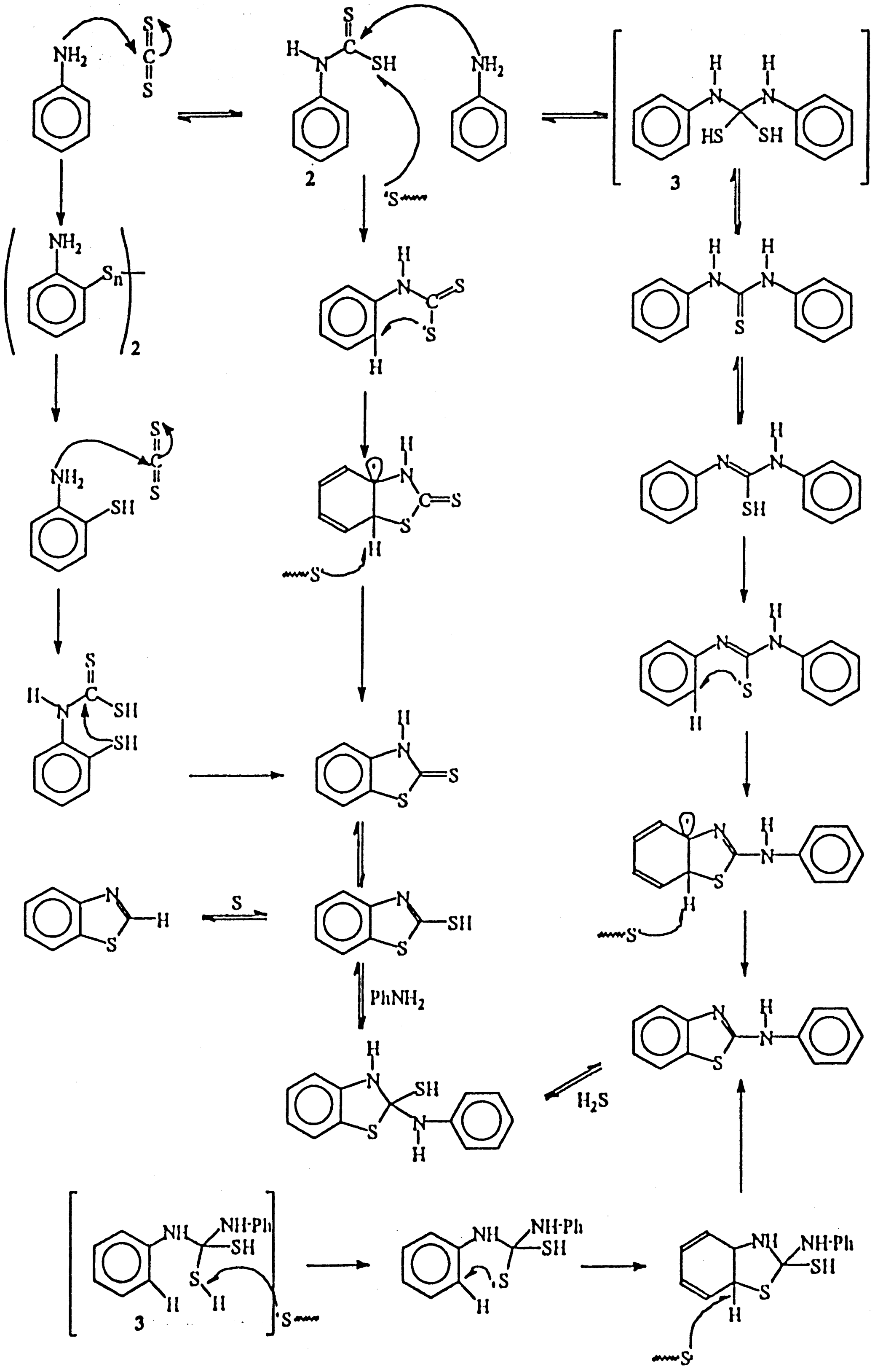
While the aniline and thiocarbanilide concentrations diminish with time, the major initial product appears to be 2-anilinobenzothiazole (AnBTh, **6**), which peaks after about 2 h and then diminishes; MBT steadily increases, reaching its final concentration after about 480 min. However, it should be noted that MBT begins to form from the very start of the reaction and is not delayed while the AnBTh concentration builds up.

We propose that the formation of both MBT and of AnBTh occurs by the radical cyclization of **3** and **5** under the action of sulphur radicals produced by the homolysis of S_8 (Scheme 5). It is no coincidence that both this process and the formation of benzothiazoles begins at around 180 °C and that, at 230 °C, there is an abundance of sulphur radicals of the types $\cdot S—(S_n)—S\cdot$ and $\cdot S—(S_n)—SH$ present, continually forming, dimerizing, fragmenting and abstracting hydrogen and in a state of flux.

The reaction is a radical substitution (S_RAr) by the radicals produced from **3** and **5**, followed by hydrogen

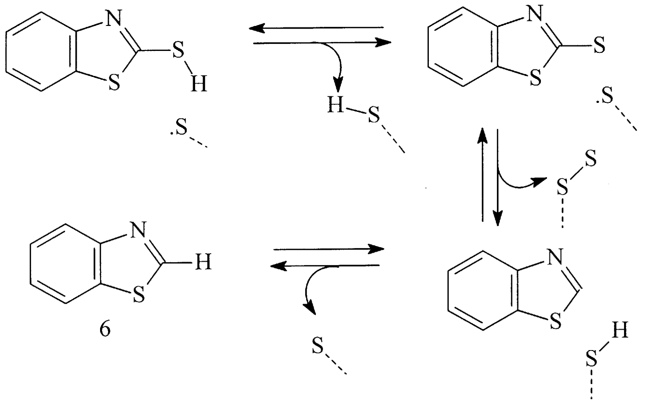


Scheme 6



Scheme 7

abstraction by elemental sulphur free radicals of varying chain lengths. The hydrogen exchange would be approximately thermoneutral and evidently the intramolecular route via a five-membered cyclic transition



Scheme 8

state is greatly favoured over direct intermolecular attack on the ring, which should be feasible but far slower.

This route accounts for the specific attachment of sulphur *ortho* to the aniline nitrogen and also for the origin of both sulphur atoms of MBT from carbon disulphide and for the role of sulphur. Cyclization of **3** would lead directly to MBT whereas **5** would initially form AnBTh, each by an aromatic radical substitution mechanism (Scheme 3). The role of the sulphur is therefore predominantly as a dynamic source of radicals which primarily abstract hydrogen from SH groups and from the C—H bonds in tetrahedral intermediates.

Attempts to use other radical sources such as benzoyl peroxide or azobisisobutyronitrile (AIBN) were not successful in promoting more than a few percent of reaction products, which must be due to the fact that, as a source of radicals, these compounds decompose irreversibly and over too short a period whereas sulphur remains a radical source throughout the reaction until it is finally reduced to hydrogen sulphide. Hydrogen abstracted by sulphur radicals must become attached to a chain of sulphur atoms which progressively shortens by S—S bond cleavage until eventually hydrogen sulphide is formed.

Conversion of AnBTh to MBT

In the standard reaction, AnBTh peaks and then decays to be replaced by MBT, the process being complete in about 3 h. This reaction was studied by allowing AnBTh and

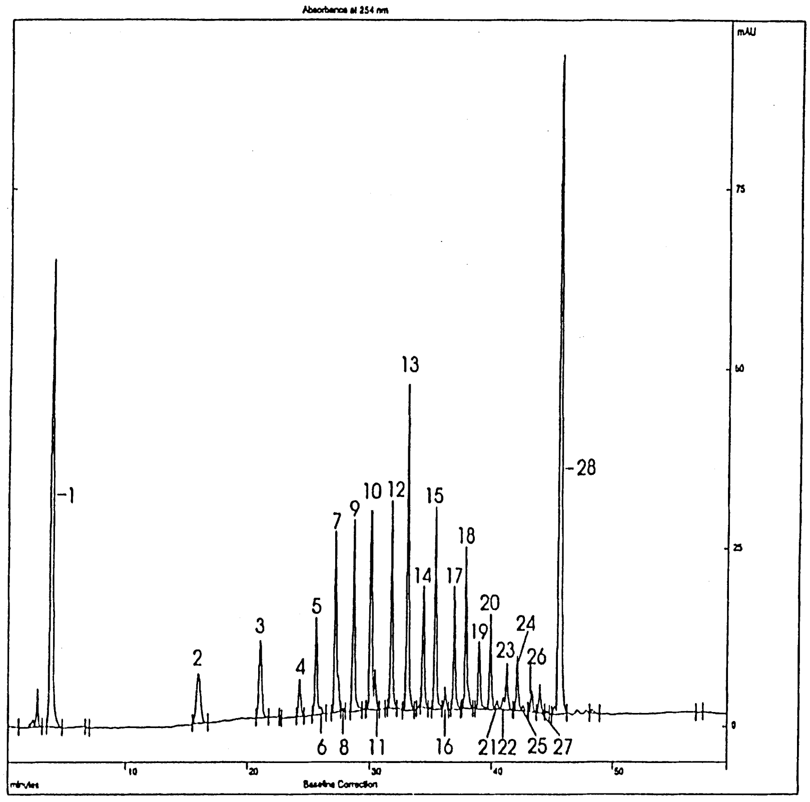
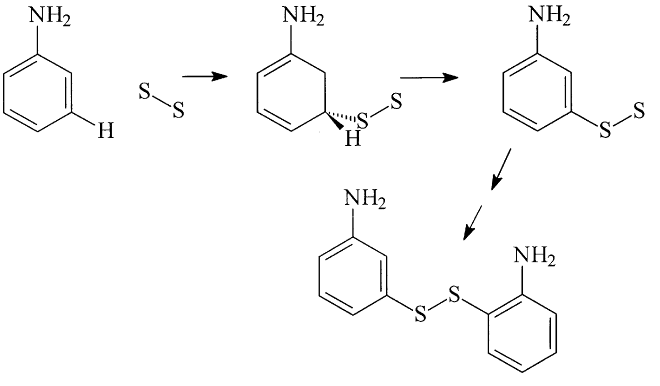


Figure 3. Liquid chromatogram of products from aniline and sulphur at 180°C. Peaks: 1, aniline; 2, bis(4-aminophenyl) sulphide; 5, bis(4-aminophenyl) disulphide; 7, bis(2-aminophenyl) disulphide; 28, sulphur; 3, 9–16, 18–20, 22, 24 and 27 are bis(aminophenyl) polysulphides and are observed as minor products in the standard reaction; 4, 6, 8, 17, 21, 23, 25 and 26 are also bis(aminophenyl) polysulphides but do not appear as products in the standard reaction, from which it is inferred that they contain at least one *ortho* sulphur group and are convertible to MBT



Scheme 9

hydrogen sulphide (10 bar) to react together at 230°C in a sealed tube, when MBT was formed. This is a polar reaction, a nucleophilic displacement presumably of the addition–elimination type (Scheme 6). The reaction is reversible but in the presence of excess hydrogen sulphide lies heavily in favour of MBT.

The end product MBT is evidently thermodynamically a very stable molecule. Measurement of its heat of formation by combustion calorimetry gave $\Delta H_f = 96 \pm 5$ kJ mol^{-1}. Further evidence for this mechanism comes from the observation that the reaction can be conducted in the opposite direction and the rates of displacement of sulphide from MBT by amines increase with increasing nucleophilic power of the amine, benzylamine > aniline. The principal route leading to the formation of MBT is summarized in Scheme 7.

Byproducts and minor pathways

Benzothiazole occurs as a byproduct of the standard reaction to the extent of about 8%. It is formed by thermal degradation of MBT and in the presence of sulphur by a route possibly as shown in Scheme 8. This is also a reversible process.

Reaction between aniline and sulphur

This reaction has been studied previously[7,8] but hitherto not well elucidated. When equimolar amounts of aniline and sulphur react together at the reflux temperature (around 180°C), there is formed within about 4 h a greenish oily product which by HPLC (Figure 3) was shown to contain over 25 products, all showing more or less identical UV spectra each with a weak maximum at 330 nm. By injecting authentic samples of bis(2-aminophenyl) sulphide and disulphide and the corresponding 4-amino derivatives, each of these compounds was found to be present by comparison of retention times and UV spectra. Neither 2- nor 4-aminobenzenethiol was among the products. We conclude that these products are of the general structure, $NH_2C_6H(S_n)C_6H_4NH_2$, in which connections between sulphur and the aniline ring are randomized at *ortho, meta* and *para* positions and *n* is up to perhaps 5, This would allow for 30 such products which are formed by radical substitutions on aniline by sulphur chains (Scheme 9).

Furthermore, many but not all of these species are found as minor byproducts in the standard reaction. The missing products are those which disappear when the mixture of compounds obtained from reaction of aniline with sulphur is heated with carbon disulphide above 180 °C when MBT forms. Evidently, the missing compounds must be those which have an aniline residue thiolated at an *ortho* position and are convertible to MBT. In a separate experiment, bis(2-aminophenyl) disulphide was allowed to react with carbon disulphide at 230 °C when a good yield of MBT was obtained together with small amounts of some of the other products. Evidently under these conditions a certain amount of reorganization occurs in addition to cyclization.

We conclude that any of the compounds formed from the action of sulphur on aniline which has at least one sulphur in an *ortho* position of an aniline ring will be converted in MBT during the course of the standard reaction whereas those having no such *ortho* connection remain as byproducts, and this contributes a minor pathway to MBT amounting to perhaps 2% of the total.

Role of phenyl isothiocyanate

Very small amounts of phenyl isothiocyanate are found in the products of the standard reaction and this has been seen as an intermediate implicated in the formation of MBT. It arises from the thermal decomposition of thiocarbanilide with which it is in equilibrium. However, when PhNCS and sulphur were heated together at 230 °C, no MBT was formed; indeed, no reaction at all was observed. If 10 mol% of water was added, however, thiocarbanilide was formed with a small yield of AnBTh together with some diphenylurea. The latter is observed as a minor product in the MBT reaction and is related to adventitious water. It may be concluded that phenyl isothiocyanate is not directly involved in any process leading to MBT or AnBTh.

Formation of 2-methylbenzothiazole

Very small amounts of this compound are detected in the standard reaction under conditions such that their origin from methyl-containing impurities can be excluded. When pure benzothiazole was heated with hydrogen sulphide and carbon disulphide at 230 °C for 2 h, a very small yield of 2-methylbenzothiazole was observed, confirmed by retention time and UV spectrum in comparison with an authentic specimen. It appears that the reducing conditions are able to convert CS_2 into a methyl group to a very small degree.

Dibenzothiazolyl sulphide and disulphide are observed and their presence is readily rationalized by dimerization of intermediate radicals described above.

Acknowledgements

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