

PREPARATION OF 3-DIMETHYLAMINO-7-METHYL-
1, 2, 4-BENZOTRIAZINE-1-OXIDE

This invention relates to an improved process for the preparation of 3-dimethylamino-7-methyl-1,2,4-benzotriazine-1-oxide, hereinafter referred to for simplicity as "benzotriazine oxide", and to benzotriazine oxide prepared by the improved process, and derivatives thereof.

Benzotriazine oxide is of commercial importance because it is an intermediate in the preparation of the anti-inflammatory drug azapropazone. The conventional preparation of benzotriazine oxide involves the reaction of 4-methyl-2-nitroaniline with phosgene and the subsequent treatment of the resulting urea derivative with ammonia to neutralise excess phosgene, followed by purification and treatment with sodium hydroxide. This procedure is disadvantageous in view of the highly toxic nature of phosgene and also because it is necessary to carry out the reaction in several stages involving separate reaction vessels.

We have devised a process for the preparation of benzotriazine oxide by the cyclization of a defined class of guanidinyl compounds which themselves are prepared by reaction of a substituted nitro-benzene compound with a cyanamide. In one form of the invention the preparation of the guanidinyl compound involves the reaction of 4-methyl-2-nitroaniline and dimethyl cyanamide. In another form of the invention the preparation of the guanidinyl compound involve the reaction of 4-methyl-2-nitroaniline and cyanamide. Both sequences produce a guanidinyl

compound which is then cyclized and in the case of the second sequence also methylated. These processes can be carried out safely with good yields.

According to one preferred aspect of the present invention, a process for the preparation of benzotriazine oxide (compound III below) as herein defined comprises reacting a solution of 4-methyl-2-nitroaniline (compound I below) with dimethylcyanamide at elevated temperature and in the presence of a salt forming moiety whereby there is obtained an N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidinyll salt (e.g. compound II below) as an intermediate convertible to benzotriazine oxide, and converting the guanidinyll salt to benzotriazine oxide by subjecting it to a dehydroxylation reaction to effect ring closure and form the said benzotriazine oxide.

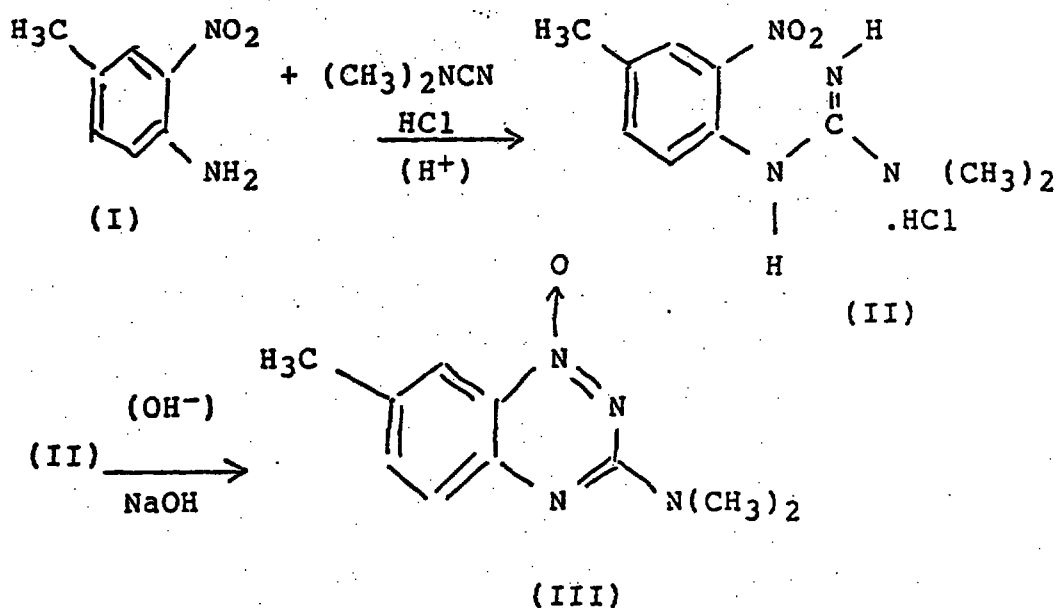
The solvent for the 4-methyl-2-nitroaniline is preferably a non-polar solvent, e.g. toluene and desirably excess solvent is used. The initial reaction mixture at 20°C may conveniently contain 15 to 20% by weight of the aniline compound or more broadly 5 to 50% by weight and 5 to 15% or more broadly 1 to 30% by weight of the dimethyl cyanamide so long as the solution remains free flowing and adapted to be refluxed. The solvent is preferably one also having solvent action for dimethylcyanamide. The elevated temperature may be the reflux temperature of the solvent, e.g. 110°C in the case of toluene. The reaction may also be carried out at an elevated temperature below reflux and is then desirably accompanied by stirring, especially by vigorous stirring.

The salt forming moiety is preferably an acid such as hydrogen chloride or hydrochloric acid. When hydrogen chloride is used it may be desirable to have some water present in the reaction vessel, e.g. a small amount of water.

Toluene has a very slight solubility in water:

The dehydroxylation reaction may be carried out by raising the guanidinyll intermediate to elevated temperature in the presence of alkali e.g. NaOH, for example by boiling it with alkali.

The scheme of the reaction according to this aspect of the invention is as follows:-



According to a preferred form of this aspect of present invention a process for the preparation of benzotriazine oxide comprises reacting together dimethylcyanamide and 4-methyl-2-nitroaniline with the introduction of gaseous hydrogen chloride in excess non-polar solvent and at a temperature above 100°C and less than 160°C to obtain a precipitate of N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine hydrochloride, and then reacting that compound with an alkali to effect a ring closure reaction and obtain the desired benzotriazine oxide derivative.

The reaction between the dimethyl cyanamide and the methylnitroaniline is preferably carried out at a temperature between 100°C and 145°C and more preferably at about 135°C. This reaction is preferably carried out under reflux conditions, in which case a solvent that forms a reaction mixture with an appropriate boiling point is chosen. Preferred examples are toluene, naphtha and p-xylene bpt 137-138°C, although in the latter two cases the temperature is preferably somewhat below the reflux temperature which is above the preferred temperature for this reaction.

The above reaction may be carried out under anhydrous conditions, or in the presence of a small quantity of water.

In order to allow the whole process to be performed in a single reaction vessel, the liquid residue may be decanted or pumped off from the precipitate of N,N-dimethyl-N'-(4-methyl-2-nitro-

phenyl) guanidine hydrochloride and an alkali such as NaOH added to the precipitate in the same reaction vessel, in order to bring about the ring closure dehydroxylation reaction.

The precipitated intermediate product N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine hydrochloride may be purified before addition of the alkali which brings about the ring closure reaction. Such purification may involve washing and/or refluxing the precipitate with a suitable solvent, e.g. chloroform.

The molar ratio of the dimethylcyanamide to the 4-methyl-2-nitroaniline is preferably from about 0.8:1 to about 2:1. Higher molar ratios within the above range seem to lead to higher yields of the desired product, but a molar ratio as high as 2.5:1 seems to be accompanied by a decrease in yield in comparison with a ratio of 2:1.

The reaction between dimethylcyanamide and 4-methyl-2-nitroaniline is preferably carried out with stirring.

According to a second preferred aspect of the present invention, a process for the preparation of benzotriazine oxide (compound III below) as herein defined comprises reacting a solution of 4-methyl-2-nitroaniline (compound I below) with cyanamide at elevated temperature and in the presence of a salt forming

moiety whereby there is obtained an amino-N'-(4-methyl-2-nitrophenyl) guanidinyll salt (e.g. compound IV below) as an intermediate convertible to benzotriazine oxide, and converting the guanidinyll salt to benzotriazine oxide by subjecting it to a dehydroxylation reaction to effect ring closure, followed by methylation to form the said benzotriazine oxide.

The solvent for the 4-methyl-2-nitroaniline is preferably a non-polar solvent, e.g. toluene and desirably excess solvent is used. The initial reaction mixture at 20°C may conveniently contain 15 to 20% by weight of the aniline compound or more broadly 5 to 50% by weight and 5 to 15% or more broadly 1 to 30% by weight of the cyanamide so long as the solution remains free flowing and adapted to be refluxed. The elevated temperature may be the reflux temperature of the solvent, e.g. 110°C in the case of toluene. The reaction may also be carried out at an elevated temperature below reflux and is then desirably accompanied by stirring, especially by vigorous stirring.

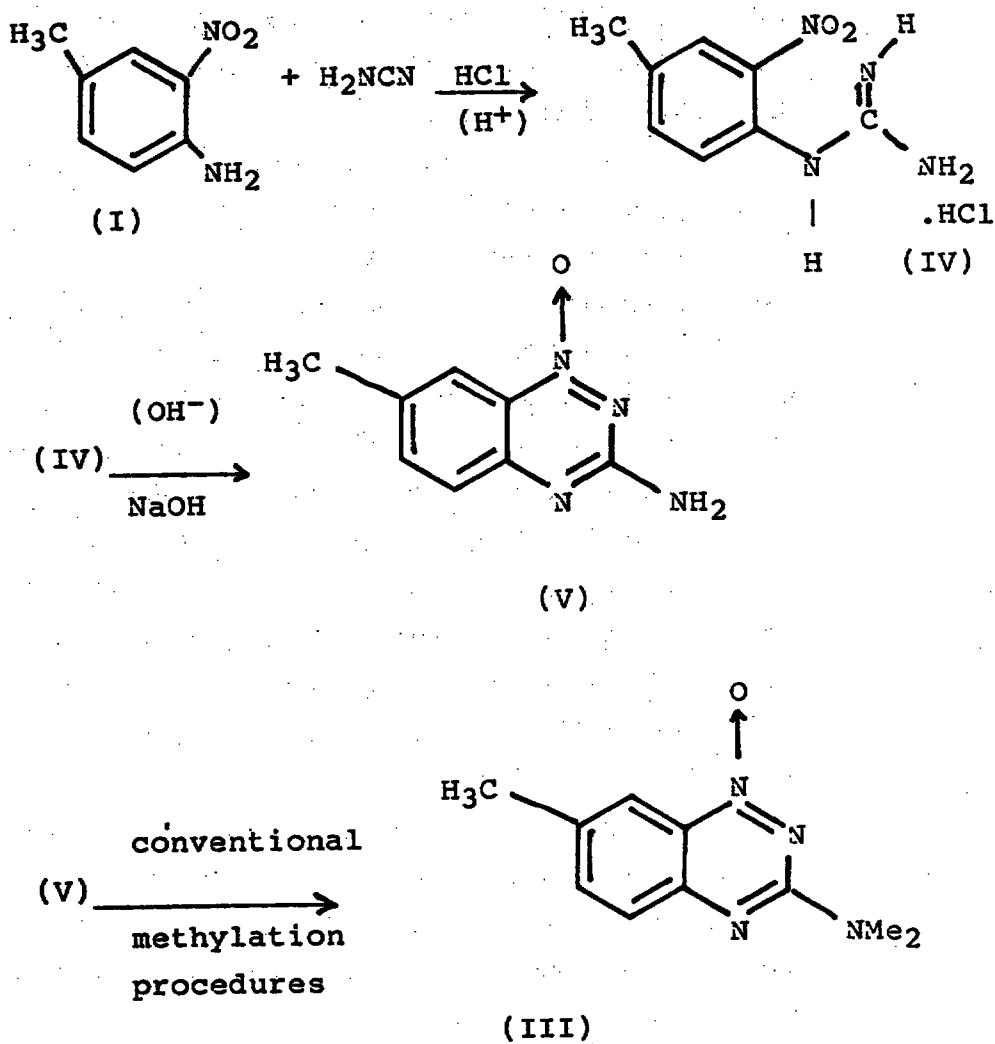
The salt forming moiety is preferably an acid such as hydrogen chloride or hydrochloric acid. When hydrogen chloride is used it may be desirable to have some water present in the reaction vessel, e.g. a small amount of water.

Toluene has a very slight solubility in water.

The dehydroxylation reaction may be carried out by raising the guanidinyll intermediate to elevated

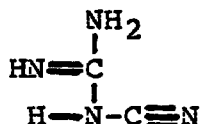
temperature in the presence of alkali e.g. NaOH, for example by boiling it with alkali.

The scheme of the reaction according to the invention is as follows:-



One conventional methylation procedure involves a number of steps and is described below in Example 19.

We believe that the purity of the cyanamide is very important. Impurities are thought likely to result in production of a dimerized form of the guanidinyll intermediate and thus much lower yields because this is thought likely to interfere with or prevent the ring closure to benzotriazine oxide. It is thus preferred to have present in the cyanamide or in the reaction mixture or in both, a stabilizer to inhibit dimerization of the cyanamide. Whilst the invention is not dependant on the accuracy or otherwise of the hypothesis it is thought that the dimer has the following formula:



This dicyanodiamidine is thought capable of reacting to form a guanidino- compound rather than a guanidinyll compound and such compound is then thought likely not to cyclize readily to benzotriazine oxide.

The reaction between the cyanamide and the methylnitroaniline is preferably carried out at a temperature between 100°C and 145°C and more preferably at about 135°C. This reaction is preferably carried out under reflux conditions, in which case a solvent for the methyl nitroaniline that forms a reaction mixture with an appropriate boiling point is chosen. Preferred examples are toluene, naphtha and p-xylene bpt 137-138°C, although in the latter two cases the temperature is preferably somewhat below the reflux temperature which is above the preferred temperature for this reaction.

The molar ratio of the cyanamide to the 4-methyl-2-nitroaniline is preferably from about 0.8:1 to about 2:1.

The invention may be put into practice in various ways and a number of specific embodiments will be described to illustrate the invention with reference to the accompanying examples.

Examples 1 to 10 were laboratory scale preparations of N,N-dimethyl-N-(4-methyl-2-nitrophenyl) guanidine hydrochloride (compound II above).

Example 1

4-methyl-2-nitroaniline (20 g, 0.13 mole) and dimethylcyanamide (10 g, 0.14 mole) were stirred in toluene (120 ml density 0.866 i.e. 104 g) and water (0.12 ml, 0.0067 mole), then heated to reflux to give a clear orange/red solution. The initial reaction solution at room temperature contained about 19% by weight of the aniline compound and 9.6% by weight of dimethyl cyanamide.

Hydrogen chloride gas (50 g total) was bubbled through the solution at reflux temperature (115°C) with stirring for 2 hours, to give a red liquor containing a yellow precipitate flecked with red oil. This mixture was refluxed for a further four hours and then allowed to cool.

The toluene was decanted off, the crude product slurried with chloroform (120 ml), and boiled under reflux for 5-10 minutes. The cooled mixture was filtered and the residue washed with ice cold chloroform (2 x 25 ml).

The yellow solid was dried at 50°C and weighed.

IR, NMR and elemental analysis were performed.

Solvent was removed from the filtration liquors, by heating in the rotary evaporator, leaving a thick red/black oil.

Typical yield of N,N-dimethyl
N'-(4-methyl-2-nitrophenyl)
guanidine hydrochloride = 19.5 g (57%).
Melting point = 222-224°C
Weight of residual oil = 16 g.

Examples 2 to 7

These were concerned with the effect of using various molar ratios of reactants.

Example 1 was repeated except that different molar ratios of dimethylcyanamide : 4-methyl-2-nitroaniline were used. (Example 1 used a ratio of 1.08:1).

The molar ratios used and the yields of N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine hydrochloride obtained are shown in Table I below:

TABLE I

<u>Example</u>	<u>Molar ratio</u> <u>dimethylcyanamide :</u> <u>4-methyl-2-nitroaniline</u>	<u>Yield</u>
2	1.5:1	23.5g (69%)
3	2:1	25.2g (74%)
4	2:1	26.7g (78%)
5	2.5:1	21.0g (62%)
6	1.75:1	23.5g (69%)
7	1:1.2 or 0.83:1	22.0g (62%)

Thus, a molar ratio of about 2:1 seems to give the highest yield.

Examples 8 to 10

These were concerned with the effect of using different solvents and reaction temperature.

The reaction described in Example 1 was repeated, subject to the variations shown in Table 2 below.

TABLE 2

<u>Example</u>	<u>Solvent</u>	<u>Reaction Temperature</u>	<u>Yield</u>
8	p-xylene	130-135°C	21.5 g (63%)
9	p-xylene	145°C	20.6 g (60%)
10	dry toluene (anhydrous reaction)	115°C	19.9 g (58%)

Example 11

This was a laboratory-scale preparation of benzotriazine oxide (compound III).

Recrystallised N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine hydrochloride (compound II above) (25 g, 0.097 mole) was boiled under reflux in molar sodium hydroxide solution (706 ml, 0.706 mole) for five minutes. The solution was allowed to cool to room temperature and the orange yellow solid filtered off, dried, ground to powder and washed with water (50 ml) and then dried at 70°C.

Crude weight of benzotriazine
oxide = 18.8 g
Crude yield = 95%
Melting point of crude compound = 124-126°C.

The product seemed pure from IR and NMR analysis and melting point, but 10 g of it was purified further by dissolving in boiling ethanol (15 ml), cooling, filtering and washing the solid with ice cold ethanol (10 ml) and drying at 70°C.

Weight of purified benzotriazine
oxide = 9.6 g
Yield = 91%
Melting point = 126.5°C.

Analysis of recrystallized product

	Expected for $C_{10}H_{12}N_4O$	Found in Sample
%C	58.80	58.7
%H	5.92	5.9
%N	27.43	27.4

Example 12

This was a larger scale preparation of N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine hydrochloride carried out on ten times the scale of Example 1.

Method: The 4-methyl-2-nitroaniline (400 g, 2.63 mole) and dimethylcyanamide (200 g, 2.85 mole) were dissolved in toluene (2400 ml) and heated to reflux (117°C) in a 5 litre flanged flask fitted with a stirrer, a temperature controller-recorder, a B34 Liebig condenser, an HCl gas inlet and an isomantle. Hydrogen chloride gas was bubbled through the refluxing mixture for a total of 12 hours over a period of 2 days. When it was necessary to interrupt the reaction at the end of the day, the reaction mixture was left to cool under a stream of nitrogen. At the completion of the run, the total quantity of hydrogen chloride used was 330 g (9.04 mole). The mixture was then refluxed for a further 6 hours.

During the course of the reaction, a white solid formed in the condenser and had to be removed occasionally to prevent blockage of the condenser.

After cooling the mixture, the solid was isolated by filtration and stirred with chloroform (1 litre) whilst boiling under reflux for 30 minutes. The mixture was cooled to 10°C, filtered and the solid on the filter was washed with chloroform (3 x 100 ml).

Yield of N,N-dimethyl-N'-
(4-methyl-2-nitrophenyl)
guanidine hydrochloride = 400.3 g (59%)

Melting point = 224-225°C.

Example 13

This was a larger scale preparation of benzotriazine oxide.

Benzotriazine oxide was prepared on sixteen times the scale of Example 11 using the product from Example 12 without further purification.

The product (440 g, 1.55 mole) and molar sodium hydroxide solution (11.24 litres) were mixed in a 20 litre flange-neck flask fitted with anchor stirrer, heating mantle, and reflux condenser. The orange/red suspension was boiled under reflux for 10 minutes then allowed to cool to 20°C with stirring. The solid was isolated by vacuum filtration and washed on the filter with water (2 x 400 ml). After drying at 70°C, the product was broken up and lightly ground in a mortar.

Weight of benzotriazine oxide	= 295 g
Yield	= 93%
Melting point	= 125.5-126°C.

EXAMPLE 14

4-methyl-2-nitroaniline (20 g, 0.13 mole) (compound I) and cyanamide (NCNH_2) (5.9 g, 0.14 mole) are stirred in toluene (120 ml density 0.866 i.e. 104 g) and water (0.12 ml, 0.0067 mole), then heated to

reflux to give a clear orange/red solution. The cyanamide used is ordinary pure commercial material. The initial reaction solution at room temperature contains about 19% by weight of the aniline compound and 9.6% by weight of cyanamide.

Hydrogen chloride gas (50 g total) is bubbled through the solution at reflux temperature (115°C) with stirring for 2 hours, to give a red liquor containing a yellow precipitate flecked with red oil. This mixture is refluxed for a further four hours and then allowed to cool.

The toluene is decanted off, the crude product slurried with chloroform (120 ml), and boiled under reflux for 5-10 minutes. The cooled mixture is filtered and the residue washed with ice cold chloroform (2 x 25 ml).

The yellow solid is dried at 50°C.

Example 15

The product of Example 14 recrystallized, namely amino-N'-(4-methyl-2-nitrophenyl) guanidine hydrochloride (compound II above) (25 g, 0.097 mole) is boiled under reflux in molar sodium hydroxide solution (706 ml, 0.706 mole) for five minutes. The solution is allowed to cool to room temperature and the orange yellow solid filtered off, dried, ground to powder and washed with water (50 ml) and then dried at 70°C.

EXAMPLE 16

4-methyl-2-nitroaniline (20 g, 0.13 mole) (compound I) and cyanamide (NCNH_2) (FLUKA) (5.9 g, 0.14 mole) are stirred in toluene (120 ml density 0.866 i.e. 104 g) and water (0.12 ml, 0.0067 mole), then heated to reflux at 115°C to give a clear red solution. The cyanamide used is ordinary pure material, supplied by FLUKA AG of Buchs, Switzerland under catalogue number 28330 and stated to have a purity of greater than 98% by weight, a m.pt. of $44-46^\circ\text{C}$, and to be stabilized with 0.05% by weight of phosphate and to contain less than 2% by weight water.

Hydrogen chloride gas is bubbled rapidly through the mixture with rapid stirring for 2 hours, to give a red liquor containing a yellowish precipitate. The mixture is refluxed for a further four hours and then allowed to cool.

The precipitate is filtered off and slurried with chloroform (120 ml), and boiled under reflux for 5-10 minutes, cooled to room temperature, filtered and washed with ice cold chloroform (2 x 50 mls).

The yellow solid is dried in vacuo in a dessicator to give 22gr of compound III (yeild 75%). Recrystallization from ethanol gives a sample having a m.pt. of $205-208^\circ\text{C}$.

I.R. and N.M.R spectral analyses agree with the assigned structure. However, a satisfactory elemental analysis could not be obtained, probably due to the product containing some hydrochloride of the starting material.

Example 17

Example 16 is repeated, but using a 100% molar excess of cyanamide. A yield of 75% of the crude product is obtained. Again a satisfactory elemental analysis could not be obtained.

Example 18

The crude product of Example 17 was refluxed for 10 minutes with an excess of molar sodium hydroxide solution. The resulting product was 3-amino-7-methyl-1,2,4-benzotriazine-1-oxide (compound III) in 63% yield having a m.pt. of 271-273°C. I.R. and N.M.R. analyses indicated it to be pure. A sample recrystallized from a mixture of ethanol and one drop of acetic acid gave a satisfactory elemental analysis.

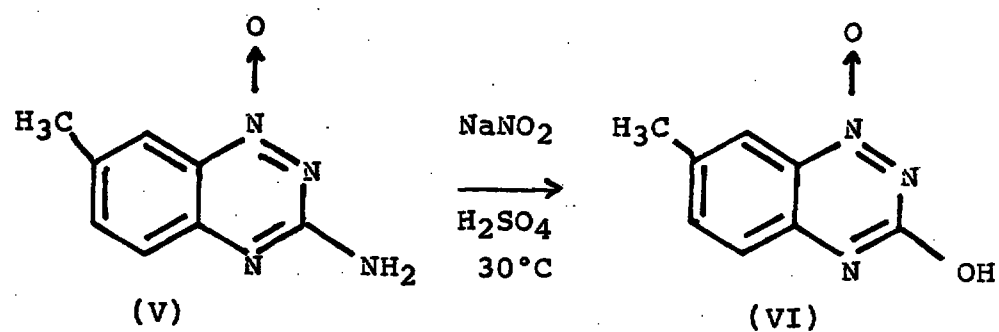
(Found: C 53.6%, H 4.4%, N 31.2%.)

(Expected: C 54.5%, H 4.5%, N 31.8%.)

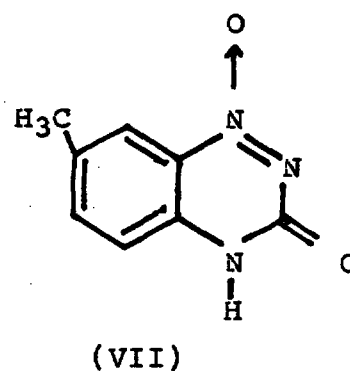
Example 19

The product of Examples 15 and 18 may then be converted to benzotriazine oxide by the following methylation procedure.

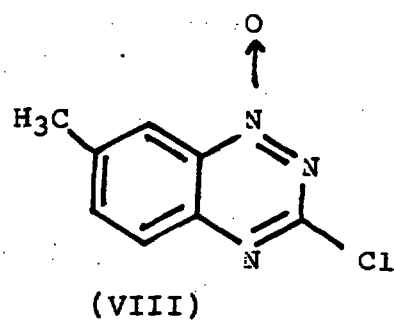
The 3-amino-7-methyl-1,2,4-benzotriazine-1-oxide (V) from Example 15 or Example 18 is converted to 3-dimethylamino-7-methyl-1,2,4-benzotriazine-1-oxide (III) as shown in the reaction sequence below. This is achieved by reaction of (V) with sodium nitrite and sulphuric acid at 30°C. The product (VI) undergoes tautomeric shift to a lactam (VII) and this is converted by reaction with phosgene and dimethyl aniline at 120°C to compound (VIII). This is converted to compound (III) by refluxing with dimethylamine in alcohol.



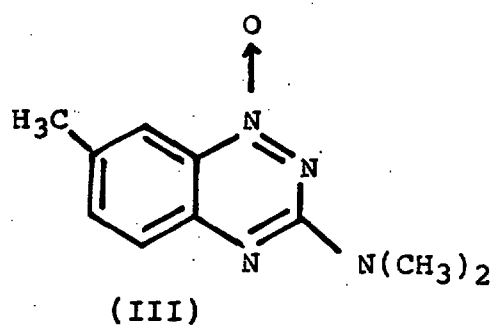
(VI) tautomeric
 shift



(VII) POCl_3
 $\xrightarrow[\text{PhN}(\text{CH}_3)_2, 120^\circ\text{C}]{}$



(VIII) $(\text{CH}_3)_2\text{NH}$
 $\xrightarrow[\text{alcohol, reflux}]{}$



CLAIMS

1. A process for the preparation of benzo-triazine oxide which comprises reacting a solution of 4-methyl-2-nitroaniline with dimethylcyanamide at elevated temperature and in the presence of a salt forming moiety whereby there is obtained an N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidinyll salt as an intermediate convertible to benzotriazine oxide and converting the guanidinyll salt to benzotriazine oxide by subjecting it to a dehydroxylation reaction to effect ring closure and form the said benzotriazine oxide.

2. A process for the preparation of benzo-triazine oxide which comprises heating a solution of 4-methyl-2-nitroaniline in a substantially anhydrous non-polar solvent with dimethyl cyanamide in the presence of gaseous hydrogen chloride whereby there is obtained an N,N-dimethyl -N'-(4-methyl-2-nitrophenyl) guanidinyll salt as an intermediate convertible to benzotriazine oxide, and heating the guanidinyll salt with alkali to effect a dehydroxylation reaction to produce ring closure and form the said benzotriazine oxide.

3. A process as claimed in Claim 1 in which the solvent for the 4-methyl-2-nitroaniline is a non-polar solvent.

4. A process as claimed in Claim 1, 2 or 3 in which the initial reaction mixture at 20°C contains 5 to 50% by weight of the aniline compound



and 1 to 30% by weight of the cyanamide the amounts being such that the mixture remains free flowing and adapted to be refluxed.

5. A process as claimed in anyone of Claims 1 to 4 in which the solvent is one also having solvent action for the cyanamide.

6. A process as claimed in any one of Claims 1 to 5 in which the elevated temperature is the reflux temperature of the solvent.

7. A process as claimed in any one of Claims 1 to 5 in which the reaction is carried out at an elevated temperature below reflux and is accompanied by vigorous stirring.

8. A process as claimed in any one of Claims 1 to 7 in which the salt forming moiety is an acid.

9. A process as claimed in Claim 8 in which the acid is hydrogen chloride or hydrochloric acid.

10. A process as claimed in any one of Claims 1 to 9 in which the dehydroxylation reaction is carried out at elevated temperature in the presence of alkali.

11. A process for the preparation of benzo-triazine oxide which comprises reacting together dimethylcyanamide and 4-methyl-2-nitroaniline with



the introduction of gaseous hydrogen chloride in excess non-polar solvent and at a temperature above 100°C and less than 160°C to obtain a precipitate of N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine hydrochloride, and then reacting that compound with an alkali to effect a ring closure reaction and obtain the desired benzo-triazine oxide derivative.

12. A process as claimed in Claim 11 in which the reaction between the cyanamide and the methylnitroaniline is carried out at a temperature between 100°C and 145°C.

13. A process as claimed in any one of Claims 1 to 12 in which the solvent is toluene, naphtha or p-xylene.

14. A process as claimed in any one of Claims 1 to 13 in which the molar ratio of the cyanamide to the 4-methyl-2-nitroaniline is from 0.8:1 to 2:1.

15. A process as claimed in Claim 1 substantially as specifically described herein with reference to Example 11 or Example 13.

16. Benzotriazine oxide whenever made by a process as claimed in any one of Claims 1 to 15.
