



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification<sup>4</sup> : C07D 253/08, 487/04 // (C07D 487/04, 253:00, 231:00)</p>	A1	<p>(11) International Publication Number:      <b>WO 87/ 04432</b>  (43) International Publication Date:        30 July 1987 (30.07.87)</p>
<p>(21) International Application Number:    PCT/GB87/00055 (22) International Filing Date:        28 January 1987 (28.01.87)  (31) Priority Application Number:         8602038 (32) Priority Date:                    28 January 1986 (28.01.86) (33) Priority Country:                    GB</p> <p>(71) Applicants (for all designated States except US): A.H. ROBINS COMPANY LIMITED [GB/GB]; Langhurst Wood Road, Horsham, West Sussex RH13 5QP (GB). UNIVERSITY COLLEGE CARDIFF CONSULTANTS LTD. [GB/GB]; P.O. Box 78, Cardiff (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : HEWLINS, Michael, John, Edward [GB/GB]; 5 Emmerdale Close, Penylan, Cardiff CF2 5NZ (GB). JONES, Huw, Onllwyn [GB/GB]; 129 Arabella Street, Roath, Cardiff CF2 4SY (GB).</p>		<p>(74) Agent: KEARNEY, Kevin, David, Nicholas; Kilburn &amp; Strode, 30 John Street, London WC1N 2DD (GB).</p> <p>(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: PREPARATION OF 3-DIMETHYLAMINO-7-METHYL-1,2,4-BENZOTRIAZINE-1-OXIDE AND AZAPROPAZONE</p>		
<p>(57) Abstract</p> <p>Process for the preparation of benzotriazine oxide from 1-chloro-2-nitro-4-methyl-benzene and monosodium cyanamide, via a guanidinyll compound which is then cyclized. Azapropazone is then made from the benzotriazine oxide produced by the novel process.</p>		

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1.

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

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  
5 benzotriazine oxide prepared by the improved process, and azapropazone made therefrom.

Benzotriazine oxide is of commercial importance because it is an intermediate in the preparation of the anti-inflammatory drug azapropazone. The  
10 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  
15 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  
20 reaction vessels.

We have devised a process for the preparation of benzotriazine oxide from 1-chloro-2-nitro-4-methyl-  
25 benzene and monosodium cyanamide, which can be carried out safely with good yields.

According to one aspect of the present invention,  
25 a process for the preparation of benzotriazine oxide (compound IV below) as herein defined comprises reacting a solution of 1-chloro-2-nitro-4-methyl-  
benzene (compound I below) with alkali metal cyanamide, preferably monosodium cyanamide at elevated temperature, cooling the reaction mixture,

## 2.

adding HCl to produce 4-methyl-2-nitro-carbanilino-  
nitrile (Compound II below) which is reacted with  
dimethylamine in solution, preferably in alcohol at  
elevated temperature whereby there is obtained an  
5 N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine  
(compound III below) as an intermediate convertible  
to benzotriazine oxide. The guanidine compound may  
be converted to benzotriazine oxide by subjecting it  
to a dehydroxylation reaction to effect ring closure  
10 and form the said benzotriazine oxide.

The solvent for the 1-chloro-2-nitro-4-methyl-  
benzene is preferably an aprotic solvent such as N,N  
dimethyl formamide (DMF) and desirably excess solvent  
is used. The initial reaction mixture at 20°C may  
15 conveniently contain 15 to 20% by weight of the  
benzene compound or more broadly 5 to 50% by weight  
and 5 to 15% or more broadly 1 to 30% by weight of  
the alkali metal cyanamide so long as the solution  
remains free flowing and adapted to be refluxed. The  
20 solvent is preferably one also having solvent action  
for the alkali metal cyanamide. The elevated  
temperature may be the reflux temperature of the  
solvent. The reaction may also be carried out at an  
elevated temperature below reflux and is then  
25 desirably accompanied by stirring, especially by  
vigorous stirring.

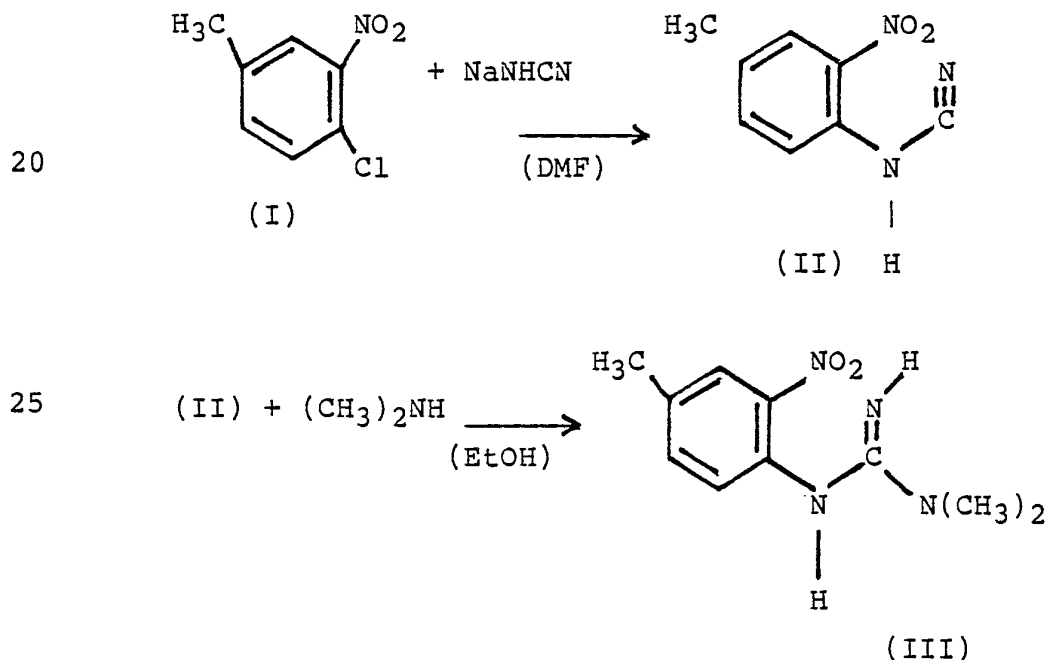
The dehydroxylation reaction may be carried out  
by raising the guanidine compound to elevated  
temperature in the presence of alkali e.g. NaOH, for  
example by boiling it with alkali.

3.

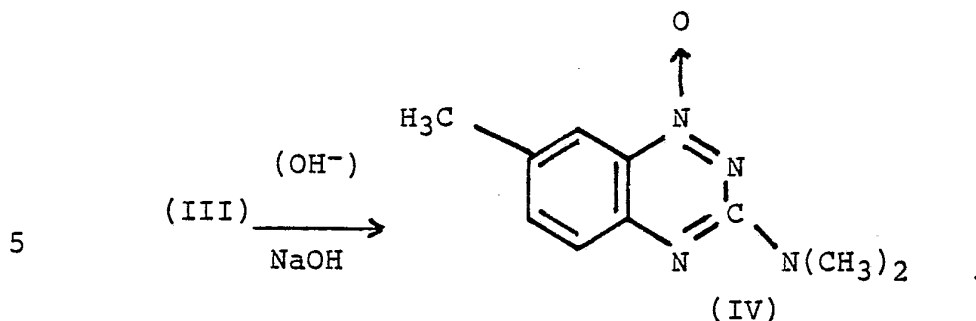
In a preferred form of the invention the alkali ring closure reaction is carried out using an excess of hydroxyl group containing phase transfer catalyst, e.g. a quaternary ammonium salt catalyst such as tetrabutyl ammonium hydroxide. The guanidine intermediate may be taken up in an organic solvent phase and the 1-oxide product recovered from an aqueous phase, the phase transfer catalyst having solubility in both phases and promoting the ring closure reaction.

The invention also extends to this aspect independently of how the guanidine intermediate is arrived at.

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



4.



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

10

EXAMPLE 1

4-chloro-3-nitrotoluene (1-chloro-2-nitro-4-methyl benzene) (10 g) and monosodium cyanamide (10 g) in dimethylformamide (30 ml) were heated under reflux for one hour. The mixture was cooled and filtered. The filtrate was concentrated under reduced pressure and water (50 ml) was added to the residue. The mixture was acidified with hydrochloric acid (2M) and the yellow solid which separated was filtered off, dried, washed with cold hexane, and dried to give a pale yellow crude product. This was recrystallised from ethanol to give pale yellow crystals of 4-methyl-2-nitrocarbanilone (compound II above) (6.4 g, 62%), m.p. 177-80°. (Found C, 54.38; H, 4.00; N, 23.71.  $\text{C}_8\text{H}_7\text{N}_3\text{O}_2$  requires C, 54.24; H, 3.95; N, 23.73%).

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20

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The above carbanilone (4.73 g) and dimethylamine (25 g) in industrial methylated spirits (75 ml) was heated at reflux for twenty hours.

5.

The mixture was cooled and evaporated under reduced pressure to give N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine (Compound III above) (5.9 g, 95%), m.p. 83-4°.

5           The guanidine compound was refluxed with 1M sodium hydroxide solution to produce ring closure and give the desired 1-oxide (compound IV above).

EXAMPLE 2

Monosodium cyanamide was made as follows:

10           An equivalent of sodium ethoxide in ethanol was added slowly to an ethanolic solution of cyanamide. The mixture was stirred for an hour after which the crystalline product was filtered, washed with ethanol and dried to give an 86% yield of the required sodium cyanamide. Infrared absorption showed nitrile  
15           absorption at 2200  $\text{cm}^{-1}$ , and a sample of the compound gave a positive flame test for sodium.

          One equivalent of sodium cyanamide was added to 4-chloro-3-nitrotoluene (1-chloro-2-nitro-4 methyl  
20           benzene) in dimethylformamide. The mixture was heated, cooled, filtered, and the crude product worked up to give a 23% yield of 4-methyl-2-nitro-carbanilonitrile. The structure was confirmed by spectroscopic techniques. The molecular weight was  
25           confirmed by the EI spectrum which showed the molecular ion at  $m/z$  177 ( $\text{C}_8\text{H}_7\text{N}_3\text{O}_2$ ).

          This preparation was repeated with two and a half equivalents of sodium cyanamide added to 4-chloro-3-nitrotoluene in dimethylformamide and the reaction carried out as before to give a 62% yield

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after recrystallisation of 4-methyl-2-nitrocarbanilone nitrile. The structure was confirmed by spectroscopic techniques.

5 The carbanilonitrile was added to a large excess of dimethylamine in industrial methylated spirits, and the mixture heated at reflux for 20 hours. The mixture was cooled and the solvent removed under reduced pressure to give a 95% yield of N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine. The structure  
10 was confirmed spectroscopically.

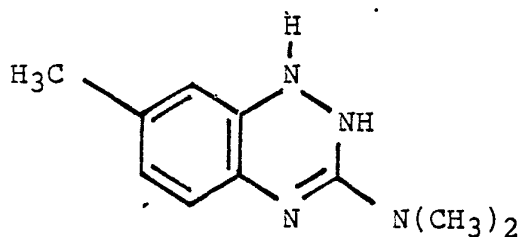
The guanidine was cyclised to the desired 1-oxide (Compound IV above) as follows:

The guanidine in toluene was heated at reflux for thirty minutes with an excess of tetrabutylammonium hydroxide as a 40% aqueous solution. The  
15 mixture was cooled and the organic layer washed and evaporated to dryness to give the crude product which was recrystallised from ethanol to give an 82% yield of the required 3-dimethylamino-7-methyl-1,2,4--  
20 benzotriazine 1-oxide. The structure was confirmed spectroscopically.

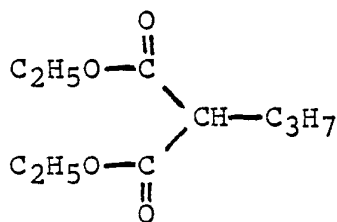
This method gives the required 1-oxide (compound IV above) which is a precursor to Azapropazone in 48% yield from the 4-chloro-3-nitrotoluene. This route  
25 is of advantage commercially in the synthesis of Azapropazone since it involves only three steps to the 1-oxide from readily available materials.

As mentioned above the present invention extends to azapropazone produced from benzotriazine oxide made by the processes of the present invention.

Thus according to a further aspect of the present invention a process for making azapropazone comprises making benzotriazine oxide by a process in accordance with the present invention and then hydrogenating the benzotriazine oxide, e.g. with Pd/C catalyst, to produce a compound of the formula:



and then reacting this compound with mono-n-propyl malonic acid diethyl ester, namely:



in the presence of sodium methoxide,  $\text{CH}_3\text{ONa}$ , and xylene to produce azapropazone, optionally as the dihydrate.

8.

CLAIMS

1. A process for the preparation of benzotriazine oxide (as herein defined) which comprises reacting a solution of 1-chloro-2-nitro-4-methylbenzene with alkali metal cyanamide, at elevated temperature, cooling the  
5 reaction mixture, adding HCl to produce 4-methyl-2-nitro-carbanilino-nitrile which is reacted with dimethylamine in solution, at elevated temperature whereby there is obtained an N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine as an  
10 intermediate convertible to benzotriazine oxide.

2. A process as claimed in Claim 1 in which the alkali metal cyanamide is monosodium cyanamide.

15 3. A process as claimed in Claim 1 or Claim 2 in which the guanidine compound is converted to benzotriazine oxide by subjecting it to a dehydroxylation reaction to effect ring closure and form the said benzotriazine oxide.  
20

4. A process as claimed in any one of Claims 1 to 3 in which the initial reaction mixture at 20°C contains 5 to 50% by weight of the benzene compound and 1 to 30% by weight of the alkali metal cyanamide,  
25 the amounts being such that the solution remains free flowing and adapted to be refluxed.

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5. A process as claimed in any one of Claims 1 to 4 in which the dehydroxylation reaction is carried out by raising the guanidine compound to elevated temperature in the presence of alkali.

5

6. A process as claimed in any one of Claims 1 to 5 in which the alkali ring closure reaction is carried out using an excess of hydroxyl group containing phase transfer catalyst.

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7. A process for forming benzotriazine oxide which comprises carrying out a ring closure reaction on N,N-dimethyl-N'-(4-methyl-2-nitrophenyl) guanidine using an excess of hydroxyl group containing phase transfer catalyst.

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8. A process as claimed in Claim 6 or Claim 7 in which the phase transfer catalyst is a quaternary ammonium salt catalyst.

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9. A process as claimed in Claim 8 in which the phase transfer catalyst is tetrabutyl ammonium hydroxide.

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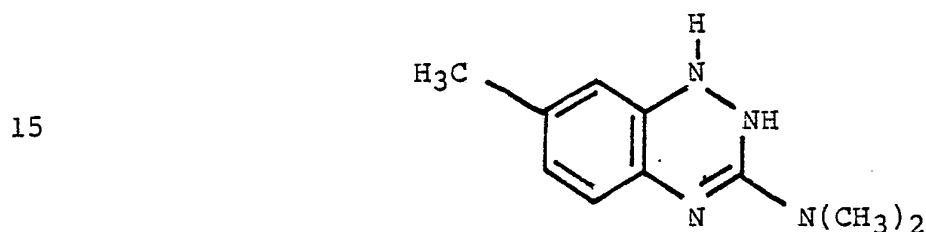
10. A process as claimed in any one of Claims 6 to 9 in which the guanidine compound is taken up in an organic solvent phase and the 1-oxide product recovered from an aqueous phase, the phase transfer catalyst having solubility in both phases and promoting the ring closure reaction.

10.

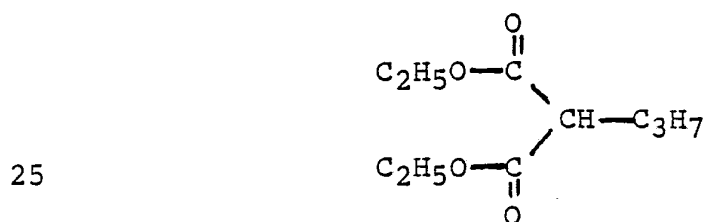
11. Benzotriazine oxide whenever made by a process as claimed in any one of Claims 1 to 10.

5 12. Azapropazone whenever made from benzotriazine oxide as claimed in Claim 11.

10 13. A process for making azapropazone which comprises making benzotriazine oxide by a process as claimed in any one of the preceding process claims and then hydrogenating the benzotriazine oxide to produce a compound of the formula:




20 and then reacting this compound with mono-n-propyl malonic acid diethyl ester, namely:



in the presence of sodium methoxide,  $\text{CH}_3\text{ONa}$ , and xylene to produce azapropazone, optionally as the dihydrate.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 87/00055

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC <sup>4</sup> : C 07 D 253/08; C 07 D 487/04// (C 07 D 487/04, 253/00, 231/00)		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC <sup>4</sup>	C 07 D 253/00; C 07 D 487/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
Y	Berichte der Deutschen Chemischen Gesellschaft, volume 46-III, 1913, (Berlin, DE) F. Arndt: "Ringschluss zwischen Nitro- und Aminogruppe unter Bildung von Triazinen", see pages 3522-3524	1-5
Y	Helvetica Chimica Acta, volume 55, Fasc. 3, 1972, Verlag Helvetica Chimica Acta, (Basle, CH), G. Mixich: "105. Isolierung, Struktur und Synthese des Metaboliten von Azapropazon-dihydrat", see pages 1031-1038	1-13
Y	EP, A, 0001090 (BAYER) 21 March 1979 see page 5	1-5
Y	The Journal of Organic Chemistry, volume 24, June 1959, Mack Printing Co., (Easton, Pennsylvania, US), J. Jiu et al.: "Syntheses in the 1,2,4-benzotriazine series", ./.	
<p><sup>9</sup> Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10th April 1987	25 MAY 1987	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	M. VAN MOL 	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	pages 813-818, see pages 814-815	1-5
A	-- US, A, 3349088 (I. MOLNAR) 24 October 1967 see claims -----	1,13

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 87/00055 (SA 15940)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/04/87

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0001090	21/03/79	DE-A- 2740887	22/03/79
		JP-A- 54049329	18/04/79
		US-A- 4206212	03/06/80
		AU-A- 3973578	20/03/80
		AU-B- 518038	10/09/81
US-A- 3349088		DE-A, B, C 1470296	08/01/70
		US-A- 3482024	02/12/69
		CH-A- 487171	15/03/70
		FR-M- 4165	
		GB-A- 1087831	
		FR-A- 1440629	

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