

EUROPEAN QUALIFYING EXAMINATION 2002

PAPER A CHEMISTRY

This paper comprises:

- * Client's Letter 2002/A(C)/e/1-9
- * Document A 2002/A(C)/e/10-14

CLIENT'S LETTER

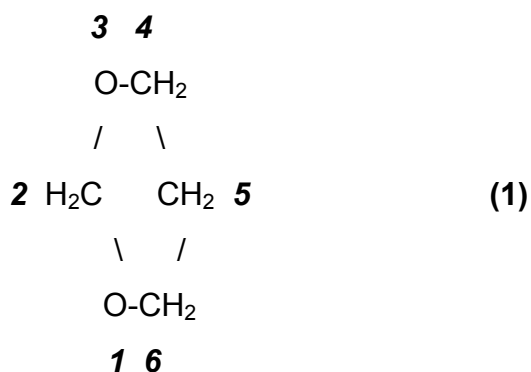
From : Herb E. Syde & Co.

To: Candy Date

Dear Candy,

I know you are very busy. Nevertheless I would be grateful to you if you could work out a draft for a patent application on one of my inventions. This is very urgent, so please deal with this as soon as you can.

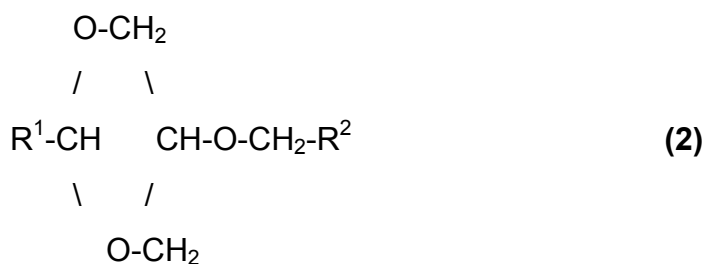
Our lab is currently working on the synthesis and use of 1,3-dioxane derivatives. 1,3-dioxane has a six-membered ring with oxygen atoms in positions 1 and 3. Its formula is depicted below.



where the numbers of the positions of the carbon and oxygen atoms are indicated in **bold** type.

1,3-dioxane and many of its derivatives are known. For your convenience I enclose Document A which has been published recently.

The novel compounds synthesized in our lab are those of formula **(2)**:



where

R¹, i.e. the substituent in the 2-position on the ring, means alkyl, haloalkyl, alkoxyalkyl, aryl, heteroaryl or substituted aryl;

the group of the formula **-O-CH₂-R²** is situated at the 5-position;

and the radical **R²** is a phenyl radical which is optionally substituted with up to three radicals **X** selected from halogen, -CN, -CF₃, C₁-C₄-alkyl and C₁-C₄-alkoxy.

Preferred compounds of formula (2) are those where

R¹ is phenyl, furyl or an alkyl or haloalkyl radical having from 1 to 4 carbon atoms.

R² is preferably phenyl, optionally substituted with a radical **X** in the 2-position (i.e. ortho). **R**² is more preferably phenyl, 2-chlorophenyl, 2-fluorophenyl or 2-methylphenyl.

You will have noted that the radicals **R**¹ and **-O-CH₂-R²** in formula (2) are different. As a consequence of this, the compounds of formula (2) exist in two stereoisomeric forms.

In one isomer, the radicals **R**¹ and **-O-CH₂-R²** are in a *cis* relationship, i.e. both radicals are above, or both radicals are below, the 1,3-dioxane ring.

In the other isomer, the radicals **R**¹ and **-O-CH₂-R²** are in a *trans* relationship, i.e. one of the radicals is above and the other below the 1,3-dioxane ring.

In the following, I will refer to these stereoisomers as the *cis* and the *trans* isomers.

These isomers can be easily separated and isolated since they have different physical properties, e.g. different melting and boiling points.

As you will recall, one of our major fields of interest is chemicals for use in agriculture.

The *cis* isomers of formula (2) proved to be quite effective as herbicides. Herbicides are

weed killers, i.e. compounds that control undesired plant growth. Said *cis* isomers are effective as herbicides when applied before the emergence of the weeds (i.e. as pre-emergence herbicides) or after the emergence of the weeds (i.e. as post-emergence herbicides). The *trans* isomers show no or only a negligible herbicidal effect.

The compounds of formula (2) may be prepared by

- (1) first reacting an aldehyde of formula (3)



with **glycerol** and then

- (2) reacting the product of step (1) with a compound of the formula



where R^2 has the same meaning as given above (see under formula (2)) and Y means a halogen atom.

The products of step (1) are known from GB-A-1 001 001.

As is evident, the aldehyde of formula (3) could also be reacted with a reaction product of glycerol with the compound of formula (4). However, such a process yields products of formula (2) where more than 50 % is in the form of the *trans* isomer.

This invention provides a new class of herbicidal materials, having both pre-emergence and post-emergence activity. The materials are highly suitable for the control and elimination of grassy plants, particularly annual grasses, in the presence of broad-leaved crops, such as cotton, sugar beets, peanuts, soya beans, snap beans, lima beans or tomatoes.

For use as a herbicide it is most economical to use materials of high *cis* content made by a process which reduces, or avoids, the formation of the *trans* isomer. The higher the *cis* content the greater is the herbicidal effect of the given mixture of *cis* and *trans* isomers. In the most preferred forms of the invention, the *cis* compound is present in an amount at least equal to that of the corresponding *trans* compound, preferably the *cis:trans* ratio is more than 1.5:1, more preferably over 2:1 and still more preferably at least 3:1.

The products of formula (2) may be combined with other herbicides. The research department informed me yesterday that combinations of the *cis* isomers of formula (2) with the known herbicides bromoxynil and/or ioxynil show a synergetic effect against weeds whilst having a good crop tolerance. I will send you a summary of these experiments as soon as possible.

The preparation, properties, and herbicidal activities of representative compounds of this invention are illustrated further in the following Examples. Temperatures indicated are in °C, pressures in mm Hg unless indicated otherwise.

Example 1

5-benzyloxy-2-methyl-1,3-dioxane (R^1 =methyl; R^2 =phenyl in formula (2))

A. Preparation of 5-hydroxy-2-methyl-1,3-dioxane

In a 500-ml three-necked flask equipped with a stirrer, a condenser and a Dean-Stark trap (for azeotropic removal of water), 44 g of **acetaldehyde** was slowly added to a stirred mixture of 92 g of **glycerol** and 6 drops of concentrated sulphuric acid. The reaction mixture was heated at 100 °C for 3 hours, then cooled to room temperature and neutralised with potassium carbonate. The mixture was washed with 100 ml of petroleum ether and then distilled at 58-60 °C/100 Pa to give 68.4 g of **5-hydroxy-2-methyl-1,3-dioxane**. The infrared spectrum of the product was consistent with the assigned structure.

B. Preparation of 5-benzyloxy-2-methyl-1,3-dioxane

1.6 g of sodium hydride in portions was added to a mixture of 4.8 g of **5-hydroxy-2-methyl-1,3-dioxane** and 100 ml of benzene.

This mixture was stirred at room temperature for 9 hours, after which 5.1 g of **benzyl chloride** ($C_6H_5-CH_2-Cl$, i.e. R^2 =phenyl and $Y=Cl$ in formula (4)) was added in portions over a 15 minute period. The reaction mixture was heated, with stirring, at 80 °C for 24 hours. The reaction mixture was washed with two 100-ml portions of water, and the organic layer was dried over magnesium sulphate. Solvent was removed under reduced

pressure to give 7.5 g of oil, which was distilled to give 4.1 g of 5-benzyloxy-2-methyl-1,3-dioxane, boiling point: 111-112 °C /50 Pa. The IR and NMR spectra were consistent with the assigned structure.

Analysis:	Calculated for C ₁₂ H ₁₆ O ₃ :	C 69.21; H 7.69;
	Found:	C 68.97; H 7.73.

Examples 2 to 6

In a completely analogous manner the following compounds were prepared:

(2) **5-benzyloxy-2-phenyl-1,3-dioxane** (R¹=phenyl; R²=phenyl):

melting point: 73-75 °C;

Analysis:	Calculated for C ₁₇ H ₁₈ O ₃ :	C 75.56; H 6.67;
	Found:	C 75.48; H 6.65.

NMR studies revealed the product to be 80-90% *cis*-5-benzyloxy-2-phenyl-1,3-dioxane.

(3) **5-benzyloxy-2-(2-furyl)-1,3-dioxane** (R¹=2-furyl; R²=phenyl):

melting point: 50-52 °C;

Analysis:	Calculated for C ₁₅ H ₁₆ O ₄ :	C 69.21; H 6.20;
	Found:	C 69.44; H 6.00.

The NMR spectrum of the product indicated it to be a mixture of *cis* and *trans* isomers in a ratio of about 70:30. Separation of the isomers by fractional crystallization from hexane and benzene resulted in isolation of the pure *cis* compound, melting point 63-64 °C.

(4) **5-benzyloxy-2-chloromethyl-1,3-dioxane** (R¹=chloromethyl; R²=phenyl):

boiling point: 100-105 °C/0.025 mm Hg;

The NMR spectrum was consistent with the assigned structure and showed the *cis* isomer content to be 52 %, the remainder being the *trans* isomer.

Analysis:	Calculated for C ₁₂ H ₁₅ ClO ₃ :	C 59.38; H 6.23;
	Found:	C 59.56; H 6.49.

The preparation was repeated and the isomeric mixture separated by column chromatography. The pure *cis* isomer was a solid, melting point 38-39 °C, and the *trans* isomer was a liquid, n_D²²: 1.5200.

(5) **5-(2-methylbenzyloxy)-2-chloromethyl-1,3-dioxane**(R¹=chloromethyl; R²=2-methyl-phenyl):

The product was recrystallized twice from benzene and petroleum ether yielding 2.2 g of 5-(2-methylbenzyloxy)-2-chloromethyl-1,3-dioxane, melting point: 62-63 °C, analyzing 98% *cis* isomer by NMR spectroscopy.

Analysis:	Calculated for C ₁₃ H ₁₇ ClO ₃ :	C 60.82; H 6.82;
	Found:	C 60.84; H 6.66.

(6) **5-(2-fluorobenzyloxy)-2-(methoxymethyl)-1,3-dioxane**(R¹=methoxymethyl; R²=2-fluoro-phenyl):

The isomers were separated by passage through a silica gel column using mixtures of petroleum ether and ethyl acetate as eluting solvents.

The first fractions were combined and concentrated to give 3.0 g of *trans*-5-(2-fluorobenzyloxy)-2-(methoxymethyl)-1,3-dioxane, boiling point 151-152 °C/1.5 mm Hg. The later fractions were combined and concentrated to give 5.2 g of *cis*-5-(2-fluorobenzyloxy)-2-(methoxymethyl)-1,3-dioxane, melting point: 31-32 °C. The IR and NMR spectra of the two products were consistent with the assigned structures.

Analysis:	Calculated for C ₁₃ H ₁₇ FO ₄ :	C 62.21; H 7.09;
	Found (<i>trans</i> -isomer):	C 62.44; H 6.85;
	Found (<i>cis</i> -isomer):	C 62.25; H 6.85.

Example 7**Pre-emergence and Post-emergence Herbicidal Activity**

The pre- and post-emergence herbicidal activity of substituted 5-benzyloxy-1,3-dioxanes was tested in the following manner:

Lima beans, corn, lettuce, cotton, crabgrass and barnyard grass were planted side by side in rows. The material to be tested was dissolved in an acetone-water mixture and was sprayed on the soil at a concentration of 4.48 or 6.72 kilograms per hectare for

pre-emergence screening. In post-emergence screening, plants were sprayed with the same acetone-water mixture at a concentration of 4.48 or 6.72 kilograms of material to be tested per hectare approximately 2 weeks after planting. Two weeks after application, the effectiveness of the material was evaluated for both pre- and post-emergence tests. Untreated plants were maintained for comparison in both procedures. Pre-emergence results are presented in Table I and results of post-emergence tests are presented in Table II. Where no results are given in Tables I and II, measurements were not taken of the herbicidal activity.

For herbicidal applications, the active 1,3-dioxanes of formula (2) are formulated by admixture, with the adjuvants and carriers, normally employed for agricultural applications. Thus, these active herbicidal compounds may be formulated as granules, as powders, as emulsifiable concentrates, as solutions, or as any of several other known types of formulations, depending on the desired mode of application. Preferred formulations for both pre- and post-emergence herbicidal application are powders, emulsifiable concentrates, and granules. These formulations may contain as little as 0.5% to as much as 95% by weight of active ingredient.

TABLE I

Pre-emergence Herbicidal Activity (in **percent kill at test concentration**) of Substituted 1,3-dioxanes of Formula (2)

Compound of Example	Test Concentration kg/hectare	Test Plant Species						
		crops				weeds		
		A	B	C	D	E	F	
		percent of killed plants at the test concentration						
1	6.72*	0	0		0	100	100	
2	4.48	75	100	0		100		<i>cis</i> isomer
2	4.48	0	0	0		10		<i>trans</i> isomer
3	4.48		35		0	100	90	<i>cis</i> isomer
4	4.48		50		0	100	95	<i>cis</i> isomer

5	4.48*	0	100	0	100	
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Test plants are:

- A - Lima beans
- B - Corn
- C - Lettuce
- D - Cotton
- E - Crabgrass
- F - Barnyard grass

* Isomer mixture as obtained in the example; concentration is that of *cis* content applied.

TABLE II

Post-emergence Herbicidal Activity of Substituted 1,3-dioxanes of Formula (2)

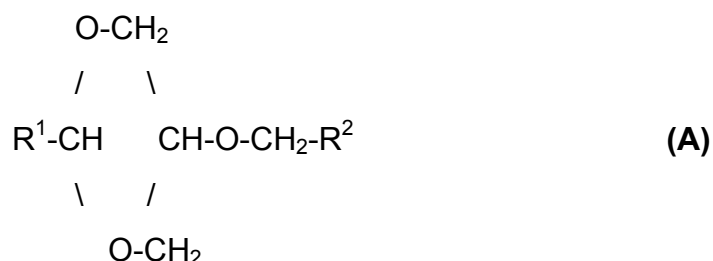
Compound of Example	Test Concentration* kg/hectare	Test Plant Species (Percent kill at test concentration)			
		crops		weeds	
		Corn	Cotton	Crabgrass	Barnyard Grass
1	4.48	100	0	100	100
2	4.48	0		20	80
3	4.48	100	0	100	100
4	6.72**		0	60	20
5	6.72	0		80	70

* Concentration is of the isomeric mixture as produced.

** Concentration is that of *cis* content applied.

DOCUMENT A

The present application relates to novel compounds of formula **(A)**:



where

R¹, i.e. the substituent in 2-position on the ring, means alkyl, haloalkyl, alkoxyalkyl, heteroaryl or optionally substituted aryl;

the group of the formula **-O-CH₂-R²** is situated at the 5-position;

the radical **R**² is a monovalent aromatic phenyl, furyl or thienyl radical which is optionally substituted with up to three radicals **X** selected from halogen, -CN, -CF₃, C₁-C₄-alkyl and C₁-C₄-alkoxy.

Preferred compounds of formula **(A)** are those where

R¹ is phenyl, furyl or an alkyl or haloalkyl radical having from 1 to 4 carbon atoms.

R² preferably is phenyl, optionally substituted with a radical **X** in 2-position (i.e. ortho), especially phenyl, 2-chlorophenyl, 2-fluorophenyl or 2-methylphenyl.

The compounds of formula **(A)** are useful as preservatives for aqueous compositions which normally spoil due to the action of bacteria and fungi. They are effective at low concentrations and non-toxic in the amounts employed.

The compounds of formula **(A)** exist in two stereoisomeric forms. In one isomer, the radicals **R**¹ and **-O-CH₂-R²** are in a *cis* relationship, in the other, they are in a *trans* relationship.

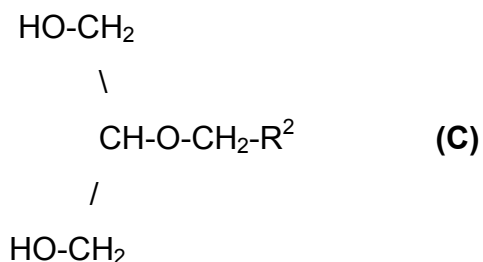
It is not worthwhile to separate or isolate these isomers as both are equally suitable for the given purpose.

It is well known that many aqueous compositions are subject to a pronounced tendency to decompose and spoil through the action of bacteria and fungi. Examples of such compositions include emulsions such as cosmetic compositions, emulsion paints and cutting oils or products such as kerosene and fuel oil which acquire water due to condensation.

The products of the present invention may be produced by reacting an aldehyde of the formula **(B)**



with a compound of formula **(C)**



under standard condensation conditions.

Compounds **(C)** are obtained by the reaction of **glycerol** with a compound of formula **(D)**



where **R²** has the same meaning as given above (see formula **(A)**) and **Y** means a halogen atom.

The invention is illustrated by the following examples:

Example 1

(1) **5-benzyloxy-2-phenyl-1,3-dioxane** (R^1 =phenyl; R^2 =phenyl in formula (A)).

A mixture of 5.0 g of 2-benzyloxy-1,3-propanediol (prepared by reacting glycerol with benzyl chloride), 3.3 g of benzaldehyde and 0.3 g of p-toluene-sulfonic acid in a three-necked, round-bottomed flask equipped with a stirrer, a thermometer and a condenser was heated in an oil bath until it reached 130 °C. The reaction mixture was cooled to room temperature and dissolved in ether. The ether solution was washed with 10% sodium carbonate and then with water. After drying over anhydrous sodium sulphate, the ether was removed under reduced pressure. Distillation of the crude oil gave 3.3 g of 5-benzyloxy-2-phenyl-1,3-dioxane.

Analysis:	Calculated for $C_{17}H_{18}O_3$:	C 75.56; H 6.67;
	Found:	C 75.49; H 6.64.

Examples 2 to 5

Under analogous conditions the following compounds were prepared:

(2) **5-benzyloxy-2-(2-furyl)-1,3-dioxane** (R^1 =2-furyl; R^2 =phenyl):

Analysis:

Calculated for $C_{15}H_{16}O_4$:	C 69.21; H 6.20;
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Found:	C 69.44; H 6.00.
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(3) **5-benzyloxy-2-chloromethyl-1,3-dioxane** (R^1 =chloromethyl; R^2 =phenyl):

Analysis:

Calculated for $C_{12}H_{15}ClO_3$:	C 59.38; H 6.23;
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Found:	C 59.56; H 6.49.
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(4) **2-chloromethyl-5-(2-methylbenzyloxy)-1,3-dioxane**

(R^1 =chloromethyl; R^2 =2-methyl-phenyl):

Analysis:

Calculated for $C_{13}H_{17}ClO_3$:	C 60.82; H 6.82;
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Found:	C 60.84; H 6.66.
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(5) **5-(2-fluorobenzyloxy)-2-(methoxymethyl)-1,3-dioxane**(R¹=methoxymethyl; R²=2-fluoro-phenyl).

Analysis:

Calculated for C₁₃H₁₇FO₄: C 62.21; H 7.09;

Found: C 62.34; H 6.85.

Example 6

To illustrate the effectiveness of **5-benzyloxy-2-phenyl-1,3-dioxane** as a preservative in a standard emulsion paint, formulations containing 0.1% **5-benzyloxy-2-phenyl-1,3-dioxane** (I) and 0.1% methyl p-hydroxybenzoate (II) were compared with paints containing no added preservative (III). Methyl p-hydroxybenzoate is a standard preservative.

The method employed to test the preserving properties of compositions under consideration is as follows:

Fifty gram samples were inoculated with 0.05 ml of a 24 hour broth culture of *Pseudomonas aeruginosa* which results in the samples having an initial bacterial count of approximately one million per gram. The inoculated samples were then held at 30 °C and bacterial counts made at 1, 24 and 72 hours after the inoculations.

The results are shown in the following table:

Emulsion paint no.	bacterial count after		
	1 h	24 h	72 h
I	74 x 10 ⁴	< 100	< 100
II*	100 x 10 ⁴	240 x 10 ⁵	520 x 10 ³
III*	380 x 10 ⁴	> 300 x 10 ⁵	> 300 x 10 ⁵

* Comparative.