

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Purification of Halothane

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED of Imperial Chemical House, Millbank, London, S.W.1., a British Company, do hereby declare the invention, for which we

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pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

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This invention relates to a purification process and more particularly it relates to a process for the purification of 2,2,2-trifluoro-1-chloro-1-bromethane hereinafter referred to as halothane.

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Halothane is a valuable inhalation anaesthetic used for the production of anaesthesia in men and in animals. However, depending on the manner of manufacture of halothane, it may contain small amounts of certain impurities and it is an object of the present invention to remove such impurities.

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According to the present invention we provide a process for the purification of impure halothane containing as impurity at least one compound of the formula $CF_3 \cdot CX=CY \cdot CF_3$, wherein X stands for hydrogen, bromine or chlorine and Y stands for bromine or chlorine and/or at least one compound of the formula $CF_2=CClZ$ where Z is hydrogen, bromine, chlorine or fluorine which comprises intimately

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contacting said impure halothane in the liquid phase with a metal permanganate and recovering the purified halothane.

It is to be understood that any compound of the above-stated formula $CF_3 \cdot CX=CY \cdot CF_3$ may be present as impurity in the form of a cis isomer or a trans isomer or a mixture thereof.

The permanganate treatment can be carried out using aqueous, or non-aqueous solvents, particularly organic solvents (for example acetone), or mixtures of such solvents, which are not appreciably attacked by permanganate. The use of organic solvents can increase the rate of attack on the impurities in the halothane but can also complicate subsequent isolation

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tion of the purified halothane, however, so it is generally preferred to use the permanganate in the form of an aqueous solution.

The relative proportions of halothane and aqueous solution may be varied considerably, and the optimum proportions in any particular circumstances will depend upon such factors as the thoroughness of mixing, the particular impurities present and the amounts of these which have to be removed, and the temperature of treatment. Suitable proportions are in the range 1:5 and 5:1 by volume, though proportions outside this range may be used if desired. Proportions of about 1:1, i.e. approximately equal volumes of halothane and aqueous solution, are usually found to be suitable and convenient.

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The permanganate may be in particular an alkali metal or alkaline earth metal permanganate, and the permanganate solution may be acid, neutral or alkaline. Of the latter a neutral or alkaline solution is preferred. If the solution is to be alkaline, this may be achieved most conveniently by addition of an alkali metal hydroxide, though other bases may be used if desired, for example, alkaline earth metal hydroxides or ammonia. If the solution is to be acid, this may be conveniently achieved by addition of, for example, sulphuric acid.

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Useful results can be obtained when using up to 10% by weight in the aqueous phase of sodium hydroxide or potassium hydroxide although higher concentrations than this could be used if desired. However lower rather than higher proportions than 10% by weight of NaOH or KOH are preferred and it is particularly preferred to employ concentrations of up to 2% by weight NaOH or KOH, for example 0.1% to 2% by weight NaOH, in the aqueous phase.

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Sodium and potassium permanganates are particularly useful metal permanganates to be used in the process of the invention. Useful results may be obtained with various concentrations of permanganate in the aqueous phase.

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[Price 4s. 6d.]

For example, good results are obtained when using a substantially saturated solution of potassium permanganate in the aqueous phase, that is about 60 g/l. potassium permanganate at ambient temperature.

- 5 Preferably the impure halothane is vigorously agitated with the aqueous solution of the permanganate. Thus is one suitable method the impure halothane is vigorously agitated with an aqueous solution of the permanganate at a temperature ranging from 0°C. to the boiling point of the mixture, for example, at ambient temperature, the agitation is stopped and the mixture is allowed to separate into two distinct layers, and the lower halothane layer is fractionally distilled.

- 10 The process may be carried out in a batch or continuous manner. Again the present process may be used in conjunction with other purification procedures, for example, those based on fractional distillation which can be carried out before or after the present process.

- 20 The following Example illustrates but does not limit the invention. All parts are to be read as parts by weight.

EXAMPLES

The following table illustrates the removal of various impurities from halothane under a variety of conditions wherein the halothane was vigorously agitated with an aqueous solution of permanganate. Some of the impurities were purposely added and sometimes in large amounts in order to illustrate the efficiency of the process. The purified halothane was analysed by gas/liquid chromatography. The impurities were:—

- A. 2-Chloro-1,1,1,4,4,4-hexafluoro butene-2. (trans).
B. 2-Chloro-1,1,1,4,4,4-hexafluoro butene-2. (cis).
C. 2-Bromo-1,1,1,4,4,4-hexafluoro butene-2. (trans).
D. 2,3 - Dichloro-1,1,1,4,4,4-hexafluoro butene-2. (cis).
E. 2,3 - Dichloro-1,1,1,4,4,4-hexafluoro butene-2. (trans).
F. 1-Chloro-1-bromo-2,2-difluoro ethylene.
G. 1-Chloro-2,2-difluoro ethylene.

Example No.	HALOTHANE		PERMANGANATE SOLUTION					Temperature °C	Time hours	Total Impurities Remaining p.p.m.
	Parts	Impurities present	Permanganate		Water Parts	Additive				
			Cation	Parts		Compound	Parts			
1	100	50 p.p.m. C	Ca	5	50	Nil	Nil	22	2	<5
2	145	95 p.p.m. C	K	4.5	75	NaOH	1.5	0	1.5	<5
3	190	35 p.p.m. A 190 p.p.m. C	K	3	100	H ₂ SO ₄	2	48	3	<5
4	200	60 p.p.m. A 95 p.p.m. C	K	3	100	NH ₃	1	23	2.5	<5
5	200	60 p.p.m. A 95 p.p.m. C	Ba	4	100	Ba(OH) ₂	2	22	2.5	<5
6	100	60 p.p.m. A 95 p.p.m. C	K	5	108	KOH	0.5	50	1	<5
7	8000	110 p.p.m. A 185 p.p.m. C	K	255	4250	NaOH	85	20	1	<5

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TABLE (continued)

Example No.	HALOTHANE		PERMANGANATE SOLUTION					Temperature °C	Time hours	Total Impurities Remaining p.p.m.
	Parts	Impurities present	Permanganate		Water Parts	Additive				
			Cation	Parts		Compound	Parts			
8	200	100 p.p.m. A 170 p.p.m. C 210 p.p.m. D 150 p.p.m. E	Ba	3	54	NaOH	1	21	8	<5
9	200	100 p.p.m. A 170 p.p.m. C 210 p.p.m. D 150 p.p.m. E	Na	4	108	NaOH	2	21	7	<5
10	589000	120 p.p.m. A 130 p.p.m. C 220 p.p.m. D 110 p.p.m. E	K	14000	300000	NaOH	4000	27	5.5	<10
11	200	75 p.p.m. G	K	4	100	NaOH	1.5	22	0.25	<5
12	100	65 p.p.m. F	K	1.5	27	NaOH	0.5	21	0.75	<5
13	100	70 p.p.m. A 375 p.p.m. C 725 p.p.m. D 620 p.p.m. E 25 p.p.m. F	Na	10	100	NaOH	2	50	5	<5
14	589000	205 p.p.m. A 70 p.p.m. B 125 p.p.m. C 75 p.p.m. F	K	12315	300000	NaOH	4870	22	2	<5

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WHAT WE CLAIM IS:—

1. A process for the purification of impure halothane containing as impurity at least one compound of the formula $CF_3.CX=CYCF_3$, wherein X stands for hydrogen, bromine or chlorine and Y stands for bromine or chlorine and/or at least one compound of the formula $CF_2=CClZ$ where Z is hydrogen, bromine, chlorine or fluorine, which comprises intimately contacting said impure halothane in the liquid phase with a metal permanganate and recovering the purified halothane.
2. A process as claimed in Claim 1 in which an aqueous solution of the metal permanganate is employed.
3. A process as claimed in Claim 2 in which the solution is neutral or alkaline.
4. A process as claimed in Claim 3 in which up to 10% by weight sodium or potassium hydroxide is present in the aqueous phase.
5. A process as claimed in Claim 4 in which up to 2% by weight sodium or potassium hydroxide is present in the aqueous phase.
6. A process as claimed in any of the preceding claims in which sodium or potassium permanganate is employed as the metal permanganate.
7. A process as claimed in Claim 6 in which a substantially saturated solution of potassium permanganate in the aqueous phase is employed.
8. A process as claimed in any of the preceding claims in which the purification process is carried out at ambient temperature.
9. A process as claimed in any of the preceding claims 2 to 8 in which the relative proportions of halothane to aqueous solution of permanganate is in the range 1:5 to 5:1 by volume.
10. A process as claimed in any of the preceding claims 1 to 9 which comprises vigorously agitating the impure halothane with an aqueous alkaline solution of the permanganate at a temperature ranging from 0°C. to the boiling point of the mixture, for example at ambient temperature, stopping the agitation and allowing the mixture to separate into two distinct layers, and fractionally distilling the lower halothane layer.
11. A process for the purification of impure halothane substantially as described with reference to the Examples.
12. Halothane whenever purified by a process as claimed in any of the preceding claims.

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