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CA 94(12): 93631 K

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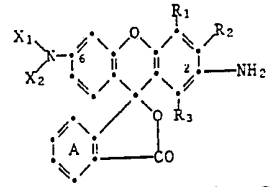
CAS online

(54) Preparation of N-aralkylated and N-aryloxyalkylated aminofluoranes

(57) N-aralkylated and N-aryloxyalkylated aminofluoranes, are prepared by reacting a 2-aminofluorane of formula

(1) 

wherein the ring A is unsubstituted or substituted by halogen, nitro, amino, C_{1-5} alkylamino or di-C_{1-5} alkylamino,
R_1 and R_3 are each independently of the other hydrogen, halogen, C_{1-5} alkyl or C_{1-5} alkoxy,
R_2 is hydrogen, C_{1-5} alkyl or C_{1-5} alkoxy,
X_1 and X_2 are each independently of the other hydrogen, alkyl containing not more than 12 carbon atoms which is unsubstituted or substituted by halogen, hydroxy, cyano or C_{1-5} alkoxy; or are cycloalkyl, tetrahydrofuryl, aryl or acyl, or $-NX_1X_2$ is a 5– or 6–membered, preferably saturated, heterocyclic radical, with an aralkylarlsulfonate of formula

(2) $Z-SO_2-O-Y$,

wherein Z is an aryl radical and Y is an arylalkyl or aryloxyalkyl radical.

The N-aryloxyalkylated aminofluorane compounds are also claimed *per se*

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Process for the preparation of N-aralkylated aminofluoranes

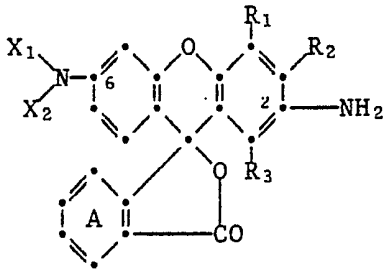
The present invention relates to a process for the preparation of N-aralkylated aminofluoranes.

The aralkyl group is usually introduced by reacting the amino compound with an aralkyl halide, for example benzyl chloride or benzyl bromide, the reaction being carried out in polar media as well as in non-polar solvents and in the presence of alkali compounds. These methods, however, have the drawback that the final product is sometimes obtained in insufficient yield when using polycyclic amino compounds.

It is the object of the present invention to provide an improved process which permits an increase in yield and simultaneously affords products for technical use in excellent purity without complicated purification steps.

Specifically, the invention relates to a process for the preparation of N-aralkylated aminofluoranes, which comprises reacting a 2-aminofluorane of formula

(1)



wherein the ring A is unsubstituted or substituted by halogen, nitro, amino, lower alkylamino or di-lower alkylamino,
R_1 and R_3 are each independently of the other hydrogen, halogen, lower alkyl or lower alkoxy,
R_2 is hydrogen, lower alkyl or lower alkoxy,

X_1 and X_2 are each independently of the other hydrogen, alkyl containing not more than 12 carbon atoms which is unsubstituted or substituted by halogen, hydroxy, cyano or lower alkoxy; or are cycloalkyl, tetrahydrofuryl, aryl or acyl, or $-NX_1X_2$ is a 5- or 6-membered, preferably saturated, heterocyclic radical,
with an aralkylarylsulfonate of formula

(2) $Z-SO_2-O-Y$,

wherein Z is an aryl radical and Y is an arylalkyl or aryloxyalkyl radical.

Halogen is, for example, fluorine, bromine, iodine or, preferably, chlorine.

In the definition of the radicals of the fluoranes, lower alkyl and lower alkoxy normally denote those groups or moieties which contain 1 to 5, preferably 1 to 3, carbon atoms. Lower alkyl groups are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl or amyl, while lower alkoxy groups are, for example, methoxy, ethoxy, isopropoxy, tert-butoxy or tert-amyloxy.

Acyl is preferably formyl, lower alkanoyl such as acetyl or propionyl, or benzoyl. Further acyl radicals can be lower alkylsulfonyl, for example methylsulfonyl or ethylsulfonyl as well as phenylsulfonyl. Cycloalkyl is, for example, cyclopentyl and, preferably, cyclohexyl.

In the meaning of X_1 or X_2 aryl is preferably phenyl or tolyl.

A heterocyclic radical $-NX_1X_2$ is, for example, pyrrolidino, piperidino, pipecolino, morpholino, thiomorpholino or piperazino, for example methylpiperazino. Preferred saturated heterocyclic radicals $-NX_1X_2$ are pyrrolidino, piperidino or morpholino.

X_1 and X_2, each independently of the other, are preferably C_1-C_8-alkyl, cyclohexyl, phenyl or tolyl or most preferably lower alkyl or as $-NX_1X_2$ pyrrolidino

The ring A is preferably not further substituted. If it does contain substituents, then these are preferably halogen or di-lower alkylamino.

Particularly good results are obtained by the process of the invention by using a fluorane of the indicated formula in which R_2 is hydrogen or, preferably, lower alkyl or, most preferably, methyl.

Suitable aralkylarylsulfonates of formula (2) are those in which the aryl radical Z as well as the arylalkyl or aryloxyalkyl radical Y are unsubstituted or ring-substituted. Preferred substituents are halogens, nitro, trifluoromethyl, lower alkyl, preferably methyl, or lower alkoxy such as methoxy.

Particularly suitable sulfonates are those of formula (2), wherein Y is arylalkyl, for example benzenesulfonates, p-toluenesulfonates, p-bromobenzenesulfonates or p-nitrobenzenesulfonates.

Examples of suitable sulfonates for introducing the aralkyl group are:
benzyl p-toluenesulfonate,
phenethyl benzenesulfonate,
phenethyl p-toluenesulfonate,
phenpropyl p-toluenesulfonate,
α-methylbenzyl p-toluenesulfonate,
phenpropyl benzenesulfonate,
phenisopropyl p-toluenesulfonate,
4-chlorbenzyl p-toluenesulfonate,
4-methylbenzyl p-toluenesulfonate,
2,5-dimethylbenzyl p-toluenesulfonate,
2,5-dichlorbenzyl p-toluenesulfonate,
benzyl p-nitrobenzenesulfonate,
benzyl p-bromobenzenesulfonate,
2,4-dimethylbenzyl p-toluenesulfonate,
4-trifluoromethylbenzyl p-toluenesulfonate,
4-methoxybenzyl p-toluenesulfonate,
2-phenoxyethyl p-toluenesulfonate,
2-phenoxyethyl benzenesulfonate.

The preferred alkylsulfonate is benzyl p-toluenesulfonate. 2-Phenoxyethyl p-toluenesulfonate is also preferred.

The aminofluorane and the sulfonate are generally used in approximately stoichiometric proportions such that one aralkyl group, or preferably two aralkyl groups, are introduced per amino group. An excess of, for example, 10-15 % of one of the components is, however, also possible.

The reaction is conveniently carried out at elevated temperature preferably in the range from 80° to 120°C and in the presence of an acid acceptor.

Examples of suitable acid acceptors are alkali metal hydroxides, alkaline earth metal hydroxides, alkali metal bicarbonates, alkali metal carbonates or tertiary nitrogen bases such as pyridine, N-methylpyridine or trialkylamines or also mixtures of these compounds. The preferred acid acceptor is sodium carbonate.

The reaction is preferably conducted in a non-polar, preferably aromatic, solvent, for example, benzene, toluene, xylene, a chlorobenzene such as dichlorobenzene or trichlorobenzene, or nitrobenzene. The preferred solvent is toluene or xylene.

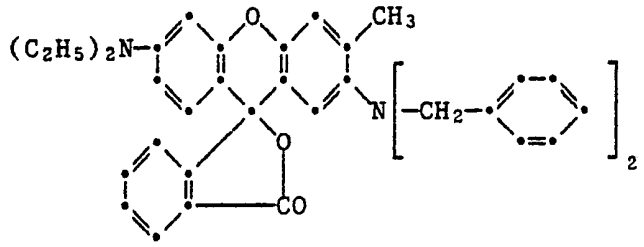
After the condensation reaction the N-aralkylated aminofluorane is isolated in conventional manner, for example removing the solvent by steam distillation, collecting the product by filtration and drying it. If necessary, the aralkylated aminofluorane can be purified by recrystallisation, for example from isopropanol.

In the following Examples, percentages are by weight.

Example 1: 12 g of 2-amino-3-methyl-6-diethylaminofluorane (prepared in accordance with DE-B-2 001 864, Example 6) and 8.7 g of sodium carbonate are stirred in 28 g of toluene and the mixture is heated to 100°C. Then a solution of 23.6 g of benzyl p-toluenesulfonate (prepared in accordance with Monatshefte-Chemie 82, pp. 452-459, 1951) in toluene is added

dropwise at 100°-105°C over 2 hours. The reaction mixture is stirred for 8 hours at 100°C and then poured into 100 g of water. The toluene phase is separated and washed three times with 50 g of water, dried over sodium sulfate and filtered. The toluene is distilled off under reduced pressure. The crude product is taken up in a small amount of isopropyl alcohol, isolated in the form of a crystalline product at 20°C and dried, affording 12 g of a fluorane of formula

(11)



Yield: 69 % of theory
Melting point: 154-155°C.

This compound immediately develops a red colour on acid-modified silica gel.

Example 2: 12 g of 2-amino-3-methyl-6-diethylaminofluorane and 12.4 g of potassium carbonate are heated to 100°C in 60 ml of toluene. Then a solution of 39.3 g of benzyl p-toluenesulfonate in 51 g of toluene is added at 100-105°C over 1 hour. Analysis by liquid chromatography of a sample taken from the reaction mixture shows already the presence of 68.8 % of the condensate of formula (11). The reaction is kept for 1 hour at reflux temperature. Analysis of a fresh sample shows 99.2 % of reaction product.

The reaction product is filtered to remove inorganic salts, the filtrate is concentrated, and the residue is stirred in 75 ml of isopropanol. The crystallised condensate is isolated by filtration and dried, to give 10.5 g of product. Analysis by liquid chromatography shows that the filtrate contains a further 2.1 g of dibenzylaminofluorane of formula (11), but no corresponding monobenzylaminofluorane.

Comparison Example

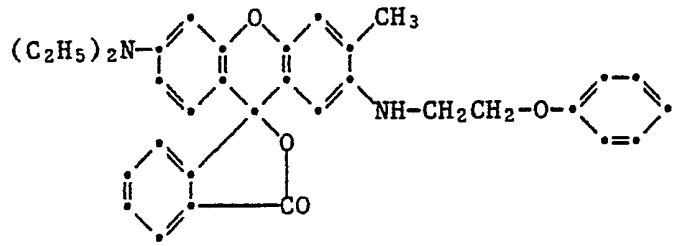
12 g of 2-amino-3-methyl-6-diethylaminofluorane and 12.4 g of potassium carbonate are heated to 100°C in 60 ml of toluene. Then a solution of 19 g of benzyl chloride in 51 g of toluene are added at 100-105°C over 1 hour. Analysis by liquid chromatography of a sample taken from the reaction mixture shows that there is still no trace of the condensate of formula (11). The reaction mixture is kept for 1 hour at reflux temperature. Analysis of a fresh sample still shows no trace of dibenzylaminofluorane of formula (11), but only 3.2 % of the corresponding N-monobenzylated aminofluorane.

The reaction mixture is filtered to remove inorganic salts, the filtrate is concentrated, and the residue is stirred in 75 ml of isopropanol. 8.3 g of the starting 2-amino-3-methyl-6-diethylaminofluorane are recovered by isolating the crystallised product by filtration.

The condensation progresses slightly by concentrating the filtrate. Analysis by liquid chromatography shows a yield of 1.7 g of monobenzylaminofluorane and 1.1 g of dibenzylaminofluorane.

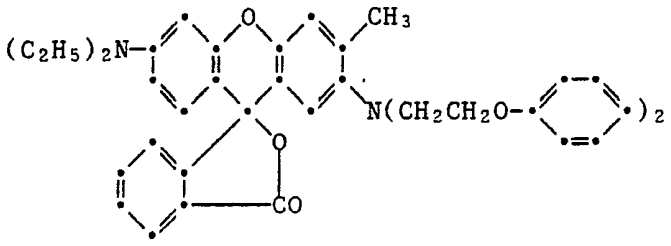
Example 3: 10 g of 2-amino-3-methyl-6-diethylaminofluorane, 10.4 g of potassium carbonate and 21.9 g of 2-phenoxyethyl p-toluenesulfonate (prepared in accordance with J. Org. Chem. 9 (1944), 235, 238-240) are stirred in 40 ml of xylene (mixture of isomers) for 11 hours at 137-140°C under reflux. A further 50 ml of xylene are added and the reaction mixture is extracted repeatedly with 100 ml of water at 50°C. The xylene phase is then concentrated until the condensate crystallises. The product is isolated by filtration, washed with isopropanol and dried, affording 3.1 g of the compound of formula

(12)



in the form of colourless crystals which melt at 189-191°C. A solution of this compound in toluene develops an instant black colour on acid-modified silica gel.

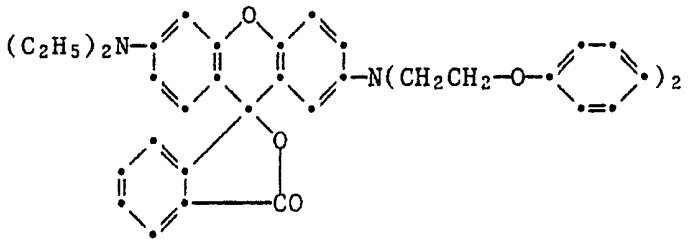
Example 4: Column chromatography of the filtrate obtained according to Example 3 (silica gel; elution with a 20:1 mixture of toluene/ethyl acetate) gives 2.8 g of the fluorane of formula

(13) 

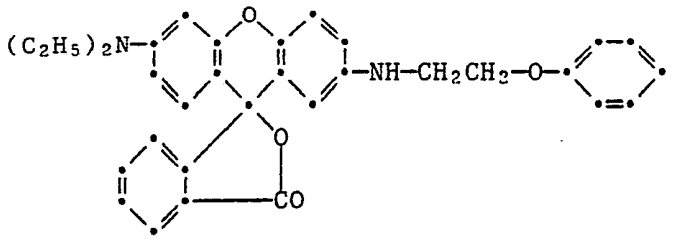
with a melting point of 117-119°C after recrystallisation from isopropanol/toluene (10:1).

This compound immediately develops a red colour on acid-modified silica gel.

Example 5: With efficient stirring, 9.6 g of 2-amino-6-diethylamino-fluorane, 6.9 g of potassium carbonate and 14.6 g of 2-phenoxyethyl p-toluenesulfonate are heated in 50 ml of xylene and the mixture is kept under reflux for 22 hours at 133-137°C. To the reaction mixture are added 50 ml of xylene and, at 80°C, 100 ml of water. The xylene phase is then separated, washed repeatedly with water and concentrated, to give 20 g of crude reaction mixture. The fluorane compounds of formulae (14) and (15) are separated by column chromatography (silica gel; elution with a 10:1 mixture of toluene/ethyl acetate) and are each recrystallised from isopropanol:

(14) 

m.p. 124-127°C.

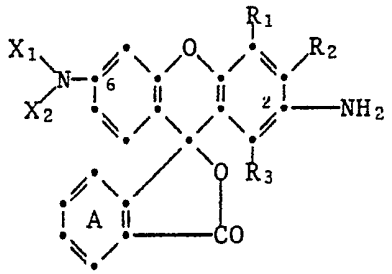
(15) 

m.p. 143-146°C.

The compound of formula (14) develops a green colour, and the compound of formula (15) a black colour, on acid-modified clay.

What is claimed is:

1. A process for the preparation of a N-aralkylated aminofluorane, which comprises reacting a 2-aminofluorane of formula

(1) 

wherein the ring A is unsubstituted or substituted by halogen, nitro, amino, lower alkylamino or di-lower alkylamino,
R_1 and R_3 are each independently of the other hydrogen, halogen, lower alkyl or lower alkoxy,
R_2 is hydrogen, lower alkyl or lower alkoxy,
X_1 and X_2 are each independently of the other hydrogen, alkyl containing not more than 12 carbon atoms which is unsubstituted or substituted by halogen, hydroxy, cyano or lower alkoxy; or are cycloalkyl, tetrahydrofuryl, aryl or acyl, or $-NX_1X_2$ is a 5- or 6-membered heterocyclic radical,
with an aralkylarylsulfonate of formula

(2) $Z-SO_2-O-Y$,

wherein Z is an aryl radical and Y is an arylalkyl or aryloxyalkyl radical.

2. A process according to claim 1, which comprises the use of an aralkylarylsulfonate of formula (2), wherein Y is the arylalkyl radical.

3. A process according to claim 1, wherein the aralkylarylsulfonate is an arylalkyl p-toluenesulfonate, an arylalkyl p-bromobenzenesulfonate or an arylalkyl p-nitrobenzenesulfonate.

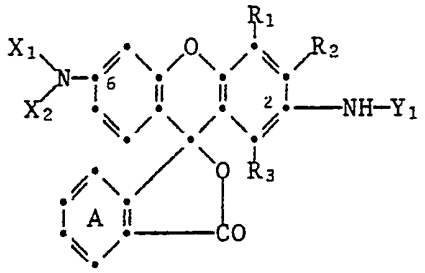
4. A process according to claim 1, wherein the aralkylarylsulfonate is benzyl p-toluenesulfonate.

5. A process according to claim 1, wherein the aralkylarylsulfonate is 2-phenoxyethyl p-toluenesulfonate.

6. A process according to claim 1, which comprises the use of a fluorane compound of formula (1), wherein R_2 is hydrogen or lower alkyl.

7. A process according to claim 1, which comprises the use of a fluorane compound of formula (1), wherein R_2 is methyl.

8. An aminofluorane of the formula



wherein the ring A is unsubstituted or substituted by halogen, nitro, amino, lower alkylamino or di-lower alkylamino,
R_1 and R_3 are each independently of the other hydrogen, halogen, lower alkyl or lower alkoxy,
R_2 is hydrogen, lower alkyl or lower alkoxy,
X_1 and X_2 are each independently of the other hydrogen, alkyl containing not more than 12 carbon atoms which is unsubstituted or substituted by halogen, hydroxy, cyano or lower alkoxy; or are cycloalkyl, tetrahydrofuryl, aryl or acyl, or $-NX_1X_2$ is a 5- or 6-membered heterocyclic radical, and
Y_1 represents an aryloxyalkyl radical.

9. The aminofluorane of claim 8, wherein Y_1 is 2-phenyloxyethyl.

10. The aminofluorane of claim 8, wherein R_2 is methyl.

11. The aminofluorane of claim 8, wherein X_1 and X_2 are lower alkyl or $-NX_1X_2$ is pyrrolidino, piperidino or morpholino.

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