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2,647,895

5-ARALKYLAMINO-9-DIALKYLAMINOBENZO[a]PHENOXAZINE COMPOUNDS AND METHOD OF PREPARING SAME

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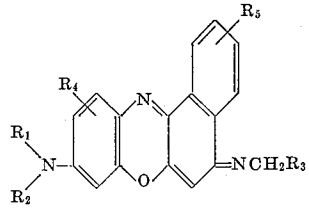
6 Claims. (Cl. 260—244)

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This invention relates to 5-aralkylamino-9-dialkylaminobenzo[a]phenoxazines, and processes of preparing the same.

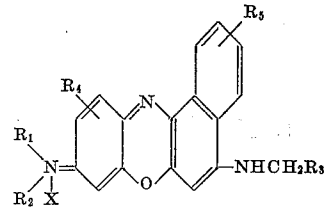
5-benzylamino - 9 - diethylaminobenzo[*a*]phenoxazine has been prepared as a blue dye. It has some activity against tubercle bacilli. It is substantially useless for differential fat staining in vivo. According to the present invention it has been found that a remarkable increase in antitubercular activity is obtained when one of the alkyl groups on the 9-amino nitrogen is from 3–6 carbon atoms, and the other from 2–5 carbon atoms, reaching a very sharp peak when the two alkyl groups have 4 carbon atoms. The longer chain alkyl groups on the 9-nitrogen also endow the compounds with the ability to preferentially stain fatty tissue in living animals; such as, for example, mice, and renders the compounds useful for biological studies. A very effective differential staining is possible with the compounds of the present invention.

The compounds of the present invention may be represented in the form of their free bases by the following formula



where R_1 is alkyl of 3 to 6 carbon atoms; R_2 is alkyl of 2 to 5 carbon atoms; R_3 is phenyl or phenyl substituted with halo, alkyl, alkoxy or alkylenedioxy, and R_4 and R_5 are hydrogen or lower alkyl.

Since the compounds are bases they are capable of forming addition salts with ordinary strong acids such as hydrochloric, hydrobromic, nitric, sulfuric, phosphoric, etc. In the salt form several formulations have been proposed. In the present application, we prefer to use the following form which seems to be most likely from experimental evidence:

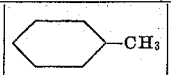
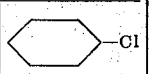


X representing the anion of the acid and the R's having the same significance as above. It should be understood that the invention is not intended to be limited to any theory of the exact structural form of the addition salts. The

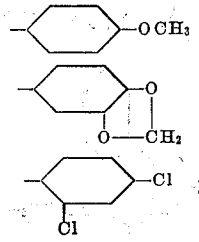
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formula given is merely the one used for convenience. Other formulations in which the anion is connected to the oxygen of the ring have also been proposed.

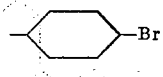
The following table gives a representation of the relative anti-tuberculosis activity of three typical series of compounds when administered to the mice infected with a bovine strain of tubercle bacillus. The activities are relative to the 5-benzylamino-9-diethylamino compound.

R_1	R_2	R_3		
Number of Carbon Atoms				
1	1	0.25	0.5	0.5
2	2	1.0	0.5	1.0
3	3	2.0	2.0	4.0
4	4	8.0	4.0	8.0
5	5	2.0	1.0	4.0
6	6	1.0	0.25	1.0

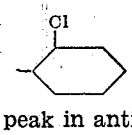
The most active compounds, such as those in which R_1 and R_2 have 3 and 4 carbon atoms, possess an activity in mice markedly greater than that of streptomycin. The antitubercular activity depends primarily on the total number of carbon atoms represented by R_1 and R_2. Thus while it will be seen that, in general, the dihexylamino compounds are inferior to, or no better than, the diethylamino compounds, compounds such as ethylhexyl or propylhexyl show activities which are considerably higher. As will appear from the table, the activity will vary somewhat with R_3. Other typical compounds which also show the increased activities in their series are those in which R_3 is



Slightly less active are compounds in which R_3 is



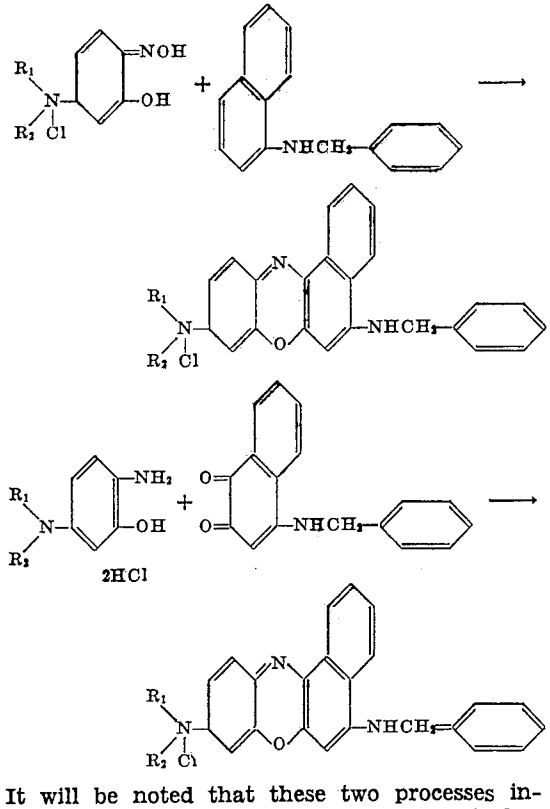
and



The very sharp peak in antitubercular activity for the 9-dibutylamino compounds is quite different from the case presented by the corre-

sponding 5-arylamino compounds which are described and claimed in the copending application, Serial No. 109,625, filed August 10, 1949, now Patent No. 2,528,862, in which the sharp peak occurred with the dipropylamino compound, the dibutylamino compound being no better than the diethyl. It is not known why an entirely different point of maximum activity is to be found in the compounds of the present invention. The variation of antitubercular activity with structure modification is different with the two series. It is not known why there should be the different sharp peaks of maximum activity in the two different series and it is not intended to limit the present invention to any theory of why certain structures should have the surprisingly high antitubercular activity. Also, it is not known why the compounds of the present invention can be used effectively either in the form of their free bases or salts for differential tissue staining in vivo simply by including the compounds in the animals' food. The mechanism by which this differential tissue staining occurs is not at present known except that it seems certain that part, at least, of the color is carried in the blood stream. The invention is therefore likewise not limited to any theory of why the effective differential staining takes place, through the discovery has resulted in the addition of an important research tool in animal experimentation.

The products of the present invention may be prepared by two processes of ring closure resulting in the first instance, in the production of the addition salts of the bases with acids, the free base itself being readily prepared therefrom by the action of an alkaline agent. The two mechanisms will be illustrated generally by equations showing the preparation of the 5-benzylamino compounds.



It will be noted that these two processes involve a ring closure reaction using a meta-hydroxy substituted dialkylaniline with a nitrogen-containing radical ortho to the hydroxy group. When the nitrogen-containing group is amino, the other reactant is an o-quinone derivative of a substituted naphthylamine, whereas when the nitrogen-containing group is a nitroso or oximino group, the substituted naphthylamine itself is used. In each case, the condensation reaction is accompanied by the elimination of water. The first method is preferred for the preparation of most of the compounds because the simple N-aralkyl-naphthylamine is used which is easier to prepare than the corresponding o-quinones.

The invention will be described in greater detail in conjunction with the following specific examples, the parts being by weight unless otherwise specified.

EXAMPLE 1

2-nitroso-5-dipropylaminophenol hydrochloride

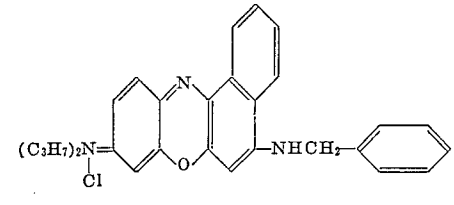
To 218 parts of m-aminophenol are added 300 parts of ethyl alcohol forming a dark colored slurry. To this slurry are added 369 parts of n-propyl bromide and the whole is then heated to a gentle reflux for approximately 5 hours. After removal of alcohol and some unchanged propyl bromide by distillation, the residue is poured into water and treated with soda ash to cause separation of the aminophenol derivatives. The oil layer is taken up in ether, the ether solution is dried and the ether is finally removed by distillation leaving a residue to which is added the alcohol and unchanged propyl bromide removed from the original reaction mixture plus 123 parts of fresh propyl bromide. The resulting solution is then heated to the reflux temperature with stirring for approximately 22 hours, and finally alcohol and a small amount of unchanged propyl bromide are again removed by distillation.

The residue is poured into 1000 parts of water and the mixture is made alkaline by the addition of solid soda ash. The product, which is present as a water insoluble oil, is removed and purified by a vacuum distillation giving the purified m-dipropylaminophenol in the form of a straw colored viscous liquid which shows a boiling point of about 132 to 133° C. at 3 mm. pressure. Upon exposure to air, this liquid acquires a deep red color.

This aminophenol derivative is dissolved in 880 parts of concentrated hydrochloric acid and to the solution is added gradually a solution of 103 parts of sodium nitrite in 210 parts of water, the temperature of the whole mixture being kept below about 10° C. throughout the addition. After the reaction is complete the water-soluble orange-colored solid which forms, consisting of the hydrochloride of the p-nitroso derivative of m-dipropylaminophenol, is removed by filtration, washed with dilute hydrochloric acid and dried. This intermediate product may be used as formed or may be purified, giving an orange-colored solid with a melting point of about 151–152° C.

EXAMPLE 2

5-benzylamino-9-dipropylaminobenzo [a]phenoxazonium chloride



To a suspension of 117 parts of N-benzyl-alpha-naphthylamine in 600 parts of ethyl alcohol are added 194 parts of 2-nitroso-5-dipropylaminophenol hydrochloride plus a few drops of concentrated hydrochloric acid. The whole is then heated to the reflux temperature with stirring for a total period of about three hours during which time the color changes through brown and green to an intense blue.

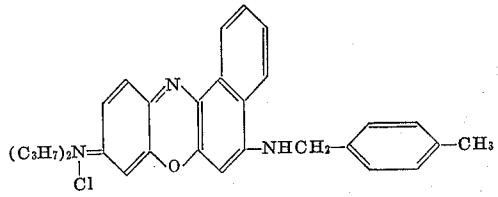
After cooling, the precipitated glistening green product consisting of the chloride salt, is separated by filtration and is purified by recrystallization from acetic acid, using at least 2.5 parts of acetic acid for each part of product.

The base is prepared by treating an ethyl alcohol slurry or suspension of the chloride salt with aqueous ammonium hydroxide solution. The base is obtained as a reddish brown solid exhibiting a reddish color in ethyl alcohol solution.

An ethyl alcohol solution of the chloride salt shows an intense blue color with a maximum absorption at about 645 millimicrons measured spectrophotometrically. An ethyl alcohol solution of the base shows a red color with a maximum absorption at about 518 millimicrons by a spectrophotometric determination.

EXAMPLE 3

5 - (4 - methylbenzylamino) -9-dipropylaminobenzo[a]phenoxazonium chloride



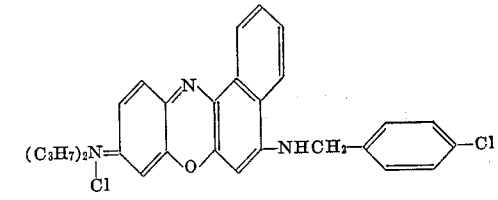
The procedure of Example 2 is followed except that 124 parts of N-(p-methylbenzyl)-alpha-naphthylamine are used instead of 117 parts of N-benzyl-alpha-naphthylamine.

The properties of the 4-methyl substituted derivative here are similar to those of the benzyl derivative described under Example 2.

The N - (p - methylbenzyl)-alpha-naphthylamine used in this example with a melting point of about 66 to 67° C., is prepared by the reduction with magnesium chips in methanol, of N-(p - methylbenzal)-alpha-naphthylamine, obtained by treatment of p-tolylaldehyde with alpha-naphthylamine in alcoholic solution at reflux temperature.

EXAMPLE 4

5-(4 - chlorobenzylamino) -9-dipropylaminobenzo[a]phenoxazonium chloride

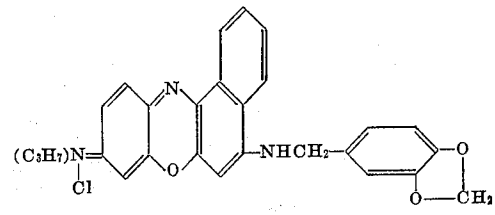


The procedure of Example 2 is followed but 134 parts of N-(p-chlorobenzyl)-alpha-naphthylamine are used in place of 117 parts of N-benzyl-alpha-naphthylamine.

The addition of excess ammonium hydroxide solution to the blue alcoholic solution of the salt of the product precipitates the red-brown base form.

EXAMPLE 5

5 - (3,4-methylenedioxybenzylamino) - 9 - dipropylaminobenzo[a]phenoxazonium chloride



The procedure of Example 2 is followed but 139 parts of N-(3,4-methylenedioxybenzyl)-alpha-naphthylamine are used in place of 117 parts of N-benzyl-alpha-naphthylamine.

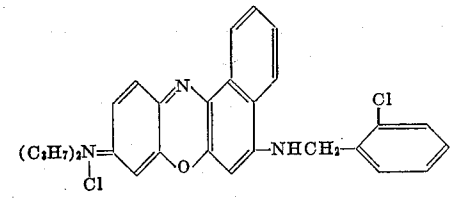
The N-(3,4 - methylenedioxybenzyl) - alpha-naphthylamine which has a melting point of about 65 to 67° C. is prepared as follows:

To a suspension of 273 parts of N-(3,4-methylenedioxybenzal)-alpha-naphthylamine in 8000 parts of methyl alcohol are added in small portions, 420 parts of magnesium chips, the whole being kept at the reflux temperature. The excess methyl alcohol is then removed by distillation and the benzylnaphthylamine derivative is obtained by treatment with acetic acid and water which causes the magnesium compounds to be dissolved leaving the water-insoluble N-(3,4-methylenedioxybenzyl) - alpha-naphthylamine. This is purified by crystallization from alcohol.

The N-(3,4 - methylenedioxybenzal) - alpha-naphthylamine used as starting material is formed by treating equimolar quantities of piperonal and alpha-naphthylamine in ethyl alcohol solution at the reflux temperature for about one-half hour. The anil separates on heating and has a melting point of about 110 to 111° C.

EXAMPLE 6

5-(2-chlorobenzylamino) - 9 - dipropylaminobenzo[a]phenoxazonium chloride



The procedure of Example 2 is used but 134 parts of N - (o-chlorobenzyl)-alpha-naphthylamine are used in place of 117 parts of N-benzyl-alpha-naphthylamine.

In alcohol or acetic acid solution, the product shows a blue color. Addition of ammonium hydroxide solution to an alcoholic solution of the salt gives a brownish red solution of the base which is recovered in the solid form as a dark red-brown material.

The o-chlorobenzylnaphthylamine which is used in this preparation has a melting point of about 110 to 112° C. and is prepared by the reduction of N-(o-chlorobenzal)-alpha-naphthylamine with magnesium chips in methyl alcohol using a procedure similar to that described under Example 5 for the preparation of N-(3,4-methylenedioxybenzyl)-alpha-naphthylamine.

EXAMPLE 7

2-amino-5-dipropylaminophenol dihydrochloride

To an acidic solution of 1350 parts of stannous chloride dihydrate are added gradually 776 parts of 2-nitroso-5-dipropylaminophenol hydrochloride. The mixture is agitated and the reduction is carried out at about room temperature or below.

After passing hydrogen chloride gas into the mixture, the white crystalline solid is removed by filtration. The separation of the product from the tin salt complex is effected by treatment of an aqueous solution of the complex with hydrogen sulfide gas which causes precipitation of the tin as tin sulfide.

The metal-free aqueous solution is then concentrated by distillation, yielding a light solid product which after removal by filtration is purified by crystallization from ethyl alcohol to give the dihydrochloride in the form of snow white crystalline material. This decomposes when heated to temperatures somewhat above 200° C. and generally acquires a bluish color upon exposure to the atmosphere.

EXAMPLE 8

5-benzylamino-9-dipropylaminobenzo[a]-phenoxazonium chloride

To approximately 3000 parts of ethyl alcohol are added 281 parts of 2-amino-5-dipropylaminophenol dihydrochloride and 263 parts of 4-benzylamino-1,2-naphthoquinone. The mixture is heated to the reflux temperature with occasional agitation for about 1½ to 2 hours. There results an intensely blue solution from which precipitates on cooling, a glistening green solid product. This crystalline material which is a chloride salt, is removed by filtration and may be purified by recrystallization from acetic acid.

The green product is somewhat soluble in ethyl alcohol to which it imparts a deep blue color. The base compound is formed by treatment of a slurry of the chloride salt in alcohol with excess ammonium hydroxide. The red-brown solid base at times tends to decompose on storage and the salt form such as the chloride, is therefore more easily handled. The product here is identical with that obtained by using the process described under Example 2.

EXAMPLE 9

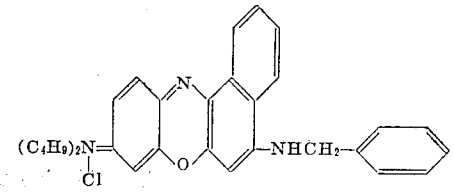
3-dibutylaminophenol

To 218 parts of m-aminophenol are added 300 parts of ethyl alcohol forming a dark-colored slurry. To this slurry are added 411 parts of n-butyl bromide and the whole is then heated to a gentle reflux for approximately 5 hours. After removal of alcohol and some unchanged butyl bromide by distillation, the residue is poured into water and treated with soda ash to cause separation of the aminophenol derivatives. The oil layer is taken up with ether, the ether solution is dried and the ether is finally removed by distillation, leaving a residue to which is added the alcohol and unchanged butyl bromide removed from the original reaction mixture plus 137 parts of fresh butyl bromide. The resulting solution is then heated to the reflux temperature with stirring for approximately 22 hours, and finally alcohol and a small amount of unchanged butyl bromide are again removed by distillation.

The residue is poured into 1000 parts of water and the mixture is made alkaline by the addition of solid soda ash. The product, which is present as a water insoluble oil, is removed and purified by a vacuum distillation giving the purified product in the form of a straw-colored viscous liquid with a boiling range of approximately 173 to 176° C. at 6 mm. pressure. Exposure of this m-dibutylaminophenol to the atmosphere causes it to acquire a deep red color.

EXAMPLE 10

5-benzylamino-9-dibutylaminobenzo[a]-phenoxazonium chloride



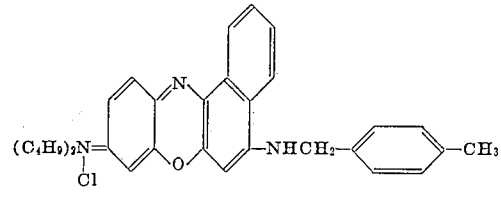
A solution of 88.4 parts of m-dibutylaminophenol in 60 parts ethyl alcohol and 120 parts of concentrated hydrochloric acid is cooled to about 5° C. A paste prepared from 30.4 parts of sodium nitrite and about 2 parts of water is then added to the solution with stirring in small portions over a period of about one hour, the temperature being maintained at 5° C. throughout the addition. The resulting red-orange mixture is stirred another one-half hour and the suspended sodium chloride is removed by filtration and discarded.

The filtate is slowly added to a solution of 62 parts of N-benzyl-alpha-naphthylamine in 400 parts of ethyl alcohol and the whole is heated to the reflux temperature with stirring for two hours. The green solid product which forms on cooling this reaction mixture is removed by filtration and purified by recrystallization from about 500 parts of ethyl alcohol. This product, which is a chloride salt, is obtained as bright green crystalline material which gives an intense blue color in alcohol solution. This shows a maximum absorption at about 647 millimicrons measured spectrophotometrically. An ethyl alcohol solution of the freshly prepared base shows a maximum absorption at about 519 millimicrons.

The base of this product is formed by the addition of ammonium hydroxide solution to an alcoholic suspension or solution of the above chloride, the base being obtained as a red-brown solid. This base in the solid form tends to undergo decomposition and the salt form such as the chloride is therefore preferred if the material is to be stored for any appreciable length of time.

EXAMPLE 11

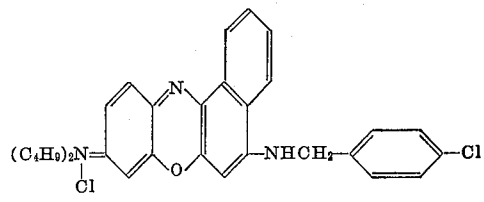
5-(4-methylbenzylamino)-9-dibutylamino-benzo[a]phenoxazonium chloride



This product and the corresponding base are prepared by the procedure described under Example 10 except that 65 parts of N-(p-methylbenzyl)-alpha-naphthylamine are used instead of 62 parts of N-benzyl-alpha-naphthylamine.

EXAMPLE 12

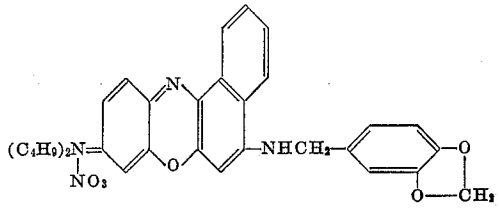
5-(4-chlorobenzylamino)-9-dibutylamino-benzo[a]phenoxazonium chloride



This product and the corresponding base are prepared by the procedure described under Example 10 except that 71 parts of N-(p-chlorobenzyl)-alpha-naphthylamine are used instead of 62 parts of N-benzl-alpha-naphthylamine.

EXAMPLE 13

5-(3,4-methylenedioxybenzylamino)-9-dibutyl-aminobenzo[a]phenoxazonium nitrate



A solution of 88.4 parts of m-dibutylaminophenol in 60 parts of ethyl alcohol and 120 parts of concentrated hydrochloric acid is cooled to about 5° C. A paste prepared from 30.4 parts of sodium nitrite and about 2 parts of water is then added to the solution with stirring in small portions over a period of about one hour the temperature being maintained at 5° C. throughout the addition. The resulting red-orange mixture is stirred another one-half hour and the suspended sodium chloride is removed by filtration and discarded.

The filtrate is slowly added to a solution of 73 parts of N-(3,4-methylenedioxybenzyl)-alpha-naphthylamine in 400 parts of ethyl alcohol and the whole is heated to the reflux temperature with stirring for two hours. After cooling the reaction mixture, about 30 parts of nitric acid are added with stirring, causing the nitrate salt to precipitate.

After removal by filtration, the nitrate is purified by recrystallization from 1000 parts of ethyl alcohol.

The base of this product is obtained by the addition of ammonium hydroxide solution to a slurry of the nitrate in alcohol.

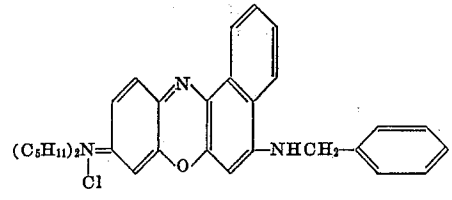
EXAMPLE 14

3-diamylaminophenol

A solution of 109.1 parts of meta-aminophenol, 151 parts of amyl bromide and 150 parts of alcohol is refluxed for a period of about 4 hours with stirring. 151 parts of amyl bromide, 106 parts of soda ash and 200 parts of water are then added and the mixture is refluxed about 16 hours longer. The dark oily product is separated from the water layer, and distilled. There is obtained 221 parts of product boiling at about 170–189° C. at 5 mm. with a refractive index of $n_D^{26}=1.5253$.

EXAMPLE 15

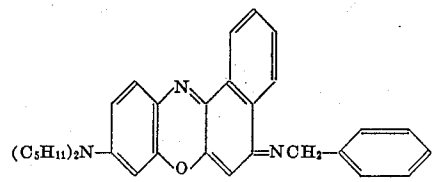
5-benzylamino-9-diamylaminobenzo[a]-phenoxazonium chloride



A solution of 24.9 parts of m-diamylaminophenol, 65 parts of alcohol and 30 parts of concentrated hydrochloric acid is cooled to about 5° C., and treated with 7.6 parts of sodium nitrite added over a period of about 1½ hours. After stirring for ½ hour longer the mixture is filtered to remove the salt and then added to a solution of 15.4 parts of N-benzyl-alpha-naphthylamine and 100 parts of alcohol. The resulting solution is refluxed for 4 hours and stirred for about 15 hours at room temperature, then cooled and filtered. The product is obtained as a dark red crystalline material after recrystallization from 50 parts of ethyl alcohol. This product gives a blue solution in alcohol, and is insoluble in water.

EXAMPLE 16

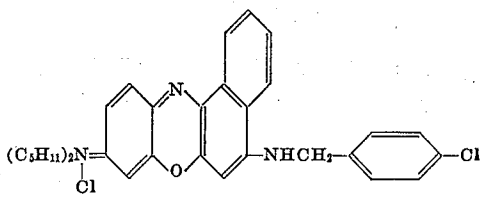
5-benzylamino-9-diamylaminobenzo[a]-phenoxazine base



A mixture of 14.6 parts of 5-benzylamino-9-diamylaminobenzo[a]phenoxazonium chloride, prepared as described under Example 15 and 100 parts of alcohol is warmed gently and treated with about 3 parts of concentrated ammonium hydroxide solution (which is an excess). During this preparation the mixture is stirred vigorously. The base, a dark solid, is obtained by filtration and is soluble in butanol, slighly soluble in methanol and ethanol and insoluble in water. This base is unstable and slowly decomposes on standing, giving a black sticky mass with a foul odor.

EXAMPLE 17

5-(4-chlorobenzylamino)-9-diamylamino-benzo[a]phenoxazonium chloride

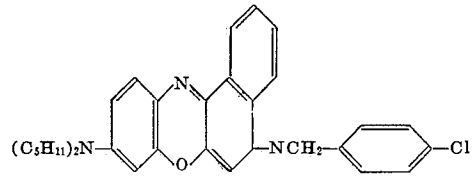


This compound is prepared in a manner similar to that described in Example 15 except that in this case 17.6 parts of N-(p-chlorobenzyl)-alpha-naphthylamine are used instead of 15.4 parts of N-benzyl-alpha-naphthylamine.

The purified chloride salt is obtained; this dissolves in alcohol to give a blue solution.

EXAMPLE 18

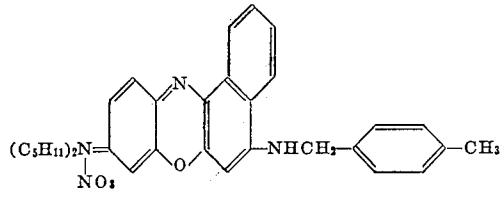
5-(4-chlorobenzylamino)-9-diamylamino-benzo[a]phenoxazine base



A mixture of 17.7 parts of 5-(4-chlorobenzylamino) - 9 - diamylaminobenzo[a]phenoxazonium chloride, prepared as described under Example 17, and 350 parts of alcohol is warmed gently and filtered; to the filtrate are added 20 parts of concentrated ammonium hydroxide solution, while stirring vigorously. After filtering, the brown-green base is obtained which melts at about 74–75° C. This base is unstable and gradually decomposes to a black tarry mass with a foul odor.

EXAMPLE 19

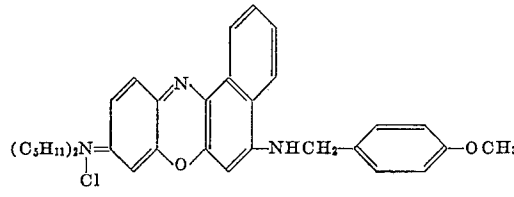
5-(4-methylbenzylamino)-9-diamylamino-benzo[a]phenoxazonium nitrate



A solution of 12.5 parts of m-diamylaminophenol, 35 parts of ethyl alcohol and 15 parts of concentrated hydrochloric acid is cooled to 5° C. and treated with 3.8 parts of sodium nitrite over a period of about 2 hours. After stirring about ½ hour longer, the mixture is filtered and the filtrate is added to a solution of 8.2 parts of N-(p-methylbenzyl)-alpha-naphthylamine and 50 parts of ethyl alcohol. The resulting solution is refluxed for about one hour, then stirred for about 15 hours at room temperature and then allowed to stand in the refrigerator. After adding 25 parts of 6N nitric acid the nitrate is obtained as a green solid. This nitrate, after drying and grinding is a red-brown color; it is soluble in alcohol and insoluble in water.

EXAMPLE 20

5-(4-methoxybenzylamino)-9-diamylamino-benzo[a]phenoxazonium chloride



A solution of 24.9 parts of m-diamylaminophenol, 65 parts of ethyl alcohol and 30 parts of concentrated hydrochloric acid is cooled to 5° C. and treated with 7.6 parts of sodium nitrite over a period of about 2 hours. After stirring an additional half-hour, the mixture is filtered to remove the salt and the filtrate is added to a solution of 17.4 parts of N-(p-methoxybenzyl)-alpha-naphthylamine, and 100 parts of ethyl alcohol. After refluxing for about an hour, and stirring

at room temperature for about 15 hours the solution is allowed to stand. The alcohol evaporates causing the product to solidify; this in insoluble in water, slightly soluble in benzene, fairly soluble in dioxane and soluble in alcohol.

EXAMPLE 21

3-ethylpropylaminophenol

To a solution of 274 parts of 3-ethylaminophenol in 400 parts of ethyl alcohol are added 246 parts propyl bromide. The whole is heated to a temperature of about 70 to 90° C. for five hours and is then poured into two liters of iced water. Sufficient sodium carbonate is added to cause a slightly alkaline reaction and release the product from its hydrobromide. The product in the form of a viscous oil is removed and distilled in vacuum for purification. The light yellow oil obtained has a boiling point of about 138 to 140° C. at 3 millimeters pressure.

EXAMPLE 22

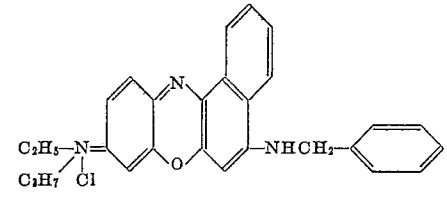
2-nitroso-5-ethylpropylaminophenol hydrochloride

A solution of 179 parts of 3-ethylpropylaminophenol in 570 parts of concentrated hydrochloric acid is cooled to about 5° C. and to it is added dropwise with stirring a solution of 69 parts of sodium nitrite in 150 parts of water. The addition takes about one hour and the reaction mixture is kept below about 10° C. throughout the addition.

After stirring for about one more hour, some precipitated sodium chloride is removed by filtration. On further cooling, the nitroso hydrochloride precipitates and is removed by filtration. More of the orange-yellow crystalline product is obtained by concentration of the mother liquor.

EXAMPLE 23

5-benzylamino-9-ethylpropylaminobenzo[a]phenoxazonium chloride



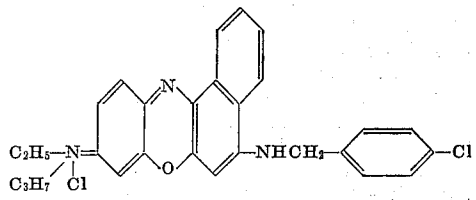
A solution containing 600 parts of ethyl alcohol, 117 parts of N-benzyl-alpha-naphthylamine and 7 parts of concentrated hydrochloric acid is prepared and heated to its boiling point. To the warm solution are added 184 parts of 2-nitroso-5-ethylpropylaminophenol hydrochloride, prepared as described under Example 22 and the whole is then heated to the reflux temperature with stirring for about three hours.

After cooling in an ice-bath, the product precipitates in the form of a glistening green solid. This is removed by filtration and purified by recrystallization from about 2000 parts of acetic acid.

An intensely blue solution is formed by dissolving this chloride salt in ethyl alcohol. Addition of an alkaline reagent to the solution causes a color change to red with the liberation of the base.

EXAMPLE 24

5-(4-chlorobenzylamino)-9-ethylpropylaminobenzo[a]phenoxazonium chloride



The procedure of Example 23 is followed but 134 parts of N-(4-chlorobenzyl) alpha-naphthylamine are used in place of 117 parts of N-benzyl-alpha-naphthylamine.

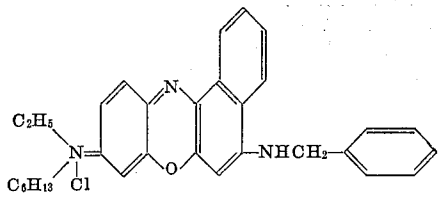
EXAMPLE 25

m-Ethylhexylaminophenol

A solution of 109 parts of m-aminophenol, 182 parts of n-hexyl bromide and 300 parts of ethanol is refluxed for about 4 hours, then the alcohol is removed by distillation and the residue is poured into 700 parts of water. The mixture is made alkaline by the addition of soda ash, and the thick brown mass is separated from the aqueous layer and dissolved in 300 parts of ethanol. 120 parts of ethyl bromide are added and the solution is refluxed for about 8 hours, then the alcohol is removed by distillation and the residue is poured into 1000 parts of water. After making alkaline with soda ash, the dark brown layer is separated from the aqueous layer and fractionally distilled. The product has a boiling point of about 165–185° C. at about 5 millimeters.

EXAMPLE 26

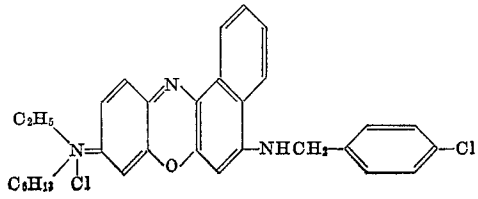
5-benzylamino-9-ethylhexylaminobenzo[a]phenoxazonium chloride



A solution of 22.1 parts of m-ethylhexylaminophenol, 65 parts of ethyl alcohol and 30 parts of concentrated hydrochloric acid is cooled to about 5° C. and treated with 7.6 parts of sodium nitrite added in small portions during a period of 1½ hours. After stirring about an hour longer, the dark red mixture is filtered, to remove the salt, and then added to a refluxing solution of 15.4 parts of N-benzyl-alpha-naphthylamine and 100 parts of ethyl alcohol over a period of about 40 minutes. After refluxing for an additional hour and allowing to stand at room temperature for about 24 hours the mixture is filtered. The product after recrystallizing from 300 parts of glacial acetic acid is obtained as a green crystalline solid, insoluble in water and soluble in alcohol giving a blue solution.

EXAMPLE 27

5-(4-chlorobenzylamino)-9-ethylhexylaminobenzo[a]phenoxazonium chloride



This compound is prepared in a manner similar to that described in Example 26 except that in this case 17.6 parts of N-(p-chlorobenzyl)-alpha-naphthylamine are used in place of the 15.4 parts of N-benzyl-alpha-naphthylamine.

The green crystalline chloride is recrystallized from hot formic acid for purification. It is insoluble in water, and soluble in alcohol giving a blue solution.

EXAMPLE 28

3-ethylpropylamino-4-methylbenzene sulfonic acid

A solution containing 406 parts of N-ethyl-o-toluidine and 492 parts of n-propyl bromide is heated for a total of about fifty hours with stirring to a temperature of 70 to 90° C. The mixture containing some white crystalline material is then treated with about 2000 parts of water and sufficient concentrated caustic soda solution is added to produce a lasting alkaline reaction.

The oil which separates is distilled giving a product which boils at about 218 to 221° C.

This ethylpropylamino derivative is then added gradually with stirring over about 2½ hours to 2400 parts of 25 percent oleum cooled below 10° C. After stirring another hour, the whole is added to sufficient ice to give a total volume of about 5000 parts. Addition of about 1500 parts of 50 percent sodium hydroxide solution causes precipitation of the sulfonic acid derivative in the form of a white solid. This is removed by filtration and recrystallized from about 2000 parts of water.

EXAMPLE 29

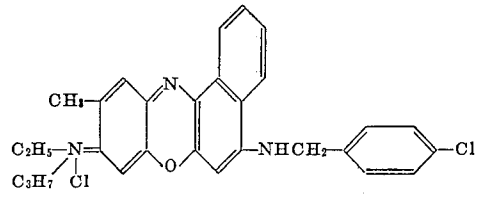
2-nitroso-4-methyl-5-ethylpropylaminophenol hydrochloride

In a stainless steel crucible, a melt of 705 parts of potassium hydroxide and 46 parts of water is prepared. With stirring, 514 parts of 3-ethylpropylamino-4-methylbenzene sulfonic acid, prepared as described under Example 28 are then added over a ten-minute period, the temperature of the mixture being kept at about 290 to 310° C. Before the mixture has cooled below about 200° C., it is poured into a mixture of ice and water to give a total volume of about 4000 parts. Sufficient hydrochloric acid is added to cause an acid reaction and the mixture is filtered to remove impurities. Enough solid sodium carbonate is then added to the filtrate to cause a slightly alkaline reaction. The oil which separates, containing the newly-formed phenol derivative, is removed and distilled for further purification.

The 292 parts of this oil are then dissolved in 1500 parts of normal hydrochloric acid and the solution is cooled to below 10° C. A solution of 69 parts of sodium nitrite in 200 parts of water is added gradually at 10° C. and after stirring several hours more, the supernatant liquid is decanted from the thick dark product. This crude nitroso derivative is taken up in ether and dried and then treated with 55 parts of a saturated alcoholic solution of hydrogen chloride. The solid orange nitroso derivative which forms, melts at about 134° C., with decomposition; this is purified by recrystallization from ethyl alcohol to give the purified yellow-colored hydrochloride.

EXAMPLE 30

5 - (4 - chlorobenzylamino) - 9 - ethylpropylamino - 10 - methylbenzo[a]phenoxazonium chloride

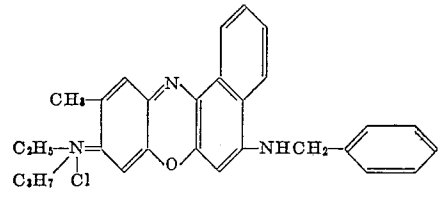


To a suspension of 267 parts of N-(p-chlorobenzyl)-alpha-naphthylamine in 1500 parts of ethyl alcohol are added 488 parts of 2-nitroso-4 - methyl - 5 - ethylpropylaminophenol hydrochloride, prepared as described in Example 29. This is then heated to the reflux temperature for about four hours and then the deep blue solution is cooled and kept under refrigeration. The product slowly separates and is removed in the form of a mixture of green glistening solid along with some blue solid product. The purified chloride salt is obtained by recrystallization from acetic acid.

It is sufficiently soluble in ethyl alcohol to form a deep blue solution. Addition of aqueous ammonia solution causes liberation of the base giving a reddish brown solution. Addition of a small excess of hydrochloric acid to a blue alcoholic solution of the chloride salt causes a loss of the blue color with the formation of a deep yellow-brown solution. The blue color of the monochloride salt is again regenerated by the partial neutralization with ammonium hydroxide solution.

EXAMPLE 31

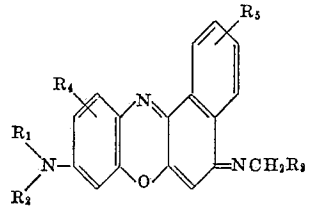
5 - benzylamino - 9 - ethylpropylamino - 10-methylbenzo[a]phenoxazonium chloride



The procedure outlined under Example 30 is followed except that 233 parts of N-benzyl-alpha-naphthylamine are used in place of 267 parts of N-(p-chlorobenzyl)-alpha-naphthylamine.

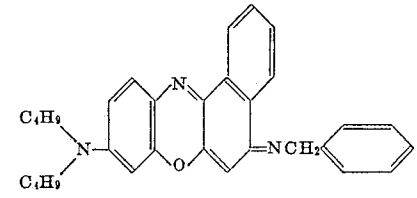
We claim:

1. 5 - aralkylamino - 9 - dialkylamino benzo-[a]phenoxazine compounds selected from the group consisting of free bases having the following formula



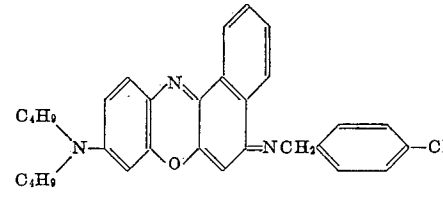
where R_1 is an alkyl group having not less than 3 nor more than 6 carbon atoms, R_2 is an alkyl group having not less than 2 and not more than 5 carbon atoms, R_3 is selected from the group consisting of phenyl, halogen substituted phenyl, lower alkyl substituted phenyl, lower alkoxy substituted phenyl, and methylenedioxy substituted phenyl, R_4 and R_5 are selected from the group consisting of hydrogen and lower alkyl radicals and addition salts of the bases with acids.

2. 9 - di - n - butylamino - 5 - benzylamino benzo[a]phenoxazine, having the formula:



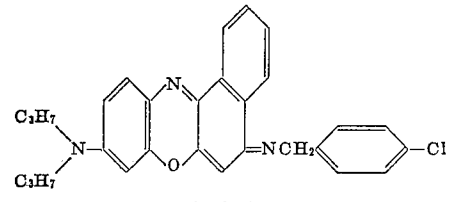
3. Addition salts of 9 - di - n - butylamino-5-benzylamino benzo[a]phenoxazine with strong acids.

4. 9 - di - n - butylamino - 5 - p - chlorobenzylamino benzo[a]phenoxazine, having the formula:



5. Addition salts of 9 - di - n - butylamino-5 - p - chlorobenzylamino benzo[a]phenoxazine with strong acids.

6. 9 - di - n - propylamino - 5 - p - chlorobenzylamino benzo[a]phenoxazine, having the formula:



MOSES L. CROSSLEY.
PAUL F. DREISBACH.

References Cited in the file of this patent

UNITED STATES PATENTS

Number	Name	Date
2,528,863	Crossley et al.	Nov. 7, 1950

OTHER REFERENCES

Sloviter Science, vol. 110 (December 1949), pp. 687–688.