

PATENT SPECIFICATION

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(72) Inventors EDWARD J. CRAGOE JR. and EVERETT M. SCHULTZ

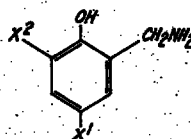


(54) 2-AMINOMETHYLPHENOL DERIVATIVES

(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we 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:—

This invention is concerned with 2-aminomethylphenols useful in the treatment of edema and inflammation, processes for preparing them, compositions containing them and methods of treating inflammation in non-human animals using such compounds.

The compounds of this invention have the following formula:



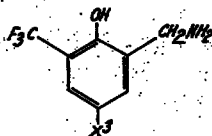
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where X¹ is C₁₋₆ alkyl such as methyl, ethyl, *n*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl or 1-methylhexyl, cyclopentyl or cyclohexyl and X² is trihalomethyl such as trifluoromethyl or trichloromethyl. Also included are their non-toxic pharmaceutically acceptable salts, preferably the non-toxic pharmaceutically acceptable acid-addition salts derived from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, methanesulfonic acid or isethionic acid; salts may also be prepared from the alkali metal bases such as sodium hydroxide and potassium hydroxide.

Pharmacological studies using rats and dogs as the experimental animals indicate that active products of the present invention and compositions containing the active products are effective diuretic and saluretic agents which can be used in the treatment of conditions associated with electrolyte and fluid retention. When administered in therapeutic dosages in conventional vehicles, the products effectively reduce the amount of sodium and chloride ions in the body, lower dangerous excesses of fluid level to acceptable levels and, in general, alleviate conditions usually associated with edema. Further, studies involving the mouse ear test and the carrageenin edema test indicate that these compounds are effective anti-inflammatory agents useful both topically and systemically.

In accordance with the present invention, compositions are provided containing a compound of formula I or a non-toxic salt thereof and a pharmaceutically acceptable carrier, which may be either a solid or a liquid. Examples of solid carriers are lactose, corn starch, gelatin, talc, stearic acid, magnesium stearate, terra alba, sucrose, agar, pectin and acacia. Examples of liquid carriers are peanut oil, olive oil, sesame oil and water. Similarly, the carrier or diluent may include a time-delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

Preferred compounds have the following formula:



where X^3 is C_{1-7} , alkyl, particularly *tert*-butyl; and the non-toxic pharmaceutically acceptable acid-addition salts thereof.

Compositions containing compounds in this class have been found to exhibit particularly good diuretic, saluretic and anti-inflammatory activity.

The compositions containing the 2-aminophenols (I) as the active ingredient and also the 2-aminophenols (I) themselves useful as diuretic and saluretic agents, can be administered in a wide variety of therapeutic dosages in conventional vehicles as, for example, by oral administration in the form of a tablet, capsule (including soft gelatin capsules), powder, troche or lozenge, by intravenous injection or oral solutions or suspensions, e.g. a syrup or aqueous solution. Also, the daily dosage of the products may be varied over a wide range varying from 50 to 2,000 mg. The product is preferably administered in subdivided doses in the form of scored tablets containing 5, 10, 25, 50, 100, 150, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from 1 mg to 50 mg/kg of body weight (5 mg to 3.5 g of body weight per day). Preferably the range is from about 1 mg to 7 mg/kg of body weight. These dosages are well below the toxic or lethal dose of the products. A suitable unit dosage form of the products of this invention can be administered by mixing 50 milligrams of a 2-aminomethylphenol (I) or a suitable salt thereof, with 149 mg of lactose and 1 mg of magnesium stearate and placing the 200 mg mixture into a No 1 gelatin capsule (U.S. standard). Similarly, by using more of the active ingredient and less lactose, other dosage forms can be put up in No 1 gelatin capsules and, should it be necessary to mix more than 200 mg of ingredients together, larger capsules may be used. Tablets may be prepared by mixing the active ingredient with conventional tableting ingredients such as calcium phosphate, lactose, corn starch or magnesium stearate. The liquid forms in which the active ingredients may be incorporated include suitably flavoured suspending or dispersing agents such as glycerin or a synthetic or natural gum, for example, tragacanth, acacia and methylcellulose. For parenteral administration sterile suspensions and solutions are desired. Isotonic preparations which generally contain a suitable preservative are used when intravenous administration is desired.

The compositions containing the 2-aminophenols as the active ingredient and also the 2-aminophenols themselves, useful as topical anti-inflammatory agents are particularly effective in topical treatment of dermatological disorders and like conditions, such as dermatitis (actinic, atopic, contact, eczematoid, seborrheic and stasis), dermatitis herpetiformis, lichen planus, neuro-dermatitis, intitrigo, lichen simplex chronicus, pruritus and psoriasis, as well as for topical treatment of inflammations of the respiratory and intestinal mucosa such as allergic rhinitis, bronchitis, bronchial asthma, bronchiectasis and colitis. These 2-aminophenols are ordinarily administered in the form of a pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable carrier adapted for topical administration. These topical pharmaceutical compositions may be in the form of a cream, ointment, gel, lotion or aerosol formulation adapted for application to the skin for treatment of dermatoses; or it may be in the form of a solution, suspension or aerosol adapted for topical spray application to respiratory passages, for example for treatment of nasal allergies or bronchial inflammations; or in the form of suppositories or enclosed in enteric capsules for treatment of intestinal inflammations. Suppositories may be prepared in a conventional manner by mixing the compound of the invention with a suitable non-irritating excipient which is solid at room temperature, but liquid at the rectal temperature. Such materials are cocoa butter and polyethylene glycol. For treatment of dermatological disorders, these topical pharmaceutical compositions containing the 2-aminophenols of the invention ordinarily include 0.01% to 0.25%, preferably about 0.10%, of the active compound, in admixture with 99.75% to 99.99% of gel

5 vehicle comprising water, at least one organic solvent, and at least one thickening agent. The water ordinarily constitutes from 8% to 18% of the gel vehicle, preferably about 13%. The organic solvent ordinarily constitutes 60% to 90% of the gel vehicle. Representative solvents are ethyl alcohol, isopropyl alcohol, propylene glycol, glycerine, 2-octyl dodecanol and methyl pyrrolidine, but preferably mixtures of isopropyl alcohol and propylene glycol in a ratio of 0.5 to 0.6 part by weight isopropyl alcohol to 1.0 part propylene glycol. The solubility of the 2-aminophenol compound in the solvent system selected should be such as to obtain maximum partitioning of the active compound from the vehicle to the skin. 10 The thickening agent, preferably hydroxyethyl cellulose or hydroxypropyl cellulose, ordinarily constitutes from 0.5 to 4.0% of the gel vehicle. Optionally, a stabilizing agent, such as disodium edetate, sodium citrate, dipotassium edetate or citric acid, in the proportion of 0.02% to 0.1% of the gel vehicle, may be used if desired.

15 A preferred topical pharmaceutical composition is prepared as follows: 2.60 g of hydroxypropyl cellulose is added to a solution of 0.05 g of disodium edetate in 13.00 g purified water while agitating the mixture and maintaining the temperature at about 60°C, and the agitation is continued until the hydroxypropyl cellulose is completely dispersed and wetted. To the resulting dispersed mixture is added, with agitation, a solution containing 0.1 g of, for example, 2-aminomethyl-4-*t*-butyl-6-trifluoromethylphenol hydrochloride dispersed in a mixture of 30.00 g of anhydrous isopropyl alcohol and 54.25 g of propylene glycol. The resulting gel mixture is stirred vigorously at room temperature for a period of approximately 15 minutes thereby forming a pharmaceutical composition adapted for the treatment of topical anti-inflammatory conditions. 20 25

Various tests have been carried out to show the ability of the compounds described herein to exhibit reactions that can be correlated with anti-inflammatory activity in humans. One such test used is the carrageenin test which is known to correlate well with anti-inflammatory activity in humans and is a standard test used to determine anti-inflammatory activity. This test shows the ability of compounds to inhibit edema induced by injection of an inflammatory agent into the tissue of the foot of a rat against non-inflamed controls. This test is generally outlined by C. A. Winter, Proc. Soc. Exptl. Biolog. & Med., 1962, III, 544. The correlation has been shown by the activities of compounds known to be clinically active, including indomethacin, aspirin, phenylbutazone, *p*-hydroxyphenylbutazone, cortisone, hydrocortisone, and dexamethasone. 30 35

The following Examples, in which parts are by weight, are illustrative of how to prepare various compositions containing the active ingredients of this invention.

40 **EXAMPLE 1.**
Tablets containing 100 mg. of active ingredient per tablet. 40

	Per Tablet	
	100 mg.	
45 2-Aminomethyl-4- <i>tert</i> -butyl-6-trifluoromethylphenol hydrochloride	40 mg.	
Calcium Phosphate	38 mg.	45
Lactose	20 mg.	
Corn Starch	2 mg.	
Magnesium Stearate	200 mg.	

50 The 2-aminomethyl-4-*tert*-butyl-6-trifluoromethylphenol hydrochloride is mixed with the calcium phosphate and lactose for ten minutes and then passed through a mill to reduce the particle size. The combined ingredients are remixed for five minutes and corn starch is passed through a No. 60 sieve (U.S. Sieve Series) onto the ingredients. The combined ingredients are again remixed for five minutes and then magnesium stearate is added through a No. 60 sieve. After remixing for two minutes the ingredients are compressed into tablets. 55

Similar dry-filled capsules, tablets, elixirs and suspensions can be prepared by replacing the active ingredient of the above example by any of the other compounds described in the foregoing general disclosure and the specific examples which follow.

EXAMPLE 2.

A mixture of 250 parts of 2-aminomethyl-4-tert-butyl-6-trifluoromethylphenol hydrochloride and 25 parts of lactose is granulated with suitable water, and to this is added 100 parts of maize starch. The mass is passed through a 16 mesh screen. The granules are dried at a temperature below 60°C. The dry granules are passed through a 16 mesh screen, and mixed with 3.8 parts of magnesium stearate. They are then compressed into tablets suitable for oral administration.

25, 100 or 500 parts of 2-aminomethyl-4-tert-butyl-6-trifluoromethylphenol hydrochloride may be used in place of 250 parts above to produce tablets suitable for oral administration according to the method of this invention.

EXAMPLE 3.

A mixture of 50 parts of 2-aminomethyl-4-methyl-6-trifluoromethylphenol hydrochloride, 3 parts of the calcium salt of lignin sulfonic acid and 237 parts of water is ball-milled until the size of substantially all of the particles is less than 10 microns. The suspension is diluted with a solution containing 3 parts of sodium carboxymethylcellulose and 0.9 parts of the butyl ester of p-hydroxybenzoic acid in 300 parts of water. There is thus obtained an aqueous suspension suitable for oral administration for therapeutic purposes.

2-aminomethyl-4-tert-butyl-6-trichloromethylphenyl hydrochloride may be used in place of the compound in the above example to obtain a suspension suitable for oral administration.

EXAMPLE 4.

(1) *Tablets*—10,000 scored tablets for oral use, each containing 500 mg. of active ingredient are prepared from the following ingredients:

	Gm.	
2-aminomethyl-4-tert-butyl-6-trifluoro-		
methylphenol hydrochloride	5000	
Starch, U.S.P.	350	
Talc, U.S.P.	250	
Calcium Stearate	35	

The 2-aminophenol compound is granulated with a 4% w/v. aqueous solution of methylcellulose U.S.P. (1500 cps.). To the dried granules is added a mixture of the remainder of the ingredients and the final mixture compressed into tablets of proper weight.

(2) *Capsules*—10,000 two-piece hard gelatin capsules for oral use, each containing 250 mg. of active ingredient are prepared from the following ingredients:

	Gm.	
2-aminomethyl-4-tert-butyl-6-trifluoro-		
methylphenol hydrochloride	2500	
Lactose, U.S.P.	1000	
Starch, U.S.P.	300	
Talc, U.S.P.	65	
Calcium Stearate	25	

The 2-aminomethyl compound is mixed with the starch lactose mixture followed by the talc and calcium stearate. The final mixture is then encapsulated in the usual manner. Capsules containing 10, 25, 50 and 100 mg. of active ingredient are also prepared by substituting 100, 250, 500 and 1000 gm. for 2500 gm. in the above formulation.

(3) *Soft elastic capsules*—One-piece soft elastic capsules for oral use, each containing 500 mg. of active material are prepared in the usual manner by first dispersing the active material in sufficient corn oil to render the material capsulatable.

(4) *Aqueous suspension*—An aqueous suspension for oral use containing in each 5 ml., 1 gm. of active ingredient is prepared from the following ingredients:

		Gm.	
	2-aminomethyl-4-tert-butyl-6-trifluoro-		
	methylphenol hydrochloride	20000	
	Methylparaben, U.S.P.	7.5	
5	Propylparaben, U.S.P.	2.5	5
	Saccharin sodium	12.5	
	Glycerin	30000	
	Tragacanth powder	10	
	Orange oil flavor	10	
10	F.D. & C. orange dye	7.5	10
	Deionized water, q.s. to 10,000 ml.		

EXAMPLE 5.

Gel Formulation

15	0.1 mg. disodium edetate		15
	1.30 mg. of purified H ₂ O		
	300 mg. isopropanol		
	26 mg. hydroxypropylcellulose		
	q.s.a.d. 1 gm. propylene glycol		
20	1.09 mg. 2-aminomethyl-4-tert-butyl-6-trifluoromethylphenol		20
	hydrochloride		

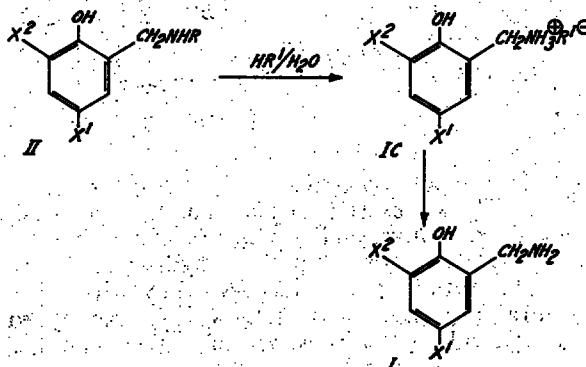
EXAMPLE 6.

Ointment Formulation

25	50 mg. wool alcohols B.P.		25
	150 mg. amichol C		
	350 mg. wax white Be square 170/175°C.		
	q.s.a.d. 1 gm. isopropyl myristate		
	1.09 mg. 2-aminomethyl-4-tert-butyl-6-trifluoromethylphenol hydro-		
	chloride		
30	0.4% citric acid anhydrous		30
	0.58% sodium phosphate dibasic anhydrous		

The 2-aminomethylphenols (I) described above may be prepared by (1) treating an N-(2-hydroxybenzyl)carboxamide (II) with an aqueous solution of an acid or base or (2) subjecting a substituted 2-hydroxybenzaloxime (III) to reduction.

The first of the above mentioned processes comprises treating an N-(2-hydroxybenzyl)carboxamide (II, infra) with an aqueous solution of an acid, preferably a mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid or hydroiodic acid, in addition to the mineral acids, bases may also be used, for example, the alkali metal bases such as sodium hydroxide and potassium hydroxide. Any solvent which is inert or substantially inert to the reactants may be used such as ethanol or acetic acid, but some water must be present. The reaction may be conducted at a temperature in the range of from 20°C to 110°C for a period of time of from 15 minutes to five hours; however, the reaction is generally conducted at the reflux temperature of the particular solvent for about 1½ hours. The following equation illustrates this reaction using a mineral acid, HR¹, such as hydrochloric acid, hydrobromic acid, hydroiodic acid or sulfuric acid.



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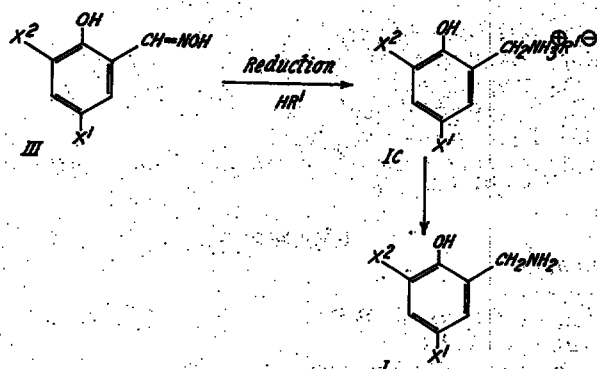
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where X^1 and X^2 are as defined for Formula I above; R is an acyl radical, for example, C_2 , alkanoyl, formyl, haloacetyl such as chloroacetyl, carbamoyl, mononuclear aroyl such as benzoyl, hydroxy-substituted mononuclear aroyl such as *o*-hydroxybenzoyl, or trihalomethylcarbonyl such as trichloromethylcarbonyl, and R^{1-} is the anion derived from an acid, for example, a mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid or sulfuric acid. The product is usually obtained in the form of an acid addition salt and the free amine can be generated by known neutralization methods.

The second method for preparing the 2-aminomethylphenols (I) comprises subjecting a substituted 2-hydroxybenzaldoxime (III, *infra*) to reduction, for example, by hydrogenation such as catalytic hydrogenation over a noble metal such as rhodium or ruthenium, preferably on a carrier such as carbon. The reduction is generally conducted using as the solvent a lower alkanol such as ethanol or methanol in the presence of mineral acid such as sulfuric acid. The following equation illustrates this process:



where X^1 and X^2 and R^{1-} are as defined above. The product is usually obtained in the form of an acid addition salt and the free amine can be generated by known neutralization methods.

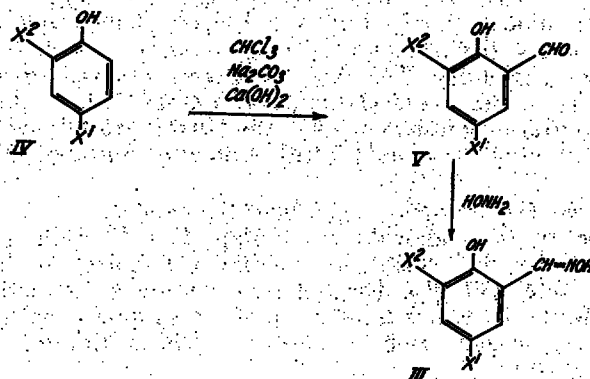
The N-(2-hydroxybenzyl)carboxamides (II, *supra*) used as starting materials in the preparation of the 2-aminomethylphenols (I) are prepared by treating an appropriately substituted phenol (IV, *infra*) with an N-hydroxymethylcarboxamide, for example, N-hydroxymethylurea, a 2-halo-N-hydroxymethylacetamide such as 2-chloro-N-hydroxymethylacetamide, and N-hydroxymethyl mononuclear arylcarboxamide, such as N-hydroxymethylbenzamide, an N-hydroxymethyl hydroxy substituted arylcarboxamide such as N-hydroxymethylsalicylamide or an N-hydroxymethyltrihaloacetamide such as N-hydroxymethyltrichloroacetamide, in the presence of a strong mineral acid such as hydrochloric acid or sulfuric acid. The reaction may be conducted using as the solvent an excess of the mineral acid used or with a solvent that is inert or substantially inert to the reactants, for example, a C_{1-3} alkanol such as ethanol or a C_2 alkanoyl acid such as acetic acid. The N-(2-hydroxybenzyl)carboxamides (II) may be isolated and purified; however, it has been found that by using the crude N-(2-hydroxybenzyl)carboxamides satisfactory results are obtained. The following equation illustrates this process:



where X^1 , X^2 and R are as defined above.

The 2-hydroxybenzaldoximes (III, *supra*) may be prepared by treating an appropriate phenol with chloroform in the presence of a base or a mixture of bases such as sodium carbonate and calcium hydroxide, which yields the correspondingly substituted 2-hydroxybenzaldehyde. The 2-hydroxybenzaldehyde (V, *infra*) is treated with a hydroxylamine hydrohalide such as hydroxylamine hydrochloride in the presence of a base such as sodium acetate.

This reaction is generally conducted in a C_{1-3} alkanol solvent such as ethanol. The reaction is conveniently conducted at the boiling point of the solvent. The following equation illustrates this process:



where X^1 and X^2 are as defined above.

The following examples illustrate the preparation of the 2-aminomethylphenols (I).

EXAMPLE 7.

Preparation of 2-aminomethyl-4-tert-butyl-6-trifluoromethylphenol hydrochloride.

A. Preparation of 2-trifluoromethyl-4-tert-butylphenol.

A mixture of 2-trifluoromethylphenol (25 g., 0.15 mole), *tert*-butyl alcohol (12 g., 0.16 mole), trifluoroacetic acid (100 ml.) and 96% sulfuric acid (2 ml.) is stirred at about 20°C for 48 hours. The mixture then is evaporated as far as possible under reduced pressure at 35–40°C. The residue is dissolved in benzene (500 ml.) and the solution is washed with water, saturated NaHCO_3 solution and saturated brine, and dried over anhydrous MgSO_4 . The dried solution is again evaporated under reduced pressure and the temperature is finally raised to 140–150°C under 65 mm. pressure to remove unchanged 2-trifluoromethylphenol. The residue is distilled at 65 mm. after collecting a small fore-run (75% unchanged starting phenol and 25% product). 2-trifluoromethyl-4-tert-butylphenol (13.6 g) is collected at 120–132°C as a pale pink oil that is 98% pure by gas liquid chromatographic analysis and can be used directly in the next step.

Following the above procedure but using an equivalent amount of isopropyl alcohol, *sec*-butyl alcohol or cyclohexyl alcohol in place of *tert*-butyl alcohol, there is produced an equivalent amount of 2-trifluoromethyl-4-isopropylphenol, 2-trifluoromethyl-4-*sec*-butylphenol or 2-trifluoromethyl-4-cyclohexylphenol.

B. Preparation of 2-aminomethyl-4-tert-butyl-6-trifluoromethylphenol hydrochloride.

2-Trifluoromethyl-4-tert-butylphenol (15.6 g., 0.062 mole) is dissolved in a mixture of glacial acetic acid (200 ml.) and 96% sulfuric acid (150 ml.). The mixture is stirred and finely powdered *N*-hydroxymethyl-2-chloroacetamide (8 g., 0.065 mole) is added in small portions at 20–25°C. Stirring then is continued for 5 hours after which the mixture is poured into water (3 l.). The 2-(2-chloroacetamidomethyl)-4-tert-butyl-6-trifluoromethylphenol that separates is collected and dried by suction to obtain a solid (19 g., m.p. about 85–100°C).

This solid is dissolved in a mixture of ethanol (75 ml.) and 12 N hydrochloric acid (25 ml.). The mixture is refluxed for 5 hours, cooled to 20°C and diluted with 12 N hydrochloric acid (150 ml.). Upon cooling –20°C, the product separates (14 g.). It is crystallized from ethanol-12 N hydrochloric acid (1:4) to obtain pure 2-aminomethyl-4-tert-butyl-6-trifluoromethylphenol hydrochloride, m.p. 202–204°C.

Anal. Calc.: C, 50.80 H, 6.04 N, 4.94

Found: C, 50.75 H, 6.01 N, 4.72

Following the above procedure but using an equivalent amount of 2-trifluoromethyl-4-isopropylphenol, 2-trifluoromethyl-4-*sec*-butylphenol or 2-trifluoromethyl-4-cyclohexylphenol in place of 2-trifluoromethyl-4-tert-butylphenol, there is obtained an equivalent amount of 2-aminomethyl-4-isopropyl-6-trifluoromethylphenol hydrochloride, 2-aminomethyl-4-*sec*-butyl-6-trifluoromethylphenol hydrochloride or 2-aminomethyl-4-cyclohexyl-6-trifluoromethylphenol hydrochloride.

EXAMPLE 8.

2-Aminomethyl-4-*tert*-butyl-6-trifluoromethylphenol hydrochloride.

A. 3-Trifluoromethyl-5-*tert*-butyl salicylaldehyde.

0.1 mole of 2-trifluoromethyl-4-*tert*-butylphenol and 0.1 mole of hexamethylenetetramine is dissolved in trifluoroacetic acid (150 ml.) and the mixture refluxed for 8 hours. After this time, 150 ml. of water and 50 ml. of concentrated hydrochloric acid is added. This mixture is then refluxed for half an hour. The reaction mixture is cooled and extracted with ether (5 x 50 ml.) and the ethereal extract is dried over magnesium sulfate. The ether is evaporated and the residue is crystallized from ethanol to yield 3-trifluoromethyl-5-*t*-butyl salicylaldehyde.

B. 3-Trifluoromethyl-5-*tert*-butyl salicylaldehyde oxime.

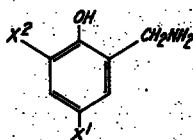
0.05 mole of the aldehyde from Step A, 0.12 mole of hydroxylamine hydrochloride and sodium acetate (0.12 mole) are dissolved in a mixture of ethanol (100 ml.) and water (30 ml.). The reaction mixture is refluxed for 2 hours and cooled, and water is added until no more precipitate forms. The solid that separates is crystallized from ethanol to yield 3-trifluoromethyl-5-*tert*-butyl salicylaldehyde oxime.

C. 2-Aminomethyl-4-*tert*-butyl-6-trifluoromethylphenol hydrochloride.

The oxime of Step B (0.02 mole) is dissolved in ethanol (200 ml.) to which concentrated H_2SO_4 (0.05 moles) is added. To this solution is added 5% Ruthenium on carbon (100 mg.). The mixture is hydrogenated at 40 lbs./sq. in. until the calculated amount of hydrogen is taken up. The catalyst is removed by filtration and the filtrate is evaporated to dryness, giving the sulfate salt of the title compound. The sulfate is suspended in water and neutralized with 28% ammonium hydroxide. The free base is taken up in ethanol and an equivalent amount of 6N ethanolic HCl is added. On addition of ether the title product is precipitated. The precipitate is collected and crystallized from a mixture of ethanol and concentrated HCl.

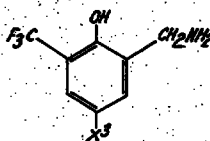
WHAT WE CLAIM IS:—

1. A compound of the formula:



where X^1 is C_{1-7} alkyl or C_{3-6} cycloalkyl and X^2 is trihalomethyl, or a non-toxic pharmaceutically acceptable salt thereof.

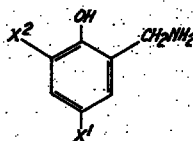
2. A compound of the formula:



where X^3 is C_{1-7} alkyl, or a pharmaceutically acceptable non-toxic acid-addition salt thereof.

3. A compound as claimed in Claim 2 in which X^3 is *tert*-butyl.

4. A method of preparing a compound of the formula:



that comprises treating a compound of the formula:



EXAMPLE 8.

2-Aminomethyl-4-*tert*-butyl-6-trifluoromethylphenol hydrochloride.

A. 3-Trifluoromethyl-5-*tert*-butyl salicylaldehyde.

0.1 mole of 2-trifluoromethyl-4-*tert*-butylphenol and 0.1 mole of hexamethylenetetramine is dissolved in trifluoroacetic acid (150 ml.) and the mixture refluxed for 8 hours. After this time, 150 ml. of water and 50 ml. of concentrated hydrochloric acid is added. This mixture is then refluxed for half an hour. The reaction mixture is cooled and extracted with ether (5 x 50 ml.) and the ethereal extract is dried over magnesium sulfate. The ether is evaporated and the residue is crystallized from ethanol to yield 3-trifluoromethyl-5-*t*-butyl salicylaldehyde.

B. 3-Trifluoromethyl-5-*tert*-butyl salicylaldehyde oxime.

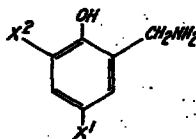
0.05 mole of the aldehyde from Step A, 0.12 mole of hydroxylamine hydrochloride and sodium acetate (0.12 mole) are dissolved in a mixture of ethanol (100 ml.) and water (30 ml.). The reaction mixture is refluxed for 2 hours and cooled, and water is added until no more precipitate forms. The solid that separates is crystallized from ethanol to yield 3-trifluoromethyl-5-*tert*-butyl salicylaldehyde oxime.

C. 2-Aminomethyl-4-*tert*-butyl-6-trifluoromethylphenol hydrochloride.

The oxime of Step B (0.02 mole) is dissolved in ethanol (200 ml.) to which concentrated H_2SO_4 (0.05 moles) is added. To this solution is added 5% Ruthenium on carbon (100 mg.). The mixture is hydrogenated at 40 lbs./sq. in. until the calculated amount of hydrogen is taken up. The catalyst is removed by filtration and the filtrate is evaporated to dryness, giving the sulfate salt of the title compound. The sulfate is suspended in water and neutralized with 28% ammonium hydroxide. The free base is taken up in ethanol and an equivalent amount of 6N ethanolic HCl is added. On addition of ether the title product is precipitated. The precipitate is collected and crystallized from a mixture of ethanol and concentrated HCl.

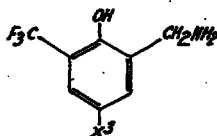
WHAT WE CLAIM IS:—

1. A compound of the formula:



where X^1 is C_{1-7} alkyl or C_{3-6} cycloalkyl and X^2 is trihalomethyl, or a non-toxic pharmaceutically acceptable salt thereof.

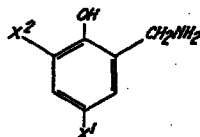
2. A compound of the formula:



where X^3 is C_{1-7} alkyl, or a pharmaceutically acceptable non-toxic acid-addition salt thereof.

3. A compound as claimed in Claim 2 in which X^3 is *tert*-butyl.

4. A method of preparing a compound of the formula:

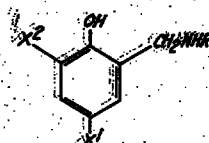


that comprises treating a compound of the formula:



1,420,572

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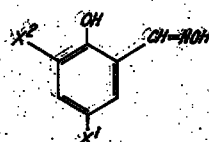
in which X^1 and X^2 are as defined in Claim 1 and R is acyl with an aqueous solution of an acid or base.

5. A method as claimed in Claim 4 in which R in the starting material is formyl, haloacetyl, carbamoyl, mononuclear aroyl, hydroxy-substituted mononuclear aroyl or trihalomethyl carbonyl, and a mineral acid is used.

6. A method as claimed in Claim 4 or 5 in which X^1 is C_{1-7} lower alkyl and X^2 is trifluoromethyl.

7. A method as claimed in Claim 6 in which X^1 is *tert*-butyl and X^2 is trifluoromethyl and the product is 2-aminomethyl-4-*tert*-butyl-6-trifluoromethylphenol.

8. A method for preparing a compound as claimed in Claim 1 that comprises treating a compound of the formula:



in which X^1 and X^2 are as defined in Claim 1 with a reducing agent.

9. A method as claimed in Claim 8 in which X^1 is C_{1-7} alkyl and X is trifluoromethyl.

10. A method as claimed in Claim 9 in which X^1 is *tert*-butyl and the product is 2-aminomethyl-4-*tert*-butyl-6-trifluoromethylphenol.

11. A method of treating a condition in a non-human animal exhibiting the symptoms of inflammation which comprises the administration to the animal of a therapeutically effective amount of a compound as claimed in any one of Claims 1—3.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound as claimed in any one of Claims 1—3 in a pharmaceutically acceptable carrier.

13. A composition as claimed in Claim 12, in orally administrable form.

14. A composition as claimed in Claim 13, in the form of a tablet, capsule, powder, troche, lozenge or syrup.

15. A composition as claimed in Claim 12, in injectable form.

16. A composition as claimed in Claim 15, in the form of an isotonic intravenously injectable solution.

17. A composition as claimed in Claim 12, in topically administrable form.

18. A composition as claimed in Claim 17, in the form of a cream, ointment, gel, lotion or aerosol.

19. A composition as claimed in Claim 12, in the form of a suppository or an enteric capsule.

20. A method of preparing a compound as claimed in claim 1, substantially as hereinbefore described in Example 7 or 8.

21. A compound as claimed in claim 1, when prepared by a method as claimed in any one of claims 4—10 and 20.

22. A composition as claimed in any one of claims 12—19, substantially as hereinbefore described in any one of Examples 1—6.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 and 10 Staple Inn, London WC1V 7RD.