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3,712,925

ACENAPHTHENE DERIVATIVES

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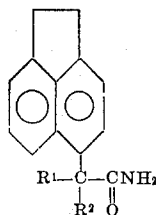
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U.S. Cl. 260—558 A

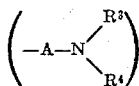
4 Claims

ABSTRACT OF THE DISCLOSURE

Acenaphthene derivatives are provided having the general structure



wherein at least one of R¹ and R² is alkyl or substituted aminoalkyl



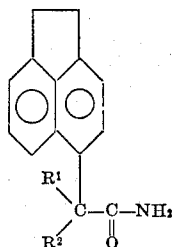
and the other can be hydrogen, wherein R³ and R⁴ are hydrogen or a hydrocarbon radical, and A is alkylene. These compounds possess anti-inflammatory activity.

The present invention relates to acenaphthene derivatives and more particularly to acenaphthene nitriles and amides having anti-inflammatory activity and to intermediates for the preparation of these new compounds.

The compounds of this invention are useful as anti-inflammatory agents and are effective in the prevention and inhibition of granuloma tissue formation in warm blooded animals, for example, in a manner similar to indomethacin. They may be used to decrease joint swelling tenderness, pain and stiffness, in mammalian species, e.g., in conditions such as rheumatoid arthritis. A compound of Formula I or a physiologically acceptable salt (when applicable) of the character described herein-after may be compounded according to accepted pharmaceutical practice in oral dosage forms such as tablets, capsules, elixirs or powders for administration of about 100 mg. to 2 gm. per day, preferably 100 mg. to 1 gm. per day in two to four divided doses. For example, about 150 mg./kg./day is effective in reducing paw swelling in rats.

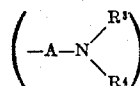
The acenaphthene derivatives of the invention have the general formula

(I)



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wherein R¹ and R² are the same or different and at least one must be alkyl having from one to about eight carbon atoms and preferably from about one to about three carbon atoms, or substituted aminoalkyl



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and the other can be hydrogen. R³ and R⁴ can be the same or different and can be hydrogen or a hydrocarbon radical including alkyl having from one to about eight and preferably from one to about six carbon atoms, alkenyl having from two to about eight and preferably from two to about five carbon atoms, phenyl and alkylphenyl or phenylalkyl having from seven to about fifteen and preferably from seven to about ten carbon atoms, and A is alkylene having from one to about six and preferably from one to about four carbon atoms in the linking group.

The alkyl radicals included in the compounds of the invention are straight, branched chain or cyclic radicals containing from about one to about eight carbon atoms and preferably from about three to about eight carbon atoms, and include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, t-butyl, n-pentyl, 2-methyl-n-butyl, neopentyl, n-hexyl, 2-methyl-n-pentyl, 3-methyl-pentyl, 2,2-dimethyl-2-butyl, 2,3-dimethyl-n-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Examples of suitable alkenyl radicals include ethenyl, 1-butenyl, 2-propenyl and 3-pentenyl.

Examples of suitable alkylphenyl radicals include all isomers of tolyl, xylyl, mesityl, and butylphenyl.

The phenylalkyl radicals are preferably phenyl lower alkyl radicals, wherein the lower alkyl group contains up to about six carbon atoms, such as benzyl, phenethyl, and phenylbutyl.

Examples of suitable alkylene radicals (A) include methylene, ethylene, trimethylene, and tetramethylene as well as any of these containing alkyl side chains.

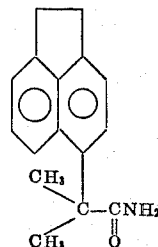
Preferred are those compounds wherein R¹ is dimethyl-aminoethyl or dimethylaminopropyl and R² is isopropyl.

As to the salts of the compounds of the invention, where applicable, those coming within the purview of this invention include the non-toxic physiologically acceptable acid-addition salts. Acids useful for preparing these acid-addition salts include, inter alia, inorganic acids, such as the hydrohalic acids (e.g., hydrochloric and hydrobromic acid), sulfuric acid, nitric acid, and phosphoric acid, and organic acids, such as maleic, methane sulfonic, cyclohexane sulfamic, tartaric, citric, acetic and succinic acids.

Examples of compounds falling within the present invention include, but are not limited to, the following:

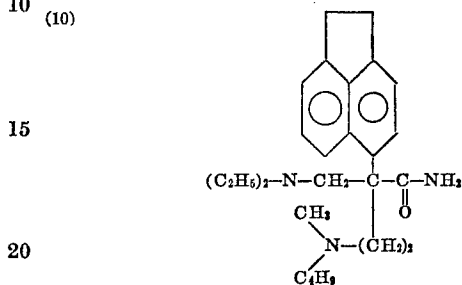
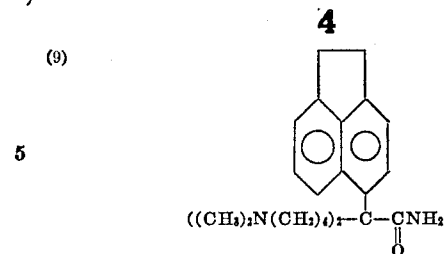
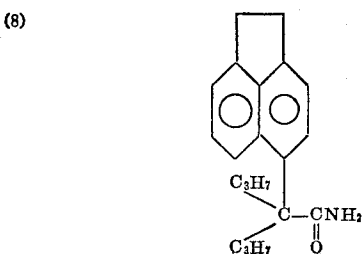
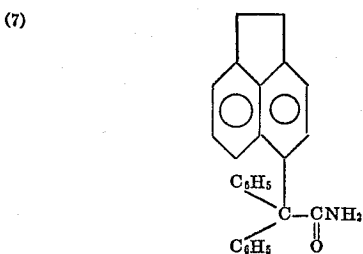
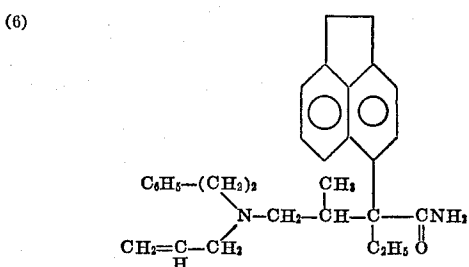
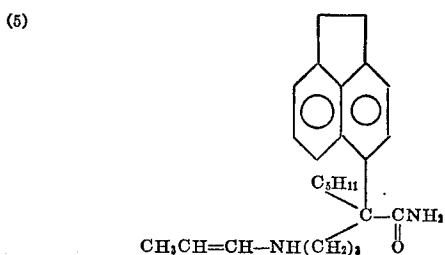
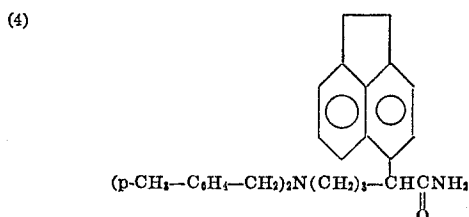
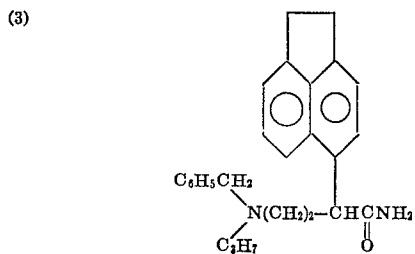
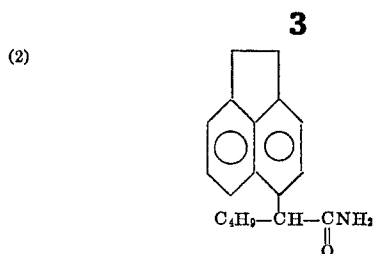
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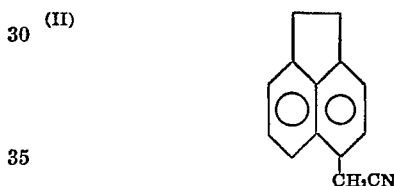


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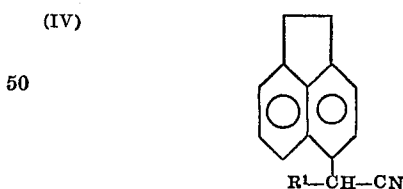
Further in accordance with the present invention a process is provided for preparing the compounds of claim 1, which comprises, dehydrating 5-acenaphtheneacetamide, for example, by reacting it with phosphorus pentoxide or thionyl chloride to form 5-acenaphtheneacetonitrile having the structure



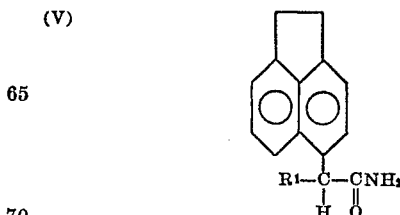
then alkylating the nitrile II by reacting it in the presence of a base such as, for example, sodium hydride or sodium amide with an alkylating agent of the structure



wherein X is Cl, Br or I, and R^1 is as defined hereinbefore, in a molar ratio of II:III of within the range of from about 4:1 to about 1:1 at a temperature within the range of from about 20 to about 40° C. to form a nitrile of the structure



and finally hydrolyzing the nitrile IV by reacting it with an acid such as polyphosphoric acid, a mineral acid such as sulfuric acid, or an organic acid such as acetic acid or mixtures of such acids or an alkali metal alkoxide such as potassium-t-butoxide to form a compound of the structure



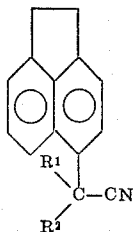
Nitrile IV can be further alkylated by reacting it in the presence of a base such as sodium amide with an alkylating agent of the structure



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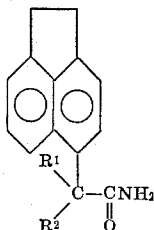
wherein R² and X are as defined above in a molar ratio of IV:IV of within the range of from about 4:1 to about 1:1 to form a nitrile of the structure

(VII)



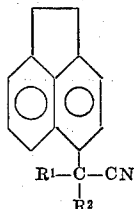
which is hydrolyzed by reacting it with polyphosphoric acid or any of the acids mentioned hereinbefore to form a compound of the structure

(VIII)



The intermediates II, IV and VII are novel compounds and as such are a part of the present invention and can be represented by the formula

(IX)



in which case R¹ and R² are as defined hereinbefore with the exception that each can be hydrogen. Examples of such compounds include compound II and compounds IV and VII wherein R¹ and R² can be any of the radicals set out hereinbefore within respect to compounds of Formula I.

The following examples further illustrate the invention.

EXAMPLE 1

5-acenaphtheneacetoneitrile

A solution of 5-acenaphtheneacetamide (3.8 g.) in toluene (400 ml.) is treated with phosphorus pentoxide (12 g.) and refluxed for 90 min. The mixture is evaporated and the residue treated with water and extracted with chloroform. The chloroform extracts are washed with saturated sodium bicarbonate solution, 8% salt solution, dried (Na₂SO₄) and evaporated. The residue in benzene is added to a dry-packed alumina column (75 g.) and eluted with benzene and benzene-chloroform (9:1 and 4:1). The nitrile containing fractions are evaporated and the residue is crystallized from chloroform-isopropyl ether to give the title compound (2.03 g., M.P. 95-95.5°). Recrystallization from isopropyl ether gives the analytical sample: M.P. 95-95.5°;

$\lambda_{\text{KBr}}^{\text{IR}}$ 4.45 μ ; $\tau_{\text{TMS}}^{\text{CDCl}_3}$ 6.60 (S, 1,2-CH₂-CH₂-); 5.97 (S, 5-CH₂CN)

Analysis.—Calcd. for C₁₄H₁₇N (percent): C, 87.01; H, 5.74; N, 7.25. Found (percent): C, 86.93; H, 5.87; N, 7.09.

EXAMPLE 2

 α -Isopropyl-5-acenaphtheneacetoneitrile

A solution of 500 mg. of 5-acenaphtheneacetoneitrile in 10 ml. of dimethylformamide is cooled in an ice bath and treated with 111 mg. of sodium hydride and stirred

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for 0.5 hr. The mixture is treated with 0.44 ml. of isopropyl iodide and stirred at room temperature overnight. The mixture is poured into water and extracted with ether. The ether extracts are washed with water, 8% salt solution, dried (Na₂SO₄) and evaporated. Plate chromatography of the residue on silica gel using chloroform-hexane (1:1) as the developing solvent gives a major band which is eluted with ethyl acetate and evaporated to give the title compound (382 mg. as an oil). The analytical sample is prepared by distillation at 100° (0.02 mm.):

λ_{neat} 4.46 μ ; $\tau_{\text{TMS}}^{\text{CDCl}_3}$ 6.60 (S, 1,2-CH₂-CH₂-), 5.68 (d., J=5.5 cps., 5-CHCN)

Analysis.—Calcd. for C₁₇H₁₇N (percent): C, 87.48; H, 7.28; N, 5.95. Found (percent): C, 87.14; H, 7.32; N, 5.53.

EXAMPLE 3

 α -[2-(dimethylamino)ethyl]-5-acenaphtheneacetoneitrile, hydrochloride

A solution of 4.13 g. of 5-acenaphtheneacetoneitrile in 80 ml. of dimethylformamide is cooled in an ice bath and treated with 1.0 g. of sodium hydride and stirred for 45 min. The mixture is treated with 2.3 g. of dimethylaminoethylbromide and stirred at room temperature overnight. The mixture is diluted with water and extracted with ether. The ether extracts are washed with 8% salt solution and then extracted with 2 N HCl. The acidic fraction is made alkaline and extracted with ether. The ether extracts are washed with 8% salt solution, dried (Na₂SO₄) and evaporated. The residue is distilled to give 3.5 g. of an oil which is dissolved in ether and converted to a hydrochloride salt with HCl in methanol. The product is crystallized from ethanol-ether to give the title compound (3.72 g., M.P. 171-173°). The analytical sample is prepared by recrystallization from ethanol-ether: M.P. 171-173°;

$\lambda_{\text{KBr}}^{\text{IR}}$ 4.48 μ

Analysis.—Calcd. for C₁₈H₂₁N₂Cl (percent): C, 71.89; H, 7.08; N, 9.32; Cl, 11.79. Found (percent): C, 71.63; H, 7.34; N, 9.15; Cl, 11.78;

EXAMPLE 4

 α -[2-(dimethylamino)ethyl]- α -isopropyl-5-acenaphtheneacetoneitrile

A solution of 3.31 g. of α -[2-(dimethylamino)ethyl]-5-acenaphtheneacetoneitrile in 50 ml. of ether is treated with 0.48 g. of sodium amide and stirred and refluxed for 7 hours. The suspension is cooled and treated with 3.5 ml. of isopropyl bromide and stirred and refluxed for three days. The mixture is treated with water and ether and the ether layer is separated. The aqueous layer is extracted with additional ether. The combined ether fractions are washed with 8% salt solution, dried (Na₂SO₄) and evaporated. The residue is crystallized from isopropyl ether-hexane to give the title compound (2.05 g., M.P. 89-90°). Recrystallization from isopropyl ether gives the analytical sample: M.P. 90-91°;

$\lambda_{\text{KBr}}^{\text{IR}}$ 4.48 μ ; $\tau_{\text{TMS}}^{\text{CDCl}_3}$ 7.90 (S, Me₂N), 6.60 (S, 1,2-CH₂-CH₂)

Analysis.—Calcd. for C₂₁H₂₆N₂ (percent): C, 82.31; H, 8.55; N, 9.14. Found (percent): C, 82.04; H, 8.71; N, 9.16.

EXAMPLE 5

 α -[2-(dimethylamino)ethyl]-5-acenaphtheneacetamide

A suspension of 250 mg. of α -[2-(dimethylamino)ethyl]-5-acenaphtheneacetoneitrile, hydrochloride in 5 ml. of polyphosphoric acid is stirred at 120° for 1.5 hrs. The mixture is poured into ice water and stirred until solution is achieved. The aqueous fraction is extracted with ether and then made alkaline. The alkaline fraction is extracted

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with chloroform and the chloroform extracts washed with 8% salt solution, dried (Na_2SO_4) and evaporated. The residue is crystallized from acetone-isopropyl ether to give the title compound (196 mg., M.P. 183–184°). Recrystallization from acetone gives the analytical sample: M.P. 188–189°;

$\lambda_{\text{KBr}}^{\text{IR}}$ 6.00 μ ; $\tau_{\text{TMS}}^{\text{CDCl}_3}$ 7.79 (S, Me_2N) and 6.60 (S, 1,2- $\text{CH}_2\text{—CH}_2$)

Analysis.—Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$ (percent): C, 76.56; H, 7.85; N, 9.92. Found (percent): C, 76.29; H, 8.06; N, 9.76.

EXAMPLE 6

α -[2-(dimethylamino)ethyl]- α -isopropyl-5-acenaphtheneacetamide

A solution of 500 mg. of α -[2-(dimethylamino)ethyl]- α -isopropyl-5-acenaphtheneacetonitrile in 1.5 ml. of acetic

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(1:1) and evaporated to give 121 mg. of the title compound. The analytical sample is prepared by distillation and solidifies on standing: M.P. 77–79°;

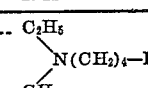
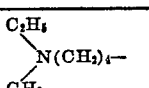
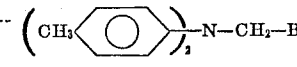
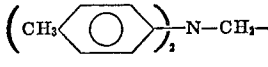
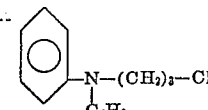
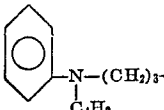
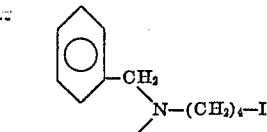
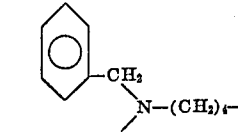
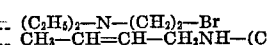
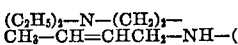


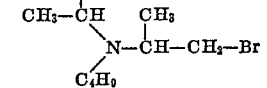
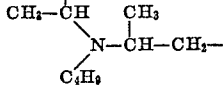
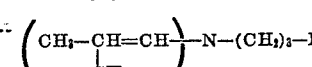
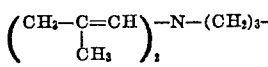
$\lambda_{\text{KBr}}^{\text{IR}}$ 6.01 μ

Analysis.—Calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}$ (percent): C, 77.73; H, 8.70; N, 8.63. Found (percent): C, 77.65; H, 8.59; N, 8.55.

EXAMPLES 7 TO 14

Following the procedure of Examples 1, 3 and 5 but substituting for the dimethylaminoethyl bromide the compound shown in the left hand column of Table I below the product shown in the right hand column is obtained.

TABLE I

Ex. No.	R ¹ X	R ¹
7.....		
8.....		
9.....		
10.....		
11.....		
12.....		
13.....		
14.....		

acid, 1.5 ml. water and 1.5 ml. sulfuric acid is refluxed for 70 hrs. The mixture is poured into water, made alkaline with potassium carbonate and extracted with chloroform. The chloroform extracts are washed with 8% salt solution, dried (Na_2SO_4) and evaporated. Plate chromatography of the residue on silica gel using ethyl acetate-methanol (7:3) as the developing solvent gives a major band which is eluted with ethyl acetate-methanol

EXAMPLES 15 TO 20

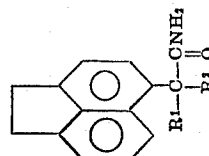
Following the procedure of Examples 1, 3, 4 and 6 but substituting for the dimethylaminoethyl bromide in Example 3 the R¹X compound shown in Column 1 of Table II and substituting for the isopropyl bromide the R²X compound shown in Column 2, the product shown in Column 3 is obtained.

TABLE II

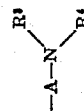
Example number	R ¹ X	R ² X	R ¹	R ²
15	(C ₆ H ₁₃) ₂ N(CH ₂) ₅ -Br	(CH ₂) ₂ N(CH ₂) ₅ -I	(C ₆ H ₁₃) ₂ N(CH ₂) ₅ -	(CH ₂) ₂ N(CH ₂) ₅ -
16	C ₂ H ₅ N(CH ₂) ₅ -Cl	C ₄ H ₉ N(CH ₂) ₅ -I	C ₂ H ₅ N(CH ₂) ₅ -	C ₄ H ₉ N(CH ₂) ₅ -
17	H ₂ N(CH ₂) ₅ -I	CH ₃ CH=CH H ₂ N(CH ₂) ₅ -Br	H ₂ N(CH ₂) ₅ -	CH ₃ CH=CH H ₂ N(CH ₂) ₅ -
18	C ₆ H ₁₁ -Br	(CH ₂) ₂ N(CH ₂) ₅ -Cl	C ₆ H ₁₁ -	(CH ₂) ₂ N(CH ₂) ₅ -
19	i-C ₄ H ₉ -Cl	CH ₃ N(CH ₂) ₅ -Br	i-C ₄ H ₉ -	CH ₃ N(CH ₂) ₅ -
20	CH ₃ CH=CH N(CH ₂) ₅ -I	CH ₃ -I	CH ₃ CH=CH N(CH ₂) ₅ -	CH ₃ -

What is claimed is:

1. A compound having the structural formula

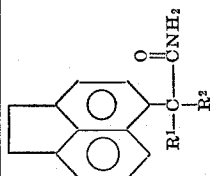


wherein R¹ and R² are phenyl or R¹ and R² are the same or different and at least one is substituted aminoalkyl of the structure



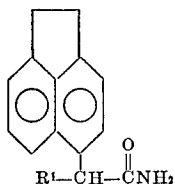
and the other can be alkyl having from one to eight carbon atoms or hydrogen; wherein R³ and R⁴ can be

the same or different and are selected from the group consisting of hydrogen, alkyl having from one to eight carbon atoms, alkenyl having from two to five carbon atoms, phenyl and alkylphenyl having from one to four carbon atoms in the alkyl group and phenylalkyl having from one to six carbon atoms in the alkyl group and p-methylbenzyl, and A is alkylene having from one to six carbon atoms and non-toxic physiologically acceptable acid-addition salts thereof.

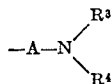


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2. A compound according to claim 1 having the formula



wherein R¹ is



3. A compound of claim 1 having the name α [2-(dimethylamino)ethyl]- α -isopropyl - 5 - acenaphtheneacetamide.

4. A compound of claim 1 having the name α [2-(dimethylamino)propyl]- α -isopropyl - 5 - acenaphtheneacetamide.

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HENRY R. JILES, Primary Examiner

15 H. I. MOATZ, Assistant Examiner

U.S. Cl. X.R.

260—465 R, 465 E, 558 R; 424—324

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