United States Patent [19]

Zinnes et al.

[11] **3,835,156**

[45] **Sept. 10, 1974**

[54] **ACYL DERIVATIVES OF 4-HYDROXY-2H-1-BENZOTHIOPYRAN-3-CARBOXAMIDE 1,1-DIOXIDE**

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[73] Assignee: **Warner-Lambert Company,** Morris Plaines, N.J.

[22] Filed: **Mar. 23, 1973**

[21] Appl. No.: **344,380**

[52] **U.S. Cl.** ..... **260/327 TH,** 260/244 R, 424/275, 424/248

[51] **Int. Cl.** **A61k 27/00,** C07d 65/08

[58] **Field of Search** ..... 260/327 TH

[56] **References Cited**

UNITED STATES PATENTS

3,769,292 10/1973 Zinnes et al. ..... 260/294.8 C

Primary Examiner—Henry R. Jiles
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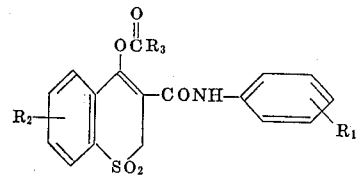
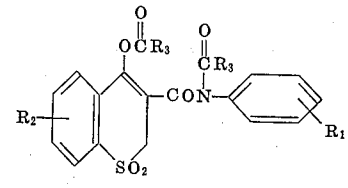
[57] **ABSTRACT**

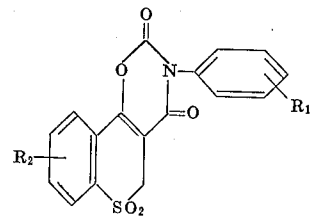
Acyl derivatives of 4-hydroxy-2H-1-benzothiopyran-3-carboxamide 1,1-dioxide having the following structural formulas are disclosed:



II



III



IV

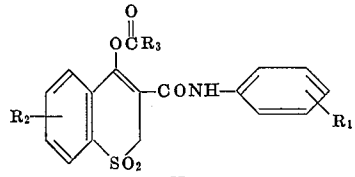
wherein R_1 and R_2 are hydrogen, alkyl, aryl, aralkyl, alkoxy, halogen, cyano, nitro, trifluoromethyl, and the like.

These compounds are useful as anti-inflammatory agents.

3 Claims, No Drawings

ACYL DERIVATIVES OF 4-HYDROXY-2H-1-BENZOTHIOPYRAN-3-CARBOXAMIDE 1, 1-DIOXIDE

The present invention relates to acyl derivatives of 4-hydroxy-2H-1-benzothiopyran-3-carboxamide 1,1-dioxide having the following structural formulas:



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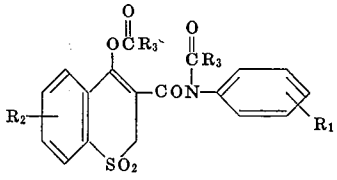

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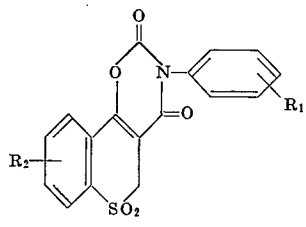


IV

wherein R_1 and R_2 are hydrogen, alkyl, aryl, aralkyl, alkoxy, halogen, cyano, nitro, trifluoromethyl, and the like.

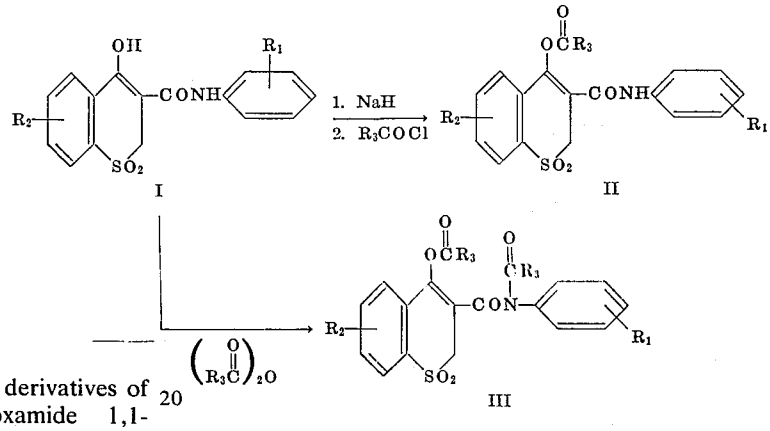
The compounds of this invention are useful as anti-inflammatory agents for mammals, i.e. cats, dogs, monkeys and the like. For example, when they are administered orally or intraperitoneally to laboratory animals such as rats, at a dose of 25–200 mg/kg, they reduce the swelling in the paw which has been previously induced by injection of an irritant such as carrageenin.

These compounds are indicated in conditions where the soft tissues are inflamed, such as rheumatoid arthritis in mammals. A dose of 25–200 mg/kg in several divided doses daily orally or by injection is recommended. This dose regimen may be varied depending on the weight, age, sex, and the species of the mammal being treated.

In order to use these compounds, they are formulated with pharmaceutical diluents such as lactose and compounded into dosage forms such as tablets. Alternatively, they can be formulated with a sterile vehicle

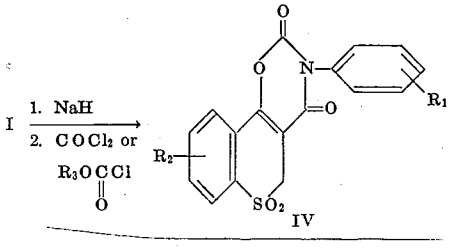
such as water for injection and compounded into suspensions suitable for parenteral administration.

According to the present invention, the above compounds are produced by the following reaction scheme:



I II

III

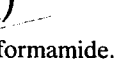


IV

wherein R_3 is alkyl or aryl.

Referring now to the above scheme, a compound of structure I is successively treated with a base such as sodium hydride and an acid chloride in a solvent such as dimethylformamide to form a monoacyl derivative of formula II. Diacyl derivatives such as III are formed by heating I with an acid anhydride.

The cyclic derivatives of formula IV are formed as a result of an internal diacylation reaction. This is achieved by the treatment of I with a base such as sodium hydride followed by the addition of either phosgene ($COCl_2$) or an alkyl- or aralkylchloroformate



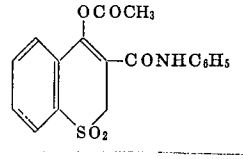
in a solvent such as dimethylformamide.

The starting material I is prepared as described in copending application Ser. No. 163,076 filed July 15, 1971, now abandoned.

In the above definitions for R_1, R_2 and R_3 "alkyl" and "alkoxy" have 1 to 7 carbon atoms such as methyl, ethyl, propyl, isopropyl and the like, "aryl" has 6 to 8 carbon atoms such as phenyl or tolyl, and "aralkyl" is aryl as defined substituted by an alkyl group as defined.

To further illustrate the practice of this invention, the following examples are included:

EXAMPLE 1



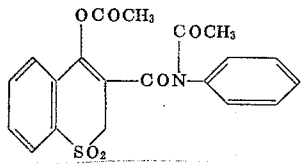
4-Hydroxy-2H-1-benzothiopyran-3-carboxanilide acetate 1,1-Dioxide. A slurry of 0.044 mol of sodium hydride in 30 ml of dimethylformamide was cooled to 5°

and a solution of 12.6 g (0.4 mol) of 4-hydroxy-2H-1-benzothiopyran-3-carboxanilide 1,1-dioxide in 30 ml of dimethylformamide was slowly added over a 15 minute period. When gas evolution had ceased, a solution of 3.4 ml of acetyl chloride in 10 ml of dimethylformamide was added and the reaction mixture was stirred at room temperature for 1.5 hr. It was poured into ice water containing excess hydrochloric acid and the resulting precipitate was collected and dissolved in dichloromethane. The solution was washed with water, dried, and evaporated to dryness. The solid residue was recrystallized from methanol to give 7.8 g (55%) of product; mp 152.5°–154.5°. Ir:

$\nu\nu^{max}$ 3300, 1680, 1660 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.49; H, 4.23; N, 3.92; S, 8.97. Found: C, 60.71; H, 4.37; N, 3.64; S, 9.03.

EXAMPLE 2

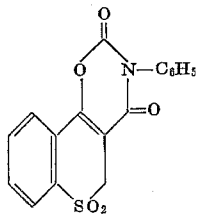


N-Acetyl-4-hydroxy-2H-1-benzothiopyran-3-carboxanilide acetate 1,1-Dioxide. A mixture of 10 g of 4-hydroxy-2H-1-benzothiopyran-3-carboxanilide 1,1-dioxide, 20 ml of acetic anhydride, and 2 ml of pyridine was heated on a steam bath for 5 minutes, cooled to room temperature, and diluted with ether. The resulting precipitate was recrystallized from acetic acid to give 5 g of product; mp 188-192° dec. (starts to darken at 180°).

Anal. Calcd for $C_{20}H_{17}NO_6S$: C, 60.14; H, 4.29; N, 3.51; S, 8.03. Found: C, 60.18; H, 4.40; N, 3.49; S, 8.07.

ν^{Nujol}_{max} 1775, 1715 cm^{-1}, absence of NH band.

EXAMPLE 3



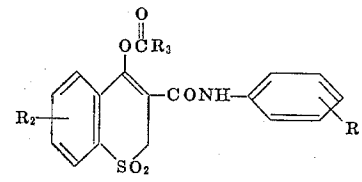
3,4-Dihydro-3-phenyl-2H,5H-1-benzothiopyrano-[3,4-e][1,3]oxazine-2,4-dione 6,6-dioxide. To a cooled, stirred slurry of 0.022 mol of sodium hydride in 50 ml of dimethylformamide was slowly added a solution of 6.3 g (0.02 mol) of 4-hydroxy-N-phenyl-2H-1-benzothiopyran-3-carboxamide 1,1-dioxide in 100 ml of dimethylformamide. When gas evolution had ceased, a solution of 3.6 g of hexylchloroformate in 25 ml of dimethylformamide was added slowly with cooling. The mixture was stirred at room temperature for 1 hour and poured into ice-water containing excess hydrochloric acid. The resulting gummy precipitate was collected and dissolved in dichloromethane. The solution was washed well with water, dried, evaporated to dryness, and the residue was dissolved in 600 ml of methanol. Concentration to a volume of 400 ml and cooling gave 3.7 g of product; mp 208°–209.5°. It gave a negative ferric chloride test and was insoluble in dilute aqueous sodium hydroxide.

ν^{Nujol}_{max} 1780, 1700 (sh), 1680 cm^{-1}.

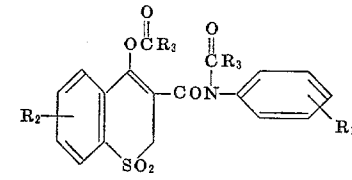
Anal. Calcd for $C_{17}H_{11}NO_5S$: C, 59.82; H, 3.25; N, 4.10; S, 9.39. Found: C, 59.54; H, 3.16; N, 4.09; S, 9.18.

We claim:

1. A member selected from the group consisting of compounds of the formulas:



II



III

in which R_1 and R_2 are hydrogen, alkyl of 1 to 7 carbon atoms, aryl of 6 to 8 carbon atoms, aralkyl in which alkyl is as defined and substituted by an alkyl group as defined, alkoxy of 1 to 7 carbon atoms, halogen, cyano, nitro and trifluoromethyl.

2. 4-Hydroxy-2H-1-benzothiopyran-3-carboxanilide acetate 1,1-dioxide.

3. N-Acetyl-4-hydroxy-2H-1-benzothiopyran-3-carboxanilide acetate 1,1-dioxide.

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