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ANTICOAGULANT, AMIDE OF 3,3'-CARBOXYMETHYLENE BIS(4-HYDROXYCOUMARIN)

Joseph J. Lovas, Ridgewood, N. Y., assignor to Specific Pharmaceuticals, Inc., New York, N. Y., a corporation of New York

No Drawing. Application June 3, 1950, Serial No. 166,070

10 Claims. (Class 260—344.6)

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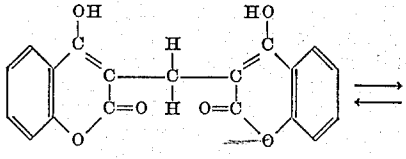
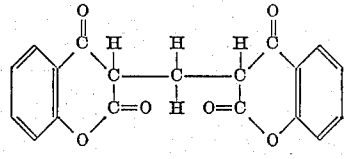
This invention relates to new amides of 3,3' - carboxymethylenebis(4 - hydroxycoumarin) which are useful as anti-coagulants.

This application is a continuation-in-part of my application Serial No. 103,318, filed July 6, 1949, now abandoned.

U. S. Patent No. 2,345,635 refers to application Serial No. 414,688 which describes the compound 3,3'-methylenebis (4-hydroxycoumarin) as an anti-coagulant suitable for administration to man. It is synthesized by condensing 4-hydroxycoumarin with formaldehyde. As explained in said patent, the compound 3,3'-methylenebis (4-hydroxycoumarin) exists in the enol and keto forms as is indicated by the following formula:



3,3'-methylenebis (4-hydroxycoumarin)



3,3'-methlenebis (2,4-diketo-chroman)

The said patent also describes esters of the enol form made by reacting the compound with anhydrides or acid halides.

The compound 3,3'-methylenebis (4-hydroxycoumarin) is well known under the trade name "Dicoumarol," and has been investigated extensively. It is an anti-coagulant for oral use, but has two important disadvantages. The first is that the onset of the anti-coagulant action is delayed after oral administration usually for some 12 to 48 hours. This delay is undesirable in conditions requiring immediate effective treatment. The second disadvantage is the persistent and protracted anti-coagulant effect in the body after withholding administration of the drug. In many cases dangerously low prothrombin levels persist to such an extent as to require special measures such as blood transfusion or high dosages of vitamin K to restore the prothrombin level to normal in order to avoid the danger of hemorrhage after the therapy has been accomplished.

The esters of the 3,3'-methylenebis (4-hydroxycoumarin), according to said Patent No. 2,345,635, prolong the action for a greater period of time. The patent also recognizes that excessive amounts of the esters may produce hemorrhage. The esters are indicated as having the same general anti-coagulant properties as 3,3'-methylenebis (4-hydroxycoumarin), namely prophylaxis and treatment in blood circulatory and vascular disturbances, including thrombosis, embolism, phlebitis, Buerger's disease, etc.

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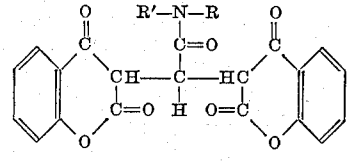
We have found that the amides of 3,3'-carboxymethylenebis (4-hydroxycoumarin) do not possess the disadvantages of 3,3'-methylenebis (4-hydroxycoumarin) or the slower acting esters thereof. More particularly, said amides accomplish a rapid lowering of prothrombin to any desired level, depending upon the dosage administered. While the reason for this has not been established, it appears likely that the amides may be more rapidly absorbed. Thus the onset of the action is very rapid after administration of the amides. The amides also have a less protracted effect and are accompanied by a rapid normalization of the prothrombin level when the drug is withheld, thereby minimizing dangers due to hemorrhage. While the exact reason for this advantage also is not known, it appears likely that this may be due to quicker elimination of the amides from the bloodstream.

The novel compounds of my invention have the following general formula, where R and R' are hydrogen or a hydrocarbon radical preferably having not more than 5 carbon atoms, such as ethyl, propylene, butyl, amyl, etc.



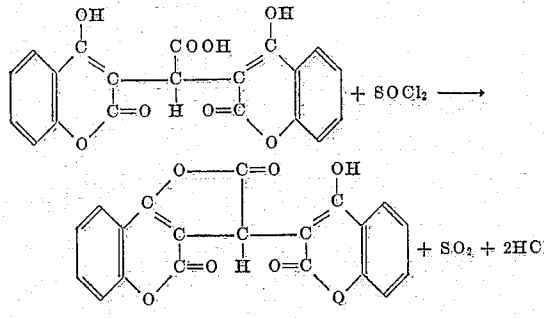
These may exist in the enol or keto form and reference to the latter is intended to include either form alone or in equilibrium.

The amides may be made in accordance with the invention by reacting an ester of 3,3'-carboxymethylenebis (4-hydroxycoumarin) with an ammoniacal compound, i.e., ammonia or an amine as described hereinafter. Alternatively, the amides may be prepared by reacting a lactone of 3,3'-carboxymethylenebis (4-hydroxycoumarin) with the ammoniacal compound as described in copending application, Serial No. 142,936, filed February 7, 1950, and also described more particularly hereinafter.

Example I

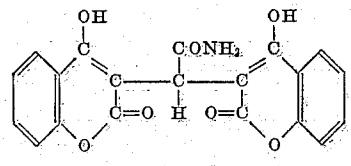
As described in said copending application, the lactone of 3,3'-carboxymethylenebis (4-hydroxycoumarin) may be made by reacting the above carboxy compound with a dehydrating agent such as an acid halide or an acid anhydride.

In accordance with an illustrative embodiment, 4.2 grams of 3,3'-carboxymethylenebis (4-hydroxycoumarin) was added to and dissolved in 40 cc. of thionyl chloride ($SOCl_2$). The 3,3'-carboxymethylenebis (4-hydroxycoumarin) is soluble in the thionyl chloride and an excess of the latter can be used as a reaction medium as well as a reaction component. The mixture was heated and refluxed for eight minutes following which the solution was cooled and a crystalline solid was filtered from the solution and washed with benzene. The yield was 4 grams of a crystalline solid having a melting point at 302° C. It is insoluble in most organic solvents. The reaction is thought to proceed as follows:



As an alternative method of preparing the lactone, a mixture of 0.2 grams of 3,3'-carboxymethylenebis (4-hydroxycoumarin) and 2 cc. of glacial acetic acid was heated to reflux. 0.1 cc. of acetic anhydride was added to the solution and the heating was continued for five minutes. The hot mixture was filtered and the precipitate was washed with ethanol. The yield was 0.1 gram, M. P. 305° with decomposition.

In preparing the simple amide in accordance with my invention, 1.8 grams of the lactone (prepared as described above using thionyl chloride) was dissolved in 10 cc. of concentrated (28%) aqueous ammonia. The solution was permitted to stand at room temperature for about one hour following which the product was precipitated by acidifying with dilute sulfuric acid. It was washed with water and dried. The yield of the crude material was 1.8 grams having a melting point of 205 to 210° C. with decomposition. After recrystallization from acetone, the product weighed 1.5 grams and had a melting point of 210 to 215° C. with decomposition.. It is thought to have the following formula:



This amide may be compared with 3,3'-methylenebis (4-hydroxycoumarin). This latter compound, according to Patent No. 2,345,635, and its manufacturer under the name "Dicoumarol," decreases the prothrombin concentration of the blood. The compound is intended for the prophylaxis and treatment of intravascular clotting; in postoperative, post-traumatic and postinfectious thrombophlebitis; pulmonary embolism;

acute embolic or thrombotic occlusion of peripheral arteries; recurrent idiopathic thrombophlebitis. It retards intravascular clotting and propagation of the thrombus but has not been shown to resolve formed thrombi or to increase the blood supply to infarcted areas. After a latent period of from 24 to 48 hours, the prothrombin time slowly increases to a maximum in 3 to 5 days and remains increased from 2 to 10 days after the cessation of therapy.

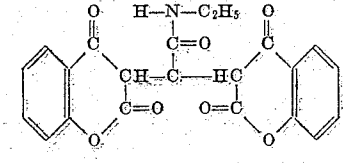
These properties of 3,3'-methylenebis (4-hydroxycoumarin) are pointed out in Patent No. 2,482,510, and are included in the warnings of the manufacturer. It will be seen, therefore, that the compound has two important disadvantages. The first is the delayed onset (1 to 2 days) of the anti-coagulant action, and the long time necessary to reach the maximum effect (3 to 5 days). This delay is undesirable in conditions requiring immediate effective treatment. The second disadvantage is the persistent and protracted anti-coagulant effect in the body after discontinuing the administration of the drug (2 to 10 days). For this reason strict precautions are to be taken in order to avoid severe and dangerous action. The effects are cumulative and over-dosage may cause severe hemorrhage. In many cases dangerous prothrombin levels persist after use of 3,3'-methylenebis-(4-hydroxycoumarin) to such an extent following administration of the drug as to require blood transfusions or high dosages of vitamin K to restore the prothrombin level to normal after the therapy has been accomplished.

The amides do not possess the disadvantages of the 3,3'-methylenebis-(4-hydroxycoumarin). In contrast with the slow onset, the long time to reach the maximum effect and persistent after effects, the amides accomplish a more rapid decrease of the prothrombin concentration of the blood apparently due to a more rapid absorption. Thus, the onset of the action is very rapid after the administration of the amides. Furthermore, the latter have a less protracted effect and are accompanied by a rapid return of the prothrombin level to normal when the administration of the drug is discontinued, apparently due to a quicker elimination of the compound. A comparison of the amide described in Example II with 3,3'-methylenebis-(4-hydroxycoumarin) is shown in the following table:

Action	Amide of 3,3'-carboxymethylenebis-(4-hydroxycoumarin)	3-3'-methylenebis-(4-hydroxycoumarin)
Onset of action	6 hours in most cases, never later than 9 hours.	24 to 48 hours.
Maximum action (peak).	15 hours	3 to 5 days.
Return to Initial value.	36 hours after administration.	2 to 10 days after administration.

Example II

The ethyl amide of 3,3'-carboxymethylenebis-(4-hydroxycoumarin), having the formula:



was prepared from 3,3'-carboxymethylenebis (4-hydroxycoumarin) which can be made by the condensation of 4-hydroxycoumarin and glyoxylic

acid (OHC—COOH) in a manner analogous to the condensation of 3,3'-methylenebis (4-hydroxycoumarin) with formaldehyde. The 3,3'-carboxymethylenebis (4-hydroxycoumarin) is converted to its ester by reaction with an alcohol and by refluxing for 6–10 hours with a 5% anhydrous alcoholic solution of HCl. The alcohol is then distilled off and the residue crystallized from acetone.

The ester is then converted to the corresponding ethyl amide following the customary procedures for conversion with ethyl amine as follows:

One part of the ethyl ester is refluxed for 8 hours with 5 parts of a 70% solution of ethyl amine. The solution is acidified to a pH of 3–4 and the precipitate is filtered off. This precipitate is then recrystallized from acetone.

The ethyl amide of 3,3'-carboxymethylenebis (4-hydroxycoumarin) is a white crystalline solid. When the solid is finely ground it melts at 203 to 204° C. with decomposition. It has been observed that when a melting point is taken of the crystalline material before grinding, it melts as high as 215 to 216° C. with decomposition. It is soluble in sodium carbonate and bases of the same or greater strength, insoluble in dilute mineral acids and insoluble in water. It is intended for oral administration, and for this reason may be compounded in tablets.

Controlled experiments have shown that when administering similar amounts of the ethyl amide above described and the 3,3'-methylenebis (4-hydroxycoumarin), the return of the prothrombin time to normal is quicker in cases treated with the said ethyl amide than in those treated with the 3,3'-methylenebis (4-hydroxycoumarin). This is shown in the following table:

	Percent Normal Prothrombin Time—			
	24 hours	48 hours	72 hours	96 hours
	Per cent	*Per cent*	*Per cent*	*Per cent*
Ethyl amide of 3,3'-carboxymethylenebis (4-hydroxycoumarin)	20	60	90	95
3,3'-methylenebis (4-hydroxycoumarin)	40	10	5	5

Thus it will be seen from a consideration of the first column at 24 hours, the same amount of said ethyl amide has reduced the prothombin level to a greater extent, and from the other columns that the effect wears off much more rapidly.

Other amides may be made following the same general procedure and using ammonia or the corresponding amine. For example, other amides may be prepared by reacting ammonia, butyl amine, amyl amine, diethyl amine, etc., with the ethyl ester or other esters as the starting material.

Example III

The butylamide of 3,3'-carboxymethylenebis (4-hydroxycoumarin) was prepared by dissolving 5 grams of the lactone (made with thionyl chloride in accordance with Example I) in a solution of 25 cc. of butyl amine and 25 cc. of water, and permitted to stand at room temperature. An excess of hydrochloric acid was then added, and the oily precipitate crystallized on standing. The precipitate was filtered, washed with water, dried at room temperature and recrystallized from acetone. The yield was 4.45 grams having a melting point of 202° C. with decomposition.

A comparison of the action of this butylamide

with 3,3'-methylenebis-(4-hydroxycoumarin) is shown in the following table:

Action	Butylamide of 3,3'-carboxymethylenebis-(4-hydroxycoumarin)	3,3'-methylenebis-(4-hydroxycoumarin)
Onset of action	6 hours in all cases	24 to 48 hours.
Maximum action (peak).	9 to 15 hours in a majority of cases.	3 to 5 days.
Return to initial value.	24 hours in a majority of cases, 36 hours in all cases after administration.	2 to 10 days after administration.

Example IV

The diethylamide of 3,3'-carboxymethylenebis (4-hydroxycoumarin) was prepared by dissolving 2 grams of the lactone (made with acetic anhydride in accordance with Example I) in a solution of 5 cc. of diethylamine and 5 cc. of water. After standing at room temperature for one hour the product was precipitated with an excess of hydrochloric acid and washed with water. The compound was then dried at room temperature and recrystallized from acetone. The yield was 1.4 grams having a melting point of 148° with decomposition.

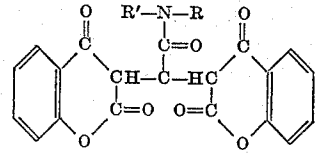
A comparison of the action of this diethylamide with 3,3'-methylenebis-(4-hydroxycoumarin) is shown in the following table:

Action	Diethylamide of 3,3'-carboxymethylenebis-(4-hydroxycoumarin)	3,3'-methylenebis-(4-hydroxycoumarin)
Onset of action	6 hours	24 to 48 hours.
Maximum action (peak).	9 to 15 hours	3 to 5 days.
Return to initial value.	36 hours after administration.	2 to 10 days after administration.

Other amides may be prepared in accordance with my invention as indicated generally herein, and have the same uses as 3,3'-methylenebis-(4-hydroxycoumarin), but with the advantages of quicker onset of the effect and a less protractive action as explained herein.

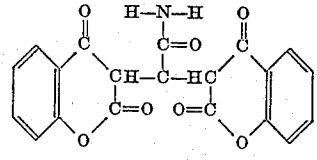
I claim:

1. Amides of 3,3'-carboxymethylenebis (4-hydroxycoumarin) of the following general formula:

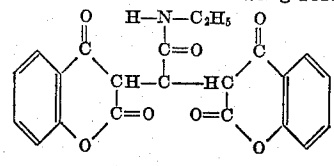


where R and R' are selected from the group consisting of hydrogen and alkyl and alkylene radicals having not over 5 carbon atoms.

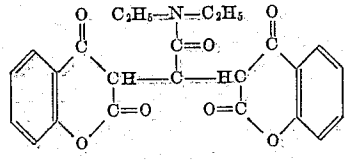
2. An amide of 3,3'-carboxymethylenebis (4-hydroxycoumarin) of the following formula:



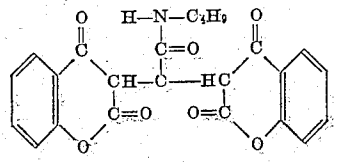
3. An amide of 3,3'-carboxymethylenebis (4-hydroxycoumarin) of the following formula:



4. An amide of 3,3'-carboxymethylenebis (4-hydroxycoumarin) of the following formula:



5. An amide of 3,3'-carboxymethylenebis (4-hydroxycoumarin) of the following formula:



6. The method of making the compounds of claim 1 in which an ester 3,3'-carboxymethylenebis (4-hydroxycoumarin) is reacted with an ammoniacal compound selected from the group consisting of ammonia and non-tertiary amines having not over 5 carbon atoms.

7. The method of making the compound of claim 2 in which the ethyl ester of 3,3'-carboxymethylenebis (4-hydroxycoumarin) is reacted with ammonia.

8. The method of making the compound of claim 3 in which the ethyl ester of 3,3'-carboxymethylenebis (4-hydroxycoumarin) is reacted with ethyl amine.

9. The method of making the compound of claim 4 in which the ethyl ester of 3,3'-carboxymethylenebis (4-hydroxycoumarin) is reacted with diethyl amine.

10. The method of making the compound of claim 5 in which the ethyl ester of 3,3'-carboxymethylenebis (4-hydroxycoumarin) is reacted with butyl amine.

JOSEPH J. LOVAS.

REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
2,482,510	Rosicky	Sept. 20, 1949

FOREIGN PATENTS

Number	Country	Date
580,084	Great Britain	Aug. 27, 1946