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3,136,753 DERIVATIVES OF CARDENOLIDES AND BUFADIENOLIDES

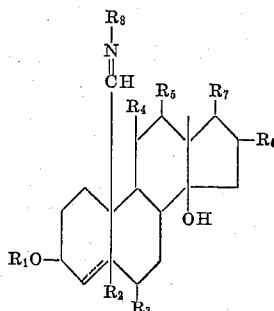
Klaus Irmscher, Darmstadt, Germany, assignor to E. Merck Aktiengesellschaft, Darmstadt, Germany, a corporation of Germany

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13 Claims. (Cl. 260—210.5)

This invention relates to derivatives of the 19-oxo-cardenolides and 19-oxo-bufadienolides. More particularly it is directed to Schiff bases derived from said oxo-compounds having the following formula:



(Formula I)

wherein:

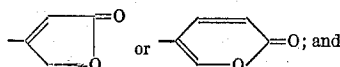
The symbol $\diagup$ in position 4—5 designates the inclusion in said group of bases of the corresponding compounds containing a double bond in the 4,5 position;

R_1 designates H, an acyl or a glycosidic radical;

R_2 designates α -H, β -H or β -OH;

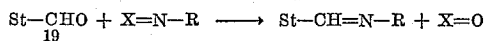
R_3 through R_6 designate H or OH;

R_7 designates



R_8 designates a member of the group consisting of alkyl and hydroxylated alkyl radicals having from 1 to 5 carbon atoms.

Said Schiff bases may be derived from the 19-oxo compounds by interaction thereof with primary amines or with Schiff bases of an aliphatic carbonyl compound in accordance with the following equation:



wherein:

St designates the steroidal structure of Formula I to which the unit $-\text{CH}=\text{N}-\text{R}_8$ is attached at position 10;

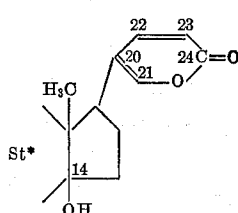
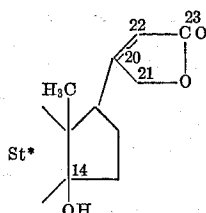
X designates H, H or a lower alkylidene radical; and

R designates an alkyl, cyclohexyl, aryl or hydroxy alkyl radical, which radical may contain substituents.

It is to be understood that the term "cardenolides" designates steroids which have an OH-group in the 14 β -position and which have as a side chain, an α,β -unsaturated, 5-membered lactone ring. The bufadienolides have a 14 β -hydroxyl group and as side chain a bis-unsaturated, 6-membered lactone ring.

Cardenolide

Bufadienolide



wherein:

St* designates the structure consisting of the A, B and C rings constituting the steroidal structure of Formula I.

Orally effective cardio-glycosides are already known. Thus, for instance, the natural cardio-glycoside digitoxin, based on clinical experience, is 100% absorbed upon oral application. All the cardio-glycosides of good oral activity known heretofore have the great disadvantage, however, that they are removed from the body again only very slowly. In this way, the danger of a cumulation in case of repeated treatment is greatly increased. Furthermore, in all known orally active cardio-glycosides, the action is only very slow.

For an acute therapy, however, rapid removal from the body, no cumulation and rapid action is necessary. These requirements are met by another group of natural cardio-glycosides, namely 19-oxo-compounds, such as k-strophanthine- β . Thus the daily decrease of the activity level present in the body is 7% in the case of digitoxin, while it is 40% in the case of strophanthine (cf. W. Küssner, Archiv der Pharmacie, vol. 294/66, page 137 (1961)).

The cardio-glycosides of the strophanthine type are, however, only of very weak action when administered per os (strophanthins, convallatoxin about 0-5%, cf. W. Küssner, loc. cit.), so that this important method of application was heretofore not possible.

Accordingly, it is among the principal objects of this invention to provide:

Schiff bases of cardenolides and bufadienolides as well as their 3-glycosides and esters;

Orally active cardio-glycosides of rapid action, rapid removal from the body and low cumulation; and methods for the preparation of said substances.

The methods consist in reacting a steroid of the cardenolide or bufadienolide series having an aldehyde group attached to the 10 C-atom of the steroid structure, with a nitrogen-containing compound of the formula $\text{R}-\text{N}=\text{X}$, in which X is H, H or a lower alkylidene radical and R is an alkyl, cyclohexyl, aryl-, aralkyl or hydroxy alkyl radical, possibly substituted, and isolating the reaction product from the reaction mixture under approximately neutral conditions.

In the conversion of the bufadienolides and cardenolides having an aldehyde group on the 10 C-atom, with a primary amine, only a slight excess of primary amine is used. It is preferred to carry the reaction out in the presence of a solvent or of a solvent mixture. As a solvent, there are suitable, for instance, alcohols such as methanol, ethanol or isopropanol; hydrocarbons such as benzene, toluene; ethers, such as tetrahydrofuran or dioxane; chlorinated hydrocarbons such as methylene chloride, chloroform, etc. It is advisable or preferable that at least one of these solvents be capable of forming an azeotropically boiling mixture with water so that when the solvent is distilled off, the reaction equilibrium is displaced in the desired direction. The use of strong acids and alkalis should be avoided in the purification. Prolonged action of water can in itself cause hydrolysis of the Schiff bases formed. It is preferable only to remove the solvents from the reaction mixture and to purify the crude product by crystallization. Surprisingly, the glycosides are not split in the reaction. The characteristic band of the aldehyde group in the IR-spectrum is at 1715 cm^{-1} . The reaction can be applied very generally to all cardenolides and bufadienolides having an aldehyde group attached to the 10 C-atom. Both the aglycones and the corresponding 3-glycosides and esters can be used for the reaction. Preferred starting materials are the 19-oxo-steroids corresponding to the above Formula

I, i.e., the steroids in which the group attached at position 10 is

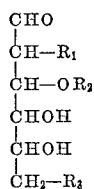


Cardio-active 19-oxo-steroids, which can be obtained from plants of the families of Strophanthus, Corchorus or Bowica are particularly suitable.

For example, the following cardenolides, aglycones and glycosides or esters derived from them can be used as starting material: strophanthidin, antiarigenin, adonitoxigenin, sarmentosigenin A, corotoxigenin and canno-

genin. Furthermore, for example, the following bufadienolide-aglycones and glycosides or esters derived from them can be used: hellebrigenin, scilliglaucosidin, bovogenin A and bovocryptogenin.

As glycoside radical, there enter into consideration in principle all mono- and oligo-saccharides. Preferred radicals are mono-, di- and trisaccharides which are derived from hexoses of the following Formula II:



Formula II

wherein:

R₁ and R₃ designate H or OH; and
R₂ designates H or CH₃.

Thus, for instance, C₆-sugars of the following types enter into consideration: aldohexoses, such as D-glucose, 6-deoxy-aldohexoses, such as L-rhamnose, D-antiarose, D-allomethylse as well as the corresponding 3-O-methylethers, such as L-thevetose, and furthermore, 2,6-bis-desoxy-aldohexoses, such as D-boivinose and D-diglitoxose, as well as the 3-O-methylethers derived therefrom, such as D-diginose, D-cymarose and D-sarmentose.

However, there can also be used glycosides which are formed with other sugars, such as with pentoses like D-arabinose, D-xylose and D-lyxose.

In individual cases, the following glycosides for instance enter into consideration: corchoroside, convallatoxin, helveticoside, desglucocheirotoxin, cymarine, cheirotoxin, k-strophanthin-β, convallalloside, k-strophanthoside, sarmentoside A, β-antiarin, adonitoxin, α-antiarin, gofruside, stroboside, paulioside, milloside, thevetin A, peruvoside, scilliglaucoside, bovocryptoside, desglucohellebrin, hellebrin and bovoside A.

The 3-hydroxyl group of the aglycones can also be esterified. For the method in accordance with the invention, the lower aliphatic carboxylates are preferably used, such as acetates, propionates or butyrates. The 3-hydroxyl group can, however, also be esterified with carboxylic acids which, in addition, contain basic substituents capable of forming salts, such as amino groups. Mention may be made by way of illustration in this connection of the glycine, alanine, serine and valine esters. As salts of these esters, the hydrochlorides enter preferably into consideration.

As amine components of the reaction, there enter into consideration all primary aliphatic, araliphatic and aromatic amines. The following amines are, for instance, particularly suitable: methylamine, ethylamine, n-propylamine, n-butylamine, isopropylamine, isobutylamine, tert-butylamine, cyclohexylamine, benzylamine, sec-butylamine, isoamylamine, n-hexylamine, n-octylamine, cetylamine, stearylamine, 2-ethylhexylamine, allylamine, oleylamine, cyclopentenylamine, dicyclohexylmethylamine, dimethylaminopropylamine, 3-stearylaminopropylamine, 1-methyl-2-carbethoxyvinylamine, 2-methyl-2-carbethoxypropylamine, 2-ethyl-2-carbethoxy-n-butylamine, 2-methyl-2-carbethoxyheptylamine, β-hydroxyethylamine or other

lower aliphatic primary amines substituted one or more times by OH, O-alkyl or O-acyl, such as 2-aminopropanol-1; 2-aminobutanol-1; 2-aminopentanol-1; 1-aminopropanol-2; 1-aminobutanol-2; 1-aminopentanol-2, etc.; 3-aminopropanol-1,4-aminobutanol-1; 5-aminopentanol-1, etc.; 2-aminopropanediol-1,3; 2-aminobutanetriol-1,3,4; 2-aminopentanetriol-1,3,4,5, etc.; 1-aminopropane-diol-2,3; 1-aminobutanetriol-2,3,4; 1-aminopentanetriol-2,3,4,5 (for instance arabamine or D-xylamine); D-glucamine, 3-methoxypropylamine.

Furthermore, it is possible to prepare the Schiff bases of the cardenolides and bufadienolides of the invention by reacting the starting compounds with the Schiff bases on an aliphatic carbonyl compound. In this way, there are obtained the Schiff bases of the cardenolides and bufadienolides, while the carbonyl compound which constituted the precursor of the intermediate Schiff bases used in the reaction is liberated.

In accordance with the invention, particularly good yields are obtained if one does not accept the reaction equilibrium which automatically takes place, but rather removes during the course of the reaction one of the resultant reaction products from the reaction mixture. Thus, practically quantitative yields are obtained if the carbonyl compound which is liberated is distilled off from the reaction mixture. Of course, it is also possible simply to wait until the reaction stops at a given equilibrium and then to separate the reaction mixture by customary methods, for instance by chromatography, crystallization or distillation. The carbonyl compound thereby isolated can finally be converted again into a Schiff base, and serve as new starting material. This reaction can possibly also be carried out continuously.

As a rule, it is advisable to carry out this reaction in the presence of an ordinary inert solvent. There are suitable for this purpose, for instance, benzene, toluene, xylene; or alcohols, such as methanol and ethanol; or chloroform, carbon tetrachloride, dioxane or methylene chloride. The presence of a solvent is, however, not absolutely necessary since the Schiff base used for the reaction can itself act as solvent. The Schiff base used for the reaction can be employed in excess. The reaction, however, proceeds in good yield also when operating with equivalent quantities. Particularly, in such case, it is advantageous to remove the resultant carbonyl compound from the reaction mixture during the course of the reaction.

As starting material, there is preferably used a Schiff base of a low-boiling carbonyl compound, since it is then readily possible after the reaction is complete to distill from the reaction mixture the low-boiling carbonyl compound which has been liberated. As low boiling carbonyl compounds, there enter into consideration particularly, compounds which have a boiling point below 100° C. The carbonyl compound can be distilled off in a simpler and considerably gentler manner than the removal of the water produced in the reaction of a primary amine with the 3-keto-19-oxo-steroids (the starting material). In this way, any possible side reactions are substantially avoided.

As low molecular weight carbonyl compound, there enter into consideration, particularly, carbonyl compounds having 2 to 5 C-atoms, such as: acetone, diethylketone, di-n-propylketone, methylethylketone and other homologs, as well as formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde and their homologs.

These carbonyl compounds give as starting material particularly suitable Schiff bases when reacted with amines of the formula R—NH₂ (R has the meaning indicated above), and therefore, for instance, with: methylamine, ethylamine, n-propylamine, n-butylamine, isopropylamine, isobutylamine, tert-butylamine, cyclohexylamine, sec-butylamine, isoamylamine, N-hexylamine, n-octylamine, 2-ethylhexylamine, N-hydroxyethylamine or other lower aliphatic primary amines, substituted once or several times by OH, such as, for instance, 2-aminopropanol-1;

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2-aminobutanol-1; 2-aminopentanol-1; 1-aminopropanol-2; 1-aminobutanol-2; 1-aminopentanol-2, etc.; 3-aminopropanol-1; 4-aminobutanol-1; 5-aminopentanol-1, etc.; 2-aminopropanediol-1,3; 2-aminobutanetriol-1,3,4; 2-aminopentantetriol-1,3,4,5, etc.; 1-aminopropanediol-2,3; 1-aminobutanetriol-2,3,4; 1-aminopentantetriol-2,3,4,5 (for instance, L-arabamine or D-xylamine), D-glucamine.

For pharmacological testing, the substances of this invention are applied in the form of a 5% alcoholic-aqueous solution applied intraduodenally to female cats narcotized with ether (weight 2 to 4 kg.) Two hours thereafter, the animal is after-titrated with g-strophanthin solution until death, 1 cc. per kilogram of body weight of a solution of 0.1 mg. g-strophanthin in 15 cc. of 0.85% solution of NaCl in 5% aqueous alcohol being introduced every 5 minutes into the *Vena femoralis*. From the required dose of strophanthin, the percentage of the test substance of cardio-activity after absorption is determined.

While, for instance, oximes and acetals of 19-oxo-compounds of the cardio-glycosides were entirely inactive per os, the following absorption percentages were determined for the instant Schiff bases:

	Percent
19-desoxo-19-(n-butyl)-imino-cymarin	26.4
19-desoxo-19-(n-propyl)-imino-cymarin	26.7
19-desoxo-19-(β -hydroxyethyl)-imino-cymarin	29.8
19-desoxo-19-(n-amyl)-imino-cymarin	35.4

The new compounds, useful as cardio-active drugs, can be put into all customary pharmaceutical forms, such as tablets, pills, dragees, and suppositories, for use, particularly, in oral application.

The following are examples in accordance with this invention:

EXAMPLE 1

19-Desoxo-19-(β -Hydroxyethyl)-Imino-Cymarin

2.5 grams of cymarin are dissolved in 50 cc. of absolute ethanol and 50 cc. of chloroform, and then treated with 320 mg. of monoethanolamine and 50 cc. of benzene. Distillation is then slowly effected and the traces of solvent removed under reduced pressure. The residue crystallizes upon being boiled out with benzene. M.P. 98° C. (decomposition), (α)_D²⁵: +24° (chloroform). IR-bands at 1650 cm.⁻¹, 1735 cm.⁻¹ and 1785 cm.⁻¹.

EXAMPLE 2

19-Desoxo-19-(β,γ -Dihydroxy-n-Propyl)-Imino-Cymarin

5.5 grams cymarin are dissolved in 100 cc. of absolute ethanol and treated with 1 gram of 1-aminopropane-2,3-diol, as well as 50 cc. of benzene. The mixture is slowly concentrated and all the solvent finally removed under reduced pressure. The residue crystallizes upon trituration with benzene. M.P. 120° C. (decomposition), (α)_D²⁵: +45° (chloroform), $\lambda_{\max}$ 216-218 m μ ,

$E_{1\text{ cm.}}^{1\%}$ 240 (ethanol)

IR-bands at 1650 cm.⁻¹, 1735 cm.⁻¹ and 1785 cm.⁻¹.

EXAMPLE 3

19-Desoxo-19-(n-Butyl)-Imino-Cymarin

4 grams cymarin are dissolved in 50 cc. of chloroform and treated with 600 mg. of n-butylamine. Distillation is slowly carried out and the chloroform is removed finally under reduced pressure. The residue crystallizes out upon trituration with benzene. M.P. 90° C., $\lambda_{\max}$ 217-218 m μ ,

$E_{1\text{ cm.}}^{1\%}$ 230 (ethanol)

IR-bands at 1775, 1735 and 1655 cm.⁻¹.

EXAMPLE 4

19-Desoxo-19-(1'-Desoxo-D-Sorbityl-1')-Imino-Cymarin

4 grams of cymarin are dissolved in 100 cc. of ethanol and then treated with a solution of 1.45 grams D-glu-

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camine in 100 cc. of methanol and with 50 cc. of toluene. The solvents are slowly distilled off, and finally under reduced pressure to dryness. The residue is recrystallized from ethyl acetate. M.P. 92°, $\lambda_{\max}$ 216 m μ ,

$E_{1\text{ cm.}}^{1\%}$ 262 (ethanol)

IR-bands at 1775, 1740 and 1660 cm.⁻¹.

EXAMPLE 5

19-Desoxo-19-(Isopropyl)-Imino-Hellebrigenin

370 mg. of hellebrigenin are dissolved in 15 cc. of chloroform and treated with 15 cc. of absolute ethanol and 275 mg. of 2-(iso-propyl)-imino-propane. The solution is slowly concentrated to dryness, using reduced pressure at the end. The residue crystallizes and absorbs in the ultra-violet at 300 m μ

($E_{1\text{ cm.}}^{1\%}$ 135)

IR-bands of the C=N-double bond at 1650 cm.⁻¹.

EXAMPLE 6

19-Desoxo-19-(β -Hydroxy-n-Propyl)-Imino-Strophanthidin-3-Acetate

2.2 grams strophanthidin-3-acetate are dissolved in 50 cc. of absolute ethanol and 50 cc. of chloroform, and then treated with 360 mg. of 1-amino-propanol-2 and 50 cc. of benzene. Distillation is effected slowly and the traces of solvent removed under reduced pressure. $\lambda_{\max}$ 216-218 m μ ,

$E_{1\text{ cm.}}^{1\%}$ 250 (ethanol)

IR-bands at 1650, 1735 and 1785 cm.⁻¹.

EXAMPLE 7

19-Desoxo-19-(β -Hydroxy-n-Butyl)-Imino-k-Strophanthin- β

7.3 grams k-strophanthin- β are dissolved in 100 cc. of absolute ethanol and treated with 1 gram of 1-aminobutanol-2 and 50 cc. of benzene. Concentration is slowly effected and all the solvents finally removed under reduced pressure. The residue crystallizes upon trituration with benzene. $\lambda_{\max}$ 216-218 m μ ,

$E_{1\text{ cm.}}^{1\%}$ 220 (ethanol)

IR-bands at 1650, 1735 and 1785 cm.⁻¹.

EXAMPLE 8

19-Desoxo-19-(Isobutyl)-Imino-Convallatoxin

4 grams convallatoxin are treated with 300 cc. of chloroform and 930 mg. of 2-(isobutyl)-imino-propane. Distillation is slowly effected and the chloroform removed. The residue crystallizes upon trituration with benzene. $\lambda_{\max}$ 217-218 m μ ,

$E_{1\text{ cm.}}^{1\%}$ 230 (ethanol)

IR-bands at 1775, 1735 and 1655 cm.⁻¹.

EXAMPLE 9

19-Desoxo-19-(β -Hydroxy-Isopropyl)-Imino-k-Strophanthoside

4.45 grams of k-strophanthoside are dissolved in 50 cc. of ethanol and treated with a solution of 390 mg. of 2-amino-propanol-1 in 25 cc. of toluene. The solvents are then slowly distilled off. The crystalline residue absorbs at $\lambda_{\max}$ 216 m μ ,

$E_{1\text{ cm.}}^{1\%}$ 262 (ethanol)

IR-bands at 1775, 1740 and 1660 cm.⁻¹.

EXAMPLE 10

19-Desoxo-19-(n-Amyl)-Imino-Cymarin

4 grams of cymarin are dissolved in a mixture of 50 cc. absolute ethanol and 50 cc. chloroform and treated with 0.7 grams n-amylamine as well as 50 cc. of benzene. Distillation is slowly effected, finally under reduced

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pressure. The residue crystallizes upon trituration in benzene. Melting point 98° (decomposition); $\lambda_{\max}$ 218 m μ ,

$E_{1\text{ cm}}^{1\%}$ 230 (ethanol)

(α)_D²⁰: +16°; IR-bands at 1780, 1740, 1660 and 1625 cm.⁻¹.

EXAMPLE 11

19-Desoxo-19-(Isobutyl)-Imino-Cymarín

In a manner similar to Example 8, 3 grams of cymarín are reacted with isobutylamine. The resultant product exhibits IR-bands at 1775, 1735 and 1655 cm.⁻¹. $\lambda_{\max}$ 217 m μ ,

$E_{1\text{ cm}}^{1\%}$ 240

EXAMPLE 12

19-Desoxo-19-(Sec.-Butyl)-Imino-Cymarín

In a manner similar to Example 3, 4 grams of cymarín are reacted with 600 mg. sec.-butylamine. The resultant product has IR-bands at 1775, 1740 and 1655 cm.⁻¹. $\lambda_{\max}$ 217-218 m μ ,

$E_{1\text{ cm}}^{1\%}$ 230

EXAMPLE 13

19-Desoxo-19-(n-Hydroxy-n-Propyl)-Imino-Cymarín

In a manner similar to Example 2, 5 grams of cymarín are reacted with 1 gram of 1-aminopropanol-(2). The residue has IR-bands at 1650, 1735 and 1785 cm.⁻¹. $\lambda_{\max}$ 216-217 m μ ,

$E_{1\text{ cm}}^{1\%}$ 240

When using 1-aminopropanol-(3), 19-desoxo-19-(γ -hydroxy-n-propyl)-imino-cymarín is correspondingly obtained.

EXAMPLE 14

19-Desoxo-19-(β -Hydroxyethyl)-Imino-k-Strophanthin- β

In a manner similar to Example 1, 5 grams of k-strophanthin- β are reacted with monoethanolamine. The resultant final product has IR-bands at 1655, 1735 and 1785 cm.⁻¹. $\lambda_{\max}$ 217 m μ ,

$E_{1\text{ cm}}^{1\%}$ 230

EXAMPLE 15

19-Desoxo-19-(n-Butyl)-Imino-k-Strophanthin- β

In a manner similar to Example 3, 1 gram of k-strophanthin- β is reacted with n-butylamine. The resultant product has IR-bands at 1655, 1735 and 1775 cm.⁻¹. $\lambda_{\max}$ 217-218 m μ ,

$E_{1\text{ cm}}^{1\%}$ 240

EXAMPLE 16

19-Desoxo-19-(n-Amyl)-Imino-k-Strophanthin- β

In a manner similar to Example 10, 2 grams of k-strophanthin- β are reacted with n-amylamine. There is obtained a product which has IR-bands at 1660, 1735 and 1780 cm.⁻¹. $\lambda_{\max}$ 217 m μ ,

$E_{1\text{ cm}}^{1\%}$ 230

EXAMPLE 17

19-Desoxo-19-(β -Hydroxyethyl)-Imino-k-Strophanthoside

In a manner similar to Example 1, 2.5 grams of k-strophanthoside are reacted with monoethanolamine. The resultant compound has IR-bands at 1655, 1740 and 1785 cm.⁻¹. $\lambda_{\max}$ 218 m μ ,

$E_{1\text{ cm}}^{1\%}$ 230

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EXAMPLE 18

19-Desoxo-19-(n-Butyl)-Imino-k-Strophanthoside

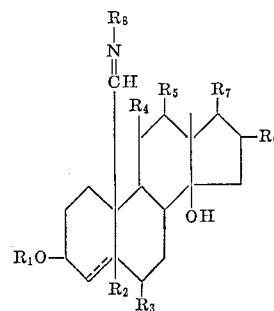
In a manner similar to Example 3, 1 gram of k-strophanthoside is reacted with n-butylamine. The resultant product has IR-bands at 1660, 1735 and 1780 cm.⁻¹. $\lambda_{\max}$ 217 m μ ,

$E_{1\text{ cm}}^{1\%}$ 240

It will be observed that the Schiff bases of this invention are readily formed by the interaction of the aforesaid 19-oxo-steroids with the primary amine or the intermediate Schiff base upon the addition of the latter, i.e., the mixing of the two interactants; and that one may proceed immediately slowly to distill off the solvent.

What I claim is:

1. Compounds having the formula:



(Formula I)

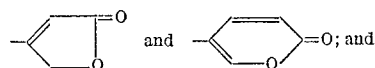
wherein:

R₁ is a member of the group consisting of H, acetyl and monovalent radicals of a glycoside selected from the group consisting of mono-, di- and tri-saccharides;

R₂ is a member of the group consisting of α -H, β -H and β -OH;

R₃, R₄, R₅ and R₆ are members of the group consisting of H and OH;

R₇ is a member of the group consisting of



R₈ is a member of the group consisting of alkyl and hydroxylated alkyl radicals having from 1 to 5 carbon atoms.

2. 19-desoxo-19-(2-hydroxyethyl)-imino-cymarín.

3. 19-desoxo-19-(n-butyl)-imino-cymarín.

4. 19-desoxo-19-(n-amyl)-imino-cymarín.

5. 19-desoxo-19-(iso-butyl)-imino-cymarín.

6. 19-desoxo-19-(sec.-butyl)-imino-cymarín.

7. 19-desoxo-19-(2-hydroxy-n-propyl)-imino-cymarín.

8. 19-desoxo-19-(3-hydroxy-n-propyl)-imino-cymarín.

9. 19-desoxo-19-(2-hydroxyethyl)-imino-k-strophanthin- β .

10. 19-desoxo-19-(n-butyl)-imino-k-strophanthin- β .

11. 19-desoxo-19-(n-amyl)-imino-k-strophanthin- β .

12. 19-desoxo-19-(2-hydroxyethyl)-imino-k-strophanthoside.

13. 19-desoxo-19-(n-butyl)-imino-k-strophanthoside.

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