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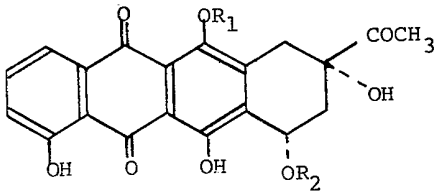
(54) ANTHRACYCLINES

(71) We, SOCIETA FARMACEUTICI ITALIA S.p.A., a Body Corporate orgainsed and existing under the laws of Italy, of 1/2 Largo Guido Donegani-1 20121 Milan, Italy, 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:—

The invention relates to anthracyclines.

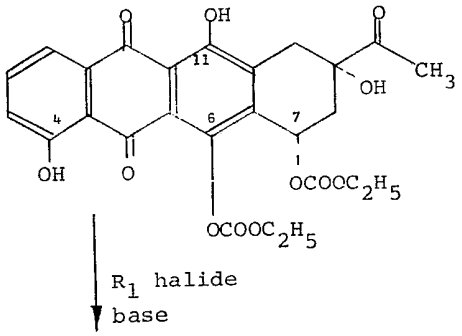
The invention provides anthracyclones and anthracycline glycosides having the general formula I



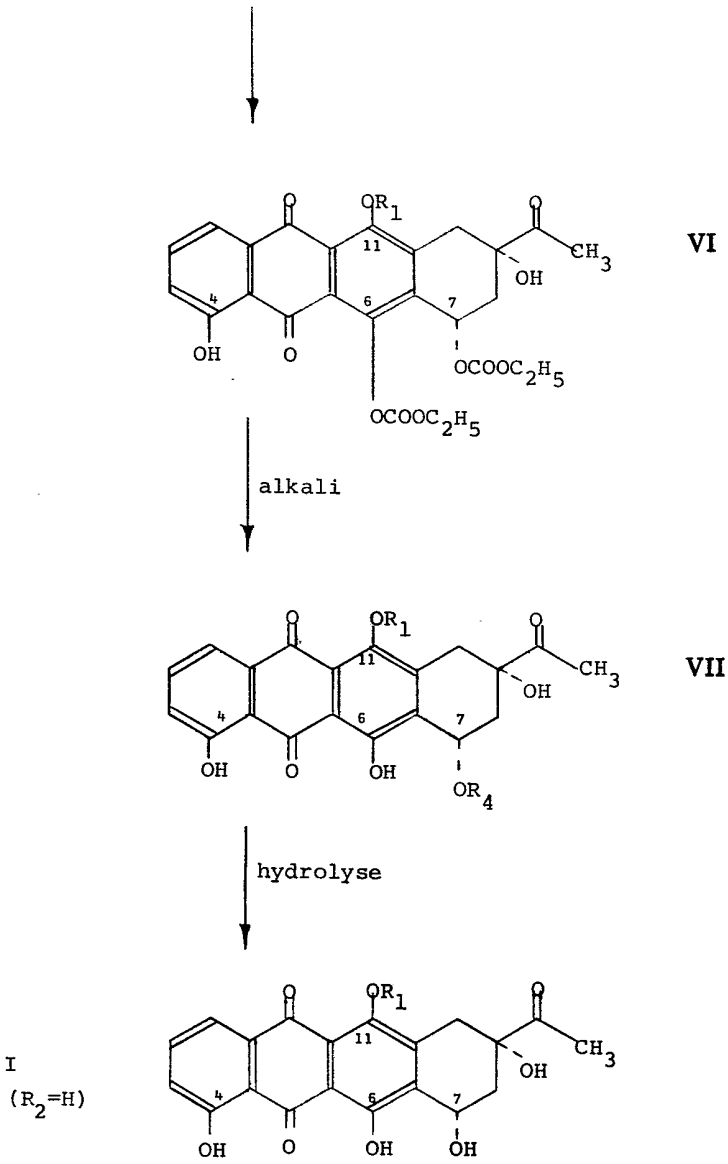
I

wherein R_1 represents an alkyl group having from 1 to 4 carbon atoms and R_2 represents a hydrogen atom, a daunosaminyl group or an N-trifluoroacetyl-daunosaminyl group, and further provides hydrochloride salts of those of the above compounds in which R_2 represents a daunosaminyl group.

Our British Patent Specification No. 18777/77 (Serial No. 1,573,037) of even date describes, inter alia, the preparation of 4-demethoxy-4-hydroxy-O^6,O^7-bis-ethoxycarbonyl-daunomycinone V. This bis-phenol V is the starting material for a process for the preparation of the new compounds I. The characterising feature of the process, which is itself within the scope of the invention, is the reaction of the bisphenol V under carefully controlled mild conditions with an alkyl halide having from 1 to 4 carbon atoms to introduce the group R_1 at position 11 and yield the monoethers VI. This reaction is performed in an organic solvent in the presence of a base. The process is outlined in the following scheme in which the above Roman numerals and some others are used:



V



The reaction of the bis-phenol V with the alkyl halide involves both phenolic hydroxyl groups in formation of diethers. Under carefully controlled conditions, the bis-phenols V can react in a highly specific manner with a halide of general formula R_1—Y, where R_1 has the above meaning and Y is Cl, Br or I, to give the monoethers VI. Such a selectivity is completely unexpected, as a much higher reactivity of the C—11—OH than the C—4—OH is unpredictable. The reaction can be carried out in dichloromethane or chloroform, for example in the presence of one equivalent of a base, for example silver oxide, and a slight excess of the halide.

Monoethers VI, on treatment with dilute alkali metal hydroxides or with an activated basic resin, for example AG1-X2 which is an anion exchange resin having quaternary ammonium groups attached to a styrene-divinylbenzene coplymer lattice and is supplied by Bio-Rad Laboratories, give the bis-phenols VII, R_4 being hydrogen if the reaction is carried out in an aqueous medium or preferably an alkyl group if an alcohol such as methanol is used as the solvent. In the latter case, the bis-phenols VII are hydrolyzed by mild exposure to aqueous trifluoroacetic acid to yield the new aglycones I (R_2=H) together with small amounts of their 7-epimers. These 7-epimers can be transformed into aglycones I (R_2=H) having a 7-α-OH group by the equilibration procedure of J. Amer. Chem. Soc., 1976, *98*, 1967.

The biologically active glycosides I (R_2=daunosaminyl or N-trifluoroacetyl-

daunosaminyl) can be prepared by the synthesis of the glycoside linkage described in our British Patent Specification No. 1,509,875. The anthracyclinone I (R_2=H) is condensed with 1-chloro-N,O-bis-trifluoroacetyldaunosamine in an organic solvent, for example dichloromethane or chloroform, in the presence of a soluble silver salt as a catalyst. The resultant N,O,-bis-trifluoroacetyldaunosaminyl derivative of the anthracyclinone on treatment with methanol and a catalytic amount of triethylamine is converted to the N-trifluoroacetyldaunosaminyl derivative (I, R_2=N-trifluoroacetyldaunosaminyl). The latter can be hydrolyzed to give the daunosaminyl derivative (I, R_2=daunosaminyl) by mild exposure to a dilute alkali. This daunosaminyl derivative can be isolated as its hydrochloride by treating it with methanolic hydrogen chloride.

The new compounds I display antimitotic activity and are useful therapeutic agents for the treatment of tumour diseases in mammals.

The following Examples illustrate the invention.

EXAMPLE 1.

4-Demethoxy-4-hydroxy-11-deoxy-11-methoxy-O⁶,O⁷-bis-ethoxycarbonyldaunomycinone

5 g of 4-demethoxy-4-hydroxy-O⁶,O⁷-bis-ethoxy-carbonyl-daunomycinone are dissolved in 100 ml of dichloromethane and treated with 1.5 ml of methyl iodide and 1.5 g of silver oxide. After refluxing for 2 h, the reaction mixture is filtered and evaporated to dryness. The residue is chromatographed (silica gel; dichloromethane) to yield pure 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-O⁶,O⁷-bis-ethoxy-carbonyl-daunomycinone.

PMR ($CDCl_3$):

1.33 and 1.46 δ (two t, CH_3—C(H_2)), 2.36 δ (s, CH_3CO), 3.83 δ (s, CH_3O)), 4.23 and 4.36 δ (two q, CH_2—C(H_3)), 6.13 δ (broad s, C-7-H), 7.0—7.8 δ (m, 3 aromatic protons), 12.2 δ (s, phenolic hydroxy).

IR (KBr):

1765, 1740, 1715, 1675, 1635, 1580 cm^{-1}.

EXAMPLE 2.

4-Demethoxy-4-hydroxy-7,11-bis-deoxy-7,11-bis-methoxy-daunomycinone

A solution of 1.5 g of 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-O⁶,O⁷-bis-ethoxycarbonyldaunomycinone in a 1:1 mixture of dichloromethane:methanol is treated with an excess of AG1-X2 resin previously activated with aqueous sodium hydroxide and washed with methanol. The reaction mixture is stirred until the starting material has completely disappeared, and is then filtered and evaporated to dryness. The residue is chromatographed (silica gel; chloroform:acetone 95:5 by volume) to give 4-demethoxy-4-hydroxy-7,11-bis-deoxy-7,11-bis-methoxy-daunomycinone.

PMR ($CDCl_3$):

2.40 δ (s, CH_3CO), 3.56 and 3.80 δ (two s, two CH_3O), 4.85 δ (broad s, C-7-H), 6.9—8.3 δ (m, 3 aromatic protons), 11.7 and 12.9 δ (two s, phenolic hydroxys).

IR (KBr):

1716, 1670, 1622, 1598 and 1585 cm^{-1}.

EXAMPLE 3.

4-Demethoxy-4-hydroxy-11-deoxy-11-methoxydaunomycinone and its 7-epimer

1.2 g of 4-demethoxy-4-hydroxy-7,11-bis-deoxy-7,11-dimethoxy-daunomycinone are dissolved in 40 ml of trifluoroacetic acid containing 2% of water and the resulting solution is stood overnight at room temperature. After removal of the solvent in vacuo, the residue is dissolved in acetone and hydrolyzed with conc. aqueous ammonia. The reaction mixture is diluted with chloroform, washed with water and evaporated to dryness. The residue is chromatographed to yield two products: 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-daunomycinone (Rf 0.54 on silica gel plate; chloroform:acetone 4:1 by volume) and its 7-epimer (Rf = 0.3). The 7-epimer can be converted to the natural configuration by treatment with dilute trifluoroacetic acid. PMR and IR of 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-daunomycinone:

PMR ($CDCl_3$):
2.45 δ (s, CH_3CO), 3.96 δ (s, CH_3O), 5.27 δ (broad s, C-7-H), 7.0—7.9 δ (m, 3 aromatic protons), 11.7 and 13.0 δ (two s, phenolic hydroxys).

IR (KBr):
1715, 1670, 1625, 1600 and 1580 cm^{-1}.

EXAMPLE 4.

4-Demethoxy-4-hydroxy-11-deoxy-11-methoxydaunomycinone and its 7-epimer

The title compounds can be obtained directly by treatment of 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-O^6,O^7-bis-ethoxycarbonyldaunomycinone with AG1-X2 resin as in Example 3, except that the reaction is carried out in aqueous, instead of methanolic, dichloromethane and using wet resin.

EXAMPLE 5.

4-Demethoxy-4-hydroxy-11-deoxy-11-methoxy-N-trifluoroacetyldaunonorubicin

To a solution of 1.5 g of 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-daunomycinone and 1.25 g of 2,3,6-trideoxy-3-trifluoroacetamido-4-O-trifluoroacetyl-δ-L-lyxopyranosyl chloride (1-chloro-N,O-bis-trifluoroacetyldaunosamine) in 100 ml of anhydrous dichloromethane, a solution of 0.95 g of silver trifluoromethanesulphonate in anhydrous diethyl ether is added dropwise at room temperature with stirring. After 1 h, the reaction mixture is washed with aqueous sodium bicarbonate and evaporated to dryness. The residue is dissolved in methanol containing a catalytic amount of triethylamine and stood at room temperature for 2 h. The solvent is removed in vacuo and the residue chromatographed (silica gel chloroform:acetone 95:5 by volume) to give 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-N-trifluoroacetyl-daunorubicin.

PMR ($CDCl_3$):
1.29 δ (d, CH_3—C(H)), 2.40 δ (1, CH_3CO), 3.83 δ (s, CH_3O), 5.15 δ (s, C-7-H), 5.39 δ (s, C-1'-H), 7.0—8.0 δ (m, NH and aromatic H), 11.76 e 13.04 δ (2s, phenolic H).

EXAMPLE 6.

4-Demethoxy-4-hydroxy-11-deoxy-11-methoxydaunorubicin hydrochloride

0.9 g of 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-N-trifluoroacetyldaunorubicin are dissolved in 40 ml of aqueous 0.15 N sodium hydroxide and stood for 1 h at room temperature. After acidification with oxalic acid and rapid neutralization with aqueous sodium bicarbonate the product is extracted with chloroform and the organic solution evaporated to dryness. The residue is dissolved in dichloromethane and treated with 1 equivalent of hydrogen chloride in methanol. By addition of diethyl ether 4-demethoxy-4-hydroxy-11-deoxy-11-methoxy-daunorubicin hydrochloride is precipitated, and the precipitate is collected by filtration.

Rf in chloroform:methanol:water (13:6:1 by volume) = 0.58.
m.p. 174° C—176° C with decomposition.
λ_{max} = 446 nm.

BIOLOGICAL ACTIVITY

4-Demethoxy-4-hydroxy-11-deoxy-11-methoxy-daunorubicin has been tested under the auspices of N.C.I., National Institute of Health, Bethesda, Maryland, U.S.A., against Lymphocitic Leukemia P_{388} according to the procedure described in Cancer Chemotherapy Reports, Part 3, Vol. 3, page 9 (1972). The new compound was compared with daunorubicin in a test on mice infected with tumour cells: intraperitoneal injections were made on days 5, 9 and 13 from the transplantation of the tumour cells into the mice. The following Table illustrates the antitumour activity of the new anthracycline.

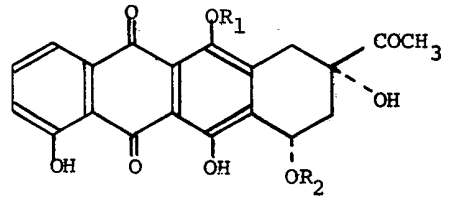
TABLE

Compound	Dose mg/kg	T/C %
Daunorubicin.HCl NSC 82151	32.0	
	16.0	86
	8.0	108
	4.0	134
	2.0	131
4-Demethoxy-4-hydroxy-11-deoxy-11-methoxy-daunorubicin.HCl MAR 81 – NSC 94399	50.0	125
	25.0	122
	12.5	119
	6.25	119
	3.13	118

T/C% is the median survival time of the treated mice expressed as a percentage of that of untreated (control) mice.

WHAT WE CLAIM IS:—

1. A compound having the general formula I



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wherein R_1 represents an alkyl group having from 1 to 4 carbon atoms and R_2 represents a hydrogen atom, a daunosaminyl group or an N-trifluoroacetyl-daunosaminyl group; or a hydrochloride salt of such a compound in which R_2 represents a daunosaminyl group.

2. 4-Demethoxy-4-hydroxy-11-deoxy-11-methoxy-daunomycinone.

3. 4-Demethoxy-4-hydroxy-11-deoxy-11-methoxy-N-trifluoroacetyl-daunorubicin.

4. 4-Demethoxy-4-hydroxy-11-deoxy-11-methoxy-daunorubicin or its hydrochloride.

5. A method for the preparation of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents a hydrogen atom, the method comprising reacting 4-demethoxy-4-hydroxy-O^6,O^7-bis-ethxoycarbonyl-daunomycinone with an alkyl halide having from 1 to 4 carbon atoms in an organic solvent in the presence of a base, and treating the resultant 4-demethoxy-4-hydroxy-11-deoxy-11-alkoxy-O^6,O^7-bis-ethoxycarbonyl-daunomycinone with a dilute alkali metal hydroxide or with an activated basic resin in an aqueous or alcoholic solvent and, if the treatment is in an alcoholic solvent, hydrolysing the resultant 4-demethoxy-4-hydroxy-7,11-bis-deoxy-7,11-bis-alkoxy-daunomycinone with aqueous trifluoroacetic acid.

6. A method for the preparation of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents a hydrogen atom, the method being substantially as described herein with reference to Examples 1 to 3.

7. A method for the preparation of a compound having the general formula I wherein R_1 is as dfined in claim 1 and R_2 represents a hydrogen atom, the method being substantially as described herein with reference to Examples 1 and 4.

8. A compound having the general formula I wherein R_1 is as dfined in claim 1 and R_2 represents a hydrogen atom prepared by a method according to any of claims 5 to 7.

9. A method for the preparation of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents an N-trifluoroacetyl-daunosaminyl group, the method comprising condensing a 4-demethoxy-4-hydroxy-11-deoxy-11-alkoxy-daunomycinone according to claim 8 with 1-chloro-N,O-bis-trifluoroacetyl-

daunosamine in an organic solvent in the presence of a soluble silver salt and treating the resultant 4-demethoxy-4-hydroxy-11-deoxy-11-alkoxy-N,O-bis-trifluoroacetyl-daunorubicin with methanol and a catalytic amount of triethylamine.

10. A method for the preparation of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents an N-trifluoroacetyl-daunosaminyl group, the method being substantially as described herein with reference to Example 5.

11. A compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents an N-trifluoroacetyl-daunosaminyl group prepared by a method according to claim 9 or claim 10.

12. A method for the preparation of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents a daunosaminyl group, the method comprising hydrolysing a 4-demethoxy-4-hydroxy-11-deoxy-11-alkoxy-N-trifluoroacetyl-daunorubicin according to claim 11 with a dilute alkali.

13. A method for the preparation of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents a daunosaminyl group, the method being substantially as described herein with reference to Example 6.

14. A compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents a daunosaminyl group prepared by a method according to claim 12 or claim 13.

15. A method for the preparation of a hydrochloride salt of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents a daunosaminyl group, the method comprising treating a 4-demethoxy-4-hydroxy-11-deoxy-11-alkoxy-daunorubicin according to claim 14 with methanolic hydrogen chloride.

16. A method for the preparation of a hydrochloride salt of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents a daunosaminyl group, the method being substantially as described herein with reference to Example 6.

17. A hydrochloride salt of a compound having the general formula I wherein R_1 is as defined in claim 1 and R_2 represents a daunosaminyl group prepared by a method according to claim 15 or claim 16.

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