

ALKYLSPECTINOMYCINS AND THEIR PREPARATION

The invention relates to a method for the synthesis of 6'-alkylspectinomycin and analogues thereof, and to intermediates utilised in the method. Some alkylspectinomycin analogues are novel and exhibit anti-bacterial activity.

Spectinomycin A is a known antibiotic. It was first prepared by the microbiological process disclosed in U.S. Patent Specification No. 3,234,092.

Some analogues of spectinomycin are described by Rosenbrook et al., J. Antibiotics 28, 953 and 960 (1975) and J. Antibiotics 31, 451 (1978). In addition, Carney et al. describe chlorodeoxy derivatives of spectinomycin in J. Antibiotics 30, 960 (1977). Further, 9-epi-4(R)-dihydrospectinomycin is reported by Foley et al., J. Org. Chem. 43, 22, 4355-4359 (1978). No biological activity is reported for any of these spectinomycin analogues and derivatives.

Lemieux, Can. J. Chem. 51, 53 (1973) discloses a preferential reaction at the 5-hydroxyl of 2-deoxystreptomamine with tri-O-acetyl-2-deoxy-2-nitroso- α -D-glycopyranosyl chloride to give a α -pseudodisaccharide. Mallams et al., J. Chem. Soc. Perkin I, 1118 (1976), extend the Lemieux reaction to synthesise di- and tri-saccharides.

The removal of oximes is disclosed by Lemieux et al., Can. J. Chem. 51, 19 (1973) and Mallams et al., J. Chem. Soc. Perkin I, 1097 (1976).

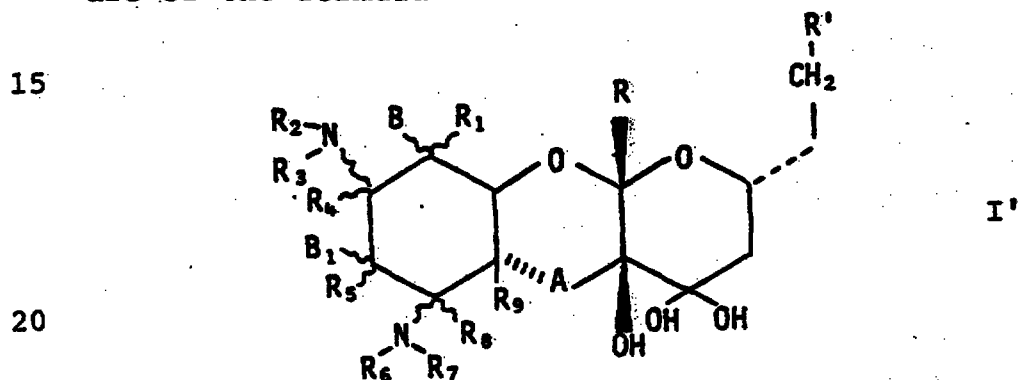
Hannessian et al. (1979) describe a chemical synthesis of spectinomycin.

White et al., Tetrahedron Letters (July 1979), disclose a chemical synthesis of spectinomycin and analogues thereof. The same synthesis is disclosed in British Patent Publication No. 2,050,348A.

The process of the present invention involves the conversion of a dienone to a large variety of 6'-alkylspectinomycin analogues, by copper-catalysed Grignard

addition. The sequence employs several versatile intermediates. The process involves modification at C-6' using an enone acylate.

A process according to the present invention gives compounds of formula I (see Scheme 1, on page 33), wherein R is hydrogen or lower alkyl; R' is a straight, cyclic or branched chain alkyl system; R₁ through R₉ are independently selected from hydrogen, lower alkyl, lower alkenyl and lower alkynyl; A is oxygen or sulfur; and B and B₁ are independently selected from hydrogen, hydroxy, alkoxy, lower alkenyloxy, thio, lower alkylthio and lower alkenylthio; and hydrated forms thereof. The hydrates are of the formula



Compounds of this invention are of formula I wherein R' is R'', i.e. a straight, cyclic or branched chain alkyl system and the longest extension of any branch or cyclic system in R'' has 1 to 4 carbon atoms, and hydrated forms and pharmaceutically acceptable salts thereof. R'' is preferably C₁₋₁₈ alkyl.

Further novel compounds of the invention are the intermediates of formulae II', III and IV. The dienones of formula IV are highly versatile Michael acceptors and are thus very suitable for modification.

Various formulae are given at the end of the description. In the given formulae, R, R', R₁ through R₉, A, B and B₁ are as defined above. R'₂, R'₃, R'₆ and R'₇ are independently selected from lower alkyl, lower

alkenyl, lower alkynyl and a blocking group which is aralkoxycarbonyl, halogenated alkoxy carbonyl and alkoxy carbonyl, with the proviso that one of R_2' and R_3' and one of R_6' and R_7' are blocking groups. R_{10} is acyl.

5 "Lower alkyl" means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and the isomeric forms thereof. "Lower alkenyl" means ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and the isomeric forms thereof. "Lower alkynyl" means ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl
10 and the isomeric forms thereof. "Acyl" means formyl, acetyl, propionyl, butyryl and pentanoyl.

"Halogenated alkoxy carbonyl" means mono-, di- and tri-halomethoxycarbonyl, mono-, di- and tri-haloethoxycarbonyl, mono-, di- and tri-halopropoxycarbonyl, mono-,
15 di- and tri-halobutoxycarbonyl, mono-, di- and tri-halopentoxycarbonyl and isomeric forms thereof.

"Halo" means fluoro, chloro, bromo and iodo.

"Aralkoxycarbonyl" means benzyloxycarbonyl, phenylethoxycarbonyl, phenylpropoxycarbonyl, diphenyloctoxycarbonyl and isomeric forms thereof, and fluoroenylmethoxycarbonyl. "Alkoxy carbonyl" means isopropylloxycarbonyl, tertiary-butyloxycarbonyl and tertiary-pentylloxycarbonyl.
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25 Alkyl means an alkyl group containing from 1 to 20 carbon atoms, which may be straight or branched-chain.

When more than one alkoxy group is present on the sugar moiety herein, they may be the same or different.

The term " α -anomer" means a 1' substituent below the plane of the ring system, and the term " β -anomer" means
30 that anomer having the C-1' configuration corresponding to spectinomycin. β -Anomers of formula I exhibit desirable biological activity. This glycosidic configuration is found in spectinomycin.
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The carbon atom numbering shown in formula I will be used throughout the specification.

5 The process of the present invention relates to the preparation of compounds of formula I from enone acylates of formula VII. The reaction sequence is given in Scheme I. Some of the intermediates and processes between formulae VI and I are disclosed in GB-A-2048243.

10 The starting materials for Step 1 are enone acylates of formula VII which are disclosed in US-A-4420624 and/or US-A-4351771.

In Step 1, the enone acylate VII is reacted with a dimethylformamide acetal, e.g. the di-t-butyl acetal but preferably excess dimethylformamide dimethyl acetal, in a solvent, to yield the enamine VI, generally at 25°C to 15 reflux, preferably 40 to 80°C. The reaction may be conducted for from 1 to 48, preferably 2 to 10, hours. The preferred reaction time and solvent are 7 hours and dimethylformamide.

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5 The enamine can be isolated from the mixture by conventional procedures such as extraction, chromatography and combinations thereof.

In Step 2 side-chain reduction of the enamine VI is effected under standard cyanoborohydride conditions, e.g. at pH4. The
10 amine can be isolated from the reaction mixture by conventional means such as extraction, chromatography and combinations thereof.

Step 3 involves reacting amine V with an alkyl halide in the presence of a solvent to yield dienone IV. The reaction can be conducted at a temperature of about 0° to about 100°, for a time
15 period of about 1 hr. to about 30 hrs., and using an excess of methyl iodide. The preferred reaction temperature and times are 20°C. to 40°C., 1 hr. to 20 hrs. Solvents that can be used include methylene chloride, CHCl_3 , THF, and ether. The preferred solvent is methylene chloride.

20 An alternative, preferred method for conducting step 3 involves reacting amine V with meta-chloroperbenzoic acid in a solvent to yield dienone IV. The reaction can be conducted at a temperature of about -20° to 50°, for a time period of about 1 min. to about 60 min. The preferred reaction temperatures and times are 20°C to 30°C, and 5 min.
25 to 20 min. Solvents that can be used include ethyl acetate/Skellysolve B, tetrahydrofuran, dioxan, and CH_2Cl_2 . The preferred solvent is ethyl acetate/Skellysolve B.

In Step 4, dienone IV is reacted with Grignard reagent, e.g. $\text{R}'\text{MgHal}$ with a copper catalyst to yield III. This reaction is
30 conducted with a solvent at a temperature of about -130° to 0° for a period of about 1 min. to 2 hours. The preferred temperature and reaction time ranges are -78° to -50° and 1 min. to 10 min., respectively. Solvents that may be used include diethyl ether, 1,2-dimethylethane, tetrahydrofuran and diisopropyl ether. The preferred solvent
35 is tetrahydrofuran.

In Step 5, enone III is subjected to reduction to yield blocked 6'-alkylspectinomycin II. This is a very critical step in the process for several reasons. It is very difficult to reduce the 4',5' double

bond without reducing the 3' carbonyl. Palladium catalysts, i.e. 10% palladium-on-barium sulfate (ionic palladium, brown catalyst), can be used with partial success, as described above, but the blocking groups, especially carbobenzyloxy groups, are removed so the separation problem is made more difficult. Furthermore, palladium catalysts do not work well on analogs with more highly substituted sugar side chains. Therefore, platinum oxide in the presence of a solvent and a base is preferred. Triethylamine may be used.

A second major advantage is that the protecting groups remain so that products can be purified by chromatography before using one of several deprotecting methods. The reaction is conducted by dissolving enone III in the solvent, adding the base, platinum oxide and then contacting the mixture with hydrogen. The reduction is conducted at a temperature of from about 20° to 40°, for a period of about 1 hr. to 4 hrs. Preferred temperature and reaction times are 20°C. to 40°C. and 2 hrs. to 3 hrs., respectively.

An alternative and preferred method for conducting step 5 involves reducing didehydrospectinomycin III to the protected 6'-spectinomycin II by reacting it with Li-selectride, a solution of lithium tri-sec-butylborohydride. The reaction is conducted by dissolving didehydrospectinomycin III in a solvent, adding the lithium solution and then base and water. The reduction is conducted at a temperature of from about 100° to -10° for 5 min. to 40 min. Preferred temperatures and reaction times are -78°, -10°, and 5 min. to 60 min., respectively. Solvents that can be used include tetrahydrofuran, dioxane, 1,2-dimethoxyethane and diethyl ether. The preferred solvent is tetrahydrofuran.

In Step 6 the compound of Formula II is deprotected to yield the compound of Formula I. The particular conditions of deprotection depends upon the particular groups, i.e. group R'₂ or R'₃ and R'₆ or R'₇ that block the amine on the actinamine ring. Where that group is benzyloxy-carbonyl or aralkoxy-carbonyl, the deprotection can be conducted under from -10 psi to +200 psi of hydrogen over a conventional catalyst such as palladium black, palladium-on-carbon, palladium-on-barium sulfate, or palladium-on-barium carbonate, while suspended in a solvent, for example, isopropanol, absolute ethanol, methanol, ethyl acetate, toluene or tetrahydrofuran. In situ generation of hydrogen from formic acid in methanol is sometimes

preferred.

Alternatively, deblocking of compounds wherein R'_2 , R'_3 and R'_6 or R'_7 are alkoxycarbonyl or aryloxycarbonyl can be conducted in the presence of an acid in solvent such as nitromethane and methylene chloride.

When R'_2 or R'_3 and R'_6 or R'_7 are haloalkoxycarbonyl, the deblocking is preferably conducted in the presence of zinc.

A particularly effective process for preparing the compound of Formula VI is depicted by the schematic outline in Scheme II. Step 1 involves reacting X, say N,N'-dibenzylloxycarbonyl spectinomycin (JACS 85, 2652, 1963), with formic acid in the presence of acetic acid anhydride, ethyl acetate and pyridine. The reaction is conducted at a temperature of about -70° to 10° for a period of about 1/2 to 30 hours in the presence of a solvent. The preferred temperature range is about -40 to 0° and the preferred reaction time is about 10 to 18 hours. Solvents that can be used include ethyl acetate, tetrahydrofuran, methylene chloride, chloroform and 1,2-dimethylethane. The preferred solvent is ethyl acetate.

In Step 2, the compound of Formula IX is reacted with an anhydride $(R_{10})_2O$, e.g. acetic anhydride, and base, e.g. pyridine. DMAP may be used. The reaction is conducted in the absence or the presence of a solvent, at a temperature of about 20° to 90° , and preferably 50° to 70° , for a period of time of about 2 to 30 hours, preferably 10 to 20 hours. Solvents that may be used include ethyl acetate, tetrahydrofuran, 1,2-dimethyloxyethane and chloroform. The preferred solvent is ethyl acetate.

In Step 3, compound VIII is subjected to treatment with light in the presence of dibromodimethyl hydantoin to generate a C_3 carbonyl in the form of a compound of Formula VII. The reaction is conducted at a temperature of about 10° to 100° , preferably 40° to 80° and a reaction time of 2 to 60 min., preferably 10 to 20 minutes. This step also generates unsaturation at the 4,5-positions.

In Step 4, the compound of Formula VII is reacted with dimethylformamide acetal in the presence of dimethylformamide, and the product reacted with methanol or water to yield a compound of Formula VI. Step 4 is conducted at a temperature of about 30° to 90° , preferably 40° to 70° , and for a time of about 2 to 6, preferably 3 to 5 hours. Each of the products prepared in the above steps can be

removed from the reaction mixture by conventional methods.

Any method within the skill in the art may be used for isolation of an analog or asteric mixture of a compound having Formula I and methods disclosed herein are not meant to be limiting. If isolation
5 is conducted under anhydrous conditions, compounds having a carbonyl group at the 3' position (Formula I) are obtained. If conducted under aqueous conditions, compounds hydrated at the 3' position (Formula I') may be obtained, with the exclusion of compounds VII and VI which do not hydrate.

10 The crude analogs may be purified by adsorption on a column of a weakly acidic ion-exchange resin such as Amberlite ^{IR-50} IRC-50 or CG-50 followed by elution with a solvent such as water, methanol, ethanol, ether, tetrahydrofuran, 1,2-dimethoxyethane or p-dioxane containing hydrochloric acid, hydrobromic acid, hydroiodic acid or sulfuric
15 acid.

Acid salts can be made by neutralizing compounds of Formula I with the appropriate acid to below about pH 7.0, and advantageously to about pH 2 to pH 3. Suitable acids for this purpose include hydrochloric, sulfuric, phosphoric, sulfamic and hydrobromic
20 acids. Acid and base salts of the compounds can be used for the same biological purposes as the parent compound.

The compounds of Formula I inhibit the growth of microorganisms in various environments. For example, Formula I compounds having the β configuration are active against Escherichia coli and can be used to
25 reduce, arrest, and eradicate slime production in papermill systems caused by its antibacterial action against this microorganism. These β anomers also can be used to prolong the life of cultures of Trichomonas foetus, Trichomonas hominis, and Trichomonas vaginalis by freeing them of Escherichia coli contamination. Still further,
30 β -anomers are active against Bacillus subtilis so it can be used to minimize or prevent odor in fish or fish crates caused by this organism. Also, the β -anomers can be used to swab laboratory benches and equipment in a mycological laboratory. β -anomers are also effective against Klebsiella pneumoniae.

35 The compounds of Formula I are also effective for treating bacterial infections, such as gonorrhea in mammals, including humans.

Compounds that show corresponding good antibacterial activity are compounds of Formula I wherein R' is an alkyl group, straight, cyclic,

or branched chain system, in which the longest extension of the branch or cyclic system contains from 1 to 4 carbon atoms. Examples of R' include ethyl, propyl, isopropyl, butyl, t-butyl and cyclohexyl. The compounds
5 6'-n-propylspectinomycin, 6'-n-butylspectinomycin and 6'-pentylspectinomycin are particularly preferred.

A pharmaceutical composition of the invention comprises an active compound of the invention in association with a physiologically acceptable excipient.
10 Examples of suitable fluid compositions are sterile parenteral solutions or suspensions, eye drops and water-in-oil emulsions. Discrete, unit dosage forms such as vials or ampoules may be used.

For parenteral administration, fluid dosage forms
15 are prepared utilising the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved in water for
20 injection and filter-sterilised before filling into a suitable vial or ampoule, and sealing. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen
25 after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial or water for injection is supplied to reconstitute the liquid prior to use. Parenteral suspensions can be prepared in substantially
30 the same manner, except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the
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composition to facilitate uniform distribution of the compound.

An effective quantity of the compound is employed in treatment. The dosage of the compound for treatment depends on many factors which are well known to those skilled in the art. They include, for example, the route of administration and the potency of the particular compound. A single dose, for humans, of from 2 to 4000, preferably 5 to 200, mg of compound, e.g. administered parenterally, may be effective for bacterial infections.

The following Preparations and Examples illustrate how compounds of the invention may be prepared. All temperatures are in degrees Centigrade. In any given case, the procedure may be repeated using any combination of the following substituents:

	<u>R₁ and/or R₅</u>	<u>R₁₀</u>	<u>B and/or B₁</u>	<u>A</u>
	☐ H-	CH ₃ CO-	H-	O
	CH ₃ -	C ₂ H ₅ CO-	HO-	S
	C ₂ H ₅ -	CH ₃ (CH ₂) ₂ CO-	CH ₃ O-	
20	C ₃ H ₇ -	(CH ₃) ₂ CHCO-	C ₂ H ₅ O-	
	C ₄ H ₉ -	C ₄ H ₉ CO-	HS-	
	C ₅ H ₁₁ -	C ₅ H ₁₁ CO-	CH ₃ S-	
	C ₈ H ₁₇ -	C ₆ H ₁₃ CO-	C ₂ H ₅ S-	
	CH ₂ =CH-	C ₇ H ₁₅ CO-		
25	CH≡C-	C ₈ H ₁₇ CO-		

Preparation 1: N,N'-dibenzyloxycarbonyl-2,6-di-O-formylspectinomycin

A 5 l flask, fitted with a stirrer and thermometer, is charged with ethyl acetate (1.33 l) and 97% formic acid (255 ml). Acetic anhydride (618 ml) is added, with dry ice/acetone cooling, so the temperature stays below -40°C. Pyridine (1.09 l) is slowly added so

the temperature is about -40°C . N,N'-dibenzyloxyspectinomycin (100 g) is added and the cooling bath is allowed to come to room temperature with stirring being continued overnight. The solution is diluted with ethyl acetate (1.65 l), washed with 0.5N hydrochloric acid (5 x 675 ml), water (2 x 675 ml), 10% aq. sodium bicarbonate (2 x 675 ml) and brine (2 x 175 ml). Drying and concentration of the organic layer gives 105 g of N,N'-dibenzyloxycarbonyl-2,6-di-O-formylspectinomycin.

CMR (d_6 -acetone): 201.6, 161.4, 161.0, 157.1, 13.6, 129.1, 128.4, 128.1, 97.1, 92.1, 73.7, 71.7, 68.3, 67.7, 67.6, 65.9, 56.1 ppm.

10 Preparation 2: N,N'-dibenzyloxycarbonyl-2,6-di-O-formyl-2'-O-acetylspectinomycin enol acetate

N,N'-dibenzyloxycarbonyl-2,6-di-O-formylspectinomycin (7.0g), acetic anhydride (15.0 ml), pyridine (30.0 ml), dimethyl aminopyridine (0.5 g) are added to ethyl acetate (50 ml) in a 250 ml flask and heated at 55° overnight. The reaction mixture is diluted with ethyl acetate (500 ml) and hexane (500 ml) and extracted with 0.6 hydrochloric acid (3 x 1 l), (1 x 0.5 l) then saturated sodium bicarbonate (2 x 500 ml) and brine (2 x 500 ml). The organics are dried over sodium sulfate and concentrated to 7.0 g of N,N'-dibenzyloxycarbonyl-2,6-di-O-formyl-2'-O-acetylspectinomycin enol acetate.

CMR (d_6 -acetone): 168.9, 167.7, 161.4, 161.0, 157.1, 139.9, 137.8, 129.1, 128.4, 128.2, 128.1, 122.8, 94.7, 92.2, 74.1, 71.3, 69.1, 67.6, 67.2, 56.3, 55.5, 31.4, 30.7, 21.1, 21.0, 20.7 ppm.

Preparation 3: N,N'-dibenzyloxycarbonyl-2,6-di-O-formyl-2'-O-acetyl-4',5'-didehydrospectinomycin

N,N'-dibenzyloxycarbonyl-2,6-di-O-formyl-2'-O-acetylspectinomycin enol acetate (5.26 g) is dissolved in carbon tetrachloride (75 ml) and
5 dibromodimethylhydantoin (1.05 g) is added. The solution was brought to reflux under visible light as initiator. After 20 minutes, the solution is cooled, diluted with chloroform (200 ml) and water (100 ml). Phases are separated and organics are washed with aqueous sodium chloride (60 ml). The organics are dried over sodium sulfate and
10 concentrated to give 5.65 g of N,N'-dibenzyloxycarbonyl-2,6-di-O-formyl-2'-O-acetyl-4',5'-didehydrospectinomycin.

CMR (d_6 -acetone): 182.4, 173.4, 170.0, 161.6, 161.0, 157.0, 137.6, 129.2, 128.6, 128.2, 103.4, 95.7, 93.1, 73.7, 72.1, 67.8, 66.9, 56.1, 55.7, 31.8, 30.6, 21.0 ppm.

Preparation 4: N,N'-dicarbobenzyloxy-2'-O-acetyl-6-[(dimethyl-amino)methylene]-4',5'-didehydrospectinomycin

A solution of N,N'-dicarbobenzyloxy-2'-O-acetyl-4',5'-didehydrospectinomycin (22.00 g, 34.4 mmole) and dimethylformamide dimethylacetal (100 ml) in dimethylformamide (100 ml) is stirred for 7 hours at 50-55°C with drierite protection. The brown solution is concentrated under vacuum and the residue chromatographed on silica gel (250 g) which has been wet packed in a 2 liter sintered glass funnel. The mixture is eluted with 5% acetonitrile in chloroform (2 liters), 7% (3 liters), 33% (3 liters), 50% (6 liters) over a period of 1 1/2 hours. Half liter fractions are taken. The fractions are evaluated by TLC (1/1 acetonitrile in chloroform) and combined to give 19.78 g of pure N,N'-dicarbobenzyloxy-2'-O-acetyl-6-[(dimethyl-amino)-methylene]-4',5'-didehydrospectinomycin and 3.30 g of N,N'-dicarbobenzyloxy-2'-O-acetyl-6-[(dimethyl-amino)-methylene]-4',5'-didehydro-
 15 spectinomycin containing some DMF (dimethyl formamide). The latter fraction was rechromatographed as above (but using 60 g of silica gel) to give 2.75 g of pure N,N'-dicarbobenzyloxy-2'-O-acetyl-6-[(dimethyl-amino)-methylene]-4',5'-didehydrospectinomycin. Total yield is 22.53 g (94% yield).
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CD(CH₃OH)[θ]_{311nm} - 10,400 $\pm$ 1,200, [θ]₂₈₅ - 2,500 $\pm$ 1,200,
 [θ]₂₄₆ - 1,200 $\pm$ 1,200.

IR(mu11): 3380, 1750, 1695, 1675sh, 1600, 1555, 1500, 1385, 1350,
 1280, 1240, 1195, 1185, 1145, 1110, 1085, 1065, 1025, 1000,
 25 960, 770, 740, 645 cm⁻¹.

PMR (CDCl₃): 2.13 (3H, s), 2.82 (3H, s), 2.89 (6H, br.s), 2.91 (3H, s), 5.10 (4H, br.s), 5.16 (1H, s), 5.97 (1H, s), 7.30s (10H, s).

CMR (CD₃COCD₃): 20.9, 31.2, 31.5, 30-44 br, 36.3, 59.6, 66.2, 67.3,
 30 74.6, 75.4, 88.7, 94.9, 95.0, 95.1, 95.5, 128.3, 129.1, 137.9, 138.0, 150.3, 157.2, 157.7, 163.3, 169.8, 171.2, 180.3 PPM.

Mass spectrum, m/c (diTMS): 839 (M⁺), 824, 797, 779, 730, 688. Peak matched calcd: 839.3480; Found: 839.3466.

Preparation 5: N,N'-dicarbobenzyloxy-2'-O-acetyl-6-[(dimethyl-
amino)methylene]-4',5'-didehydrospectinomycin

N,N'-dibenzyloxycarbonyl-2,6-di-O-formyl-2'-O-acetyl-4',5'-didehydrospectinomycin (5.50 g) is dissolved in dimethylformamide (39.0 ml) and dimethylformamide dimethyl acetal (36.0 ml) is added. After heating at 55°-60° for 4 hours, methanol (36 ml) is added and heating at 55°-60° continued for 3 hours. The residue is taken up in chloroform (15 ml) and applied to silica gel (200 ml) in a filter. The product is washed off after the remaining DMF by elution with 10 chloroform (1/2 l), 5% acetonitrile in chloroform (0.8 l), 30% acetonitrile in chloroform (150 ml) and acetonitrile (1 l). Fractions are combined to give 2.71 g of N,N'-dicarbobenzyloxy-2'-O-acetyl-6-[(dimethylamino)methylene]-4',5'-didehydrospectinomycin.

CMR (d₆-acetone): 180.3, 171.2, 169.8, 157.0, 150.3, 137.9, 129.0,
15 128.2, 95.5, 95.2, 95.1, 94.8, 88.7, 75.3, 67.3, 66.2, 59.9,
56.7, 41.0, 31.4, 30.7, 21.2 ppm.

Preparation 6: N,N'-dicarbobenzyloxy-2'-O'-acetyl-6'-(dimethylaminomethyl)-4',5'-didehydrospectinomycin

N,N'-dicarbobenzyloxy-2'-O'-acetyl-6'-[(dimethylamino)methylene]-4',5'-didehydrospectinomycin (20.00 g, 28.78 mmole) and methyl orange (5 mg) are dissolved in methanol (200 ml). The pH is adjusted to 4 with 2N methanolic hydrogen chloride and sodium cyanoborohydride is added in portions over 20 minutes with frequent readjustment to pH using 2N methanolic hydrogen chloride. After a total of 2.00 g (31.83 mmole) of sodium cyanoborohydride has been added, the solution is stirred an additional hour at room temperature; TLC (1:9 methanol/chloroform) shows starting material has been consumed. The solution is concentrated, diluted with ethyl acetate (500 ml), 0.1N sodium hydroxide (250 ml), 1.0 N NaOH (25 ml) and saturated brine (250 ml). The organic phase is washed with brine (200 ml + 100 ml). The three aqueous phases are washed in sequence with ethyl acetate (2 x 200 ml). Organic extracts are dried over sodium sulfate and concentrated to yield N,N'-dicarbobenzyloxy-2'-O'-acetyl-6'-dimethylaminomethyl)-4',5'-didehydrospectinomycin as a foam (17.93 g, 89% yield).

CD (CH₃OH): $[\theta]_{321} = 12,000 \pm 1,100$, $[\theta]_{270} \pm 1,100$.

UV (C₂H₅OH): 273 nm (8,800), 377 nm(sh) (63).

PMR (CDCl₃): 2.13 (3H, s), 2.17 (6H, s), 2.46 (3H, s), 3.05 (3H, s), 3.06 (3H, s), 5.05 (4H, d), 5.34 (1H, s), 5.89 (1H, s), 7.26 (10H, d).

CMR (CD₃COCD₃): 20.9, 31.3, 45., 56.1, 57.1, 61.3, 66.1, 67.3, 74.0, 75.4, 93.7, 96.0, 103.1, 128.3, 129.1, 137.9, 157.2, 170.0, 174.9, 183.1 ppm.

Preparation 6a: N,N'-dicarbobenzyloxy-2,0'-acetyl-6'-(dimethylaminomethyl)-4',5'-didehydrospectinomycin

N,N'-dicarbobenzyloxy-2'-O'-acetyl-6'-[(dimethylamino)methylene]-4',5'-didehydrospectinomycin (57.0 g, 78.7 mmole) ethyl acetate (450 ml) and methanol (105 ml) are mixed. The pH is adjusted to 4, with 2N hydrochloric acid and sodium cyanoborohydride (7.3 g) added in five

portions over five minutes with frequent readjustment to pH of 4 using 2N hydrochloric acid. After completion of addition of sodium cyanoborohydride the pH is held at 4 for an additional 15 minutes. TLC (1:9 methanol/chloroform) shows starting material has been consumed.

- 5 The solution is then mixed with water (350 ml) in sodium hydroxide (175) and the phases separated. The upper phase is exhausted with brine (250 ml) and Skellysolve B (150 ml) added to break the emulsion. The two aqueous phases are backwashed in sequence with ethyl acetate (300 ml) plus Skellysolve B (75 ml) and the total organics are dried
- 10 over sodium sulfate. The sodium sulfate is filtered to yield a filtrate containing N,N'-dicarbobenzyloxy-2,0'-acetyl-6'-(dimethylaminomethyl)-4',5'-didehydrospectinomycin.



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Preparation 7: N,N'-dicarbobenzyloxy-2-O'-acetyl-6'-methylene-4',5'-didehydrospectinomycin

N,N'-dicarbobenzyloxy-2-O'-acetyl-6'-(dimethylaminomethyl)-4',5'-didehydrospectinomycin (17.43 g, 25.00 mmole) is dissolved in 5 methylene chloride (200 ml) and methyl iodide (18.0 ml, 41.04 g, 289 mmole) and stirred at room temperature for 6 hours. After standing at 10°C. for an additional 16 hours the solution is concentrated and then dissolved in 1/9 acetonitrile/chloroform. The mixture is chromatographed on silica gel (300 g) using the same solvent (4 liters), then 10 1/3 acetonitrile/chloroform (4 liters). The first pure substance eluted is obtained by combining fractions and concentrating to yield 10.03 g of N,N'-dicarbobenzyloxy-2-O'-acetyl-6'-methylene-4',5'-didehydrospectinomycin (61% yield).

CD (CH₃OH): $[\theta]_{334} - 26,100 \pm 2,300$, $[\theta]_{240} - 44,800 \pm 2,300$,
15 $[\theta]_{244nm} - 10,800 \pm 2,300$.

UV (C₂H₅OH): 204sh (22,500), 241 (6,750) 250sh (5,900), 256sh (4,900), 293nm (14,650).

PMR (CDCl₃): 2.13 (3H, s), 3.03 (3H, s), 3.06 (3H, s), 5.05 (4H, d),
5.44 (1H, s), 5.61 (1H, q), 5.95 (1H, s), 6.11 (1H, s), 6.19
20 (1H, s), 7.29pp (10H, s).

CMR (CD₃COCD₃): 20.9, 31.4, 57.2, 60.1, 66.2, 67.4, 74.1, 74.7, 75.6,
94.0, 96.1, 104.3, 125.3, 128.4, 129.2, 131.1, 138.0, 138.1,
157.6, 166.6, 170.2, 184.0 ppm.

Preparation 7a: N,N'-dicarbobenzyloxy-2-O'-acetyl-6'-methylene-4',5'-didehydrospectinomycin

To the N,N'-dicarbobenzyloxy-2-O'-acetyl-6'-(dimethylamino-methyl)-4',5'-didehydrospectinomycin in ethyl acetate/Skellysolve B prepared in Preparation 6a is added m-chloroperbenzoic acid (15 g). After stirring the solution for 10 minutes saturated sodium 30 bicarbonate (300 ml) is added with mixing and the phases separated. The organic layer is washed with brine (250 ml) and then methanol is added to break the emulsion. The two aqueous fractions are washed in sequence with ethyl acetate (250 ml) and Skellysolve B (75 ml). The

organics are combined, dried with sodium sulfate and then concentrated to a solid. The solid is dissolved in chloroform and the solution chromatographed on silica (1 liter wet packed in a 1 liter sintered glass funnel) using chloroform (4 liter), 2% acetonitrile/chloroform (2 liters), 5% acetonitrile/chloroform (2 liters), 10% acetonitrile (4 liters) and 15% acetonitrile (4 liters). Fractions 10-14 are combined and concentrated to yield 15.7 g of a mixture containing N,N'-dicarbo-benzyloxy-2-O'-acetyl-6'-methylene-4',5'-didehydrospectinomycin.

Preparation 8: N,N'-dibenzylloxycarbonyl-2'-O-acetyl-4',
5'-didehydro-6'-n-octylspectinomycin

A dried 15 ml three neck flask is equipped with a magnetic stir bar and a serum cap. N,N'-dicarbobenzyloxy-2-O'-acetyl-6'-methylene-
5 4,5'-didehydrospectinomycin (332 mg, 0.5 mmole) is dissolved in tetrahydrofuran (10 ml) and cupric bromide (25 mg) is added. After cooling the slurry to -78° under a nitrogen atmosphere, heptylmagnesium bromide (1.2 ml, 2.1 M) is added by injection through the serum cap. A TLC probe (1:4 CH₃CH:CHCl₃) shows starting material
10 has been converted to a slightly less polar major product. The reaction mixture is poured onto a solution of ethyl acetate (20 ml) and acetic acid (0.3 ml). After dilution with water (10 ml) and mixing, the organic phase is separated and washed with saturated sodium bicarbonate (15 ml) and saturated brine (10 ml). The aqueous
15 extracts are, in turn, washed with ethyl acetate (20 ml). Organic extracts are dried over sodium sulfate and concentrated to a foam. Chromatography on 6.0 g silica in 1:9 acetonitrile-chloroform gives (0.32 g) purified N,N'-dibenzylloxycarbonyl-2'-O-acetyl-4',5'-di-
didehydro-6'-n-octylspectinomycin.

20 CMR (CD₃COCD₃): 183.1, 178.4, 170.0, 157.7, 138.0, 124.1, 128.3, 102.5, 96.0, 93.8, 75.6, 73.4, 67.3, 66.1, 59.7, 57.2, 35.0, 32.4, 31.4, 30.0, 29.8, 29.6, 26.7, 23.2, 20.4, 14.3 ppm.

Mass spectrum (silylated): M/e 856 (M⁺), 841, 769, 671, 600, 484, 356, 313, 284, 243, 217, 199, 171, 145, 73.

25 Utilizing a procedure similar to that used in Preparation 8 but substituting the appropriately substituted alkyl magnesium bromide for heptyl magnesium bromide there is obtained:

N,N'-dibenzylloxycarbonyl-2'-O-acetyl-4',5'-didehydro-6'-ethyl-
spectinomycin.

30 CMR 183.1, 176.2, 170.0, 151.3, 137.81, 129.0, 128.1, 102.6, 95.9, 93.6, 75.3, 74.2, 67.3, 66.1, 60.0, 57.1, 36.8, 31.3, 20.8, 20.0, 13.6 ppm.

N,N'-dibenzoyloxycarbonyl-2'-O-acetyl-4',5'-didehydro-6'-n-propyl spectinomycin.

5 CMR 183.3, 176.5, 170.1, 157.2, 138.2, 129.2, 128.4, 102.6, 96.1, 93.8, 75.6, 74.6, 67.4, 66.2, 60.1, 57.3, 34.8, 32.2, 28.8, 22.7, 20.9, 13.9 ppm.

N,N'-dibenzoyloxycarbonyl-2'-O-acetyl-4',5'-didehydro-6'-n-butyl spectinomycin.

10 CMR 183.1, 176.4, 170.0, 157.9, 138.2, 129.1, 128.7, 102.5, 96.0, 93.8, 75.6, 74.6, 67.3, 66.1, 60.0, 57.2, 35.0, 31.7, 31.4, 26.3, 22.8, 20.9, 14.1 ppm.

N,N'-dibenzoyloxycarbonyl-2'-O-acetyl-4',5'-didehydro-6'-n-pentyl spectinomycin.

15 CMR 183.1, 176.5, 170.0, 157.8, 138.4, 129.1, 128.3, 102.6, 96.0, 93.7, 75.6, 74.8, 67.3, 66.0, 60.2, 57.1, 35.0, 32.0, 31.4, 29.2, 26.6, 23.0, 20.9, 14.2 ppm.

Another compound of this type is N,N'-dibenzoyloxycarbonyl-2'-O-acetyl-4',5'-didehydro-6'-n-undecyl spectinomycin.

Preparation 9: N,N'-dibenzylloxycarbonyl-6'-octyl-spectinomycin

N,N'-dicarbobenzyloxy-2'-O-acetyl-4',5'-didehydro-6'-n-octyl-spectinomycin (0.32 g) is dissolved in 2-propanol (12.0 ml) and triethylamine (0.12 ml) is added. The solution is divided into four equal parts and placed in test tubes each containing 30 mg of platinum oxide. The test tubes are placed in a Parr bottle carefully and allowed to shake at 20 pounds per square inch (psi) of hydrogen for 2 hours. The catalyst is filtered and water (0.7 ml) is added to the combined filtrates. After standing 16 hours the filtrate is heated an additional 3/4 hours at 65°, concentrated and chromatographed on silica (6 g). N,N'-dibenzylloxycarbonyl-6'-n-octylspectinomycin is eluted with 1/2% methanol chloroform (200 ml), 1% (100 ml), 1 1/2% (150 ml), 2% (200 ml) and 3% (100 ml). The desired fractions are found by TLC analysis; the product gives a purple spot when sprayed with DNP spray, then sulfuric acid spray and heated. Weight of product is 0.09 g.

CMR (CD_3COCD_3): 201.5, 157, 138.1, 129.1, 128.3, 97.5, 92.3, 75.1, 74.7, 74.6, 71.8, 67.2, 66.4, 65.6, 61.1, 60.1, 57.5, 44.1, 36.1, 32.4, 31.7, 31.4, 30.7, 30.1, 29.8, 25.7, 23.1, 14.3 ppm.

Mass Spectrum (silylated): $M/e = 928 (M^+)$, 913, 901, 837, 823, 793, 745, 624, 611, 539, 493, 449, 359, 91.

Preparation 9a: N,N'-dibenzylloxycarbonyl-6'-propylspectinomycin

A solution of 4',5'-didehydro-2'-O-acetyl-N,N'-dibenzylloxycarbonyl-6'-propylspectinomycin (0.70 g) is dissolved in tetrahydrofuran (10 ml) and cooled to -78°. A 1 M solution of lithium tri-sec-butylborohydride in tetrahydrofuran (3.0 ml) is added. After stirring under nitrogen for 25 min. at -78° the solution is poured into ethyl acetate (10 ml) plus acetic acid (0.2 ml). More ethyl acetate (10 ml), water (1.0 ml) and triethylamine (1.0 ml) are added. After two hours additional triethylamine (1.0 ml) is added and the solution is stirred at room temperature for 16 hours. Skellysolve B (20 ml) and sodium bicarbonate (saturated aqueous solution 15 ml) are added and phases are separated. The upper phase is washed with aqueous saturated NaCl (15 ml). The organic phase is dried over

sodium sulfate and concentrated to an oil. This is chromatographed on silica gel (40 ml), packed in methylene chloride. The product is eluted with methylene chloride (50 ml), 1:1 methylene chloride/chloroform (60 ml), chloroform (50 ml), 1/2% methanol in chloroform (100 ml), 1% methanol in chloroform (100 ml), 2 1/2% methanol in chloroform (100 ml), 5% methanol in chloroform (200 ml). Concentration of appropriate fractions gives 0.45 g (68.3%) of N,N'-dibenzyloxycarbonyl-6'-propylspectinomycin.

Utilizing procedures similar to those used in Preparations 9 or 9a but substituting the appropriately substituted N,N'-dicarbobenzyloxy-6'-alkylspectinomycin analog for N,N'-dicarbobenzyloxy-6'-octylspectinomycin there is obtained

N,N'-dibenzyloxycarbonyl-6'-ethylspectinomycin.

CMR 201.0, 158.2, 138.2, 129.1, 128.4, 97.6, 92.3, 75.2, 74.7, 74.6,
71.5, 67.2, 66.2, 65.6, 61.1, 60.2, 57.6, 57.3, 44.1, 38.2, 31.7,
31.4, 18.2, 14.1 ppm.

N,N'-dibenzyloxycarbonyl-6'-n-propylspectinomycin.

CMR 201.8, 156.7, 138.1, 129.1, 128.3, 97.5, 92.3, 75.1, 74.7, 74.6,
71.8, 67.2, 66.4, 65.6, 60.9, 59.9, 57.5, 44.1, 35.7, 31.4, 30.8,
27.7, 23.0, 14.2 ppm.

N,N'-dibenzyloxycarbonyl-6'-n-butylspectinomycin.

CMR 201.5, 156.2, 138.2, 129.4, 128.6, 97.7, 92.6, 75.3, 75.1, 74.8,
72.1, 67.6, 66.7, 66.0, 61.0, 60.0, 57.8, 44.3, 35.3, 31.6, 32.5,
32.1, 31.8, 31.2, 30.2, 29.2, 25.6, 23.3, 14.6 ppm.

N,N'-dibenzyloxycarbonyl-6'-isobutylspectinomycin.

N,N'-dibenzyloxycarbonyl-6'-n-pentylspectinomycin.

CMR 202.0, 158.1, 138.2, 129.1, 128.4, 97.6, 92.4, 75.2, 74.6, 74.0,
71.8, 67.2, 66.4, 65.7, 61.1, 60.1, 57.5, 57.3, 44.1, 36.1, 32.3,
31.7, 31.4, 29.7, 25.6, 23.2, 14.3 ppm.

N,N'-dibenzoyloxycarbonyl-6'-(3,3-dimethyl)-n-butyl spectinomycin.

N,N'-dibenzoyloxycarbonyl-6'-cyclopentenyl spectinomycin.

N,N'-dibenzoyloxycarbonyl-6'-cyclohexylmethyl spectinomycin.

5 CMR 202.0, 157.5, 138.0, 129.1, 178.3, 97.5, 92.3, 75.1, 74.7, 72.1,
67.2, 66.4, 65.6, 60.9, 60.7, 57.5, 57.3, 44.1, 38.2, 33.8, 33.5,
31.7, 31.4, 27.2, 26.9, ppm,

N,N'-dibenzoyloxycarbonyl-6'-undecyl spectinomycin.

Example 1: 6'-n-octylspectinomycin

N,N'-dibenzylloxycarbonyl-6'-n-octylspectinomycin (0.09 g) is dissolved in methanol (7.0 ml) and stirred under a nitrogen atmosphere. Palladium black (60 mg) is added followed by 97% formic acid (0.45 ml). After stirring well for 40 minutes the catalyst is filtered and the filtrate is concentrated at high vacuum. The residue is taken up in H₂O (8 ml) and acidified to pH 1.5 with 0.1 N hydrogen chloride (0.35 ml). The sample is freeze-dried to prepare a CMR sample. After CMR the sample was diluted with H₂O and freeze-dried to give 0.05 g 6'-n-octylspectinomycin as its dihydrochloride.

CMR (D₂O, referenced to internal CH₃CN): 92.9, 92.6, 91.1, 70.9, 68.8, 65.1, 64.7, 60.6, 58.7, 57.5, 38.2, 33.4, 30.8, 30.1, 29.5, 28.5, 28.2, 24.2, 21.5, 12.8 ppm.

Utilizing a procedure similar to that used in Example 1 but substituting the appropriately substituted protected 6'-alkylspectinomycin for N,N'-dicarbobenzyloxy-6'-n-octylspectinomycin, there is obtained as the dihydrochloride:

6'-ethylspectinomycin

CMR 29.8, 29.4, 60.6, 58.6, 57.6, 64.6, 70.7, 65.0, 92.7, 92.7, 91.0, 58.5, 68.8, 35.0, 16.6, 12.4 ppm.

6'-n-propylspectinomycin

CMR 29.8, 29.4, 60.6, 58.6, 57.6, 64.6, 70.9, 64.9, 92.6, 92.6, 91.0, 38.5, 68.7, 32.5, 25.4, 21.0, 12.3 ppm.

6'-n-butylspectinomycin

CMR 29.9, 24.4, 60.4, 58.5, 57.4, 64.5, 70.7, 64.9, 92.5, 92.5, 90.9, 38.7, 68.7, 32.9, 30.1, 23.1, 20.4, 12.5 ppm.

6'-iso-butylspectinomycin

6'-n-pentylspectinomycin

CMR 29.8, 29.3, 60.6, 58.6, 57.7, 64.7, 71.0, 65.0, 92.7, 92.7, 91.1,
38.6, 68.8, 32.9, 30.1, 23.2, 21.0, 20.8, 12.5 ppm.

6'-(3,3-dimethyl)-n-butyl spectinomycin

6'-cyclopentylmethyl spectinomycin

5 6'-cyclohexylmethyl spectinomycin

CMR 30.1, 29.5, 60.6, 58.6, 57.5, 64.7, 70.9, 65.1, 92.6, 92.6, 91.1,
38.2, 68.8, 33.4, 30.7, 28.5, 28.5, 28.2, 28.2, 24.2, 21.5, 12.8
ppm.

6'-n-undecyl spectinomycin

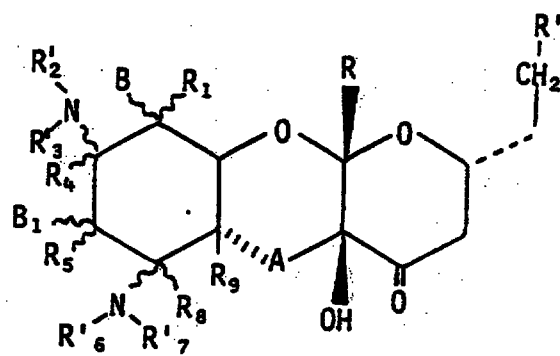
10 CMR 60.5, 58.6, 57.5, 64.9, 70.9, 65.2, 97.7, 92.8, 91.2, 38.8, 68.8,
33.4, 30.9, 28.4, 28.8, 28.8, 28.8, 28.8, 28.8, 28.8, 24.4, 21.5,
12.8, 30.2, 24.6 ppm.

Example 2 6'-n-propylspectinomycin sulfate

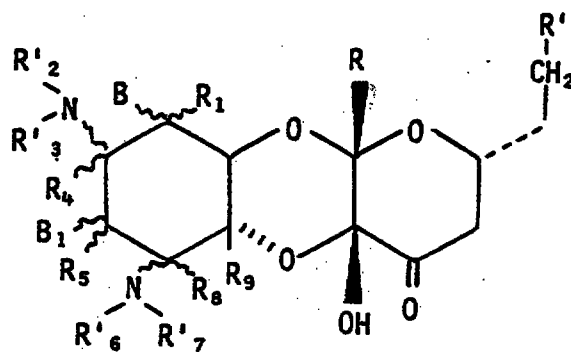
N,N'-dibenzoyloxycarbonyl-6'-n-octylspectinomycin (2.20 g) is dissolved in methanol (100 ml) and stirred under a nitrogen atmosphere. Palladium black (1.39 g) is added followed by 97% formic acid (4.3 ml). After stirring well the catalyst is filtered and the filtrate is concentrated at high vacuum. The residue is taken up in H₂O (10 ml) and acidified with 1 M aqueous hydrogen sulfate. (3.5 ml). The sample is freeze-dried and then recrystallized from acetone:water to give 0.87 g 6'-n-propylspectinomycin sulfate pentahydrate.

10 CMR (D₂O, referenced to internal CH₃CN):

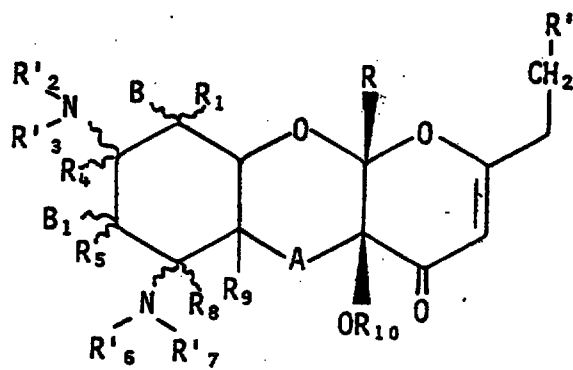
118.07, 92.67, 91.24, 91.06, 70.73, 68.94, 65.01, 64.74, 60.78, 59.15, 57.69, 38.77, 32.83, 30.35, 29.77, 25.78, 21.18 and 12.45 ppm.



II

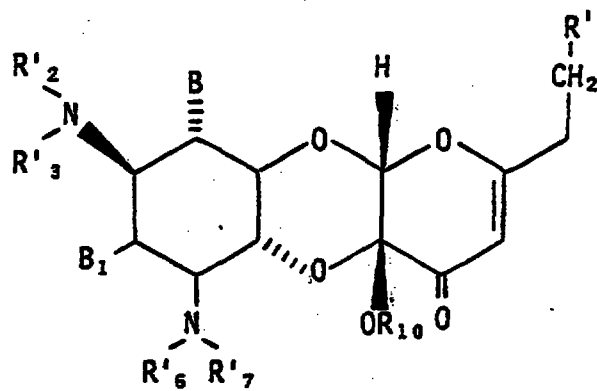


II'

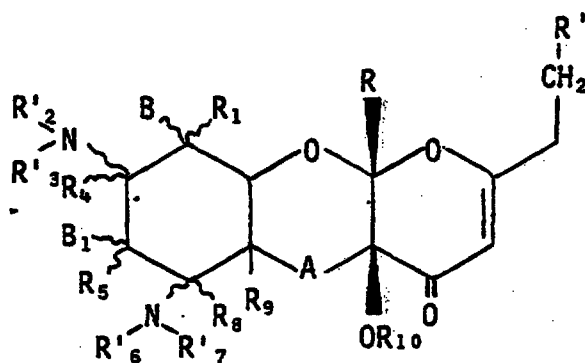


III

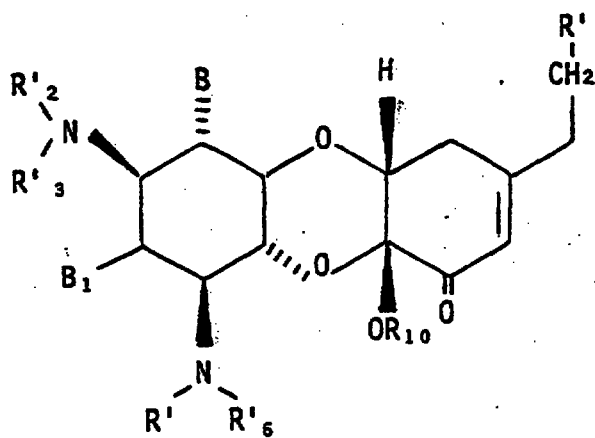
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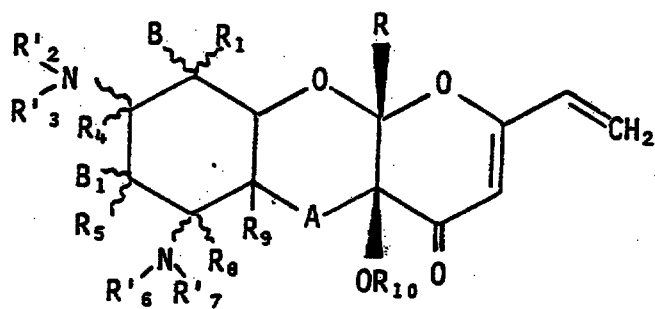
IIIa



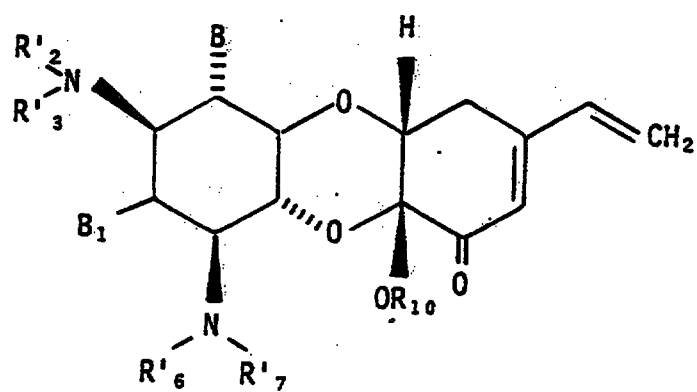
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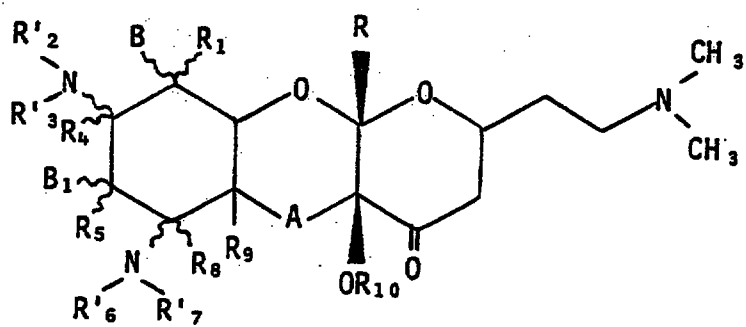
III'a



IV

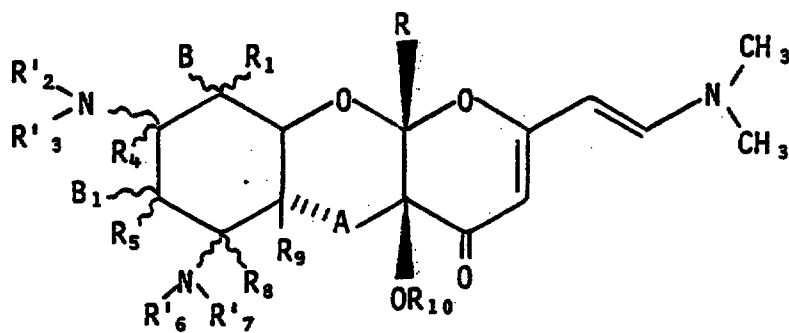


IVa

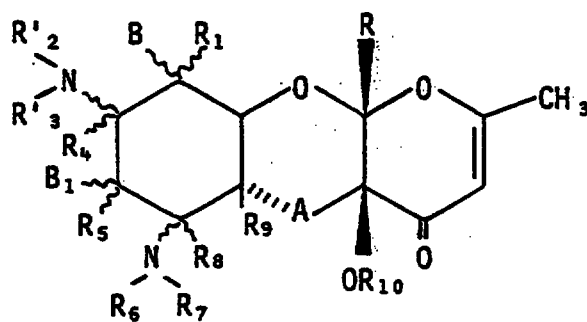


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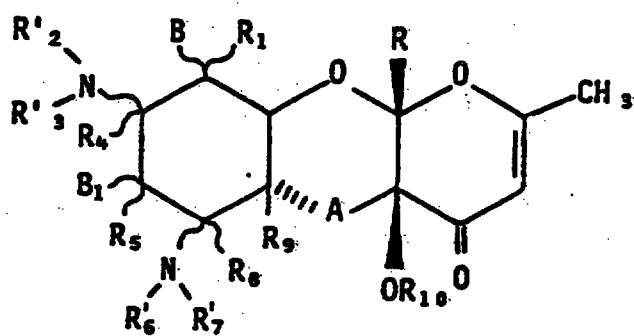
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VI

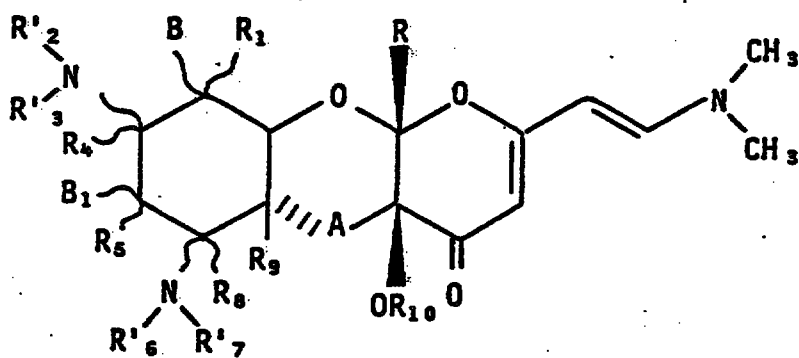


VII

Scheme 1

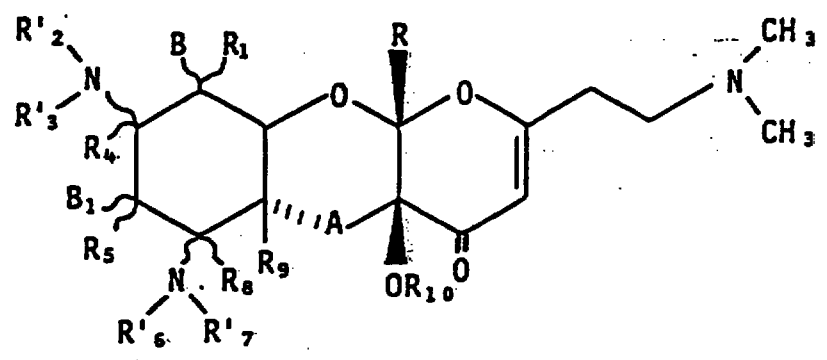
VII

STEP 1

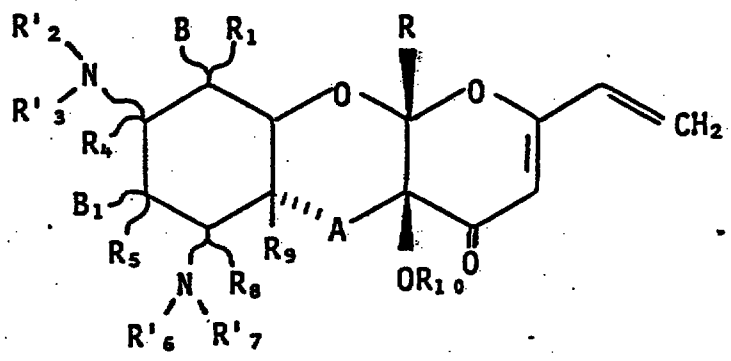


VI

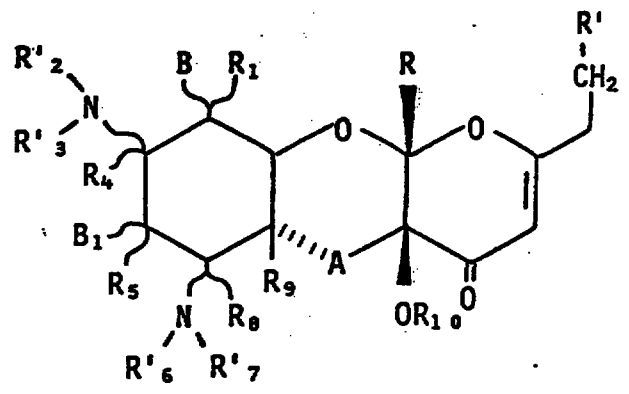
STEP 2



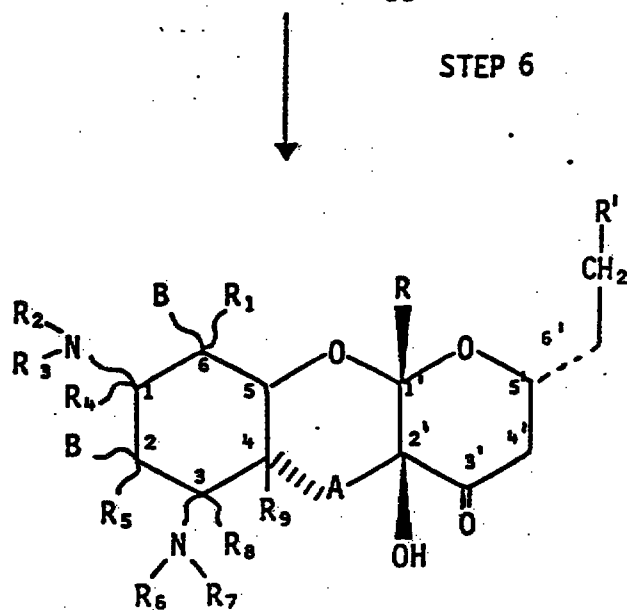
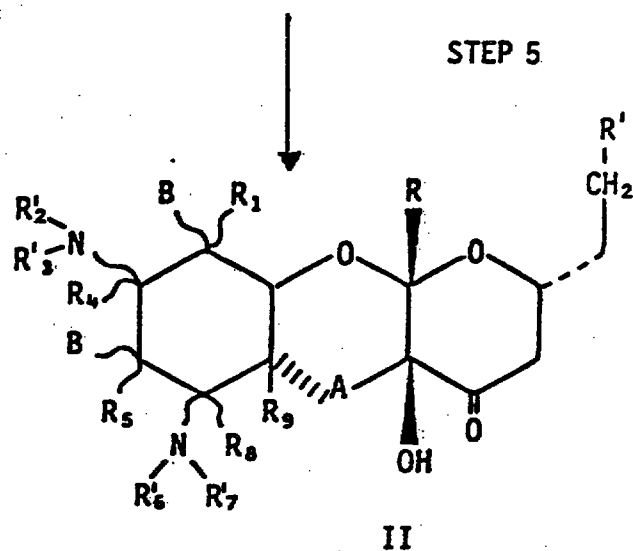
V
STEP 3



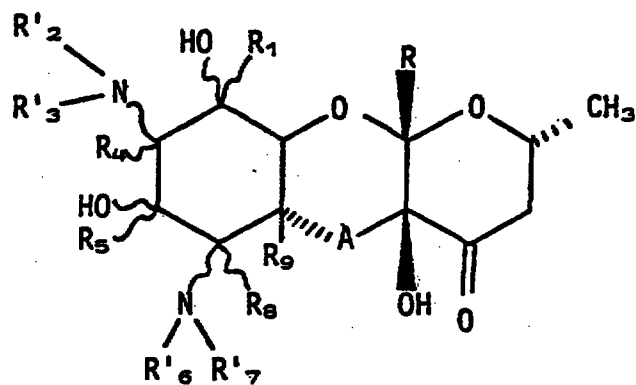
IV
STEP 4



III

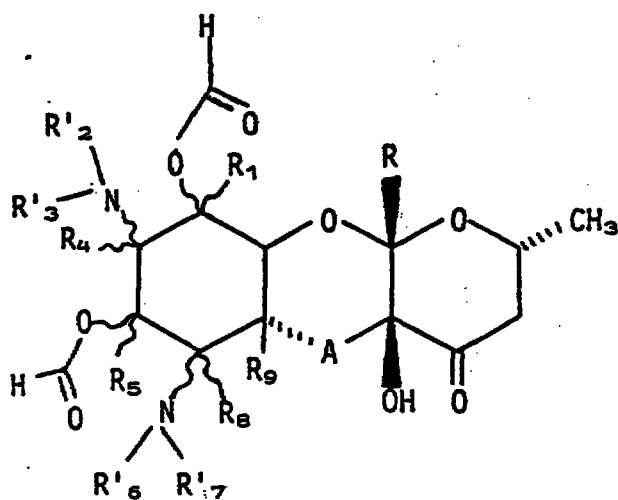


Scheme II



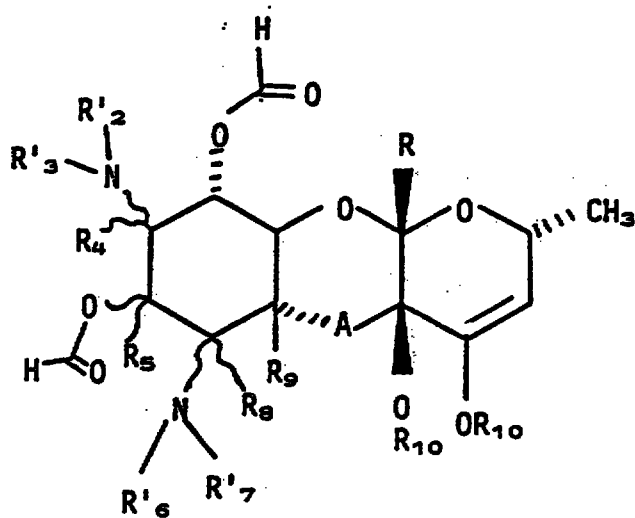
X

Step 1



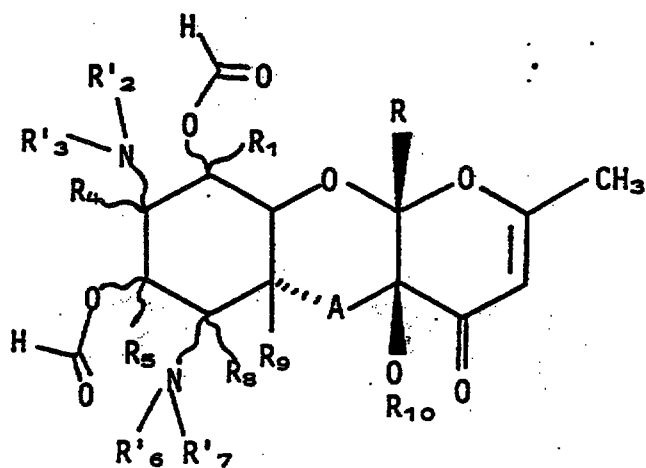
IX

Step 2



VIII

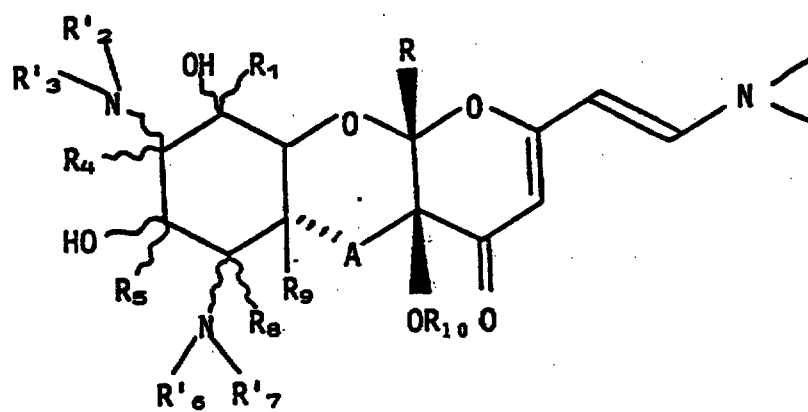
Step 3



VII

Step 4

- 1) DMF
DMF acetal
- 2) CH_3OH or water

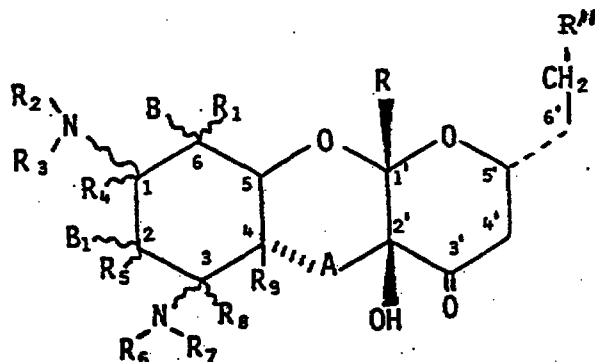


VI



CLAIMS

1. A compound having the formula



I

wherein R is hydrogen or lower alkyl; R'' is a straight, cyclic or branched chain alkyl system and the longest extension of any branch or cyclic system in R has 1 to 4 carbon atoms; R₁ through R₉ are independently selected from hydrogen, lower alkyl, lower alkenyl and lower alkynyl; A is oxygen or sulfur; and B and B₁ are independently selected from hydrogen, hydroxy, alkoxy, lower alkenyloxy, thio, lower alkylthio and lower alkenylthio; a hydrated form thereof; or a pharmaceutically acceptable salt of the compound or hydrated form thereof.

2. A compound according to claim 1, wherein R'' is C₁₋₁₈ alkyl.

3. A compound according to claim 1 or claim 2, wherein one of R₂ and R₃ and one of R₆ and R₇ are hydrogen.

4. A compound according to any preceding claim, wherein R, R₁, R₄, R₅ and R₈ are hydrogen and R'' is ethyl, n-propyl or n-butyl.

5. A compound according to any preceding claim, wherein B and B₁ are each hydroxy.

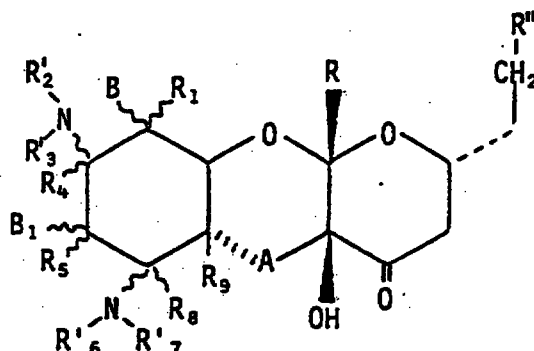
6. 6'-Ethylspectinomycin or its dihydrochloride.



* C L M S *

7. 6'-n-Propylspectinomycin or its dihydrochloride or sulphate.
8. 6'-n-Butylspectinomycin or its dihydrochloride.
9. 6'-Isobutylspectinomycin or its dihydrochloride.
- 5 10. 6'-n-Pentylspectinomycin or its dihydrochloride.
11. 6'-(3,3-Dimethylbutyl)spectinomycin or its dihydrochloride.
12. 6'-n-Octylspectinomycin or its dihydrochloride.
13. 6'-Cyclopentylmethylspectinomycin or its
- 10 dihydrochloride.
14. 6'-Cyclohexylmethylspectinomycin or its dihydrochloride.
15. 6'-n-Undecylspectinomycin or its dihydrochloride.
16. A compound of the formula

15

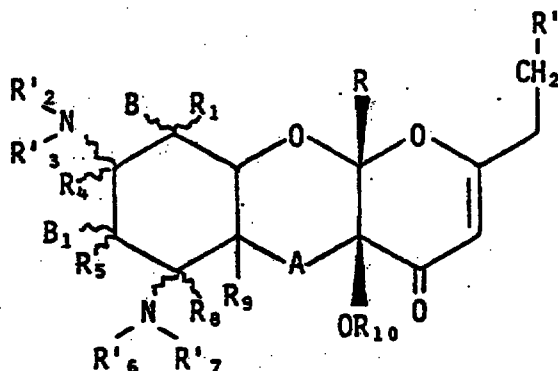


II

- wherein R, R₁, R₄, R₅, R₈, R₉, R'', A, B and B₁ are as defined in any preceding claim; and R'₂, R'₃, R'₆ and R'₇ are independently selected from lower alkyl, lower alkenyl, lower alkynyl and a blocking group which is
- 20 aralkoxycarbonyl, halogenated aralkoxycarbonyl or alkoxy-carbonyl, with the proviso that one of R'₂ and R'₃ and one of R'₆ and R'₇ are blocking groups.
17. A compound according to claim 16, wherein R'₂ and R'₆ are each hydrogen and R'₃ and R'₇ are each carbobenzyloxy.
- 25 18. N,N'-Dicarbobenzyloxy-6'-methylspectinomycin.
19. N,N'-Dicarbobenzyloxy-6'-ethylspectinomycin.
20. N,N'-Dicarbobenzyloxy-6'-n-propylspectinomycin.

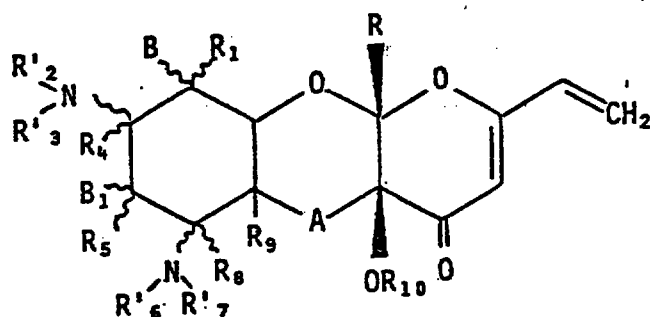


21. N,N'-Dicarbobenzyloxy-6'-n-pentylspectinomycin.
22. N,N'-Dicarbobenzyloxy-6'-n-octylspectinomycin.
23. N,N'-Dicarbobenzyloxy-6'-n-undecylspectinomycin.
24. N,N'-Dicarbobenzyloxy-6'-cyclohexylspectinomycin.
- 5 25. A compound of the formula



III

- wherein R, R₁, R₄, R₅, R₈, R₉, A, B and B₁ are as defined in any of claims 1 to 5; R' is straight, cyclic or branched chain alkyl; R'₂, R'₃, R'₆ and R'₇ are as defined in claim 16 or claim 17; and R₁₀ is acyl.
26. A compound as claimed in claim 25, wherein R' is as defined for R" in any of claims 1, 2 and 4.
 27. N,N'-Dicarbobenzyloxy-2'-O-acetyl-4',5'-didehydro-6'-ethylspectinomycin.
 - 15 28. N,N'-Dicarbobenzyloxy-2'-O-acetyl-4',5'-didehydro-6'-n-propylspectinomycin.
 29. N,N'-Dicarbobenzyloxy-2'-O-acetyl-4',5'-didehydro-6'-n-butylspectinomycin.
 30. N,N'-Dicarbobenzyloxy-2'-O-acetyl-4',5'-didehydro-6'-n-pentylspectinomycin.
 - 20 31. N,N'-Dicarbobenzyloxy-2'-O-acetyl-4',5'-didehydro-6'-n-octylspectinomycin.
 32. N,N'-Dicarbobenzyloxy-2'-O-acetyl-4',5'-didehydro-6'-n-undecylspectinomycin.
 - 25 33. A process for preparing a compound according to claim 25, which comprises reacting a compound of the formula



IV

wherein the variables are as defined in claim 25, with an alkylmagnesium halide.

34. A process for preparing a compound according to claim 16, but in which R" and R' as defined in claim 25 or claim 26, which comprises reducing a compound according to claim 25 or the product of a process according to claim 33.

35. A process for preparing a compound according to claim 1, but in which R" and R' as defined in claim 25 or claim 26, which comprises deprotecting a compound according to claim 16 or the product of a process according to claim 34.

~~36. A compound or process substantially as herein described.~~

36. A pharmaceutical composition which comprises a compound according to any of claims 1 to 15 in association with a physiologically acceptable excipient.