

PATENT SPECIFICATION

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(54) PROCESS FOR 11a-DEHALOGENATION OF 11a-HALOTETRACYCLINES

(71) We, PFIZER INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, 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 11a - halo - 6 - demethyl - 6 - deoxy - 6 - methylenetetracyclines, referred to herein for convenience as 11a - halo - 6 - methylenetetracyclines, form an important class of intermediates for further synthesis of tetracycline-type antibiotics, such as the valuable and widely used antibiotics 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline and 6 α - deoxy - 5 - hydroxytetracycline which are prepared from 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline; the former by 11a - dehalogenation and the latter by 11a - dehalogenation and reduction of the 6 - methylene group.

The previously known methods for 11a - dehalogenation of 11a - halotetracyclines, including 11a - halo - 6 - methylenetetracyclines, are discussed in U.S. Patent Specification No. 3,043,875; issued July 10, 1962. These methods comprise a variety of reactions, such as treatment of the 11a - halotetracyclines:

- (a) With dilute aqueous hydriodic acid,
- (b) With zinc metal in the presence of a proton donor, such as acetic acid,
- (c) In the case of 11a - bromo and 11a - iodo compounds, by boiling the product with a solvent capable of reacting with bromine or iodine (acetone, methanol, etc.),
- (d) Alternatively, treatment with sodium iodide in an organic solvent, followed by treatment of the resultant iodo compound with metallic zinc,
- (e) Treatment with metal sulfites and hydrosulfites, particularly the alkali metal (Na, K, Li) salts, and

(f) By catalytic hydrogenation of the 11a - halotetracycline in a reaction-inert medium with hydrogen gas in the presence of a noble metal catalyst.

A further procedure, described in French Patent Specification No. 2,136,138, comprises electrochemical dehalogenation.

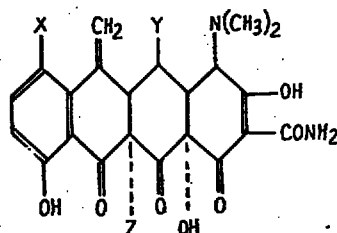
The dehalogenation of α - halo organo compounds, e.g., ketones and nitriles, by means of tertiary phosphines is reported by Borowitz *et al.*, Tetrahedron Letters, No. 11, 471—4 (1962), Partos *et al.*, J. Am. Chem. Soc. 87, 5068—75 (1965) and Borowitz *et al.*, J. Org. Chem. 33, 3686—90 (1968). The use of diphenylphosphine, a secondary phosphine, as dehalogenating agent for α - halo ketones is described by Borowitz *et al.*, J. Org. Chem. 34, 2687—92 (1969). Triethylphosphite has been shown by Pudovik *et al.*, Zhur. Obschei Khim. 28, 1496—1500 (1958), (C.A. 53, 216 g) and Kreutzkamp *et al.*, Ann. 609, 39 (1957), to function as a dehalogenating agent.

The known methods of 11a - dehalogenation of 11a - halotetracyclines are subject to disadvantages arising from the use of expensive catalysts (method f) or equipment (electrochemical dehalogenation); reaction mixtures which are frequently difficult to separate from by-products and, frequently, incomplete conversions to 11a - dehalogenated product.

It has now been found that 11a - halotetracyclines can be readily dehalogenated by contacting them with a secondary or a tertiary phosphine or a tertiary phosphite. The present invention accordingly provides a process for the production of 6 - methylenetetracycline compounds by 11a - dehalogenation of 11a - halo - 6 - methylenetetracycline compounds which comprises contacting the 11a - halo - 6 - methylenetetracycline compound in a reaction-inert solvent with at least an equimolar amount of a phosphorus compound selected from secondary phosphines, tertiary phosphines and tertiary phosphites.

Major interest exists in 11a - halo - 6 - methylene - tetracyclines of the formula shown below because of the general importance of

the 11a - dehalogenated analogues thereof as antibacterial agents and intermediates:



and the acid addition salts thereof wherein X is a hydrogen or chlorine atom; Y is a hydrogen atom or a hydroxy or alkanoyloxy group, wherein the alkanoyloxy group has from 1 to 8 carbon atoms; and Z is a chlorine or a bromine atom.

Particular interest resides in those 11a - halo - 6 - methylenetetraacyclines of the above formula wherein Z is a chlorine atom for the above-mentioned reason, plus the fact that the 11a - chloro derivatives are conveniently prepared and, because of their stability relative to that of the corresponding 11a - bromo and 11a - iodo derivatives, easily isolated and stored without decomposition.

Special interest exists in 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylenetetraacycline (X=H, Y=OH, Z=Cl) which serves as an intermediate in the production of 6 α - deoxy - 5 - hydroxytetraacycline, a broad spectrum antibacterial agent of great value to mankind.

The process of this invention comprises treating an 11a - halotetraacycline of the above formula or an acid addition salt thereof in a suitable solvent with a secondary or tertiary phosphine or a tertiary phosphite. Suitable solvents are hydroxylic solvents such as water, alkanolic acids and substituted alkanolic acids wherein the substituent is selected from lower alkoxy, hydroxy and cyano groups; alcohols and substituted alcohols wherein the substituent is selected from hydroxy and lower alkoxy. Favored solvents are water, methanol, ethanol and mixtures of these. Further, mixtures of such hydroxylic solvents with non-hydroxylic solvents such as lower alkyl esters of lower alkanolic acids e.g. methyl acetate, ethyl acetate and methyl propionate, tetrahydrofuran, dioxane, aromatic hydrocarbons, e.g. benzene, toluene and xylene, ketones, e.g. acetone and methyl isobutyl ketone, and di-(lower alkyl)alkanoic acid amides, e.g. N,N - dimethylformamide and N,N - dimethylacetamide, can be used. Additionally, when the phosphine or phosphite dehalogenating agent is a liquid at the temperature of the reaction, it can serve as both reactant and solvent.

The temperature of the reaction is not critical. The reaction is operative over a wide temperature range, that is, from about 20°C.

to the boiling point of the solvent system when using secondary or tertiary phosphines as dehalogenating agents. Lower temperatures can be used but are of no advantage since the reaction appears to be relatively slow at lower temperatures. The favored reaction temperature, from the standpoint of convenience, is room temperature, that is, from about 20°C. to about 30°C. Higher temperatures have, of course, the advantage of accelerating the reaction and the disadvantage, albeit relatively minor, of requiring greater caution in operating the reaction on a large scale when volatile solvents are employed. When using tertiary phosphites as dehalogenating agents, temperatures of from about 50°C. to the boiling point of the solvent system are operative. The reaction is so slow below 50°C. as not to be practical.

The 11a - halo - 6 - methylenetetraacycline reactants can be used in amphoteric or base form, or as an acid addition salt. In practice, they are generally used as an acid addition salt since this is the form in which they are normally isolated. The nature of the acid addition salt is immaterial to the reaction. The hydrochloride and p - toluenesulfonate salts are the salt forms in which the 11a - halo - 6 - methylenetetraacyclines are generally isolated, especially in large-scale preparations and are, therefore, the form in which the 11a - halo - 6 - methylenetetraacyclines are usually used.

The 11a - halo - 6 - methylenetetraacycline need not dissolve completely in the solvent medium used. The reaction proceeds satisfactorily in mixtures in which the 11a - halo - 6 - methylenetetraacycline is only partially soluble.

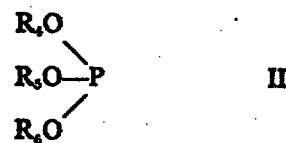
The phosphines of value in the present invention are secondary and tertiary phosphines of the formula



wherein each of R_1 and R_2 is an alkyl group containing from 1 to 10 carbon atoms, a cyclohexyl, benzyl or aryl group wherein the aryl group is a phenyl, methyl-substituted phenyl, methoxy-substituted phenyl or halo-substituted phenyl group; and R_3 is a hydrogen atom or as R_1 .

Principal interest exists in the tertiary aryl phosphines because of the favorable yields afforded by such agents.

The phosphites of interest in the process of this invention have the formula



wherein each of R_4 , R_5 and R_6 is an alkyl

2	3	1,459,861	3
		group containing from 1 to 10 carbon atoms, a cyclohexyl, benzyl or aryl group wherein the aryl group is a phenyl, methyl-substituted phenyl, methoxy-substituted phenyl or halo-substituted phenyl group.	
60	5	In this series of dehalogenating agents those wherein the variables R ₁ , R ₂ and R ₃ are lower alkyl are favored because of their ready availability.	
65	10	The terms "lower alkyl" and "lower alkoxy" as used herein are intended to include alkyl and alkoxy groups of from 1 up to and including 4 carbon atoms.	
70	15	The 11a - halo - 6 - methylenetetraacycline reactant and the dehalogenating agent are generally reacted in a molar ratio of from about 1:1 to about 1:3. The favored molar ratio of 11a - halo - 6 - methylenetetraacycline compound to dehalogenating agent is from about 1:1 to about 1:1.5. Higher ratios can be used but serve no useful purpose. The use of less than one mole of dehalogenating agent per mole of 11a - halo compound is not desired since it gives incomplete reaction and poor yields.	
75	20	The products are isolated by methods commonly used for isolation of 6 - methylene-tetraacyclines, such as extraction and precipitation. The dehalogenating agents and the products to which they are converted do not appear to interfere in the isolation procedures.	
80	25		
85	30		
90		EXAMPLE I	
95	35	6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetraacycline p - Toluenesulfonate	
	40	A. To a stirred solution of 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetraacycline p - toluenesulfonate (6.4295 g., 10 mM) in N,N - dimethylformamide (12 ml.) and benzene (7 ml.) at room temperature is added triphenylphosphine (3.9343 g., 15 mM). The mixture becomes warm and is heated at 90°C. for fifty minutes. It is then cooled and poured into benzene (375 ml.). The yellow solid, the dehalogenated product, which precipitates is removed by filtration, washed with diethyl ether and air-dried (4.275 g., 70.6%). It is identified by NMR as 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetraacycline.	
100	45	The filtrate and wash solutions are combined, washed successively with water (2x100 ml.) and brine (1x50 ml.) and dried with anhydrous sodium sulfate. Removal of the solvent affords a brownish residue (3.306 g.). The residue is dissolved in chloroform and chromatographed on a silica gel column. Elution with chloroform followed by 15% ethyl acetate/chloroform and evaporation of the eluate gives triphenylphosphine oxide in 93% yield. (M.P. 155°-157°C.).	
105	50	Based upon the yield of triphenylphosphine oxide recovered, conversion of the 11a - chloro compound to the deschloro analog is also at least 93%. The fact that less than a 93%	
110	55		
	60		
		yield of 11a - deshalo analog is isolated is attributable to incomplete precipitation of the product by benzene.	65
		B. Repetition of this procedure but without the application of external heat to the reaction mixture produces substantially the same results.	70
		EXAMPLE II	
		6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetraacycline Sulfosalicylate	
		A. A methanol solution of tri(n - butyl)-phosphine (0.62 ml. of 5 mM) is added at room temperature to a solution of 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetraacycline hydrochloride (1.536 g., 3.1 mM) in methanol (15 ml.) and the mixture stirred for twenty hours. One-third of the reaction mixture is treated with a solution of sulfosalicylic acid (2 - hydroxydithiosalicylic acid) (1 ml. of 1 M aqueous solution), and the mixture stirred for 15 minutes and then filtered to recover the title compound (0.424 g., 61%), identified by ultraviolet, infrared and nuclear magnetic resonance spectroscopy.	75
		The filtrate is evaporated under reduced pressure and the residue partitioned between water and chloroform. The aqueous phase is separated, extracted with chloroform (2x10 ml.) and the combined extracts decolorized, dried (Na ₂ SO ₄) and evaporated under reduced pressure. The residue, a viscous oil, crystallized upon storage in a high vacuum (0.135 g., 62% yield).	80
		Mass spectra showed it to be tri(n - butyl)-phosphine oxide.	85
		B. Repetition of this procedure but using triphenylphosphine in place of tri(n - butyl)-phosphine produces a similar result.	90
		EXAMPLE III	
		6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetraacycline Hydrochloride	95
		The remaining two-thirds of the reaction mixture of Example II, upon standing for three days, deposited a yellow solid. The solid is filtered off, washed with benzene and air-dried (0.658 g., 69% yield of the title compound, identified by thin layer chromatography in the system tetrahydrofuran/water (95/5) on silica gel plates at pH 6.0).	100
		EXAMPLE IV	105
		6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetraacycline Sulfosalicylate	
		A. To a solution of 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetraacycline hydrochloride (2.052 g., 4.0 mM) in acetone (10 ml.)-water (2 ml.) at room temperature is added tris(4 - methoxyphenyl)phosphine (1.61 g., 4.2 mM) over a five-minute period. A slight exothermic reaction occurs and a water bath is used to maintain the temperature at room temperature.	110
			115
			120
			125

After stirring for one hour, the reaction mixture is concentrated under reduced pressure to remove the acetone. Methanol (20 ml.) is added followed by a 10% methanolic solution of sulfosalicylic acid (15 ml.). The mixture is stirred for four hours and then cooled to about 15°C. The solid product is filtered off, washed with cold methanol (2×5 ml.) and dried *in vacuo* (2.54 g. of title product, 96.2%). It is identical to the product of Example II.

B. Repetition of this procedure but using molar ratios of 11a - chloro reactant to phosphine of 1:2, 1:3 and 1:5 affords substantially the same results.

EXAMPLE V

6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetracycline Hydrochloride

The procedure of Example IV-A is repeated but using hydrochloric acid in place of sulfosalicylic acid and 4.2 mM of dimethylphenylphosphine in place of tris(4 - methoxyphenyl)phosphine affords 1.598 g. (84%) of the title product.

EXAMPLE VI

6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetracycline Sulfosalicylate (via Triethyl Phosphite Dehalogenation)

A mixture of triethyl phosphite (3.82 g., 23.0 mM) and 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline *p* - toluenesulfonate (3.214 g., 4.51 mM) in ethanol (34 ml.) is heated to reflux for one hour. It is then cooled to room temperature and stirred for three hours, after which it is chilled to 0°C. and the solid removed by filtration. The filtrate is treated with sulfosalicylic acid (20 ml. of 10% aqueous solution) and stirred at room temperature overnight. The title product is recovered by filtration, washed with cold methanol and dried *in vacuo* (2.163 g., 73%).

An additional 0.148 g. is recovered from the filtrate upon removal of the alcohol. (Total yield: 2.311 g., 78%). It is identified by its ultraviolet, infrared and nuclear magnetic resonance spectra.

EXAMPLE VII

6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetracycline Sulfosalicylate

A mixture of 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline *p* - toluenesulfonate (2.927 g., 4.51 mM), methanol (30 ml.), water (4 ml.) and triphenylphosphine (1.205 g., 4.60 mM) is stirred under an atmosphere of nitrogen at room temperature for three hours. Methanol (18 ml.) and an aqueous solution of sulfosalicylic acid (20 ml. of 10% solution) are added to the mixture, which is thoroughly stirred and allowed to crystallize by standing for 18 hours. The product is filtered off,

washed with cold methanol (0°—5°C.) and dried. Yield=2.671 g., 88% yield.

EXAMPLE VIII

Diphenylphosphine (27.21 mg., 0.1575 mM) is added to a solution of 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline hydrochloride (25.7 mg., 0.050 mM) in methanol (1.5 ml.) under an atmosphere of nitrogen. The mixture is stirred for 28 hours and then evaporated to dryness *in vacuo*. The oily residue is washed with ether (3×1 ml.) and then dissolved in methanol (0.32 ml.). An aqueous solution of sulfosalicylic acid (0.16 ml. of 10% solution) is added and the mixture stirred overnight. The mixture is warmed to 38°—40°C. and the liquid phase evaporated to about 0.5 ml. by exposing the warm mixture to a stream of nitrogen gas. It is then centrifuged, the supernatant liquid pipetted off and the crystals washed with ether (1 ml.). The supernatant solution is then passed through a column of Amberlite IR-45 (hydroxide form of a weakly basic anion exchange resin available from Rohm and Haas Co.), ('Amberlite' is a Registered Trade Mark). The ion exchange resin is slurried in 1N methanolic hydrogen chloride, and the column packed and rinsed thoroughly with methanol. The supernatant solution is passed through the column, and the eluate collected and evaporated to dryness *in vacuo*. The residue is taken up in the minimum volume of ethanol and the solution evaporated under reduced pressure to thoroughly dry the 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline hydrochloride. Yield=15 mg., 45.4%.

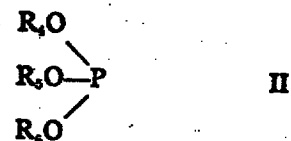
WHAT WE CLAIM IS:—

1. A process for the production of 6 - methylenetetracycline compounds by 11a - dehalogenation of 11a - halo - 6 - methylenetetracycline compounds which comprises contacting the 11a - halo - 6 - methylenetetracycline compound in a reaction-inert solvent with at least an equimolar amount of a phosphorus compound selected from secondary phosphines, tertiary phosphines and tertiary phosphites.

2. A process as claimed in claim 1, wherein the phosphorus compound is selected from compounds of the formulae:



and



wherein each of R_1 , R_2 , R_3 and R_4 is one

(13)

After stirring for one hour, the reaction mixture is concentrated under reduced pressure to remove the acetone. Methanol (20 ml.) is added followed by a 10% methanolic solution of sulfosalicylic acid (15 ml.). The mixture is stirred for four hours and then cooled to about 15°C. The solid product is filtered off, washed with cold methanol (2×5 ml.) and dried *in vacuo* (2.54 g. of title product, 96.2%). It is identical to the product of Example II.

B. Repetition of this procedure but using molar ratios of 11a - chloro reactant to phosphine of 1:2, 1:3 and 1:5 affords substantially the same results.

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The procedure of Example IV-A is repeated but using hydrochloric acid in place of sulfosalicylic acid and 4.2 mM of dimethylphenylphosphine in place of tris(4 - methoxyphenyl)phosphine affords 1.598 g. (84%) of the title product.

EXAMPLE VI

6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetracycline Sulfosalicylate (via Triethyl Phosphite Dehalogenation)

A mixture of triethyl phosphite (3.82 g., 23.0 mM) and 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline *p* - toluenesulfonate (3.214 g., 4.51 mM) in ethanol (34 ml.) is heated to reflux for one hour. It is then cooled to room temperature and stirred for three hours, after which it is chilled to 0°C. and the solid removed by filtration. The filtrate is treated with sulfosalicylic acid (20 ml. of 10% aqueous solution) and stirred at room temperature overnight. The title product is recovered by filtration, washed with cold methanol and dried *in vacuo* (2.163 g., 73%).

An additional 0.148 g. is recovered from the filtrate upon removal of the alcohol. (Total yield: 2.311 g., 78%). It is identified by its ultraviolet, infrared and nuclear magnetic resonance spectra.

EXAMPLE VII

6 - Demethyl - 6 - Deoxy - 6 - Methylene - 5 - Hydroxytetracycline Sulfosalicylate

A mixture of 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline *p* - toluenesulfonate (2.927 g., 4.51 mM), methanol (30 ml.), water (4 ml.) and triphenylphosphine (1.205 g., 4.60 mM) is stirred under an atmosphere of nitrogen at room temperature for three hours. Methanol (18 ml.) and an aqueous solution of sulfosalicylic acid (20 ml. of 10% solution) are added to the mixture, which is thoroughly stirred and allowed to crystallize by standing for 18 hours. The product is filtered off,

washed with cold methanol (0°—5°C.) and dried. Yield=2.671 g., 88% yield.

EXAMPLE VIII

Diphenylphosphine (27.21 mg., 0.1575 mM) is added to a solution of 11a - chloro - 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline hydrochloride (25.7 mg., 0.050 mM) in methanol (1.5 ml.) under an atmosphere of nitrogen. The mixture is stirred for 28 hours and then evaporated to dryness *in vacuo*. The oily residue is washed with ether (3×1 ml.) and then dissolved in methanol (0.32 ml.). An aqueous solution of sulfosalicylic acid (0.16 ml. of 10% solution) is added and the mixture stirred overnight. The mixture is warmed to 38°—40°C. and the liquid phase evaporated to about 0.5 ml. by exposing the warm mixture to a stream of nitrogen gas. It is then centrifuged, the supernatant liquid pipetted off and the crystals washed with ether (1 ml.). The supernatant solution is then passed through a column of Amberlite IR-45 (hydroxide form of a weakly basic anion exchange resin available from Rohm and Haas Co.), ('Amberlite' is a Registered Trade Mark). The ion exchange resin is slurried in 1N methanolic hydrogen chloride, and the column packed and rinsed thoroughly with methanol. The supernatant solution is passed through the column, and the eluate collected and evaporated to dryness *in vacuo*. The residue is taken up in the minimum volume of ethanol and the solution evaporated under reduced pressure to thoroughly dry the 6 - demethyl - 6 - deoxy - 6 - methylene - 5 - hydroxytetracycline hydrochloride. Yield=15 mg., 45.4%.

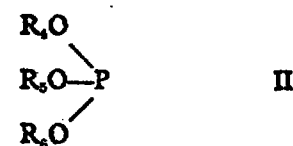
WHAT WE CLAIM IS:—

1. A process for the production of 6 - methylenetetracycline compounds by 11a - dehalogenation of 11a - halo - 6 - methylenetetracycline compounds which comprises contacting the 11a - halo - 6 - methylenetetracycline compound in a reaction-inert solvent with at least an equimolar amount of a phosphorus compound selected from secondary phosphines, tertiary phosphines and tertiary phosphites.

2. A process as claimed in claim 1, wherein the phosphorus compound is selected from compounds of the formulae:



and

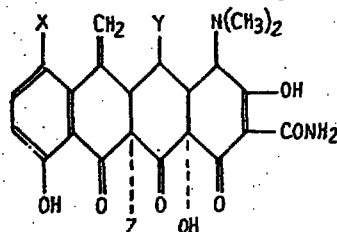


wherein each of R_1 , R_2 , R_3 , R_4 and R_5 is one



of the following: an alkyl group of from 1 to 10 carbon atoms, a cyclohexyl, benzyl or aryl group wherein the aryl group is phenyl, methyl - substituted phenyl, methoxy - substituted phenyl or halo - substituted phenyl; and R_3 is a hydrogen atom or as R_1 .

3. A process as claimed in either claim 1 or claim 2, wherein the 11a - halo - 6 - methylenetetraacycline is of the formula:



or is an acid addition salt thereof wherein X is a hydrogen or chlorine atom; Y is a hydrogen atom, or a hydroxy or alkanoyloxy group wherein the alkanoyloxy group has from 1 to 8 carbon atoms; and Z is a chlorine or a bromine atom.

4. A process as claimed in claim 3, wherein Z is a chlorine atom.

5. A process as claimed in claim 4, wherein Y is a hydroxy group and X is a hydrogen atom.

6. A process as claimed in claim 4, wherein Y is a hydroxy group and X is a chlorine atom.

7. A process as claimed in claim 5, wherein the phosphorus compound is of Formula I wherein R_3 is as R_1 .

8. A process as claimed in claim 7, wherein each of R_1 , R_2 and R_3 is an alkyl group of from 1 to 10 carbon atoms.

9. A process as claimed in claim 7, wherein each of R_1 , R_2 and R_3 is an aryl group.

10. A process as claimed in claim 9, wherein each of R_1 , R_2 and R_3 is a phenyl group.

11. A process as claimed in any one of claims 1 to 10 substantially as hereinbefore described.

12. 11a - Dehalogenated tetracyclines whenever prepared by the process claimed in any one of claims 1 to 11.

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