1 582 864

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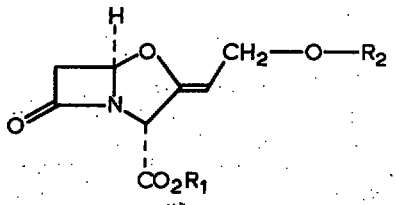
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(54) CHEMICAL PROCESS FOR THE PREPARATION OF CLAVULANIC ACID DERIVATIVES

(71) We, BEECHAM GROUP LIMITED, a British Company of Beecham House, Great West Road, Brentford, Middlesex, 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 present invention relates to a process for the preparation of ethers.

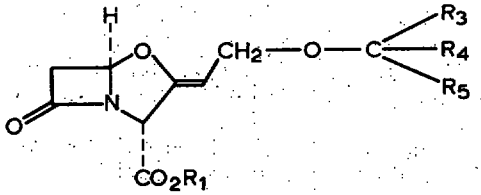
British Patent Application No. 41897/75—02629/76 (Serial No. 1565209) (which corresponds to Belgian Patent No: 847045) discloses *inter alia* ethers of clavulanic acid of the formula (I):



(I)

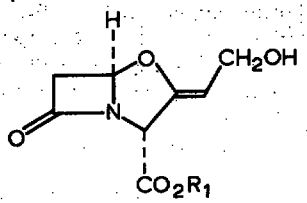
wherein R_1 is a group such that CO_2R_1 is an esterified carboxyl group and R_2 is a inert organic group of up to 18 carbon atoms.

This invention provides a process for the preparation of a compound of the formula (II):



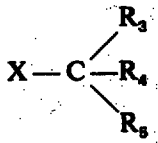
(II)

wherein R_1 is as defined in relation to formula (I), R_3 is a hydrogen atom or an alkyl group of 1—4 carbon atoms, R_4 is a hydrogen atom or an alkyl group of 1—4 carbon atoms and R_5 is a group such that the $CR_3R_4R_5$ moiety is an inert organic group of up to 18 carbon atoms; which process comprises the reaction of a compound of the formula (III):



(III)

wherein R_1 is as defined in relation to formula (II) with a compound of the formula (IV):



(IV)

wherein X is I, Br, or Cl and R_3, R_4 and R_5 are defined in relation to formula (II); in the presence of a source of silver ions. When used herein the term "inert" has the normal meaning of inert under the reaction conditions of the process.

Optionally, an alkaline earth metal oxide may also be present. Preferably, the oxide is calcium oxide. Preferably the oxide is powdered.

The preferred source of silver ions is silver oxide. Generally 1—2 equivalents of silver ions are employed per equivalent of compound of the formula (III).

When calcium oxide is also present it is generally employed in the proportion of 1—2 equivalents per equivalent of compound of the formula (III).

Suitable values for R_3 include the hydrogen atom and the methyl, ethyl, n-propyl and n-butyl groups.

Suitable values for R_4 include the hydrogen atom and the methyl, ethyl, n-propyl and n-butyl groups.

A preferred value for R_3 is the hydrogen atom and a preferred value for R_4 is the hydrogen atom so that it will be appreciated that certain preferred processes of this invention are adapted to provide compounds of the formula (II) wherein the $CR_3R_4R_5$ moiety is a $CH_2—R^1$ group where CH_2R^1 is an inert organic group of up to 18 carbon atoms.

Suitable value for R_5 include the hydrogen atom and the methyl, ethyl, n-propyl, n-butyl, n-pentyl, iso-propyl, vinyl, phenyl and *p*-methoxybenzyl groups.

Particularly suitable values for R_5 include the hydrogen atom and the methyl, ethyl, phenyl and vinyl groups.

Favoured values for R_5 include the hydrogen atom and the methyl and ethyl groups.

A preferred value for R_5 is the hydrogen atom.

A further preferred value for R_5 is the methyl group.

Highly favoured processes of this invention are those adapted to the preparation of the compounds of the formula (II) wherein $CR_3R_4R_5$ is a methyl group or wherein $CR_3R_4R_5$ is an ethyl group. Hence a prefered compound of the formula (IV) is methyl iodide and a further prefered compound of the formula (IV) is ethyl iodide.

Suitable esters of the formula (II) include those wherein R_1 is a group A^1 or CHA^2A^3 wherein A^1 is an alkyl group of 1—8 carbon atoms, optionally substituted by halogen or by a group of the formula OA^4, $OCOA^4$, SA^4 or SO_2A^4 wherein A^4 is a hydrocarbon group of up to 6 carbon atoms; A^2 is a hydrogen atom, an alkyl group of up to 4 carbon atoms or a phenyl group optionally substituted by halogen or by a group A^5 or OA^5 where A^5 is an alkyl group of up to 6 carbon atoms; and A^3 is a phenyl group optionally substituted by halogen or by a group A^5 or OA^5 where A^5 is an alkyl group.

Other suitable esters are those of the formula (II) wherein R_1 is an alkenyl group of up to 8 carbon atoms. Examples of such esters are the allyl esters.

Esters of this invention are preferably *in-vivo* hydrolysable. Suitable esters include those described in Belgian Patent No: 827926 as being *in-vivo* hydrolysable esters of clavulanic acid. Particularly suitable *in-vivo* hydroysable esters include acetoxymethyl, α-acetoxyethyl, pivaloyloxymethyl, phthalidyl, ethoxycarbonyloxymethyl and ethoxycarbonyloxyethyl esters.

Most suitably the ester forming group is one readily convertible to a salt corresponding to the compound of the formula (II) by mild hydrolysis or hydrogenolysis as described in the said Belgian patent specification.

Particularly suitable esters include benzyl, *p*-methoxybenzyl, methyl and methoxymethy esters. Nitrobenzyl esters, for example, *p*-nitrobenzyl esters are also suitable.

The etherification reaction is generally carried out in an inert medium at non-extreme temperatures.

Suitable media for the reaction include hydrocarbon solvents such as benzene and toluene and other conventional solvents such as ethyl acetate, tetrahydrofuran or acetone.

The reaction may be best effected at a temperature of from 10° to 100°C, for example 30°—80°C.

It is desirable that the reaction mixture is maintained under anhydrous conditions.

Once the reaction is over (for example as judged by tlc) the mixture is allowed to cool, filtered to remove suspended solids and then evaporated. If desired the resulting material can be purified by such conventional procedures as column chromatography.

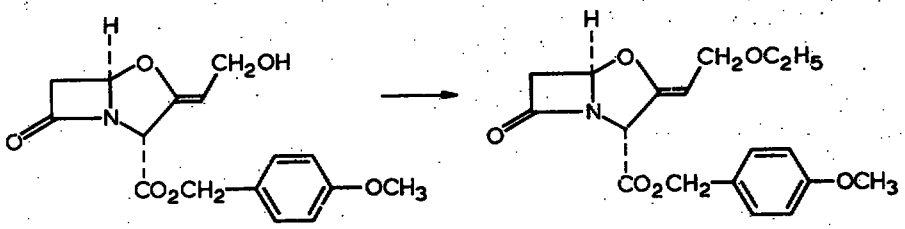
In those cases where the product of the reaction is a compound of the formula (II) wherein R_1 is a group $CR_3R_4R_5$, the starting material may be a salt of clavulanic acid, when the reaction may be regarded as proceeding via the formation of an ester of clavulanic acid followed *in-situ* etherification. Normally, such a reaction will be carried out in the presence of a crown ether to solubilise the salt of clavulanic acid.

This is a less preferred aspect of the invention.

The following examples illustrate the invention.

Example 1

p-Methoxybenzyl O-Ethylclavulanate



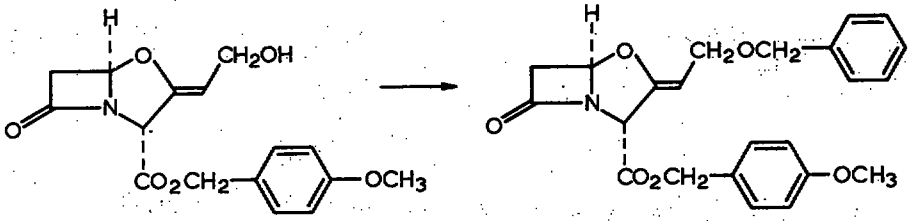
A mixture of *p*-methoxybenzyl clavulanate (3.19 g), powdered calcium oxide (4.0 g), silver oxide (4.0 g), and ethyl iodide (6 ml) in benzene (50 ml) was boiled under reflux for 2 h. The cooled reaction mixture was filtered and the filtrate evaporated to give an oil which was chromatographed over silica gel (30 g). Elution of the column with ethyl acetate-cyclohexane (1:4) afforded the title compound (0.74 g) in pure form, identical to an authentic sample (ir. and ^1H n.m.r. comparisons).

A similar result may be obtained by replacing the ethyl iodide with ethyl bromide and carrying out the reaction at 40°C for a longer period.

The corresponding methyl ether can also be prepared by substituting methyl iodide for the above ethyl iodide.

Example 2

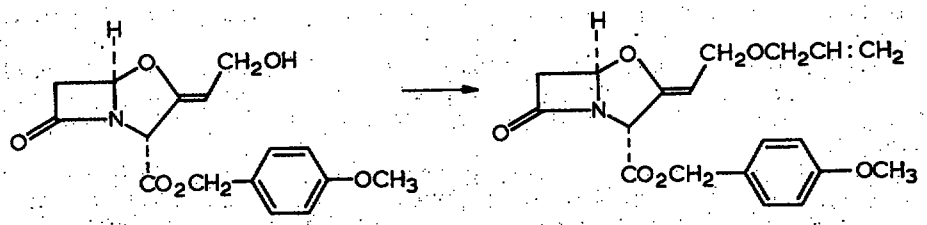
p-Methoxybenzyl O-Benzylclavulanate



A mixture of *p*-methoxybenzyl clavulanate (3.19 g), powdered calcium oxide (4.0 g), silver oxide (4.0 g) and benzyl bromide (5 ml) in benzene (50 ml) was boiled under reflux for 2 h. The cooled reaction mixture was filtered and the filtrate evaporated to give an oil which was chromatographed over silica gel (30 g). Elution of the column with ethyl acetate-cyclohexane (1:4) afforded the title compound (1.0 g), ν_{max} (liquid film) 1810, 1750, 1700, 1310, 1250, 1180 and 1040 cm^{-1}, δ ($CDCl_3$) 7.22 (5H, s, Ar*H*), 7.19 (2H, d, J = Ar*H*), 6.76 (2H, d, J =9Hz, Ar*H*), 5.58 (1H, d, J = 2.5Hz, 5-C*H*), 5.08 (2H, s, —CH_2Ar), 5.00 (1H, broad s, 3-C*H*), 4.80 (1H, broad t, J = 8Hz, 8-C*H*), 4.38 (2H, s, —CH_2Ar), 4.05 (2H, broad d, J = 8Hz, 9-CH_2), 3.70 (3H, s, OCH_3), 3.40 (1H, dd, J = 17Hz, J' × 2.5Hz, 6α-C*H*), and 2.96 (1H, d, J = 17Hz, 6β-C*H*).

Example 3

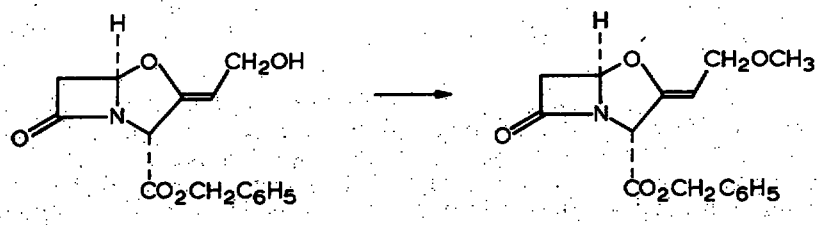
p-Methoxybenzyl O-Allylclavulanate



A mixture of *p*-methoxybenzyl clavulanate (3.19 g), powdered calcium oxide (4.0g), silver oxide (4.0g), and allyl bromide (4 ml) in benzene (30 ml) was stirred at room temperature for 66 h. The mixture was filtered and the filtrate evaporated to give an oil which was chromatographed over silica gel (20 g). Elution of the column with cyclohexane-ethyl acetate (4:1) afforded the title compound (0.65 g), ν_{max} (liquid film) 3020, 1810, 1750, 1700, 1310, 1255, 1080 and 1040 cm^{-1}, δ ($CDCl_3$) 7.30 (2H, d, J = 9Hz, Ar*H*), 6.86 (2H, d, J = 9Hz, Ar*H*), 5.95 (1H, m, C=C*H*), 5.67 (1H, d, J = 2.5Hz, 5-C*H*), 5.32 (2H, m, C=C*H*), 5.13 (2H, s, —CH_2Ar), 5.06 (1H, s, 3-C*H*) 4.83 (1H, broad t, J = 8Hz, 8-C*H*), 4.06 (2H, broad d, J = 8Hz, 9-CH_2), 3.92 (2H, m, —OCH_2—CH=CH_2), 3.80 (3H, s, OCH_3), 3.50 (1H, dd, J = 17Hz, J' = 2.5Hz, 6α-C*H*), and 3.00 (1H, d, J = 17 Hz, 6β-C*H*).

Example 4

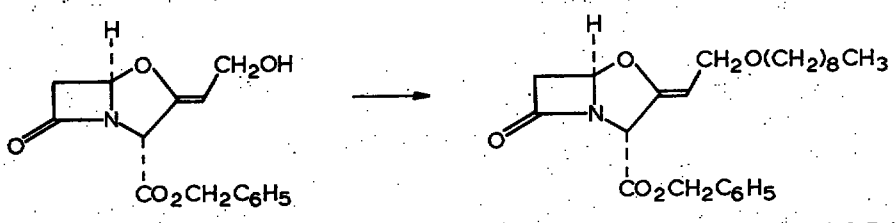
Benzyl O-methylclavulanate



A mixture of benzyl clavulanate (8.67g), calcium oxide (12g), silver oxide (12g) and methyl iodide (15ml) in benzene (50ml) in benzene (50ml) was heated under reflux for 2 hours. The mixture was allowed to cool, was filtered and filtrate evaporated to give an oil which was chromatographed over silica gel (50g), eluting with ethyl acetate/cyclohexane (1/4) to give the title compound 2.81g).

Example 5

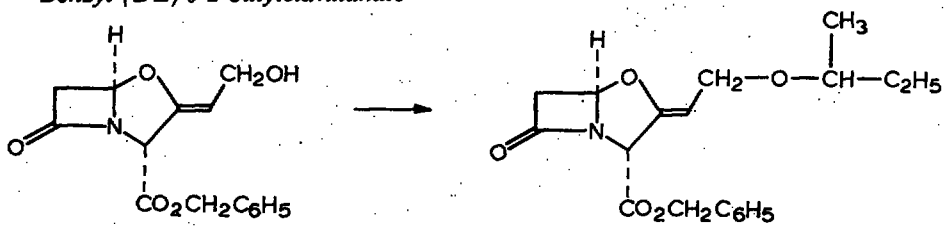
Benzyl O-Nonylclavulanate



Benzyl clavulanate (2.89g) in ethyl acetate (10ml) and iodononane (12.7g) were heated under reflux with stirring in presence of silver oxide (4g) and calcium oxide (4g) for 3 hours. Tlc showed a fast-running zone and a much diminished zone due to starting material. The mixture was filtered, the insolubles washed with ethyl acetate (50ml) and the filtrate evaporated under reduced pressure to a dark oil. This was subjected to column chromatography in silica gel, using ethyl acetate and cyclohexane graded from 1:10 to 1:2 as eluents. Fractions after the nonyl iodide had been eluted contained the product, which was isolated as a pale yellow oil by evaporation of the solvents; yield 0.64g. Ir. (1/f): 1805, 1750, 1695cm^{-1}. n.m.r. ($CDCl_3$) δ:0.86 (3H, t, *J*7Hz, CH_3), 1.25 (14H, m, O—$CH_2(CH_2)_7CH_3$), 2.98 (1H, d, J 17Hz, 6-β-C*H*), 3.31 (2H, *t*, J 7Hz, $OCH_2(CH_2)_7$), 3.43 (1H, dd, J 17Hz and 3Hz, 6-α-C*H*), 3.98 (2H, d, J 7Hz, CH_2CH=), 4.78 (1H, t, J 7Hz, C*H*=), 5.02 (1H, s, 3-C*H*), 5.12 (2H, s, PhCH_2), 5.61 (1H, d, J 3Hz, 5-C*H*) and 7.27 (5H, s, C_6H_5).

Example 6

Benzyl (DL)-0-2-butylclavulanate

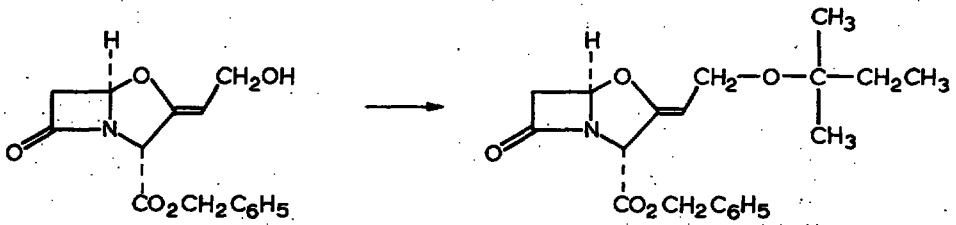


Benzyl clavulanate (2.89g) in ethyl acetate (7ml) and 2-iodobutane (9g) were refluxed with stirring in the presence of silver oxide (4g) and calcium oxide (4g) for 2½ hr. The insoluble materials were filtered off, and the filtrate concentrated *in vacuo* to a yellow oil, which was subjected to column chromatography on silica gel using ethyl acetate and cyclohexane graded from 1:10 to 1:2 ratio. The ether was eluted after the 2-iodobutane. Fractions containing the ether (by tlc) were evaporated *in vacuo* to yield the compound (0.57g) as a pale yellow oil. I.r. (2/f) 1808, 1753, 1698 cm^{-1}.

Nmr ($CDCl_3$) δ 0.84 (3H, t, *J* 7Hz, CH_2CH_3), 1.07 (3H, d, J 7Hz, $CH—CH_3$), 1.26—1.63 (2H, m, CH_2CH_3), 2.96 (1H, d, *J* 17Hz, 6-β-C*H*), 3.26 (1H, qt, *J*, 7Hz OC*H*), 3.41 (OH, dd, 17Hz, 6-α-C*H*), 3.8—4.25 (1H, m, 9-CH_2), 4.77 (1H, t, *J* 8Hz 8-C*H*) 5.20 (1h, s, 3-C*H*), 5.12 (2H, s, CH_2Ph), 5.90 (1H, d, *J* 3Hz, 5-C*H*) 7.28 (5H, s, C_6H_5).

Example 7

Benzyl O-t-Amyl clavulanate



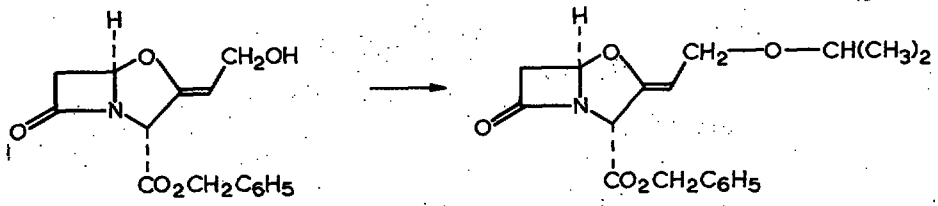
Benzyl clavulanate (2.89g) in ethyl acetate (20ml) and 2-iodo-2-methylbutane (6.5ml, 9.9g) were stirred at room temperature in the presence of silver oxide (4g) and calcium oxide (4g) for 3 hr. The insoluble material was filtered off, washed with ethyl acetate (50ml) and the filtrate evaporated under reduced pressure to a dark oil, which was subjected to column chromatography on silica gel, eluting with cyclohexane-ethyl acetate graded from 10:1 to 3:1, to yield 0.43g of the title product as a pale yellow oil.

I.r. 1805, 1755, 1698 cm^{-1}; (liquid film).

nmr. ($CDCl_3$) δ 0.83 (3H, t, *J* 7Hz, CH_2CH_3), 1.11 (6H, s, $(CH_3)_2$), 1.46 (2H, q, *J* 7Hz, CH_2CH_3), 2.96 (1H, d, J 17Hz, 6-β-C*H*), 3.40 (1H, dd, *J* 17 and 3Hz, 6-α-CH), 3.6—4.3 (2H, m, $=CHCH_2$), 4.74 (1H, dt, *J* 7 and ~2Hz, C*H*=), 5.0 (1H, d, *J* ~2Hz, 3-C*H*), 5.12 (2H, s, $PhCH_2$), 5.59 (1H, d, *J*3Hz, 5-C*H*), 7.27 (5H, s, C_6H_5).

Example 8

Benzyl 9-0-(2-propyl)clavulanate



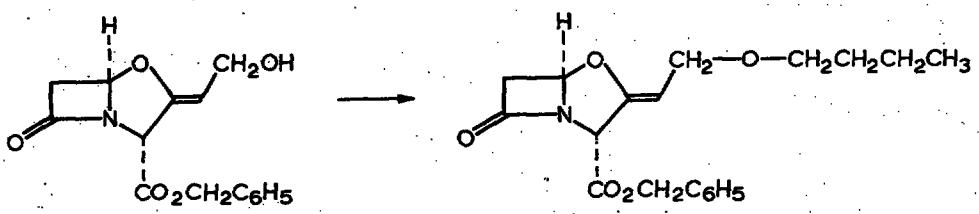
The process used for the preparation of the title compound (0.47g) was as described in Example 6, replacing the iodobutane with 2-iodopropane (5ml).

I.r. 1805, 1750 1698 cm^{-1}.

N.m.r. ($CDCl_3$) δ : 1.10 (6H, d, J 7Hz), 2.96 (1H, d, *J 17Hz), 3.40 (1H, dd, J*17Hz and 3Hz), 3.51 (1H, dq. *j* 7Hz), 3.80—4.30 (2H, m),4.77 (1H, t *J* 7Hz), 5.02 (1H, s), 5.13 (2H,s), 5.59 (1H, d, *J* 3Hz), 7.26 (5H, s).

Example 9

Benzyl 9-0-n-butylclavulanate



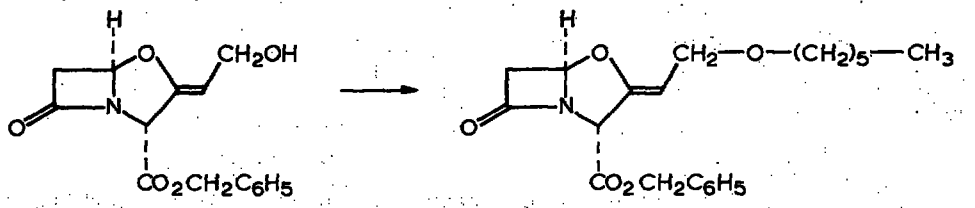
A mixture of benzyl clavulanate (2.89g) silver oxide (4g) calcium oxide (4g) and 1-iodobutane (5.7ml) in ethyl acetate (7ml) was heated and stirred under reflux for 2½ hour. At this time tlc (cyclopentane-methyl acetate 2:1) showed a mixture of starting material and product. The insoluble materials were filtered off, and washed with ethyl acetate (10ml). The filtrate was evaporated under reduced pressure to an orange oil, which was subjected to column chromatography on silica gel using cyclohexane and ethyl acetate graded from 10:1 to 1:1 ratio as eluents. Fractions containing the ether (by tlc) were collected, combined, and evaporated to a pale yellow oil under reduced pressure, to yield 0.34 g pure ether and 0.4 g slightly less pure material.

I.r. 1805, 1750, 1695cm^{-1}.

N.m.r. ($CDCl_3$) δ : 0.90 (3H, t, *J* 6.5Hz, CH_2CH_3), 1.12—1.70 (4H, m, $(CH_2)_2CH_3$), 2.99 (1H, d, *J* 17Hz, 6-β-C*H*), 3.33 (2H, t, *J* 6.5 Hz, OCH_2CH_2) 3.44 (1H, dd, *J* 17Hz and 3Hz, 6-α-C*H*), *3.83—4.19 (2h, m, 9-CH_2)* 4.66—4.91 (1H, m, 8-C*H*), 5.05 (1H, s, 3-C*H*), 5.15 (2H, s, CH_2Ph), 5.63 (1H, d, *J* 3Hz, 5-C*H*) and 7.29 (5H, s, $CH_2C_6H_5$).

Example 10

Benzyl 9-0-n-hexylclavulante



The title compound (0.4g) was prepared as an oil by the method of Example 9, replacing the 1-iodobutane by 1-iodohexane (10.6 g).

I.r. 1805, 1757, 1698cm^{-1}.

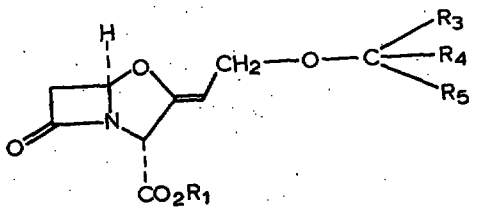
N.m.r. ($CDCl_3$) δ 0.88 (3H, t J 6Hz), 1.12—1.50 (8H, bm), 2.99 (1H, d, *J* 17Hz) 3.32 (2H, t, *J* 6Hz), 3.43 (1H, dd, *J*17 and 3Hz), 4.02 (2H, db, J 7Hz), 4.79 (1H, t, *J* 7Hz), 5.05 (1H, s), 5.15 (2H, s), 5.64 (1H, bs) and 7.29 (5H, s).

Examples 11—13

The reactions described in Examples 1—3 were repeated, but without the use of calcium oxide. The desired compounds were produced in each instance, but in reduced yields.

WHAT WE CLAIM IS:—

1. A process for the preparation of a compound of the formula (II):

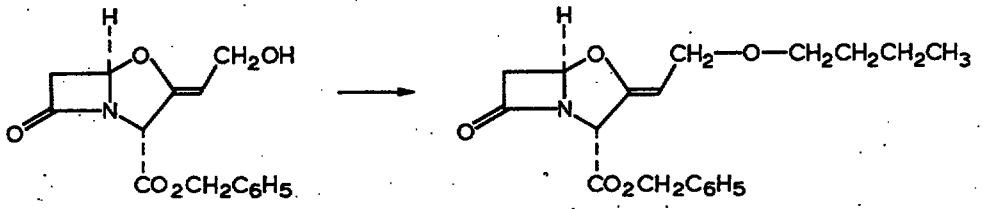


(II)

wherein R_1 is a group such that CO_2R_1 is an esterified carboxyl group, R_3 is a hydrogen atom or an alkyl group of 1—4 carbon atoms, R_4 is a hydrogen atom or an alkyl group of 1—4 carbon atoms and R_5 is a group such that the $CR_3R_4R_5$ moiety is an inert organic group of up to 18 carbon atoms; which process comprises the reaction of a compound of the formula (III):

Example 9

Benzyl 9-0-n-butylclavulanate



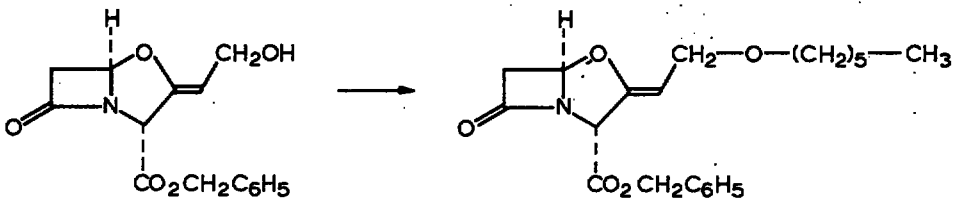
A mixture of benzyl clavulanate (2.89g) silver oxide (4g) calcium oxide (4g) and 1-iodobutane (5.7ml) in ethyl acetate (7ml) was heated and stirred under reflux for 2½ hour. At this time tlc (cyclopentane-methyl acetate 2:1) showed a mixture of starting material and product. The insoluble materials were filtered off, and washed with ethyl acetate (10ml). The filtrate was evaporated under reduced pressure to an orange oil, which was subjected to column chromatography on silica gel using cyclohexane and ethyl acetate graded from 10:1 to 1:1 ratio as eluents. Fractions containing the ether (by tlc) were collected, combined, and evaporated to a pale yellow oil under reduced pressure, to yield 0.34 g pure ether and 0.4 g slightly less pure material.

I.r. 1805, 1750, 1695cm^{-1}.

N.m.r. ($CDCl_3$) δ : 0.90 (3H, t, *J* 6.5Hz, CH_2CH_3), 1.12—1.70 (4H, m, $(CH_2)_2CH_3$), 2.99 (1H, d, *J* 17Hz, 6-β-C*H*), 3.33 (2H, t, *J* 6.5 Hz, OCH_2CH_2) 3.44 (1H, dd, *J* 17Hz and 3Hz, 6-α-C*H*), *3.83—4.19 (2h, m, 9-CH_2)* 4.66—4.91 (1H, m, 8-C*H*), 5.05 (1H, s, 3-C*H*), 5.15 (2H, s, CH_2Ph), 5.63 (1H, d, *J* 3Hz, 5-C*H*) and 7.29 (5H, s, $CH_2C_6H_5$).

Example 10

Benzyl 9-0-n-hexylclavulante



The title compound (0.4g) was prepared as an oil by the method of Example 9, replacing the 1-iodobutane by 1-iodohexane (10.6 g).

I.r. 1805, 1757, 1698cm^{-1}.

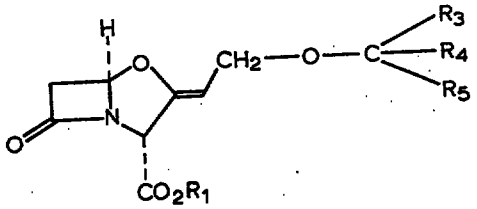
N.m.r. ($CDCl_3$) δ 0.88 (3H, t J 6Hz), 1.12—1.50 (8H, bm), 2.99 (1H, d, *J* 17Hz) 3.32 (2H, t, *J* 6Hz), 3.43 (1H, dd, *J*17 and 3Hz), 4.02 (2H, db, J 7Hz), 4.79 (1H, t, *J* 7Hz), 5.05 (1H, s), 5.15 (2H, s), 5.64 (1H, bs) and 7.29 (5H, s).

Examples 11—13

The reactions described in Examples 1—3 were repeated, but without the use of calcium oxide. The desired compounds were produced in each instance, but in reduced yields.

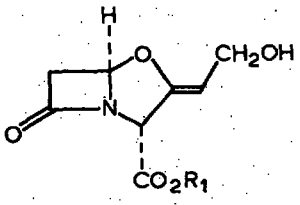
WHAT WE CLAIM IS:—

1. A process for the preparation of a compound of the formula (II):



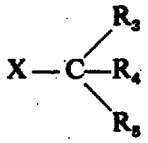
(II)

wherein R_1 is a group such that CO_2R_1 is an esterified carboxyl group, R_3 is a hydrogen atom or an alkyl group of 1—4 carbon atoms, R_4 is a hydrogen atom or an alkyl group of 1—4 carbon atoms and R_5 is a group such that the $CR_3R_4R_5$ moiety is an inert organic group of up to 18 carbon atoms; which process comprises the reaction of a compound of the formula (III):



(III)

wherein R_1 is as defined in relation to formula (II) with a compound of the formula (IV):



(IV)

wherein X is I, Br, or Cl and R_3, R_4 and R_5 are defined in relation to formula (II); in the presence of a source of silver ions.

2. A process as claimed in claim 1 wherein an alkaline earth metal oxide is also present.

3. A process as claimed in claim 2 wherein the oxide is calcium oxide.

4. A process as claimed in any of claims 1—3 wherein the source of silver ions is silver oxide.

5. A process as claimed in any of claims 1—4 wherein from 1 to 2 equivalents of silver ions are employed per equivalent of compound of the formula (III).

6. A process as claimed in any of claims 3—5 wherein from 1 to 2 equivalents of calcium oxide are employed per equivalent of compound of the formula (III).

7. A process as claimed in any of claims 1—6 wherein R_3 is a hydrogen atom or a methyl, ethyl, n-propyl or n-butyl group.

8. A process as claimed in any of claims 1—7 wherein R_4 is a hydrogen atom or a methyl, ethyl, n-propyl or n-butyl group.

9. A process as claimed in any of claims 1—8 wherein R_3 is a hydrogen atom.

10. A process as claimed in any of claims 1—9 wherein R_4 is a hydrogen atom.

11. A process as claimed in any of claims 1—6 wherein the $CR_3R_4R_5$ moiety is a CH_2R^1 group where CH_2R^1 is an inert organic group of up to 18 carbon atoms.

12. A process as claimed in any of claims 1—11 wherein R_5 is a hydrogen atom or a methyl, ethyl n-propyl, n-butyl, n-pentyl, iso-propyl, vinyl, benzyl or p-methoxybenzyl group.

13. A process as claimed in any of claims 1—11 wherein R_5 is a hydrogen atom or a methyl, ethyl, benzyl or vinyl group.

14. A process as claimed in any of claims 1—11 wherein R_5 is a hydrogen atom or a methyl or ethyl group.

15. A process as claimed in any of claims 1—11 wherein R_5 is a hydrogen atom.

16. A process as claimed in any of claims 1—11 wherein R_5 is a methyl group.

17. A process as claimed in any of claims 1—6 adapted to the preparation of a compound of the formula (II) as defined in claim 1 wherein $CR_3R_4R_5$ is a methyl or ethyl group.

18. A process as claimed in claim 17 wherein the adaption comprises the use of methyl iodide or ethyl iodide.

19. A process as claimed in any of claims 1—18 wherein R_1 is a group A^1 or CHA^2A^3 wherein A^1 is an alkyl group of 1—8 carbon atoms, optionally substituted by halogen or by a group of the formula OA^4, $OCOA^4$, SA^4, SO_2A^4 wherein A^4 is a hydrocarbon group of up to 6 carbon atoms; A^2 is a hydrogen atom, an alkyl group of up to 4 carbon atoms or a phenyl group optionally subsituted by halogen or by a group A^5 or OA^5 where A^5 is a alkyl group of up to 6 carbon atoms; and A^3 is a phenyl group optionally substituted by halogen or by a group A^5 or OA^5 where A^5 is an alkyl group.

20. A process as claimed in any of claims 1—18 wherein R_1 is an alkenyl group of up to 8 carbon atoms.

21. A process as claimed in coam 20 wherein R_1 is an allyl group.

22. A process as claimed in any of claims 1—19 adapted to the preparation of an *in-vivo* hydrolysable ester of the formula (II).

23. A process as claimed in claim 22 wherein the *in-vivo* hydrolysable ester is the acetoxymethyl, α-acetoxyethyl, pivaloyloxymethyl, phthalidyl, ethoxycarbonyloxymethyl, or ethoxycarbonyloxyethyl ester.

24. A process as claimed in any of claims 1—19 adapted to the preparation of a benzyl, *p*-methoxybenzyl, methyl or methoxymethyl ester of the formula (II).

25. A process as claimed in any of claims 1—18 adapted to the preparation of a *p*-nitrobenzyl ester of the formula (II).

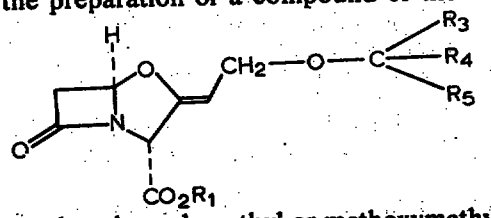
26. A process as claimed in any of claims 1—25 wherein the reaction is carried out in an inert medium at a temperature of from 10° to 100°C.

27. A process as claimed in claim 26 wherein the medium is benzene, toluene, ethyl acetate, tetrahydrofuran or acetone.

28. A process as claimed in claim 27 wherein the reaction is effected at a temperature of 30—80°C.

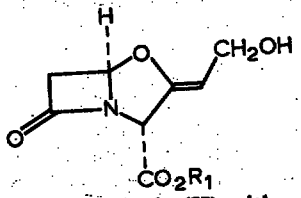
29. A process as claimed in any of claims 1—28 wherein a compound of the formula (III) wherein R_1 is a group $CR_3R_4R_5$ in situ by the esterification of a salt of clavulanic acid.

30. A process for the preparation of a compound of the formula (II):



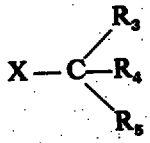
II

wherein R_1 is benzyl, *p*-methoxybenzyl, methyl or methoxymethyl and $CR_3R_4R_5$ is methyl or ethyl, which comprises the reaction of a compound of the formula (III):



III

wherein R_1 is as defined in relation to formula (II) with a compound of the formula (IV):



(IV)

wherein $CR_3R_4R_5$ is a methyl or ethyl group and X is I, Br or Cl in the presence of a source or silver ions.

31. A process as claimed in claim 30 wherein $CR_2R_3C_4$ is a methyl group.

32. A process as claimed in claim 30 wherein the compound of the formula (IV) is methyl iodide.

33. A process as claimed in claim 30 wherein $CR_2R_3R_4$ is an ethyl group.

34. A process as claimed in claim 30 wherein the compound of the formula (IV) is ethyl iodide.

35. A process as claimed in any of claims 30—34 wherein the source of silver ions is silver oxide.

36. A process as claimed in any of claims 30—35 carried out in the presence of calcium oxide.

37. A compound of the formula (II) as defined in claim 1 whenever prepared by the process of any of claims 1—36.

38. A process as claimed in any of claims 1—36 substantially as described in the Examples.

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