

PATENT SPECIFICATION

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 (72) Inventors LUCIANO RE, ALBERTO BRANDT and LUCIANO
 BASSIGNANI



(54) DEHYDROPENICILLINS

(71) We, SNAMPROGETTI S.P.A., an Italian company, of Corso Venezia 16, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

5 This invention relates to dehydropenicillins and to their preparation.
 The dehydropenicillins of the invention have the formula:



wherein X is an amino group, a monosubstituted amino group or a disubstituted amino group, and R is a carboxyl group or a salt, amide, ester or thioester thereof.

10 The dehydropenicillins of the invention are characterized by the presence of an unsaturated double bond in the beta-lactam ring. They belong to the class of 2-azetidine-4-ones.

15 The invention provides a process for the preparation of a dehydropenicillin of the invention, which process comprises (a) irradiating a 4-acylmethylthio-2-azetidinone having the formula:



or the formula:



20 wherein R' is an alkyl, aryl or aralkyl group and X and R are as defined in claim 1, thereby to obtain respectively a 4-thioxo-2-azetidinone having the formula:



or the formula:



and (b) effecting cyclization of the 4-thioxo-2-azetidinone thus obtained.

The group R can be, for example, a carboxylic ester or thioester of an alkyl group (for example a methyl, ethyl, propyl or butyl group), of an aralkyl group (for example a benzyl or substituted benzyl group) or of an aryl group (for example a phenyl or substituted phenyl group), or a 2,2,2-trichloroethyl ester or thioester of a carboxylic acid. The group R can also be, for example, a mono- or dialkyl carboxylic amide group (such as a mono- or diethylamide carboxylic amide group), a mono- or diaralkyl carboxylic amide group (for example a mono- or dibenzylamide carboxylic amide group), or a mono- or diaryl carboxylic amide group (such as a mono- or diphenylamide carboxylic amide group).

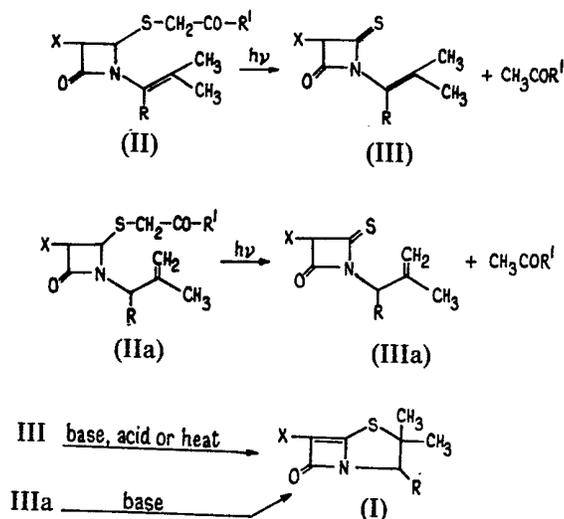
The selection of an ester the cleavage of which can be carried out under mild conditions (for example a benzyl ester or a 2,2,2-trichloroethyl ester) is preferred when it is desired to prepare from esters of the general formula (I) the corresponding free carboxylic acids from which, in their turn, it is possible to prepare other carboxyl derivatives with procedures known to those skilled in the art.

Both the basic salts with respect to the carboxyl group and the acidic salts with respect to the amino group of the dehydropenicillins of the general formula (I) can be prepared by methods known to those skilled in the art from the corresponding precursors.

In the general formula (I), particular examples of substituted amino groups with regard to X are aralkylamino groups (such as benzylamino or triphenylmethylamino groups), and acylamino groups (such as those present in natural penicillins or cephalosporins, such as phenylacetamido or phenoxyacetamido). A particular example of a disubstituted amino group X is the phthalimido group.

According to the present invention, the preparation of the dehydropenicillins is carried out, as shown in scheme I, by irradiation of substituted 4-acylmethylthio-2-azetidinones of the formula II or IIa to give, by a photochemical reaction of the Norris II type, the corresponding 4-thioxo-2-azetidinone derivatives of the formula III or IIIa, and by subsequent basic treatment (in the case of compound III also acidic or merely a heat-treatment) to give the dehydropenicillin I.

SCHEME I



In the above scheme I, X and R have the same meaning as above and R' is an alkyl, aryl or aralkyl group.

It should be noted that in the synthesis shown in scheme I, the groups X or R of the starting compound II or IIa need not necessarily be the same as those of the desired product I, since it is possible to effect, by conventional methods, a modification of such groups at the level of the intermediate III or IIIa or after the cyclization of such intermediate to I.

It is to be noted, moreover, that for such a synthesis, it is possible to use starting compounds II and IIa in both the cis or trans form relative to the

substituents on the C₃ and the C₄ of the lactam ring.

The derivatives I obtained by the method shown in scheme I are optically inactive chiral products which can be split into their enantiomers by conventional procedures known to those skilled in the art.

An interesting aspect of the method according to the present invention is the fact that compounds III and IIIa of scheme I are novel compounds. These compounds are claimed in our Application No. 1747/79 (Serial No. 1,572,140).

The starting compounds II and IIa are, on the contrary, known compounds and can be prepared from derivatives of natural penicillins or by total synthesis, for example as follows:

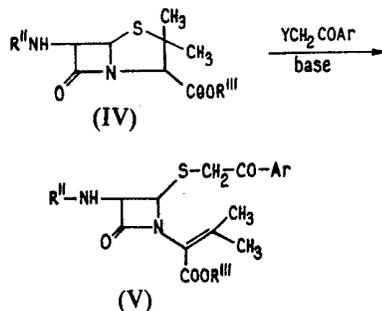
(a) Compounds II in which X, R and R' have the meaning as indicated above, can be prepared from derivatives of penicillins according to German Offenlegungsschriften Nos. 2,204,105 and 2,254,632, or by total synthesis according to R. Lattrel, Liebigs Ann. Chem. 1974, 1361 and the references cited therein;

(b) Compounds II and IIa in which X is a mono- or diacylamino group, R is an ester group and R' is as above, can be prepared from penicillins according to M. Yashimoto et al., Tetrahedron Letters, 1972, 4387, or from penicillin sulphoxides according to German Offenlegungsschrift No. 2,138,320 or R. Lattrel, Liebigs Ann. Chem. 1974, 1937;

(c) Compounds IIa in which X and R are other groups and in which R' is as above, can be prepared from the above-mentioned derivatives in which X is a mono- or diacylamino group, R is an ester group and R' is as above, using chemical and/or enzymatic procedures as known to those skilled in the art.

Compounds II in which R' is an aryl group, X is an R''NH group (in which R'' is an aralkyl group) and R is a COOR''' group (wherein R''' is an alkyl, aralkyl or aryl group) (i.e. compounds V below) can also be prepared by a method which is more direct than those above, such method being shown by scheme II (wherein Y = halogen and AR = aryl) by reacting 6-aralkylaminopenicillates (IV) with halomethyl aryl ketones in the presence of a strong base.

SCHEME II



Also, from the compounds V, by conventional procedures known to those skilled in the art, it is possible to prepare other compounds II in which R' is an aryl group.

For the preparation of the dehydropenicillins I according to the present invention, a compound II or IIa is subjected to irradiation, preferably from an ultraviolet lamp, preferably of the kind with an average mercury pressure and equipped with a filter, e.g. a "Pyrex" or "Corex" filter. The words "Pyrex" and "Corex", and the word "Hanovia" used below, are registered Trade Marks.

The reaction is preferably carried out in an atmosphere of an inert gas (for example nitrogen) in an inert solvent (such as an aromatic solvent) or in acetonitrile which is anhydrous and oxygen-free, and is preferably carried out at a temperature in the range of from -10°C to +40°C (preferably at room temperature) to give the derivative III or IIIa in generally high yields. Preferably, the intermediate III or IIIa is then treated in an anhydrous inert solvent (such as a halo-aliphatic solvent or an aromatic solvent) with a quantity, which can be a catalytic quantity (when III or IIIa is a neutral molecule), of an organic base (preferably triethylamine) at a temperature in the range of from -10°C to +40°C (preferably at room temperature) to give, with generally high yields, the dehydropenicillin I. In an alternative preferred procedure, the cyclization of compound III to compound I is

carried out in an inert anhydrous solvent (such as an aliphatic or aromatic solvent), also with a Brønsted or a Lewis acid, preferably silica gel, or in a neutral environment by merely heating to a temperature between 50°C and 150°C.

With regard to the preparation of starting compound V, a compound IV may be reacted with a halomethyl aryl ketone (preferably a bromo- or iodomethyl aryl ketone) in an inert anhydrous solvent (such as dimethylformamide, dimethylsulphoxide, tetrahydrofuran or mixtures thereof with tert-butyl alcohol, but preferably tetrahydrofuran alone) in the presence of a strong base which is capable of cleaving the thiazolidine ring of compound IV but incapable of cleaving the lactam ring of compound IV or V (such as an alkali metal hydride, preferably sodium hydride, or an alkali metal salt of a tertiary alcohol, preferably potassium tert-butyrate), at a temperature between -80°C and +30°C (preferably at -40°C).

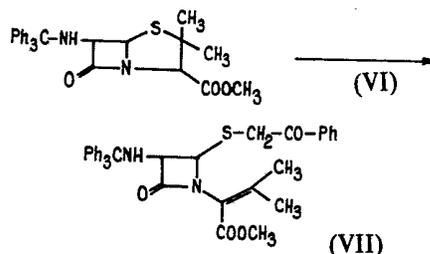
Compounds IV which are particularly suitable as starting compounds for the preparation of compounds V according to scheme II are those in which R' is a triphenylmethyl group, both from the point of view of the yield of the reaction and the ease with which such a group can be removed from the compound V to give the free amine from which it is possible to prepare, according to conventional procedures, other amine derivatives.

The dehydropenicillins of the invention are useful intermediates for the preparation of other penicillin derivatives and cephalosporins of pharmaceutical interest. In addition, some of the dehydropenicillins of the invention have a mild antibacterial activity.

The first step of the process of the invention is illustrated by the following Examples 4, 5, 6, 7 and 8, and the second step of the process of the invention is illustrated by the following Examples 9, 10, 11, 12 and 13. The following Examples 1, 2 and 3 illustrate the preparation of starting materials for use in Examples 6 and 7.

Example 1.

Preparation of cis - 1 - (1 - methoxycarbonyl - 2 - methyl - 1 - propenyl - 3 - triphenylmethylamino - 4 - phenacylthio - 2 - azetidione (VII).



To a solution of 3.78 grams (8 millimols) of methyl-6beta-triphenylmethylaminopenicillanate (VI) and 1.75 grams (8 millimols) of phenacylbromide in 30 mls of anhydrous tetrahydrofuran are added during 30 mins. with stirring, in a nitrogen atmosphere and at a temperature of -40°C, 0.898 grams (8 millimols) of potassium tert-butyrate dissolved in 40 mls of anhydrous tetrahydrofuran.

On completion of the addition, the mixture is stirred during 5 additional hours at the same temperature. Then, still under nitrogen, neutralization is effected with a few drops of glacial acetic acid diluted in anhydrous tetrahydrofuran, filtration is carried out and the filtrate is evaporated under vacuum.

The thus-obtained residue is chromatographed on a silica-gel column (3 x 60 cm) eluting with benzene which contains 5% of ethyl acetate.

From the first eluates are isolated 1.71 grams of the starting compound (VI) which did not react (recovery 45.2%) and from the subsequent eluates 1.52 grams of the pure product (yield 58.7% relative to the converted VI) in the form of a white foam.

IR (CHCl₃):

ν_{max} 3340 (NH), 3040 and 3020 (phenyls), 1760 (CO of the beta-lactam), 1720 (CO of the ester), 1673 (CO of the phenacyl), 1625 (C = C), 1595, 1580 and 1495 cm⁻¹ (phenyls).

NMR (CDCl₃):

δ 1.83 (3H,s) and 2.03 (3H,s) [(CH₃)₂C = C], 3.00 (1H,d, J = 8Hz, NH), 3.42 (2H,q, J = 14Hz, SCH₂), 3.80 (3H,s,COOCH₃), 4.60 (1H,q, J = 4 and 8Hz, 3-H), 4.92 (1H,d, J = 4Hz, 4-H), 6.90-7.90 (20 H,m,aromatics).

Mass spectrum:

m/e 590, 485, 243, 228, 155, 105, 77, 68.

Analysis for $C_{38}H_{34}N_2O_4S$:

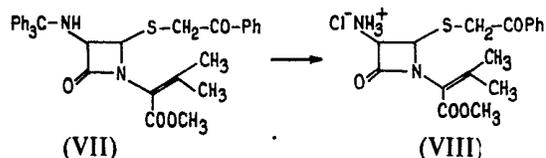
Calcd. $C\% = 73.19$ $H\% = 5.80$ $N\% = 4.74$

5 Found 72.80 6.02 4.91

5

Example 2.

Preparation of cis - 1 - (1 - methoxycarbonyl - 2 - methyl - 1 - propenyl) - 3 - amino - 4 - phenacylthio - 2 - azetidinone hydrochloride (VIII).



10 To 0.673 gram (1.14 millimol) of the product VII, prepared according to Example 1, dissolved in 10 mls of anhydrous methylene chloride, are added at $-20^{\circ}C$ with stirring and in an anhydrous atmosphere (nitrogen), 7.0 mls of a 0.326-normal solution (2 equivalents) of gaseous hydrogen chloride in anhydrous methylene chloride.

15 The solution is stirred during 2 hours at the same temperature under nitrogen, then evaporated to dryness under vacuum and the gummy residue is taken up with a few mls of a mixture of ethyl ether and petroleum ether (anhydrous).

20 The precipitate is collected by filtration under nitrogen and dried in vacuo to give 0.390 gram of the hydrochloride VIII (yield 89%) as a white solid which is very hygroscopic, and is sufficiently pure to be used in the following reaction (Example 3) and for being spectrophotometrically identified.

I R ($CHCl_3$):

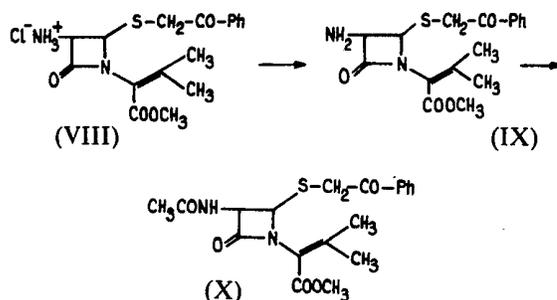
25 ν_{max} 3060 and 3020 (phenyl), 1775 (CO of the beta-lactam), 1720 (CO of the ester), 1675 (CO of the phenacyl), 1620 (C=C), 1595, 1580 and 1490 cm^{-1} (phenyl).

NMR ($CDCl_3$):

30 δ 2.05 (3H,s) and 2.22 (3H,s) [(CH_3)₂C=C], 3.80 (3H,s,COOCH₃), 4.23 (2H,s,SCH₂), 5.87 (1H, d wide band, 4-H), 6.40 (1H,m wide band,3H), 7.00—7.90 (5H,m, aromatics), 8.35 (3H, wide band,NH₃⁺).

Example 3.

30 Preparation of cis - 1 - (1 - methoxycarbonyl - 2 - methyl - 1 - propenyl) - 3 - acetamido - 4 - phenacylthio - 2 - azetidinone (X).



35 To 0.385 gram (1 millimol) of the hydrochloride VIII, prepared according to Example 2, dissolved in 5 mls of anhydrous methylene chloride are added at $0^{\circ}C$ with stirring and in an anhydrous atmosphere (nitrogen), 140 microliters (millimol) of triethylamine.

40 After 30 mins. the mixture which contains the free amine IX is further cooled to $-20^{\circ}C$ and there are added, still with stirring and in a nitrogen atmosphere, 140 additional microliters of triethylamine followed by 71 microliters (1 millimol) of acetyl chloride dissolved in 2 mls of anhydrous methylene chloride. Stirring is carried out for a few hours at $0^{\circ}C$.

Upon dilution with 10 additional mls of methylene chloride, the mixture is

washed with water to neutrality and the organic phase is dried over sodium sulfate and evaporated to dryness in vacuo.

The raw product is purified by chromatography on a thin preparative layer of silica gel, by eluting with ethyl ether-ethyl acetate (2:1) and extracting the product from the silica with chloroform.

There is obtained 0.085 gram of the product X, pure (yield 22%) in the form of a white foam.

I R (film):

ν_{\max} 3320 (NH), 3050 and 3020 (phenyl), 1760 (CO of the beta-lactam, 1720 (CO of the ester), 1682 (shoulder, CO of the acetamide), 1673 (CO of the phenacyl), 1625 (C=C), 1595 and 1585 (phenyl), 1523 (NH), 1500 cm^{-1} (phenyl).

NMR(CDCl_3):

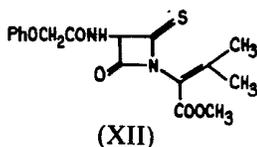
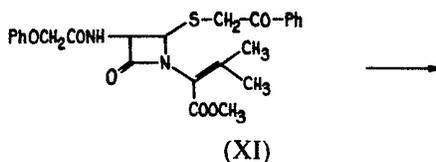
δ 1.86 (3H,s) and 2.13 (3H,s) [$(\text{CH}_3)_2 \text{C}=\text{C}$], 1.93 (3H,s, CH_3CO), 3.75 (3H,s, COOCH_3), 3.80 (2H,s, SCH_2), 5.25 (1H,q, $J=8$ and 4 Hz, 3—H), 5.40 (1H,d, $J=4$ Hz, 4—H—), 7.10—8.00 (6H, aromatics and NH).

Mass spectrum:

m/e 390, 291, 271, 239, 105, 84, 77, 68.

Example 4.

Preparation of 1 - (1 - methoxycarbonyl - 2 - methyl)1 - propenyl - 3 - phenoxy - acetamido - 4 - thioxo - 2 - azetidinone (XII).



A conventional apparatus for photometric reactions with an immersion lamp having a cooling jacket of quartz and a water jacket, equipped with a magnetic stirrer, a capillary tube for nitrogen dipping to the bottom and an outlet placed laterally and connected to a mercury layer, is charged under nitrogen 0.965 gram (2 millimols) of the product XI dissolved in 150 mls of anhydrous and degasified acetonitrile.

Purging is effected during 5 mins. in nitrogen stream, then irradiation is effected at room temperature and with stirring during 45 mins. with a "Hanovia" lamp at average pressure of mercury, 500 Watts power, and with a "Pyrex" glass filter.

The solution is then transferred into a flask and, at room temperature, the solvent is first evaporated off under a vacuum of 13 mmHg and then the predominant fraction of the formed acetophenone under a vacuum of 0.1 mmHg during a few hours. The glassy residue of 0.645 gram (yield 89%) is formed nearly exclusively by the product XII and contains traces of acetophenone and very little (10% approx.) of the starting compound, XI. The product obtained, which cannot be crystallized and is chromatographically unstable, is pure enough for the next reaction (Example 9) and for being chromatographically identified.

I R (CHCl_3):

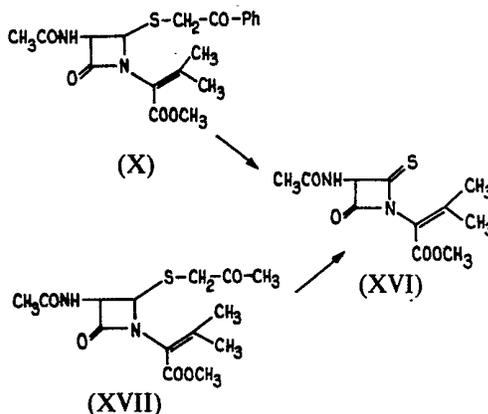
ν_{\max} 3340 (NH), 3060 and 3040 (shoulder, phenyl), 1820 (CO of the beta-lactam); 1720 (CO of the ester), 1682 (CO of the phenoxyacetamide), 1635 (shoulder, C=C), 1595 and 1580 (shoulder, phenyl), 1528 (NH), 1490 cm^{-1} (phenyl).

NMR (CDCl_3):

δ 2.06 (3H,s) and 2.28 (3H,s) [$(\text{CH}_3)_2 \text{C}=\text{C}$], 3.80 (3H,s, COOCH_3), 4.36 (2H,s, OCH_2CO), 4.91 (1H,s, $J=8$ Hz, 3—H), 6.60—7.60 (5H,m, aromatics), 7.94 (1H,d, $J=8$ Hz, NH).

Example 7.

Preparation of 1 - (1 - methoxycarbonyl - 2 - methyl - 1 - propenyl) - 3 - acetamido - 4 - thioxo - 2 - azetidinone (XVI).



a) The procedure is similar to that disclosed in Example 4 for the preparation of XII from XI, starting from the product X prepared according to Example 3.

The thus-obtained product XVI (yield 84.5%) in the form of a glassy solid is sufficiently pure for the next reaction (Example 12a) and for being spectrophotometrically identified.

I R (CHCl₃):

ν_{\max} 3320 (NH), 1820 (CO of the beta-lactam), 1722 (CO of the ester), 1675 (CO of the acetamide), 1635 (C=C), 1530 cm⁻¹ (NH).

NMR (CDCl₃):

δ 2.00 (3H,s) and 2.32 (3H,s) [(CH₃)₂ C=C], 2.08 (3H,s,CH₃CO), 3.73 (3H,s,COOCH₃), 4.93 (1H,d, J = 8Hz, 3-H), 7.53 (1H,d, J = 8Hz, NH).

b) The procedure is similar to that disclosed in Example 4 for the preparation of XII from XI, starting from the product XVII by using, instead, a filter of "Corex" glass and irradiating for 4 hours. In addition, at the end of the reaction, the evaporation at 0.1 mmHg is not required since, in this case, the formed ketone is acetone rather than acetophenone.

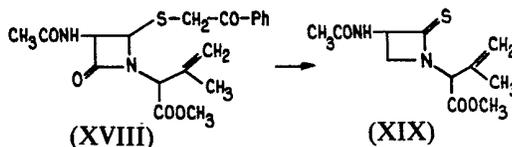
The gummy raw-product which is obtained cannot be crystallized and is unstable to chromatography and is conveniently used as such for the next reaction (Example 12a).

From the IR and NMR spectra it can be seen that the raw product contains about 40% of the product XVI and that the yield referred to the pure product is about 37%.

From a partial purification test of the raw material by repeated solubilizations in ethyl ether and precipitations with petroleum ether there is obtained, with very low yields, a gummy product which is purer and the IR and NMR spectra of which compared with those of the product obtained from X confirm the structure XVI.

Example 8.

Preparation of 1 - (1 - methoxycarbonyl - 2 - methyl - 2 - propenyl) - 3 - acetamido - 4 - thioxo - 2 - azetidinone (XIX).



The procedure is similar to that disclosed in Example 4 for the preparation of XII from XI, starting from the product XVIII. The product XIX which is obtained (yield 78.5%) as a glassy solid is sufficiently pure for the next reaction and for being identified spectrophotometrically.

I R (film):

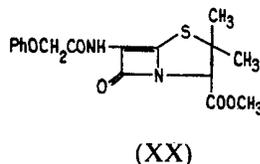
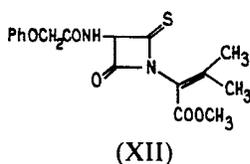
ν_{\max} 3300 (NH), 1818 (CO of the beta-lactam), 1740 (CO of the ester), 1670 (CO of the acetamide), 1530 cm⁻¹ (NH).

NMR (CDCl₃):

δ 1.88 (3H,s, CH₃-C=C), 2.07 (3H,s,CH₃CO-), 3.80 (3H,s,COOCH₃)
4.90—5.25 (4H,m,CH₂=C, 3-H and CHCOO), 7.50 (1H,d, J = 8Hz, NH).

Example 9.

5 Preparation of methyl - 6 - phenoxyacetamidodehydropenicillanate (XX). 5



10 a) To 0.645 gram (1.78 millimol) of the product XII, prepared according to
Example 4, dissolved in 30 mls of methylene chloride are added 0.08 ml of
triethylamine and the solution stirred at room temperature in an anhydrous
atmosphere (nitrogen) until observing from the IR spectra the total discharge from
the solution of the band at 1820 cm⁻¹ which is typical of the starting product XII
(about 4 hours). The mixture is then dried in vacuo and the raw product is purified
by chromatography on a silica-gel column (2 x 20 cm) eluting with benzene and
ethyl acetate (4:1). After the elution of a few impurities, there are isolated from the
successive eluates 0.460 grams of the product XX (yield 71% from XII and 63.5%
15 from XI) and then 0.05 gram approx. of the starting product XI of the previous
reaction (Example 4). 15

20 The dehydropenicillin XX is obtained as an amorphous white solid which is
pure at the chromatography on thin layer and can be crystallized from ethyl ether-
petroleum ether, m.p. 138°C—139°C. 20

UV (EtOH):

λ_{\max} (log E) 220 (3.88, 245 (3.87) and 328 millimicrons (4.41).

IR (CHCl₃):

25 ν_{\max} 3300(NH), 3060 and 3020 (phenyl), 1742 (CO of the ester), 1720 (CO of
the beta-lactam), 1630 (CO of the phenoxyacetamide), 1595 and 1585
(shoulder, phenyl), 1565 (NH) 1493 cm⁻¹ (phenyl). 25

NMR (CDCl₃):

δ 1.47 (3H,s) and 1.73 (3H,s) [(CH₃)₂Cl], 3.80 (3H,s,COOCH₃) 4.52 (1H,s,3—4),
4.80 (2H,s,OCH₂CO), 6.80—7.50 (5H, aromatics), 7.85 (1H,s,wide band, NH).

30 Mass spectrum: 30

m/e 362, 269, 209, 199, 167, 139, 94, 66.

Analysis for C₁₇H₁₈N₂O₅S:

Calcd.	C% = 56.34	H% = 5.01	N% = 7.73
Found	55.92	4.88	7.52

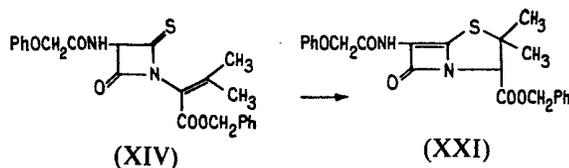
35 b) To 0.100 gram (0.28 millimol) of the product XII, prepared according to
Example 4, dissolved in 10 mls of chloroform are added 5 grams of silica gel. The
slurry is stirred at room temperature overnight, then filtered, washing the silica
repeatedly with chloroform. 35

40 The filtrate, evaporated in dryness in vacuo shows at the IR the discharge of
the band at 1820 cm⁻¹. The raw product is purified by chromatography on a
preparative thin layer of silica gel eluting with benzene and ethyl acetate (7:3) and
extracting the product from the silica with chloroform. There is obtained 0.038
gram of the product XX, identical to that obtained under (a). 40

Yield 38% from XII and 34% from XI.

45 c) A solution in 10 mls of tetrachloroethylene of 0.100 gram (0.28 millimol) of
the product XII, prepared according to Example 4, is stirred for 10 hours at
90°C—100°C. The cooled solution shows in its IR spectra the discharge of
the band at 1820 cm⁻¹ and is dried in vacuo and the residue purified as under (b). There
is obtained 0.036 gram of the product XX, identical to that obtained under (a). The
50 yield is 36% from XII and 32% from XI. 50

Example 10.
Preparation of benzyl-6-phenoxyacetamidodehydropenicillanate (XXI).



5 The procedure is similar to that described in Example 9(a) for the preparation of XX from XII with triethylamine, starting from the benzyl ester XIV prepared according to Example 5. The product XXI which is obtained (yield 72.5%) as a white amorphous solid, pure at the thin layer chromatography, can be crystallized from ethyl ether-petroleum ether, m.p. 129°C—131°C. 5

IR (CHCl₃):

10 ν_{\max} 3300 (NH), 3040 and 3020 (phenyls), 1745 (CO of the ester), 1720 (CO of the beta-lactam), 1630 (CO of the phenoxy-acetamide), 1600 and 1590 (shoulder, phenyls), 1565 (NH), 1495 cm⁻¹ (phenyls). 10

NMR (CDCl₃):

15 δ 1.35 (3H,s) and 1.63 (3H,s) [(CH₃)₂Cl], 4.50 (H,s,3—4), 4.80 (2H,s, OCH₂CO), 5.18 (2H,s,COOCH₂), 6.70—7.50 (10H,m,aromatics), 7.85 (1H, s, wide band, NH). 15

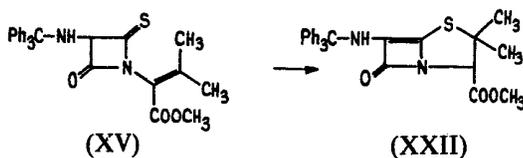
Mass spectrum:

m/e 439, 438, 345, 303, 209, 94, 91, 66.

Analysis for C₂₃H₂₂N₂O₅S

20 Calcd. C% = 63.00 H% = 5.05 N% = 6.39
Found 62.58 5.06 6.17 20

Example 11.
Preparation of methyl-6-triphenylmethylaminodehydropenicillanate (XXII).



25 The procedure is similar to that disclosed in Example 9 (a) for the preparation of XX from XII with triethylamine, starting from the product XV prepared according to Example 6. 25

30 In such case, however, to observe from the IR spectra the discharge of the band at 1810 cm⁻¹ longer times are required (about 24 hours). The thus-obtained raw material is purified on neutral alumina, eluting with benzene. The product which is obtained (yield 23%) in the form of a foam is pure at the chromatography on thin layer, but it is poorly stable. 30

IR (CHCl₃):

35 ν_{\max} 3320 (NH), 3060 and 3020 (phenyls), 1750 (CO of the ester), 1730 (CO of the beta-lactam), 1595, 1580 (shoulder), and 1490 cm⁻¹ (phenyls). 35

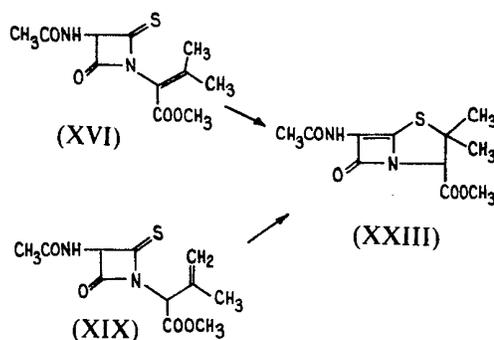
NMR (CDCl₃):

40 δ 1.35 (3H,s), and 1.72 (3H,s) [(CH₃)₂Cl], 3.20 (1H,s, wide band, NH), 3.80 (3H,s,COOCH₃), 4.58 (1H, s, 3—4), 7.10—7.68 (15H,m,aromatics). 40

Analysis for C₂₈H₂₈N₂O₃S:

Calcd. C% = 71.47 H% = 5.57 N% = 5.95
Found 71.01 5.5 5.75 40

Example 12.
Preparation of methyl-6-acetamidodehydropenicillanate (XXIII).



5 a) The procedure is similar to that disclosed in Example 9 (a) for the preparation of XX from XII with triethylamine, starting from the product XVI prepared according to Example 7 (a) or 7 (b). The product which is obtained is purified in the first case by column chromatography as described in Example 9(a), eluting, however, with ethyl ether-ethyl acetate (2:1) (yield 50.5% from XVI and 43% from X) and, in the second case by chromatography on a preparatory thin layer of silica gel but eluting with ethyl ether-ethyl acetate (3:1) and extracting from the silica with chloroform (yield 24% from XVII). The product which is obtained as a glassy solid in both cases is pure and can be crystallized from ethyl ether-petroleum ether, m.p. 98°C—100°C.

15 I R (CHCl₃):
 ν_{\max} 3300 (NH), 1740 (CO of the ester), 1715 (CO of the beta-lactam), 1630 (CO of the acetamide), 1570 cm⁻¹ (NH).

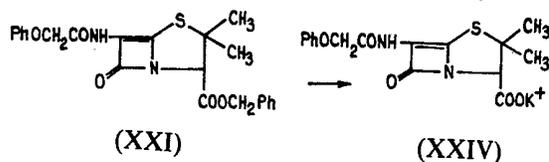
20 NMR (CDCl₃):
 δ 1.47 (3H,s), and 1.75 (3H,s) (CH₃)₂C, 2.20 (3H,s,CH₃CO), 3.80 (3H,s,COOCH₃), 4.48 (1H,s,3—4), 7.60 (1H,s,COOCH₃), 4.48 (1H,s,3—4), 7.60 (1H,s, wide band, NH).

25 Mass spectrum:
m/e 270, 238, 211, 199, 167, 139, 98, 39.

Analysis for C₁₁H₁₄N₂O₄S
Calcd. C% = 48.88 H% = 5.22 N% = 10.36
Found 48.55 5.48 9.88

30 b) The procedure is similar to that in Example 9 (a) for the preparation of XX from XII with triethylamine, starting from the product XIX prepared according to Example 8. The product which is obtained (yield 32% from XIX and 25% from XVIII) as an amorphous solid after chromatography on a thin layer preparatory layer as described in Example 12(a) is identical to the product prepared according to Example 12(a).

Example 13.
Preparation of potassium-6-phenoxyacetamidodehydropenicillanate (XXIV).



35 A solution in 20 mls of a mixture of ethanol-ethyl acetate (4:1) of 0.438 gram (1 millimol) of the product XXI prepared according to Example 10, is hydrogenated in the presence of 0.430 gram of 10% palladium on activated charcoal under atmospheric pressure and at room temperature for 30 mins. The catalyst is then filtered off and to the filtrate is added 0.430 gram of fresh catalyst and the hydrogenolysis is continued during 40 additional minutes under the same conditions. The catalyst is filtered off again and the solution is immediately brought

to a pH of 7.8—8.0 with a 5% aqueous solution of potassium bicarbonate and cooling with an ice bath. The mixture is evaporated to dryness in vacuo at room temperature and the solid residue is taken up in ethylacetate, filtered, and the product XXIV is precipitated with ethyl ether from the solution. There is obtained 0.330 grams of XXIV (yield 85%).

IR (KBr):

ν_{\max} 3400 (wide band, H_2O), 3320 (shoulder, NH), 3060 and 3040 (shoulder, phenyl), 1703 (CO of the beta-lactam), 1620 (CO of the phenoxyacetamide), 1602 (wide band, CO of the carboxylate), 1590 (shoulder, phenyl), 1555 (NH), 1493 cm^{-1} (phenyl).

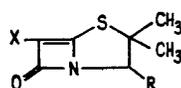
NMR (CD_3OD):

δ 1.51 (3H,s) and 1.76 (3H,s) (CH_3)₂C, 4.38 (1H,s,3—4), 4.86 (2H,s,OCH₂CO), 6.85—7.40 (5H,m, aromatics).

The compound XXIV shows mild antibacterial activity to *B. subtilis* and *Staph. aureus* in the vitro dosage (agar plate diffusion test).

WHAT WE CLAIM IS:—

1. A dehydropenicillin having the formula:



(I)

wherein X is an amino group, a monosubstituted amino group or a disubstituted amino group, and R is a carboxyl group or a salt, amide, ester or thioester thereof.

2. Methyl-6-phenoxyacetamidodehydropenicillanate.

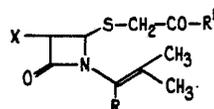
3. Benzyl-6-phenoxyacetamidodehydropenicillanate.

4. Methyl-6-triphenylmethylaminodehydropenicillanate.

5. Methyl-6-acetamidodehydropenicillanate.

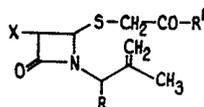
6. Potassium-6-phenoxyacetamidodehydropenicillanate.

7. A process for the preparation of a dehydropenicillin as claimed in claim 1, which comprises (a) irradiating a 4-acylmethylthio-2-azetidinone having the formula:



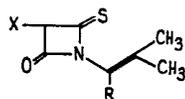
(II)

or the formula:



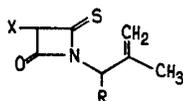
(IIa)

wherein R' is an alkyl, aryl or aralkyl group and X and R are as defined in claim 1, thereby to obtain respectively a 4-thioxo-2-acetidinone having the formula:



(III)

or the formula:



(IIIa)

and (b) effecting cyclization of the 4-thioxo-2-acetidinone thus obtained.

8. A process according to claim 7, wherein the irradiation is effected at a temperature of from -10 to 40°C.

9. A process according to claim 7 or 8, wherein the irradiation is effected in an anhydrous oxygen-free inert solvent.
10. A process according to claim 9, wherein the irradiation is effected under an inert atmosphere.
- 5 11. A process according to any of claims 7 to 10, wherein a 4-acylmethylthio-2-azetidinone of formula II is used, and wherein the cyclization of the 4-thioxo-2-azetidinone of the formula III is effected by treatment thereof with a base or acid. 5
12. A process according to claim 11, wherein the treatment is effected at a temperature of from -10 to 40°C .
- 10 13. A process according to claim 11 or 12, wherein the treatment is effected in an anhydrous inert solvent. 10
14. A process according to any of claims 7 to 10, wherein a 4-acylmethylthio-2-azetidinone of formula II is used, and wherein the cyclization of the 4-thioxo-2-azetidinone of formula III is effected by heating it to a temperature of from 50 to 150°C .
- 15 15. A process according to claim 14, wherein the heating is effected in an anhydrous inert solvent. 15
16. A process according to any of claims 7 to 10, wherein a 4-acylmethylthio-2-azetidinone of formula IIa is used, and wherein the cyclization of the 4-thioxo-2-azetidinone of formula IIIa is effected by treatment thereof with a base.
- 20 17. A process according to claim 16, wherein the treatment is effected at a temperature of from -10 to 40°C . 20
18. A process according to claim 16 or 17, wherein the base is an organic base.
- 25 19. A process for the preparation of a dehydropenicillin as claimed in claim 1, substantially as described in any of Examples 4 and 9, or Examples 5 and 10, or Examples 6 and 11, or Examples 7 and 12, or Example 13. 25
20. A dehydropenicillin as claimed in claim 1, whenever prepared by a process according to any of claims 7 to 19.

HASELTINE, LAKE & CO.,
Chartered Patent Agents,
28 Southampton Buildings,
Chancery Lane,
London WC2A 1AT.
— and —
Temple Gate House,
Temple Gate,
Bristol BS1 6PT.
— and —
9 Park Square,
Leeds LS1 2LH.
Agents for the Applicants.