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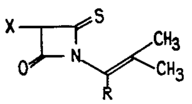
(54) 4-THIOXO-2-AZETIDINONES

(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:—

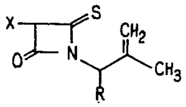
This invention relates to 4-thioxo-2-azetidinones and to their preparation.

The 4-thioxo-2-azetidinones of the invention have the formula:



(III)

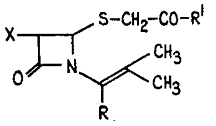
or the formula:



(IIIa)

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.

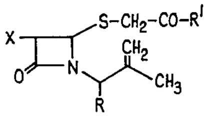
The invention provides a process for the preparation of a 4-thioxo-2-azetidinone of formula III, which process comprises irradiating a 4-acylmethylthio-2-azetidinone having the formula:



(II)

wherein R′ is an alkyl, aryl or aralkyl group, and X and R are as defined above.

The invention also provides a process for the preparation of a 4-thioxo-2-azetidinone of formula IIIa, which process comprises irradiating a 4-acylmethylthio-2-azetidinone having the formula:



(IIa)

wherein R′, X and R are as defined above.

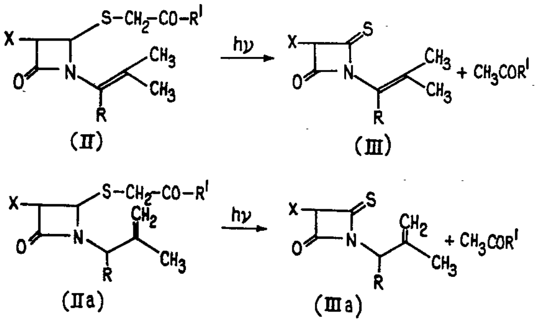
The group R can be, for example, a carboxylic ester or thioester of an alkyl group (for example a methyl, ethyl, propyl or butyl group), of an aralkyl group (for example a benzyl or substituted benzyl group) or of an aryl group (for example a phenyl or substituted phenyl group), or a 2,2,2-trichloroethyl 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 diethyl-amide 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 formulae III and IIIa 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.

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 phenoxylacetamido). A particular example of a distributed amino group X is the phthalimido group.

According to the present invention, the preparation of the 4-thioxo-2-azetidinones 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.

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 III or IIIa, since it is possible to effect, by conventional methods, a modification of such groups after formation of compound III or IIIa.

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 C_3 and the C_4 of the lactam ring.

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

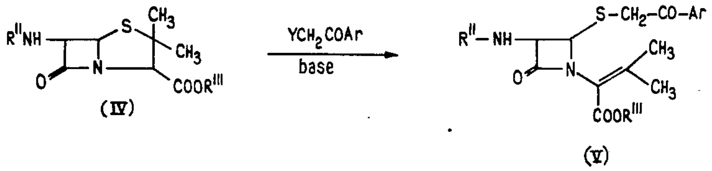
(a) Compounds II in which X, R and R′ have the meaning as indicated above, can be prepared from derivatives of penicillins according to German Offenlegungsschriften Nos. 2,204,105 and 2,254,632, or by total synthesis according to R. Lattrel, Liebigs Ann. Chem. *1974*, 1361, and the reference cited therein;

(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 4-thioxo-2-azetidinones 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 and +40°C (more preferably at room temperature) to give the derivative III or IIIa in generally high yields.

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-butylate), at a temperature between –80°C and +30°C (preferably at –40°C).

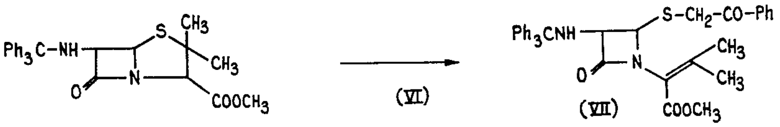
Compounds IV which are particularly suitable as starting compounds for the preparation of compounds V according to scheme II are those in which R″ is a triphenylmethyl group, both from the point of view of the yield of the reaction and the ease with which such a group can be removed from the compound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

The 4-thioxo-2-azetidinones of the invention are useful intermediates for the preparation of other penicillin derivatives and cephalosporins of pharmaceutical interest. They are obtained as intermediate products in the preparation of the dehydropenicillins claimed in our Application No. 7500/77. (Serial No. 1572139).

The invention will now be illustrated by the following Examples 4, 5, 6, 7 and 8. 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-azetidinone (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-butylate 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 ($CHCl_3$):
νmax 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 ($CDCl_3$):
δ1.83 (3H,s) and 2.03 (3H,s)[$(CH_3)_2C$ = C], 3.00 (1H,d, J = 8Hz, NH), 3.42 (2H,q, J = 14Hz SCH_2), 3.80 (3H,s,$COOCH_3$), 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).

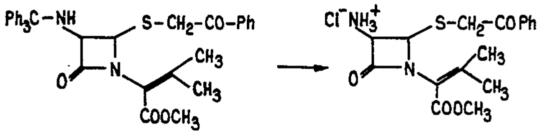
Mass spectrum:
m/e 590, 485, 347, 243, 228, 155, 105, 77, 68.

Analysis for $C_{36}H_{34}N_2O_4S$:

Calcd.	C% = 73.19	H% = 5.80	N% = 4.74
Found	72.80	6.02	4.91

Example 2.

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



(VII) (VIII)

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°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.

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).

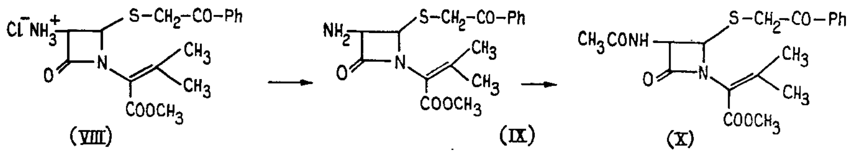
The precipitate is collected by filtration under nitrogen and dried in vacuo to give 0.390 gram of the hydrochloride VIII (yield 89%) as a white solid which is very hygroscopic, and is sufficiently pure to be used in the following reaction (Example 3) and for being spectrophotometrically identified.

IR ($CHCl_3$):
νmax 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 ($CDCl_3$):
δ2.05 (3H,s) and 2.22 (3H,s) [$(CH_3)_2C$ = C] 3.80 (3H,s,$COOCH_3$), 4.23 (2H,s,SCH_2), 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,NH_3^+).

Example 3.

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



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°C with stirring and in an anhydrous atmosphere (nitrogen), 140 microliters (millimol) of triethylamine.

After 30 mins. the mixture which contains the free amine IX is further cooled to –20°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°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.

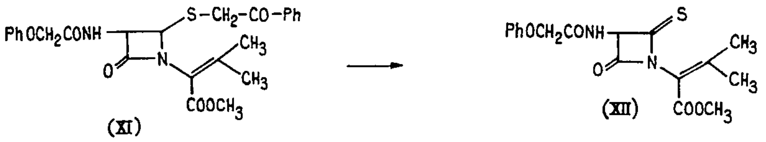
IR (film):
ν_{max} 3320 (NH), 3050 and 3020 (phenyl), 1760 (CO of the beta-lactam, 1720 (CO of the ester), 1682 (shoulder, CO of the acetamide), 1673 (CO of the phenacyl), 1625 (C = C), 1595 and 1585 (phenyl), 1523 (NH), 1500 cm^{-1} (phenyl).

NMR ($CDCl_3$):
δ 1.86 (3H,s) and 2.13 (3H,s) [$(CH_3)_2$ C = 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 = 4Hz, 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-phenoxyacetamido-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.

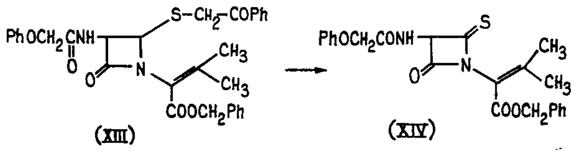
The solution is then transferred into a flask and, at room temperature, the solvent is first evaporated off under a vacuum of 13 mmHg and then the predominant fraction of the formed acetophenone under a vacuum of 0.1 mmHg during a few hours. The glassy residue of 0.645 gram (yield 89%) is formed nearly 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.

IR ($CHCl_3$):
νmax 3340 (NH), 3060 and 3040 (shoulder, phenyl), 1820 (CO of the beta-lactam); 1720 (CO of the ester), 1682 (CO of the phenoxy-acetamide), 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) [$(CH_3)_2$ C = C], 3.80 (3H,s,$COOCH_3$), 4.36 (2H,s,OCH_2CO), 4.91 (1H,s, J = 8Hz, 3-H), 6.60 – 7.60 (5H,m, aromatics), 7.94 (1H,d, J = 8Hz, NH).

Example 5.

Preparation of 1-(1-benzyloxycarbonyl-2-methyl-1-propenyl)-3-phenoxyacetamido-4-thioxo-2-azetidinone (XIV)



The procedure is similar to that disclosed in Example 4 for the preparation of XII starting from XI, the initial starting compound being the benzyl ester XIII.

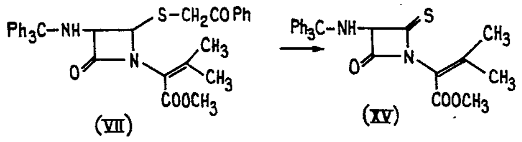
The obtained product XIV (yield 86%) in the form of a glassy solid, is sufficiently pure for the subsequent reaction (Example 10) and for being spectrophotometrically identified.

IR:
similar to that of XII

NMR ($CDCl_3$):
δ 2.06 (3H,s) and 2.28 (3H,s) $(CH_3)_2$ C = C, 4.36 (2H,s,OCH_2CO), 4.91 (1H,d, J = 8Hz,3-H), 5.17 (2H,s,$COOCH_2$), 6.60—7.60 (10H,m,aromatics), 7.94 (1H,d, J = 8Hz, NH).

Example 6.

Preparation of 1-(1-methoxycarbonyl-2-methyl-1-propenyl)-3-triphenylmethylamino-4-thioxo-2-azetidinone (XV).



The procedure is similar to that disclosed in Example 4 for the preparation of XII from XI, starting from the product VII prepared according to Example 1.

The thus-obtained product XV (yield 81%) in the form of a homogeneous foam is sufficiently pure for the next reaction (Example 11) but can be purified again, with low yields, by chromatography on a preparatory thin layer of silica gel eluting with benzene which contains 5% of ethyl acetate and extracting from the silica with chloroform the pure product in the form of a white foam.

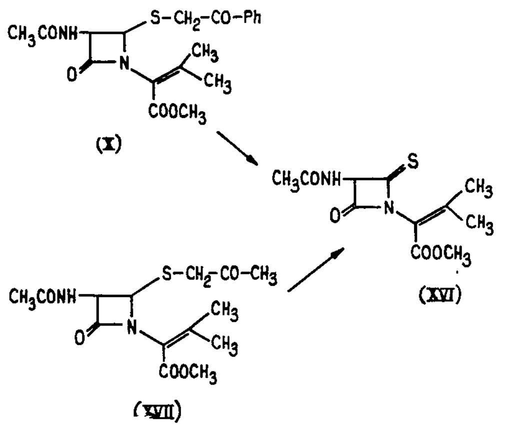
IR ($CHCl_3$):
ν max 3330 (NH), 3050 and 3020 (phenyls), 1810 (CO of the beta-lactam), 1720 (CO of the ester), 1620 (shoulder, C = C), 1595, 1590 and 1490 cm^{-1} (phenyls).

NMR ($CDCl_3$):
δ 1.81 (3H,s) and 2.26 (3H,s), $(CH_3)_2$ C = C, 2.80 (1H,d, J = 8Hz, NH), 3.67 (3H,s,$COOCH_3$), 4.75 (1H,d, J = 8Hz, 3-H), 7.10—7.70 (15H,m, aromatics).

Rotatory power:
$[\alpha]_D^{25}$ −1.4 (C = 1.00, $CHCl_3$).

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.

IR (CHCl$_3$):

νmax 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 (CDCl$_3$):

δ 2.00 (3H,s) and 2.32 (3H,s) [(CH$_3$)$_2$C = C], 2.08 (3H,s,CH$_3$CO), 3.73 (3H,s,COOCH$_3$), 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.

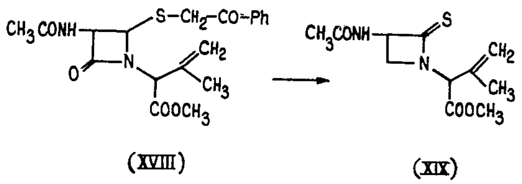
The gummy raw-product which is obtained cannot be crystallized and is unstable to chromatography and is conveniently used as such for the next reaction (Example 12a).

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)

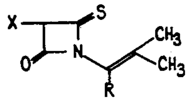


The procedure is similar to that disclosed in Example 4 for the preparation of XII from XI, starting from the product XVIII. The product XIX which is obtained (yield 78.5%) as a glassy solid is sufficiently pure for the next reaction and for being identified spectrophotometrically.

IR (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 ($CDCl_3$)
δ 1.88 (3H,s, CH_3—C = C), 2.07 (3H,s,CH_3CO—), 3.80 (3H,s,$COOCH_3$) 4.90—5.25 (4H,m,CH_2= C, 3-H and CHCOO), 7.50 (1H,d, J = 8Hz, NH).

WHAT WE CLAIM IS:—

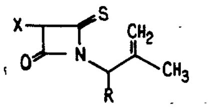
1. A 4-thioxo-2-azetidine having the formula:



(III)

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. A 4-thioxo-2-azetidinone having the formula:



(IIIa)

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.

3. 1-(1-methoxycarbonyl-2-methyl-1-propenyl)-3-phenoxyacetamido-4-thioxo-2-azetidinone.

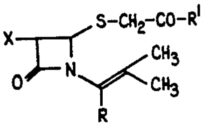
4. 1-(1-benzyloxycarbonyl-2-methyl-1-propenyl)-3-phenoxyacetamido-4-thioxo-2-azetidinone.

5. 1-(1-methoxycarbonyl-2-methyl-1-propenyl)-3-triphenylmethylamino-4-thioxo-2-azetidinone.

6. 1-(1-methoxycarbonyl-2-methyl-1-propenyl)-3-acetamido-4-thioxo-2-azetidinone.

7. 1-(1-methoxycarbonyl-2-methyl-2-propenyl)-3-acetamido-4-thioxo-2-azetidinone.

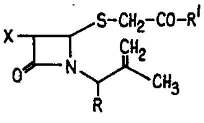
8. A process for the preparation of a 4-thioxo-2-azetidinone as claimed in claim 1, which comprises irradiating a 4-acylmethylthio-2-azetidinone having the formula:



(II)

wherein R' is an alkyl, aryl or aralkyl group, and X and R are as defined in claim 1.

9. A process for the preparation of a 4-thioxo-2-azetidinone as claimed in claim 2, which comprises irradiating a 4-acylmethylthio-2-azetidinone having the formula:



(IIa)

wherein R' is an alkyl, aryl or aralkyl group, and X and R are as defined in claim 2.

10. A process according to claim 8 or 9, wherein the irradiation is effected at a temperature of from −10 to 40°C.

11. A process according to any of claims 8 to 10, wherein the irradiation is effected in an anhydrous oxygen-free inert solvent.

12. A process according to claim 11, wherein the irradiation is effected under an inert atmosphere.

13. A process for the preparation of a 4-thioxo-2-azetidinone as claimed in claim 1 or 2, substantially as described in any of the foregoing Examples 4, 5, 6, 7 and 8.

14. A 4-thioxo-2-azetidinone as claimed in claim 1 or 2, whenever prepared by a process according to any of claims 8 to 13.

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