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Preparation and Isomerization of 3*S*-Benzylpenicilloamides[1]

J. J. Herak, M. Kovačević, and B. Gašpert

Research Department, Pliva Pharmaceutical and Chemical Works, Zagreb, Croatia, Yugoslavia

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The isomerization of 3*S*-benzylpenicillobenzylamide in aprotic solvents was studied by using ^{1}H NMR spectroscopy. The lack of isomerization of the *N*-acetyl derivative of I indicated that the epimerization at *C*-5 and *C*-6 position[2] proceeded through the open chain imine tautomer (III) of I or II. Since the isomerization at the *C*-6 position occurred after the opening of the thiazolidine ring, it was concluded that isomerization at this centre preceeded through penamaldic acid (IV) as an intermediate. All four isomers of 3*S*-benzylpenicillobenzylamide were prepared and isolated as methyl esters (II).

In the course of the preparation of D-penicillamine from the derivatives of penicilloic acid[3], we detected the isomerization of penicilloamides in aprotic solvents. The isomerization of penicilloamides in aqueous medium at different pH values has been reported[4,5]. It has been assumed that isomerization at pH 5 takes place through penamaldic acid to give all the four posible diastereoisomers as the product[4]. On the other hand, it was found that penicilloamides mutarotate in alkaline medium at a rate different from that of penicilloic acid and it was concluded that they isomerized by different mechanism, probably via carbanion resulting from the deprotonation of the asymmetric carbon alpha to carboxamide[5].

To study the isomerization of penicilloamides in aprotic solvents and to determine the product formed in the course of the isomerization, we prepared 6-epimers: 5R,6R- (Ia) and 5R,6S- (Ic) benzylpenicilloic acid alpha benzylamide.

5R,6R-isomer (Ia) was prepared according to the procedure described in »Chemistry of Penicillin« for alpha benzylamide[6] designated as »natural«. It has been shown that in the reaction of benzylamine with benzylpenicillin in ether, the obtained benzylpenicilloic acid alpha benzylamide had the same configuration as the natural benzylpenicillin, i. e, 3S,5R,6R[7].

This procedure was also used for the preparation of 5R,6S-isomer (Ic). In the reaction of benzylamine on 6-*epi*-benzylpenicillin, obtained according to Vanderhaeghe at al.[8], only one product was obtained, with the same R_f value on TLC as that of Ia, a higher melting point and a higher optical rotation. The ^{1}H NMR spectra of isomers Ia and Ic exhibited a significant difference only in the chemical shifts of C_3-H (Ia 3.60 ppm and Ic 3.83 ppm).

The heating of isomer Ia in benzene for a short time yielded a mixture of two products, detected on TLC as the starting isomer (Ia), with R_f value 0,79,

and a new one with R_f 0.77. The ^1H NMR spectrum of this mixture revealed the presence of 5R,6R-isomer (Ia) and of a new one, different from the 5R,6S--isomer (Ic). This was indicated by the presence of additional signals in the region (δ 4—5 and 1—2) assigned to the *C*-5 and *C*-6 protons and methyl groups, and by the lack of 3.8 ppm signal belonging to C_3-H of the isomer (Ic).

Since the reaction of phenylhydrazine with this mixture of isomers in benzene gave D-penicillamine in a high yield and purity, the isomerization at *C*-3 was improbable. It was concluded, therefore, that the isomerization occurred at the *C*-5 position due to the opening of the thiazolidine ring, and that 5S,6R-isomer was formed. This conclusion was also supported by the evidence that the thiazolidine ring in penilloic acid was opened under the same reaction conditions[9].

The obtained mixture of beta acids could not be well separated, therefore the mixture was transformed into beta methyl esters by treatment with diazomethane and then separated by column chromatography. Two esters were isolated: one with R_f value 0.44 on TLC, identified as 5R,6R-isomer (IIa) by correlation with the ester prepared by the treatment of the 5R,6R-isomer (Ia) with diazomethane[10], and another with R_f value 0.24, i. e. 5S,6R-isomer (IIb).

The mixture of two isomers obtained in the isomerization of the 5R,6S--isomer (Ic) was separated in the same way. The first one, with R_f 0.26, was identical to the ester (IIc) obtained in the reaction of diazomethane on the 5R,6S-isomer (Ic) and the second one, with R_f 0.41, was supposed to be the 5S,6S-isomer (IId).

Some data on the four prepared isomers of the alpha benzylamide of penicilloic acid beta methyl esters (IIa, b, c, d) are given in the Table.

The correlation between the chemical shift of the *C*-3 proton and the configuration at *C*-5 observed previously in carboxythiazolidines[11] was not noted in our case. This lack of correlation was previously noted with benzylpenicilloates[12].

Further study of isomerization revealed that any of the isomers of penicillobenzylamides, as beta acid or ester, yielded all the four isomers in the reaction product, upon prolonged heating in the low boiling solvents or short heating in the high boiling solvents.

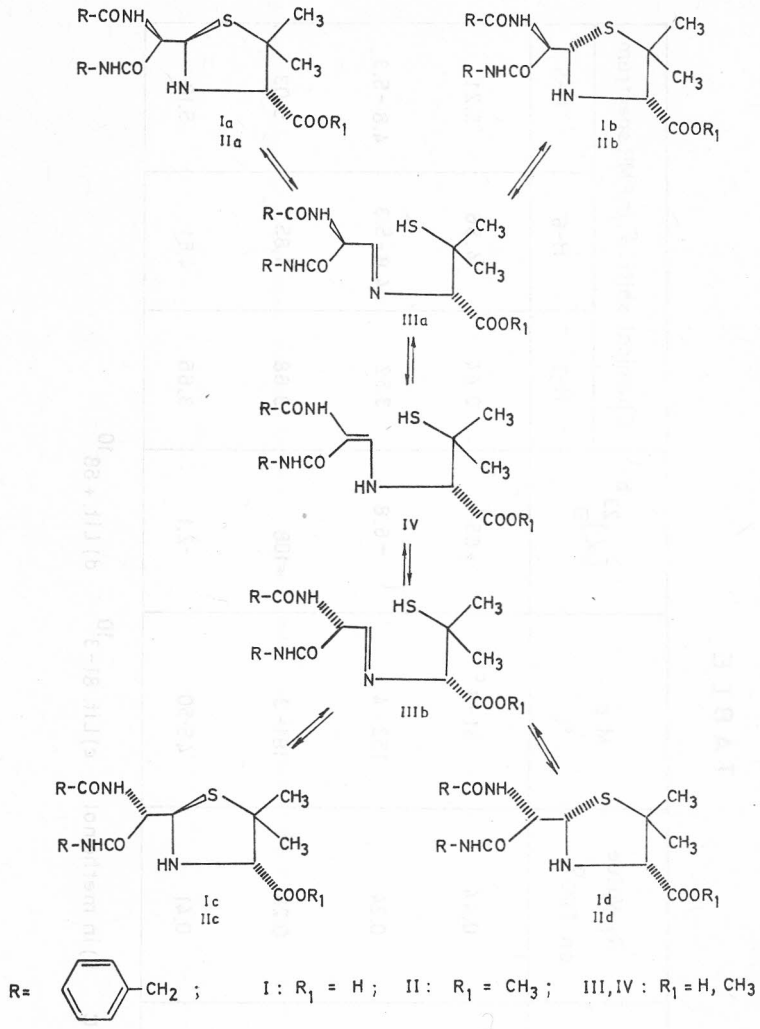
It can be concluded that epimerization takes place at the *C*-6 position only after the isomerization at the *C*-5 position has taken place, namely after the opening of the thiazolidine ring. In our previous report[9] we presented some evidence in favour of the idea, that in the course of the epimerization of benzylpenilloic acid in aprotic solvents or melted, the imine form could be one of the intermediates.

The isomerization of penicilloamides in aprotic solvents at low temperatures can be explained in terms of an imine intermediate III, formed by the opening of the thiazolidine ring. During prolonged heating or at a higher temperature another intermediate IV, in the form of penamaldic acid, is formed. The formation of intermediate IV explains the presence of all the four isomers in the obtained product.

TABLE

Compound	Configuration	R_f Value on TLC[a]	M.p °C	$[\alpha]_D^{23}$[b]	Chemical shift, δ, in PMR spectrum		
					H-3	H-6	H-5
IIa	5R,6R	0.44	81-3[c]	+65[d]	3.44	4.56	5.21
IIb	5S,6R	0.24	152-4	−6.8	3.52	4.8-5.3	4.8-5.3
IIc	5R,6S	0.26	181-3	+108	3.68	4.85	5.03
IId	5S,6S	0.41	45-50	-2.1	3.66	4.61	5.10

a) solvent system C b) in methanol c) Lit. 81-3[10] d) Lit. +68[10]



So far, no direct evidence of the existence of either of the given intermediates has been obtained. However, the proposed assumption is supported by the evidence that the *N*-acyl derivative of isomer (I) did not isomerize under the same reaction conditions as for isomers (I). The *N*-acyl group would prevent the opening of the thiazolidine ring into the open chain imine intermediate (III) and, consequently, also the formation of penamaldic acid (IV) as an intermediate in the equilibrium between two open chain imines.

EXPERIMENTAL

Melting points are uncorrected. The IR spectra were recorded with a Model 257 G Perkin-Elmer spectrometer. The ^{1}H NMR measurements were done with an A-60 Varian in DMSO-d_6 with TMS as the internal standard or in $CDCl_3$. TLC was conducted on silica gel plates (Merck, Kieselgel HF_{254}) followed by detection with

iodine vapour. Solvent systems, A: dichloromethane-methanol (4 : 1); B: *n*-buthanol--acetic acid- water (4 : 1 : 1); C: dichloromethane-ether (5 : 3).

3S,5R,6S-Benzylpenicillin

6-*epi*-benzypenicillin was obtained according to the method (b) given by Vanderhaeghe et al.[8]. Yield 70%, m. p. 153—6 °C; $[\alpha]_D^{23}$ + 198° (c 0.5, H_2O). Lit. m. p. 154—6 °C; $[\alpha]_D^{23}$ + 201° (c 0.5, H_2O).

3S,5R,6R-Benzylpenicilloic Acid Alpha Benzylamide (Ia)

3S,5R,6R-Benzylpenicilloic acid alpha benzylamide (Ia) was prepared according to the method described in »Chemistry of Penicilin«[6]. Yield 88%, m. p. 110—2 °C; $[\alpha]_D^{23}$ + 76.1° (c 0.5, MeOH); R_f 0.79 (system B). Lit. m. p. 110—3 °C; $[\alpha]_D^{22}$ + 88° (MeOH).

IR spectrum: 3300(vs), 1720(s), 1655(s), 1645(s), 1530(s), 1330(m), 1220(m), 720(m), 694(m) cm^{-1}.

^1H NMR spectrum (DMSO-d_6) δ : 1.20 (s, alpha CH_3), 1.51 (s, beta CH_3), 3.53 (s, $PhCH_2CO$), 3.60 (s, C_3—H), 4.27 (d, J = 6 Hz, $PhCH_2N$), 4.48 (dd, J = 9 and 9 Hz, C_6—H, 4.92 (d, J = 9 Hz, C_5—H), 7.30 (s, C_6H_5), 8.20—8.80 (m, CONH and NHCO).

3S,5R,6S-Benzylpenicilloic Acid Alpha Benzylamide (Ic)

(Ic) was prepared according to the method for (Ia) starting from 6-*epi*-benzylpenicillin. Yield 68% $[\alpha]_D^{23}$ + 135° (c 0.5, MeOH); R_f 0.79 (system B); m. p. 105—8 °C.

Anal. $C_{23}H_{27}N_3O_4S$ (441.53) calc'd.: C 62.56; H 6.18; N 9.52%
found: C 62.50; H 6.10; N 9.73%

IR spectrum: 3290(s), 1710(s), 1665(vs), 1630(vs), 1545(s), 1315(m), 1225(m), 725(m), 695(m) cm^{-1}.

^1H NMR spectrum (DMSO-d_6) δ: 1.24 (s, alpha CH_3), 1.58 (s, beta CH_3), 3.50 (s, $PhCH_2CO$), 3.83 (s, C_3—H), 4.30 (d, J = 7 Hz, $PhCH_2N$), 4.44 (dd, J = 10 and 10 Hz, C_6—H), 4.93 (d, J = 10 Hz, C_5—H), 7.35 (s, C_6H_5), 8.20—8.80 (m, CONH and NHCO).

N-*Acetyl-3S,5R,6R-benzylpenicilloic Acid Alpha Benzylamide (V)*

To a solution of 3S,5R,6R-benzylpenicilloic acid alpha benzylamide (Ia; 4.41 g, 0.01 mol) and triethylamine (3.0 g, 0.03 mol) in dichloromethane (50 ml), acetylchloride (2.35 g, 0.03 mol) was added dropwise at 15 °C. The reaction mixture was stirred at 20 °C for 3 hours and 0.1 mol/dm^3 hydrochloric acid (40 ml) was added. The dichloromethane layer was separated and water was (30 ml) added. After addition of 10% sodium hydroxide to pH 10, the water layer was separated, dichloromethane was added again (20 ml) and acidified with 10% hydrochloric acid to pH 2. The dichloromethane extract was dried over sodium sulphate and evaporated to dryness. Yield 3.22 g (67%). M. p. 101—5 °C.

Recrystallization from ether-petrolether gave an analytical sample with m. p. 103—7 °C; $[\alpha]_D^{23}$ — 193° (c 0.05, MeOH); R_f 0.67 (system B).

Anal. $C_{25}H_{29}N_3O_5S$ (483.56) calc'd.: C 62.09; H 6.04; N 8.69%
found: C 61.81; H 5.88; N 8.49%

IR spectrum: 3280(s), 1725(s), 1670(vs), 1640(vs), 1520(s), 1335(m), 1195(m), 723(m) cm^{-1}. ^1H NMR spectrum ($CDCl_3$) δ : 1.35 (s, alpha CH_3), 1.58 (s, beta CH_3), 1.80 (s, $COCH_3$), 3.48 (s, $PhCH_2CO$), 4.19 (s, C_3—H), 4.35 (d, J = 6 Hz, $PhCH_2N$) 5.13 (dd, J = 9 and 9Hz C_6—H), 5.90 (d, J = 9 Hz, C_3—H), 7.08 (d, J = 6 Hz, NHCO), 7.20 (s, $2C_6H_5$), 7.72 (d, J = 9 Hz, CONH).

3S,5R,6R-Benzylpenicilloic Acid Alpha Benzylamide Beta Methylester (IIa)

Beta methylester (IIa) was prepared from the corresponding beta acid (Ia) according to the procedure described in »Chemistry of Penicillin«[10]. Yield 80%; m. p. 81—3 °C; $[\alpha]_D^{23}$ + 65° (c 0.5, MeOH); R_f 0.44 (system C). Lit. m. p. 81—3 °C; $[\alpha]_D^{23}$ + 68° (c 0.45, MeOH).

IR spectrum: 3300(s), 1740(vs), 1645(vs), 1530(s), 1335(m), 1210(m), 740(m), 695(m) cm^{-1}. ^1H NMR spectrum ($CDCl_3$) δ : 1.20 (s, alpha CH_3), 1.50 (s, beta CH_3), 2.89 (s, N_4—H), 3.44 (s, C_3—H), 3.61 (s, $PhCH_2CO$), 3.79 (s, OCH_3), 4.39 (d, $J = 6$ Hz, $PhCH_2N$), 4.56 (dd, $J = 6$ and 14 Hz, C_6—H), 5.21 (d, $J = 6$ Hz, C_5—H), 6.7—6.9 (2 C_6H_5 and 2 CONH).

3S,5R,6S-Benzylpenicilloic Acid Alpha Benzylamide Beta Methylester (IIc)

Into a solution of beta acid (Ic; 2.2 g, 0.005 mol) in methanol (50 ml), an ether solution of diazomethane was added dropwise at 15 °C over 30 minutes. Reaction solution was stirred for an additional hour and then the solvent evaporated under reduced pressure. The residue was reprecipitated from aqueous ethanol. Yield 1.9 g (84 %); m. p. 168—172 °C.

Several reprecipitations from aqueous methanol gave the analytical sample with m. p. 181—3 °C; $[\alpha]_D^{23}$ + 108.3° (c 0.5, MeOH); R_f 0.26 (system C).

Anal. $C_{24}H_{29}N_3O_4S$ (455.55) calc'd.: C 63.27; H 6.42; N 9.22%
found: C 62.92; H 6.13; N 9.00%

IR spectrum: 3300(vs), 1740(s), 1640(vs), 1550(s), 1330(m), 1215 (s), 725(m), 695(m) cm^{-1}. ^1H NMR spectrum ($CDCl_3$) δ : 1.17 (s, alpha CH_3), 1.45 (s, beta CH_3), 3.33 (s, N_4—H), 3.53 (s, $PhCH_2CO$), 3.68 (s, C_3—H), 3.76 (s, OCH_3), 4.30 (d, $J = 6$ Hz, $PhCH_2N$), 4.85 (dd, $J = 6$ and 14 Hz, C_6—H), 5.03 (d, $J = 6$ Hz, C_5—H), 6.70—7.80 (2 C_6H_5 and 2 CONH).

3S,5S,6R-Benzylpenicilloic Acid Alpha Benzylamide Beta Methylester (IIb)

3S,5R,6R-Benzylpenicilloic acid alpha benzylamide beta methylester (IIa; 228 mg, 0.5 mmol) was dissolved in benzene (20 ml) and heated under reflux for four hours. The solvent was evaporated and the residue dissolved in dichloromethane and chromatographed on a silica gel column (20 g). The starting material was eluted with dichloromethane-ether (108 mg, 47.5%); R_f 0.44 (system C) followed by and oil (112 mg, 49%); R_f 0.24 (system C), which upon addition of ether crystallised. M. p. 152—4 °C; $[\alpha]_D^{23}$ — 6.86° (c 0.2, MeOH).

Anal. $C_{24}H_{29}N_3O_4S$ (455.55) calc'd.: C 63.27; H 6.42; N 9.22%
found: C 63.02; H 6.22; N 9.43%

IR spectrum: 3280(vs), 1740(s), 1640(vs), 1560(s), 1270(m), 1170(m), 875(m), 730(m), 695(s) cm^{-1}.

^1H NMR spectrum ($CDCl_3$) δ : 0.92 (s, alpha CH_3), 1.61 (s, beta CH_3), 3.40 (s, N_4—H), 3.52 (s, C_3—H), 3.62 (s, $PhCH_2CO$), 3.77 (s, OCH_3), 4.43 (d, $J = 6$ Hz, $PhCH_2N$), 4.80—5.30 (m, C_6—H and C_5—H), 6.70—7.70 (m, 2 C_6H_5 and 2 CONH).

3S,5S,6S-Benzylpenicilloic Acid Alpha Benzylamide Beta Methylester (IId)

3S,5R,6S-Benzylpenicilloic acid alpha benzylamide beta methylester (IIc; 228 mg, 0.5 mmol) was dissolved in benzene (20 ml) and heated under reflux for four hours. The solvent was evaporated and the residue dissolved in dichloromethane and chromatographed on a silica gel, column (20 g). Elution with dichloromethane gave the starting material (1.25 mg, 55%); R_f 0.26 (system C) and an oily product (92 mg, 40%) which upon addition of ether gave a crystalline product. M. p. 45—50 °C; R_f 0.41 (system C); $[\alpha]_D^{23}$ — 2.11 (c 0.2, MeOH).

Anal. $C_{24}H_{29}N_3O_4S$ (455.55) calc'd.: C 63.27; H 6.42; N 9.22%
found: C 63.00; H 6.13; N 9.02%

IR spectrum: 3290(s), 1740(s), 1650(vs), 1540(s), 1260(m), 1030(m), 800(m), 695(s) cm^{-1}. ^1H NMR spectrum ($CDCl_3$) δ: 1.23 (s, alpha CH_3), 1.58 (s, beta CH_3), 2.83 (s, N_4—H), 3.63 (s, $PhCH_2CO$), 3.66 (s, C_3—H), 3.76 (s, OCH_3), 4.33 (d, $J = 6$ Hz, $PhCH_2N$), 4.61 (dd, $J = 5$ and 8 Hz, C_6—H), 5.10 (d, $J = 5$ Hz, C_5—H), 6.90—8.10 (m, 2 C_6H_5 and 2 CONH).

N-Acetyl-3S,5R,6R-Benzylpenicilloic Acid Alpha Benzylamide Beta Methylester (VI)

Into a solution of *N*-acetyl-3S,5R,6R-benzylpenicilloic acid alpha benzylamide (1.20 g, 0.004 mol) in methanol (50 ml), an ether solution of diazomethane was added

dropwise at 15 °C over 30 minutes. The reaction solution was stirred for additional hour and then the solvent evaporated under reduced pressure. Yield 1.23 g (100%); m. p. 60—7 °C.

For analysis the crude product was chromatographed on a silica gel column (10 g). Elution with dichloromethane-ether gave the product with m. p. 65—8 °C; $[\alpha]_D^{23}$ — 37.2° (c 0.05, MeOH); R_f 0.49 (system C).

Anal. $C_{26}H_{31}N_3O_5S$ (497.59) calc'd.: C 62.75; H 6.28; N 8.44%
found: C 62.73; H 6.00; N 8.84%

IR spectrum: 3280(s), 1750(s), 1650(vs), 1520(s), 1335(m), 1200(m), 1025(v), 725(m), 695(s) cm^{-1}.

^1H NMR spectrum ($CDCl_3$) δ: 1.33 (s, alpha CH_3), 1.67 (s, beta CH_3), 1.80 (s, OCH_3), 3.45 (s, $PhCH_2CO$), 3.72 (s, OCH_3), 4.20 (s, C_3—H), 4.32 (d, J = 6 Hz, $PhCH_2N$), 4.87 (dd, J = 8 and 9 Hz, C_6—H), 5.88 (d, J = 9 Hz, C_5—H), 6.70—7.70 (m, 2 C_6H_5 and 2 CONH).

Epimerization of Benzylpenicilloic Acid Alpha Benzilamide (I)

1. a) 3S,5R,6R-isomer (Ia; 0.2 g) was heated in benzene (10 ml) under a reflux for an hour. The reaction mixture was evaporated to dryness under reduced pressure (two spots by TLC, with R_f 0.79 and 0.77, in solvent system B). A part of the residue (60 mg) was dissolved in DMSO-d_6 and the ^1H NMR spectrum recorded (mixture of Ia and Ib).
The other part was dissolved in methanol (10 ml), an ether solution of diazomethane was added and stirred for an hour at room temperature. The solvent was evaporated and the residue was chromatographed on a silica gel column. The physical and spectral data of the separated isomers were identical with those reported for IIa and IIb.

   b) 3S,5R,6R-isomer (Ia) was heated in xylene for an hour under reflux. The reaction mixture was evaporated to dryness under reduced pressure (two spots by TLC, with R_f 0.79 and 0.77, in solvent system B).
The sample (60 mg) was dissolved in DMSO-d_6 and the ^1H NMR spectrum recorded (mixture of isomers I). One part was dissolved in methanol (10 ml), an ethereal solution of diazomethane was added and then it was stirred at 25 °C for an hour. Four isomers (II) with R_f values 0.44, 0.41, 0.26 and 0.24 were detected (solvent system C).
The other part (441 mg, 1 mmol) was dissolved in xylene (10 ml), phenylhydrazine (216 mg, 2 mmol) was added and the mixture was heated under reflux for an hour. D-penicillamine was separated. Yield 120 mg (83.7%); $[\alpha]_D^{23}$ — 60° (c 5, 4%, NaOH).

2. a) 3S,5R,6*S*-isomer (Ic; 0.2 g) was heated in benzene (10 ml) under reflux for an hour. The reaction mixture was treated as in 1.a. (Two spots by TLC, with R_f 0.79 and 0.77 in solvent system B). After reaction with diazomethane and column chromatography as in 1.a. the physical and spectral data of the separated isomers were identical with those reported for IIc and IId.

   b) 3S,5R,6*S*-isomer (Ic) was heated in xylene for an hour and the product treated as in 1.b. (two spots by TLC, with R_f 0.79 and 0.77, solvent system B). After reaction with diazomethane as in 1.b. TLC detected four isomers, with R_f values 0.44, 0.41, 0.26 and 0.24 (solvent system C).

   c) The reaction with phenylhydrazine gave D-penicillamine as in 1.b.

3. 3S,5R,6R-isomer (V) was treated as in 1.b. The ^1H NMR spectrum, optical rotation and R_f value of the reaction product were identical to those of starting material. After reaction with diazomethane ester (VI) was obtained. There was no reaction with phenylhidrazine, treated as in 1.b.

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SAŽETAK

Dobivanje i izomerizacija 3*S*-benzilpeniciloamida

J. J. Herak, M. Kovačević i B. Gašpert

Proučavana je izomerizacija 3*S*-benzilpeniciloamida u aprotičnim otapalima primjenom ^{1}H NMR-spektroskopije. Budući da *N*-acil derivati od I ili II (V) ne izomeriziraju u položaju *C*-5 i *C*-6, pretpostavlja se da je iminski tautomer III međuprodukt u toj reakciji. Kako do izomerizacije u položaju *C*-6 dolazi tek nakon epimerizacije u položaju *C*-5, tj. nakon otvaranja tiazolidinskog prstena to se pretpostavlja da je penamaldinska kiselina (IV) daljnji međuprodukt u reakciji izomerizacije u položaju *C*-6. Sva četiri izomera 3*S*-benzilpeniciloben zilamida priređeni su kao kiseline i kao metilesteri.

PLIVA — TVORNICA FARMACEUTSKIH
I KEMIJSKIH PROIZVODA
41000 ZAGREB

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