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Isomerisation of *N*-Acyl Benzylpenilloic Acid in Acetic Anhydride and Formation of 7,7-Dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octan-2-one

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The heating of *N*-acyl benzylpenilloic acids (II) in acetic anhydride gave an equilibrium mixture of C-4 epimers, due to the epimerisation at C-4 position. Cyclisation of the 2-amidomethyl and 4-carboxylic group of IIb or IIc into a 2-ketopiperazine ring gave 1*S*,5*S* or 1*R*,5*R* enantiomer of III. Alkaline hydrolysis of III gave IV and II. When *N*-formyl group was present, IV and II upon acid hydrolysis yielded V and I. The C-4 epimers (Ib or Ic) can be prepared from *trans* C-2, C-4 substituted C-4 epimers (Id or Ia) via II and III.

INTRODUCTION

The recent study of the isomerisation of benzylpenilloic acid in aprotic solvents revealed the epimerisation of 2-amidomethyl derivatives of thiazolidine-4-carboxylic acid at the C-2 position due to opening of the thiazolidine ring.[1] The same course of the isomerisation took place when benzylpenicilloamides were heated for a short time in low boiling aprotic solvents. After prolonged heating, the isomerisation occured also at the asymmetric carbon alfa to the C-2 position due to the formation of a penamaldic acid intermediate[2]. The isomerisation at C-4 position was not detected during the heating of these compounds in aprotic solvents.[1,2] However, the epimerisation at this position occured when thiazolidine-4-carboxylic acid derivatives were heated in inert solvents above 60 °C in the presence of catalytic amounts of acetic anhydride, acetyl chloride or phosphorus trichloride.[3] On the other hand, 2--amidomethyl derivatives of thiazolidine-4-carboxylic acid submitted to acetylation procedure resulted in the cyclisation of the amido and carboxylic group into 2-ketopiperazine ring to give 6-thia-3,8-diazabicyclo-(3,2,1)octan-2--one.[4,6,7] D. J. Cram et al. isolated racemic 8-acetyl-7,7-dimethyl-6-thia-3,8--diazabicyclo-(3,2,1)octan-2-one (IV), by treatment of residues from commercial production of penicillin with acetic anhydride.[5] They confirmed this structure by synthesis from penicillamine and demonstrated that the same, but optically active product was formed when benzylpenilloic acid was submitted to acetylation procedure. A. S. Khokhlow et al. obtained 3,8-diacyl derivatives (III) in the reaction of *N*-acyl penilloic acid with acyl anhydrides.[6,7]

The stereochemistry and configuration of the two asymmetric centers of IV have been discussed by Cram et al. Although this molecule can theoreti-

cally exist in four stereochemical forms, two were clearly eliminated on geometric grounds. Since IV was obtained from D-(+)-benzylpenilloic acid, with uncertain C-2 but definite 4*S* configuration, the projection formula IVb with 1*S*, 5*S* configuration was suggested for the optical active 8-acetyl derivative.[4] However, the epimerisation at C-4 position during acetylation of D-(+)-benzylpenilloic acid cannot be excluded on the basis of the procedure reported for the racemisation of *N*-formyl-L-penicillamine, by the treatment of *N*-formyl-2,2,5,5-tetramethyl-thiazolidine-4-carboxylic acid with acetic anhydride.[8] It seemed of interest to study the epimerisation at the C-4 position of 2-amidomethyl derivatives of thiazolidine -4-carboxylic acid in the presence of acetic anhydride and to prove the configuration of 6-thia-3,8-diazabicyclo(3,2,1)octan-2-one structure. The results of a research of this kind using D-benzylpenilloic acid are presented here and the mechanism of the epimerisation is also discussed.

A recent X-ray crystallografic analysis of D-alfa-benzylpenilloic acid enabled us to determine the configuration of the epimers of benzylpenilloic acid and the corresponding *N*-acetyl derivatives.[9,1]

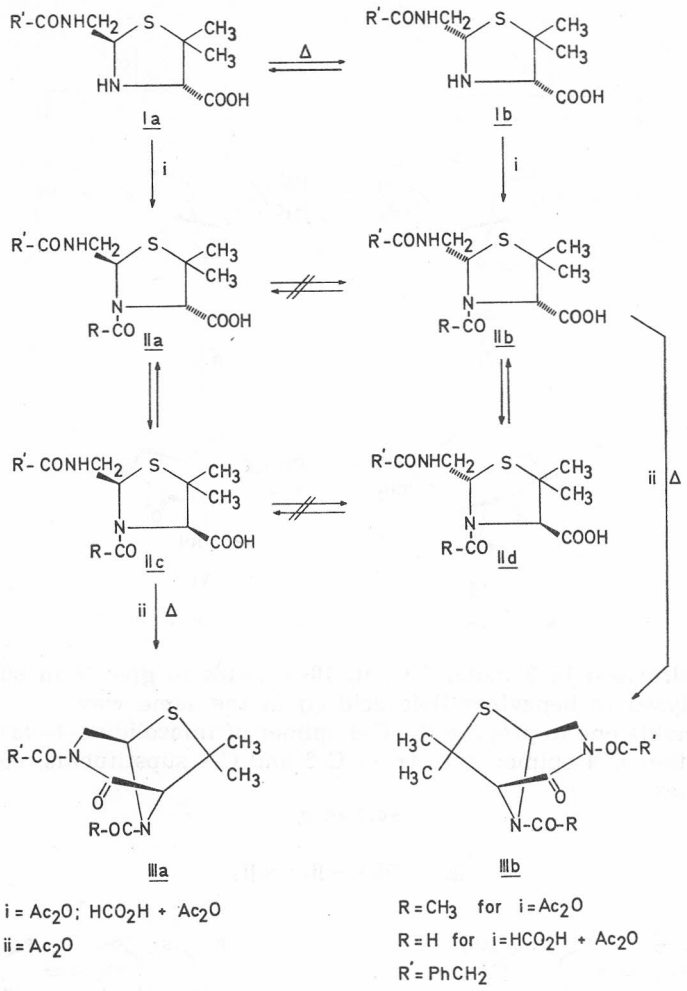
The heating of 2*R*, 4*S* (Ia) or 2*S*, 4*S* (Ib) epimer of benzylpenilloic acid in acetic anhydride, gave racemic 3,8-diacyl derivatives of 7,7-dimethyl-6--thia-3,8-diazabicyclo(3,2,1)octan-2-one (III). It can be concluded that in the course of the reaction, isomerisation occured at the C-2 and C-4 position. However, *N*-acyl derivatives of 2*R*, 4*S* or 2*S*, 4*S* epimer of benzylpenilloic acid (IIa, IIb) heated in acetic anhydride under the same reaction conditions as above mentioned, gave the optical active product. The same melting point R_f value, IR and ^{1}H NMR spectra, and the same value of optical rotation but of opposite sign, indicated the enantiomeric relationship of IIIa and IIIb.

It has been shown that the isomerisation of *N*-acyl derivatives of penilloic acid was prevented at the C-2 position when the *N*-acyl group was present.[1] Thus, the formation of 6-thia-3,8-diazabicyclo(3,2,1)octan-2-one from 2*R*,4*S*--*N*-acyl benzylpenilloic acid (IIa), clearly indicates that the 2*R*, 4*R* isomer (IIc) should also be present in the reaction, because only a *cis* stereoisomer can give a 2-ketopiperazine ring. It follows, that in the course of the reaction the epimerisation of *N*-acyl penilloic acid takes place at C-4 position, to give the equillibrium mixture of C-4 epimers prior to cyclisation into the 2-ketopiperazine ring. The lack of optical activity of the product obtained from benzylpenilloic acid could be in part explained in terms of the epimerisation of 2*R*,4*S* (Ia) and 2*S*,4*S* (Ib) epimers at the C-2 position prior to acetylation.

It should be noted that additional evidence supporting the mechanism proposed in scheme I are the products obtained after hydrolysis of the enantiomers IIIa and IIIb.

Of the three amide groups present in III, only two are readily hydrolysed. Alkaline hydrolysis of the 3-acyl group and the cleavage of the 2-ketopiperazine ring proceed in aqueous alcohol at a similar rate, while in aqueous solution hydrolysis of the 3-acyl group is predominant.[7] An enantiomer of III subjected to alcaline hydrolysis provided the corresponding enantiomer of IV and enantiomer of II. It is significant that only the enantiomer IIIb upon hydrolysis gave the starting epimer of *N*-acyl benzylpenilloic acid (IIb). The enantiomer IIIa on the contrary yielded 2*R*,4*R*-*N*-acyl benzylpenilloic acid (IIc), i. e. the C-4 epimer of the starting 2*R*,4*S*-*N*-acyl benzylpenilloic acid.

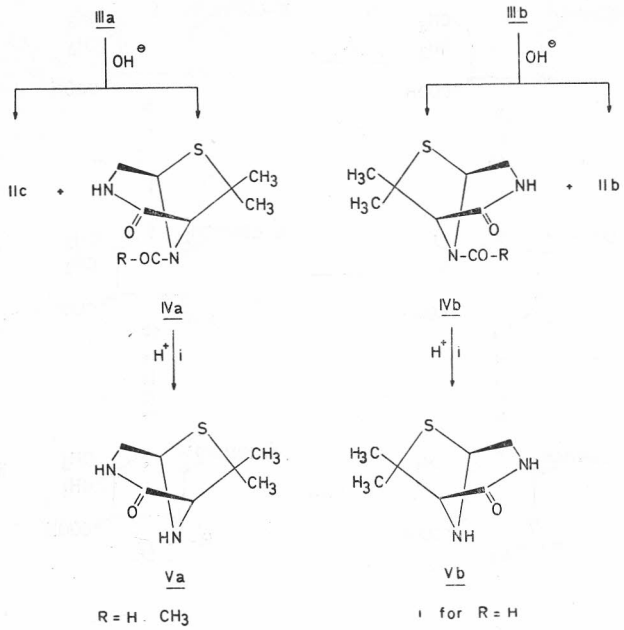
SCHEME I



The obtained results can be compared to those obtained by Cram et al. The sign and the value of the optical rotation ([α] — 87.7°) of 1*R*,5*R* enantiomer (IVa; R = CH_3) coresponds to that of ([α] — 80°) reported by Cram for the optical active product assignated as 1*S*,5*S* enantiomer. The high value of optical rotation of this product in relation to the racemic product obtained from Ia or Ib in our case may be rationalised in terms of the use of pyridine in the acetylation procedure, which favours the formation of *N*-acetyl derivatives prior to epimerisation at C-2 position. In fact, 2*R*,4*S*-benzylpenilloic acid subjected to the acetylation procedure reported by Cram, gave IIIa (R = CH_3) and only after chromatography on alumina, was the optical active product IVa obtained.

It was found that hydrolysis of the third amido group at *N*-8 position was facilitated when *N*-formyl was present as the *N*-acyl group. In this case

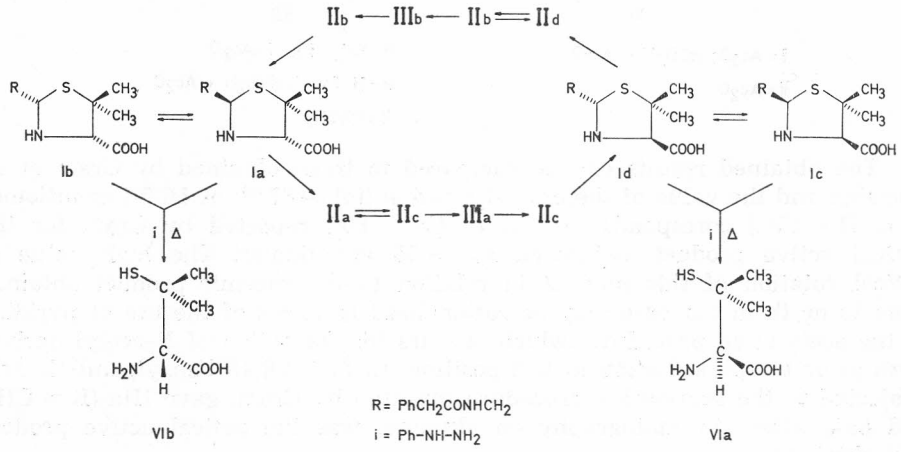
SCHEME II



IV was hydrolysed in 2 molar HCl in 10 minutes to give V in 90% yield. II was hydrolysed to benzylpenilloic acid (I) in the same way.

This enable one to prepare the C-4 epimer of thiazolidine-4-carboxylic acid from the other C-4 epimer with *trans* C-2 and C-4 supstituents, *via* II and III intermediates.

SCHEME III



Furthermore, this procedure can be used as a method for the preparation of one enantiomer of beta-mercapto alfa-amino-acids from the other one via

II and III.[10] In this method one avoids the use of the racemic procedure followed by the resolution of racemic mixture with an optical active agent as reported for 2,2,5,5-tetramethyl-thiazolidine-4-carboxylic acid.[8] By using this procedure D-penicillamine (VIb) can be prepared from L-benzylpenilloic acid (Id), via IId, IIIb and IIb, followed by the reaction of Ia or Ib with phenylhydrazine. On the same way L-penicillamine (VIa) can be prepared from D-benzylpenilloic acid (Ia) via IIa, IIIa and IIc.

EXPERIMENTAL

Melting points stand uncorrected. The IR spectra were recorded in potassium bromide plates with a Model 257G Perkin Elmer spectrometer. The ^{1}H NMR measurements were done with an A-60 Varian in $CDCl_3$, unless otherwise stated, with TMS as the internal standard. TLC was conducted on original plates (Merck, Kieselgel HF_{254}) followed by detection with iodine vapour in the solvent system: n-butanol-acetic acid-water (4 : 1 : 1).

2*R*,4*S*-2-Phenylacetamidomethyl-5,5-dimethyl-thiazolidine-4-carboöylic acid (D--alfa-benzylpenilloic acid monohydrate) (Ia), 2*S*,4*S*-2-Phenylacetamidomethyl-5,5- dimethyl-thiazolidine-4-carboxylic acid (D-beta-benzylpenilloic acid) (Ib), 2*R*,4*S*-2-Phenylacetamidomethyl-3-acetyl-5,5-dimethyl-thiazolidine-4-carboxylic acid hemihydrate (*N*-acetyl-D-alfa-benzylpenilloic acid hemihydrate) (IIa; R=CH_3), and 2*S*,4*S*-2-Phenylacetamidomethyl-3-acetyl-5,5-dimethyl-tiazolidine-4-carboxylic acid (*N*-acetyl-D--beta-benzylpenilloic acid) (IIb; R=CH_3) were prepared according to procedure described in a previous publication.[1]

2R,4S-2-Phenylacetamidomethyl-3-formyl-5,5-dimethyl-thiazolidine-4-carboxylic acid (N-formyl-D-alfa-benzylpenilloic acid) (IIa; R=H)

2*R*,4*S*-Benzylpenilloic acid monohydrate (Ia; 25.86 g, 0.0793 mol) was dissolved in formic acid (164 ml, 3.23 mol), cooled to 10 °C and acetic anhydride (66.5 ml, 0.705 mol) added dropwise during 2 hours. The reaction mixture was stirred for additional 2 hours and then submitted to distillation under reduced pressure. The residue was dissolved in dichloromethane (120 ml), extracted with water (60 ml) and made alkaline with 10% NaOH till pH=10. The aqueous layer was washed with dichloromethane (2 × 60 ml) and then acidified with 2 molar HCl till pH=2, followed by extraction with dichloromethane (2 × 60 ml). The organic layer was dried over sodium sulphate and evaporated to dryness; yield 24.85 g (93%) of IIa (R=H); R_f 0.70; m. p. (70—6) °C.

For analysis, the crude product was reprecipitated from alkaline solution with acid; m. p. (74—6) °C; $[\alpha]_D^{23}$ + 83.3° (c = 0.5, MeOH).

Anal. $C_{16}H_{20}N_2O_4S$ (336.5) calc'd: C 57.10; H 5.99; N 8.33%
found: C 56.85; H 6.20; N 8.39%

^{1}H NMR spectrum δ: 1.36, 1.45, 1.52 (3 s, C_5—$(CH_3)_2$, 3.58 (s, $PhCH_2$), 3.50—3.90 (m, 720 (s), 690 (s) cm^{-1}.

^{1}H NMR spectrum δ: 1,36, 1.45, 1.52 (3 s, C_5—$(CH_3)_2$, 3.58 (s, $PhCH_2$), 3.50—3.90 (m, N—CH_2), 4.29, 4.56 (2 s, C_4—H), 5.15—5.50 (m, C_2—H), 7.10—7.50 (m, C_6H_5, CONH), 8.32 (s, NCHO). Lit.[11]

2S,4S-2-Phenylacetamidomethyl-3-formyl-5,5-dimethyl-thiazolidine-4-carboxylic acid (N-formyl-D-beta-banzylpenilloic acid) (IIb; R=H)

According to the above procedure 2*S*,4*S*-benzylpenilloic acid (Ib) gave 82% of IIb (R=H); m. p. 179—182 °C; $[\alpha]_D^{23}$ + 13.66° (c = 0.5, MeOH); R_f = 0.78.

Anal. $C_{16}H_{20}N_2O_4S$ (336.5) calc'd: C 57.10; H 5.99; N 8.33%
found: C 56.80; H 6.00; N 8.07%

IR spectrum: 3340 (s), 2740 (m), 2460 (s), 1720 (vs), 1660 (vs), 1610 (vs), 1540 (s), 1365 (vs), 1265 (vs), 1196 (s), 1120 (m), 986 (m), 725 (s), 690 (s) cm^{-1}.

^1H NMR spectrum δ: 1.48 (s, C_5—$(CH_3)_2$), 3.54 (s, $PhCH_2CO$), 3.45—4.00 (m, NCH_2), 4.30, 4.69 (2s, C_4—H), 5.10—5.50 (m, C_2—H), 7.23 (s, C_6H_5), 7.30—7.70 (b, CONH), 8.10 (s, NCHO).

1R,5R-3-Phenylacetyl-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octane-2-one (IIIa; R=CH_3)

N-Acetyl 2*R*,4*S*-benzylpenilloic acid hemihydrate (IIa; R=CH_3) (3.59 g, 0.01 mol) in acetic anhydride (20 ml) was stirred under reflux for 10 minutes. After cooling the reaction mixture to 5 °C, the precipitate was filtered; yield 3.1 g (93.5%) of IIIa (R=CH_3); m. p. (150—4) °C.

For analysis, the crude product was re-crystallized from ethanol; m. p. (154—6) °C; $[\alpha]_D^{23}$ — 76.6° (c = 0.5, CH_2Cl_2); R_f = 0.88. Lit[6] m. p. (121—3) °C; lit[7] m. p. 134—136.5 °C. IR and ^1H NMR spectral data correspond to spectral data given in literature.[7]

1S,5S-3-Phenylacetyl-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octan-2-one (IIIb; R=CH_3)

According to the above procedure, *N*-acetyl-2*S*,4*S*,-benzylpenilloic acid (IIb; R=CH_3) gave 90% of IIIb (R=CH_3); m. p. (154—6) °C; $[\alpha]_D^{23}$ + 77.7° (c = 0.5, CH_2Cl_2); R_f = 0.88.
IR and ^1H NMR spectra identical to spectra of IIIa (R=CH_3).

3-Phenylacetyl-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octan-2-one (III; R=CH_3)

2*R*,4*S*-Benzylpenilloic acid monohydrate (Ia) or 2*S*,4*S*-benzylpenilloic acid (Ib) heated in acetic anhydride according to the above procedure gave a 90% yield of III (R=CH_3); m. p. (154—6) °C; $[\alpha]_D^{23}$ 0° (c = 0.5, CH_2Cl_2); R_f = 0.88.
IR and ^1H NMR spectra identical to spectra of IIIa and IIIb (R=CH_3).

1R,5R-3-Phenylacetyl-8-formyl-7,7-dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octan-2-one (IIIa; R=H)

N-Formyl 2*R*,4*S*-benzylpenilloic acid (IIa; R=H) (29.55 g, 0.087 mol) in acetic anhydride (295 ml) was heated under reflux for 15 minutes. The reaction mixture was cooled to 25 °C and evaporated under reduced pressure. The residue was dissolved in benzene and evaporated again to dryness, dissolved in methanol and the solution stirred at 25 °C for 30 minutes. IIIa (R=H) crystallized from the solution and was collected by filtration; yield 20.2 g (72%); m. p. 156—160 °C.

Re-crystallization from methanol gave an analytical sample with m. p. 159—161 °C; $[\alpha]_D^{23}$ — 108.7° (c = 0.5, $CHCl_3$); R_f = 0.91.

Anal. $C_{16}H_{18}N_2O_3S$ (318.23) calc'd: C 60.34; H 5.70; N 8.80%
found: C 60.47; H 5.49; N 8.55%

IR spectrum: 2960 (m), 1675 (vs), 1420 (s), 1400 (s), 1375 (s), 1290 (m), 1275 (s), 1260 (s), 1215 (vs), 1185 (vs), 1085 (s), 740 (s), 725 (s) cm^{-1}.

^1H NMR spectrum δ: 1.39 (s, C_7—$(CH_3)_2$), 3.87 (d, J = 3, C_4—H_2), 4.10, 4.87 (2 s, C_1—H), 4.30 (s, $PhCH_2CO$), 5.46, 6.40 (2 t, J = 3, C_5—H), 7.25 (s, C_6H_5), 8.06, 8.30 (2 s, NCHO).

1S,5S-3-Phenylacetyl-8-formyl-7,7-dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octan-2-one (IIIb; R=H)

N-Formyl 2*S*,4*S*-benzylpenilloic acid (IIb; R=H) heated in acetic anhydride according to the above procedure gave the product IIIb (R=H), re-crystallized from methanol; m. p. (160—2) °C; $[\alpha]_D^{23}$ + 110° (c = 0.5, $CHCl_3$); R_f = 0.91.
IR and ^1H NMR spectra identical to spectra of IIIa (R=H).

Hydrolysis of IIIb ($R=CH_3$)

(a) 1S,5S-8-Acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo-(3,2,1)-octan-2-one (IVb; $R=CH_3$). — IIIb ($R=CH_3$) (6.65 g, 0.02 mol) was suspended in 2% NaOH (100 ml) and stirred at 25 °C for 15 hours. Traces of undissolved material were filtered and the filtrate was extracted with dichloromethane (3 × 50 ml). The organic layer was dried over sodium sulphate and evaporated to dryness; yield 1.33 g (31%) of IVb ($R=CH_3$); m. p. 217—223 °C.

For analysis, the crude product was re-crystallized from ethylacetate; m. p. 228—230 °C; $[\alpha]_D^{23}$ + 98.32° (c = 0.5, CH_2Cl_2); R_f = 0.65.

Anal. $C_9H_{14}N_2O_2S$ (214.28) calc'd: C 50.45; H 6.59; N 13.07%
found: C 50.71; H 6.76; N 13.23%

IR spectrum: 3200 (s), 1680 (vs), 1650 (vs), 1390 (s), 1300 (s), 1225 (m), 1010 (m), 960 (m), 880 (m), 670 (w) cm^{-1}.

^1H NMR spectrum (DMSO-d_6; at 78 °C) δ: 1.38, 1.53 (2 s, C_7—$(CH_3)_2$), 2.15 (s, $COCH_3$), 3.00—4.00 (m, C_4—H_2), 4.45 (s, C_1—H), 5.70—6.15 (m, C_5—H), 7.5—7.8 (b, NH).

(b) N-Acetyl 2S,4S-benzylpenilloic acid (IIb; $R=CH_3$). — The aqueous layer, after extraction, was acidified with 1 molar HCl till pH = 2 and then extracted with dichloromethane (3 × 30 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The oily residue was dissolved in methanol (10 ml) and water added till the crystallization of IIb ($R=CH_3$); yield 4.7 g (66.4%); m. p. (182—4) °C; $[\alpha]_D^{23}$ — 27.5° (c = 0.5, MeOH).

Hydrolysis of IIIa ($R=CH_3$)

(a) 1R,5R-8-Acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo-(3,2,1)octan-2-one (IVa; $R=CH_3$) — IIIa ($R=CH_3$) hydrolysed according to the above procedure gave 40% of IVa; m. p. 228—230 °C; $[\alpha]_D^{23}$ — 87.7° (c = 0.5, CH_2Cl_2); R_f = 0.65.

IR and ^1H NMR spectra identical to spectra of IVb.

(b) N-Acetyl 2R,4R-benzylpenilloic acid (IIc; $R=CH_3$). — IIc ($R=CH_3$) was isolated from the aqueous layer in 55% yield; m. p. (180—2) °C; $[\alpha]_D^{23}$ + 26.5° (c = 0.5, MeOH).

IR and ^1H NMR spectra identical to spectra of IIb ($R=CH_3$).

Hydrolysis of III ($R=CH_3$)

III ($R=CH_3$) hydrolysed according to the above procedure, gave the product IV ($R=CH_3$) in a 45% yield; m. p. 228—230 °C; $[\alpha]_D^{23}$ 0° (c = 0.5, CH_2Cl_2); R_f = 0.65. IR and ^1H NMR spectra identical to spectra of IVa and IVb ($R=CH_3$)

Preparation of IIIa and IVa According to Cram's Procedure[4]

D-alfa-Benzylpenilloic acid monohydrate (Ia) (3.26 g, 0.01 mol) was added to acetic anhydride (20 ml) and pyridine (20 ml), and heated at 100 °C for 4 hours. The product was cooled, poured on ice an made basic with saturated sodium carbonate solution. The product was extracted with chloroform (40 ml), while the organic layer was washed with water, with diluted sulfuric acid, with water and dried. Evaporation of chloroform gave an oil which crystallized upon addition of ether. Yield 2.4 g (72%) of IIIa ($R=CH_3$). Recrystallization from ethanol gave m. p. (152—4) °C; $[\alpha]_D^{23}$ — 60° (c = 0.5, CH_2Cl_2); R_f = 0.88.

A sample (200 mg) in dichloromethane was adsorbed on a column of basic alumina, and eluted with dichloromethane-benzene solution. Evaporation of the eluate gave 130 mg of crystalline material (98%); m. p. 228—230 °C; $[\alpha]_D^{23}$ — 82° (c = 0.5, CH_2Cl_2); R_f = 0.65. Lit.[4]: m. p. 210—231 °C; $[\alpha]_D^{23}$ — 80° (c = 2, $CHCl_3$).

Hydrolysis of IIIa (R=H)

(a) 1R,5R-8-Formyl-7,7-dimethyl-6-thia-3,8-diazabicyclo(3,2,1)-octan-2-one (IVa; R=H). — IIIa (R=H) hydrolysed according to the above procedure gave 36.6% of IVa (R=H).

Re-crystallization from ethylacetate gave an analytical sample with m. p. 169—171 °C; $[\alpha]_D^{23}$ — 161.2° (c = 0.5, CH_2Cl_2); R_f = 0.74.

Anal. $C_8H_{12}N_2O_2S$ (200.0) calc'd: C 48.00; H 6.00; N 14.00%
found: C 47.77; H 6.16 N 14.19%

IR spectrum: 3190 (vs), 3060 (s), 1665 (vs), 1400 (vs), 1330 (s), 1260 (s), 1010 (s), 780 (m), 640 (m) cm^{-1}.

^1H NMR spectrum δ: 1.44, 1.65 (2 s, C_7—/CH_3/$_2$), 3.20—4.01 (m, C_4—H_2), 4.03, 4.77 (2s, C_1—H), 5.48, 6.04 (2 d, C_5—H), 6.30—7.10 (m, CONH), 8.15, 8.37 (2 s, NCHO)

(b) N-Formyl 2R,4R-benzylpenilloic acid (IIc; R=H). — IIc (R=H) was isolated from the aqueous layer in a 57.8% yield; m. p. 179—182 °C; $[\alpha]_D^{23}$ — 13.9° (c= 0.5, MeOH); R_f = 0.78.

IR and ^1H NMR spectra identical to spectra of IIb (R=H).

Hydrolysis of IIIb (R=H)

(a) 1S,5S-8-Formyl-7,7-dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octan-2-one (IVb; R=H). — IIIb (R=H) hydrolysed according to the above procedure, gave IVb (R=H) in a 23.3% yield.

Re-crystallization from ethylacetate gave a sample with m. p. 169—171 °C; $[\alpha]_D^{23}$ + 162.7° (c = 0.5, CH_2Cl_2); R_f = 0.74.

IR and ^1H NMR spectra identical to spectra of IVa (R=H).

(b) N-Formyl 2S,4S-benzylpenilloic acid (IIb; R=H). — From the aqueous layer IIb (R=H) was isolated in a 69.7% yield; m. p. 178—180 °C; $[\alpha]_D^{23}$ + 16.2° (c = 0.5, MeOH); R_f = 0.78.

IR and ^1H NMR spectra identical to spectra of IIb (R=H).

1R,5R-7,7-Dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octan-2-one(Va)

A mixture of IVa (R=H) (1 g, 0.005 mol) and 2 molar HCl (10 ml) was heated under reflux for 10 minutes. 1 molar NaOH was added till pH = 7 and evaporated to dryness under reduced pressure. The dry residue was extracted with dichloromethane, (3 × 10 ml) and after drying ($MgSO_4$), dichloromethane was evaporated. Yield 0.79 g (92%) of Va; m. p. (150—3) °C; R_f = 0.64.

Re-crystallization from benzene gave a sample with m. p. 158—160 °C; $[\alpha]_D^{23}$ — — 24.3° (c = 0.5, $CHCl_3$).

Anal. $C_7H_{12}N_2O_2S$ (172.24) calc'd: C 48.80; H 7.04; N 16.25%
found: C 49.03; H 7.26; N 16.52%

IR spectrum: 3330 (s), 3280 (s), 1650 (vs), 1480 (m), 1310 (s), 1255 (m), 1210 (s), 880 (m), 800 (s) cm^{-1}.

^1H NMR spectrum δ: 1.42, 1.64 (2 s, C_7—(CH_3)$_2$), 2.90 (s, N_8—H), 3.02—3.90 (m, C_4—H_2), 3.49 (s, C_1—H), 5.03 (d, J = 3, C_5—H), 6.94 (s, N_3—H).

1S,5S-7,7-Dimethyl-6-thia-3,8-diazabicyclo(3,2,1)octan-2-one(Vb)

IVb (R=H) hydrolysed in 2 N HCl according to the above procedure, gave Vb in a 79.7% yield; m. p. 158—160 °C; $[\alpha]_D^{23}$ + 23.9° (c = 0.5, $CHCl_3$); R_f = 0.64. IR and ^1H NMR spectra were identical to spectra of Va.

Hydrolysis of N-formyl Benzylpenilloic Acids (II; R=H)

(a) 2*R*,4*R*-Isomer (IIc; R=H) (5 g, 0.0149 mol) in 1 molar HCl (60 ml) was heated under reflux for 15 minutes. After cooling, the solution was extracted with

dichloromethane, the organic layer separated, and 10% NaOH was added till pH=2. The separated product was re-crystallized from water to yield 2*S*,4*R*-benzylpenilloic acid (Id); m. p. 95—103 °C; $[\alpha]_D^{23}$ — 62.6° (*c* = 0.5, EtOH); 5.22% water (K. F.); R_f = 0.74.

IR and ^{1}H NMR spectra identical to spectra of Ia.

Re-crystallization of obtained product (Id) from methanol gave 2*R*,4*R*-benzylpenilloic acid (Ic) in a 35% yield; m. p. 158—160 °C; $[\alpha]_D^{23}$ — 36.6° (*c* = 0.5, MeOH); R_f = 0.74.

IR and ^{1}H NMR spectra identical to spectra of Ib.

(*b*) 2*S*,4*S*-Isomer (IIb; R=H), hydrolysed in 1 molar HCl according to the above procedure, gave a product which, re-crystallized from water gave 2*R*,4*S*-benzylpenilloic acid (Ia) in a 65% yield; m. p. 95 —103 °C; $[\alpha]_D^{23}$ + 65.2° (*c* = 0.5, EtOH); R_f = 0.74.

IR and ^{1}H NMR spectra identical, to spectra of Ia.

Several re-crystallizations of the Ia obtained, from methanol gave 2*S*,4*S*-benzylpenilloic acid (Ib) in a 37.4% yield; m. p. 161—163 °C; $[\alpha]_D^{23}$ + 32.2° (*c* = 0.5, MeOH); IR and ^{1}H NMR spectra identical to spectra of Ib.

D-*Penicillamine (VIb)*

VIb was prepared from 2*R*,4*S*- or 2*S*,4*S*-benzylpenilloic acid (Ia or Ib) according to the procedure described in previous publicaction[1].

L-*Penicillamine (VIa)*

2*R*,4*R*- or2*S*,4*R*-Benzylpenilloic acid (Ic or Id) heated in xylene with phenylhydrazine according to the procedure described in a previous publication for D-penicillamine (VIb) gave L-penicillamine (VIa) in a 70% yield; m. p. (200—5 °C; $[\alpha]_D^{23}$ + + 61° (*c* = 0.5, NaOH).

IR an ^{1}H NMR spectra identical to spectra of VIb.

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SAŽETAK

Izomerizacija *N*-acil benzilpenilojevih kiselina u acetanhidridu i nastajanje 7,7-dimetil-6-tia-3,8-diazabiciklo(3,2,1)oktan-2-ona

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

Grijanjem *N*-acil benzilpenilojevih kiselina (II) u acetanhidridu dobivena je smjesa C-4 epimera uslijed epimerizacije u položaju C-4. Ciklizacijom 2-amidometil i 4-karboksilne grupe u 2-ketopiperazin, od IIb ili IIc nastaje 1*S*,5*S* odnosno 1*R*,5*R* enantiomer od III.

Alkalnom hidrolizom III daje IV i II. U slučaju kada je *N*-acilna grupa formil, IV i II hidrolizom u kiselini daje V i I. C-4 epimeri sa *cis* supstituentima u položaju C-2, C-4 (Ib ili Ic) mogu se prirediti polazeći iz *trans* supstituiranih C-4 epimera (Id ili Ia) preko intermedijera II i III.

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