A FACILE PREPARATION OF D-PENICILLAMINE. REACTION OF BENZYLPENILLOIC ACID WITH ARYLAMINES[1]

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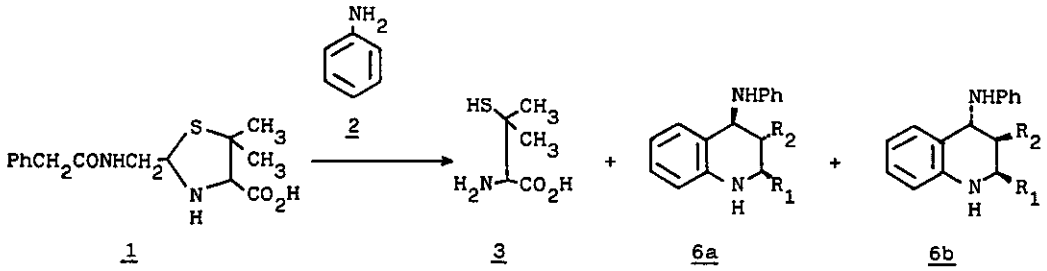
Abstract —— The preparation of D-penicillamine (3) was achieved by the reaction of benzylpenilloic acid (1) with arylamines (2, 7, 13, 15) through ring fission of thiazolidine. The structures of the by-products formed in these reactions were determined.

D-Penicillamine (3), a degradation product of penicillin, is clinically used for the treatment of cystinuria, Wilson's and rheumatoid disease.[2] Various methods[3] for the preparation of 3 from penicillins have been reported. Such processes generally use penicilloic acid and/or the penilloic acid (1) as intermediates, which may subsequently be converted into 3 through ring fission of thiazolidine.

A typical procedure for the preparation of 3 involves treatment of the penilloic acid (1) prepared from benzylpenicillin with a mercuric salt, such as mercuric chloride, followed by treatment of the resulting a D-penicillamine-mercuric complex with hydrogen sulfide.[4] However, the use of heavy metal compounds such as mercuric chloride is commercially unattractive because of potentially poisonous contaminants. An alternative procedure involves treatment of 1 with carbonyl reagents such as hydroxylamine[5] or hydrazines[6] to give 3.

We have now found that 3 can also be obtained by raction of 1 with arylamines. Treatment of 1 with 2 in a mixture of water, acetic acid and toluene under reflux gave D-penicillamine (3) in 79% yield along with 1,2,3,4-tetrahydroquinoline derivatives (6a and 6b) as a 1:1 mixture of diastereomers (Chart 1).

Chart 1



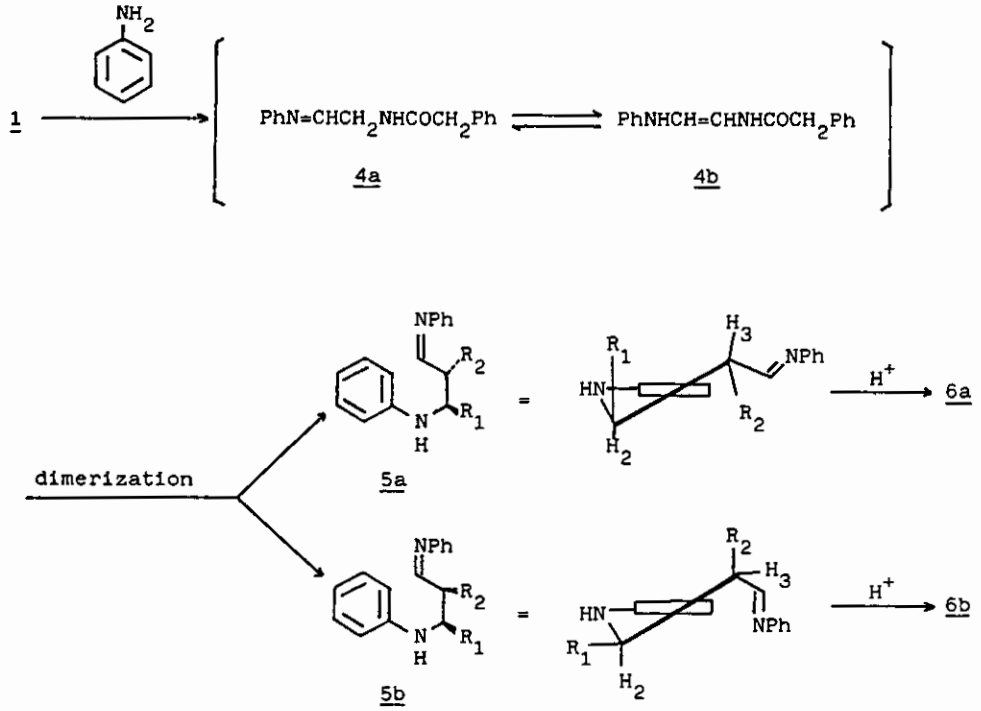
6a, 6b: R_1 = $-CH_2NHCOCH_2Ph$

R_2 = $-NHCOCH_2Ph$

The ratio of 6a and 6b in the crude product was estimated from the intensity of each 4-*H* proton signal in the ^{1}H-nmr spectra. Assignment of the stereochemistry[7] for 6a and 6b was based on the comparison of the ^{1}H-nmr (DMSO-d_6) spectra. The vicinal coupling parameters for $J_{2,3}$ (8 Hz) and $J_{3,4}$ (8 Hz) of 6a indicate the relative configuration of 2-H and 3-H to be trans and that of 3-H and 4-H to be trans, from the consideration of the Karplus relation[8] and Funabashi's report.[9] On the other hand, the vicinal coupling parameters for $J_{2,3}$ (2 Hz) and $J_{3,4}$ (5 Hz) of 6b indicate that the relative configuration of 2-H and 3-H is cis and that of 3-H and 4-H is trans.

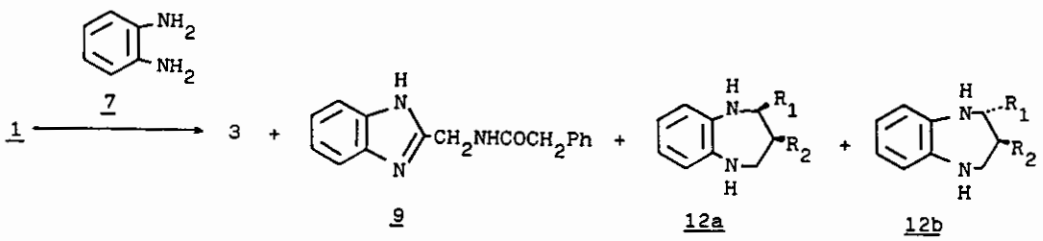
The formation of 6a and 6b can be explained as follows: First, the reaction includes the formation of the Schiff base (4a) through the ring fission reaction of thiazolidine by nucleophilic attack of aniline (2). The formation of the products (5a, 5b) occurs by the dimerization of its tautomer (4b) of 4a. Then threo and erythro isomers (5a, 5b) can be converted into 6a and 6b by cyclization similar to that of Skraup synthesis[10] (Chart 2).

Chart 2



We next examined the reaction of benzylpenilloic acid (1) with arylamines containing the nucleophilic group, such as the amino or mercapto group at the ortho or peri position. The reaction of o-phenylenediamine (7) with 1 in a mixture of water and acetic acid afforded 3, benzimidazole derivative (9), benzodiazepine derivative (12a) and its isomer (12b) in 68, 15, 2 and 2% yields, respectively (Chart 3). The structures of 12a and 12b were determined based on their ^{1}H-nmr.[11]

Chart 3

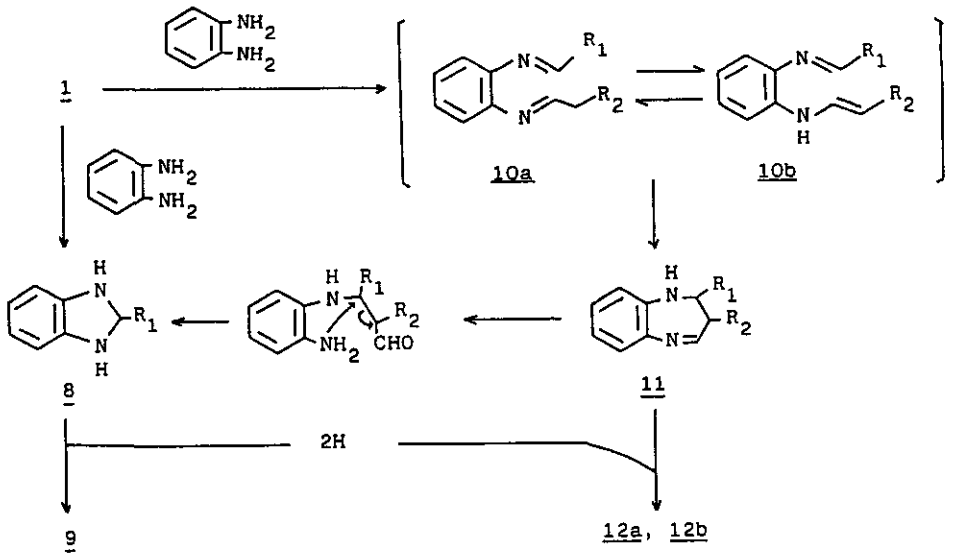


12a, 12b: R_1 = $-CH_2NHCOCH_2Ph$

R_2 = $-NHCOCH_2Ph$

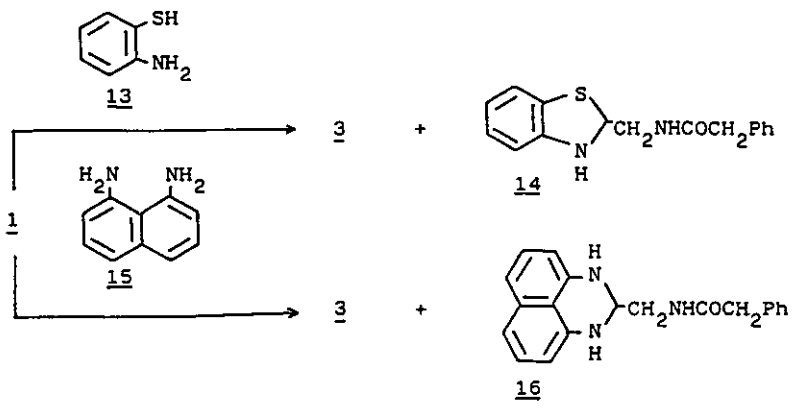
The reaction mechanism for the formation of 12a and 12b is assumed to proceed by cyclization of the Schiff base (10) obtained from the reaction of two moles of benzylpenilloic acid (1) with 7, followed by the reduction of 11.
On the other hand, the formation of 9 is assumed to proceed by the elimination of the hydrogen of the intermediate (8). Two raction mechanisms have been postulated for 8: Compound 1 reacts with one mole of 7 to give 8. Another reaction mechanism includes the ring contraction of the intermediate (11) through hydrolysis in aqueous solution and concomitant ring closure to the corresponding 2-substituted benzimidazolidine (8) (Chart 4).

Chart 4



The formation of 9 and the stereoisomer (12a, 12b) appears to indicate the disproportionation of oxidation-reduction. The reaction of o-aminothiophenol (13) with 1 proceeded smoothly to afford 3 and benzothiazolidine derivative (14) in 86 and 93% yields, respectively. Futhermore, we also investigated the reaction of 1 with 1,8-naphthalenediamine (15). Treatment of 15 with 1 gave 3 in 93% yield and perimidine derivative (16) in 87% yield without the formation of other by-products (Chart 5).

Chart 5



In conclusion, we have developed new methods for preparation of 3. These methods may be more practical for the commercial production of 3 than previous methods. In particular, it is best considered to use o-aminothiophenol as an agent from the points of the high yield of 3, and the easy separation of the desired product 3 from a by-product.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded on a JASCO DS-301 spectrometer. ^{1}H Nmr spectra were recorded on a Varian XL-200 spectrometer, unless otherwise noted. Mass spectra (ms) were taken on a Shimadzu LKD 9000 spectrometer, and $[\alpha]_D$ was determined on a JASCO-140 instrument.

Reaction of Benzylpenilloic Acid Hydrate (1) with Aniline (2)

Benzylpenilloic acid hydrate (1) (16.32 g, 50 mmol) and aniline (2) (24.96 g, 268 mmol) were added to a mixture of water (100 ml), acetic acid (23 ml, 402 mmol) and toluene (50 ml). The mixture was heated under reflux with stirring for 4 h under a nitrogen atmosphere. After cooling, the organic layer was removed, aqueous layer was washed with three 30 ml portions of chloroform and evaporated under reduced pressure. The remaining solid was triturated with methanol to yield D-penicillamine (3) (5.89 g, 79%), mp 201-202 °C (lit.[6] 200—205 °C), $[\alpha]_D^{20}$= -63.62° (1N

NaOH, c=1) (lit.[6] $[\alpha]_D^{22}$ -61°). ^{1}H Nmr (CF_3COOH, 60 Hz)[12] δ : 1.65 (3H, s, CH_3), 1.81 (3H, s, CH_3), 2.26 (1H, br s, SH), 4.30 (1H, m, methine proton), 7.60 (2H, br s, NH_2). Anal. Calcd for $C_5H_{11}NO_2S$: C, 40.24; H, 7.43. Found: C, 40.28; H, 7.53.

The organic layer was dried over sodium sulfate and evaporated. The remaining residue was chromatographed on silica gel (500 g). The first eluate with ether gave (2R*, 3S*, 4R*)-3-phenylacetylamino-2-phenylacetylaminomethyl-4-phenylamino-1,2,3,4-tetrahydroquinoline (6a) (905 mg, 7%) as colorless crystals, mp 133-135°C (from methanol). ^{1}H Nmr (DMSO-d_6) δ : 3.08 (1H, m, $-CH_2-$), 3.38 (2H, s, $-CH_2Ph$), 3.44 (1H, m, $-CH_2-$), 3.46 (2H, s, $-CH_2Ph$), 4.01 (1H, m, 3-H), 4.59 (1H, t, J=8 Hz, 4-H), 5.62 (1H, s, NH), 5.68 (1H, d, J=8 Hz, NHPh), 6.48-7.38 (19H, m, ArH), 7.98 (1H, t, J=4 Hz, $-CH_2NHCO-$), 8.10 (1H, d, J=8 Hz, NH). Signals due to 2-H are concealed between other signals. Ir $\nu_{max}^{KBr}cm^{-1}$: 1638 (C=O), 3230, 3240 (NH). Ms m/z: 504 (M^+). Anal. Calcd for $C_{32}H_{32}N_4O_2$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.39; H, 6.42; N, 11.02.

The second fraction eluted with the same solvent gave a mixture of 6a and 6b (3.9 g, 31%). The third fraction eluted with the same solvent gave (2R*, 3R*, 4S*)-3-phenylacetylamino-2-phenylacetylaminomethyl-4-phenylamino-1,2,3,4-tetrahydroquinoline (6b) (1.15 g, 9%) as a white powder, mp 204-206°C (from acetone). ^{1}H Nmr (DMSO-d_6) δ : 2.85, 3.30 (1Hx2, each m, $-CH_2NH-$), 3.44 (2H, s, $-CH_2Ph$), 3.52 (2H, s, $-CH_2Ph$), 4.36 (1H, m, 3-H), 5.03 (1H, dd, J=10 and 5 Hz, 4-H), 5.22 (1H, d, J=10 Hz, NH), 5.68 (1H, s, -NHPh), 6.50-7.38 (19H, m, ArH), 7.82 (1H, t, J=6 Hz, NH). Signals due to 2-H are concealed between other signals. Ir $\nu_{max}^{KBr}cm^{-1}$: 1634 (C=O), 3260, 3380 (NH). Ms m/z: 504 (M^+). Anal. Calcd for $C_{32}H_{32}N_4O_2$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.86; H, 6.55; N, 10.95.

Reaction of Benzylpenilloic Acid Hydrate (1) with o-Phenylenediamine (7)

Benzylpenilloic acid hydrate (1) (3.26 g, 10 mmol) and o-phenylenediamine (7) (1.19 g, 11 mmol) were added to a solution of acetic acid (0.7 ml, 12 mmol) in water (20 ml). The mixture was heated under reflux with stirring for 2 h under a nitrogen atmosphere. After cooling, the mixture was extracted with chloroform. Aqueous layer was evaporated and residue was washed with methanol to give D-penicillamine (3) (1.01 g, 68%). The organic extract was dried over sodium sulfate and evaporated. The resulting residue was chromatographed on silica gel (50 g) using methanol-chloroform (1:99). The first fraction of eluate gave (2S*, 3S*)-3-phenyl-

acetylamino-2-phenylacetylaminomethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (12a) (47 mg, 2%) as a white powder, mp 198-201°C (from benzene). ^{1}H Nmr (DMSO-d_6) δ: 2.84 (1H, dd, J=12 and 4 Hz, $-CH_2-$), 2.95 (1H, m, $-CH_2-$), 3.24 (3H, m, 2-H and $-CH_2-$), 3.52 (2H, d, J=14 Hz, $-CH_2Ph$), 3.57 (2H, d, J=14 Hz, $-CH_2Ph$), 4.10 (1H, m, 3-H), 4.42 (1H, s, NH), 5.06 (1H, br s, NH), 6.45-6.70 (4H, m, ArH), 7.16-7.32 (10H, m, ArH), 7.88 (1H, d, J=9 Hz, NH), 8.18 (1H, t, J=5 Hz, NH). Ir ν_{max}^{KBr} cm^{-1}: 1632 (C=O), 3330 (NH). Ms m/z: 428 (M^+). Anal. Cacld for $C_{26}H_{28}N_4O_2$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.73; H, 6.65; N, 13.13.

The second eluate gave (2R*, 3S*)-3-phenylacetylamino-2-phenylacetylaminomethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (12b) (51 mg, 2%) as a white amorphous powder, mp 145-148°C (from benzene). ^{1}H Nmr (DMSO-d_6) δ: 2.83 (1H, dd, J=14 and 3 Hz, $-CH_2-$), 3.07 (1H, m, $-CH_2-$), 3.19 (1H, m, $-CH_2-$), 3.31 (1H, m, 2-H), 3.43 (2H, s, $-CH_2Ph$), 3.49 (2H, s, $-CH_2Ph$), 3.60 (1H, dd, J=14 and 3 Hz, $-CH_2-$), 3.73 (1H, m, 3-H), 4.62 (1H, m, NH), 5.06 (1H, s, NH), 6.38-6.60 (4H, m, ArH), 7.18-7.34 (10H, m, ArH), 8.21 (1H, d, J=8 Hz, NH), 8.26 (1H, t, J=6 Hz, NH). Ir ν_{max}^{KBr} cm^{-1}: 1640 (C=O), 3310 (NH). Ms m/z: 428 (M^+). Anal. Calcd for $C_{26}H_{28}N_4O_2.1/2H_2O$: C, 71.37; H, 6.68; N, 12.81. Found: C, 71.38; H, 6.54; N, 12.82.

The third eluate gave 2-(1-phenylacetylaminomethyl) benzimidazole (9) (389 mg, 15%) as colorless crystals, mp 185-187°C (from benzene). ^{1}H Nmr (DMSO-d_6) δ: 3.56 (2H, s, $-CH_2Ph$), 4.52 (2H, d, J=6 Hz, $-CH_2-$), 7.11-7.62 (9H, m, ArH), 8.76 (1H, t, J=6 Hz, NH), 12.25 (1H, br s, NH). Ir ν_{max}^{KBr} cm^{-1}: 1650 (C=O), 3320 (NH). Ms m/z: 265 (M^+). Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.43; H, 5.77; N, 16.02.

Reaction of Benzylpenilloic Acid Hydrate (1) with o-Aminothiophenol (13)

Benzylpenilloic acid hydrate (1) (3.26 g, 10 mmol) and o-aminothiophenol (13) (1.38 g, 11 mmol) were added to a solution of acetic acid (0.7 ml, 12 mmol) in water (20 ml). The mixture was heated under reflux with stirring for 2 h under a nitrogen atmosphere. After standing the resulting mixture at room temperature for 1 h, the precipitated solid was filtered and washed with water. Recrystallization from toluene gave 2-(1-phenylacetylaminomethyl)-2,3-dihydrobenzothiazole (14) (2.64 g, 93%), mp 127-129°C. ^{1}H Nmr ($CDCl_3$) δ: 3.16 (1H, m, $-CH_2-$), 3.39, 3.50 (1Hx2, each d, J=14 Hz, $-CH_2Ph$), 3.65 (1H, m $-CH_2-$), 4.46 (1H, br s, NH), 5.28 (1H, t, J=4.5 Hz,

2-H), 6.06 (1H, br s, NH), 6.56-7.36 (9H, m, ArH). Ir ν_{max}^{KBr} cm^{-1}: 1635 (C=O), 3230, 3330 (NH). Ms m/z: 284 (M^+). Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.57; H, 5.67; N, 9.85. Found: C, 67.63; H, 5.66; N, 9.86.

The filtrate and washing were evaporated under reduced pressure. The residue was triturated with 10 ml of ethanol to give D-penicillamine (3) (1.28 g, 86%), mp 203-204 °C.

Reaction of Benzylpenilloic Acid (1) with 1,8-Naphthalenediamine (15)

Benzylpenilloic acid hydrate (1) (3.26 g, 10 mmol) and 1,8-naphthalenediamine (15) (1.58 g, 10 mmol) were added to a solution of acetic acid (1.4 ml, 24 mmol) in water (50 ml). The mixture was heated under reflux with stirring for 2 h under a nitrogen atmosphere. After cooling, the mixture was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated. The remaining residue was chromatographed on silica gel (30 g). Elution with chloroform-methanol (99:1) gave 2-(1-phenylacetylaminomethyl)-2,3-dihydro-1H-perimidine (16) (2.76 g, 87%), mp 128-130 °C (from methanol-petroleum ether). ^1H Nmr (DMSO-d_6) δ: 3.41 (2H, m, $-CH_2-$), 3.54 (2H, s, CH_2Ph), 4.46 (1H, t, J=5 Hz, 2-H), 6.49, 6.53 (1Hx2, each s, NH), 6.49-7.42 (11H, m, ArH), 8.22 (1H, t, J=5 Hz, NH). Ir ν_{max}^{KBr} cm^{-1}: 1637 (C=O), 3320 (NH). Ms m/z: 317 (M^+). Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.68; H, 6.03; N, 13.24. Found: C, 75.45; H, 5.83; N, 13.27.

The aqueous layer was evaporated and remaining solid was triturated with methanol to give D-penicillamine (3) (1.38 g, 93 %), mp 203-205 °C.

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7. Assignment of the cis- and trans-stereochemistry of 6a and 6b were made by means of the irradition technique in the ^{1}H-nmr spectra.

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11. The small coupling constant (J=~0 Hz) between 2-H and 3-H in the double irradition methods in the ^{1}H-nmr spectra indicated a cis-configuration by comparison of that (J=8 Hz) of 12b.

12. The nmr spectrum was taken at 60 MHz using a Hitachi-Perkin-Elmer R-20 spectrometer.

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