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A New Method for Preparing D-Penicillamine. Reaction of Benzylpenicilloic Acid α -Amides with Arylamines¹⁾

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Benzylpenicilloic acid α -amides (**1a—d**) prepared by aminolysis of benzylpenicillin were treated with arylamines (**2**, **7**, **9** and **13a—f**) in the presence of acetic acid to give D-penicillamine (**3**) in good yield and high purity. The structures of the by-products formed in these reactions were also determined.

Keywords—D-penicillamine; benzylpenicillin; benzyl penicilloic acid α -amide; ring fission; arylamine

D-Penicillamine (**3**) is useful in the treatment of cystinuria, Wilson's disease and rheumatoid disease.²⁾ Various methods for preparation of **3** from benzylpenicillin have been reported.³⁾ Such processes generally proceed *via* penicilloic acid and penilloic acid derivatives as intermediates, which may subsequently be converted into **3**. For example, treatment of penilloic acid with a mercuric salt, such as mercuric chloride, yielded a D-penicillamine–mercuric salt complex and conversion of the complex to **3** was carried out by treatment with hydrogen sulfide.⁴⁾ This result shows that heavy metal salts and carbonyl reagents are effective for the fission of the thiazolidine ring in penilloic acid derivatives. The reactions of penicilloic acid with dimedone⁵⁾ or 4-hydroxycoumarins,⁶⁾ and of penilloic acid with hydroxylamine⁷⁾ or hydrazines⁸⁾ afforded **3**. It was also prepared directly from the reactions of benzylpenicillin with hydrazines, through penicilloic hydrazide as an intermediate.⁹⁾

We now describe a convenient method for the preparation of **3** using arylamines (**2**, **7**, **9**

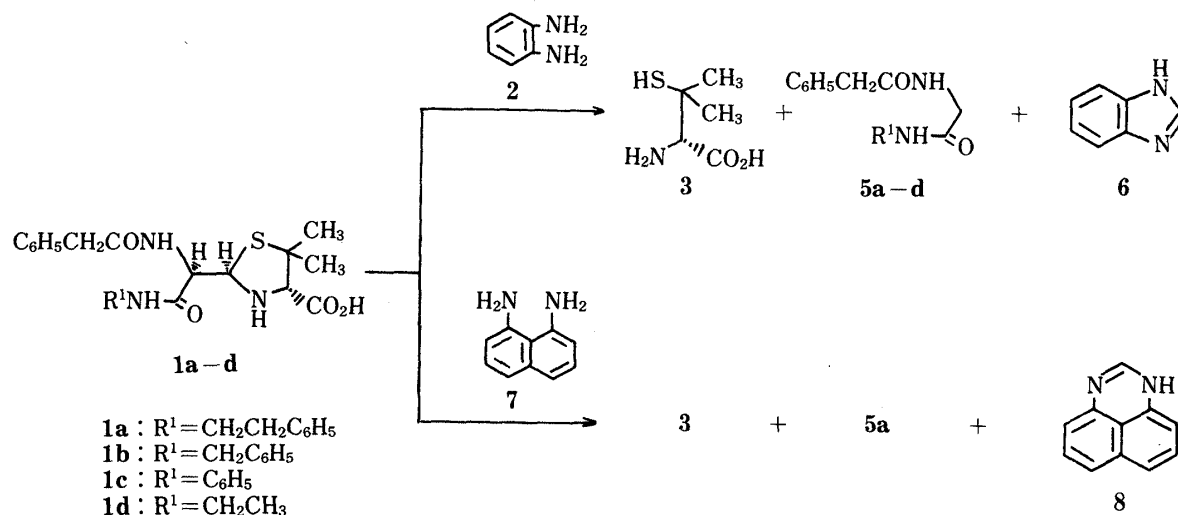


Chart 1

and **13a—f**) as reagents for fission of the thiazolidine ring in penicilloic acid α -amides (**1a—d**), which were readily prepared by aminolysis¹⁰⁾ of benzylpenicillin.

We investigated first the reaction of α -amides (**1a—d**) with arylamines containing a nucleophilic group such as an amino group at the *ortho* or *peri* position (Chart 1).

When benzylpenicilloic acid α -phenethylamide (**1a**) was heated under reflux with *o*-phenylenediamine (**2**) in a mixture of water and acetic acid for 1.5 h, compound **3** was obtained in 87% yield accompanied with phenaceturic acid α -phenethylamide (**5a**) and benzimidazole (**6**) in 91 and 59% yields, respectively. The structures of **3** and **5a** were confirmed by comparison with authentic samples.^{3,11)}

Similarly, the other amides (**1b—d**) also reacted with **2** to give **3**, **6** and the corresponding **5b—d**^{12–14)} in good yields (Table I).

The mechanism for the formation of **3**, **5** and **6** is proposed to be as follows. It seems

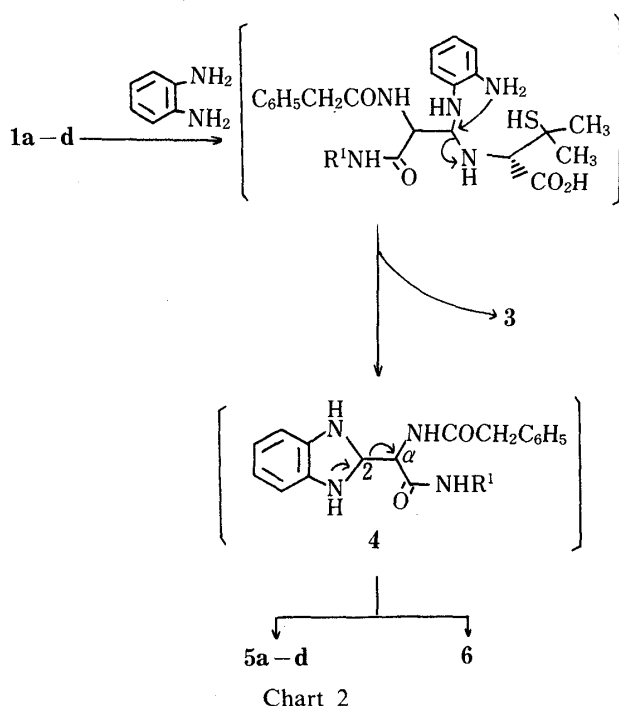


TABLE I. Reaction of Amides **1a—d** with Diamines (**2** and **7**)

Substrate No.	R ¹	Diamine	Yields (%)		
			3	5a—d	6 (or 8)
1a	CH ₂ CH ₂ Ph	2	87	91	59
		7	69	74	85
1b	CH ₂ Ph	2	80	85	57
1c	Ph	2	86	81	58
1d	CH ₂ CH ₃	2	71	79	55

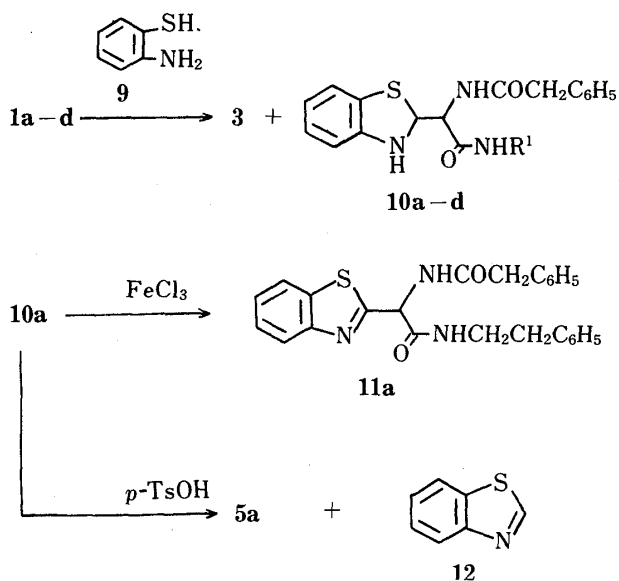


TABLE II. Reaction of Amides **1a—d** with *o*-Aminothiophenol (**9**)

Substrate No.	R ¹	Yields (%)	
		3	10a—d
1a	CH ₂ CH ₂ Ph	83	89
1b	CH ₂ Ph	81	86
1c	Ph	71	68
1d	CH ₂ CH ₃	74	79

likely that the reaction takes place in two stages. Firstly, **1** reacts with **2** to yield **3** and the benzimidazolidine intermediate **4**. The C-C bond between the 2- and α -position of **4** is then cleaved by transfer of the lone pair of the nitrogen atom and subsequently the two products, **5** and **6**, are formed. (Chart 2).

When 1,8-naphthalenediamine (**7**) was treated with **1a** under the same conditions as used in the former reaction, a similar reaction took place, and **3**, **5a** and perimidine (**8**) were obtained in 69, 74, and 85% yields, respectively.

We next examined the reactions of **1a—d** with *o*-aminothiophenol (**9**) under the same conditions (Chart 3). In these cases, **3** was obtained in 71–83% yields, but **5** and **12** were not formed, and benzothiazolidine derivatives (**10a—d**) were isolated in 68–89% yields (Table II).

Each of **10a—d** was a mixture of two diastereomers and attempts to separate them by column chromatography or fractional recrystallization were unsuccessful. Consequently, the structure of **10a** was confirmed by means of the following experiments. Compound **10a** was dehydrogenated by treatment with iron (III) chloride in methanol to give the benzothiazole derivative **11a**, the structure of which was determined from spectral data. In addition, when **10a** was heated in ethanol with *p*-toluenesulfonic acid, **5a** and benzothiazole (**12**) were obtained in high yields.

Finally, we investigated the reactions of **1a** with anilines (**13a—f**). Refluxing of **1a** with **13a** in a mixture of water, toluene and acetic acid for 4 h afforded **3** in 51% yield and (*Z*)-3-anilino-*N*-phenethyl-2-phenylacetamidoacrylamide (**15a**).^{15,16} Compound **15a** should be produced through isomerization of the Schiff base intermediate **14a** (Chart 4).

The effect of a substituent on the benzene ring of aniline upon the reaction with **1a** was also examined. Electron-releasing groups on the benzene ring increase the nucleophilicity of aniline, so that the reaction afforded **3** in high yield. On the other hand, reaction of aniline having an electron-attracting group afforded **3** in poor yield (Table III).

The present results demonstrate that arylamines are useful reagents to prepare D-penicillamine (**3**) by the fission reaction of the thiazolidine ring in penicilloic acid α -amides.

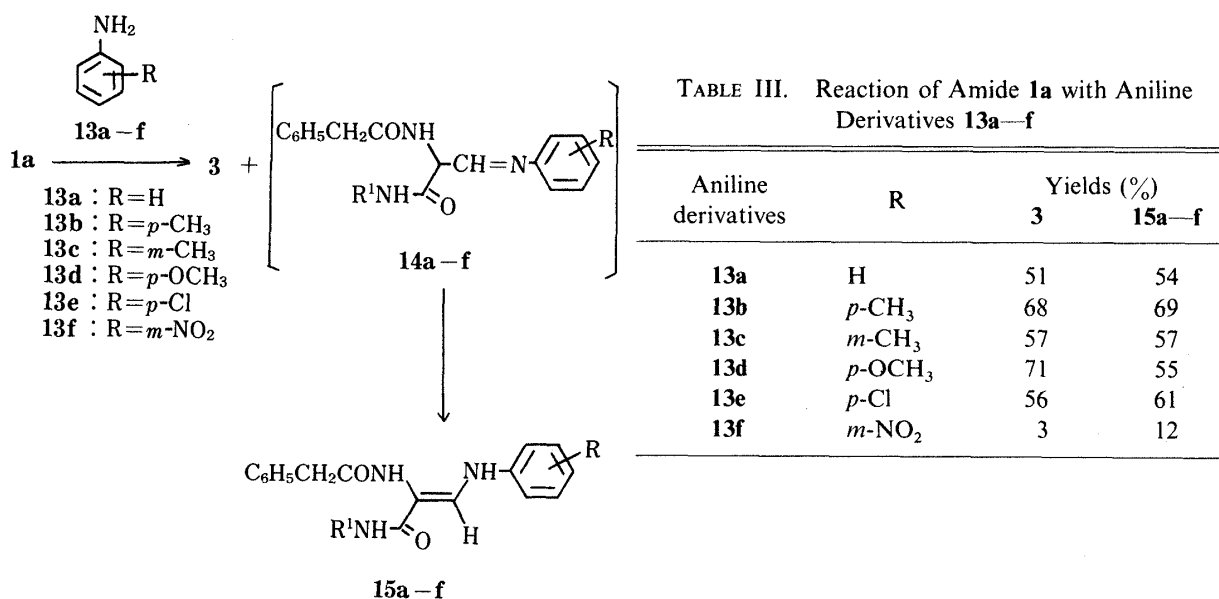


Chart 4

Experimental

All melting points are uncorrected. The infrared (IR) spectra were recorded on a JASCO DS-301 spectrometer.

Nuclear magnetic resonance (NMR) spectra were taken at 200 MHz with tetramethylsilane as an internal standard using a Varian XL-200 spectrometer, unless otherwise noted. Chemical shifts were expressed in (ppm) values.

Typical Procedure for Preparation of Benzylpenicilloic Acid α -Amides (1a–d). Benzylpenicilloic Acid α -Phenethylamide (1a)—Benzylpenicillin potassium salt (37.25 g, 100 mmol) was dissolved in water (500 ml). To this solution, phenethylamine (12.12 g, 100 mmol) was added dropwise with stirring at room temperature over 30 min, and then stirring was continued for 3 h. The mixture was acidified with 50% phosphoric acid and filtered, and the resulting crystals were washed with water. Recrystallization from water–methanol (1 : 1) gave the amide hydrate **1a** (43.99 g, 93%) as a white powder, mp 101–106 °C. ¹H-NMR (DMSO-*d*₆) δ : 1.16 (3H, s, –CH₃), 1.49 (3H, s, –CH₃), 2.65 (2H, t, *J* = 7.5 Hz, –CH₂CH₂Ph), 3.18 (2H, m, –CH₂CH₂Ph), 3.48 (1H, d, *J* = 9 Hz, –COCH₂Ph), 3.56 (1H, d, *J* = 9 Hz, –COCH₂Ph), 4.41 (1H, m, methine proton), 4.85 (1H, d, *J* = 7.5 Hz, methine proton), 7.16–7.40 (10H, m, ArH), 8.15 (1H, t, *J* = 6 Hz, NH), 8.28 (1H, d, *J* = 7.5 Hz, NH). MS *m/z*: 455 (M⁺). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{–1}: 1630 (C=O), 2900, 3280 (NH). *Anal.* Calcd for C₂₄H₂₉N₃O₄S·H₂O: C, 60.86; H, 6.60; N, 8.87. Found: C, 60.88; H, 6.32; N, 8.85.

Benzylpenicillin potassium salt was also treated with ethylamine to give the α -ethylamide **1d** in 95% yield, mp 99–101 °C. ¹H-NMR (DMSO-*d*₆) δ : 1.02 (3H, t, *J* = 6 Hz, –CH₂CH₃), 1.16 (3H, s, CH₃), 1.50 (3H, s, CH₃), 3.07 (2H, m, –CH₂CH₃), 3.55 (2H, s, –COCH₂Ph), 4.38 (1H, m, methine proton), 4.84 (1H, m, methine proton), 7.16–7.42 (5H, m, ArH), 8.00 (1H, t, *J* = 6 Hz, NH), 8.25 (1H, d, *J* = 8 Hz, NH). MS *m/z*: 380 (M + H). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{–1}: 1635 (C=O), 2960, 3280 (NH).

The other amide derivatives (**1b** and **1c**) were similarly prepared by the procedure described in the literature. Benzylpenicilloic acid α -benzylamide (**1b**); 95% yield, mp 113–115 °C (lit.¹⁰ 134–135.5 °C), benzylpenicilloic acid α -anilide (**1c**), 94% yield, mp 60–83 °C (lit.¹⁰ 65–80 °C).

Typical Procedure for the Reaction of Benzylpenicilloic Acid α -Amides (1a–d) with *o*-Phenylenediamine (2)—The amide hydrate **1a** (14.21 g, 30 mmol) and the diamine **2** (3.24 g, 30 mmol) were added to a solution of acetic acid (1.0 ml) in water (100 ml). The mixture was heated under reflux with stirring for 1.5 h under a nitrogen atmosphere. After standing of the resulting mixture at room temperature for 1 h, the precipitated product was filtered off, washed with water, and then dried *in vacuo*. Recrystallization from methanol–petroleum ether gave **5a** (8.09 g, 91%) as colorless crystals, mp 144–145 °C (lit.¹¹ 141–144 °C). Subsequently, the filtrate and washing were evaporated and the resulting residue was triturated with methanol (10 ml). The separated crystals were collected by filtration, washed with methanol and dried to give D-penicillamine (**3**) (3.89 g, 87%) as colorless crystals, mp 205–206 °C, $[\alpha]_{\text{D}}^{20} = -62.5$ (1 N, NaOH, *c* = 1). ¹H-NMR (60 MHz, CF₃CO₂H): 1.65 (3H, s, CH₃), 1.81 (3H, s, CH₃), 2.26 (1H, brs, SH), 4.30 (1H, m, methine proton), 7.60 (2H, brs, NH₂). *Anal.* Calcd for C₃H₁₁NO₂S: C, 40.24; H, 7.43. Found: C, 40.27; H, 7.52.

The filtrate was evaporated under reduced pressure. The residue was recrystallized from methanol to give benzimidazole (**6**) as colorless crystals (2.10 g, 59%), mp 166–168 °C.

The other amides **1b–d** were also treated with **2** to give **3**, **5b–d** and **6**. Compound **5b**, mp 174–176 °C (lit.¹² 172–173 °C); **5c**, mp 157–159 °C (lit.¹³ 158–160 °C); **5d**, mp 166–168 °C (lit.¹⁴ 170–171 °C). The results are summarized in Table I.

Reaction of α -Phenethylamide Hydrate (1a) with 1,8-Naphthalenediamine (7)—The amide hydrate **1a** (9.47 g, 20 mmol) and the diamine **7** (3.16 g, 20 mmol) were added to a solution of acetic acid (1 ml) in water (60 ml). The mixture was heated under reflux with stirring for 2 h under a nitrogen atmosphere. After standing of the resulting mixture at room temperature for 1 h, the precipitated product was filtered off, washed with water, and then dried *in vacuo*. Recrystallization from methanol–petroleum ether gave **5a** (4.38 g, 74%) as colorless crystals. The filtrate was evaporated, and the resulting residue was dissolved in methanol, then acidified with 6N hydrochloric acid. The

TABLE IV. Physicochemical Properties and Analytical Data for the Benzothiazolidine Derivatives **10a–d**^{a)}

Compound	R ¹	Formula	mp (°C) (Recryst. solvent ^{b)})	MS (<i>m/z</i> : M ⁺)	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ^{–1}		Analysis (%) Calcd (Found)		
					C=O	NH	C	H	N
10a	CH ₂ CH ₂ Ph	C ₂₅ H ₂₅ N ₃ O ₂ S	135–140 (M)	431	1635	3030	69.58	5.84	9.74
10b	CH ₂ Ph	C ₂₄ H ₂₃ N ₃ O ₂ S	95–129 (D–W)	417	1636	3020	69.36	5.85	9.82
10c	Ph	C ₂₃ H ₂₁ N ₃ O ₂ S	168–177 (D–W)	403	1657	3040	69.04	5.55	10.07
10d	CH ₂ CH ₃	C ₁₉ H ₂₁ N ₃ O ₂ S	141–147 (D–W)	355	1645	3040	69.10	5.58	9.99
					3250		68.46	5.25	10.42
					1635	3020	68.29	5.38	10.21
					3060		64.20	5.96	11.82
							64.19	5.93	11.85

a) Compounds **10a–d** are diastereomeric mixtures. b) D, DMSO; M, MeOH; W, H₂O.

mixture was stirred for 30 min in an ice bath. Insoluble substances were filtered off and washed with a small amount of methanol. Recrystallization from 6*N* hydrochloric acid gave perimidine (**8**) hydrochloride (3.46 g, 85%) as yellow crystals, mp 265–270 °C (dec.). ¹H-NMR (D₂O): 6.02–7.13 (6H, m, ArH), 7.43 (1H, s, –CH=NH–). Concentration of the filtrate under reduced pressure afforded crude D-penicillamine hydrochloride, which was treated with triethylamine in methanol to give **3** (2.06 g, 69%), mp 199–200 °C.

Typical procedure for the Reaction of Benzylpenicilloic Acid α -Amides (1a–d) with *o*-Aminothiophenol (9)—The amide hydrate **1a** (4.74 g, 10 mmol) and *o*-aminothiophenol (**9**) (1.25 g, 10 mmol) were added to a solution of acetic acid (1 ml) in water (30 ml). The mixture was heated under reflux with stirring for 2 h under a nitrogen atmosphere. After standing of the resulting mixture at room temperature for 1 h, the precipitated solid was filtered off and washed with water. Recrystallization from methanol gave *N*-phenethyl- α -phenylacetamido-2-benzothiazolidineacetamide (**10a**) (3.84 g, 89%) as colorless crystals. The filtrate and washing were evaporated under reduced pressure and the resulting residue was triturated with methanol (10 ml) to give **3** (1.24 g, 83%) as colorless crystals, mp 206–207 °C.

The other amides **1b–d** were also treated with **9** to give **3** and **10b–d**. Yields and physical data are listed in Tables II and IV.

Typical Procedure for the Reaction of Benzylpenicilloic Acid α -Phenethyl Amide (1a) with Anilines 13a–f—The amide hydrate **1a** (4.74 g, 10 mmol) and aniline (**13a**) (1.86 g, 20 mmol) were added to a mixture of water (20 ml), toluene (30 ml) and acetic acid (1 ml). The mixture was heated under reflux with stirring for 4 h under a nitrogen

TABLE V. Physicochemical Properties and Analytical Data for Acrylamides **15a–f**

Compound	R	Formula	mp (°C) (Recryst. solvent ^{a, b})	M (<i>m/z</i> : M ⁺)	IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$		Analysis (%) Calcd (Found)		
					C=O	NH	C	H	N
15a	H	C ₂₅ H ₂₅ N ₃ O ₂	133–136 (M–P)	399	1670	3010 3200	75.16 (74.97)	6.31 6.39	10.52 10.64
15b	<i>p</i> -CH ₃	C ₂₆ H ₂₇ N ₃ O ₂ ·H ₂ O	99–101 (M–R)	413	1658	3010 3260 3360	72.36 (72.30)	6.77 6.53	9.74 9.78
15c	<i>m</i> -CH ₃	C ₂₆ H ₂₇ N ₃ O ₂	64–68 (E–P)	413	1665	3010 3200	75.52 (75.47)	6.58 6.67	10.16 10.16
15d	<i>p</i> -OCH ₃	C ₂₆ H ₂₇ N ₃ O ₃	124–126 (M–P)	429	1670	3010 3180 3380	72.70 (72.50)	6.34 6.47	9.78 9.87
15e	<i>p</i> -Cl	C ₂₅ H ₂₄ N ₃ O ₂ Cl	142–145 (M)	433	1668 1689	3040 3220 3360	69.19 (69.21)	5.58 5.73	9.68 9.77
15f	<i>m</i> -NO ₂	C ₂₅ H ₂₄ N ₄ O ₄	190–193 (H–L)	444	1650	3010 3350	67.55 (67.71)	5.44 5.67	12.61 12.46

a) E, EtOH; H, Hexane; L, AcOEt; P, petroleum ether; R, Et₂O. b) See footnote a in Table IV.

TABLE VI. ¹H-NMR Data for Acrylamides **15a–f**

Compound	Chemical shifts (200 MHz, DMSO- <i>d</i> ₆)
15a	2.72 (2H, t, <i>J</i> = 7.5 Hz), 3.32 (2H, m), 3.70 (2H, s), 6.75–7.38 (15H, m), 7.56 (1H, d, <i>J</i> = 12 Hz), 8.12 (1H, d, <i>J</i> = 12 Hz), 8.99 (1H, s)
15b	2.22 (3H, s), 2.70 (2H, t, <i>J</i> = 7.5 Hz), 3.50 (2H, m), 3.68 (2H, s), 6.92–7.46 (14H, m), 7.58 (1H, d, <i>J</i> = 12 Hz), 7.94 (1H, d, <i>J</i> = 12 Hz), 8.80 (1H, s)
15c	2.27 (3H, s), 2.70 (2H, t, <i>J</i> = 8 Hz), 3.31 (2H, m), 3.68 (2H, s), 6.68–8.48 (14H, m), 7.60 (1H, d, <i>J</i> = 12 Hz), 7.95 (1H, d, <i>J</i> = 12 Hz), 8.83 (1H, s)
15d	2.69 (2H, t, <i>J</i> = 7.5 Hz), 3.30 (2H, m), 3.67 (2H, s), 3.71 (3H, s), 6.88–7.43 (14H, m), 7.58 (1H, d, <i>J</i> = 12 Hz), 8.22 (1H, d, <i>J</i> = 12 Hz), 8.86 (1H, s)
15e	2.71 (2H, t, <i>J</i> = 7.5 Hz), 3.36 (2H, m), 3.69 (2H, s), 7.04–7.44 (14H, m), 7.58 (1H, d, <i>J</i> = 12 Hz), 8.23 (1H, d, <i>J</i> = 12 Hz), 8.86 (1H, s)
15f	2.75 (2H, t, <i>J</i> = 7.5 Hz), 3.39 (2H, m), 3.62 (2H, s), 7.18–7.42 (14H, m), 7.48 (1H, d, <i>J</i> = 12 Hz), 7.97 (1H, d, <i>J</i> = 12 Hz), 8.94 (1H, s)

atmosphere. After standing of the mixture at room temperature for 1 h, the precipitated product was filtered off, washed with a small amount of water, and then dried. Recrystallization from methanol gave (Z)-3-anilino-N-phenethyl-2-phenylacetamidoacrylamide (**15a**) (2.15 g, 54%). Toluene was removed from the filtrate. Subsequently, the aqueous layer was washed with three 30 ml portions of chloroform and evaporated under reduced pressure. The resulting residue was triturated with methanol-ethanol (1:1) (10 ml) to give **3** (760 mg, 51%), mp 206–207°C.

The other anilines (**13b–f**) were also treated with **1a** to give **3** and the corresponding **15b–f**. Yields and physical data are listed in Tables III, V and VI.

Treatment of N-Phenethyl- α -phenylacetamido-2-benzothiazolidineacetamide (10a) with p-Toluenesulfonic Acid—A solution of **10a** (2.16 g, 5 mmol) and p-toluenesulfonic acid (10 mg, 0.06 mmol) in ethanol (20 ml) was heated under reflux with stirring for 3 h. After cooling, the solvent was evaporated off and the residue was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (30 g). The chloroform eluate gave **5a** (1.30 g, 88%), mp 139–142°C. The methanol-chloroform (1:99) eluate gave benzothiazole (**12**) as a colorless oil (514 mg, 76%).

N-Phenethyl- α -phenylacetamido-2-benzothiazoleacetamide (11a) from 10a—A mixture of **10a** (4.31 g, 10 mmol), iron (III) chloride (2.43 g, 15 mmol) and methanol (50 ml) was heated under reflux for 3 h. After cooling, the solvent was evaporated off and the residue was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and concentrated. The residue was purified by short column chromatography on silica gel with methanol-chloroform (1:99) as an eluent to give **11a**. Recrystallization from methanol-petroleum ether afforded colorless prisms (644 mg, 15%), mp 142–143°C. $^1\text{H-NMR}$ (CDCl_3) δ : 2.75 (2H, t, $J=7.5$ Hz, $-\text{CH}_2\text{CH}_2\text{Ph}$), 3.50 (2H, m, $-\text{CH}_2\text{CH}_2\text{Ph}$), 3.75 (2H, m, $-\text{COCH}_2\text{Ph}$), 5.80 (1H, d, $J=8$ Hz, methine proton), 6.94–7.58 (10H, m, ArH), 7.88 (2H, m, $2 \times \text{NH}$). MS m/z : 429 (M^+). Anal. Calcd for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$: C, 69.90; H, 5.40; N, 9.78. Found: C, 69.80; H, 5.60; N, 9.82. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1635 (C=O), 3270 (NH).

References and Notes

- 1) This work was presented at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, August 1979, p. 270.
- 2) J. D. Schulman and K. H. Bradley, *Science*, **169**, 595 (1970); I. A. Jaffe, *Ann. Rheum. Dis.*, **22**, 71 (1963); Y. Shiokawa, Y. Horiuchi, M. Kageyama, T. Okada, and T. Azuma, *Arthritis. Rheum.*, **20**, 1464 (1977).
- 3) W. M. Weigert, H. Offermanns, and P. Scherberich, *Angew. Chem.*, **87**, 372 (1975).
- 4) A. R. Restivo, F. A. Dondzila, and H. Murphy, Jr., U.S. Patent 3281461 (1966) [*Chem. Abstr.*, **66**, 29045s (1967)]; U. Eberhardt, J. Depner, and Schaumann, Ger. (East) 80921 (1971) [*Chem. Abstr.*, **76**, 86145e (1972)]; M. Boch, Ger. Offen. 2114329 (1972) [*Chem. Abstr.*, **78**, 4520c (1973)].
- 5) U. Eberhardt, J. Depner, and J. Schaumann, Ger. (East) 82718 (1971) [*Chem. Abstr.*, **77**, 34506z (1972)].
- 6) K. Fucik, Czech. 127553 (1968) [*Chem. Abstr.*, **70**, 77959x (1969)]; K. Fucik, Czech. 163055 (1976) [*Chem. Abstr.*, **86**, 72441t (1977)].
- 7) K. Kashiwa, Y. Hattori, and M. Fujii, Japan Kokai Tokkyo Koho Japan. Patent 75-129518 (1975) [*Chem. Abstr.*, **84**, 165191k (1976)].
- 8) B. Gaspert and J. Herak, Ger. Offen. 2512608 (1975) [*Chem. Abstr.*, **84**, 44667m (1976)]; J. J. Herak, M. Kovacevic, and B. Gaspert, *Croat. Chem. Acta*, **49**, 141 (1977).
- 9) J. Elks, N. G. Weir, T. L. Gane, and B. Burton, U.S. Patent 3960940 (1976) [Ger. Offen. 2440117 (1975), *Chem. Abstr.*, **82**, 170905j (1975)]; S. Xu and W. Wu, *Kangshengsu*, **7**, 338 (1982) [*Chem. Abstr.*, **98**, 107714m (1983)]; S. Smolik, Czech. 219413B (1985) [*Chem. Abstr.*, **103**, 215007m (1985)]; M. Szarvas, J. Balint, K. Punkosti, G. Farkas, A. Kovacs, G. Bacsá, M. Eszteró, and C. Kovacs Hungary Teljes 34205 (1985) [*Chem. Abstr.*, **103**, 160300w (1985)].
- 10) H. Hitomi, *Yakugaku Zasshi*, **73**, 428 (1953); B. B. Levin, *J. Med. Chem.*, **5**, 1025 (1962); A. F. Martin, J. J. Morris, and M. I. Page, *J. Chem. Soc., Chem. Commun.*, **1979**, 298.
- 11) H. Hitomi, *Yakugaku Zasshi*, **79**, 1611 (1959).
- 12) H. Hitomi, *Yakugaku Zasshi*, **74**, 188 (1954).
- 13) H. Hitomi, *Yakugaku Zasshi*, **74**, 185 (1954).
- 14) T. E. David, Ger. Offen. 1927692 (1969) [*Chem. Abstr.*, **72**, 55885j (1970)].
- 15) Stereochemistry of **15a–f** was assigned based on the chemical shifts of the amino proton ($-\text{NHPh}$) in the $^1\text{H-NMR}$ spectra; R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966); W. Bottomley, J. N. Phillips, and J. G. Wilson, *Tetrahedron Lett.*, **31**, 2957 (1967); A. P. Morgenstern, C. Schutij, and W. Th. Nauta, *J. Chem. Soc., Chem. Commun.*, **1969**, 321. The amino proton signals in *E* isomers were observed at lower field than the corresponding signals of *Z* isomers on account of the hydrogen bond between the amino proton and carbonyl oxygen. The *E* isomers **15a–f** showed a doublet absorption assignable to NH at 10.5–10.7, while the *Z* isomers **15a–f** exhibited a doublet absorption at 7.94–8.23.
- 16) Treatment of **15a–f** with silica gel in methanol under reflux for 12 h gave a mixture of **15a–f** and their *E* isomers. The *E* isomers were isolated by chromatography on silica gel with methanol-chloroform.