PREPARATION OF D-PENICILLAMINE. REACTION OF PENILLOIC ACID, PENICILLOIC ACID α-AMIDES AND BENZYLPENICILLIN WITH *N,N'*-DIPHENYLETHYLENEDIAMINE

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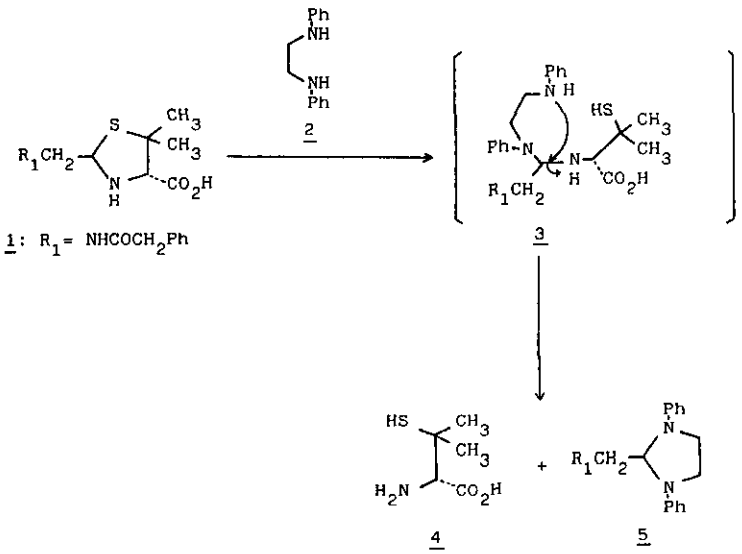
Abstract —— Reaction of benzylpenilloic acid (1) with *N,N'*-diphenylethylenediamine (2) in mixture of water, acetic acid and toluene under reflux yielded D-penicillamine (4). In a similar way, 4 was also obtained from benzyl- and phenoxymethylpenicilloic acid α-amides (6a-f) and benzylpenicillin potassium salt (13). The structures of the by-products formed in these reactions were also determined.

D-Penicillamine (4) is clinically used as drugs of cystinuria, Wilson's disease and rheumatoid disease.[1] As a part of our attempts to develop a facile preparative route to 4, we previously reported the ring-cleavage method of thiazolidine in benzylpenilloic acid (1) and benzylpenicilloic acid α-amides (6a-d) by using arylamines such as anilines, *o*-phenylenediamine, 1,8-naphthalenediamine and *o*-aminothiophenol.[2,3]

We next focussed on the reaction of 1, 6a-f and 13 with *N,N'*-diphenylethylenediamine (2) instead of arylamines mentioned, because 2 possessing two reactive amino groups is also considered to be a useful reagent for nucleophilic fission of thiazolidine ring.

First, we explored the reaction of benzylpenilloic acid (1) with 2. Treatment of 1 with 2 in a mixture of water, acetic acid and toluene for 6 h under reflux gave D-penicillamine (4) and 2-substituted 1,3-diphenylimidazolidine derivative (5) in 23 and 22% yields, respectively (Chart 1).

Chart 1



The reaction pathway for the formation of 4 and 5 can be rationalized as follows: the intermediate (3) is formed through cleavage of C-S bond of thiazolidine in 1 by the nucleophilic attack of one amino group of 2.

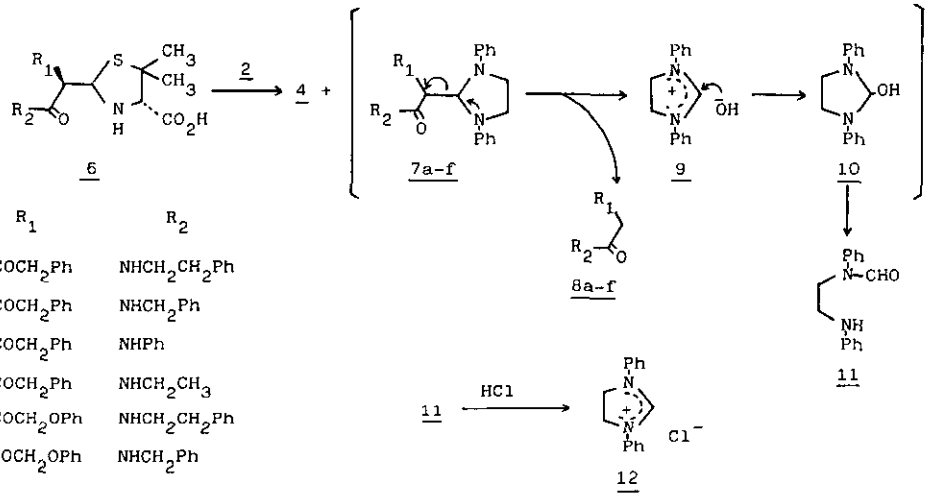
Further nucleophilic attack of the another amino group to N-C-N moiety gives rise to a formation of 5 through elimination of 4.

Next, the reactions of benzylpenicilloic acid α-amides (6a-d) and phenoxymethylpenicilloic acid α-amides (6e, 6f) with 2 were investigated. When 6a-f were treated with 2 in the same manner as described for the reaction of 1 with 2, D-penicillamine (4), *N*-2-anilinoethylformanilide (11)[4] and amides (8a-f) were obtained in 42-51, 47-63 and 63-76% yields, respectively (Chart 2). The structure of 11 was confirmed by converting it to 1,3-diphenyl-2-imidazolidinium chloride (12) by cyclization with hydrochloric acid according to the literature method.[5] The results are summarized in Table 1.

Table 1. Reaction of Amides (6a-f) with *N,N'*-Diphenylethylenediamine (2)

Starting Material	Products (% yield) 4	8	11	$[\alpha]_D^{22}$ degree of 4 (c=1.0, 1N NaOH)
6a	51	76	63	-63.2
6b	47	72	58	-63.5
6c	49	75	60	-62.8
6d	42	71	58	-63.2
6e	47	69	47	-63.5
6f	43	63	48	-62.9

Chart 2

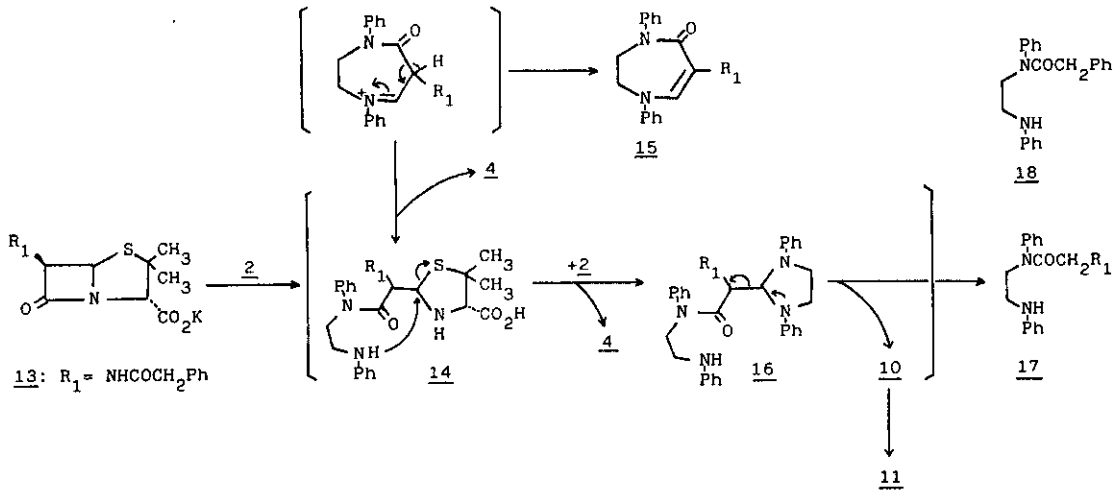


6	R_1	R_2
a	$NHCOCH_2Ph$	$NHCH_2CH_2Ph$
b	$NHCOCH_2Ph$	$NHCH_2Ph$
c	$NHCOCH_2Ph$	NHPh
d	$NHCOCH_2Ph$	$NHCH_2CH_3$
e	$NHCOCH_2OPh$	$NHCH_2CH_2Ph$
f	$NHCOCH_2OPh$	$NHCH_2Ph$

The mechanism for the formation of 4, 8 and 11 is postulated as shown in Chart 2. It seems likely that the reaction takes place in two stages: first, 4 and the intermediate (7) are formed by the nucleophilic attack of amino groups, accompanied with ring fission of thiazolidine in 6. Then, C-C bond between 2- and α-position is cleaved by the participation of lone pair of nitrogen atom to give two products, 8 and the 1,3-diphenylimidazolidinium intermediate (9). Compound 11 was probably derived from further addition of hydroxy anion to the intermediate (9), followed by the tetrahedral intermediate[6] 10 and concomitant ring cleavage.

As described above, the formation of 4 and 8a-f proceeded through two step sequences via 6a-f from penicillins. We investigated the same reaction by using two equivalents of 2, in the expectation that treatment of penicillin with two equivalents of 2 would give 4 through penicilloic acid α-amide (14) as an intermediate. Treatment of benzylpenicillin potassium salt (13) with two equivalents of 2 in a mixture of water and acetic acid under reflux for 6 h gave 4, 11, *N*-(2-anilinoethyl)-2-phenylacetamidoacetanilide (17) and a diazepine derivative (15) along with a small amount of *N*-(2-anilinoethyl)phenylacetanilide (18) (yield: 4, 29%; 11, 49%; 17, 47%; 15, 6.5%; 18, 2.8%, respectively) (Chart 3).

Chart 3



The mechanism for the formation 4, 11, 15 and 17 is postulated as shown in Chart 3. First, 13 reacts with 2 to cleave the ß-lactam ring and yields a benzylpenicilloic acid α-amide intermediate (14). It partly undergoes intramolecular cyclization to afford 15, accompanied by the elimination of 4. The intermediate (14) undergoes ring fission of thiazolidine by the nucleophilic attack of another molecule of 2 to yield the desired 4 and the 2-substituted 1,3-diphenylimidazolidine intermediate (16).

Compound 17 and the intermediate (10) are formed by C-C bond cleavage between 2- and α-position of 16. Compound 11 is formed from the intermediate (10). The minor product 18 seems to be formed by the reaction of phenylacetyl group in R_1 with 2. Attempts to prepare 4 from 6a by using aliphatic diamine such as ethylenediamine in similar conditions were unsuccessful.

From the results described above, it became clear that 2 reacts with 1, 6, and 13 to give 4.

EXPERIMENTAL

Melting points are uncorrected. Mass spectra (ms) were taken on a Shimazu LKB 9000 spectrometer, and ir spectra were recorded on a JASCO DS-301 spectrometer. ^{1}H Nmr and ^{13}C nmr spectra were recorded on a Varian XL-200 instrument. $[\alpha]_D$ was determined on a JASCO DIP-360 instrument.

Phenoxymethylpenicilloic Acid α-Amides 6e and 6f[7]

Phenoxymethylpenicillin potassium salt (7.74 g, 20 mmol) was dissolved in water (50 ml). To this solution phenethylamine (2.42 g, 20 mmol) was added dropwise with stirring at room temperature over 30 min, and then stirring was continued for 5 h. The mixture was acidified with 50% phosphoric acid, and the resulting crystals were filtered and washed with water.

Recrystallization from methanol-water (1:1) gave α-phenethylamide (6e) as a white powder. Yield, 7.3 g (75%), mp 99-102 °C. ^{1}H Nmr (DMSO-d_6) δ : 1.18 (3H, s, CH_3), 1.53 (3H, s, CH_3), 2.72 (2H, t, J=6 Hz, $-CH_2\underline{CH_2}Ph$), 3.29 (2H, m, $-\underline{CH_2}CH_2Ph$), 3.57 (1H, s, H-4), 4.43 (1H, dd, J=8 and 6 Hz, methine proton), 4.54 (2H, s, $-CH_2OPh$), 4.89 (1H, d, J=6 Hz, methine proton), 6.89-7.39 (10H, m, ArH), 8.06 (1H, d, J=8 Hz, NH), 8.25 (1H, t, J=5 Hz, NH), 12.91 (1H, br s, CO_2H). Signals due to 3-NH are concealed in other signals. Ir ν_{max}^{KBr} cm^{-1}: 1645 (C=O), 2910, 3280 (NH). Ms m/z: 472 (M^++1). Anal. Cacld for $C_{24}H_{29}N_3O_5S\cdot H_2O$: C, 58.87; H, 5.97; N, 8.58. Found: C, 59.15; H, 6.15; N, 8.64.

Amide hydrate (6f) was similarly prepared by using benzylamine instead of phenethylamine. Yield, 75%, mp 65-71 °C. ^{1}H Nmr (DMSO-d_6) δ : 1.09 (3H, s, CH_3), 2.55 (3H, s, CH_3), 3.57 (1H, s, H-4), 4.30 (2H, d, J=7 Hz, $-CH_2Ph$), 4.50 (1H, t,[8]

J=8 Hz, methine proton), 4.57 (2H, s, $-CH_2Ph$), 4.96 (1H, d, J=8 Hz, H-2), 6.94-7.41 (10H, m, ArH), 8.13 (1H, d, J=8 Hz, NH), 8.67 (1H, t, J=7 Hz, NH). Signals due to 3-NH and CO_2H are concealed in other signals. Ir $\nu_{max}^{KBr}cm^{-1}$: 1645 (C=O), 2910, 3280 (NH). Ms m/z: 458 (M^++1).

Reaction of Benzylpenilloic Acid (1) with *N,N'*-Diphenylethylenediamine (2)

Benzylpenilloic acid hydrate (1) (3.26 g, 10 mmol) and *N,N'*-diphenylethylenediamine (2) (2.55 g, 12 mmol) were added to a mixture of water (30 ml), acetic acid (60 mg, 1 mmol) and toluene (20 ml).

The mixture was heated under reflux with stirring for 6 h under a nitrogen atmosphere. After the resulting mixture was allowed to stand at room temperature for 2 h, the precipitated product formed was filtered and washed with water, dried in vacuo to give the recovered 1 (2.15 g). Then toluene layer was removed from the filtrate by decantation, and aqueous layer was washed with two times of 10 ml portions of chloroform and evaporated under reduced pressure. The remaining solid was washed with methanol to give D-penicillamine (4) (340 mg, 23%), mp 198-200 °C, (lit.[9] mp 200-205 °C), $[\alpha]_D^{25}$ -62.90° (1N-NaOH, c=1) (lit.[9] $[\alpha]_D^{22}$ -61°). The toluene layer was washed with water and dried over anhydrous sodium sulfate and evaporated. The remaining residue was chromatographed on silica gel (50 g) with hexane-ethyl acetate (1:1, v/v) as an eluent. The first fraction of the eluate gave the recovered 2 (1.50 g). The second fraction eluted with the same solvent gave 2-(1-phenylacetylaminomethyl)-1,3-diphyenylimidazolidine (5) (830 mg, 22%) as a white powder, mp 131-133 °C (from ether). ^1H Nmr ($CDCl_3$) δ: 3.42 (2H, t, J=7 Hz, $-CH_2CH_2-$), 3.48 (2H, s, $-CH_2Ph$), 3.50 (2H, t, J=7 Hz, $-CH_2CH_2-$), 3.55 (2H, q, J=5 and 6 Hz, $-CH_2NH-$), 5.51 (1H, t, J=5 Hz, H-2), 5.57 (1H, t, J=6 Hz, NH), 6.66-7.38 (15H, m, ArH). Ir $\nu_{max}^{KBr}cm^{-1}$: 1642 (C=O), 2920, 3300, (NH). Ms m/z: 371 (M^+). Anal. Calcd for $C_{24}H_{25}N_3O$: C, 77.60; H, 6.78; N, 11.31. Found: C, 77.47; H, 6.73; N, 11.28.

Typical Procedure for the Reaction of Penicilloic Acid α-Amide Hydrate (6a-f) with *N,N'*-Diphenylethylenediamine (2)

α-Phenethylamide hydrate (6a) (4.74 g, 10 mmol) and *N,N'*-diphenylethylenediamine (2) (2.55 g, 12 mmol) were added to a mixture of acetic acid (60 mg, 1 mmol) and water (30 ml). The mixture was heated under reflux with stirring for 5 h under a nitrogen atmosphere. After being cooled, the mixture was extracted with chloroform. Aqueous

layer was evaporated under reduced pressure. The remaining solid was washed with methanol to give D-penicillamine (4) (760 mg, 51%), mp 201-202 °C. The organic extract was dried over sodium sulfate and evaporated. The resulting residue was chromatographed on silica gel (50 g) with methanol-chloroform (1:99, v/v) as an eluent. The first fraction of the eluate gave *N*-2-anilinoethylformanilide (11) (1.52 g, 63%) as colorless prisms, mp 59-60 °C (from ether-petroleum ether), (lit.[4] mp 65-66 °C). The second fraction of the eluate gave phenaceturic acid α-phenethylamide (8a) (2.25 g, 76%) as colorless prisms, mp 143-145 °C (from methanol-petroleum ether), (lit.[10] mp 141-144 °C).

The other amides (6b-f) were also treated with 2 to give 4, 8b-f and 11. The results are summarized in Table 1. 8b; mp 172-173 °C (lit.[11] mp 174-176 °C), 8c; mp 158-160 °C (lit.[12] mp 158-160 °C), 8d; mp 170-171 °C (lit.[13] mp 170-171 °C), *N*-phenoxyacetylglycine α-phenethylamide (8e); colorless prisms, 159-161 °C (from ether-petroleum ether). ^{1}H Nmr (DMSO-d_6) δ: 2.72 (2H, t, J=8 Hz, $-CH_2Ph$), 3.30 (2H, m, $-CH_2CH_2Ph$), 3.75 (2H, d, J=6 H, $-NHCH_2CO-$), 4.54 (2H, s, $-CH_2OPh$), 6.94-7.42 (10H, m, ArH), 7.98 (1H, t, J=6 Hz, NH), 8.27 (1H, t, J=6 Hz, NH). Ir ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 3240 (NH). Ms m/z: 313 (M^++1). Anal. Cacld for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.35; H, 6.45; N, 8.99.

N-phenoxyacetylglycine α-benzylamide (8f): colorless prisms, mp 148-149 °C (from ether-petroleum ether). ^{1}H Nmr (DMSO-d_6) δ: 3.82 (2H, d, J=7 Hz, $-NHCH_2CO$), 4.30 (2H, d, J=7 Hz, $-NHCH_2Ph$), 4.54 (2H, s, $-CH_2OPh$), 6.92-7.40 (10H, m, ArH), 8.34 (1H, t, J=7 Hz, NH), 8.40 (1H, t, J=7 Hz, NH).

Ir ν_{max}^{KBr} cm^{-1}: 1670 (C=O), 3280, 3390 (NH). Ms m/z: 299 (M^++1). Anal. Cacld for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.50; H, 6.04; N, 9.39.

Reaction of Benzylpenicillin Potassium Salt (13) with *N,N'*-Diphenylethylenediamine (2)

Benzylpenicillin potassium salt (13) (7.44 g, 20 mmol) and *N,N'*-diphenylethylenediamine (2) (8.49 g, 40 mmol) were added to a mixture of acetic acid (2.40 g, 40 mmol) and water (60 ml). The mixture was heated under reflux with stirring for 6 h under a nitrogen atmosphere. After being cooled, the mixture was extracted with chloroform. Aqueous layer was evaporated under reduced pressure and the resulting residue was triturated with methanol. The separated crystals were collected by filtration, washed with methanol and dried to give D-penicillamine (4)

(860 mg, 29%), mp 197-198 °C, $[\alpha]_D^{25}$ -65.80°. The organic extract was dried over sodium sulfate and evaporated. The resulting residue was chromatographed on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) gave four fractions; fr. 1: starting material 2, 4.8 g, fr. 2: *N*-(2-anilinoethyl)phenylacetanilide (18) (184 mg, 2.8%), colorless prisms, mp 93-95 °C (from benzene-hexane). ^{1}H Nmr ($CDCl_3$) δ: 3.26 (2H, t, J=6 Hz, $-C\underline{H}_2CH_2-$), 3.44 (2H, s, $-CH_2Ph$), 3.99 (2H, t, J=6 Hz, $-CH_2C\underline{H}_2-$), 4.26 (1H, br s, NH), 6.48-7.52 (15H, m, ArH). Ir ν_{max}^{KBr} cm^{-1}: 1645 (C=O), 3340 (NH). Ms m/z 330 (M^+). Anal. Cacld for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.09; H, 6.73; N, 8.40., fr. 3: *N*-2-anilinoethylformanilide (11) (2.51 g, 49%), and fr. 4: a mixture of 15 and 17.

Fr. 4 was rechromatographed with chloroform-methyl isobutyl ketone-acetic acid (6: 3.5: 0.5, v/v) as an eluent. The first fraction of the eluate gave *N*-(2-anilinoethyl)-2-phenylacetamidoacetanilide (17) (3.63 g, 47%) as colorless prisms, mp 91-93 °C (ether-petroleum ether). ^{1}H Nmr ($CDCl_3$) δ: 3.25 (2H, t, J=5 Hz, $-CH_2C\underline{H}_2-$), 3.58 (2H, s, $-CH_2Ph$), 3.68 (2H, t, J=4 Hz, $-C\underline{H}_2NH$), 3.95 (2H, t, J=5 Hz, $-C\underline{H}_2CH_2-$), 4.20 (1H, br s, NH), 6.43 (1H, t, J=4 Hz, NH), 6.48-7.52 (15H, m, ArH). ^{13}C Nmr ($CDCl_3$, 50.43 MHz) δc: 170.7, 169.1, 147.8, 140.0, 134.7, 130.3 (2C), 129.3 (2C), 129.2 (2C), 129.0, 128.9 (2C), 128.1 (2C), 127.3, 117.4, 112.5 (2C), 48.9, 43.5, 42.4, 42.0. Ir ν_{max}^{KBr} cm^{-1}: 1670, 1645 (C=O), 3318 (NH). Ms m/z 338 (M^++1). Anal. Cacld for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.85. Found: C, 74.30; H, 6.45; N, 10.78.

The latter fraction of eluate gave 6,7-dihydro-6*H*-3-phenylacetylamino-1,5-diazepin-2-one (15) (517 mg, 6.5%) as colorless prisms, mp 171-173 °C (from benzene-hexane). ^{1}H Nmr ($CDCl_3$) δ: 3.64 (2H, s, $-CH_2Ph$), 3.99 (4H, s, $-C\underline{H}_2C\underline{H}_2$), 7.38-7.77 (15H, m, ArH), 7.88 (1H, s, NH), 8.41 (1H, s, H-4). ^{13}C Nmr ($CDCl_3$, 50.3 MHz) δc: 169.3, 165.1, 146.8, 144.1, 134.9, 134.3, 129.5 (2C), 129.4 (2C), 129.3 (2C), 128.9 (2C), 127.2, 126.8, 126.2 (2C), 124.1, 119.8 (2C), 105.8, 53.1, 49.7, 45.0, Ir ν_{max}^{KBr} cm^{-1}: 1630 (C=O), 3270 (NH). Ms m/z: 398 (M^++1). Anal. Cacld for $C_{25}H_{23}N_3O_2$: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.67; H, 5.82; N, 10.50.

REFERENCES AND NOTES

1. J. M. Walshe, Am. J. Med., 21, 487 (1956); I. A. Jaffe, Ann. Rheum. Dis., 22, 71 (1963); F. M. Andrews, D. N. Golding, A. M. Freeman, J. R. Golding, A. T. Day, A. G. S. Hill, A. V. Camp, E. Lewis-Faning, and W. H. Lyle, Lancet., 1, 275 (1973).
2. T. Ogawa, K. Tomisawa, and K. Sota, Chem. Pharm. Bull., 36, 1957 (1988).
3. T. Ogawa, K. Tomisawa, and K. Sota, Heterocycles, 27, 1421 (1988).
4. F. B. Zienty, J. Am. Chem. Soc., 68, 1388 (1946).
5. M. May, T. J. Bardos, F. L. Barger, M. Lansford, J. M. Ravel, G. L. Sutherland, and W. Shive, J. Am. Chem. Soc., 73, 3067 (1951).
6. D. R. Robinson, Tetrahedron Lett., 48, 5007 (1968); D. R. Robinson, J. Am. Chem. Soc., 92, 3138 (1970).
7. 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., 298 (1979).
8. It might be better to treat it as doublet of doublet (J=8 and 8 Hz).
9. J. J. Herak, M. Kovacevic, and B. Gaspert, Croat. Chem. Acta, 49, 141 (1977).
10. H. Hitomi, Yakugaku Zasshi, 79, 1611 (1959).
11. H. Hitomi, Yakugaku Zasshi, 74, 188 (1954).
12. H. Hitomi, Yakugaku Zasshi, 74, 185 (1954).
13. T. E. David, Ger. Offen. 1,927,692 (1969) [Chem. Abstr., 72, 555885j (1970)].

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