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METABOLITES OF FELBAMATE: SYNTHESIS OF 2-(4-HYDROXYPHENYL)-1,3-PROPANEDIOL DICARBAMATE, 2-PHENYL-2-HYDROXY-1,3-PROPANEDIOL DICARBAMATE, AND 2-PHENYL-1,3-PROPANEDIOL MONOCARBAMATE

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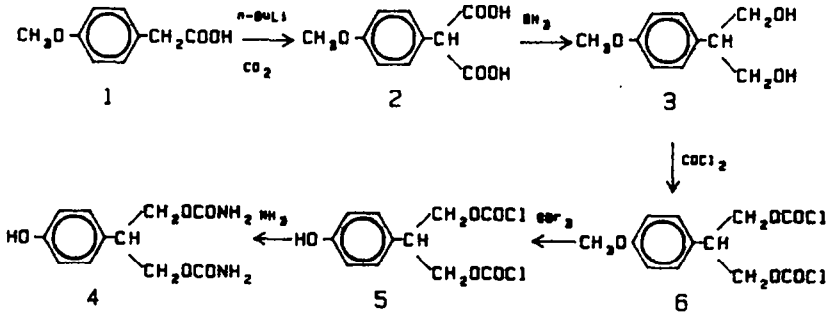
Abstract -- Three major metabolites of felbamate, namely 2-(4-hydroxyphenyl)-1,3-propanediol dicarbamate [4], 2-hydroxy-2-phenyl-1,3-propanediol dicarbamate [12], and 2-phenyl-1,3-propanediol monocarbamate [17] were prepared. The first metabolite, 4, was synthesized from p-methoxy-phenylacetic acid [1] via five steps involving carboxylation, reduction, phosgenation, demethylation, and carbamation. The second one, 12, was prepared from 2-phenyl-1,3-propanediol [7] by the following five steps: phosgenation, halogenation, carbamation, dehalogenation, and ammonolysis. The synthesis of the third metabolite, 17, started with 7, via the following five steps: methylation, phosgenation, carbamation, and demethylation.

Felbamate, 2-phenyl-1,3-propanediol dicarbamate, is a new anticonvulsant agent[1] which is currently undergoing clinical trials. The biotransformation of felbamate has been studied in the rat *in vitro*[2] and in the rat, dog, and rabbit *in vivo*[3]. The three major metabolites identified were 2-(4-hydroxyphenyl)-1,3-propanediol dicarbamate, 2-hydroxy-2-phenyl-1,3-propanediol dicarbamate, and 2-phenyl-1,3-propanediol monocarbamate. To facilitate positive identification, the above three metabolites were needed to serve as authentic reference compounds. The development of synthetic procedures for the three metabolites is described in this paper. The procedures for direct reduction of malonic acids to the corresponding propanediols and for introduction of the hydroxy group into the 2-phenylpropane chain may be of general utility.

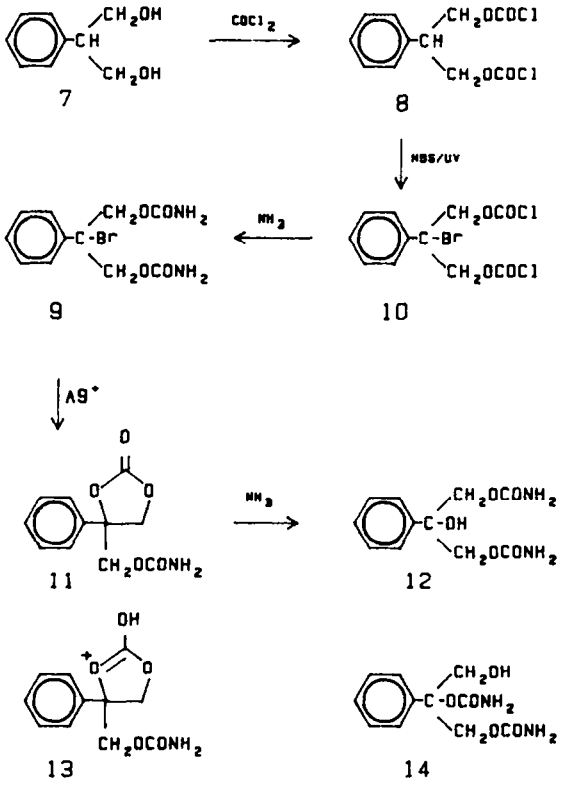
The first metabolite, 2-(4-hydroxyphenyl)-1,3-propanediol dicarbamate [4] was synthesized in five steps (Scheme I) from 4-methoxyphenylacetic acid [1] via 2-(4-methoxyphenyl)malonic acid [2], 2-(4-methoxyphenyl)-1,3-propanediol [3], its bischloroformate [6], and 2-(4-hydroxyphenyl)-1,3-propanediol bischloroformate [5] following, in part, the procedure developed for ^{14}C-labeling of felbamate[4].



SCHEME I

According to Barnes et. al[5] organic carboxylic acids can be synthesized from a compound containing an acidic C-H bond by carboxylation utilizing n-butyl lithium and carbon dioxide. Thus, the first step was successfully carried out by carboxylation of 4-methoxyphenylacetic acid [1] with the reagents mentioned above. The purification by recrystallization yielded 58% of pure 2. The borane-tetrahydrofuran complex, known to be an excellent selective reducing agent for carboxylic acids[6], reacted with 2 at low temperatures. The optimal reduction conditions were determined to be a two-step reduction with 200% excess of hydride. The yield of 3 after further recrystallization was 61%. In the third step phosgenation[7] was completed in 2 h with pure tetrahydrofuran as solvent leading to the bischloroformate of 2-(4-methoxyphenyl)-1,3-propanediol [6]. Subsequently, the demethylation by boron tribromide was carried out in methylene chloride[8], followed by addition of anhydrous ammonia[7,9], which lead to the desired 2-(4-hydroxyphenyl)-1,3-propanediol dicarbamate [4]. After further recrystallization the overall yield of the last three steps was 42%. The structure of the new compound was confirmed by ^{1}H-NMR spectra, mass spectrometry, UV, and elemental analysis.

The preparation of the second metabolite, 2-hydroxy-2-phenyl-1,3-propanediol dicarbamate [12] started with the readily available diethyl phenylmalonate[10], which was reduced to 2-phenyl-1,3-propanediol [7]. This synthesis involved a five-step procedure from 7 to the desired product via the following intermediate: bischloroformate of 2-phenyl-1,3-propanediol [8], 2-bromo-2-phenyl-1,3-propanediol bischloroformate [10], 2-bromo-2-phenyl-1,3-propanediol dicarbamate [9], and 4-phenyl-1,3-dioxolan-2-one-4-yl-methanol carbamate [11] (Scheme II). The improved preparation of 7 was developed by the reduction of diethyl phenylmalonate with lithium aluminum hydride utilizing a new technique[11] and giving a higher yield (70%). After the formation of the intermediate, 8, by the phosgenation of 7, free radical bromination[12] yielded 2-bromo-2-phenyl-1,3-propanediol

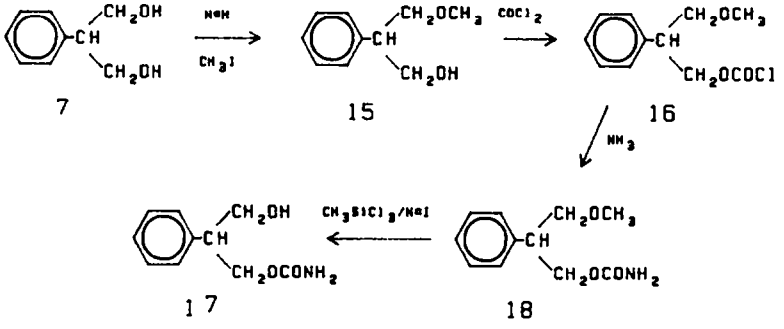


SCHEME II

bischloroformate [10]. The bromination was carried out with N-bromosuccinimide (NBS) under irradiation with UV light in the presence of dibenzoyl peroxide. Subsequently, carbamation was performed by addition of an excess amount of anhydrous ammonia to give the corresponding 9. The overall yield for the last three steps was 84%. Silver acetate, reported to be a dehalogenating agent[13], reacted with 9 in the presence of acetic acid but contrary to expectations, the product formed was 4-phenyl-1,3-dioxolane-2-one-4-yl-methanol carbamate [11] in a yield of 56%. This could be due to formation of a heterocyclic oxonium ion, 13, as indicated in Scheme II.

Ammonolysis of the cyclic carbonate, 11, was carried out in the presence of anhydrous liquid ammonia. The course of the reaction could conceivably provide two products, 2-hydroxy-2-phenyl-1,3-propanediol dicarbamate [12], and 1-hydroxy-2-phenyl-2,3-propanediol dicarbamate [14]. However, the only reaction product isolated in a quantitative yield was 12. Its structure was confirmed by ^{1}H-NMR spectra, IR spectra, UV, elemental analysis, and mass spectroscopy.

The synthesis of the third metabolite, 2-phenyl-1,3-propanediol monocarbamate [17] has been accomplished starting from the diol 7 via a four-step reaction shown in Scheme III. This procedure involved the monomethylation of 7, phosgenation of 2-phenyl-3-methoxypropanol [15], carba-



SCHEME III

mation of 2-phenyl-3-methoxypropanol chloroformate [16], and finally, demethylation of 2-phenyl-3-methoxy-propanol carbamate [18] to 17. The 2-substituted alkyl-1,3-propanediol monocarbamates have been synthesized by ammonolysis of the cyclic carbamates[9] prepared from a wide variety of 2-substituted alkyl-1,3-propanediols and phosgene. However, the procedure led to some difficulties to synthesize 17 due to polymerization of the cyclic intermediate. As shown in Scheme III, the methylation reaction was carefully controlled with a stoichiometric amount of 7 and sodium hydride, followed by addition of excess methyl iodide[14]. The crude product, 15, was used for the next step without further purification. Subsequently, the procedure used for phosgenation and carbamation was identical to that described above. The yield of 18 in the last two steps was 55%. The recently described combination of trichloromethylsilane and sodium iodide, a selective demethylation procedure for aliphatic ethers in the presence of other functional groups[15], was utilized in selective demethylation of 18 to 17 at ambient temperature. After further purification the final yield of 17 was 96%. The structure of 17 was confirmed by ^{1}H-NMR spectra, IR spectra, TLC analysis, and mass spectrometry.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a JEOL JNM-100MHR, spectrometer in chloroform-d_1, dimethylsulfoxide-d_6, and acetone-d_6 with tetramethylsilane (TMS) as internal reference. Infrared spectra were obtained on a Beckman IR-9 spectrometer. GC-Mass spectra (EI) were taken on a 5985-Hewlett Packard mass spectrometer at 70 ev. Thin layer chromatography (TLC) was performed on silica gel 60F 254 plates of 0.25 mm thickness (EM Scientific). UV spectra were recorded

tetrachloride. After stirring for a while, 93.04 mmol (16.6 g) of NBS and 0.22 mmol (0.05 g) of dibenzoyl peroxide were introduced in two portions under N_2. The mixture was refluxed for four days and simultaneously exposed to UV light (150 W bulb) for three days. The insoluble material was filtered, the clear solution in carbon tetrachloride was concentrated to 80 mL, and cooled to 0°C under N_2. Anhydrous ammonia was bubbled into the solution under stirring for 30 min at 0°C. The precipitate was filtered off and dissolved in 700 mL of refluxing acetone. After filtration and concentration of the solution, the red brownish oily material was redissolved in 500 mL of methylene chloride and cooled at 0°C. The insoluble material was filtered off, and the clear solution was concentrated. Purification by column chromatography on silica gel with a mixture of acetone and hexane (2:1) provided 13.81 g (43.54 mmol, 84%) of 9 as a colorless solid with mp 111-113°C; ^{1}H NMR (Me_2SO-d_6) δ 5.1 (d, 2H, CH_2), 4.9 (d, 2H, CH_2), 6.5 (s, 4H, $2NH_2$), and 8.0 (m, 5H, Ph).

Anal. Calcd. for $C_{11}H_{13}N_2O_4Br$: C, 41.65; H, 4.10; N, 8.83; Br, 25.19. Found: C, 41.82; H, 4.28; N, 8.64; Br, 24.91.

4-Phenyl-1,3-dioxolan-2-one-4-yl-methanol [11]. The reaction was carried out under N_2 in the dark in a 250 mL RB flask with a side arm and N_2 outlet connecting tube. To the predried three-necked flask, kept in the dark, 13.60 g (42.88 mmol) of 9 and 600 mL of glacial acetic acid were added under N_2. A suspension of 14.32 g (85.76 mmol) of silver acetate in 5 mL of water was then introduced into the flask at RT and kept stirred overnight (22 h). To prevent photo-decomposition of silver acetate, the flask was covered with aluminum foil. The heterogeneous mixture was filtered, washed twice with THF, and concentrated under reduced pressure to give a colorless oily material. Addition of cold water provided a greyish white solid in a yield of 7.18 g (71%). To it a mixture of methylene chloride, tetrahydrofuran (THF), and acetone (2:1:1) were added and the mixture heated to reflux under stirring for 20 min. Charcoal was added, and the solution filtered and concentrated to 5 mL of solution. Addition of excess ether gave a colorless white solid of 11 in a yield of 5.59 g (23.56 mmol, 56%) with a mp 132-133°C; ^{1}H NMR (Me_2SO-d_6) δ 4.41 (s, 2H, CH_2), 4.7 (d, 1H, CH), 4.95 (d, 1H, CH), 6.85 (s, 2H, NH_2), and 7.6 (s, 5H, Ph).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.91. Found: C, 56.06; H, 4.84; N, 5.97.

2-Hydroxy-2-phenyl-1,3-propanediol Dicarbamate [12]. Without stirring at RT 6.13 g (25.84 mmol) of 11 was slowly introduced into a test tube containing 7 mL of liquid ammonia giving a yellowish homogeneous solution. The tube was put in a stainless steel pressure bottle (2" diam. x 5" L) and maintained at RT for 24 h without stirring. The bottle was immersed in dry ice-acetone temperature for a while and then slowly opened by releasing the pressure. Excess ammonia was evaporated off at RT giving 6.5 g of a highly viscous yellowish oily material. The crude product was then purified by column chromatography (2.5 x 50 cm) on 160 g of silica gel with a 3:2 mixture of acetone and hexane as eluting solvent. The fractions containing the desired compound (determined by TLC analysis) were combined and the solvent was removed under reduced pressure (1 torr, RT). The yield was 6.15 g (24.19 mmol, 94%) of 12 as colorless crystals with a mp 42-43°C; ^{1}H NMR (Me_2SO-d_6) δ 4.8 (s, 4H, CH_2), 6.7 (s, 4H, NH_2), 5.4 (s, 1H, OH), and 8.3-8.7 (m, 5H, Ph); IR (Me_2SO filtered) cm^{-1} 3350 (OH, s), 3200 (NH, s), 1620 (NH, m), 1710 (C=O, s), and 1150 (C-O, bm); UV (3.9 x 10^{-3} M in MeOH) nm 212 and 255; MS, m/e (relative intensity) 91 (100), 119 (58), 137 (61), and 180 (41).

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.99; H, 5.54; N, 10.95.

3-Methoxy-2-phenylpropanol [15]. To a 500 mL three-necked flask 7.6 g (50 mm) of 7 and 100 mL of dry DMSO were added under N_2 at RT. Then 1.2 g (50 mmol) of sodium hydride (after washing the 40% oil off with hexane) was slowly added in five separate portions to the flask under stirring. After additional stirring for 5 h at RT, 3.1 mL (50 mmol) of methyl iodide was slowly introduced into the flask from a syringe at 0°C under stirring and kept stirred overnight at RT. Then 150 mL of water and 100 mL of ether were introduced and extracted twice with an additional 100 mL of ether. The combined ether was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a colorless oil corresponding to 15. The yield was 5.51 g (66%). This material was then used for the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 1H, OH), 3.20 (s, 3H, OCH_3), 3.62 (m, 4H, $2CH_2$), 3.04 (m, 1H, CH), and 7.08 (s, 5H, Ph).

3-Methoxy-2-phenylpropanol Carbamate [18]. To a predried 250 mL flask 2.77 g (16.7 mmol) of 15 and 50 mL of dry THF were added at RT. Then under N_2 at 0°C 3.60 mL (50 mmol) liquid phosgene was added to the solution in the flask. The mixture was maintained at RT for 2 h, then the solvent evaporated under reduced pressure, and 100 mL of fresh toluene was added. The flask was cooled to 0°C under N_2 and anhydrous ammonia was bubbled into the solution under stirring for 30 min at 0°C. The white precipitate was stirred for an additional 30 min at RT then filtered off to collect the filtrate. The solvent was evaporated under reduced pressure giving a slightly yellowish solid. The crude

on a Beckman model 25 spectrophotometer. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. All reactions were performed under a nitrogen atmosphere. All ether solvents were freshly distilled over lithium aluminum hydride under a nitrogen atmosphere. Methanol and DMSO were stored over Linde 3-A molecular sieves. The glassware was heated to 100°C and then cooled under nitrogen at room temperature (RT) before use.

4-Methoxyphenylglycolic Acid [2]. The entire reaction was carried out under N_2 in a 500 mL RB three-necked flask. To this flask 12.45 g (75 mmol) of 1 and 87 mL of dry THF were added at RT and cooled to dry ice temperature. Then 87 mL (200 mmol) of n-butyl lithium in hexane was slowly introduced to the flask under stirring. After additional stirring for 2 h at dry ice temperature, 50 g of solid CO_2 was slowly added in four portions and kept stirred for another 2 h at dry ice temperature and for 30 min at RT. The mixture was decomposed by the addition of 250 mL of 2N HCl under stirring causing the separation of two layers and extracted with 100 mL of ethyl ether. The organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure giving a yellow oil. To the crude product ethyl ether was added until all dissolved followed by excess hexane. After 2 h in the refrigerator, the solvent was decanted and , the residue was recrystallized from a mixture of toluene and methylene chloride, 2:1, producing a white crystalline material, corresponding to 2. The yield was 9.06 g (58%) with a mp of 141-143°C [Lit.[16], mp 137-138°C]; ^1H NMR (Me_2CO-d_6) δ 3.76 (s, 3H, OMe), 4.69 (s, 1H, CH), and 6.9-7.5 (q, 4H, Ph).

2-(4-Methoxyphenyl)-1,3-propanediol [3]. To a three-necked predried flask 6.62 g (31.5 mmol) of 2, 1 mL of methanol, and 10 mL of dry THF were added at RT. At 0°C under N_2 225 mL (189 mmol) of a 0.84M solution of borane:THF in THF was slowly introduced into the flask from a syringe under stirring and then stirred at 0°C for 6 h. Then 100 mL of dry methanol was slowly added at 0°C. The excess solvent was distilled off under reduced pressure. Then 225 mL (189 mmol) of borane:THF in THF was slowly added at 0°C. After stirring for another 6 h at 0°C, 100 mL of dry methanol was slowly introduced into the flask. The reaction mixture was kept at RT overnight. Excess solvent was removed under reduced pressure, and to the oily residue 100 mL of ethyl ether was introduced and then washed twice with a saturated potassium carbonate solution. The combined ether layers were dried over anhydrous magnesium sulfate and concentrated by reduced pressure. To this 50 mL of toluene was added to facilitate removal of the excess trimethyl borate and evaporation repeated until the contents of the flask solidified. The product was then purified by recrystallization from a mixture of toluene and trichloroethylene 2:1 yielding 3.1 g (51%) of 3, as shiny white crystalline substance, melting at 83-85°C. ^1H NMR ($CDCl_3$) δ 2.96 (m, 1H, CH), 3.4 (s, 2H, OH), 3.8 (t, 4H, $2CH_2$), and 6.76-7.14 (q, 4H, Ph).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.93; H, 7.74. Found: C, 66.21; H, 7.73.

2-(4-Hydroxyphenyl)-1,3-propanediol Dicarbamate [4]. To the predried 250 mL RB flask 3.0 g (16.46 mmol) of 3 and 50 mL of THF at RT were added. Under N_2 atmosphere at 0°C 2.9 mL (40 mmol) of liquid phosgene was added to the contents of the flask. The mixture was maintained at RT for 2½ h. The solvent was evaporated under reduced pressure and to this residue, in 25 mL of methylene chloride, 33 mL (33 mmol) of a 1.0 M solution of boron tribromide in methylene chloride were slowly added at 0°C under N_2. Then the mixture was stirred at 25°C for 2 h. The contents of the flask were cooled to 0°C and anhydrous ammonia was bubbled into the solution for 30 min at 0°C. After the precipitate was filtered, a mixture of 10 mL of distilled water and 30 mL of THF were added and the contents stirred for 10 min at RT, separating two layers. The organic layer was collected and, after saturation with sodium chloride, the aqueous layer was extracted with 50 mL of THF. The combined organic layer was dried over anhydrous magnesium sulfate and charcoal, filtered, and concentrated. To the oily residue 50 mL of fresh THF was added for dissolution, and the volume was reduced under reduced pressure to 15 mL. After addition of methylene chloride, a colorless solid precipitate formed after cooling to 0°C for 30 min. Filtration gave 1.76 g (42%) of 4, mp 181-183°C; ^1H NMR (Me_2SO-d_6) δ 3.12 (m, 1H, CH), 4.14 (d, 4H, $2CH_2$), 6.48 (s, 4H, NH_2), 6.68-7.32 (q, 4H, Ph), and 9.32 (s, 1H, OH); UV (1.2×10^{-4} M in MeOH) nm 222 and 275; MS, m/e (relative intensity), 91 (40), 120 (60), 150 (100), and 193 (15).

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.78; H, 5.77; N, 10.89.

2-Bromo-2-phenyl-1,3-propanediol Dicarbamate [9]. To a predried 250 mL three-necked flask 7.85 g (51.58 mmol) of 7 and 20 mL of dry THF were added under N_2 at RT. Then 261 mL (287.38 mmol) of a 1.1 M solution of phosgene in toluene was slowly introduced at 0°C with a syringe followed by 21.2 g (113.48 mmol) of antipyrine in 25 mL of chloroform. The mixture was kept overnight at RT. The precipitate of antipyrine hydrochloride was filtered off, and the solution evaporated under reduced pressure. The oily material corresponding to 51.58 mmol of 8 was transferred to a pre-dried, 2000 mL three-necked flask, and 0.22 mmol (0.05 g) of dibenzoyl peroxide were added in 1000 mL of carbon

product was purified by recrystallization from toluene-hexane (1:5) at 0°C for 30 min yielding 1.91 g (55%) of 18 as colorless crystals, mp 83-86°C; ^{1}H NMR (Me_2SO-d_6) δ 3.18 (m, 1H, CH), 3.20 (s, 3H, OCH_3), 3.46 (d, 2H, CH_2), 4.14 (d, 2H, CH_2), 6.42 (s, 2H, NH_2), and 7.29 (s, 5H, Ph).

Anal. Calcd. for $C_{11}H_{15}N_1O_3$: C, 63.14; H, 7.24; N, 6.69. Found: C, 62.99; H, 7.40; N, 6.69.

2-Phenyl-1,3-propanediol Monocarbamate [17]. To a predried flask 2.0 g (9.55 mmol) of 18 and 25 mL of dry acetonitrile were added under N_2 at RT, then 1.35 mL (11.46 mmol) of trichloromethylsilane was slowly introduced with a syringe and then 1.72 g (11.46 mmol) of sodium iodide in 10 mL of acetonitrile. The yellowish solution was kept at RT for 24 h, quenched with 120 mL of a 1:5 mixture of water and THF with stirring, and saturated with potassium carbonate to separate the two layers. The combined organic layers were first washed with 100 mL of aqueous sodium thiosulfate, then with saturated sodium chloride and dried over anhydrous magnesium sulfate. Concentration under reduced pressure produced a yellowish oily product which was purified by column chromatography on silica gel with a mixture of acetone and hexane (3:2). This gave 1.80 g (0.22 mmol) of a slightly yellowish solid which by recrystallization from a 1:2 mixture of ether and toluene yielded 1.78 g (9.2 mmol, 96%) of 17 as a colorless solid with a m.p. 72-74°C. TLC on silica gel (60F-254, 5 x 10 cm) with a 1:1 mixture of acetone and hexane showed only one spot (R_f=0.28); ^{1}H NMR (Me_2SO-d_6) δ 2.25 (m, 1H, CH), 3.9 (d, 2H, CH_2), 4.5 (d, 2H, CH_2), 6.05 (s, 2H, NH_2), 3.5 (s, 1H, OH), and 7.5 (s, 5H, Ph); IR (neat) cm^{-1} 3400 (O-H, s), 3200 (N-H, s), 1720 (C=O, s), and 1150 (C-O, s); MS, m/e (relative intensity) 91 (12), 104 (100), 134 (12), and 165 (5).

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