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Synthetic routes leading to the preparation of 4-substituted 1,4-benzodiazepine-3,5-diones are described. Thus, 2-carbobenzoxyaminobenzoic acid was converted to its *p*-nitrobenzyl ester (I) and the decarbobenzoxylated product (II) gave, with ethyl α -bromoacetate, *N*-(2-carboxy-*p*-nitrobenzylate)phenylglycine ethyl ester (III). The latter was hydrogenolyzed to *N*-(2-carboxy)phenylglycine ethyl ester (IV), which was coupled with benzylamine to give *N*-(2-carboxybenzylamido)phenylglycine ethyl ester (VIa). Saponification of VIa afforded *N*-(2-carboxybenzylamido)phenylglycine (VIIa) which was cyclized with DCCI to produce 4-benzyl-2*H*-1,4-benzodiazepine-3,5(1*H*,4*H*)dione (VIIIa). Alternatively, 2-nitro-*N*-phenylbenzamide (Xb) was reduced to 2-amino-*N*-phenylbenzamide (XIb) which was converted to *N*-(2-carboxanilido)phenylglycine ethyl ester (VIb). The latter was converted to 4-phenyl-2*H*-1,4-benzodiazepine-3,5(1*H*,4*H*)dione (VIIIb) in an analogous fashion described for VIIIa.

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Introduction

Since the discovery of psychophysiological activity in many compounds containing 1,4-benzodiazepine ring, the synthesis of such structures has been an elusive goal for many investigators (1). Previously it was reported that treatment of 2-amino-5-*R*-benzamides and dimethyl acetylenedicarboxylate gave high yields of Michael adducts, e.g. dimethyl 2-(*o*-carboxamidoanilino)butenedioates, which in turn were cyclized to 2-carbomethoxymethylene-1,4-benzodiazepine-3,5(1*H*,4*H*)diones (2,3). One of these products (*R* = H) displayed general central nervous system depressant activity and was nontoxic (2).

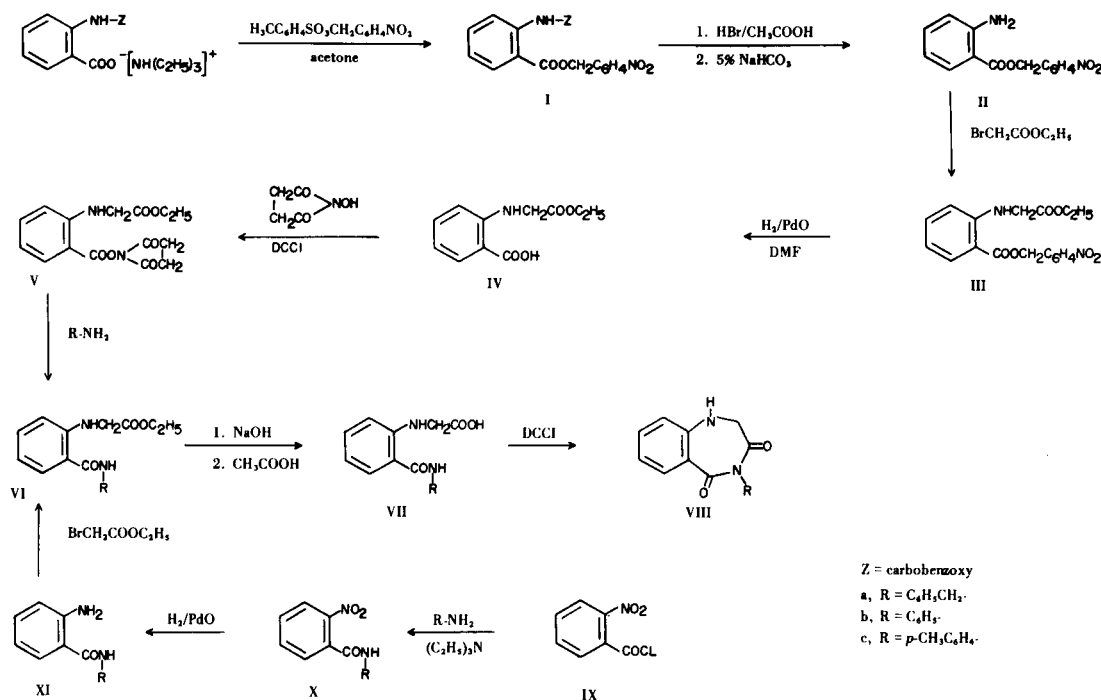
As part of a program designed to expand the chemistry of 1,4-benzodiazepine-3,5-diones, it became necessary to

explore synthetic routes leading to the synthesis of 4-substituted 1,4-benzodiazepine-3,5(1*H*,4*H*)diones. Here we present our initial results.

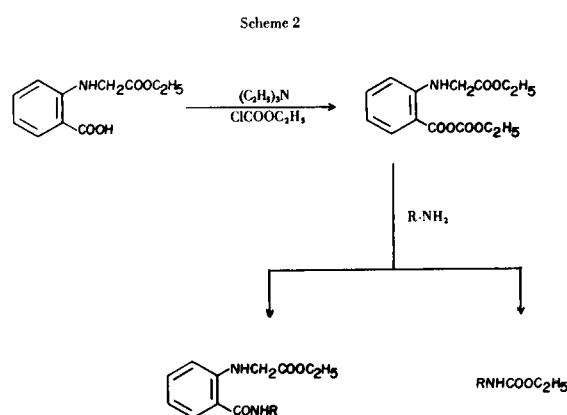
Results and Discussion

The original scheme utilized 2-carbobenzoxyamino-benzoic acid (*N*-carbobenzoxyanthranilic acid) as the starting material (Scheme 1). Treatment of the triethylammonium salt of the latter with *p*-nitrobenzyl tosylate (4) produced, by nucleophilic displacement of the tosyl moiety, *p*-nitrobenzyl 2-carbobenzoxyaminobenzoate (I) in high yield. Subsequently, the carbobenzoxo group was split off with hydrogen bromide/acetic acid and the obtained *p*-nitrobenzyl 2-aminobenzoate (II) upon treatment with ethyl α -bromoacetate, in ethanol solution and the

Scheme 1



presence of sodium carbonate, gave *N*-(2-carboxy *p*-nitrobenzylate)phenylglycine ethyl ester (III) in 50% yield. Catalytic hydrogenation of III over palladium black removed smoothly the *p*-nitrobenzyl group and afforded ethyl *N*-phenylglycinate-2-carboxylic acid (IV) in crystalline form and high yield. Attempts to activate the carboxyl group of IV *via* the mixed carbonic-carboxylic anhydride method (5) and couple it with various amines have failed. Apparently, due to steric hindrance, the nucleophilic attack of the amine upon the so-formed mixed anhydride of IV, leads mainly to formation of a carbamate instead of the desired amide derivative (6) (Scheme 2).



On the other hand, use of *N,N'*-dicyclohexylcarbodiimide (DCCI) (7), as the condensing agent of IV with amines resulted in formation of two products, which we were unable to separate by classical methods.

In a third approach, compound IV was combined with *N*-hydrosuccinimide (8) in the presence of DCCI to form the corresponding active ester (V) and the effectiveness of the latter for coupling was tested with various amines (Table I). Evidently, amines with low pK_b react with the

active ester V in high yields, while those with high pK_b values give low yields or they do not react at all. Characteristically, *p*-nitroaniline failed to react with the active ester V either at room temperature for two days or under reflux in tetrahydrofuran solution. As the next step, *N*-(2-carboxybenzylamido)phenylglycine ethyl ester (VIa) was selectively saponified with the equimolar amount of *N* sodium hydroxide at room temperature and upon acidification with acetic acid, the desired product *N*-(2-carboxybenzylamido)phenylglycine (VIIa) was obtained almost in quantitative yield. The structure of VIIa was confirmed by microanalytical and spectral data.

Attempted cyclization of VIIa with the use of thionyl chloride or phosphorus pentachloride gave no satisfactory results. Since DCCI has been successfully used for cyclization of related structures (9), this reagent was tested herein again. Indeed, the action of DCCI upon compound VIIa, in dilute tetrahydrofuran (THF) solution, led predominantly to formation of 4-benzyl-2*H*-1,4-benzodiazepine-3,5(1*H*,4*H*)dione (VIIIa) *via* intramolecular dehydration. When the thus resultant crude product (VIIIa) was checked by thin layer chromatography, a slower migrating contamination was detected. Repeated reprecipitations in various solvent systems failed to remove completely the undesirable by product, which was proven to be an acylurea derivative (7). High purity of VIIIa was secured by chromatographic separation on Sephadex LH-20 using 2-propanol as the eluant.

An alternative route for the preparation of 4-substituted 1,4-benzodiazepine-3,5-diones, employing *o*-nitrobenzoylchloride, as the starting material, has the added advantage that it eliminates the difficulties encountered during the coupling of V with a variety of amines, as previously described (Scheme 1). Thus, coupling of this chloride with aniline in a suitable solvent afforded 2-nitro-*N*-phenylbenzamide (Xb) in 89% yield. Catalytic hydro-

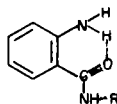
Table I

2-Carboxamide Derivatives of *N*-Phenylglycine Ethyl Ester

R	Yield %	Molecular Formula	M.p., °C	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
CH ₃ CH ₂ CH ₂ - (a)	89	C ₁₄ H ₂₀ N ₂ O ₃	88	63.61	7.62	10.60	63.58	7.69	10.72
C ₆ H ₅ CH ₂ - (b)	95	C ₁₈ H ₂₀ N ₂ O ₃	98	69.20	6.45	8.97	69.72	6.52	9.08
<i>p</i> -CH ₃ C ₆ H ₄ - (c)	58	C ₁₈ H ₂₀ N ₂ O ₃	119	69.20	6.45	8.97	69.35	6.31	9.06
C ₆ H ₅ -	12	C ₁₇ H ₁₈ N ₂ O ₃	131	68.43	6.08	9.39	68.90	6.12	9.12

(a) Ir: 3370 (NH), 1745, 1640 cm^{-1} (C=O); nmr (deuteriochloroform): δ 0.95 (t, 3H, CH₂CH₂CH₃), 1.25 (t, 3H, OCH₂CH₃), 3.95 (d, 2H, ArNCH₂), 4.2 (q, 2H, OCH₂CH₃), 6.4-7.5 (m, 4H, aromatic), 8.0 (broad s, 1H, CONH). (b) Ir: 3370 (NH), 1750, 1630 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.25 (t, 3H, CH₃), 3.95 (d, 2H, ArNCH₂), 4.25 (q, 2H, OCH₂), 4.65 (d, 2H, ArCH₂), 6.5-7.5 (m, 9H, aromatic), 8.1 (broad s, 1H, CONH). (c) Ir: 3370 (NH), 1745, 1640 (C=O); nmr (deuteriochloroform): δ 1.2 (t, 3H, CH₂CH₃), 2.25 (s, 3H, ArCH₃), 3.95 (d, 2H, NCH₂), 4.2 (q, 2H, OCH₂), 6.5-7.7 (m, 9H, aromatic), 8.1 (broad s, 1H, CONH).

genation of Xb in ethanol, over palladium black, produced 2-amino-*N*-phenylbenzamide (XIb) as a crystalline product with a salt-like high m.p. 252°. A possible explanation, supported by ir data, is that XIb contains an internal hydrogen bond. Its ir spectrum in potassium bromide



exhibits a strong absorption at the 3320 cm^{-1} region, instead of the two expected bands at 3480 and 3370 cm^{-1} for the NH_2 group. Compound XIb gives no positive ninhydrin test, but it is diazotized with β -naphthol readily.

Treatment of XIb with ethyl α -bromoacetate yielded *N*-(2-carboxanilido)phenylglycine ethyl ester (VIb) in 80% yield. Its structure was confirmed by spectral data. Thus the ir spectrum (potassium bromide discs) shows bands at 3350 cm^{-1} (secondary NH), 1750 cm^{-1} (carbonyl ester) and 1645 cm^{-1} (carbonyl amide). The ^1H nmr spectrum in deuteriochloroform shows a triplet at δ 1.25 and a quartet at δ 4.2 corresponding to the ethyl ester group. A doublet at δ 3.95, due to two CH_2 protons coupled to the NH proton, collapses to a singlet on exchange with deuterium oxide. A multiplet at δ 6.7-7.7 accounts for nine aromatic protons, while a broad signal at δ 8.1 is attributed to the CONH proton and is slowly exchangeable (24 hours).

The compound VIb was saponified as described above, with equimolar amount of *N* sodium hydroxide and, upon acidification with acetic acid, yielded *N*-(2-carboxanilido)phenylglycine (VIIb). Its ir spectrum (potassium bromide discs) shows characteristic bands at 3070-2750 cm^{-1} (carboxylic acid), 1730 cm^{-1} (carbonyl of carboxylic acid) and 1630 cm^{-1} (carbonyl amide). The ^1H nmr spectrum in DMSO-d_6 does not show the characteristic triplet and quartet of the ethyl ester VIb, but a broad singlet at δ 3.95, due to two CH_2 protons, and a multiplet at δ 6.5-7.7 attributed to the aromatic protons.

Ring closure of compound VIIb with DCCI led to formation of 4-phenyl-2*H*-1,4-benzodiazepine-3,5(1*H*,4*H*)dione (VIIIb), contaminated with a by product, which was separated again by column chromatography on Sephadex LH-20. The ir spectrum of VIIIb in potassium bromide shows bands at 3305 cm^{-1} (secondary NH) and 1670-1650 cm^{-1} (carbonyl groups). The ^1H nmr spectrum in DMSO-d_6 shows a singlet at δ 4.4, due to two CH_2 protons. This signal is shifted to lower field as compared with the same signal (δ 3.95) of the precursor compound VIIb. This should be expected (10,11) due to the formation of a neighbouring amide bond after the ring closure. A complex multiplet at δ 7.0-7.8 is attributed to the nine aromatic protons.

EXPERIMENTAL

Melting points were taken on a Buchi SMP-20 capillary melting

point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 Grating Infrared spectrophotometer. The ^1H nmr spectra were determined on a Hitachi Perkin-Elmer R-24 (60-MHz) instrument, with TMS as an internal standard and are expressed as δ values. Thin layer chromatography (tlc) was performed on silica gel Si F chromatogram plates with solvent system I (*n*-hexane-ethanol 1:1), II (*n*-hexane-ethyl acetate 3:2), III (benzene-methanol 9:1) and IV (chloroform-methanol 1:1), and visualized by uv, ninhydrin and chlorine-tolidine reagent (12). Elemental analyses were performed at the National Hellenic Research Foundation, Athens, Greece.

p-Nitrobenzyl 2-Carbobenzoxyaminobenzoate (I).

N-Carbobenzoxyanthranilic acid (5.42 g., 20 mmoles), m.p. 141°, prepared by the usual carbobenzoxylation process (13), was dissolved in 50 ml. of acetone, containing 2.77 ml. (20 mmoles) of triethylamine. Then 6.14 g. (20 mmoles) of *p*-nitrobenzyl tosylate was added and the solution was heated for 2 hours under reflux. The solvent was removed *in vacuo* and the remaining residue was washed with water and dried over phosphorus pentoxide. Recrystallization from ethanol provided 7.42 g. (91%) of product (needles), m.p. 106°; ir (potassium bromide): 3300 (NH), 1740, 1690 (C=O), 1525, 1350, 860 cm^{-1} (C-NO₂).

Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_6$: C, 65.01; H, 4.47; N, 6.89. Found: C, 64.74; H, 4.38; N, 6.85.

p-Nitrobenzyl 2-Aminobenzoate (II).

A mixture of 4.06 g. (10 mmoles) of I and 8 ml. of 2.5 *N* hydrogen bromide/acetic acid was shaken for 3 hours at room temperature. Then, ether was added and the precipitating product was filtered and washed several times with ether; yield 3.25 g. (92%), m.p. 218°. Subsequently, the hydrobromide derivative was suspended in 150 ml. of ethyl acetate and mixed with an excess of 5% sodium bicarbonate solution with shaking. The organic layer was separated, washed with water, dried (sodium sulfate) and the solvent was then removed in vacuum. The remaining yellow product was crystallized (needles) from ethanol-water (5:1), yield 2.3 g. (95%), m.p. 136°; ir (potassium bromide): 3480, 3375 (NH₂), 1690 (C=O), 1520, 1345, 860 cm^{-1} (C-NO₂).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_4$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.68; H, 4.40; N, 10.34.

Desalting of the above hydrobromide derivative through a Dowex 2-X8 column, using methanol as the eluant, afforded also the desired product with m.p. 136°.

N-(2-Carboxy-*p*-nitrobenzylate)phenylglycine Ethyl Ester (III).

To a hot solution of 2.72 g. (10 mmoles) of II in 80 ml. of absolute ethanol were added 1.06 g. (10 mmoles) of sodium carbonate and 1.67 g. (10 mmoles) of ethyl α -bromoacetate. The mixture was heated for 48 hours under reflux. Then it was filtered while warm and the ethanol removed in vacuum. The residue was taken up in ethyl acetate and the organic layer was washed with water, and dried (sodium sulfate). The solvent was evaporated to a small volume and by addition of petroleum ether, the product crystallized out, yield 1.8 g. (50%), m.p. 116°; ir (potassium bromide): 3360 (NH), 1735, 1690 (C=O), 1520, 1345, 855 cm^{-1} (C-NO₂).

Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_6$: C, 60.32; H, 5.06; N, 7.81. Found: C, 60.47; H, 5.15; N, 7.44.

Ethyl *N*-Phenylglycinate-2-carboxylic Acid (IV).

A solution of 3.58 g. (10 mmoles) of III in 20 ml. of DMF was subjected to catalytic hydrogenolysis over palladium oxide (0.4 g.). The reaction was followed by TLC. At the end, the catalyst was filtered and the solvent was removed *in vacuo*. The remaining oily residue was taken up in ethyl acetate and the desired product

was extracted from the organic layer with 5% sodium bicarbonate solution, following acidification with *N* hydrochloric acid. The thus precipitating product was washed with water and recrystallized from ethanol-water (1:1), yield 1.95 g. (87%), m.p. 148°; ir (potassium bromide): 3350 (NH), 3080-2850 (COOH), 1740, 1675 cm⁻¹.

Anal. Calcd. for C₁₁H₁₃NO₄: C, 59.18; H, 5.86; N, 6.27. Found: C, 58.95; H, 5.72; N, 6.26.

N-(2-Carboxysuccinimide)phenylglycine Ethyl Ester (V).

To a solution of IV (2.23 g., 10 mmoles) in 50 ml. of dioxane were added 1.15 g. (10 mmoles) of *N*-hydroxysuccinimide and 2.06 g. (10 mmoles) of DCCI. The mixture was permitted to remain for 8 hours at room temperature. Then *N,N'*-dicyclohexylurea was removed by filtration and the solvent was removed in vacuum. The remaining oily residue was solidified by addition of cold water, filtered and dried over phosphorus pentoxide. Finally, the desired product was obtained in crystalline form (needles) from dichloromethane-petroleum ether (1:2), yield 3 g. (95%), m.p. 115-116°.

Anal. Calcd. for C₁₅H₁₆N₂O₆: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.41; H, 4.92; N, 8.69.

N-(2-Carboxybenzylamido)phenylglycine Ethyl Ester (VIa).

A solution of V (1.6 g., 5 mmoles) and 0.64 g. (6 mmoles) of benzylamine in 30 ml. of THF was stirred for 6 hours at room temperature. Then the solvent was removed *in vacuo* and the obtained oily product was solidified with water. Crystallization from ethanol-water (2:1) afforded 2.98 g. (95%) of product, m.p. 98°; ir (potassium bromide): 3370 (NH), 1750, 1630 cm⁻¹ (C=O).

Anal. Calcd. for C₁₈H₂₀N₂O₃: C, 69.20; H, 6.45; N, 8.97. Found: C, 69.52; H, 6.52; N, 9.08.

N-(2-Carboxybenzylamido)phenylglycine (VIIa).

To a solution of 1.56 g. (5 mmoles) of VI in 20 ml. of ethanol were added 5.3 ml. of *N* sodium hydroxide and the mixture was stirred for 2 hours at room temperature. Then the solvent was removed *in vacuo* at 30° and to the residue 40 ml. of water were added. The water layer, after being extracted with ether, was acidified with acetic acid. The precipitating product was filtered, washed with water, dried (phosphorus pentoxide) and recrystallized from ethyl acetate, yield 1.3 g. (91%), m.p. 173°; ir (potassium bromide): 3370 (NH), 3070-2750 (COOH), 1730, 1630 cm⁻¹ (C=O).

Anal. Calcd. for C₁₆H₁₆N₂O₃: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.30; H, 5.50; N, 9.60.

2-Nitro-*N*-phenylbenzamide (Xb).

To a stirred solution of 2.05 g. (2.2 mmoles) of freshly distilled aniline and 2.22 g. (2.2 mmoles) of triethylamine, in 20 ml. of chloroform cooled to 0°, was added dropwise 3.71 g. (2 mmoles) of 2-nitrobenzoyl chloride dissolved in 15 ml. of chloroform. Stirring was continued, after the addition of the chloride, for 1 hour at room temperature. Then the solution was diluted with equal volume of chloroform and washed successively with *N* hydrochloric acid, 5% sodium bicarbonate solution, water and dried (sodium sulfate). After evaporation of the solvent in vacuum the remaining solid material was crystallized from ethanol-water (5:1), yield 4.32 g. (89%), m.p. 153-154°; ir (potassium bromide): 3270 (NH), 1660 (C=O), 1530, 1350, 855 cm⁻¹ (C-NO₂).

Anal. Calcd. for C₁₃H₁₀N₂O₃: C, 64.45; H, 4.16; N, 11.56. Found: C, 64.31; H, 4.24; N, 11.47.

2-Amino-*N*-phenylbenzamide (XIb).

A solution of 3.63 g. (15 mmoles) of Xb in 200 ml. of ethanol was hydrogenated over palladium oxide (400 mg.) for about 3

hours. The catalyst was filtered off and the filtrate was evaporated in vacuum. The remaining oily residue was solidified upon trituration with ethyl acetate, m.p. 245-246°. Recrystallization from 2-propanol afforded 1.8 g. (56%) of product, m.p. 252°; ir (potassium bromide): 3320 (NH), 1640 cm⁻¹ (C=O).

Anal. Calcd. for C₁₃H₁₂N₂O: C, 73.55; H, 5.70; N, 13.20. Found: C, 73.38; H, 5.63; N, 13.32.

N-(2-Carboxanilido)phenylglycine Ethyl Ester (VIb).

To a solution of 1.06 g. (5 mmoles) of XIb in 30 ml. of ethanol were added 0.53 g. (5 mmoles) of sodium carbonate and 0.84 g. (5 mmoles) of ethyl α-bromoacetate and the resulting mixture was heated for 48 hours under reflux. After filtration, the solvent was evaporated to dryness in vacuum and the remaining product was crystallized (needles) from ethanol-water (2:1), yield 1.2 g. (80%), m.p. 131°; ir (potassium bromide): 3350 (NH), 1750, 1645 cm⁻¹ (C=O); nmr (deuteriochloroform): δ 1.25 (t, 3H, CH₂CH₃), 3.95 (d, 2H, CH₂CO), 4.2 (q, 2H, CH₂CH₃), 6.5-7.7 (m, 9H, aromatic) and 8.1 (broad 1H, CONH).

Anal. Calcd. for C₁₇H₁₈N₂O₃: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.70; H, 6.12; N, 9.12.

N-(2-Carboxy-*p*-methylanilido)phenylglycine Ethyl Ester (VIc).

The desired product was prepared from 0.68 g. (3 mmoles) of 2-amino-*N-p*-methylphenylbenzamide, m.p. 147-148° (XIc) upon treatment with 0.5 g. (3 mmoles) of ethyl α-bromoacetate as previously described, yield 0.9 g. (96%), m.p. 119°; ir (potassium bromide): 3370 (NH), 1745, 1640 cm⁻¹ (C=O).

Anal. Calcd. for C₁₈H₂₀N₂O₃: C, 69.20; H, 6.45; N, 8.97. Found: C, 69.35; H, 6.31; N, 9.06.

N-(2-Carboxanilido)phenylglycine (VIIb).

This compound was prepared by saponification of VIb in a similar manner described for VIIa. Thus, from 0.89 g. (3 mmoles) of VIb were obtained 0.72 g. (88%) of the desired product, m.p. 187-188°; ir (potassium bromide): 3370, 3345 (NH), 3070-2750 (COOH), 1730, 1630 cm⁻¹ (C=O); nmr (DMSO-d₆): δ 3.95 (s, 2H, CH₂CO), 6.5-7.7 (m, 9H, aromatic).

Anal. Calcd. for C₁₅H₁₄N₂O₃: C, 66.65; H, 5.22; N, 10.36. Found: C, 66.32; H, 5.04; N, 10.51.

N-(2-Carboxy-*p*-methylanilido)phenylglycine (VIIc).

Saponification of 1.25 g. (4 mmoles) of VIc was effected as above, yield 1.05 g. (92%), m.p. 206-207°; ir (potassium bromide): 3350 (NH), 3050-2750 (COOH), 1730, 1645 cm⁻¹ (C=O).

Anal. Calcd. for C₁₆H₁₆N₂O₃: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.42; H, 5.76; N, 9.64.

4-Phenyl-2*H*-1,4-benzodiazepine-3,5(1*H*,4*H*)dione (VIIIb).

A stirred mixture of VIIIb (0.81 g., 3 mmoles) and 0.62 g. (3 mmoles) of DCCI in 30 ml. of THF was allowed to remain at room temperature for 24 hours. *N,N'*-Dicyclohexylurea was removed by filtration and the filtrate was evaporated to dryness in vacuum. The remaining residue was taken up in dichloromethane and this solution was washed with 5% sodium bicarbonate solution, water and dried (sodium sulfate). The solvent was evaporated to an oil, which upon the addition of ether, solidified, yield 0.5 g. (66%); tlc gave two spots. A portion (60 mg.) of the white solid was dissolved in 2-propanol and passed through a 1.5 x 70 cm Sephadex LH-20 column, using the same solvent as the eluant. The desired product gave m.p. 198-199°; ir (potassium bromide): 3305 (NH), 1660 cm⁻¹ (broad, C=O); nmr (DMSO-d₆): δ 4.4 (s, 2H), 7.0-7.8 (complex multiplet poorly resolved, 9H, aromatic).

Anal. Calcd. for C₁₅H₁₂N₂O₂: C, 71.41; H, 4.79; N, 11.10. Found: C, 71.29; H, 4.85; N, 11.01.

4-Benzyl-2*H*-1,4-benzodiazepine-3,5(1*H*,4*H*)dione (VIIIa).

Cyclization of 0.85 g. (3 mmoles) of VIIa as described above, gave 0.48 g. (60%) of product, m.p. 140-142°; ir (potassium bromide): 3340 (NH), 1650 cm^{-1} (broad, C=O).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$: C, 72.16; H, 5.29; N, 10.52. Found: C, 72.04; H, 5.34; N, 10.30.

4-p-Methylphenyl-2H-1,4-benzodiazepine-3,5(1H,4H)dione (VIIIc).

A portion of 0.85 g. (3 mmoles) of VIIc gave, after cyclization, 0.56 g. (70%) of the desired product, m.p. 193-194°; ir (potassium bromide): 3300 (NH), 1670 cm^{-1} (broad, C=O).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$: C, 72.16; H, 5.29; N, 10.52. Found: C, 72.07; H, 5.38; N, 10.38.

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