Synthesis of 3-Alkoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridines and their Cyclization to 5-Phenyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones

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The regiospecific reaction of 3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoylpyridine (**6a**), or 3-*t*-butoxycarbonylaminomethylcarbonylamino-4-benzoylpyridine (**6b**), with either acetyl chloride or ethyl chloroformate, and either *n*-butylmagnesium chloride or phenylmagnesium bromide afforded the respective 1-acetyl (or ethoxycarbonyl)-2-*n*-butyl (or phenyl)-3-benzyloxy (or *t*-butoxy) carbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridines **7** in 60-75% yield. Reaction of 1-acetyl (or ethoxycarbonyl)-2-*n*-butyl (or phenyl)-3-*t*-butoxycarbonylaminomethylcarbonyl-4-benzoyl-1,2-dihydropyridines **7b, 7f, 7d, 7h** with trifluoroacetic acid gave the corresponding 5-phenyl-8-acetyl (or ethoxycarbonyl)-9-*n*-butyl (or phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8a, 8b, 8c, 8d** respectively in 45-63% yield. N^1-Methylation of 5-phenyl-8-acetyl-9-*n*-butyl (or phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8a, 8b** using sodium hydride and iodomethane yielded the corresponding N^1-methyl derivatives **9a** (48%) and **9b** (54%). Oxidation of 5,9-diphenyl-8-ethoxycarbonyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8d**) using *p*-chloranil afforded 1,3-dihydro-5,9-diphenyl-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**10**). 5-Phenyl-8-acetyl-9-*n*-butyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8a**) and the corresponding 8-ethoxycarbonyl analog **8c** exhibited weak anticonvulsant activity indicating that **8a** and **8c** may be acting at the same site as the 7-halo-1,4-benzodiazepin-2-one class of compounds.

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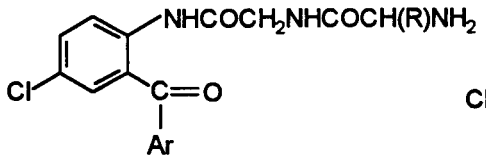
Introduction.

It has been proposed that dipeptidoaminobenzophenones **1** may act as prodrugs which undergo enzymatic hydrolysis to *ortho*-glycylaminobenzophenones **2**, followed by cyclization to biologically-active 1,4-benzodiazepin-2-ones **3** [1,2]. The dipeptidoaminobenzophenones **1** and benzodiazepin-2-ones **3** exhibit powerful effects on the central nervous system, including anticonvulsant, sedative, hypnotic and muscle relaxant properties [1-4]. Although it is well documented that an electronegative substituent at C-5 of **1** or C-7 of **3** is required for potent anxiolytic activity, very few electronically analogous pyrido analogs of **1** or **3** have been investigated [5-7]. In earlier studies we developed efficient synthetic methodologies, involving *ortho*-directed lithiation, for the preparation of 3-alkoxycarbonylaminomethylcarbonylamino-4-benzoylpyridines **4** and 1,3-dihydro-5-aryl-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **5** that exhibited anticonvulsant activity [8-10].

It was therefore of interest to prepare the 1-acetyl (or ethoxycarbonyl)-2-*n*-butyl (or phenyl)-3-alkoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridines **7** and 5-phenyl-8-acetyl (or ethoxycarbonyl)-9-*n*-butyl (or phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8**. Compounds **7** and **8** are electronically related



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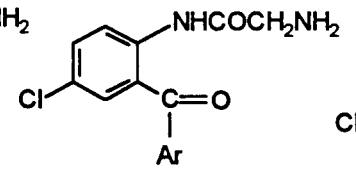

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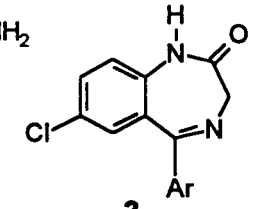

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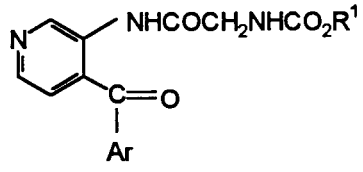

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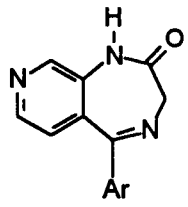

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to the chlorophenyl **1, 3** and pyridyl **4, 5** analogs since they possess similar electron-density profiles at equivalents positions. When the inductive and resonance effects of the chloro substituent **1, 3**, and the ring nitrogen in the pyridyl compounds **4** and **5** and the 1,2-dihydropyridyl derivatives **7** and **8** are compared, the resulting electron-densities are qualitatively similar for the chlorophenyl, pyridyl and 1,2-dihydropyridyl ring systems at equivalent positions as illustrated in Figure 1. This study was therefore initiated to determine whether the 1,2-dihydropyridyl, pyridyl and chlorophenyl rings are bioisosteric with respect to anticonvulsant activity since these ring systems are similar in size and shape and they possess similar electron-density profiles at equivalent positions. Accordingly, it could be expected that these chlorophenyl, pyridyl and 1,2-dihydropyridyl classes of compounds could interact with the same receptor site(s) to exhibit anticonvulsant activity.

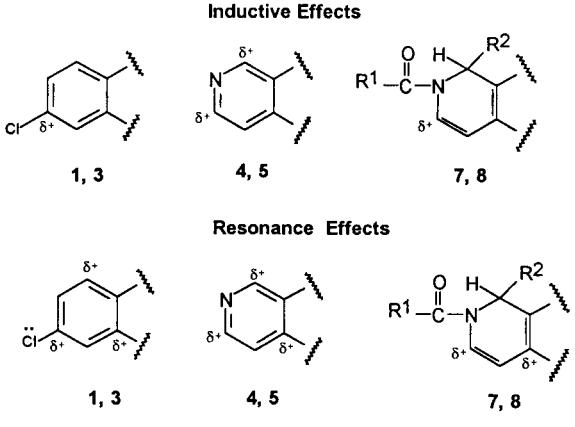


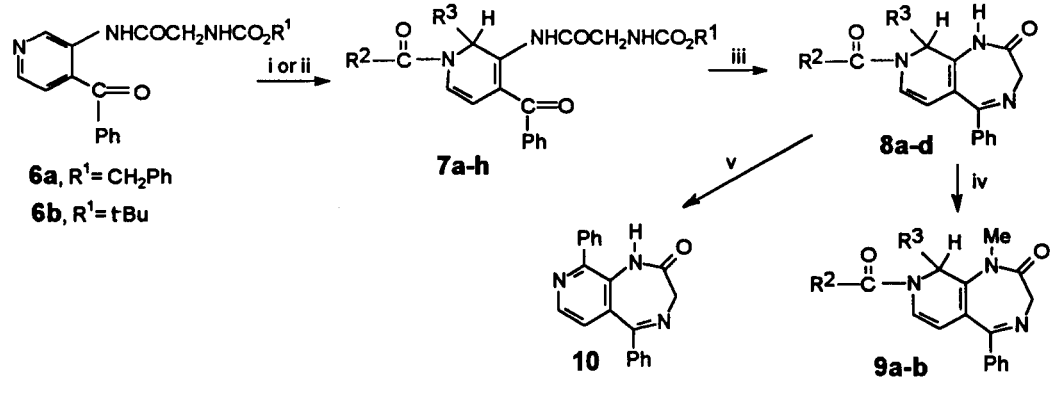
Figure 1. A comparison of the inductive and resonance effects exhibited by the chloro substituent in chlorobenzenes 1, 3, and the ring nitrogens in pyridines 4, 5 and 1,2-dihydropyridines 7, 8.

Chemistry.

The one-pot reaction of 3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoylpyridine (**6a**), or 3-*t*-butoxycarbonylaminomethylcarbonylamino-4-benzoylpyridine (**6b**) with either acetyl chloride or ethyl chloroformate in THF at −78° affords the respective intermediate 1-acetyl or 1-ethoxycarbonylpyridinium salt. Subsequent reaction with either *n*-butylmagnesium chloride or phenylmagnesium bromide (Procedure A) afforded the respective 1-acetyl (or 1-ethoxycarbonyl)-2-*n*-butyl (or 2-phenyl)-3-benzyloxy (or *t*-butoxy)carbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine **7a-d, 7f-h** in 60-68% yield as illustrated in Scheme I and summarized in Table I. A similar reaction of 3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoylpyridine (**6a**) with phenylcadmium chloride, generated from the *in situ* reaction of phenylmagnesium chloride with cadmium chloride, yielded 1-acetyl-2-phenyl-3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7e**) in 75% yield (Procedure B). The exclusive formation of the 1,2-dihydropyridyl products **7a-h** indicates that the intermediate 1-acetyl (or 1-ethoxycarbonyl)pyridinium salt undergoes regiospecific attack at the C-2 position by the Grignard or organocadmium reagent. A plausible explanation for the regiospecific reaction observed is that coordination of the Grignard reagent with the carbonylamino moiety of the 3-alkoxycarbonylaminomethylcarbonylamino substituent facilitates exclusive *ortho*-directed addition to the electron-deficient C-2 position of the intermediate pyridinium salt.

The trifluoroacetic acid catalyzed cleavage (-$NHCO_2$-*t*-Bu → -NH_2) at 25° in 1,2-dichloroethane and subsequent thermal cyclization reaction (Procedure C) of selected 1-acetyl (or 1-ethoxycarbonyl)-2-*n*-butyl (or 2-phenyl)-3-*t*-butoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-di-

Scheme I[a]

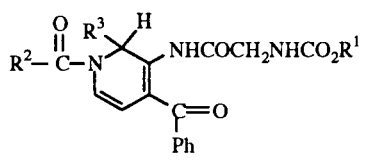


[a]Reagents: i, R^2-CO-Cl, THF, -78°, R^3-Mg-X (Procedure A); ii, R^2-CO-Cl, THF, -78°, $CdCl_2$, R^3-Mg-Cl (Procedure B); iii, CF_3CO_2H in $ClCH_2CH_2Cl$ (1:9, v/v), 25°, 2 hours, toluene-pyridine, reflux 2 hours (Procedure C); iv) NaH, MeI, 0°, 2 hours (Procedure D); v, toluene-HOAc, *p*-chloranil, reflux, 1.5 hours (Procedure E).

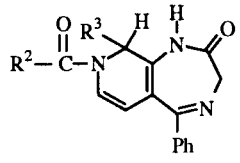
hydropyridines **7b**, **7f**, **7d** and **7h** afforded the corresponding 5-phenyl-8-acetyl (or 8-ethoxycarbonyl)-9-*n*-butyl (or 9-phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8a**, **8b**, **8c** and **8d**, respectively in 45-63% yield (Procedure C) as illustrated in Scheme I and summarized in Table I. In contrast, the 45% w/v hydrogen bromide in glacial acetic acid catalyzed cleavage (-$NHCO_2CH_2Ph$ → -NH_2) at 25° and subsequent thermal cyclization reaction of selected 1-acetyl (or 1-ethoxycarbonyl)-2-*n*-butyl (or 2-phenyl)-3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridines **7a**, **7e**, **7c** and **7g** yielded the corresponding products **8a**, **8b**, **8c** and **8d**, respectively in low yields of 8-13% due to extensive decomposition in 45% w/v hydrogen bromide in glacial acetic acid. N^1-Methylation of 5-phenyl-8-acetyl-9-*n*-butyl (or 9-phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8a** and **8b** by treatment with sodium hydride and then reaction with iodomethane gave the N^1-methyl derivatives **9a** (48%) and **9b** (54%), respectively. Oxidation of 5,9-diphenyl-8-ethoxycarbonyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8d**) using *para*-chloranil in toluene-glacial acetic acid gave 1,3-dihydro-5,9-diphenyl-2*H*-py-

Table I

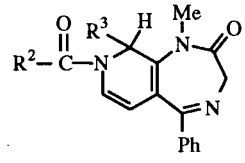
Physical Data for 1-Acetyl (or ethoxycarbonyl)-2-*n*butyl (or phenyl)-3-alkoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridines 7a-h, 5-phenyl-8-acetyl (or ethoxycarbonyl)-9-*n*-butyl (or phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepine-2-ones 8a-d and the 1-Methyl Derivatives 9a-b and 1,3-Dihydro-5,9-diphenyl-2*H*-pyrido[3,4-*e*]-1,4-diazepine-2-ones (10)



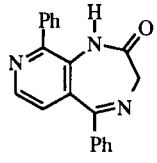
7a-h



8a-d



9a-b



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No.	R^1	R^2	R^3	Procedure	R_f	Mp, °C	Yield	Calcd./Found C	H	N	Exact Mass Calcd.	Found
7a	CH_2Ph	Me	*n*-Bu	A	0.61 [a]	80-82	66	ND [b]	ND	ND	489.2264	489.2270
								–	–	–		
7b	*t*-Bu	Me	*n*-Bu	A	0.53 [c]	90-92	68	ND	ND	ND	455.2420	455.2425
								–	–	–		
7c	CH_2Ph	EtO	*n*-Bu	A	0.54 [a]	83-85	62	ND	ND	ND	519.2369	519.2375
								–	–	–		
7d	*t*-Bu	EtO	*n*-Bu	A	0.55 [a]	81-83	65	ND	ND	ND	485.2526	485.2526
								–	–	–		
7e	CH_2Ph	Me	Ph	B	0.52 [c]	115-117	75	ND	ND	ND	509.1951	509.1954
								–	–	–		
7f	*t*-Bu	Me	Ph	A	0.58 [a]	120-122	68	ND	ND	ND	475.2107	475.2107
								–	–	–		
7g	CH_2Ph	EtO	Ph	A	0.55 [a]	98-100	60	ND	ND	ND	539.2056	539.2057
								–	–	–		
7h	*t*-Bu	EtO	Ph	A	0.55 [a]	101-103	66	ND	ND	ND	505.2213	505.2207
								–	–	–		
8a	–	Me	*n*-Bu	C	0.47 [a]	204-205	63	71.19	6.87	12.45	337.1790	337.1790
								70.88	6.87	12.34		
8b	–	Me	Ph	C	0.63 [d]	215-217	65	73.93	5.36	11.76	357.1477	357.1472
								73.59	5.35	11.63		
8c	–	EtO	*n*-Bu	C	0.48 [a]	90-92	45	ND	ND	ND	367.1895	367.1896
								–	–	–		
8d	–	EtO	Ph	C	0.40 [a]	166-168	54	71.30	5.47	10.85	387.1583	387.1588
								71.14	5.65	10.51		
9a	–	Me	*n*-Bu	D	0.47 [a]	oil	48	ND	ND	ND	351.1947	351.1947
								–	–	–		
9b	–	Me	Ph	D	0.65 [d]	125-127	54	ND	ND	ND	371.1633	371.1640
								–	–	–		
10	–	–	–	E	0.34 [d]	229-230	45	76.66	4.82	13.41	ND	ND
								76.58	4.84	13.11		

[a] EtOAc-hexane (2:1, v/v). [b] ND = not determined. [c] EtOAc-hexane (1:1, v/v). [d] EtOAc-hexane (3:1, v/v).

rido[3,4-*e*]-1,4-diazepin-2-one (**10**, 45%).

The 1,2-disubstituted-3-alkoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridines **7a-h** exhibited dual absorptions in the ^{1}H nmr spectra at 25° for the C-2H, C-5H, C-6H, $COCH_3$ or $CO_2CH_2CH_3$ resonances due to restricted rotation about the dihydropyridyl N^1-to-CO bond with rotamer ratios between 1:3 and 4:5. The absorptions for the two rotamers coalesced to a single resonance upon heating to 75° in dimethyl sulfoxide-d_6. Rotamers were also observed for the 5-phenyl-8-acetyl (or 8-ethoxycarbonyl)-9-*n*-butyl (or 9-phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8c-d, 9a-b** where dual absorptions were observed for the C-6H, C-7H, C-9H, CH_3CO or $CO_2CH_2CH_3$ resonances at 25°.

Anticonvulsant Test Results.

The anticonvulsant activities of the acyclic 1,2-disubstituted-3-alkoxycarbonylaminomethylcarbonylamino-1,2-dihydropyridines **7a-h** and bicyclic 5-phenyl-8,9-disubstituted-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8a-d, 9a-d** were determined by the Antiepileptic Drug Development (ADD) program (Adminisitered by the Section on Epilepsy, National Institute of Health, Bethesda, MD). Anticonvulsant activities against subcutaneous pentylenetetrazole (scPTZ) and maximal electroshock (MES) induced seizures, which are models for absence (petit mal) and generalized tonic clonic (grand mal seizures), respectively were measured in mice at 30 minutes and 4 hours after intraperitoneal (ip) administration of the test compound using the procedures reported previously [8]. All of the acyclic 1,2-dihydropyridyl compounds **7a-h** and the bicyclic 1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8b, 8d, 9a-b** were inactive in both the scPTZ and MES screens at a 300 mg/kg ip dose at both 30 minutes and 4 hours. In contrast, 5-phenyl-8-acetyl-9-*n*-butyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8a**) protected two out of four mice at a 300 mg/kg ip dose at 30 minutes post administration of the test compound in the scPTZ test. The 5-phenyl-8-ethoxycarbonyl-9-*n*-butyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8c**) protected one out of one mice in the MES, and two out of four mice in the scPTZ, screens at a 300 mg/kg ip dose at 30 minutes post administration of the test compound in the scPTZ test. The 5-phenyl-8-ethoxycarbonyl-9-*n*-butyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8c**) protected one out of one mice in the MES, and two out of four mice in the scPTZ, screens at a 300 mg/kg ip dose at 30 minutes post administration of the test compound. The ED_{50} values for the standard reference drugs in these screens were Clonazepam (scPTZ, ED_{50} = 0.02 mg/kg; MES, 86.6 mg/kg) and Valproic acid (scPTZ, ED_{50} = 148.6 mg/kg; MES, ED_{50} = 271.7 mg/kg). These results indicate that the bicyclic 5-phenyl-8-acetyl-9-*n*-butyl (**8a**) and 5-phenyl-8-ethoxycarbonyl-9-*n*-butyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8c**) may be acting at the same site as the 1,4-diazepin-2-one Clonazepam.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover apparatus, and are uncorrected. Nuclear magnetic resonance spectra (^{1}H nmr) were recorded on a Bruker AM-300 spectrometer using tetramethylsilane as the internal standard. The assignment of all exchangeable amide protons was confirmed by addition of deuterium oxide. The ^{13}C nmr spectra were acquired using the J modulated spin echo technique where the methyl and methine carbon resonances appear as positive peaks and methylene and quaternary carbons appear as negative peaks. Mass spectra were recorded on an AEI MS-50 mass spectrometer and when these exact mass measurements are used *in lieu* of elemental analyses, ^{13}C nmr spectra are also provided for structure confirmation and purity. All of the products gave rise to a single spot using Whatman MK6F silica gel microslides (250 μM thickness) with a solvent system of high, medium and low polarity. Preparative thin layer chromatography was performed on Camag Kieselgel DSF silica gel plates, 1.0 mm in thickness. Infrared spectra were recorded on a Nicolet 5DX FT spectrometer. Tetrahydrofuran was distilled from sodium-benzophenone immediately before use. Compounds **6a** and **6b** were prepared according to the literature procedures [9].

General Method for the Preparation of 1-Acetyl (or 1-ethoxycarbonyl)-2-*n*-butyl (or 2-phenyl)-3-alkoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridines **7a-d, 7f-h**. Procedure A.

Either acetyl chloride (1.76 g, 5.6 mmoles), or ethyl chloroformate (4.82 g, 5.6 mmoles), was added dropwise with stirring to a solution of **6a** (1.76 g, 4.52 mmoles), or **6b** (1.60 g, 4.52 mmoles), in dry tetrahydrofuran (30 ml) under an atmosphere of nitrogen at −78° and the mixture was stirred for 20 minutes. Either *n*-butylmagnesium chloride (7 ml of a 2*M* solution in tetrahydrofuran, 14 mmoles), or phenylmagnesium bromide (4.6 ml of a 3*M* solution in ether, 14 mmoles), was added dropwise. The reaction mixture was stirred for 25 minutes at −78°, quenched by addition of 20% w/v aqueous ammonium chloride (20 ml) and allowed to warm to 25°. Extraction with ethyl acetate (3 x 80 ml), washing the ethyl acetate fraction with brine (2 x 25 ml), drying the ethyl acetate fraction (sodium sulfate) and removal of the solvent *in vacuo* gave the respective product **7**. Products **7** were purified by preparative silica gel thin layer chromatography using plates 1.0 mm in thickness. The development solvent, R_f value, melting point, and % yield for each product is listed in Table I. The spectral data for **7a-d, 7f-h** prepared by Procedure A are listed below. When the compound existed as a mixture of two rotamers in solution, the chemical shift of the minor rotamer is shown in square brackets.

1-Acetyl-2-*n*-butyl-3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7a**).

This compound was obtained as a yellow solid; ^{1}H nmr (chloroform-d_1): (mixture of two rotamers in a ratio of 1:3) δ 11.46 (s, 1H, N*H*CO), 7.2-7.62 (m, 10H, phenyl hydrogens), 6.72-6.84 (m, 1H, H-2), 6.24 [6.36] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-6), 5.88-6.02 (m, 1H, CH_2NH), 5.70 [5.76] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-5),

5.1-5.2 (m, 2H, CH_2Ph), 4.02 [3.82] (two br s, 2H total, CH_2NH), 2.18 [2.30] (two s, 3H total, CO*Me*), 1.62-1.84 (m, 2H, CH_2CH$_2$CH$_2$CH$_3$), 1.12-1.45 (m, 4H, CH$_2$CH_2CH_2CH$_3$), 0.90 (t, J = 7 Hz, 3H, CH$_2$CH$_2$CH$_2$CH_3); ^{13}C nmr (chloroform-d$_1$): δ 196.22 [196.61] (*C*OPh), 168.53 and 169.45 [169.32 and 169.92] (*C*OMe, NH*C*OCH$_2$), 156.52 (*C*O$_2$), 147.48 [145.81] (C-3), 127.68-138.55 range (phenyl carbons), 119.50 [119.58] (C-6), 109.83 [110.04] (C-5), 108.99 (C-4), 67.17 [67.30] (*C*H$_2$Ph), 47.88 [52.26] (C-2), 45.63 (*C*H$_2$NH), 29.78 [30.04] (*C*H$_2$CH$_2$CH$_2$CH$_3$), 27.54 [27.45] (CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.36 [22.47] (CH$_2$CH$_2$*C*H$_2$CH$_3$), 21.19 [21.42] (CO*C*H$_3$), 13.92 [13.81] (CH$_2$*C*H$_3$).

1-Acetyl-2-*n*-butyl-3-*tert*-butoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7b**).

Compound **7b** was obtained as a yellow solid; ^{1}H nmr (chloroform-d$_1$): (mixture of two rotamers in a ratio of 1:2) δ 12.48 [12.42] (two s, 1H total, N*H*CO), 7.42-7.64 (m, 5H, phenyl hydrogens), 6.76-6.84 (two m, 1H total, H-2), 6.24 [6.40] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-6), 5.74 [5.80] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-5), 5.24 (br s, 1H, CH$_2$N*H*), 3.98 (d, $J_{CH,NH}$ = 4.8 Hz, 2H, CH_2NH), 2.18 [2.32] (two s, 3H total, COCH_3), 1.7-1.83 (m, 2H, CH_2CH$_2$-CH$_2$CH$_3$), 1.48 (s, 9H, *t*-Bu), 1.16-1.55 (m, 4H, CH_2CH_2CH$_3$), 0.90 (t, J = 7 Hz, 3H, CH$_2$CH_3); ^{13}C nmr (chloroform-d$_1$): δ 196.23 [196.59] (*C*OPh), 168.77 and 169.37 [169.70 and 170.00] (*C*OMe, NH*C*OCH$_2$), 156.10 (*C*O$_2$), 147.48 [145.74] (C-3), 126.17-138.70 range (phenyl carbons), 119.57 [119.71] (C-6), 109.89 [110.13] (C-5), 109.14 [110.25] (C-4), 80.47 [80.74] (*C*-Me$_3$), 48.03 [52.40] (C-2), 45.48 (CO*C*H$_2$NH), 30.21 [29.94] (*C*H$_2$CH$_2$CH$_2$CH$_3$), 28.24 (C-*Me*$_3$), 27.65 [27.55] (CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.47 [22.58] (CH$_2$*C*H$_2$CH$_3$), 21.31 [21.52] (CO*Me*), 13.99 [13.88] (CH$_2$*C*H$_3$).

1-Ethoxycarbonyl-2-*n*-butyl-3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7c**).

This compound was obtained as a yellow solid; ^{1}H nmr (chloroform-d$_1$): (mixture of two rotamers in a ratio of 4:5): δ 12.49 [12.46] (two s, 1H total, CON*H*), 7.2-7.65 (m, 10H, phenyl hydrogens), 6.40 [6.56] (two d, $J_{5,6}$ = 9 Hz, 1H total, H-6), 6.32-6.50 (m, 1H, H-2), 5.74-5.84 (m, 1H, CH$_2$N*H*), 5.66 [5.58] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-5), 5.12 (s, 2H, CH_2Ph), 4.16-4.40 (m, 2H, OCH_2CH$_3$), 3.92-4.04 (m, 2H, CH_2Ph), 1.58-1.94 (m, 2H, CH_2CH$_2$CH$_2$CH$_3$), 1.20-1.50 (m, 7H, CH_2CH_2CH$_3$, OCH$_2$CH_3), 0.91 (t, J = 7 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C nmr (chloroform-d$_1$): δ 196.79 [196.61] (*C*OPh), 168.41 [168.59] (NH*C*OCH$_2$), 156.47 (*C*O$_2$CH$_2$Ph), 154.10 [153.48] (*C*O$_2$Et), 145.07 [145.45] (C-3), 126.00-138.64 range (phenyl carbons), 120.41 [119.62] (C-6), 109.86 [109.39] (C-4), 108.11 [107.71] (C-5), 67.29 (*C*H$_2$Ph), 62.35 (O*C*H$_2$CH$_3$), 50.50 [50.11] (C-2), 45.64 (CO*C*H$_2$NH), 29.84 [29.58] (*C*H$_2$CH$_2$CH$_2$CH$_3$), 27.36 [27.42] (CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.30 [22.35] (CH$_2$CH$_2$*C*H$_2$CH$_3$), 14.36 (OCH$_2$*C*H$_3$), 13.95 (CH$_2$CH$_2$*C*H$_3$).

1-Ethoxycarbonyl-2-*n*-butyl-3-*tert*-butoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7d**).

Compound **7d** was obtained as a yellow solid; ^{1}H nmr (chloroform-d$_1$): (mixture of two rotamers in a ratio of 1:2) δ 11.38 [11.34] (two s, 1H total, CON*H*), 7.38-7.60 (m, 5H, phenyl hydrogens), 6.6 [6.4] (two d, $J_{5,6}$ = 9 Hz, 1H total, H-6), 6.34-6.42 (m, 1H, H-2), 5.64 [5.58] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-5), 5.36 (m, 1H, CH$_2$N*H*), 4.16-4.36 (m, 2H, OCH_2CH$_3$), 3.92 (m, 2H, CH_2NH), 1.56-1.88 (m, 2H, CH_2CH$_2$CH$_2$CH$_3$), 1.14-1.56 (m, 16H, CH$_2$CH_2CH_2CH$_3$, OCH$_2$CH_3, C*Me*$_3$), 0.88 (t, J = 7 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C nmr (chloroform-d$_1$) δ 196.58 [196.42] (*C*OPh), 169.13 [168.86] (NH*C*OCH$_2$), 155.77 (*C*O$_2$-*t*-Bu), 154.13 [153.47] (*C*O$_2$Et), 144.99 [145.34] (C-3), 128.13-138.66 range (phenyl carbons), 120.32 [119.54] (C-6), 109.85 [109.80] (C-4), 108.15 [107.75] (C-5), 80.47 [80.33] (*C*-Me$_3$), 62.31 [62.23] (O*C*H$_2$CH$_3$), 50.51 [50.15] (C-2), 45.44 (*C*H$_2$NH), 29.88 (*C*H$_2$CH$_2$CH$_2$CH$_3$), 28.17 (C-*Me*$_3$), 27.36 [27.45] (CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.30 [22.38] (CH$_2$*C*H$_2$CH$_3$), 14.37 [14.09] (OCH$_2$*C*H$_3$), 13.95 [13.80] (CH$_2$CH$_2$*C*H$_3$).

1-Acetyl-2-phenyl-3-*tert*-butoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7f**).

Compound **7f** was obtained as a yellow solid; ir (potassium bromide): 3353, 2984, 2926, 1712, 1680, 1635 and 1565 cm^{-1}; ^{1}H nmr (chloroform-d$_1$): (mixture of two rotamers in a ratio of 1:3) δ 12.38 [12.26] (two s, 1H total, CON*H*), 8.02 [7.69] (two s, 1H total, H-2), 7.18-7.67 (m, 10H, phenyl hydrogens), 6.22 [6.99] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-6), 5.73 [5.69] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-5), 5.38 [5.60] (two m, 1H total, CH$_2$N*H*), 3.82 [3.88] (two m, 2H, CH_2NH), 2.18 [2.36] (two s, 3H total, CO*Me*), 1.42 (s, 9H, C*Me*$_3$); ^{13}C nmr (chloroform-d$_1$): δ 196.97 [196.33] (*C*OPh), 168.47 and 168.90 [169.87] (*C*OMe and NH*C*OCH$_2$), 155.63 (*C*O$_2$-*t*-Bu), 144.15 [142.94] (C-3), 126.26-138.35 range (phenyl carbons), 120.31 [121.18] (C-6), 110.69 (C-4), 109.43 [109.25] (C-5), 80.18 [80.48] (*C*-Me$_3$), 50.51 [54.09] (C-2), 45.21 (*C*H$_2$NH), 28.09 (C-*Me*$_3$), 21.37 [21.53] (CO*Me*).

1-Ethoxycarbonyl-2-phenyl-3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7g**).

This compound was obtained as a yellow solid; ir (potassium bromide): 3337, 3025, 2935, 1721, 1712, 1639, 1573 and 1516 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$, 25°): (mixture of two rotamers in a ratio of 1:2) δ 11.10 and 11.18 (two s, 1H total, N*H*CO), 7.22-7.84 (m, 16H, phenyl hydrogens, N*H*CH$_2$), 7.10 [7.02] (two s, 1H total, H-2), 6.66 [6.74] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-6), 5.58 [5.62] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-5), 5.06 (s, 2H, CH_2Ph), 4.24 (br q, J = 7 Hz, 2H, OCH_2CH$_3$), 3.56 (m, 2H, CH_2NH), 1.26 (t, J = 7 Hz, 3H, OCH$_2$CH_3); ^{1}H nmr (dimethyl sulfoxide-d$_6$, 75°): δ 11.04 (s, 1H, N*H*CO), 7.24-7.90 (m, 16H, phenyl hydrogens, N*H*CH$_2$), 7.16 (s, 1H, H-2), 6.68 (d, $J_{5,6}$ = 9.0 Hz, 1H, H-6), 5.58 (d, $J_{5,6}$ = 9.0 Hz, 1H, H-5), 5.06 (s, 2H, CH_2Ph), 4.26 (q, J = 7 Hz, 2H, OCH_2CH$_3$), 3.60 (m, 2H, CH_2NH), 1.24 (t, J = 7 Hz, 3H, OCH$_2$CH_3); ^{13}C nmr (chloroform-d$_1$): δ 196.76 [196.93] (*C*OPh), 167.69 [168.05] (*C*OMe), 156.32 (*C*O$_2$-*t*-Bu), 153.26 [153.58] (*C*O$_2$Et), 142.63 (C-3), 127.71-138.46 range (phenyl carbons), 120.76 [121.74] (C-6), 111.20 [111.46] (C-4), 107.21 [107.47] (C-5), 67.35 (*C*H$_2$Ph), 62.79 [62.70] (O*C*H$_2$CH$_3$), 52.83 [53.22] (C-2), 45.57 (*C*H$_2$NH), 14.46 (OCH$_2$*C*H$_3$).

1-Ethoxycarbonyl-2-phenyl-3-*tert*-butoxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7h**).

This compound was obtained as a yellow solid; ir (potassium bromide): 3402, 2984, 2935, 1721, 1639, 1598 and 1573 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$, 25°): (mixture of two rotamers in a ratio of 1:3) δ 11.30 and 11.38 (two s, 1H total, N*H*CO), 7.18-7.76 (m, 11H, phenyl hydrogens, H-2), 6.92 [7.04] (m, 1H, N*H*CH$_2$), 6.64 [6.72] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-6), 5.48 [5.54] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-5), 4.26 (br q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 3.42 [3.52] (two br m, 2H total, CH_2NH), 1.36 (s, 9H, *t*-Bu), 1.16 and 1.22 (two br t, J = 7.0 Hz, 3H total, OCH$_2$CH_3); ^{1}H nmr (dimethyl sulfoxide-d$_6$, 75°): δ 11.14 (br s, 1H, N*H*CO), 7.24-7.74 (m, 11H, phenyl hydrogens, H-2), 6.90 (br m, 1H,

N*H*CH$_2$), 6.65 (d, $J_{5,6}$ = 9.0 Hz, 1H, H-6), 5.57 (d, $J_{5,6}$ = 9.0 Hz, 1H, H-5), 4.26 (q, J = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 3.52 (m, 2H, C*H*$_2$NH), 1.32 (s, 9H, *t*-Bu), 1.16 (t, J = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C nmr (chloroform-d$_1$): δ 196.64 [196.48] (*C*OPh), 168.69 [168.29] (NH*C*OCH$_2$), 155.63 (*C*O$_2$-*t*-Bu), 153.59 [153.24] (*C*O$_2$Et), 142.53 (C-3), 127.68-138.46 (phenyl carbons), 121.59 [120.61] (C-6), 111.14 [111.40] (C-4), 107.52 [107.23] (C-5), 80.51 (*C*-Me$_3$), 62.73 [62.64] (O*C*H$_2$CH$_3$), 52.82 [53.17] (C-2), 45.34 (*C*H$_2$NH), 28.19 (C-*Me*$_3$), 14.43 (OCH$_2$*C*H$_3$).

1-Acetyl-2-phenyl-3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoyl-1,2-dihydropyridine (**7e**). Procedure B.

Phenylmagnesium chloride (7.1 ml of a 2.0 *M* solution in tetrahydrofuran, 14.2 mmoles) was added to a suspension of dry cadmium chloride (1.3 g, 7.1 mmoles) with stirring under a nitrogen atmosphere at 25°. After stirring for 25 minutes, this mixture was added dropwise using a syringe to a solution of 1-acetyl-3-benzyloxycarbonylaminomethylcarbonylamino-4-benzoylpyridinium chloride which was prepared by dropwise addition of acetyl chloride (0.39 g, 5.0 mmoles) to a solution of **6a** (1.73 g, 4.4 mmoles) in tetrahydrofuran (20 ml) at −78° under a nitrogen atmosphere. The reaction was allowed to proceed with stirring at −78° for 25 minutes and the reaction was quenched by addition of 20% w/v aqueous ammonium chloride (20 ml) prior to warming to 25°. Extraction with ethyl acetate (3 x 80 ml), washing the ethyl acetate fraction (sodium sulfate) and removal of the solvent *in vacuo* gave a residue. Purification of this residue by preparative silica gel thin layer chromatography using plates 1.0 mm in thickness with ethyl acetate-hexane (1:1, v/v) as development solvent afforded **7e** (1.7 g, 75%, R_f 0.52) as a yellow solid; ir (potassium bromide): 3320, 3033, 3025, 2935, 2861, 1729, 1721, 1688, 1639, 1573 and 1524 cm^{-1}; ^{1}H nmr (chloroform-d$_1$): (mixture of two rotamers in a ratio of 1:3) δ 12.52 [12.38] (two s, 1H total, CON*H*), 7.20-8.04 (m, 16H, phenyl hydrogens, H-2), 6.22 [7.0] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-6), 5.74 [5.69] (two d, $J_{5,6}$ = 9.0 Hz, 1H total, H-5), 5.45-5.52 [5.62-5.73] (two m, 1H total, CH$_2$N*H*), 5.05-5.16 (m, 2H, C*H*$_2$Ph), 3.92 [4.0] (two d, $J_{CH,NH}$ = 5.4 Hz, 1H total, C*H*$_2$NH), 2.17 [2.38] (two s, 3H total, CO*Me*); ^{13}C nmr (chloroform-d$_1$): δ 196.39 [196.81] (*C*OPh), 168.96 [169.92] and 167.79 [169.11] (*C*OMe and NH*C*OCH$_2$), 156.34 (*C*O$_2$CH$_2$Ph), 144.45 [143.03] (C-3), 126.38-138.46 range (phenyl carbons), 120.53 [121.54] (C-6), 110.84 [111.71] (C-4), 109.47 [109.20] (C-5), 67.29 [67.46] (*C*H$_2$Ph), 50.64 [54.32] (C-2), 45.53 [45.79] (*C*H$_2$NH), 21.49 [21.67] (CO*C*H$_3$).

General Method for the Preparation of 5-Phenyl-8-acetyl (or 8-ethoxycarbonyl)-9-*n*-butyl (or 9-phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **8a-d**. Procedure C.

A solution of trifluoroacetic acid in 1,2-dichloroethane (1:9, v/v; 150 ml) was added to the selected 1,2-dihydropyridyl compound, **7b, 7f, 7d, 7h,** respectively (7.83 mmoles) and the resulting solution was stirred for 2 hours at 25°. The solvent was removed *in vacuo*, the residue was dissolved in chloroform (70 ml) and neutralized with 10% w/v aqueous potassium carbonate. The chloroform fraction was then washed with water (20 ml), brine (20 ml), the chloroform fraction was dried (sodium sulfate) and the solvent was removed *in vacuo*. Toluene (200 ml) and pyridine (2 ml) were added to the residue and this solution was heated at reflux for 3 hours. Removal of the solvent *in vacuo* gave the respective product, **8a, 8b, 8c, 8d** which was purified by preparative silica gel thin layer chromatography using plates 1.0 mm in thickness. The development solvent, R_f value, melting point and % yield for each product is listed in Table I. The spectral data for **8a-d** prepared by Procedure C are listed below. When the compound existed as a mixture of two rotamers in solution, the chemical shift of the minor rotamer is shown in square brackets.

5-Phenyl-8-acetyl-9-*n*-butyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8a**).

This compound was obtained as a white solid; ir (potassium bromide): 3238, 3173, 3058, 2951, 2943, 2869, 1712, 1688, 1655, 1630, 1589 and 1565 cm^{-1}; ^{1}H nmr (chloroform-d$_1$): δ 9.58 (s, 1H, N*H*CO), 7.44-7.62 (m, 5H, phenyl hydrogens), 6.33 (d, $J_{6,7}$ = 9.0 Hz, 1H, H-7), 5.60 (t, J = 7 Hz, 1H, H-9), 5.44 (d, $J_{6,7}$ = 9.0 Hz, 1H, H-6), 4.36 (br s, 2H, NC*H*$_2$CO), 2.26 (s, 3H, C*H*$_3$CO), 1.76 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.30 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.86 (t, J = 7 Hz, 3H, CH$_2$CH$_2$CH$_2$C*H*$_3$).

5,9-Diphenyl-8-acetyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**8b**).

This compound was obtained as a white solid; ^{1}H nmr (chloroform-d$_1$): δ 9.16 (s, 1H, N*H*CO), 7.2-7.74 (m, 10H, phenyl hydrogens), 7.62 (s, 1H, H-9), 6.38 (d, $J_{6,7}$ = 9.0 Hz, 1H, H-7), 5.46 (d, $J_{6,7}$ = 9.0 Hz, 1H, H-6), 4.44 and 4.28 (two broad d, J_{gem} = 11 Hz, 1H each, H-3), 2.27 (s, 3H, CO*Me*).

5-Phenyl-8-ethoxycarbonyl-9-*n*-butyl-1,3,8,9-tetrahydro-2*H*-pyrido-[3,4-*e*]-1,4-diazepin-2-one (**8c**).

Compound **8c** was obtained as a white solid; ^{1}H nmr (chloroform-d$_1$): (mixture of two rotamers in a ratio of 1:2) δ 9.63 [10.10] (two s, 1H total, N*H*CO), 7.3-7.65 (m, 5H, phenyl hydrogens), 6.48 [6.62] (two d, $J_{6,7}$ = 9.0 Hz, 1H total, H-7), 5.25 [5.32] (two d, $J_{6,7}$ = 9.0 Hz, 1H total, H-6), 5.15 [4.85] (t, J = 7 Hz, 1H, H-9), 4.18-4.48 (m, 4H, OC*H*$_2$CH$_3$, H-3), 1.6-1.95 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.1-1.55 (m, 7H, OCH$_2$C*H*$_3$, CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.90 (t, J = 7 Hz, 2H, CH$_2$CH$_2$C*H*$_3$); ^{13}C nmr (chloroform-d$_1$): δ 168.69 and 168.14 (C-2, *C*=O, C-5), 153.24 [153.38] (*C*O$_2$Et), 137.35, 137.14, 136.64 and 135.78 (C-9a, phenyl C-1), 129.99, 129.23 and 128.10 (phenyl C-2, C-3, C-4, C-5, C-6), 119.30 [120.14] (C-7), 114.99 [115.91] (C-5a), 107.45 [107.18] (C-6), 62.86 [62.44] (O*C*H$_2$CH$_3$), 57.96 [57.83] (C-3), 54.37 [54.93] (C-9), 31.73 [31.61] (*C*H$_2$CH$_2$CH$_2$CH$_3$), 27.17 (*C*H$_2$CH$_2$CH$_3$), 22.41 [22.28] (CH$_2$*C*H$_2$CH$_3$), 14.28 (OCH$_2$*C*H$_3$), 13.82 [13.91] (CH$_2$CH$_2$*C*H$_3$).

5,9-Diphenyl-8-ethoxycarbonyl-1,3,8,9-tetrahydro-2*H*-pyrido-[3,4-*e*]-1,4-diazepin-2-one (**8d**).

This compound was obtained as a white solid; ir (potassium bromide): 3246, 3197, 3107, 2967, 2959, 1721, 1680, 1639, 1606, and 1581 cm^{-1}; ^{1}H nmr (chloroform-d$_1$, 25°): (mixture of two rotamers in a ratio of 1:2) δ 8.40 (br s, 1H, N*H*CO), 7.22-7.70 (m, 10H, phenyl hydrogens), 6.64 [6.82] (two d, $J_{6,7}$ = 9.0 Hz, 1H total, H-7), 6.08 [5.76] (two s, 1H total, H-9), 5.30 (br d, $J_{6,7}$ = 9.0 Hz, 1H, H-6), 4.16-4.48 (m, 4H, NC*H*$_2$CO, OC*H*$_2$CH$_3$), 1.30 (br t, J = 7 Hz, 3H, OCH$_2$C*H*$_3$); ^{1}H nmr (dimethyl sulfoxide-d$_6$, 75°): δ 10.32 (s, 1H, N*H*CO), 7.40-7.68 (m, 10H, phenyl hydrogens), 6.70 (d, $J_{6,7}$ = 9.0 Hz, 1H, H-7), 6.18 (s, 1H, H-9), 5.26 (d, $J_{6,7}$ = 9.0 Hz, 1H, H-6), 4.38 (d, J_{gem} = 12 Hz, 1H, NC*H*H'CO), 4.26 (q, J = 7 Hz, 2H, OC*H*$_2$CH$_3$), 4.04 (d, J_{gem} = 12 Hz, 1H, NCH*H'*CO), 1.26 (t, J = 7 Hz, 3H, OCH$_2$C*H*$_3$).

General Procedure for the Preparation of 1-Methyl-5-phenyl-8-acetyl-9-*n*-butyl (or 9-phenyl)-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-ones **9a-b**. Procedure D.

Sodium hydride (0.2 g of a 60% dispersion in mineral oil, 5

mmoles) was added to a solution of either **8a** or **8b** (3.95 mmoles) in dimethylformamide (20 ml) at 0° and this mixture was stirred for 20 minutes at 0°. Iodomethane (0.68 g, 4.8 mmoles) was then added and the reaction was allowed to proceed for 2 hours at 0° prior to pouring onto ice-water (250 ml). Extraction with ethyl acetate (3 x 70 ml), washing the ethyl acetate extract with water (magnesium sulfate) and removal of the solvent *in vacuo* gave a residue. The residue was purified by preparative silica gel thin layer chromatography using plates 1.0 mm in thickness. The development solvent used, R_f value, melting point and % yield for **9a-b** are listed in Table I. Spectral data for **9a** and **9b** are listed below.

1-Methyl-5-phenyl-8-acetyl-9-*n*-butyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**9a**).

This compound was obtained as an oil; ir (film): 3017, 2959, 2935, 1680, 1639, 1598, 1573 and 1565 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6, 25°): (mixture of two rotamers in a ratio of 2:3) δ 7.40-7.70 (m, 5H, phenyl hydrogens), 6.78 [6.65] (two d, $J_{6,7}$ = 9.0 Hz, 1H total, H-7), 6.70 (t, J = 7.0 Hz, 1H, H-9), 5.26 [5.43] (two d, $J_{6,7}$ = 9.0 Hz, 1H, total, H-6), 4.66 [4.56] (two d, J_{gem} = 12.0 Hz, 1H total, NC*H*H'CO), 3.96 [3.80] (two d, J_{gem} = 12.0 Hz, 1H, NCH*H'*CO), 3.16 [3.08] (two s, 3H total, CH_3N), 2.24 [2.18] (two s, 3H total, CH_3CO), 1.57 (m, 2H, CH_2CH$_2$CH$_2$CH$_3$), 1.24 (m, 4H, CH$_2$CH_2CH_2CH$_3$), 0.84 (t, J = 7 Hz, 3H, CH$_2$CH$_2$CH$_2$CH_2); ^1H nmr (dimethyl sulfoxide-d_6, 80°): δ 7.34-7.74 (m, 5H, phenyl hydrogens), 6.74 (br d, $J_{6,7}$ = 9.0 Hz, 1H, H-7), 5.74 (br t, J = 7.0 Hz, 1H, H-9), 5.38 (br d, $J_{6,7}$ = 9.0 Hz, 1H, H-6), 4.64 (br d, J_{gem} = 12.0 Hz, 1H, NC*H*H'CO), 3.90 (br d, J_{gem} = 12.0 Hz, 1H, NCH*H'*CO), 3.16 (br s, 3H, CH_3N), 2.24 (br s, 3H, CH_3CO), 1.64 (m, 2H, CH_2CH$_2$CH$_2$CH$_3$), 1.36 (m, 4H, CH$_2$CH_2CH_2CH$_3$), 0.84 (t, J = 7.0 Hz, 3H, CH$_2$CH$_2$CH$_2$CH_3); ^{13}C nmr (chloroform-d_1): δ 169.42, 168.86, 167.91, 167.66, 167.61 and 166.77 (C-2, C-5, and *C*OMe), 141.94 [137.81] (C-9a), 136.68 [136.13] (phenyl C-1), 128.02-130.24 (phenyl C-2, C-3, C-4, C-5, C-6), 121.54 [118.61] (C-7), 118.23 [117.64] (C-5a), 109.53 [109.44] (C-6), 57.71 [57.38] (C-3), 50.94 [47.74] (C-9), 32.15 [30.03] (N*C*H$_3$), 31.68 [30.19] (*C*H$_2$CH$_2$CH$_2$CH$_3$), 27.25 [27.55] (*C*H$_2$CH$_2$CH$_3$), 22.29 [22.15] (CH$_2$*C*H$_2$CH$_3$), 21.22 [20.86] (CO*Me*), 13.63 [13.82] (CH$_2$CH$_2$*C*H$_3$.

1-Methyl-5,9-diphenyl-8-acetyl-1,3,8,9-tetrahydro-2*H*-pyrido[3,4-*e*]-1,4-diazepin-2-one (**9b**).

This compound was obtained as a white solid; ir (potassium bromide): 3058, 2984, 2926, 1680, 1639 and 1565 cm^{-1}: ^1H nmr (chloroform-d_1, 25°): (mixture of two rotamers in a ratio of 1:3) δ 7.22-7.70 (m, 10H, phenyl hydrogens), 6.32 [7.06] (two d, $J_{6,7}$ = 9.0 Hz, 1H total, H-7), 6.50 [5.92] (two s, 1H total, H-9), 4.96 [5.04] (two d, $J_{6,7}$ = 9.0 Hz, 1H total, H-6), 4.16 [4.06] (br d, J_{gem} = 12.0 Hz, 2H total, NCH_2CO), 3.08 [3.04] (two s, 3H total, CH_3N), 2.22 [2.18] (two s, 3H total, CH_3CO); ^1H nmr (dimethyl sulfoxide-d_6, 75°): δ 7.22-7.66 (m, 10H, phenyl hydrogens), 6.50 (d, $J_{6,7}$ = 9.0 Hz, 1H, H-7), 6.18 (s, 1H, H-9), 5.0 (d, $J_{6,7}$ = 9.0 Hz, 1H, H-6), 3.94 (d, J_{gem} = 12.0 Hz, 1H, NC*H*H'CO), 3.40 (d, J_{gem} = 12.0 Hz, 1H, NCH*H'*CO), 3.0 (s, 3H, CH_3N), 2.16 (s, 3H, CH_3CO); ^{13}C nmr (chloroform-d_1): δ 169.32, 168.54, 167.91, 167.63 and 167.00 (*C*OMe, C-2, C-5), 140.44, 138.07, 137.23, 136.61, 136.19 and 135.50 (C-9a and two phenyl C-1), 126.90-130.43 range (two phenyl C-2 to C-6), 119.58 [122.20] (C-7), 119.94 [119.23] (C-5a), 109.31 [107.94] (C-6), 57.29] (C-3), 50.91 [54.98] (C-9), 31.08 [31.67] (N*C*H$_3$), 21.22 [21.56] (CO*C*H$_3$).

1,3-Dihydro-5,9-diphenyl-2*H*-pyrido[3,4-*e*]1,4-diazepin-2-one (**10**). Procedure D.

A mixture of **8d** (0.25 g, 0.64 mmole) and *para*-chloranil (0.25 g, 1 mmole) in toluene (20 ml) and glacial acetic acid (15 ml) was heated at reflux for 1.5 hours and the solvent was removed *in vacuo*. Ethyl acetate (50 ml) and 10% w/v aqueous sodium hydroxide (15 ml) was added to the residue obtained and the mixture was stirred for 20 minutes at 25° after which it was filtered through celite. The filtrate obtained was neutralized with 5*N* hydrochloric acid, the ethyl acetate fraction was separated, and the aqueous layer was extracted with ethyl acetate (2 x 30 ml). The combined ethyl acetate fractions were washed with water (50 ml), brine (25 ml), the ethyl acetate solution was dried (sodium sulfate) and the solvent was removed *in vacuo*. Preparative silica gel thin layer chromatography of the residue obtained using plates 1.0 mm in thickness with ethyl acetate-hexane (3:1, v/v) as development solvent afforded **10** (90 mg, 45%, R_f 0.34); ir (potassium bromide): 3378, 3117, 2959, 2926, 2853, 1688, 1614 and 1581 cm^{-1}; ^1H nmr (chloroform-d_1): δ 8.50 (d, $J_{6,7}$ = 5.8 Hz, 1H, H-7), 7.40-7.66 (m, 11H, phenyl hydrogens, N*H*CO), 7.22 (d, $J_{6,7}$ = 5.8 Hz, 1H, H-6), 4.44 (br s, 2H, NCH_2CO).

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