Schmidt Rearrangement of 1,2,3,5,10,10a-Hexahydropyrrolo[1,2-*b*]-isoquinoline-3,10-diones

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The Schmidt rearrangement of 1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline-3,10-diones has been studied. The structure of the lactams obtained has been determined by chemical reactivity and characterized by means of ir, ^{1}H and ^{13}C nmr spectroscopy.

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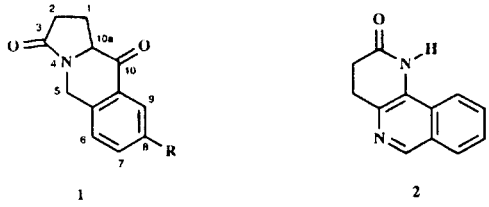
L-Pyroglutamic acid (5-pyrrolidone-2-carboxylic acid) the naturally occurring cyclized internal amide of glutamic acid is found as the amino-terminal residue of a number of biologically active neuropeptides like neurotensin [1]. Pyroglutamic acid is orally active and can permeate the blood-brain barrier so that derivatives of this acid can be active on the CNS. It is also an effective chiral template for the synthesis of nitrogen containing natural products [2-4] like cytochalasans [5], calyculins [6], anatoxinic acid [7,8] or for the design of new angiotensin-converting enzyme or renin inhibitors [9]. The need for novel pyroglutamic derivatives is of importance for improvement *inter alia* of memory and more generally as potential agents for the treatment of diseases which associated cholinergic deficits like Alzheimer's disease.

We have been involved in our research program in studying the Schmidt rearrangement of heterocyclic ketones [10,11] which is a route for lactam synthesis [12] concurrently with the Beckmann rearrangement [13-15]. The results obtained with 4-acetylpiperidone [10] or 1-acetyl-1,2-dihydro-3*H*-indol-3-one [11] prompted us to investigate the behaviour of 1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline-3,10-diones **1** which can open access to aminobenzodiazepines **15** with potential pharmacological properties.

Rigo [16] has first prepared and studied the reactivity of ketones **1**; more recently [17,18] the Beckmann rearrangement of the oxime of ketone **1a** (R = H) has been performed (polyphosphoric acid/100°); a new compound **2** has been obtained which was neither a product of the Beckmann rearrangement nor a nitrile that would result from oxime fragmentation. Compound **2**, 1,4-dihydro-benzo[*c*]-1,5-naphthyridin-2(3*H*)-one, was expected to result from a Semmler-Wolff type aromatization.



1 2

Figure 1

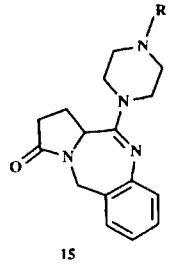


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Figure 2

We have also prepared the seven-membered ring ketone **6** in order to investigate the influence of the conformation on the migratory aptitude of substituents of the ketone moiety under the conditions of the Schmidt rearrangement. The methyl pyroglutamate anion reacted with phenacyl bromide in dimethylformamide affording the alkylated compound **4** which was hydrogenated over palladium into compound **5**; the reduction of the ketone group allowed us to obtain the methyl 1-(2-phenylethyl)-2-pyrrolidinone-5-carboxylate **5**; this two step-synthesis overcame the drawback of the basicity of the methylpyroglutamate anion [19] which only gave elimination with the 1-bromo-2-phenylethanes used as an electrophile. Unfortunately the seven membered cyclic ketone **6** was only obtained in very low yield (8%) using the standard procedure of cyclization [17,18] thus preventing further studies.

We have performed the Schmidt rearrangement on ketones **1** [16,17], prepared from methyl pyroglutamate and substituted benzyl chlorides, according to the following experimental conditions: (concentrated sulfuric acid /0°/ sodium azide, 2.2 equivalents/ketone, 1 equivalent).

A mixture of the isomeric lactams **7** and **8** was obtained where lactams **7** were always the major products. Compounds of structure **2** were not detected.

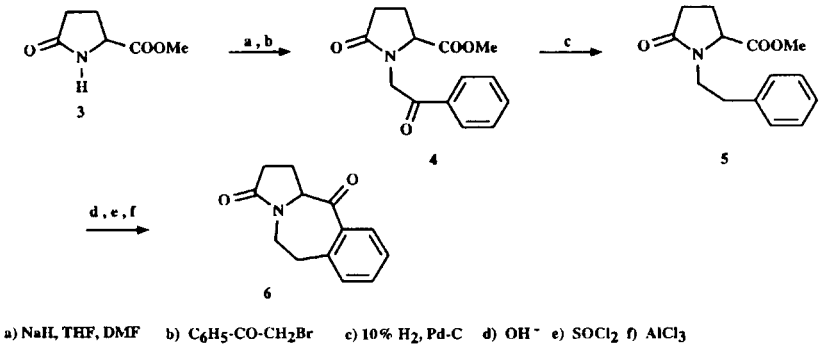


Figure 3

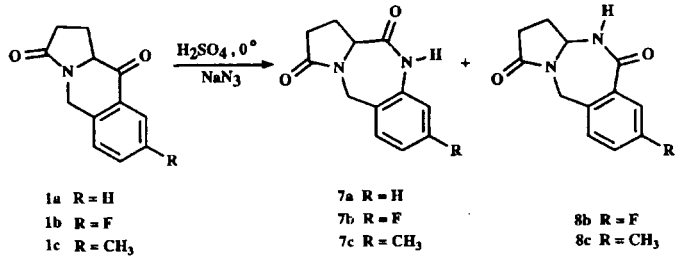


Figure 4

%	a	b	c
7	100	60	72
8	0	40	28

The migratory aptitude of the sigma bond adjacent to the ketone is known to be very sensitive to inductive effects caused by neighbouring groups in a Schmidt rearrangement [20]; it was also known that phenyl migration was generally predominant in cycloalkyl arylketones [21,22]; if 6,7-dihydro-3-phenyl-1,2-benzisoxazol-4-(5*H*)-one was subjected to a Schmidt reaction, the lactam resulting from alkyl migration predominated over lactam resulting from aryl migration [23]. Similarly 4-amino-1-benzyl-7,8-dihydro-(6*H*)pyrazolo[3,4-*b*]quinolin-5-one [24] afforded a mixture of isomeric lactams (1:3) where the pyridinyl migration predominated.

The structure of **7** or **8** was supported by chemical and spectral evidence. Comparison of the chemical shift in ^1H nmr (300 MHz) of the H_{10a} hydrogen of the ketones **1** or the H_{11a} hydrogen of the lactams **7** gave similar value (for example δ = 4.20 ppm for **1b**, δ = 4.18 ppm for **7b**). The ^{13}C chemical shift of the C_{10a} carbon of the oxoproline ring in compounds **1** and the C_{11a} carbon of compounds **7** gave rise to the same conclusion (for example δ = 61 ppm for **1a** and δ = 58 ppm for **7a**). A CH next to a carbonyl function in a lactam group absorbs at a higher field when compared to a CH next to a NH function of the lactam group. Moreover compound **7b** shows a broad amide NH signal at δ *ca* 8.6 ppm shifted upfield from the signal observed at *ca* δ = 8.9 ppm in the other isomer **8b**.

Compounds **7a,b** were submitted to sodium borohydride reduction in 2-methyl-2-propanol in the presence of a limited amount of methanol according a procedure developed for lactam reduction [25].

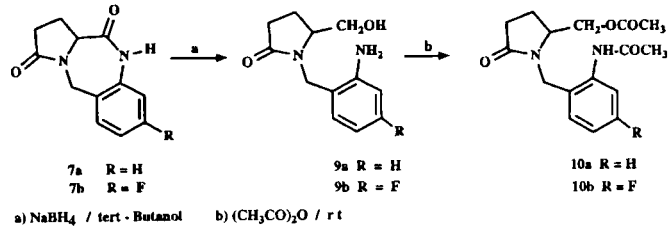


Figure 5

Opening of the lactam ring was the result of such a reduction with formation of the aminoalcohols **9a,b** which were diacetylated at room temperature to yield compounds **10a,b**; (the nmr data of compounds **9** were in agreement with the data of 1-benzyl-5-hydroxymethyl-2-pyrrolidone obtained by reduction in the same conditions of the methyl 1-benzyl-5-pyrrolidone-2-carboxylate). Under the same reduction conditions the isomeric lactam **8b** afforded a mixture of unidentified products due to the low stability of the 2-amino-5-oxoproline moiety.

The direct synthesis of **7a** from methyl pyroglutamate and 2-nitrobenzyl chloride was not possible due to the

strong basicity of the methyl pyroglutamate anion [19]; we have prepared from methyl prolinate and 2-nitrobenzyl chloride the benzodiazepine **13** precedently described in a patent [26]. The cyclization step (**12** to **13**) is very capricious and need careful experimental conditions. Unfortunately the ruthenium oxidation of the compound **13** according to standard conditions [27] did not afford compound **7a**.

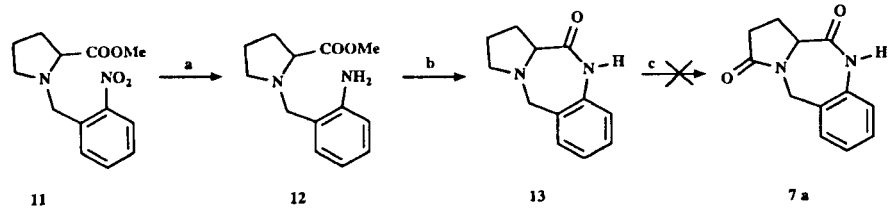
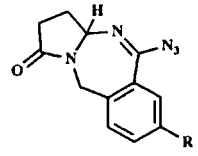


Figure 6

In the Schmidt reaction of ketones **1** we have isolated in small amount (<5% yield) the stable compounds **14** which were first eluted on flash silica gel chromatography. These compounds have a strong absorption at 2130 cm^{-1} and 1720 cm^{-1} on ir spectra with no absorption in the region 3100-3500 cm^{-1}. In the mass spectra a peak at M^+ - 42 is observed (loss of N_3). The nmr data indicated that the tricyclic structure was always present; the chemical shift at *ca* 5.0 ppm for the CH in the products **14** led us to attribute an hypothetical structure of iminoyl azides for compounds **14** with the azido group connected with the benzylic carbon atom.



14a R = H
14b R = F
14c R = CH_3

Figure 7

Until now only instable iminoylazides have been postulated due to their rapid transformation into tetrazoles [28-30]. In some cases tetrazoles are the major products in the Schmidt reactions of 2-aryl-1,2,3,4-tetrahydro-4-quinolones [31].

Reacting compound **7a** with sodium azide in sulfuric acid left **7a** unchanged; reaction of compound **1a** with only one equivalent of sodium azide always afforded **14a** in small amount. Reaction of compound **7a** with trimethylsilyl azide, diisopropyl azodicarboxylate and triphenylphosphine met with failure despite the description of the transformation of a lactam to a tetrazole by this route [28].

Compounds **7** are very interesting compounds for being key intermediates in the synthesis of amino (like piperazino)benzodiazepines **15** with very promising pharmacological properties.

EXPERIMENTAL

Melting point were obtained on a Kofler hot-stage apparatus and are uncorrected; the ^1H nmr spectra were determined on a Bruker instrument (AM 300WB, 300 MHz) with tetramethyl silane as the internal standard; ir spectra were recorded on a Perkin Elmer 257 spectrophotometer; mass spectra were obtained on a Nermag 10C apparatus. The synthesis of compounds **1a**, **1b**, and **1c** have been reported [16-18].

Methyl 1-Benzoylmethyl-5-oxopyrrolidine-2-carboxylate (**4**).

Compound **4** was prepared according a similar procedure as for alkylation of the pyroglutamate anion [16]. The product was chromatographed on a silica gel column (230-400 mesh) using dichloromethane as eluent, oil; yield 48%; ir (film): 1750, 1700 large (CO) cm^{-1}; ^1H nmr (deuteriochloroforml: δ = 2.10-2.30 (m, 2H, CH_2), 2.45-2.55 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.42 (d, J = 16, 1H, NCH_2Ar), 4.52 (m, 1H, CH), 5.37 (d, J = 16, 1H, NCH_2Ar), 7.50 (t, J = 7.9, 2H, H arom), 7.60 (m, 1H, H arom), 7.96 (d, J = 7.9, 2H, H arom).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found C, 64.31; H, 5.67; N, 5.18.

Methyl 1-(2-Phenylethyl)-5-oxopyrrolidine-2-carboxylate (**5**).

The hydrogenation of compound **4** was carried out in methanol in the presence of 10% palladium on carbon, at room temperature under 40 psi of hydrogen during 2 days and afforded compound **5** in nearly quantitative yield, mp 82-84° (ethanol/water); ir (potassium bromide): 1745, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.00-2.60 (m, 4H, CH_2), 2.70-

2.95 (m, 2H, $CH_2C_6H_5$), 3.20 (m, 1H, NCH_2Ar), 3.75 (s, 3H, OCH_3), 3.95 (m, 1H, NCH_2Ar), 4.00 (m, 1H, CH), 7.20-7.35 (m, 5H, H arom).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.17; H, 7.08; N, 5.49.

2,3,5,6,11,11a-Hexahydro-1*H*-pyrrolo[2,1-*b*][3]benzazepine-3,11-dione (**6**).

Compound **5** was treated with sodium hydroxide in water according [17] and the acid obtained (yield 82%) was dissolved in dichloromethane followed by the addition of thionyl chloride (2 equivalents) and dimethylformamide (one drop); the mixture was stirred 2 days at room temperature then cooled to 0° with an ice-bath and treated portionwise with aluminium chloride (5 equivalents); after 1 hour at 0° the mixture was stirred 2 hours at room temperature then hydrolyzed with ice/water; the organic layer was sequentielly washed with a 10% sodium carbonate solution, water, then dried over magnesium sulfate; after evaporation, the oil was chromatographed on silica gel (230-400 mesh) using dichloromethane: methanol (99:1, v/v) as eluent, oil; yield 8%; ir (chloroform): 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.20-2.40 (m, 3H, CH_2CH_2), 2.60-2.70 (m, 1H, CH_2CO), 3.02 (dq, J = 12.5, 5, 1H, $CH_2C_6H_5$), 3.29 (td, J = 13.5, 6, 1H, NCH_2), 3.40 (dd, J = 12.5, 5, 1H, $CH_2C_6H_5$), 4.02 (td, J = 13.5, 6, 1H, NCH_2), 4.40 (dd, J = 9.2, 2.5, 1H, CH), 7.23 (d, J = 7.9, 1H, H arom), 7.36 (t, J = 7.9, 1H, H arom), 7.49 (t, J = 7.9, 1H, H arom), 7.73 (d, J = 7.9, 1H, H arom); ms: (m/z) 215 (M^+).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.31; H, 6.30; N, 6.27.

General Procedure for Schmidt Rearrangement. Compounds (**7**) or (**8**).

To a solution of the ketone **1** (1.5 mmoles) in chloroform (30 ml), at 0 °, was added concentrated sulfuric acid (24.3 ml), sodium azide (3.3 mmoles) was portionwise added and the mixture stirred 3 hours at this temperature, then ice (250 g) was added. The mixture was extracted with dichloromethane (3 x 50 ml), the organic extracts were washed with water (2 x 25 ml) and dried over magnesium sulfate. After evaporation *in vacuo*, the crude product was flash chromatographed on a silica gel colum (240-400 mesh) using dichoromethane: methanol, 99:1, v/v as eluent. Compounds **14** were first eluted, then compounds **7** and last, compounds **8**.

2,3,5,10,11,11a-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-3,11-dione (**7a**).

This compound was obtained from ketone **1a**, yield 40% mp 202-204° (ethanol/water); ir (potassium bromide): 3160 (NH), 1670 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.00-2.10 (m, 2H, CH_2), 2.40-2.70 (m, 2H, CH_2), 4.18 (ft, J = 7.1, 1H, CH), 4.28 (d, J = 14, 1H, N-CH_2), 4.77 (d, J = 14, 1H, N-CH_2), 7.09 (fd, J = 8, 1H, H arom), 7.22 (fd, J = 8, 1H, H arom), 7.35 (fd, J = 8, 1H, H arom), 7.37 (ft, J = 8, 1H, H arom), 8.60 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ = 18.75 (CH_2) 29.9 (CH_2), 44.6 (CH_2-C_6H_5), 57.8 (CH), 122.1, 126.4, 129.6, 130.4 (CH arom) 127.3, 136.8 (C arom), 169.3, 173.4 (C=O); ms: (m/z) 216 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.39; H, 5.47; N, 13.18 .

8-Fluoro-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-3,11-dione (**7b**).

This compound was obtained from ketone **1b**; yield 35% mp 194-196° (ethanol/water); ir (potassium bromide): 3160 (NH), 1685 (CO), 1675 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.05-2.17 (m, 2H, CH_2), 2.4-2.7 (m, 2H, CH_2), 4.18 (dd, J = 8.5, 1.2, 1H, CH), 4.21 (d, J = 13.8, 1H, NCH_2), 4.75 (d, J = 13.8, 1H, NCH_2), 6.85 (td, J = 8.7, 2.4, 1H, H arom), 6.94 (td, J = 8.7, 2.4, 1H, H arom), 7.33 (dd, J = 8.7, 6, 1H, H arom), 8.70 (s, 1H, NH); ^{13}C nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ = 18.95 (CH_2), 29.8 (CH_2), 43.9 (CH_2N), 58.1 (CH), 109, 112, 131 (C arom), 160.5 (d, J_{CF} = 245 Hz) (C arom), 123, 139 (C arom), 168.9 (CO), 172.9 (CO); ms: (m/z) 234 (M^+).

Anal. Calcd. for $C_{12}H_{11}FN_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.66; H, 4.82; N, 11.73.

2,3,5,10,11,11a-Hexahydro-8-methyl-1*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-3,11-dione (**7c**).

This compound was prepared from ketone **1c**, yield 38% mp 225-227° (ethanol/water); ir (potassium bromide): 3170 (NH), 1690, 1680 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.05-2.10 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.40-2.70 (m, 2H, CH_2), 4.19 (dd, J = 7.6, 1.4, 1H, CH), 4.25 (d, J = 14.2, 1H, NCH_2), 4.75 (d, J = 14.2, 1H, NCH_2), 6.92 (s, 1H, H_9, arom), 7.05 (fd, J = 7.6, 1H, H arom), 7.27 (fd, J = 8.8, 1H, H arom), 8.45 (s, 1H, NH); ms: (m/z) 230 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found : C, 67.98; H, 6.03; N, 12.25.

7-Fluoro-2,3,3a,4,5,10-hexahydro-1*H*-pyrrolo[1,2-*b*][2,4]benzodiazepine-1,5-dione (**8b**).

This compound was prepared from ketone **1b**, yield 23% mp 136-138° (ethanol/water); ir (potassium bromide): 3220 (NH), 1660 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ = 1.9 (mas, 1H, CH_2), 2.35 (mas, 1H, CH_2), 2.87 (ft, J = 7.4, 1H, CH_2CO), 3.37 (ft, J = 7.4, 1H, CH_2CO), 4.37 (d, J = 15, 1H, CH_2N), 4.62 (d, J = 15, 1H, CH_2N), 5.02 (m, 1H, CH), 7.40-7.60 (m, 2H, H arom), 7.80 (dd, J = 11, 4, 1H, H arom), 8.9 (s, 1H, NH); ^{13}C nmr (deuteriochloroform + DMSO-d_6): 28.2 (CH_2), 28.6 (CH_2), 41.3 (CH_2N), 82.6 (CH) 119.2 (CHAr), 120.4 (CHAr), 131 (CHAr), 116 (C quat), 137.6 (C quat), 158- 163 (d, C-F), 174.7 (CO); ms: (m/z) 234 (M^+).

Anal. Calcd. for $C_{12}H_{11}FN_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.79; H, 4.87; N, 11.75.

2,3,3a,4,5,10-Hexahydro-7-methyl-1*H*-pyrrolo[1,2-*b*][2,4] benzodiazepine-1,5-dione (**8c**).

This compound was prepared from compound **1c**, yield 15%; mp 195° (dec) (ethanol); ir (potassium bromide): 3225 (large, NH), 1660 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.90-2.20 (m, 2H, CH_2), 2.40-2.70 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 4.29 (d, J = 14, 1H, NCH_2), 4.81 (d, J = 14, 1H, NCH_2), 4.98 (m, 1H, CH), 7.21 (d, J = 7, 1H, H arom), 7.34 (d, J = 7, 1H, H arom), 7.67 (s, 1H, H arom), 7.80 (br s, 1H, NH); ms: (m/z) 230 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.04; H, 6.32; N, 12.03.

2-Oxo-5-hydroxymethyl-1-(2-aminophenylmethyl)pyrrolidine (**9a**).

Compound **7a** (0.22 g, 1 mmole), sodium borohydride (0.458 g, 12 mmoles) in *tert*-butyl alcohol (20 ml) were refluxed; methanol (0.5 ml) was added every hour. After 3 hours of reflux water (80 ml) was added, the mixture extracted with dichloromethane (2 x 25 ml) and the organic layer dried over magnesium sulfate. Evaporation of the solvent afforded a white solid which is pure enought for acylation, yield 0.195 g (88%), mp 149-151° (ethanol/water); ir (potassium bromide): 3440, 3350 (NH_2), 3220 (OH), 1650 (CO), 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.60 (br s, 3H, NH_2 + OH), 1.90-2.20 (m, 2H, CH_2), 2.30-2.40 (m, 1H, CH_2), 2.55-2.70 (m, 1H, CH_2), 3.37 (dd, J = 10, 2.8, 1H, CH_2O), 3.47 (dd, J = 10, 2.2, 1H, CH_2O), 3.62 (m, 1H, CH), 4.21 (dd, J = 14.5, 1H, NCH_2Ar), 4.85 (dd, J = 14.5, 1H, NCH_2Ar), 6.70 (t, J = 7.7, 1H, H_5 arom), 6.68 (d, J = 8.2, 1H, H_6 arom), 7.05 (d, J = 7.7, 1H, H_3 arom), 7.12 (t, J = 7.7, 1H, H_4 arom); ms: (m/z) 220 (M^+).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.19; H, 7.43; N, 12.84.

2-Oxo-5-hydroxymethyl-1-(2-amino-4-fluorophenylmethyl-pyrrolidine (**9b**).

Similarly prepared as for compound **9a**, yield 0.210 g (89%), oil; ir (chloroform): 3460, 3360 (NH_2), 3210 (OH), 1660, (CO), 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.85-2.2 (m, 2H, CH_2), 2.3-2.45 (m, 1H, CH_2), 2.5-2.65 (m, 1H, CH_2), 3.45 (dd, J = 13.3, 3.5,1H, CH_2O), 3.68 (m, 1H, CH), 3.65 (dd, J = 12, 3.5, 1H, CH_2O), 4.33 (d, J = 13, 1H, NCH_2), 4.61 (d, J = 13, 1H, NCH_2), 6.40 (m, 1H, H arom), 7.00 (m, 1H, H arom), 7.96 (d, J = 7, 1H, H arom); ms: (m/z) 238 (M^+).

Anal. Calcd. for $C_{12}H_{15}FN_2O_2$: C, 60.49; H, 6.35; N, 11.76. Found: C, 60.72; H, 6.15; N, 11.82.

2-Oxo-5-acetyloxymethyl-1-(2-acetylaminophenylmethyl)-pyrrolidine (**10a**).

Similarly prepared as for compound **10b**, yield 89%, oil; ir (film): 3350 (NH), 1740 (OCO), 1650 (NCO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.80-2.60 (m, 4H, CH_2), 2.08 (s, 3H, $COCH_3$), 2.24 (s, 3H, $COCH_3$), 4.09 (dd, J = 12, 4, 1H, CH_2O), 4.14 (d, J = 15, 1H, NCH_2Ar), 4.30 (dd, J = 12, 4, CH_2O), 4.31 (m, 1H, CH), 4.77 (d, J = 15, 1H, NCH_2Ar), 7.03 (ft, J = 7.5, 1H, H arom), 7.21 (dd, J = 7.5, 1.2, 1H, H arom), 7.32 (td, J = 7.5, 1.2, 1H, H arom), 8.26 (fd, J = 8.3, 1H, H arom), 9.43 (s, 1H, NH); ms: (m/z) 304 (M^+).

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.32; H, 6.87; N, 9.35.

2-Oxo-5-acetyloxymethyl-1-(2-acetylamino-4-fluorophenyl-methylpyrrolidine (**10b**).

Compound **9b** (0.100 g, 0.042 mmole) was dissolved in acetic anhydride (5 ml) and reacted 20 hours at room temperature; the mixture was evaporated *in vacuo*, then treated with water (20 ml) and extracted with dichloromethane (2 x 20 ml); after drying over magnesium sulfate and evaporation of the solvent an oil was obtained which slowly crystallyzed, mp 112-114° (ethanol/water) yield 0.114 g (84%); ir (potassium bromide): 3300 (NH), 1740 (OCO), 1650 (NCO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.90-2.60 (m, 4H , CH_2), 2.07 (s, 3H, $COCH_3$), 2.26 (s, 3H, $COCH_3$), 3.79 (m, 1H, CH), 4.10 (dd, J = 12, 3.5, 1H, CH_2O), 4.14 (d, J = 15, 1H, NCH_2), 4.32 (dd, J = 12, 3.5, 1H, CH_2O), 4.71 (d, J = 15, 1H, NCH_2), 6.72 (td, J = 8, 3.2, 1H, H_5 arom), 7.17 (dd, J = 8.5, 6.3, 1H, H_6 arom), 8.16 (dd, J = 11, 3.2, 1H, H_3 arom), 9.60 (s, 1H, NH); ms: (m/z) 322 (M^+).

Anal. Calcd. for $C_{16}H_{19}FN_2O_4$: C, 59.62; H, 5.94; N, 8.69. Found: C, 59.46; H, 6.07; N, 8.72.

Methyl 1-(2-Nitrophenylmethyl)pyrrolidine-2-carboxylate (**11**).

To a suspension of methyl prolinate (15.44 g, 119.6 mmoles) and sodium carbonate (31.7 g, 299 mmoles) in 2-butanone (350 ml), cooled by an ice bath, 2-nitrobenzylchloride (19.05 g, 111 mmoles) in 2-butanone (50 ml) was dropwise added; the mixture was stirred overnight at room temperature. After filtration, the mixture was evaporated and the obtained oil was dissolved in benzene and washed with water; drying over magnesium sulfate and evaporation afforded an oil which was chromatographed on silica gel (230-400 mesh) using dichloromethane:petroleum ether, 50:50, v/v as eluent, yield 18.2 g (62%); ir (film): 1730 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.80-2.20 (m, 4H, CH_2), 2.45 (dd, J = 16, 8, 1H, CH_2N), 3.00 (m, 1H, CH_2N), 3.40 (dd, J = 8, 4.8, CH), 3.64 (s, 3H, OCH_3), 4.03 (d, J = 15, 1H, NCH_2Ar), 4.16 (d, J = 15, NCH_2Ar), 7.37 (td, J = 8, 2, 1H, H arom), 7.55 (t, J = 8, 1H, H arom), 7.73 (d, J = 8, 1H, H arom), 7.84 (d, J = 8, 1H, H arom).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H 6.10; N, 10.60. Found: C, 58.91; H, 6.22; N, 10.75.

Methyl 1-(2-Aminophenylmethyl)pyrrolidine-2-carboxylate (**12**).

Compound **7** (0.52 g, 10 mmoles) was dissolved in methanol (25 ml) and platinum oxide (0.010 g) was added to the solution which was submitted to hydrogenation (30 psi, 3 hours). The aminoester **8** was obtained in nearly quantitative yield after evaporation of the solvent, and immediately used; ir (film): 3420, 3320 (NH_2), 1730 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.6-2.0 (m, 4H, CH_2 + NH_2), 2.10-2.20 (m, 2H, CH_2), 2.30 (dd, J = 16, 8, 1H, CH_2N), 2.90 (m, 1H, CH_2N), 3.21 (dd, J = 9, 6.8, 1H, CH), 3.30 (d, J = 12, 1H, NCH_2Ar), 3.68 (s, 3H, OCH_3), 3.96 (d, J = 12, 1H, NCH_2Ar), 6.62 (d, J = 7.1, 2H, H arom), 6.98 (d, J = 7.1, 1H, H arom), 7.07 (t, J = 7.7, 1H, H arom).

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C 66.69; H, 7.83; N, 12.03.

2,3,5,10,11,11a-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**13**) [26].

The aminoester **12** (0.15 g, 0.6 mmole) was dissolved in dimethyl sulfoxide (1 ml) and cooled at 0°; sodium hydride 80% (0.180 g, 0.6 mmole) was added portionwise and the mixture stirred 5 hours at room temperature; water (20 ml) was added and the mixture was extracted with dichloromethane (2 x 20 ml). Drying over magnesium sulfate and evaporation afforded a white solid which was purified by silica gel chromatography (230-400 mesh dichloromethane as eluent), yield 0.071 g (59%), mp 171-173° (ethanol); ir (potassium bromide): 3200 (NH), 1650 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.9-2.2 (m, 2H, CH_2), 2.46 (m, 2H, CH_2), 2.63 (dd, J = 16, 8, 1H, CH_2N), 3.07 (m, 1H, CH_2N), 3.63 (d, J = 12, 1H, NCH_2Ar), 3.67 (dd, J = 8, 2.8, 1H, CH), 3.95 (d, J = 12, 1H, NCH_2Ar), 6.96 (d, J = 8, 1H, H arom), 7.17 (t, J = 8, 1H, H arom), 7.30 (td, J = 8, 2, 1H, H arom), 7.35 (dd, J = 8, 2, 1H, H arom), 7.58

(s, 1H, NH); ms: (m/z) 202 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.09; H, 7.12; N, 13.97.

5-Azido-2,3,3a,10-tetrahydro-1*H*-pyrrolo[1,2-*b*][2,4]benzodiazepin-1-one (**14a**).

This compound is an oil, yield (5%); ir (film): 2150 (N_3), 1720 (CO) (large) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.00-2.70 (m, 4H, CH_2), 4.56 (d, J = 16, 1H, NCH_2Ar), 4.91 (d, J = 16, 1H, NCH_2Ar), 5.01 (fdd, J = 7.1, 2.3, 1H, CH), 7.40-7.70 (m, 4H, H arom); ms: (m/z) 241 (M^+).

Anal. Calcd. for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.96; H, 4.76; N, 28.98.

5-Azido-7-fluoro-2,3,3a,10-tetrahydro-1*H*-pyrrolo[1,2-*b*][2,4]benzodiazepin-1-one (**14b**).

This compound is an oil; yield (5%); ir (film): 2150 (N_3), 1720 (CO) (large) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.00-2.70 (m, 4H, CH_2), 4.58 (d, J = 16, 1H, NCH_2Ar), 4.78 (d, J = 16, 1H, NCH_2Ar), 5.05 (fd, J = 7.1, 1H, CH), 7.30-7.40 (m, 2H, H arom), 7.50 (m, 1H, H arom); ms: (m/z) 259 (M^+).

Anal. Calcd. for $C_{12}H_{10}FN_5O$: C, 55.60; H, 3.89; N, 27.01. Found: C, 55.76; H, 3.76; N, 27.18.

5-azido-2,3,3a,10-tetrahydro-7-methyl-1*H*-pyrrolo[1,2-*b*]-[2,4]benzodiazepin-1-one (**14c**).

This compound is an oil, yield (6%); ir (film): 2150 (N_3), 1720 (CO) (large) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.00-2.70 (m, 4H, CH_2), 2.40 (s, 1H, CH_3); 4.49 (d, J = 16, 1H, NCH_2Ar), 4.88 (d, J = 16, 1H, NCH_2Ar), 4.98 (fd, J = 5.6, 1H, CH), 7.4-7.5 (m, 3H, H arom); ms: (m/z) 255 (M^+).

Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.32; H, 5.27; N, 27.29.

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