Furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine and Derivatives

Christophe Chédru, Bernard Decroix* and Jean Morel

Laboratoire de Chimie, UER des Sciences et des Techniques
de l'Université du Havre, 30 rue Gabriel Péri,
76600 Le Havre, France

Frantisek Povazanec

Department of Organic Chemistry, Slovak Technical University,
81237 Bratislava, Slovakia

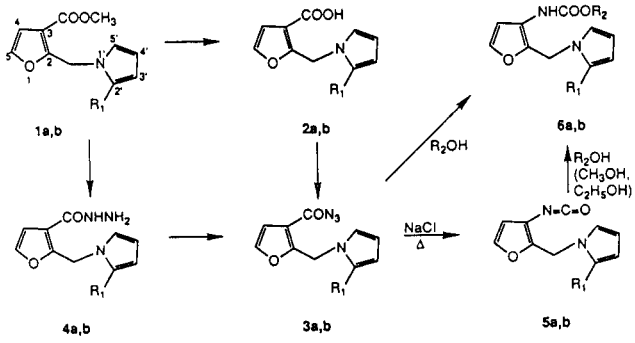
Received February 23, 1994

The 5,10-dihydro-4*H*-furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (**7**) and furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine (**10**) are synthesized from suitable isocyanates **3a,b** in acetic acid. The reactivity of **10** (*C*- and *N*-alkylation) is investigated.

J. Heterocyclic Chem., **31**, 1027 (1994).

We previously reported the synthesis of furo[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-9-one and the *C*-aminated and *N*-alkylated derivatives [1] from methyl 3-bromomethylfuran-2-carboxylate. The key step was the cyclization of a furan α substituted with a carbonylazide group in warm acetic acid [2]. Since the β-position of furan is very different from the α-position [3] compared with analogues of thiophene or pyrrole, it appears interesting to study the reactivity of a carbonylazide group substituted in the β-position of the furan ring.

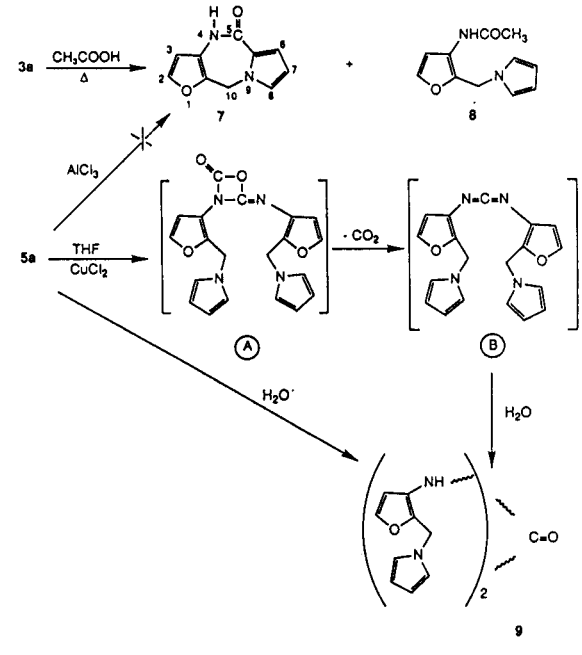
Scheme I



1-6a (R_1=H ; R_2=C_2H_5) 1-3,5,6b (R_1=CHO ; R_2=CH_3) 4b (R_1=CH=N-NH_2)

Thus, the methyl 2-(pyrrol-1-ylmethyl)furan-3-carboxylate **1a** was prepared from methyl 2-bromomethylfuran-3-carboxylate [4] and the potassium salt of pyrrole in anhydrous tetrahydrofuran in a 49% yield. An alkaline hydrolysis, followed by acidic treatment afforded 2-(pyrrol-1-ylmethyl)furan-3-carboxylic acid **2a**. This acid treated successively with triethylamine, ethyl chloroformate and sodium azide [5] led to the carbonylazide **3a** in a 73% yield. Alternatively, the azide **3a** could be obtained from the ester **1a** *via* the hydrazide **4a** in a 45% yield. Heating **3a** with an alcohol produced the corresponding carbamate **6a** which could be prepared in two steps *via* the isocyanate **5a**. The latter was distillated under vacuum from a mixture of carbonylazide **3a** and anhydrous sodium sulfate in a 80% yield. Similar reactions starting from 2-formylpyrrole and methyl 2-bromomethylfuran-3-carboxylate gave compounds **1b** to **6b** in satisfactory yields (see Experimental). Thus, reaction of the aldehyde-ester **1b** with hydrazine gave the expected hydrazone-carbohydrazide **4b** upon treatment with sodium nitrite in a solution of chlorhydric acid led to the aldehyde-carbonylazide **3b** (Scheme I). It is also interesting to notice that the aldehyde-isocyanate **5b** was stable in contrast with the isomer with the isocyanate group in the α position of the furan ring.

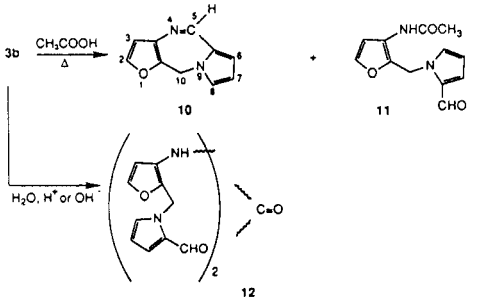
Scheme II



Heating the carbonylazide **3a** in warm acetic acid (Scheme II) gave a mixture of 5,10-dihydro-4*H*-furo[3,2-*e*]-pyrrolo[1,2-*a*][1,4]diazepin-5-one (**7**) (22%) and 2-(pyrrol-1-ylmethyl)furan-3-acetamide (**8**) (78%). On the other hand

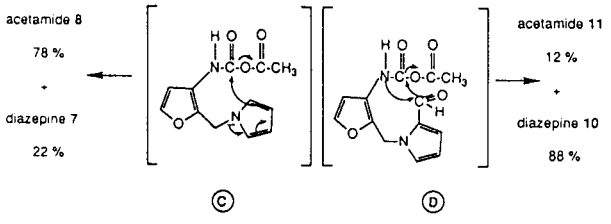
the isocyanate **5a**, upon treatment with aluminium trichloride [6] did not give the expected diazepine **7** but when heated with copper(II) chloride in tetrahydrofuran followed with an hydrolysis it gave the urea **9** in a 57% yield. The urea could be obtained by a direct hydrolysis of **5a** (86%) or **3a** (46%). It seems that the isocyanate leads first to the azalactone **A** followed by the loss of carbon dioxide to give the carbodiimide **B** which is hydrolyzed into the urea **9**. Similarly, the carbonylazide **3b** heated with acetic acid led to a mixture of 10*H*-furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]-diazepine (**10**) (88%) and 2-[(2-formylpyrrol)-1-ylmethyl]-furan-3-acetamide (**11**) (12%). An hydrolysis of **3b** with acid or base gave the expected urea **12** (Scheme III).

Scheme III



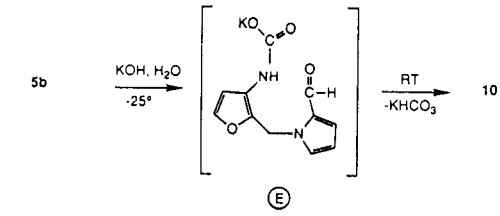
These results are very different from those found when the carbonylazide is substituted in the α position of the furan [1] because only the diazepinone or diazepine were isolated upon treatment with acetic acid. It seems that the mixed carboxylic carbamic acid anhydride **C** [7,8] loses easily a molecule of carbone dioxide to furnish the acetamide because the nucleophile character of the pyrrole ring decreases, due to the electron-withdrawing effect much more efficient in the α position of the furan ring (22% diazepine) than in the β position (100% diazepine) (Scheme IV). In contrast, the intermediate **D** gives the diazepine **10** as the major product (88%) because the formyl group is very reactive towards the carbamic function and less modified by the furan ring.

Scheme IV



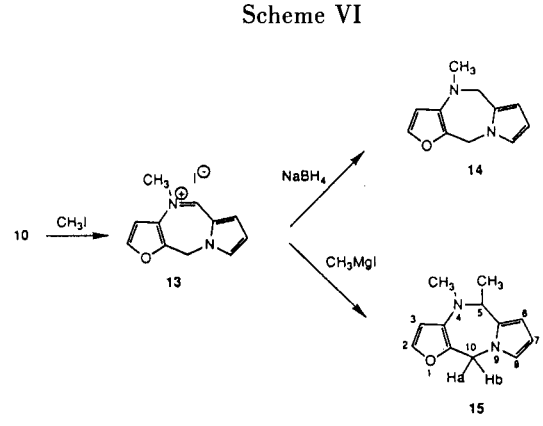
In view of this unsatisfactory result due to the presence of acetamide as a by-product and since some reports [9,10] in the literature indicated that a carbonylazide-aldehyde could be cyclized into a diazepine in a protic or basic aqueous solution, we attempted these conditions. An acidic media has been discarded rapidly because it yielded a mixture of diazepine and urea whatever the conditions of the reaction. Nevertheless the isocyanate aldehyde **5b** in a cold (−20°) solution of potassium hydroxide (50%) afforded the potassium salt **E** (Scheme V). When allowed to reach to room temperature by loss of potassium hydrogenocarbonate the latter cyclized to the diazepine **10** in good yield (70%) and no urea was detected. If the solution of potassium hydroxide is less concentrated or the temperature is up to −20° a mixture of diazepine **10** and urea **12** was obtained.

Scheme V



The diazepine is somewhat unstable so we formed the stable *N*-methyldiazepinium salt **13** by addition of methyl iodide (Scheme VI). Reduction of this salt with sodium borohydride furnished the 5,10-dihydro-4-methylfuro[3,2-*e*]-pyrrolo[1,2-*a*][1,4]diazepine (**14**). On the other hand the salt **13** treated with a Grignard reactant (methylmagnesium iodide) gave the 5,10-dihydro-4,5-dimethylfuro[3,2-*e*]-pyrrolo[1,2-*a*][1,4]diazepine (**15**). The structures of these *N*-and *C*-alkylated products were supported by their nmr spectra as well as their elemental analyses. In ^{1}H nmr, the stronger difference between the compounds **10, 13, 14** and **15** is the form of the signal of the two protons attached to the carbon C_{10} located between the furan and the pyrrole rings. Actually, for **10, 13** and **14** this signal is a singlet with a respective shift of 5.18 ppm (deuteriochloroform); 5.73 ppm (DMSO-d_6) and 5.21 (deuteriochloroform). For the dimethyl compound **15**, C_{10}-H_a and C_{10}-H_b appear as an AB system with a chemical shift of 5.01 and 5.25 ppm and a coupling constant of J = 16.1 Hz characteristic of gem-protons. Furthermore, the C_5-H appears as

Scheme VI



a quadruplet (J = 7.2 Hz due to the vicinal methyl group) with a chemical shift of 4.43 ppm. This observation allows to assign to C_5-H in compound **14** a chemical shift of 4.14 ppm (singlet). The non-equivalence of the C_{10}-H_a and C_{10}-H_b protons suggest that the conformation is somewhat locked for **15** and is moving for **10, 13** and **14.**

Further investigations concerning these tricyclic systems are in progress.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Beckman IR 20 spectrometer. The nmr spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) using tetramethylsilane as the internal standard. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60 F (70-300 mesh) was used for column chromatography. The elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 M^T.S^T. Aignan.

Methyl 2-(pyrrol-1-ylmethyl)furan-3-carboxylate (**1a**).

To a well stirred suspension of the potassium salt of pyrrole [prepared from pyrrole (4.5 g, 0.065 mole) and potassium metal (2.5 g, 0.064 g-atom)] in anhydrous tetrahydrofuran or benzene (80 ml), kept under nitrogen, a solution of methyl 2-bromomethylfuran-3-carboxylate (11.0 g, 0.05 mole) in the same solvent (100 ml) was added slowly dropwise and stirred at room temperature for 6 hours. The mixture was heated under reflux for 4 hours. After cooling to room temperature cyclohexane (150 ml) was added to the reaction mixture and was allowed to stand at room temperature 2 hours. The mixture was filtered. Evaporation of the solvents afforded 9 g of crude ester **1a** as an oily material. The oily was purified by distillation (bp 108-112°/0.09 mm) to give 5 g (49%) of the ester **1a** which solidified on standing in a cool place. An analytical sample of mp 37-38° was obtained as colorless prisms by crystallization from methanol/water (1:1); ir: 1715 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.87 (s, 3H, CH_3), 5.37 (s, 2H, CH_2), 6.15 (t, 2H, J = 2.1 Hz, H.3′ + H.4′), 6.67 (d, 1H, J = 1.9 Hz, H.4), 6.79 (t, 2H, H.2′ + H.5′), 7.31 (d, 1H, H.5); ^{13}C nmr (deuteriochloroform): 44.1 (CH_2-N), 51.3 (CH_3-O, 108.3 (C.3′ + C.4′), 110.5 (C.4), 114.9 (C.3), 120.8 (C.2′ + C.5′), 142.0 (C.5), 155.9 (C.2), 163.3 (COOR).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.57; H, 5.75; N, 6.84.

2-(Pyrrol-1-ylmethyl)furan-3-carboxylic Acid (**2a**).

A mixture of 4.4 g (0.02 mole) of methyl 2-(pyrrol-1-ylmethyl)-furan-3-carboxylate (**1a**), 1.3 g (0.03 mole) of potasssium hydroxide pellets in a mixture of methanol/water (25 ml, 1:1) was refluxed for 4 hours. After cooling, the reaction mixture was extracted twice with 25 ml of diethyl ether. The aqueous solution was treated with charcoal, filtered and acidified with hydrochloric acid (1:1, *p*H = 2.5-3). The precipitate was collected, washed with water and air dried. The 2-(pyrrol-1-ylmethyl)furan-3-carboxylic acid (**2a**) (3.2 g, 78%) after crystallization from water melted at 151-152° (colorless prisms), ir: 1680 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.5 (s, 1H, OH), 5.38 (s, 2H, CH_2), 6.00 (t, 2H, J = 2.1 Hz, H.3′ + H.4′), 6.70 (d, 1H, J = 1.9 Hz, H.4), 6.78 (t, 2H, H.2′ + H.5′), 7.64 (d, 1H, H.5); ^{13}C nmr (DMSO-d_6): 43.8 (CH_2-N), 108.3 (C.4), 111.1 (C.3′ + C.4′), 115.9 (C.3), 120.9 (C.2′ + C.5′), 143.0 (C.5), 155.9 (C.2), 164.3 (COOH).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82. H, 4.74; N, 7.33. Found: C, 62.45; H, 4.73; N, 7.06.

2-Pyrrol-1-ylmethyl)furan-3-carbohydrazide (**4a**).

A mixture of 4.4 g (0.021 mole) of methyl 2-(pyrrol-1-ylmethyl)-furan-3-carboxylate (**1a**) and 1.5 g (0.03 mole) of hydrazine hydrate in a mixture of 20 ml of methanol and 10 ml of water was stirred and refluxed for 2 hours. After cooling to room temperature, the precipitate was collected, washed with water and air dried. The 2-(pyrrol-1-ylmethyl)furan-3-carbohydrazide (**4a**) (3.2 g, 72%) after crystallization from methanol/water (2:1) melted at 108-110° (colorless plates), ir: 1650 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.62 (s, 2H, NH_2), 5.41 (s, 2H, CH_2), 5.96 (t, 2H, J = 2.1 Hz, H.3′ + H.4′), 6.77 (t, 2H, H.2′ + H.5′), 6.70 (d, 1H, J = 1.9 Hz, H.4), 7.61 (d, 1H, H.5), 9.59 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.16; H, 5.57; N, 20.37.

2-(Pyrrol-1-ylmethyl)furan-3-carboazide (**3a**).

Method A.

To a well stirred suspension of 2-(pyrrol-1-ylmethyl)furan-3-carbohydrazide (**4a**) (2.05 g, 0.01 mole) in carbon tetrachloride (100 ml) and sodium nitrite (1.0 g, 0.015 mole) in water (20 ml) was added slowly dropwise at 20-25° and the mixture was stirred under nitrogen 0.5 hour. The organic solution was separated and washed 3 times with water (100 ml). After drying (magnesium sulfate) was removed carbon tetrachloride and the solid residue was crystallized from anhydrous diethyl ether to give 1.26 g (63%) of the carboazide **3a** mp 34-36°; ir: 2150 (CON_3) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 5.39 (s, 2H, CH_2), 6.16 (t, 2H, J = 2.1 Hz, H.3′ + H.4′), 6.64 (d, 1H, J = 2.0 Hz, H.4), 6.79 (t, 2H, H.2′ + H.5′), 7.32 (d, 1H, H.5); ^{13}C nmr (deuteriochloroform): 44.3 (CH_2-N), 108.7 (C.3′ + C.4′), 110.4 (C.4), 116.3 (C.3), 121.0 (C.2′ + C.5′), 142.5 (C.5), 157.2 (C.2).

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.88; H, 3.77; N, 26.25.

Method B.

A solution of 1.9 g (0.01 mole) of 2-(pyrrol-1-ylmethyl)furan-3-carboxylic acid (**2a**), 75 ml of anhydrous acetone and 2.9 g (0.027 mole) of triethylamine was cooled in an ice-salt bath. To the well stirred and cooled solution, in a nitrogen atmosphere, a solution of 4 g (0.035 mole) of ethyl chloroformate in 7.5 ml of acetone was added over a period of 30 minutes. When the addition was stopped, the reaction mixture was allowed to stir at 0° for 15 minutes and a solution of 3 g (0.045 mole) of sodium azide in 10 ml of water was added dropwise over 20 minuts. The light orange solution obtained was allowed to stir at 0-5° for 30 minutes. The reaction mixture was poured onto crushed ice and extracted several times with diethyl ether. The combined organic layers were washed with water and dried over anhydrous magnesium sulfate. The isolation of **3a** was carried out as described above in the method A and gave 1.6 g (73%) of crude azide.

2-(Pyrrol-1-ylmethyl)furan-3-isocyanate (**5a**).

A mixture of 1.1 g (0.005 mole) of 2-(pyrrol-1-ylmethyl)furan-3-carboazide (**3a**) and 20 g of anhydrous sodium sulfate was heated and vacuum distillation gave 0.7 g (80%) of the isocyanate **5a** (bp 125-127°/0.5 mm); ir: 2267 (N=C=O) cm^{-1}; ^{1}H nmr (deu-

teriochloroform): δ 4.97 (s, 2H, CH_2), 6.19 (t, 2H, J = 2.2 Hz, H.3' + H.4'), 6.30 (d, 1H, J = 2.2 Hz, H.4), 6.73 (t, 2H, H.2' + H.5'), 7.26 (d, 1H, H.5); ^{13}C nmr (deuteriochloroform): 42.1 (CH_2), 108.3 (C.3' + C.4'), 108.9 (C.4), 116.4 (C.3), 120.0 (C.2' + C.5'), 125.4 (NCO), 141.6 (C.5), 142.4 (C.2). The instability of this compound did not allow to obtain a good elemental analyse.

Ethyl 3-[2-(pyrrol-1-ylmethyl)furyl]carbamate **6a**.

Method A.

A solution of 0.6 g (0.0028 mole) of 2-(pyrrol-1-ylmethyl)furan-3-carboazide (**3a**) and 50 ml of anhydrous ethanol was refluxed for 12 hours. After cooling and evaporation of the solvent *in vacuo*, the solid was crystallized from diethyl ether. An analytical sample of mp 86-87° was obtained as colorless needles by recrystallization from ethanol to give 0.7 g (66%) of the carbamate **6a**; ir: 3241 (NH), 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.18 (t, 3H, CH_3), 4.1 (q, 2H, J = 7.1 Hz, CH_2), 4.93 (s, 2H, CH_2-N), 6.08 (d, 1H, J = 2.0 Hz, H.4), 6.09 (t, 2H, J = 2.0 Hz, H.3' + H.4'), 6.50 (s, 1H, NH), 6.61 (t, 2H, H.2' + H.5'), 7.14 (d, 1H, H.5); ^{13}C nmr (deuteriochloroform): 23.1 (CH_3), 44.0 (CH_2-N), 61.4 (CH_2-O), 108.3 (C.4), 108.7 (C.3' + C.4'), 120.9 (C.3), 121.8 (C.2' + C.5'), 139.1 (C.2), 141.2 (C.5), 154.3 (NH COOR).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.60; H, 5.96; N, 11.85.

Method B.

A solution of 0.2 g (0.001 mole) of 2-(pyrrol-1-ylmethyl)furan-3-isocyanate (**5a**) and 15 ml of chloroform and 5 ml of anhydrous ethanol was refluxed for 15 minutes. After cooling and evaporation of the solvent *in vacuo*, the solid was crystallized from the mixture of ethanol and water to give 0.24 g (92%) of the carbamate **6a**.

3-[2-(Pyrrol-1-ylmethyl)furyl]urea (**9**).

Method A.

A solution of 1.0 g (0.005 mole) of 2-(pyrrol-1-ylmethyl)furan-3-carboazide (**3a**), 15 ml of chloroform and 5 ml of water was stirred over a period of 30 minutes at room temperature. After evaporation of the solvent *in vacuo*, the solid was crystallized from methanol to give 0.75 g (86%) of compound **9**, mp 211-212°; ir: 3250 (NH), 1627 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.10 (s, 2H, CH_2), 5.99 (t, 2H, J = 2.1 Hz, H.3' + H.4'), 6.73 (t, 2H, H.2' + H.5'), 6.75 (d, 1H, J = 2.0 Hz, H.4), 7.51 (d, 1H, H.5), 8.35 (s, 2H, NH); ^{13}C nmr (DMSO-d_6): 42.8 (CH_2), 107.9 (C.3' + C.4'), 108.4 (C.4), 120.3 (C.3), 123.0 (C.2' + C.5'), 138.1 (C.5), 141.6 (C.2), 152.9 (C=O).

Anal. Calcd. for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.23; H, 5.38; N, 16.14.

Method B.

A solution of 0.2 g (0.01 mole) of 2-(pyrrol-1-ylmethyl)furan-3-isocyanate (**5a**), 50 ml of tetrahydrofuran and 0.1 g Copper(II) chloride was stirred under reflux for 2 hours. After cooling to room temperature was added slowly 20 ml of water. The precipitate was collected, washed with water, air dried and recrystallized from methanol to give 0.1 g (57%) of urea **9**.

5,10-Dihydro-4*H*-furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (**7**) and 2-(Pyrrol-1-ylmethyl)furan-3-acetamide (**8**).

A solution of 2.2 g (0.01 mole) of 2-(pyrrol-1-ylmethyl)furan-3-carboazide (**3a**) in 15 ml of acetic acid was added dropwise to 30 ml of boiling acetic acid under a nitrogen atmosphere. After 30 minutes of reflux, the acetic acid was distillated and the residual oil **7** + **8** was chromatographed on silica gel with hexane-chloroform (1:1).

The acetamide **8** was first eluted (1.22 g, 59%), mp 132-133° (methanol); ir: 3220 (NH), 1650 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.40 (s, 3H, CH_3), 5.14 (s, 2H, CH_2), 5.97 (t, 2H, J = 2.0 Hz, H.3' and H.4'), 5.73 (t, 2H, H.2' and H.5'), 6.75 (d, 1H, J = 1.9 Hz, H.4), 7.49 (d, 1H, H.5), 9.70 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 23.1 (CH_3), 42.8 (CH_2), 107.8 (C.3' + C.4'), 108.3 (C.4), 120.4 (C.3), 122.4 (C.2' + C.5'), 138.7 (C.5), 141.6 (C.2), 168.0 (CO).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.18; H, 5.30; N, 11.98.

The diazepine **7** was then eluted (0.32 g, 17%), mp 219-220°; ir: 1635 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.31 (s, 2H, H_{10}), 6.12 (dd, 1H, J = 3.5 Hz, J = 2.5 Hz, H_7), 6.32 (d, 1H, J = 1.8 Hz, H_3), 6.84 (dd, 1H, J = 1.8 Hz, H_6), 7.06 (dd, 1H, H_8), 7.50 (d, 1H, H_2); ^{13}C nmr (DMSO-d_6): δ 44.8 (C_{10}), 107.1 (C_7), 109.0 (C_{3a}), 119.7 (C_6), 122.9 (C_3), 127 (C_8), 127.6 (C_{5a}), 136.8 (C_2), 142.0 (C_{10a}), 160.3 (C_5).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 63.85; H, 4.19; N, 14.72.

Methyl 2-[(2-Formyl)pyrrol-1-ylmethyl]furan-3-carboxylate (**1b**).

In a similar manner as described for the synthesis of **1a**, 2.0 g (0.021 mole) of pyrrole-2-carbaldehyde, 0.8 g (0.02 g atom) of potassium metal and 4.4 g (0.02 mole) of methyl-2-bromomethylfuran-3-carboxylate afforded 2.5 g (62%) of crude **1b** as an oily material. This oil was purified by crystallization from cyclohexane to give 2.1 g (45%) of methyl 2-[(2-formyl)pyrrol-1-ylmethyl)-furan-3-carboxylate (**1b**), mp 62-63°; ir: 1650 (CHO) 1715 ($COOCH_3$) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.84 (s, 3H, CH_3), 5.93 (s, 2H, CH_2), 6.20 (dd, 1H, J = 4.0 Hz, J = 2.6 Hz, H.4'), 6.64 (d, 1H, J = 2.0, H.4), 6.91 (dd, 1H, J = 1.7, H.3'), 7.01 (dd, 1H, H.5'), 7.26 (d, 1H, H.5), 9.57 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): 43.1 (CH_2), 51.6 (OCH_3), 110.2 (C.4), 110.6 (C.4'), 115.4 (C.3), 124.3 (C.3'), 131.1 (C.5'), 131.5 (C.2'), 142.3 (C.5), 155.4 (C.2), 163.5 (COOR), 179.5 (CHO).

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 62.03; H, 4.72; N, 6.06.

2-[(2-Formyl)pyrrol-1-ylmethyl]furan-3-carboxylic Acid (**2b**).

In a similar manner as described for compound **2a**, 2.0 g (0.0086 mole) of methyl 2-[1-(2-formyl)pyrrol-1-ylmethyl]furan-3-carboxylate (**1b**) afforded 1.0 g (52%) of the acid **2b**, mp 150-151°; ir: 1650 (CHO), 1685 (COOH) cm^{-1}; ^1H nmr (DMSO-d_6): δ, 5.88 (s, 2H, CH_2), 6.27 (dd, 1H, J = 4.0, J = 2.5 Hz, H.4'), 6.69 (d, 1H, J = 1.9 Hz, H.4), 7.03 (dd, 1H, J = 1.8 Hz, H.3'), 7.26 (dd, 1H, H.5'), 7.60 (d, 1H, H.5), 9.55 (d, 1H, J = 0.6 Hz, CHO); ^{13}C nmr (DMSO-d_6): 43.4 (CH_2), 110.2 (C.4), 111.0 (C.4'), 115.5 (C.3), 123.7 (C.3'), 131.5 (C.2'), 131.9 (C.5'), 143.0 (C.5), 155.1 (C.2), 164.1 (COOH), 180.0 (CHO).

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.28; H, 4.14; N, 6.39. Found: C, 60.59; H, 3.82; N, 6.46.

2-[(2-Aminoiminomethyl)pyrrol-1-ylmethyl]furan-3-carbohydrazide (**4b**).

A mixture of 2.0 g (0.0086 mole) of methyl 2-[(2-formyl)pyrrol-1-ylmethyl]furan-3-carboxylate (**1b**) and 1.5 g (0.03 mole) of hydrazine hydrate in 20 ml of methanol was stirred and refluxed for 2 hours. After evaporation of the methanol and hydrazine hydrate, the solid was recrystallized in water (yellow prisms) to yield 1.8 g (85%) of compound **4b**; ir: 1625, 1660 (CH=N, C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ, 5.74 (s, 2H, CH_2), 5.94 (s, 4H, NH_2) 6.16 (dd,

1H, J = 3.8 Hz, J = 2.3 Hz, H.4'), 6.67 (dd, 1H, J = 1.7 Hz, H.3'), 6.87 (d, 1H, J = 1.9 Hz, H.4), 7.06 (dd, 1H, H.5'), 7.58 (d, 1H, H.5), 8.53 (s, 1H, NCH), 9.57 (s, 1H, CNH).

Anal. Calcd. for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.32. Found: C, 53.22; H, 5.18; N, 28.01.

2-[(2-Formyl)pyrrol-1-ylmethyl]furan-3-carboazide (**3b**).

In a similar manner as described for the synthesis of **3a**, the carboazide **3b** was prepared from **2b** or **4b**.

Method A.

2-[(2-Formyl)pyrrol-1-ylmethyl]furan-3-carboxylic acid (**2b**) (5 g, 0.023 mole) led to 0.35 g (72%) of carboazide **3b**, mp 67-68°; ir: 1650 (CHO), 1682 (CO), 2140 (CON_3) cm^{-1}; ^1H nmr (deuteriochloroform): δ, 5.92 (s, 2H, CH_2), 6.20 (dd, 1H, J = 4.0 Hz, J = 2.6 Hz, H.4'), 6.59 (d, 1H, J = 1.9 Hz, H.4), 6.90 (dd, 1H, J = 1.6 Hz, H.3'), 6.98 (dd, 1H, H.5'), 7.23 (d, 1H, H.5), 9.53 (d, 1H, J = 1 Hz, CHO); ^{13}C nmr (deuteriochloroform): 43.4 (CH_2), 110.3 (C.4), 110.4 (C.4'), 116.5 (C.3), 124.4 (C.3'), 131.2 (C.5'), 131.4 (C.2'), 142.6 (C.5), 156.6 (C.2), 168.0 (CON_3), 179.4 (CHO).

Anal. Calcd. for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.30; N, 22.94. Found: C, 54.24; H, 3.29; N, 23.03.

Method B.

2-[1-(2-Aminoiminomethyl)pyrrol-1-ylmethyl]furan-3-carbohydrazide (**4b**), (2.4 g, 0.01 mole) led to 1.2 g (50%) of carboazide **3b**.

2-[(2-Formyl)pyrrol-1-ylmethyl]furan-3-isocyanate (**5b**).

A mixture of 5.0 g (0.02 mole) of 2-[(2-formyl)pyrrol-1-ylmethyl]-furan-3-carboazide (**3b**) and 100 g of anhydrous sodium sulfate was heated and vacuum distillation gave 3.6 g (84%) of 2-[(2-formyl)pyrrol-1-ylmethyl]furan-3-isocyanate (bp 134-138°/0.1 mm); ir: 2265 (NCO) cm^{-1}, ^1H nmr (deuteriochloroform): δ, 5.47 (s, 2H, CH_2), 6.18 (dd, 1H, J = 4.9 Hz, J = 2.6 Hz, H.4'), 6.20 (d, 1H, J = 2.0 Hz, H.4), 6.86 (dd, 1H, J = 1.6 Hz, H.3'), 6.89 (m, 1H, H.5'), 7.17 (d, 1H, H.5), 9.50 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): 41.5 (CH_2), 109.1 (C.4'), 110.0 (C.4), 117.1 (C.3), 123.3 (NCO), 124.3 (C.3'), 130.6 (C.5'), 131.0 (C.2'), 141.8 (C.5), 142.0 (C.2), 179.3 (CH=O). This compound was not stable enough to get a good elemental analysis.

Methyl 3-{2-[(2-Formyl)pyrrol-1-ylmethyl]fury}carbamate (**6b**).

Method A.

A mixture of 2.5 g (0.01 mole) of 2-[(2-formyl)pyrrol-1-ylmethyl]-furan-3-carboazide (**3b**) and 100 ml of anhydrous methanol was refluxed for 12 hours. After cooling and evaporation of the solvent *in vacuo*, the solid was crystallized from diethyl ether/methanol to give 1.8 g (73%) of carbamate **6b**. An analytic sample of mp 89-90° was obtained as colorless needles by recrystallization from methanol; ir: 3341 (NH), 1725 (CHO), 1658 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.69 (s, 3H, CH_3), 5.34 (s, 2H, CH_2), 6.16 (dd, 1H, J = 4.0 Hz, J = 2.4 Hz, H.4'), 6.79 (d, 1H, J = 2.0 Hz, H.4), 6.86 (dd, 1H, J = 1.6 Hz, H.3'), 7.12 (m, 2H, H.5, H.5'), 8.40 (s, 1H, NH), 9.34 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): 42.5 (CH_2), 52.2 (CH_3O), 107.1 (C.4'), 110.4 (C.4), 123.5 (C.3), 126.3 (C.3'), 130.2 (C.2'), 132.7 (C.5'), 136.0 (C.2), 141.5 (C.5), 154.5 (NHCOOR), 180.3 (CHO).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.86; N, 11.28. Found: C, 58.33; H, 4.97; N, 11.32.

Method B.

A solution of 0.25 g (0.001 mole) of 2-[(2-formyl)pyrrol-1-ylmethyl]furan-3-isocyanate (**5b**), 15 ml of chloroform and 5 ml of anhydrous methanol was refluxed for 15 minutes. After cooling and evaporation of the solvent *in vacuo*, the solid was crystallized from methanol to give 0.2 g (80%) of carbamate **6b**.

3-{2-[(2-Formyl)pyrrol-1-ylmethyl]furyl}urea (**12**).

Method A.

A solution of 0.25 g (0.001 mole) of 2-[(2-formyl)pyrrol-1-ylmethyl]furan-3-isocyanate (**5b**), 15 ml of chloroform and 5 ml of water was refluxed for 15 minutes. After cooling and evaporation of the solvent *in vacuo*, the solid was crystallized from methanol to give 0.17 g (84%) of urea **12**, mp 122-123°; ir: 3258 (NH), 1630 (CHO) cm^{-1}; ^1H nmr (DMSO-d_6): 5.56 (s, 2H, CH_2), 6.24 (dd, 1H, J = 4.1 Hz, J = 2.5 Hz, H.4'), 6.70 (d, 1H, J = 1.9 Hz, H.4), 7.03 (dd, 1H, J = 1.7 Hz, H.3'), 7.22 (dd, 1H, H.5'), 7.47 (d, 1H, H.5), 8.49 (s, 1H, NH), 9.54 (s, 1H, CHO); ^{13}C nmr (DMSO-d_6): 42.2 (CH_2), 108.7 (C.4'), 109.9 (C.4), 123.3 (C.3), 124.1 (C.3'), 131.1 (C.2'), 131.6 (C.5'), 137.4 (C.2), 141.6 (C.5), 153.1 (CO), 179.6 (CHO).

Anal. Calcd. for $C_{21}H_{18}N_4O_5$: C, 62.07; H, 4.46; N, 13.76. Found: C, 61.80; H, 4.88; N, 13.61.

10*H*-Furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine (**10**) and 2-[(2-Formyl)-pyrrol-1-ylmethyl]furan-3-acetamide (**11**).

In a similar manner as described for the synthesis of compounds **7** and **8**, the carboazide **3b** (2.5 g, 0.01 mole) afforded a mixture of diazepine **10** and acetamide **11** separated by chromatography.

The acetamide **11** eluted first (0.25 g, 11%), mp 129-130°; ir: 3220 (NH), 1725 (CHO), 1630 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.06 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 6.26 (dd, 1H, J = 3.0 Hz, J = 2.5 Hz, H.4'), 6.67 (dd, 1H, J = 1.8 Hz, H.3'), 6.94 (dd, 1H, H.5'), 6.96 (d, 1H, J = 2.0 Hz, H.4), 7.19 (d, 1H, H.5), 9.41 (s, 1H, CHO).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.01; H, 5.18; N, 12.27.

The diazepine **10** was then eluted (1.39 g, 81%), mp 83-84°; ir: 1640 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.21 (s, 2H, H_{10}), 6.27 (dd, 1H, J = 3.8 Hz, J = 2.8 Hz, H_7), 6.51 (d, 1H, J = 1.8 Hz, H_3) 6.60 (dd, 1H, J = 1.7 Hz, H_6), 6.77 (dd, 1H, H_8), 7.21 (d, 1H, H_2), 7.93 (s, 1H, H_5); ^{13}C nmr (deuteriochloroform): 47.1 (CH_2), 111.0 (C_{3a}), 112.6 (C_7), 120.6 (C_3), 126.7 (C_6), 130.8 (C_{5a}), 133.7 (C_8), 136.5 (C_2), 141.0 (C_{10a}), 147.5 (C_5).

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.93; H, 4.78; N, 16.11.

10*H*-Furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine (**10**).

A solution of 10 g of potassium hydroxide in 10 ml of water was cooled to −20°. To the well stirred and cooled solution in a nitrogen atmosphere, a solution of 2.5 g (0.01 mole) of 2-[(formyl)-pyrrol-1-ylmethyl]furan-3-isocyanate (**5b**) in 5 ml of tetrahydrofuran was added over a period of 30 minutes. When the addition was stopped the reaction mixture was neutralized with concentrated hydrochloric acid and extracted several times with ether. The combined organic layers were washed with water and dried over anhydrous magnesium sulfate and the solid residue was crystallized from a mixture of hexane and ether to give 1.2 g (69%) of the diazepine **10**.

4-Methyl-10*H*-furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepinium Iodide (**13**).

A solution of 1.72 g (0.01 mole) of 10*H*-furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine (**10**) and 10 ml of methyl iodide in 200 ml of ether was stirred at room temperature for 24 hours. The precipitate was collected, washed with anhydrous ether and air dried. The diazepinium iodide **13** (2.7 g, 87%) melted at 175-176°; ir: 1665 (C=N+H) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.85 (s, 3H, CH_3), 5.73 (s, 2H, H_{10}), 6.75 (dd, 1H, J = 4.3 Hz), J = 2.3 Hz, H_7), 7.10 (d, 1H, J = 2.1 Hz, H_3), 7.51 (dd, 1H, J = 1.4 Hz, H_6), 7.91-7.94 (m, 2H, H_2 and H_8), 8.87 (s, 1H, H_5); ^{13}C nmr (DMSO-d_6): 46.3 (CH_2), 46.6 (CH_3), 106.6 (C_7), 116.0 (C_{3a}), 124.3 (C_3), 126.9 (C_6), 133.8 (C_{5a}), 139.0 (C_8), 139.5 (C_2), 143.4 (C_{10a}), 148.9 (C_5).

Anal. Calcd. for $C_{11}H_{11}N_2OI$: C, 42.06; H, 3.53; N, 8.92. Found: C, 42.16; H, 3.36; N, 8.74.

4,5-Dihydro-4-methylfuro[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine (**14**).

To a well stirred solution of 3.14 g (0.01 mole) of 4-methyl-10*H*-furo[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine (**13**) in 100 ml of water was added slowly (0.02 mole) of sodium borohydride. When the addition stopped the mixture was stirred at room temperature for 2 hours. Then the reaction mixture was extracted several times with ether. The organic layers were combined and washed with water and dried (magnesium sulfate). Evaporation of the solvent gave an oily residue. The residual oil was dissolved in hexane, treated with charcoal, filtered, concentrated and left to crystallize. The solid was collected, washed with hexane to yield 1.2 g (64%) of pure diazepine **14** mp 64-65°; ^1H nmr (deuteriochloroform): δ 2.73 (s, 3H, CH_3), 4.14 (s, 2H, H_5), 5.18 (s, 2H, H_{10}), 6.01 (dd, 1H, J = 3.3 Hz, J = 2.8 Hz, H_7), 6.18 (dd, 1H, J = 1.6 Hz, H_6), 6.21 (d, 1H, J = 1.9 Hz, H_3), 6.67 (dd, 1H, H_8), 7.18 (d, 1H, H_2); ^{13}C nmr (deuteriochloroform): 41.8 (CH_3), 45.1 (CH_2), 50.1 (CH_2-NCH_3), 106.1 (C_7), 107.1 (C_6), 109.1 (C_{3a}), 121.5 (C_8), 128.4 (C_{5a}), 133.2 (C_3), 135.4 (C_2), 139.7 (C_{10a}).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.12; H, 6.29; N, 14.91.

4,5-Dimethyl-5,10-dihydrofuro[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine (**15**).

To a well stirred suspension of 4-methyl-10*H*-pyrrolo[1,2-*a*]-furo[3,2-*e*][1,4]diazepinium iodide (**13**) (3.14 g, 0.01 mole) in 100 ml of anhydrous ether, kept under nitrogen, a solution of methyl magnesium iodide (0.03 mole, 4.3 g methyl iodide, 0.73 g magnesium metal) in the same solvent (50 ml) was added slowly dropwise at room temperature. The mixture was stirred for 4 hours. After cooling (0°) 2 ml of water was added slowly to the reaction mixture and was allowed to stand at room temperature for 15 minutes. The mixture was filtered. The organic layers were dried over anhydrous magnesium sulfate and solvent was removed *in vacuo*. The oily residue was purified by crystallization from petroleum ether to give 1.2 g (59%) of 4,5-dimethyl-5,10-dihydropyrrolo[1,2-*a*]furo[3,2-*e*][1,4]diazepine (**15**), mp 32-37°; ^1H nmr (deuteriochloroform): δ 1.54 (d, 3H, J = 7.2 Hz, C-CH_3), 2.46 (s, 3H, NCH_3), 4.43 (dd, 1H, H_5), 5.01 (d, 1H, J = 16.1 Hz, H^a_{10}), 5.25 (d, 1H, H^b_{10}), 6.05 (dd, 1H, J = 3.5 Hz, J = 2.7 Hz, H_7), 6.10 (dd, 1H, J = 1.7 Hz, H_6), 6.16 (d, 1H, J = 1.8 Hz, H_3), 6.59 (dd, 1H, H_8), 7.14 (d, 1H, H_2); ^{13}C nmr (deuteriochloroform): 16.7 (CH_3), 36.9 (C_5), 45.7 (C_{10}), 52.9 (NCH_3), 105.8 (C_7), 107.6 (C_{3a}), 108.4 (C_6), 121.4 (C_8), 132.1 (C_{5a}), 133.9 (C_3), 135.8 (C_2), 139.9 (C_{10a}).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.89. Found: C, 71.30; H, 7.07; N, 13.83.

REFERENCES AND NOTES

[1] F. Povazanec, B. Decroix and J. Morel, *J. Heterocyclic Chem.*, **29**, 1507 (1992).

[2] A. Daïch, F. Povazanec and B. Decroix, *J. Heterocyclic Chem.*, **28**, 1911 (1991).

[3] M. V. Sargen and T. M. Cresp, Comprehensive Organic Chemistry, Vol **4**, D. Barton and W. D. Ollis, eds, Pergamon Press, New York, 1979, p 693.

[4] E. Bisagni and C. Rivalle, *Bull. Soc. Chim. France*, 519 (1974).

[5] J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

[6] O. Schindler, R. Blaser and F. Hunziker, *Helv. Chim. Acta*, **49**, 905 (1966).

[7] J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, **43**, 203 (1948).

[8] R. G. Arnold, J. A. Nelson, J. J. Verbanc, *Chem. Rev.*, **57**, 47 (1957).

[9] S. Rault, Y. Effi, M. Cugnon de Sevricourt, *J. Heterocyclic Chem.*, **20**, 17 (1983).

[10] B. Decroix and J. Morel, *J. Heterocyclic Chem.*, **28**, 81 (1991).