Reaction of 1,2-Diamines with 4-Hydroxycoumarin. Synthesis of 1,4-Diazepin-5-ones

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1,4-diazepin-5-ones were obtained from 4-hydroxycoumarin and substituted 1,2-diamines by heating in 2-methyl-1-propanol.

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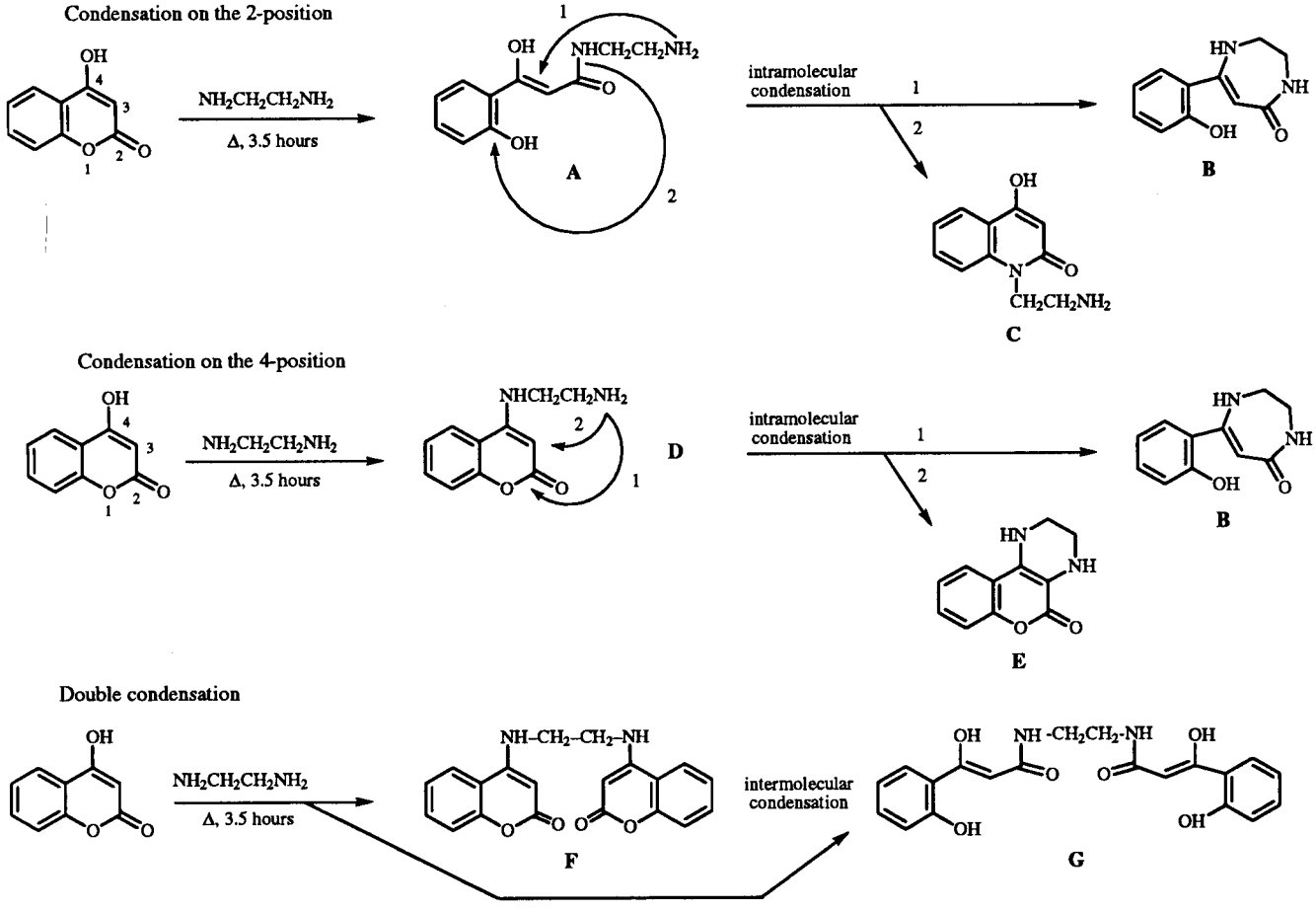
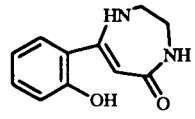
A number of investigations have been carried out on the condensation of 4-hydroxycoumarin with amines. For example, 4-aminocoumarins have been synthesized by condensation of primary and secondary amines [1], while the reaction with hydrazines has been found to give rise to pyrazoles after opening of the coumarin ring [2]. In our laboratory, we have shown that condensation of ureas, carbamates and α-aminoacids using ethyl orthoformate leads to the corresponding ureidomethylenecoumarins [3], *N*-coumarinyl carbamates [4] and *N*-coumarinyl amino acids [5]. We have also investigated the reaction with diamines. Thus the condensation of 1,2-phenylenediamines gives rise to the 1,5-benzodiazepin-2-ones [6]. In other experiments, we examined the action of aliphatic and cyclic 1,2-diamines in an attempt to obtain diazepines of potential therapeutic [7-9] and agricultural interest [10-12].



We initially refluxed 1,2-diaminoethane with 4-hydroxycoumarin in 2-methyl-1-propanol for 3.5 hours. A large amount of product, whose structure was subsequently determined, was isolated on filtration of the reaction mixture. Various possibilities of attack by the diamine may occur, which are summarized in the following reaction scheme:

The ^1H nmr spectrum at 400 MHz exhibited signals attributed to an ethylenic proton at 4.25 ppm, protons on two CH_2 groups at 3.24 and 3.36 ppm, aromatic protons between 6.76 and 7.18 ppm, three exchangeable protons at 9.45, 7.00 and 6.78 ppm. These observations ruled out the following structures: E which has no ethylenic proton, C where the chemical shift of the ethylenic proton should be similar to that in 4-hydroxyquinolin-2-one (around 6 ppm), F and G as the signals of the aromatic protons correspond to two CH_2 groups, and **A, C, D, E, F**, which have a different number of exchangeable protons to that actually observed. Only the form **B** was compatible with these observations and the product, obtained in 75% yield, was assigned as 7-(2'-hydroxyphenyl)-1,4-diazepin-5-one.



B

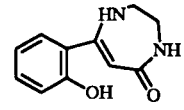
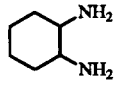
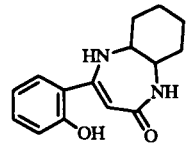
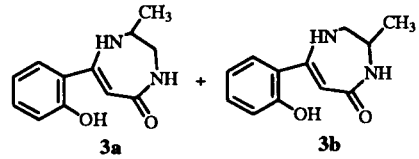
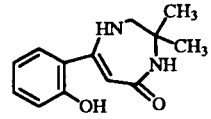
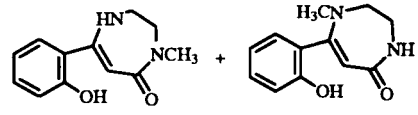
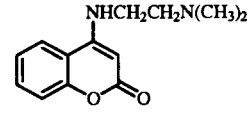
The exchangeable protons were observed by irradiation of protons at 7.00 and 9.45 ppm.

This condensation reaction was tested in other solvents and gave rise to the expected product in yields of: 85% (dioxane), 85% (toluene), 45% (propane-2-ol) but only 2-methyl-1-propanol gave rise to a product in a high degree of purity. We also found that no further reaction took place on heating for more than 3.5 hours.

We investigated the reaction with other diamines in an attempt to generalize this method of synthesis: a cyclic diamine (*trans*-1,2-diaminocyclohexane $C_6H_{11}(NH_2)_2$), diamines with substituents on the hydrocarbon chain (1,2-diaminopropane $H_2NCH_2CH(CH_3)NH_2$, 1,2-diamino-2-methylpropane $H_2NCH_2C(CH_3)_2NH_2$, diamines substituted on the nitrogen atom (*N*-methyl-1,2-diaminoethane $H_2NCH_2CH_2NHCH_3$, *N,N'*-dimethyl-1,2-diaminopropane $H_2NCH_2CH_2N(CH_3)_2$ in order to examine the influence of the position and environment of the second amino group and determine the initial stage of the reaction mechanism. The results are listed in Table 1:

It can be seen from the results that a methyl group on the hydrocarbon chain or the nitrogen atom led to the formation of two isomeric products resulting from competitive nucleophilic attack on the two amino groups. For *N*-methyl-1,2-diaminoethane the two products were separated by

Table 1
1,4-Diazepin-5-ones Prepared

Diamines	Diazepinones	Yield %
$H_2NCH_2CH_2NH_2$	 **1**	75 [a]
	 **2**	30 [b]
$H_2NCH_2CH(CH_3)NH_2$	 **3a** **3b**	50
$H_2NCH_2C(CH_3)_2NH_2$	 **4**	45
$H_2NCH_2CH_2NHCH_3$	 **5a** **5b**	45
$H_2NCH_2CH_2N(CH_3)_2$	 **6**	85

[a] 2-Propanol 45%; dioxane 85%; toluene 85%. [b] Xylene 85%.

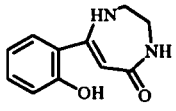
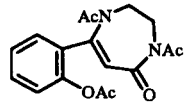
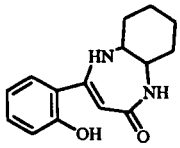
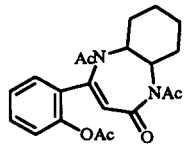
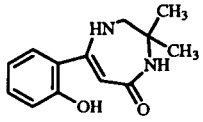
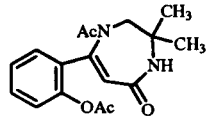
exploiting their difference in solubility in acetonitrile, the two methyl substituents at the α position to the nitrogen eliminated competition between the two amino groups for initial nucleophilic attack, giving rise to a single product, the two substituents on the nitrogen atom gave rise to the corresponding 4-aminocoumarin indicating that the initial attack on the most reactive amino group occured at position 4. This result is in agreement with our previous observations on the 1,2-phenylenediamines [6].

The mechanism is thus an initial nucleophilic attack at position 4 to the most reactive amino group, followed by an another nucleophilic attack on the second amino group with opening of the coumarin ring. This condensation reaction is of interest as it gives the diazepines in good yield. Its main limitation is the possibility of simultaneous nucleophilic attack on the two amino groups.

The diazepines obtained as a single species could be acetylated by heating the derivative with acetic anhydride

in the presence of pyridine on a water-bath [13]. The results obtained are listed in Table 2.

Table 2
Acetylated 1,4-Diazepin-5-ones Prepared

Diazepinones	Acetylated diazepinones	Yield %
 1	 7	95
 2	 8	75
 4	 9	85

We observed that the acetylation took place on all possible sites (OH or NH), except when the site was hindered sterically. This was the case in the derivatives with two methyl groups in the α position to the NH linkage. The acetylated derivatives were obtained in excellent yields. Their structures were confirmed by ^{1}H nmr and elemental analysis.

EXPERIMENTAL

Melting points were determinated in an Electrothermal apparatus. The ^{1}H nmr spectra were recorded on a Bruker AC 80, ARX 400 MHz (solvent dimethyl-d_6 sulfate), and mass spectra on a Nermag R 1010 instrument (70 ev, electron impact). Elemental analysis was carried out at the Interuniversity microanalysis center in Toulouse. All starting materials were purchased from Acros and Aldrich Chemical Company.

7-(2'-Hydroxyphenyl)-1,4-diazepin-5-ones.

General Procedure.

A solution of 4-hydroxycoumarin (1.62 g, 0.01 mole) and diamine (0.01 mole) in the solvent (35 ml) was refluxed while stirring for 3.5 hours. The precipitate, obtained from the hot solution or after partly or complete evaporation of the solvent, was collected and then crystallized.

7-(2'-Hydroxyphenyl)-1,4-diazepin-5-one (**1**).

This compound was crystallized from ethanol (yield 45% in 2-propanol, 85% in dioxane, 85% in toluene, 75% in 2-methyl-1-propanol), mp 253-254°; ^{1}H nmr: δ 3.24 (t, 2H, CH_2), 3.36 (t, 2H, CH_2), 4.25 (dd, 1H, CH, J = 1.8 Hz), 6.76-7.18 (m, 6H, Ar, NH), 9.45 (s, 1H, OH); ms: (m/z,%): 204 (M^+, 49), 175 (30), 174 (48), 162 (81), 147 (27), 146 (56), 135 (26), 133 (14), 120 (36), 119 (29), 118 (37), 107 (24), 105 (13), 104 (24), 102 (13), 92 (16), 91 (100), 90 (47), 89 (50), 86 (37), 85 (19), 78 (16), 77 (33), 65 (32), 64 (16), 63 (23), 51 (16), 44 (32), 43 (30), 42 (32), 41 (12), 39 (22), 32 (48), 31 (62), 30 (45).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.88; N, 13.72. Found: C, 64.59; H, 5.91; N, 13.75.

4-(2'-Hydroxyphenyl)-1,5-cyclohexanodiazepin-2-one (**2**).

This compound was crystallized from acetone (yield 30% in 2-methyl-1-propanol, 85% in xylene), mp 237-238°; ^{1}H nmr: δ 1.2 (m, 4H, CH_2), 1.65 (m, 2H, CH_2), 2.04 (m, 2H, CH_2), 3.00 (m, 1H, CH), 3.10 (m, 1H, CH), 4.24 (s, 1H, CH), 6.09 (s, 1H, NH), 6.53 (s, 1H, NH), 6.77-7.19 (m, 4H, Ar), 9.57 (s, 1H, OH); ms: (m/z,%) 258 (M^+, 39), 257 (5), 188 (9), 162 (15), 136 (11), 135 (100), 120 (18), 97 (38), 96 (11), 91 (31), 89 (11), 82 (10), 69 (15), 65 (13), 56 (15), 43 (17), 41 (18), 39 (12), 32 (12), 31 (11), 30 (10).

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.77; H, 6.98; N, 10.85. Found: C, 69.73; H, 6.78; N, 10.60.

2-Methyl-7-(2'-hydroxyphenyl)-1,4-diazepin-5-one + 3-Methyl-7-(2'-hydroxyphenyl)-1,4-diazepin-5-one **3a** +**3b**.

These compounds were crystallized from ethanol (yield 50%), mp 240-241°; ^{1}H nmr: δ 1.11 (dd, 3H, CH_3), 3.15 (m,3H, CH_2, CH), 4.22 (d, 1H, CH, J = 2.1 Hz), 4.31 (d,1H, CH, J = 2.1 Hz), 6.77-7.19 (m, 6H, Ar, NH), 9.45 (s, 1H, OH); ms: (m/z, %) 218 (M^+, 71), 189 (26), 188 (22), 175 (21), 174 (11), 162 (29), 161 (17), 160 (20), 147 (24), 141 (27), 119 (21), 118 (22), 91 (60), 90 (21), 89 (24), 77 (12), 57 (21), 44 (18), 41 (11).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.05; H, 6.42; N, 12.84. Found: C, 65.78; H, 6.33; N, 12.72.

3-Dimethyl-7-(2'-hydroxyphenyl)-1,4-diazepin-5-one (**4**).

This compound was crystallized from ethanol (yield 45%), mp 270-271°; ^{1}H nmr: δ 1.15 (s, 6H, CH_3), 2.98 (d, 2H, CH_2, J = 5.4 Hz), 4.19 (dd, 1H, CH, J = 2.2 Hz), 6.41-7.16 (m, 6H, Ar, NH), 9.45 (s, 1H, OH); ms: (m/z, %) 232 (M^+, 90), 203 (17), 202 (24), 176 (13), 175 (30), 174 (44), 162 (8), 161 (13), 160 (100), 158 (17), 146 (10), 135 (35), 120 (39), 119 (17), 118 (15), 102 (12), 92 (11), 91 (67), 90 (22), 89 (31), 77 (16), 71 (25), 70 (11), 65 (22), 64 (10), 63 (15), 58 (57), 57 (10), 56 (18), 55 (14), 42 (13), 39 (9).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H,6.89; N, 12.06. Found: C, 67.36; H, 7.04; N, 12.03.

4-Methyl-7-(2'-hydroxyphenyl)-1,4-diazepin-5-one (**5a**).

This compound was crystallized from ethanol (yield 15%) and was separated from **5b** by its different solubility in acetonitrile (**5a** soluble, **5b** insoluble, proportion **5b**/**5a** = 2), mp 305-306°; ^{1}H nmr: δ 2.63 (s, 3H, CH_3), 3.27 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 4.20 (d, 1H, CH, J = 2.1 Hz), 6.79-7.16 (m, 5H, Ar, NH), 9.53 (s, 1H, OH); ms: (m/z, %) 218 (M^+, 50), 217 (39), 189 (13), 188 (61), 176 (40), 172 (16), 162 (4), 160 (25), 148 (35), 146 (14), 134 (53), 133 (12), 132 (25), 131 (15), 120 (13), 119 (26), 118 (89), 117 (12), 107 (14), 105 (18), 104 (19), 103 (14), 102 (10), 91 (63), 90 (98), 89 (100), 82 (19), 78 (11), 77 (33), 65 (20), 64 (15), 63 (39), 62 (11), 56 (16), 55 (11), 51 (15), 44 (39), 43 (14), 42 (43), 41 (11), 39 (26), 30 (13).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.05; H, 6.42; N, 12.84. Found: C, 65.76; H, 6.22; N, 12.55.

1-Methyl-7-(2'-hydroxyphenyl)-1,4-diazepin-5-one (**5b**).

This compound was crystallized from ethanol (yield 30%) and was separated from **5a** by its different solubility in acetonitrile (**5a** soluble, **5b** insoluble, proportion **5b**/**5a**) = 2), mp 300-301°; ^{1}H nmr:

δ 2.87 (s, 3H, CH_3), 3.35 (t, 2H, CH_2), 3.47 (t, 2H, CH_2), 4.36 (d, 1H, CH, J = 0.6 Hz), 6.72-7.19 (m, 5H, Ar, NH), 9.45 (s, 1H, OH); ms: (m/z, %) 218 (M^+, 50), 175 (62), 174 (43), 162 (20), 147 (35), 146 (62), 135 (11), 120 (16), 119 (21), 118 (24), 107 (10), 104 (17), 92 (12), 91 (64), 90 (32), 89 (46), 78 (21), 77 (30), 75 (11), 71 (17), 69 (16), 65 (39), 64 (21), 63 (39), 58 (16), 57 (64), 56 (38), 55 (32), 52 (13), 51 (25), 44 (100), 43 (45), 42 (56), 41 (67), 40 (31), 39 (41), 38 (12), 30 (12).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.05; H, 6.42; N, 12.84. Found: C, 65.78; H, 6.26; N, 12.70.

N-Coumarinyl-*N'*-dimethyl-1,2-diaminoethane (**6**).

This compound is an highly viscous oil (yield 85%); ^1H nmr: δ 2.15 (s, 6H, CH_3), 2.42 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 4.80 (s, 1H, CH), 7.12-7.82 (m, 5H, Ar, NH); ms: (m/z, %) 232 (M^+, 1), 162 (1), 120 (2), 92 (2), 89 (2), 88 (3), 86 (14), 84 (14), 72 (1), 71 (3), 63 (2), 59 (4), 58 (100), 57 (2), 56 (2), 51 (7), 49 (22), 48 (2), 47 (5), 44 (3), 43 (3), 42 (8), 41 (2), 35 (2), 30 (4).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.89; N, 12.06. Found: C, 67.08; H, 6.66; N, 11.99.

Acetylated 7-(2'-Hydroxyphenyl)-1,4-diazepin-5-ones.

General Procedure.

A solution of diazepine **1**, **2** or **4** (0.002 mole) was heated on a water-bath for 5 hours and stirred at room temperature for 2 hours then poured into an ice/water mixture (100 ml). The acetylated diazepinone was obtained by extraction with dichloromethane and after evaporation of the solvent (compound **9**) or by concentration of the reaction mixture, the precipitate thus formed was collected by filtration and washed several times with water (compounds **7** and **8**).

N,N'-Diacetyl-7-(2'-acetoxyphenyl)-1,4-diazepin-5-one (**7**).

This compound was crystallized from ethanol (yield 95%), mp 178-179°; ^1H nmr: δ 1.64 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.9 (m, 4H, CH_2), 6.19 (s, 1H, CH), 7.2-7.6 (m, 4H, Ar); ms: (m/z, %) 330 (M^+, 9), 288 (21), 187 (8), 175 (11), 174 (18), 162 (7), 91 (6), 89 (7), 59 (8), 58 (13), 43 (100), 42 (7).

Anal. Calcd. for $C_{17}H_{18}N_2O_5$; C, 61.81; H, 5.45; N, 8.48. Found: C, 61.79; H, 5.46; N, 8.46.

N,N'-Diacetyl-4-(2'-acetoxyphenyl)-1,5-cyclohexanodiazepin-2-one (**8**).

This compound was crystallized from ethanol (yield 85%), mp 183-184°; ^1H nmr: δ 1.2-2.0 (m, 8H, CH_2), 1.61 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.7 (m, 1H, CH), 4.8 (m, 1H, CH), 6.43 (s, 1H, CH), 7.3-7.5 (m, 4H, Ar); ms: (m/z, %) 384 (M^+, 11), 342 (8), 324 (8), 299 (8), 284 (8), 283 (16), 257 (10), 241 (12), 240 (9), 204 (15), 162 (20), 159 (15), 139 (20), 135 (9), 97 (23), 96 (12), 91 (8), 79 (9), 69 (9), 43 (100), 41 (8).

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.63; H, 6.25; N, 7.29. Found: C, 65.40; H, 6.37; N, 7.40.

N'-Acetyl-3-dimethyl-7-(2'-acetoxyphenyl)-1,4-diazepin-5-one (**9**).

This compound was crystallized from ethanol (yield 75%), mp 66-68°; ^1H nmr: δ 1.17 (s, 6H, CH_3), 2.25 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.89 (s, 2H, CH_2), 4.26 (d, 1H, CH, J = 1.6 Hz), 7.55 (s, 1H, CH), 7.2-7.5 (m, 5H, Ar, NH); ms: (m/z, %) 316 (M^+, 32), 299 (9), 274 (9), 273 (10), 231 (26), 203 (25), 202 (26), 175 (10), 174 (14), 162 (25), 160 (13), 91 (10), 89 (9), 71 (13), 58 (25), 56 (11), 55 (10), 43 (100), 42 (13), 39 (7).

Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.56; H, 6.33; N, 8.86. Found: C, 64.27; H, 6.22; N, 8.58.

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