Synthesis of 1,4-Dialkyl-1,4-dihydro-1,4-benzo[*e*]diazepine-5-ones

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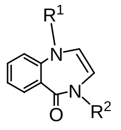
Abstract: The title heterocycles were synthesized by the reaction of *N*-alkylisatoic anhydrides with *N*-alkylaminoacetaldehyde dialkylacetals, followed by hydrolysis with Amberlyst-15 and dehydration.

Key words: bicyclic compounds, benzodiazepines, condensation, heterocycles, hydrolyses, Amberlyst-15

Since the introduction of 1,4-benzodiazepines as tranquilizer drugs in early 1960s,[3] synthesis of molecules bearing a 1,4-benzodiazepine pharmacophore unit has become increasingly important in the pharmaceutical industry. Synthesis of different analogs of 1,4-benzodiazepines has been well documented.[4,5] During the course of our research, we became interested in the preparation of 1,4-benzodiazepine **1**, in which 1- and 4-nitrogens are connected by an unsubstituted 2,3-carbon-carbon double bond. Only one analog of **1** has been reported in the literature: it was claimed that the reaction of *N*-benzylamino benzamide with 2-bromoacetaldehyde diethyl acetal under basic condition (sodium amide, toluene)[6a] afforded **1** (R^1 = benzyl, R^2 = H). However, no mass spectral data were recorded in the report.[6] To the best of our knowledge, 1,4-dialkyl version of **1** has not been reported. Here we wish to report a novel, simple synthetic route to 1,4-dialkyl version of **1**, namely 1,4-dialkyl-1,4-dihydro-1,4-benzo[*e*]diazepine-5-ones **1a−f**.



R^2 = CH_3, R^1 = CH_3 (**1a**), allyl (**1b**), benzyl (**1c**);
R^2 = benzyl, R^1 = CH_3 (**1d**), allyl (**1e**), benzyl (**1f**))

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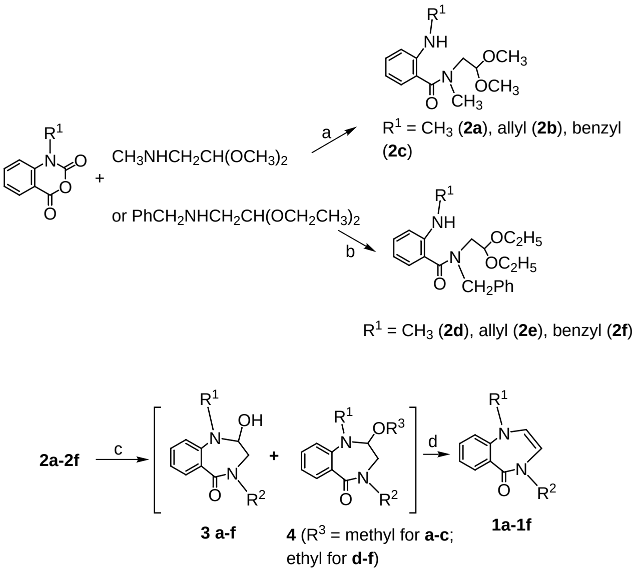
Refluxing equimolar amounts of *N*-methylaminoacetaldehyde dimethylacetal and *N*-alkyl (methyl, allyl and benzyl) isatoic anhydride in acetonitrile afforded the amide products 2-alkylamino-*N*-methyl-*N*-(2,2-dimethoxyethyl)benzamides **2a−c** as a single product in quantitative yields (Scheme).[7] The reaction of the more hindered N-benzylaminoacetaldehyde diethylacetal with *N*-alkyl isatoic anhydride required refluxing in DMF. The corresponding benzamides **2d−f** were isolated after chromatographic purification.

Hydrolysis of the acetal groups of benzamides **2a−f** in aqueous tetrahydrofuran in the presence of Amberlyst-15 as a catalyst at room temperature afforded polar crude hydrolyzed products as an inseparable mixture of hemiaminal **3** and methyl or ethyl aminal **4**. The structures of intermediates **3a** and **4a** were confirmed by mass spectral analysis of the crude mixture [for **3a** (M + 1) = 207 while **4a** (M + 1) = 221]. This mixture was then refluxed in toluene with a Dean−Stark trap to generate the benzodiazepines **1a−f** (Scheme). The products **1a,b,d,e** were isolated as oils while **1c** and **1f** as solids. The two enamide vinyl protons of **1a−f** consistently showed two doublets in the range of 5.28−5.36 and 5.55−5.62 ppm, with a coupling constant of 5.6 Hz.



Reagents and conditions: a) MeCN, reflux, 2 h, 99−100%; b) DMF, reflux, 1 h, 34−64%; c) Amberlyst-15, THF/H_2O, r.t., 2−12 h; d) toluene, reflux, Dean-Stark trap, 48−83% over 2 steps.

Scheme

In conclusion, a novel and simple procedure for the preparations of 1,4-dialkyl-1,4-dihydro-1,4-benzo[e]diazepine-5-ones **1a−f** has been completed.

Reagents and solvents were used as received from commercial suppliers. TLC was performed on pre-coated Silica Gel 60 F_{254} plates form Merck using reagent-grade solvents. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). ^1H NMR were performed at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal TMS. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer. Mass spectra were recorded on a HP 5989B spec-

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trometer. HRMS were performed by Mass Spectrometry Facility of University of California, Berkeley. Elemental analyses were conducted by Galbraith Laboratories, Inc.

2-Alkylamino-*N*-methyl-*N*-(2,2-dimethoxyethyl)benzamides 2a-c; General Procedure

N-Alkylisatoic anhydride (10 mmol) and *N*-methylaminoacetaldehyde dimethyl acetal (1.192 g, 10 mmol) were mixed in MeCN (10 mL) and the resulting mixture was heated at reflux for 2 h. Cooling and evaporation gave the oily residue as pure products **2a−c**, as confirmed by TLC and ^{1}H NMR analysis, in quantitative yield. The NMR data for **2a−f** were broad due to rotamer interconversion.[8] The elemental analysis samples were obtained by simple flash chromatographic purification on silica gel (hexane/EtOAc, 2:1).

2a

Yield: 99%; TLC (silica gel, hexane /Et_2O, 1:1); R_f 0.18.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.70 (s, 3 H), 2.94 (s, 3 H), 3.26 (br s, 6 H) 3.58 (br s, 2 H), 4.60 (br s, 1 H), 4.97 (br s, 1 H), 6.64−6.68 (m, 2 H), 7.10 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.26 (td, *J* = 7.8, 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.15, 54.40, 102.77, 110.63, 115.61, 119.95, 127.54, 130.70, 147.22, 171.60.

IR (film): ν = 3394, 2935, 2832, 1626, 1581, 1515, 1489, 1461, 1426, 1396, 1316, 1293, 1171, 1127, 1103, 1078, 980, 751 cm^{-1}.

MS (EI): *m*/*z* (%) = 253 (M + 1, 9), 252 (M, 48), 134 (100).

Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 62.06; H, 8.00; N, 10.96.

2b

Yield: 100%; TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.32.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.07 (s, 3 H), 3.38 (br s, 6 H), 3.59 (br s, 2 H), 3.78 (d, *J* = 5.2 Hz, 2 H), 4.61 (br s, 1 H), 5.10 (br s, 1 H), 5.15 (dq, *J* = 10.3, 1.5 Hz, 1 H), 5.28 (dq, *J* = 17.1, 1.6 Hz, 1 H), 5.86−5.99 (m, 1 H), 6.66 (d, *J* = 7.9 Hz, 1 H), 6.67 (t, *J* = 7.8 Hz, 1 H), 7.10 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.22 (td, *J* = 7.8, 1.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.90, 54.46, 102.78, 111.48, 115.94, 116.03, 120.21, 127.65, 130.55, 134.96, 145.91, 171.53.

IR (film): ν = 3382, 3078, 2935, 2834, 1626, 1582, 1514, 1488, 1455, 1397, 1318, 1292, 1204, 1165, 1127, 1074, 980, 920, 751 cm^{-1}.

MS (EI): *m*/*z* (%) = 279 (M + 1, 16), 278 (M, 72), 160 (100).

Anal. Calcd for: $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.59; H, 7.96; N, 9.92.

2c

Yield: 99%; TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.22.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.06 (s, 3 H), 3.31 (s, 6 H), 3.59 (br s, 2 H), 4.32 (d, *J* = 3.5 Hz, 2 H), 4.57 (br s, 1 H), 5.40 (br s, 1 H), 6.61 (d, *J* = 8.3 Hz, 1 H), 6.65 (t, *J* = 7.5 Hz, 1 H), 7.10−7.35 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.31 (br), 47.58, 49.88 (br), 54.40, 102.70, 111.59, 116.10, 120.32, 127.01, 127.16, 127.66, 128.50, 130.62, 139.10, 145.89, 171.49.

IR (film): ν = 3382, 3062, 3028, 2935, 2834, 1780, 1729, 1633, 1585, 1514, 1494, 1454, 1395, 1322, 1295, 1202, 1165, 1125, 1073, 1028, 981, 943, 920, 817, 750, 699 cm^{-1}.

MS (EI): *m*/*z* (%) = 329 (M + 1, 6), 328 (M, 26), 75 (100).

Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.85; H, 7.33; N, 8.37.

2-Alkylamino-*N*-benzyl-*N*-(2,2-diethoxyethyl)benzamides 2d-f; General Procedure

A mixture of *N*-alkylisatoic anhydride (10 mmol) and *N*-benzylaminoacetaldehyde diethylacetal (2.32 g, 10 mmol) in DMF (5 mL) was heated at the reflux temperature for 1 h. After cooling and evaporation of DMF under vacuum, the residue was flash chromatographed on silica gel, eluting with 3:1 to 1:1 hexane/Et_2O to afford **2d−e**.

2d

Yield: 64%; TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.33.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 6.4 Hz, 6 H), 2.84 (d, *J* = 4.8 Hz, 3 H), 3.46 (br s, 4 H), 3.67 (br s, 2 H), 4.72 (br s, 3 H), 4.94 (br s, 1 H), 6.64 (t, *J* = 7.5 Hz, 1 H), 6.66 (d, *J* = 8.5 Hz, 1 H), 7.13−7.34 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 15.23, 30.17, 63.05, 101.02, 110.62, 115.81, 120.18, 127.28, 127.32, 127.59, 128.53, 130.69, 137.06, 147.04, 171.89.

IR (film): ν = 3388, 2974, 2929, 1626, 1604, 1581, 1514, 1455, 1412, 1316, 1240, 1170, 1121, 1061, 976, 749, 699 cm^{-1}.

MS (EI): *m*/*z* (%) = 357 (M + 1, 6), 356 (M, 23), 103 (100).

Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.53; H, 7.95; N, 7.82.

2e

Yield: 56%; TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.33.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.20 (t, *J* = 6.0 Hz, 6 H), 3.48 (br s, 4 H), 3.68 (br s, 2 H), 3.79 (br s, 2 H), 4.73 (br s, 3 H), 5.13 (br s, 1 H), 5.16 (dd, *J* = 10.3, 1.4 Hz, 1 H), 5.28 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.86−5.95 (m, 1 H), 6.64 (t, *J* = 7.4 Hz, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 7.14−7.33 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 15.26, 45.87, 63.14, 101.11, 111.52 116.02, 116.15, 120.44, 127.36, 127.61, 128.54, 130.55, 134.95, 137.05, 145.73, 171.83 (one aromatic carbon is missing due to overlapping).

IR (film): ν = 3377, 3064, 3029, 2975, 2929, 2880, 1627, 1597, 1582, 1513, 1454, 1413, 1374, 1318, 1292, 1262, 1231, 1123, 1062, 993, 921, 750, 700 cm^{-1}.

MS (EI): *m*/*z* (%) = 383 (M + 1, 5), 382 (M, 17), 103 (100).

2f

Yield: 34%; mp 77−78°C (Et_2O/hexane); TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.44.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.18 (t, *J* = 6.7 Hz, 6 H), 3.48 (br s, 4 H), 3.65 (br s, 2 H), 4.37 (d, *J* = 5.0 Hz, 2 H), 4.75 (br s, 3 H), 5.45 (br s, 1 H), 6.63 (d, *J* = 8.9 Hz, 1 H), 6.65 (t, *J* = 8.3 Hz, 1 H), 7.14−7.41 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 15.26, 47.58, 63.18, 101.17, 111.64 116.30, 120.44, 127.02, 127.15, 127.38, 127.58, 128.51, 128.55, 130.62, 137.02, 139.08, 145.80, 171.85, (one aromatic carbon signal is missing due to overlapping).

IR (film): ν = 3381, 3028, 2974, 2928, 2880, 1627, 1596, 1582, 1513, 1496, 1452, 1413, 1374, 1322, 1295, 1231, 1126, 1064, 977, 750, 698 cm^{-1}.

MS (EI): *m*/*z* (%) = 433 (M + 1, 4), 432 (M, 14), 103 (100).

1,4-Dialkyl-1,4-benzodiazepine-5-ones 1a−f; General Procedure

To a stirred solution of **2** (1−2 mmol) in THF (3 mL) and H_2O (0.5 mL) was added Amberlyst-15 (0.5 g, Aldrich) at r.t. After the starting material was consumed (TLC analysis, for **2a−d**, 2 h; for **2e** and **2f**, 12 h), CH_2Cl_2 (15 mL) was added. After drying (Na_2SO_4), filtration and evaporation gave the residue.[In the hydrolysis of **2a**, mass spectral data were collected for these intermediates **3a** and **4a**: API-

TIS *m/z* (%): for **3a**: 207 (M + 1, 100); for **4a**: 221 (M + 1, 27)]. This residue was dissolved in toluene (15 mL) and refluxed with a Dean−Stark trap for 2−6 h (monitored by TLC). Cooling and evaporation gave the residue which was purified by flash chromatography (silica gel, hexane/Et_2O, 2:1) to afford **1a−f**.

1a

Yield: 79%; TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.25.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.92 (s, 3 H), 3.15 (s, 3 H), 5.32 (d, *J* = 5.6 Hz, 1 H), 5.57 (d, *J* = 5.6 Hz, 1 H), 6.77 (d, *J* = 8.2 Hz, 1 H), 6.97 (t, *J* = 7.5 Hz, 1 H), 7.31 (t, *J* = 7.7 Hz, 1 H), 7.76 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.16, 38.23, 114.39, 117.52, 121.78, 127.06, 130.23, 131.99, 132.67, 154.89, 169.25.

IR (film): ν = 2960, 1690, 1632, 1596, 1476, 1454, 1391, 1282, 1262, 1216, 1194, 1168, 1046, 1011, 739 cm^{-1}.

MS (EI): *m/z* (%) = 189 (M + 1, 25), 188 (M, 74), 147 (100).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.37; H, 6.49; N, 14.75.

1b

Yield: 67%; TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.48.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.15 (s, 3 H), 3.87 (d, *J* = 5.7 Hz, 2 H), 5.24 (dd, *J* = 10.3, 1.4 Hz, 1 H), 5.30 (dd, *J* = 17.3, 1.5 Hz, 1 H), 5.36 (d, *J* = 5.6 Hz, 1 H), 5.62 (d, *J* = 5.6 Hz, 1 H), 5.83−5.96 (m, 1 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.99 (td, *J* = 7.5, 0.8 Hz, 1 H), 7.30 (td, *J* = 7.5, 1.7 Hz, 1 H), 7.75 (dd, *J* = 7.8, 1.7Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.14, 53.22, 115.69, 118.18, 118.22, 121.95, 127.57, 128.80, 131.82, 132.53, 133.78, 154.18, 169.29.

IR (film): ν = 3072, 2980, 2930, 2843, 2688, 2632 (s), 1596, 1487, 1460, 1392, 1283, 1260, 1213, 1168, 1046, 992, 973, 925, 891, 827, 742 cm^{-1}.

MS (EI): *m/z* (%) = 215 (M + 1, 15), 214 (M, 84), 132 (100).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.95; H, 6.66; N, 12.95.

1c

Yield: 83%; mp 122−123°C (Et_2O/hexane); TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.48.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.16 (s, 3 H), 4.45 (s, 2 H), 5.34 (d, *J* = 5.6 Hz, 1 H), 5.56 (d, *J* = 5.6 Hz, 1 H), 6.82 (d, *J* = 8.2 Hz, 1 H), 6.99 (t, *J* = 7.3 Hz, 1 H), 7.25−7.35 (m, 6 H), 7.78 (dd, *J* = 7.7, 1.7 Hz, 1 H).

^{13}C NMR(75 MHz, $CDCl_3$): δ = 36.11, 54.48, 115.88, 118.87, 122.19, 127.34, 127.80, 127.88, 128.52, 129.36, 131.92, 132.52, 137.05, 154.32, 169.33.

MS (EI): *m/z* (%) = 265 (M + 1, 18), 264 (M, 37), 132 (100).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.30; H, 6.14; N, 10.48.

1d

Yield: 75%; TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.30.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.88 (s, 3 H), 4.79 (s, 2 H), 5.28 (d, *J* = 5.7 Hz, 1 H), 5.56 (d, *J* = 5.7 Hz, 1 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.95 (t, *J* = 7.5 Hz, 1 H), 7.23−7.33 (m, 6 H), 7.81 (dd, *J* = 7.7, 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.23, 51.45, 114.48, 116.06, 121.78, 126.92, 127.27, 127.57, 128.51, 131.27, 132.13, 132.86, 136.81, 154.95, 169.23.

IR (film): ν = 3062, 3030, 2962, 2879, 1689, 1633 (s), 1595, 1471, 1453, 1440, 1412, 1391, 1332, 1282, 1262, 1199, 1162, 1012, 887, 828, 736 cm^{-1}.

MS (EI): *m/z* (%) = 265 (M + 1, 20), 264 (M, 100).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.59; H, 6.22; N, 10.52.

1e

Yield: 72%; TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.40.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.83 (d, *J* = 5.7 Hz, 2 H), 4.80 (s, 2 H), 5.16 (dd, *J* = 10.3, 1.4 Hz, 1 H), 5.21 (dd, *J* = 17.3, 1.4 Hz, 1 H), 5.35 (d, *J* = 5.6 Hz, 1 H), 5.62 (d, *J* = 5.6 Hz, 1 H), 5.74−5.87 (m, 1 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.98 (t, *J* = 7.3 Hz, 1 H), 7.22−7.39 (m, 6 H), 7.80 (dd, *J* = 7.8, 1.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.37, 53.15, 115.78, 117.29, 118.16, 122.08, 127.24, 127.52, 127.58, 128.44, 130.88, 131.97, 132.68, 133.79, 136.88, 154.41, 169.23.

IR (film): ν = 3064, 3031, 2982, 2924, 2827, 1682, 1633 (s), 1595, 1487, 1454, 1416, 1394, 1360, 1318, 1283, 1260, 1177, 1106, 990, 925, 746, 699 cm^{-1}.

MS (EI): *m/z* (%) = 291 (M + 1, 16), 290 (M, 71), 91 (100).

Anal. Calcd for $C_{18}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 77.57; H, 6.22; N, 9.40.

1f

Yield: 48%; mp 100−101°C (Et_2O/hexane); TLC (silica gel, hexane/Et_2O, 1:1); R_f 0.51.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.41 (s, 2 H), 4.80 (s, 2 H), 5.36 (d, *J* = 5.6 Hz, 1 H), 5.55 (d, *J* = 5.6 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 7.03−7.33 (m, 11 H), 7.84 (dd, *J* = 7.8, 1.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.61, 54.51, 115.76 117.93, 122.31, 127.26, 127.75, 127.81, 128.03, 128.44, 128.46, 130.72, 132.07, 132.63, 136.96, 137.03, 154.53, 169.19 (one aromatic carbon signal is missing due to overlapping).

IR (film): ν = 3059, 3030, 1632 (s), 1594, 1495, 1453, 1413, 1296, 1220, 1165, 729, 694 cm^{-1}. MS (EI): *m/z* (%) = 342 (M + 2, 2), 341 (M + 1, 12), 340 (M, 45), 91 (100).

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.52; H, 6.00; N, 8.11.

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characterize the 1,4-benzodiazepin-5-ones bearing free NH group, since those molecules tend to form dimers according to our experience.

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