2,3,6,7,8,9-Hexahydro-8,8-dimethyl-5-phenyl-1*H*-1,4-benzodiazepin-6-one

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Several approaches for the synthesis of the title compound **1** were investigated. Treatment of the ethane-1,2-diamine derivative **2** with phosphoryl chloride afforded 3-chloro-5,5-dimethylcyclohex-2-enone (**3**) and 1-(5,5-dimethyl-3-oxocyclohex-1-enyl)-4,5-dihydro-2-phenylimidazole (**4**). The reaction of 2-benzoyldimedone (**5**) with an equimolar amount of ethane-1,2-diamine led to the 2:1 adduct **6**, whereas with an excess of ethane-1,2-diamine, 4,5-dihydro-2-phenylimidazole (**7**) and dimedone were obtained. The synthesis of the title compound **1** was achieved by reacting 2-benzoyl-3-chloro-5,5-dimethylcyclohex-2-enone (**8**) with ethane-1,2-diamine.

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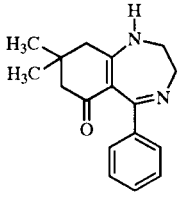
In connection with our research program with the goal to develop new central-nervous-system-active compounds, we were interested in a series of 5-aryl-2,3,6,7,8,9-hexahydro-8,8-dimethyl-1*H*-1,4-diazepin-6-ones. In order to investigate different approaches for the synthesis of this class of substances, the 5-phenyl derivative **1** was chosen as target compound.

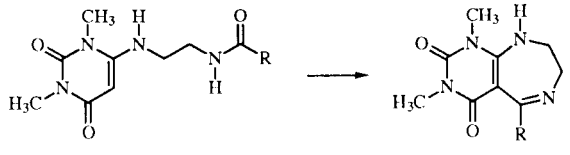


1

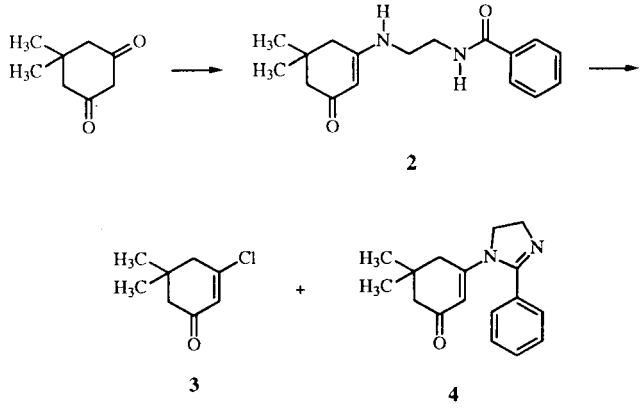
In a previous paper [1], we described the synthesis of pyrimido-[4,5-*e*][1,4]diazepines by a Bischler-Napieralski type reaction by treatment of 6-[2-(acylamino)ethylamino]pyrimidine-2,4-diones with phosphoryl chloride. (Scheme 1). However, this procedure was not amenable to the analogous reaction of *N*-[2-[(5,5-dimethyl-3-oxocyclohex-1-enyl)amino]ethyl]benzamide (**2**), obtained from 5,5-dimethylcyclohexane-1,3-dione (dimedone) and *N*-(2-aminoethyl)benzamide. Treatment of **2** with phosphoryl chloride did not yield **1**, but 3-chloro-5,5-dimethylcyclohex-2-enone (**3**) and a small amount of 1-(5,5-dimethyl-3-oxocyclohex-1-enyl)-4,5-dihydro-2-phenylimidazole (**4**) (Scheme 2).

It was shown by elemental analysis and mass spectroscopy that **4** is an isomer of the title compound **1**. It can easily be distinguished from **1** by its ^{1}H nmr spectrum, which, apart from the expected signals, displays a singlet at 5.32 ppm attributable to the 2-CH group of the cyclohexenone moiety, thus providing evidence that ring closure has occured forming an imidazoline instead of a dihydrodiazepine ring.

Scheme 1



Scheme 2

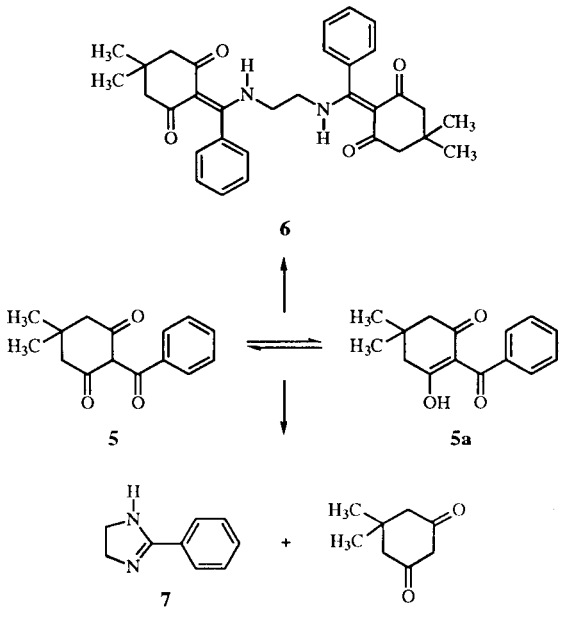


2 **3** **4**

Subsequently, the reaction of 2-benzoyldimedone (**5**) with ethane-1,2-diamine, as a feasible route to **1**, was taken into consideration. 2-Benzoyldimedone (**5**), which according to Lakhvich and coworkers [2] preferentially has the tautomeric structure **5a**, was obtained by a method described by the same authors [3]. Dimedone was treated with benzoyl chloride to yield the corresponding enol ester, which was isomerized to **5** with aluminum chloride.

When a solution of equimolar amounts of **5** and ethane-1,2-diamine in toluene was heated under reflux, a 2:1 adduct was obtained which was identified as **6** (Scheme 3). The molecular formula of **6** was shown to be $C_{32}H_{36}N_2O_4$ both by elemental analysis and mass spectroscopy, in which upon chemical ionization a $[M + H]^+$ molecular ion of 513 was observed. The proposed structure was fully established by ir, ^{1}H nmr and ^{13}C nmr spectra. The ^{1}H nmr

Scheme 3



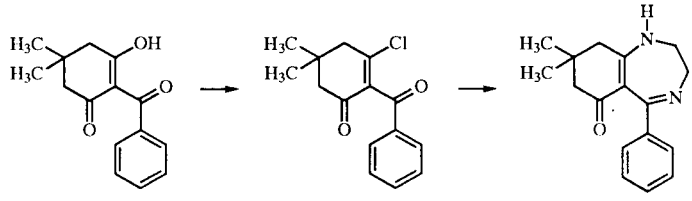
spectrum showed 3 singlets at 1.07, 2.23 and 2.49 ppm attributable to the methyl and methylene groups of the cyclohexane rings, a doublet at 3.16 ppm and a broad singlet at 7.8 ppm attributable to the ethanediamine bridge. The ^{13}C nmr spectrum of **6** consisted of the expected 13 signals, one for primary C-atoms at 28.3 ppm, three for secondary C-atoms at 43.8 (NCH_2CH_2N), 52.3 and 52.9 ppm (2 CH_2 of the cyclohexane rings), three for tertiary C-atoms at 125.8, 128.7 and 128.8 ppm (aromatic CH) and six for quaternary C-atoms at 30.2 (C-5), 108.0 (C-2), 134.0 (arom), 172.4 (benzylic C), 194.7 and 200.1 (C=O).

When benzoyldimedone (**5**) was treated with a large excess of ethane-1,2-diamine, dimedone and the known [4] 4,5-dihydro-2-phenylimidazole (**7**) were formed. Apparently, ethane-1,2-diamine, which acts as reagent and solvent as well, causes cleavage of **5** to dimedone and benzoic acid, which spontaneously condenses with ethane-1,2-diamine to yield **7**.

The basis for the successful synthesis of the target compound **1** was the finding of De Wald and coworkers [5], who synthesized antidepressive pyrazolodiazepines in a three step reaction. *C*-Alkylation of 1,3-dialkylpyrazolones with aroyl chlorides and subsequent chlorination with phosphoryl chloride or phenylphosphonic dichloride led to the corresponding 4-aroyl-5-chloropyrazoles which upon treatment with 1,2-diamines yielded pyrazolodiazepines.

According to a modified procedure by Tamura *et al.* [6] benzoyldimedone (**5**) was chlorinated with freshly distilled oxalyl chloride to form 2-benzoyl-3-chloro-5,5-dimethylcyclohex-2-enone (**8**). When **8** was dissolved in an excess of ethane-1,2-diamine at room temperature, a smooth reaction occured leading to **1**, but in relatively poor yield (Scheme 4).

Scheme 4



After purification by lc, **1** was crystallized as the purple hydrochloride. The structural assignment is based on elemental analysis and spectral data. In the ^1H nmr spectrum, the signals of the 4 methylene groups appear at 2.23 (s, C-7), 2.78 (s, C-9), 3.70 and 3.90 ppm (2 m, C-2/3), respectively. The ^{13}C nmr spectrum shows the corresponding signals at 51.1, 45.8, 46.4 and 48.8 ppm.

EXPERIMENTAL

Melting points are uncorrected and obtained on a Reichert-Kofler hot stage microscope. The ir spectra were observed with a Shimadzu IR-470 spectrometer; only selected absorptions are reported. The nmr spectra were obtained with a Bruker AM 300 reported as δ values in ppm using TMS as the internal standard or solvent signals (deuteriochloroform or DMSO-d_6) as indirect internal standards. Microanalyses were performed by the Institut für Physikalische Chemie, Universität Wien.

N-[2-[(5,5-Dimethyl-3-oxocyclohex-1-enyl)amino]ethyl]benzamide (**2**).

A solution of dimedone (1.40 g, 0.01 mole) and *N*-(2-aminoethyl)benzamide (2.13 g, 0.013 mole) in dry benzene (50 ml) was refluxed for 3 hours using a Dean Stark separator to remove the water formed during the reaction. After cooling to room temperature the brownish precipitate was collected by filtration and recrystallized from dichloromethane-hexane to yield 1.31 g of **2** (46%), mp 212-214°; ir (potassium bromide): 3290, 1640, 1600, 1575 and 1540 cm^{-1}; ^1H nmr (perdeuteriomethanol): δ 1.03 (s, 6H, CH_3), 2.13 and 2.28 (2s, 4H, CH_2 of cyclohexenone), 3.3-3.7 (m, 4H, CH_2-CH_2, 5.18 (s, 1H, CH of cyclohexenone), 7.2-7.9 ppm (m, 6H, arom and NH).

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.31; H, 7.76; N, 9.68.

3-Chloro-5,5-dimethylcyclohex-2-enone (**3**) and 1-(5,5-Dimethyl-3-oxocyclohex-1-enyl)-4,5-dihydro-2-phenylimidazole (**4**).

Phosphoryl chloride (10 ml) was added cautiously to *N*-[2-[(5,5-Dimethyl-3-oxocyclohex-1-enyl)amino]ethyl]benzamide (**2**) (1.43 g, 5 mmoles). After the addition was complete, the mixture was heated at reflux for 30 minutes, cooled to room temperature and poured on crushed ice. The resulting solution

was alkalized with concentrated aqueous sodium hydroxide and extracted with dichloromethane. The extract was dried over sodium sulfate and evaporated *in vacuo* to provide an oily residue, which consisted of unreacted **2**, **3**, **4** and two unidentified components. It was separated by lc on silica gel using dichloromethane/methanol (9:1) as eluent, to yield 0.29 g of **3** (37%) and 0.15 g of **4** (12%).

Compound **3** was a liquid of camphoraceous odor, n_D = 1.4955 (lit [7] 1.4942); ir (liquid film): 1670 and 1610 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.07 (s, 6H, CH_3), 2.22 and 2.53 (2s, 4H, CH_2), 6.17 ppm (s, 1H, CH-2).

Compound **4** had mp 107-110°; ir (potassium bromide): 1630, 1590 and 1560 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.92 (s, 6H, CH_3), 1.92 and 2.17 (2s, 4H, CH_2 of cyclohexenone), 4.00 (m, 4H, CH_2 of dihydroimidazole), 5.32 (s, 1H, CH-2 of cyclohexenone), 7.2-7.45 (m, 5H, arom).

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.07; H, 7.38; N, 10.53.

2,2'-(1,6-Diphenyl-2,5-diazahexan-1,6-diyliden)bis(5,5-dimethylcyclohexane-1,3-dione) (**6**).

A solution of 2-benzoyldimedone (**5**) (1.22 g, 5 mmoles) and 1,2-diaminoethane (0.30 g, 5 mmoles) in toluene (15 ml) was heated at reflux. After 2 hours the solvent was removed under vacuum and the residue triturated with water. The solid formed was collected by filtration and purified by crystallization from ethanol-water to yield 0.89 g of **6** (70%), mp 238-242°; ir (potassium bromide): 1650 and 1550 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.07 (s, 12H, CH_3), 2.23 and 2.49 (2s, 8H, CH_2 of cyclohexane), 3.16 (d, 4H, CH_2CH_2, J = 6.5 Hz), 6.9-7.4 (m, 10H, arom) and 7.8 ppm (broad s, 2H, NH); ^{13}C nmr (deuteriochloroform): δ 28.3 (CH_3), 30.2 (C-5), 43.8 (NCH_2CH_2N), 52.3 and 52.9 (C-4 and C-6), 108.0 (C-2), 125.8, 128.7, 128.8 and 134.0 (arom), 172.4 (benzylic C), 194.7 and 200.1 ppm (C=O).

Anal. Calcd. for $C_{32}H_{36}N_2O_4$: C, 74.97; H, 7.08; N, 5.46. Found: C, 75.08; H, 7.32; N, 5.44.

4,5-Dihydro-2-phenylimidazole (**7**).

A solution of 2-benzoyldimedone (**5**) (1.22 g, 5 mmoles) in 1,2-diaminoethane (6 g, 100 mmoles) was heated at reflux. After one hour the excess ethane-1,2-diamine was removed under vacuum and the oily residue partitioned between water and dichloromethane. The organic layer was separated, dried over sodium sulfate and evaporated under vacuum. The residue was purified by kugelrohr distillation to give 0.45 g of **7** (62%), mp 97-99° (lit [4] 100-101°); ir (potassium bromide): 3200, 1605, 1600 and 1570 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.71 (s, 4H, CH_2), 4.7 (broad s, 1H, NH), 7.4-7.75 ppm (m, 5H, arom).

2-Benzoyl-3-chloro-5,5-dimethylcyclohex-2-enone (**8**).

Freshly distilled oxalyl chloride (10 ml) was added dropwise to 2-benzoyldimedone (**5**) (7.32 g, 30 mmoles) with stirring and ice cooling. After the addition was complete, the mixture was stirred at 0° for 2 hours and at room temperature for 12 hours. The excess of oxalyl chloride was removed under vacuum to yield 6.7 g of **8** (85%), mp 97° (lit [6] 95-96°); ir (potassium bromide): 1680, 1660 and 1615 cm^{-1}.

2,3,6,7,8,9-Hexahydro-8,8-dimethyl-5-phenyl-1*H*-1,4-benzodiazepin-6-one Hydrochloride (**1**).

A solution of 2-benzoyl-3-chloro-5,5-dimethylcyclohex-2-enone (**8**) (5.25 g, 20 mmoles) in ethane-1,2-diamine (15 ml) was kept at room temperature under nitrogen for 1 hour. The excess of ethane-1,2-diamine was removed under vacuum and the residue dissolved in 2*N*-hydrochloric acid (15 ml). The dark purple solution was washed with dichloromethane, alkalized with concentrated aqueous sodium hydroxide and extracted with dichloromethane. The extract was dried over sodium sulfate and the solvent removed. The residue was purified by lc on silica gel with a 1:1 mixture of acetone and methanol as eluent. The amorphous base, thus obtained, was dissolved in dichloromethane and the solution acidified with hydrogen chloride in ether. The purple crystals, which separated, were collected by filtration, dried over potassium hydroxide and recrystallized from 1-propanol-ether to yield 1.46 g of **1** (24%), mp 270° dec; ir (potassium bromide): 2900-2500, 1635, 1600, 1565 and 1520 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.07 (s, 6H, CH_3), 2.23 (s, 2H, 7-CH_2), 2.78 (s, 2H, 9-CH_2), 3.70 and 3.90 (2m, 4H, 2- and 3-CH_2), 7.4-7.5 ppm (m, 5H, arom); ^{13}C nmr (DMSO-d_6): δ 27.5 (CH_3), 30.7 (C-8), 45.8 (C-9), 46.4 and 48.8 (C-2/3), 51.1 (C-7), 100.6 (C-5a), 128.4, 128.4, 131.4 and 136.9 (arom), 168.0 (C-9a), 175.6 (C-5) and 194.7 ppm (C=O).

Anal. Calcd. for $C_{17}H_{21}ClN_2O$: C, 66.99; H, 6.94; Cl, 11.63; N, 9.19. Found: C, 66.98; H, 6.79; Cl, 11.72; N, 9.02.

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* To whom correspondence should be addressed.

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