SEARCH FOR NEW DRUGS

SYNTHESIS AND NEUROTROPIC ACTIVITY OF HYDROGENATED DERIVATIVES OF QUINOXALINE AND DIBENZO[b,f][1,4]DIAZEPINE

É. S. Krichevskii, L. M. Alekseeva, O. S. Anisimova, V. A. Parshin, V. V. Asnina, and V. G. Granik


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Previously we have demonstrated that 5,5-dimethyl-2-nitro-3-ethoxy-cyclo-1-hexen-2-one (I) is a convenient initial compound for the synthesis of various hydrogenated derivatives of benzimidazole and condensed systems containing benzimidazole fragments [1]. The presence of the ethoxymethylene group in compound I, with two strong electron-acceptor substituents in the β-position, provides the ability of interaction between I and various nucleophilic reagents, in particular, with aliphatic and aromatic amines. These reactions proceed smoothly with the formation of enamino ketones (IIa – IIg) containing nitro groups in the β-position. Reduction of this group may be accompanied by cyclization, leading to the formation of azaheterocycles.

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\begin{align*}
\text{IIa: } R &= \text{CH}_2\text{Ph}; \\
b: R &= \text{CH}_3\text{COOEt}; \\
c: R &= \text{CH(Me)COOMe}; \\
d: R &= \text{C}_6\text{H}_4\text{COOEt-2}; \\
e: R &= \text{C}_6\text{H}_3\text{COOEt-2-Br-4}; \\
f: R &= \text{C}_6\text{H}_4\text{NH}_2-2; \\
g: R &= \text{CH}_2\text{CH}_2\text{COOMe}.
\end{align*}
\]

In the case of N-benzyl derivative IIa, the reduction of the nitro group proceeded smoothly in glacial acetic acid under the action of zinc and led to the formation of 2-acetamidino-3-benzyliminocyclo-1-hexen-2-one (III).

The structure of synthesized compounds was confirmed by the data of mass-spectrometry and \(^1\)H NMR spectroscopy (see the experimental part below).

In compounds IIb – IIe, the side chains containing alkoxycarbonyl groups provide the ability to synthesize the derivatives of quinoxalin-2-one and dibenzazepine. For example, the reduction of compound IIb by zinc in glacial acetic acid smoothly yields 6,6-dimethyl-1,2,3,4,5,6,7,8-octahydroquinoxaline-2,8-dione (IVa). The \(^1\)H NMR spectrum of this compound in DMSO-d\(_6\) shows the following signals (δ, ppm): 0.98 (s, 6H, Me₂), 2.08 (s, 2H, 7-CH₂), 2.24 (s, 2H, 5-CH₂), 3.86 (s, 2H, 3-CH₂), 7.38 (bs, 1H, 4-NH), 8.52 (bs, 1H, 1-NH). The most intense peak in the mass spectrum belongs to the molecular ion with \(m/z = 194\) (M⁺). The main decomposition channel under electron impact involves elimination of a CH₃ group, as reflected by the appearance of a peak at \(m/z = 179\) [M–CH₃]⁺ (30%), followed by the peaks with \(m/z = 165\) [M–CH₂NH]⁺ (3), 151 [M–CONH]⁺ (8), 83 [Me₂C=C–CH=C≡O]⁺ (10). Compound IIc was catalytically reduced in the presence of Pd/C with a high yield of compound IVb. Finally, the benzodiazepine cyclization was performed by treating enamine IIe with zinc in glacial acetic acid to form dibenzodiazepine V with a yield of >90%.

It should be noted that neither catalytic hydrogenation nor the reduction by zinc in an acid medium allowed us to obtain a dibenzodiazepine derivative on the basis of compound IIe.
EXPERIMENTAL PART

The mass-spectra of the synthesized compounds were obtained on a Finnigan SSQ-710 spectrometer operated at an ionizing electron energy of 70 eV and an ionization chamber temperature of 150°C. The 1H NMR spectra were measured on a Varian XL-200 spectrometer with TMS as the internal standard. The melting temperatures were determined on a Boetius heating stage. The IR absorption spectra were recorded on a Perkin-Elmer Model 450 spectrophotometer using samples prepared as nujol mulls. The course of reactions was monitored by TLC on Silufol UV-254 plates eluted in a benzene – methanol (9: 1) system and developed under UV illumination. The data of elemental analyses agreed with the results of analytical calculations by the empirical formulas.

5,5-Dimethyl-2-nitro-3-ethoxycyclo-1-hexen-2-one (I) was synthesized as described elsewhere [1].

3-Benzylamino-5,5-dimethyl-2-nitrocyclo-1-hexen-2-one (IIa). A mixture of 32 g (0.15 mole) of compound I, 5.5 g (25 mmole) of 5-bromoanthranyl acid ethyl ester, 50 ml of methyl alcohol and 4 ml of acetic acid. Then the reaction mass was evaporated in a rotor evaporator to obtain compound IIa with a yield of 75.7%; C17H17BrN2O6; m.p., 163 - 164°C (ethanol).

5,5-Dimethyl-2-nitroethoxycarbonylmethylamino
cyclo-1-hexen-2-one (IIb). A suspension of 3.2 g (15 mmole) of compound I, 2.8 g (20 mmole) of glycine ethyl ester hydrochloride, and 3.8 g sodium acetate in 200 ml of acetone was boiled for 4 h and allowed to stand overnight. Then the reaction mixture was filtered, the mother liquor was evaporated in vacuum, and the residue was mixed with 10 ml of isopropyl alcohol. The precipitate was filtered and washed with ether to obtain compound IIb with a yield of 85.3%; C17H19N2O6; m.p., 110-112°C (ethanol); mass spectrum, m/z (I/Io, %): 270 [M]+ (82), 224 [M-NO2]+ (22), 197 [M-CONMe2] (44), 196 [M-HCOOEt] (36), 182 [M-MeCOOEt] (40), 168 [M-NHC(O)Me] (28), 124 [M-NO2-N=CHCOOEt] (100), 97 [CH3CMe2C(=O)C=O]+ (70), 83 [Me2C=CHC(O)]= (67), 55 [Me2C=CH]+ (33).

5,5-Dimethyl-2-nitrocyclohexen-1-yl)-a-alanine methyl ester (IIc). A suspension of 2.1 g (10 mmole) of compound I, 2.7 g (15 mmole) of α-alanine methyl ester hydrochloride, and 2 g sodium acetate in 100 ml of acetonitrile was boiled for 8 h. Then the reaction mass was evaporated in vacuum. The residue was heated with 10 ml of an acetone – ether (1 : 1) mixture and allowed to stand overnight in a refrigerator. The precipitate was filtered and dried to obtain compound IIc with a yield of 78.3%; C12H13N2O5; m.p., 123 – 125°C (ethanol); mass spectrum, m/z (I/Io, %): 270 [M]+ (36), 224 [M-NO2]+ (10), 211 [M-COOMe]+ (45), 182 [M-EtCOOMe]+ (9), 167 [M-NH2CH(Me)COOEt]+ (15), 124 [M-NO2-N=CHCOOEt] (100), 111 [M-NH2CH(Me)COOEt-Me-CH=CH2]+ (16), 96 [M-NO2-N=C(Me)COOEt-Me]+ (30), 83 [Me2C=CHC(O)]= (40), 55 [Me2C=CH]+ (20).

N-5,5-Dimethyl-(2-nitro-3-oxocyclohexen-1-yl)-anthra
yl acid ethyl ester (IID). A mixture of 6.4 g (0.03 mole) of compound I and 9.9 g (0.06 mole) of anthranyl acid ethyl ester in 50 ml of methyl alcohol was boiled for 24 h in the presence of 3 ml of acetic acid. Then the reaction mass was evaporated in a rotov evaporator to obtain compound IIe with a yield of 79.8%; CI4H17N3O3; m.p., 218-220°C (methanol); mass spectrum, m/z (I/Io, %): 332 [M]+ (93), 317 [M-Me]+ (46), 286 [M-EOH]+ and [M-NO2]+ (41), 258 [M-HCOOEt]+ (50), 240 [M-EOH-NO2]+ (100), 225 [M-EOH-NO2-Me]+ (25), 212 [M-NO2-HCOOEt]+ (40), 83 [Me2C=CHC(O)]= (73); 1H NMR spectrum, DMSO-d6 (5, ppm): 0.93 [s, 6H, 5-(CH3)2], 2.29, 2.51 (s, 4H, 4-CH2, 6-CH2), 1.24, 4.26 (t + q, J 7.2 Hz, CH3CH2O), 7.52, 7.45, 7.70, 7.98 (m, H-arom), 11.22 (bs, NH).

N-5,5-Dimethyl-(2-nitro-3-oxocyclohexen-1-yl)-5-bromo
anthranyl acid ethyl ester (IIe). A mixture of 4.26 g (20 mmole) of compound I, 6.10 g (25 mmole) of 5-bromoanthranyl acid ethyl ester, 50 ml of methyl alcohol and 2.5 ml of acetic acid was boiled for 18 h. Then the reaction mass was evaporated in vacuum to obtain compound IIe with a yield of 75.7%; C17H13BrN2O6; m.p., 174 - 175°C (ethanol); mass spectrum, m/z (I/Io, %): 410 [M]+ (100), 395 [M-Br]+ (43), 364 [M-EOH]+ and [M-NO2]+ (15), 336 [M-HCOOEt]+ (33), 318 [M-EOH-NO2]+ (80), 303 [M-EOH-NO2-Me]+ (25), 290 [M-NO2-HCOOEt]+ (30), 83 [Me2C=CHC(O)]= (73); 1H NMR spectrum, DMSO-d6 (5, ppm): 0.93 [s, 6H, 5-(CH3)2], 2.29, 2.51 (s, 4H, 4-CH2, 6-CH2), 1.24, 4.26 (t + q, J 7.2 Hz, CH3CH2O), 7.80 (qd, J2 8.8 Hz, Ca,-H), 8.05 (d, J 1.2 Hz, C6~H), 7.41 (d, J 1.2 Hz, C5~H), 7.70, 7.98 (m, H-arom), 11.05 (bs, NH).

N-5,5-Dimethyl-(2-nitro-3-oxocyclohexen-1-yl)-phenyl
eine-1,2-diamine (III). A mixture of 1.1 g (5 mmole) of compound I, 0.8 g (7 mmole) of o-phenylenediamine, 5 ml of methyl alcohol, and 0.5 ml of acetic acid was allowed to stand for 48 h at 20°C. The precipitate was filtered and dried to obtain compound III with a yield of 79.8%; C12H13N2O5; m.p., 218 – 220°C (methanol); mass spectrum, m/z (I/Io, %): 275 [M]+ (25), 257 [M-H2O]+ (10), 229 [M-NO2]+ (100), 202 [M-H2O-Me2C=CH]+ (23), 144 [M-NO2-Me2CHCH2CO]+ (60), 132 [M-NO2-