CHLORO DERIVATIVES OF 4-PHENYL-2,3-DIHYDRO-1H-1,5-BENZODIAZEPIN-2-ONE

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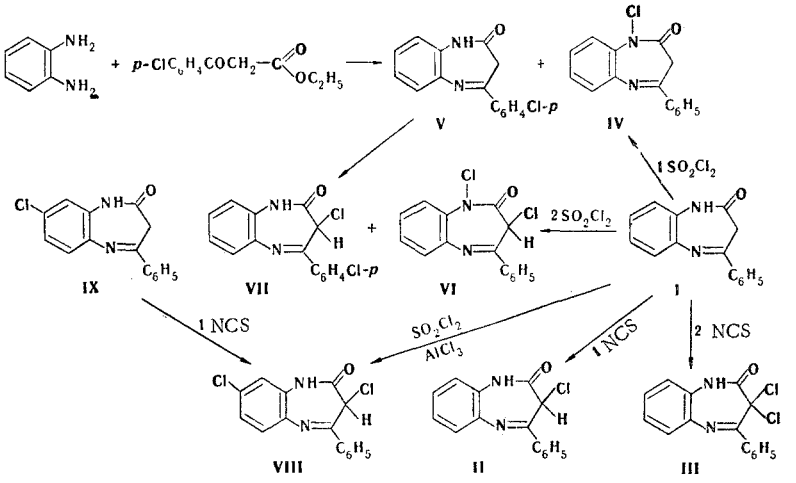
The chlorination of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one with N-chlorosuccinimide takes place at the methylene group to give mono and dichloro derivatives. In the reaction of the diazepinone with sulfuryl chloride chlorine is incorporated in the 1 or 3 position or in both the 1 and 3 positions, as well as in the para position of the phenyl substituent; in the presence of anhydrous aluminum chloride substitution takes place in the methylene group of the heteroring and in the 8 position of the annelated benzene ring.

In contrast to 1,4-benzodiazepinones, which are widely used in medicine, the 1,5 analogs are milder tranquilizers and do not give rise to a number of side effects [1-3]. The presence of electron-acceptor substituents in the annelated benzene ring is a necessary condition of the biological activity of 1,5-benzodiazepinones [4]. In this connection, it seems of interest to study the chlorination of 4-phenyl-2,3-dihydro-1H-1,5-diazepin-2-one (I) by various chlorinating agents.

Chlorination by heating with an equimolar amount of N-chlorosuccinimide (NCS) in carbon tetrachloride leads to the formation of 3-chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (II).



Bands of stretching vibrations of free and associated NH groups, as well as absorption bands of CO–NH and C=N groups at 1675 and 1620 cm^{-1}, are observed in the IR spectra of this compound at 3100-3300 cm^{-1}. Consequently, the product is not an N-chloroamide. The UV spectrum of chlorodiazepinone II is similar to the spectrum of starting diazepinone I but differs with respect to a more appreciable hypsochromic shift of all of the bands and a significant decrease in their intensities. A singlet of one methylidyne proton at 5.7 ppm is observed in the PMR spectrum. The mass spectrum of this compound in the molecular-ion region contains ion peaks with m/z 270 and 272* and an intensity ratio of 3:1, which constitutes evidence for the presence of one

* Here and subsequently, in the schemes and in the text the numbers that characterize the ions are the mass-to-charge ratios. In the case of the chlorine-containing ions the m/z values are presented for the ^{35}Cl isotope.

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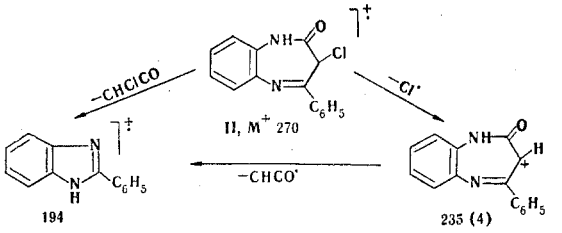
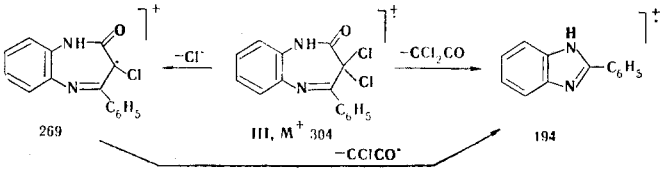
chlorine atom in the molecule. The fragmentation of the molecular ion is realized via two principal pathways: with splitting out of a CHClCO particle (76 amu), which is characteristic for such systems [5], and by successive splitting out of chlorine and a CHCO radical:



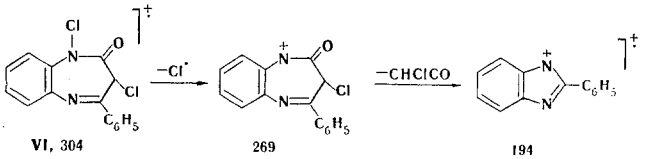
The chlorination of diazepinone I with 2 moles of NCS leads to 3,3-dichloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (III). The absence of signals of protons of a methylene group in the PMR spectrum of this compound does not contradict the adopted structure. The most intense peak in the mass spectrum is the $[M-CCl_2CO]^+$ ion peak, and the fragmentation of the molecular ion is also accompanied by the successive splitting out of a chlorine atom and a chloroketene radical:



Two monochloro derivatives with the composition $C_{15}H_{11}ClN_2O$ and mp 164-165°C (IV) and 206°C (V) are formed in the chlorination of diazepinone I with 1 mole of sulfuryl chloride. The IR spectrum of diazepinone IV does not contain bands of stretching vibrations of NH groups, and this compound is converted to starting diazepinone I upon crystallization from aqueous alcohol. The PMR spectrum of this compound contains a singlet of two methylene protons at 3.8 ppm. On the basis of these data it may be assumed that the compound obtained is 1-chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IV).

The 4-(p-chlorophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one structure (V) was assigned to the second compound on the basis of spectral data and alternative synthesis. The UV spectrum of this compound contains three absorption maxima at 210, 260, and 320 nm. The presence of a chlorine atom in the para position of the phenyl group and its participation in the conjugated system of the molecule appreciably increase the absorption intensity. A singlet of two methylene protons at 3.74 ppm is observed in the PMR spectrum of diazepinone V, and the chlorine atom is consequently contained in one of the benzene rings. For the definitive elucidation of the structure we obtained V by alternative synthesis from p-chlorobenzoylacetic ester and o-phenylenediamine.

Bright-yellow 1,3-dichloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VI) precipitates in the chlorination of diazepinone I with 2 moles of sulfuryl chloride, and 3-chloro-4-(p-chlorophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VII) is isolated from the filtrate. The IR spectrum of VI does not contain bands of stretching vibrations of an NH group, and it is converted to 3-chloro derivative II when it is purified by crystallization from aqueous alcohol. The mass-spectrometric fragmentation of this substance confirms the presence of halogens attached to the 1 and 3 atoms of the heteroring:



The structure of diazepinone VII was established on the basis of spectral data and alternative synthesis. The PMR spectrum of this compound contains the signal of one proton of a methylidyne group at 5.98 ppm. In addition, this substance was obtained by chlorination of monochloro derivative V with 1 mole of NCS.

If the chlorination of diazepinone I is carried out with sulfuryl chloride in the presence of anhydrous aluminum chloride, one can isolate 3,8-dichloro-2,3-dihydro-1,5-benzodiazepin-2-one (VIII), in the PMR spectrum of which the signal of the 3-H proton at 4.89 ppm is observed, in addition to a multiplet of aromatic pro-

tons. This compound was also obtained by chlorination of the previously described [6] 8-chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IX) with 1 mole of NCS.

EXPERIMENTAL

The IR spectra of KBr pellets or mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in trifluoroacetic acid were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were obtained with an MKh-1307 spectrometer with introduction of the substances directly into the ionization region at ionizing voltages of 50 and 70 eV and temperature close to the melting points of the substances. The course of the reactions and the purity of the substances obtained were monitored by means of TLC on plates with a fixed layer of Silufol UV-254 silica gel in a benzene–ethyl acetate system (7:3). The substances were purified with a chromatographic column filled with silica gel in the same system.

3-Chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (II). A mixture of 0.5 g (2 mmole) of diazepinone I and 0.268 g (2 mmole) of N-chlorosuccinimide in 15 ml of carbon tetrachloride was refluxed for 4 h, after which the precipitated succinimide was removed by filtration, and the solvent was removed by distillation in vacuo to give 0.11 g (23%) of diazepinone II with mp 185°C (from alcohol) and Rf 0.65. The product was soluble in chloroform, dimethylformamide (DMF), acetone, acetic acid, and hot alcohol but insoluble in water and hexane. Found: Cl 13.11; N 10.42%. $C_{15}H_{11}ClN_2O$. Calculated: Cl 13.09; N 10.35%. IR spectrum: 3160, 3200, 3300 (N–H); 1710 (C = O); 1640 cm^{-1} (C = N). PMR spectrum: 5.70 (1H, s, 3-H) and 7.01–8.36 ppm (9H, m, aromatic protons). Mass spectrum,* m/z values (%): 272 (3.7), 270 (10.9), 236 (8.9), 235 (3.8), 199 (3.8), 198 (6.3), 195 (12.2), 194 (35.9), 193 (3.8), 192 (3.5), 129 (3.1), 117 (4.0), 111 (3.2), 104 (3.5), 103 (4.5), 102 (6.0), 99 (100), 97 (3.5).

3,3-Dichloro-4-phenyl-2,3-dihydro-1,5-benzodiazepin-2-one (III). A mixture of 0.5 g (2 mmole) of diazepinone I and 0.58 g (4 mmole) of N-chlorosuccinimide (NCS) in 15 ml of carbon tetrachloride was refluxed for 4 h, after which it was worked up to give 0.26 g of III with mp 197°C (from alcohol) and Rf 0.72. Found: Cl 23.16; N 9.34%. $C_{14}H_{10}Cl_2N_2O$. Calculated: Cl 23.21; N 9.18%. IR spectrum (thin layer): 1620 (C = N); 1680 (C = O); 3130, 3200, 3230 cm^{-1} (N–H). UV spectrum, λ (log ε): 104 (4.19), 246 (3.77), and 320 nm (3.28). PMR spectrum: 7.22–8.79 ppm (m, aromatic protons). Mass spectrum, m/z (%): 308 (2.4), 306 (13.2), 304 (20.2), 271 (5.0), 269 (17.0), 268 (4.0), 241 (5.0), 234 (4.0), 227 (10.0), 205 (59.0), 206 (51.0), 207 (10.0), 199 (4.0), 196 (5.0), 195 (46.0), 194 (100), 192 (6.0), 190 (4.0), 180 (5.0), 168 (10.0), 167 (14.0), 166 (22.0), 165 (29.0), 153 (9.3), 151 (4.2), 150 (4.3), 149 (9.9), 140 (4,8), 139 (4.2), 138 (11.0), 137 (5.9), 136 (21.0), 130 (4.0), 129 (18.0).

4-(p-Chlorophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (V). A) A solution of 0.67 g (5 mmole) of sulfuryl chloride in 5 ml of acetic acid was added dropwise to a solution of 1.18 g (5 mmole) of diazepinone I in 10 ml of acetic acid, and the mixture was stirred at room temperature for 8 h. The yellow precipitate of 1-chloro-4-phenyl-2,3-dihydro-1,5-diazepin-2-one (IV) was removed by filtration to give 0.21 g (15%) of a product with mp 164–165°C (from CH_3COOH) and Rf 0.54. Found: Cl 13.23; N 10.24%. $C_{15}H_{11}ClN_2O$. Calculated: Cl 13.09; N 10.35%. The filtrate was poured into ice water, and the mixture was worked up to give 0.33 g (24%) of V with mp 106–207°C (from carbon tetrachloride) and Rf 0.44. Found: Cl 13.31; N 9.19%. $C_{15}H_{11}ClN_2O$. Calculated: Cl 13.09; N 9.35%. IR spectrum: 3250, 3210, 3120 (NH); 1690 (C = O); 1620 cm^{-1} (C = N).

B) A solution of 6.7 g (0.03 mole) of p-chlorobenzoylacetic ester in 26 ml of xylene was added dropwise to a refluxing solution of 3.2 g (0.03 mole) of o-phenylenediamine in 30 ml of xylene, and the mixture was refluxed with a water separator for 1 h. It was then worked up to give 5.7 g (71%) of diazepinone V with mp 206–207°C. No melting-point depression was observed for a mixture of this product with the substance obtained in experiment A.

3-Chloro-4-(p-chlorophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VII). A) A 1.18-g (5 mmole) sample of diazepinone I was chlorinated with 1.34 g (10 mmole) of sulfuryl chloride for 8 h, after which the yellow precipitate of 1-chloro-4-(p-chlorophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VI) was removed by filtration to give 0.71 g (46.6%) of a substance with mp 150–151°C (from CH_3COOH) and Rf 0.76. Found: Cl 23.35; N 9.29%. $C_{15}H_{10}Cl_2N_2O$. Calculated: Cl 23.25; N 9.19%. IR spectrum: 1620 (C = N) and 1680 cm^{-1} (C = O). Mass spectrum, m/z (%): 308 (3.9), 307 (3.9), 306 (20.7), 304 (30.1), 271 (12.4), 270 (22.6), 269 (56.6), 268 (6.2), 265 (17.6), 242 (10.0), 241 (5.6), 239 (4.0), 235 (10.6), 234 (18.8), 233 (8.4), 227 (9.1), 221 (21.6), 207 (18.8), 206 (73.5), 205 (66.0), 202 (17.2), 195 (27.6), 194 (79.2), 193 (30.1), 192 (12.8). Workup of the filtrate gave 0.32 g

*Here and subsequently, the peaks of ions with intensities greater than 3% of the maximum peak are presented.

(21%) of VII with mp 176-177°C and R_f 0.67. Found: Cl 23.47; N 9.2%. $C_{15}H_{10}Cl_2N_2O$. Calculated: Cl 23.25; N 9.18%. IR spectrum: 1640 (C=N), 1690 (C=O), and 3100-3260 cm^{-1} (N-H). PMR spectrum: 5.98 (1H, s, 3-H) and 6.94-7.98 ppm (8H, m, aromatic protons).

B) A 0.7-g (2 mmole) sample of diazepinone V was chlorinated with 0.26 g (2 mmole) of NCS in 20 ml of carbon tetrachloride for 5 h. Workup gave 0.24 g (39%) of diazepinone VII with mp 176-177°C. No melting-point depression was observed for a mixture of this compound with the substance obtained in experiment A.

3,8-Dichloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VIII). A solution of 0.67 g (5 mmole) of sulfuryl chloride in 5 ml of acetic acid was added dropwise to a mixture of 1.18 g (5 mmole) of diazepinone I and 0.51 g of aluminum chloride in 15 ml of acetic acid, and the mixture was stirred for 3 h. Workup gave 0.2 g (13%) of yellow chlorodiazepinone VII with mp 166-167°C and R_f 0.67. The filtrate was poured into ice water and worked up by chromatography with a column filled with silica gel to give 0.35 g (23%) of VIII with mp 190-191°C (from CCl_4) and R_f 0.72. Found: Cl 23.18; N 9.16%. $C_{15}H_{10}Cl_2N_2O$. Calculated: Cl 23.23; N 9.18%. IR spectrum: 1640 (C=N) and 3160-3280 cm^{-1} (N-H). PMR spectrum: 4.89 (1H, s, 3-H) and 6.89-7.95 ppm (7H, m, aromatic protons). Compound VIII was obtained by chlorination of 0.2 g (1.5 mmole) of 8-chloro-4-phenyl-2,3-dihydro-1,5-benzodiazepinone [5] with an equimolar amount of NCS in 15 ml of carbon tetrachloride by the method described above. Workup gave 0.15 g (33%) of diazepinone VII with mp 190°C and R_f 0.72.

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EFFECT OF SUBSTITUENTS ON THE CHEMICAL SHIFT OF THE RING PROTONS IN THE PMR SPECTRA OF MONOSUBSTITUTED sym-TRIAZINES

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A correlation equation that links the relative chemical shift of the protons of the triazine ring with the F and R constants of the substituents was obtained on the basis of data from the PMR spectra of solutions of sym-triazine and its monosubstituted derivatives [OCH_3, $N(CH_3)_2$, CH_3, C_6H_5, $COOC_2H_5$, and CN] in dimethyl sulfoxide (DMSO). The equation was analyzed by comparison with the corresponding equations for monosubstituted benzenes and pyrimidines.

Appreciable weakening of the inductive effect of substituents on the relative chemical shift of the ring protons adjacent to the nitrogen atom of the pyrimidine ring was previously noted [1, 2] during a study of the conductivity of electronic effects of substituents in the pyrimidine ring by PMR spectroscopy. To ascertain the common character of this effect we studied the dependence of the chemical shift of the protons of the sym-triazine ring on the electronic effects of the substituents in the PMR spectra of monosubstituted triazines in dimethyl sulfoxide (DMSO). We selected only monosubstituted derivatives as subjects of the investigation and

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