CHLORINATION OF 4-METHYL-8-METHOXY-2,3-DIHYDRO-1H,1,5-BENZODIAZEPIN-2-ONE

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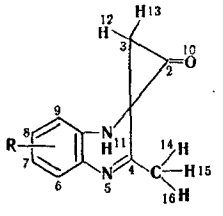
The results of the chlorination of 4-methyl-8-methoxy-2,3-dihydro-1H,1,5-benzodiazepin-2-ones are compared with the results of quantum-chemical calculations of 4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones with various substituents in the benzene ring in the case of homolytic halogenation. The chlorination of 4-methyl-8-methoxy-2,3-dihydro-1H-1,5-benzodiazepin-2-one (I) with N-chlorosuccinimide leads to 3-chloro- and 3,3-dichloro-4-methyl-8-methoxy-2,3-dihydro-1H-1,5-benzodiazepin-2-ones, whereas chlorination with sulfuryl chloride leads to 4-chloromethyl and 3,3-dichloro-4-methyl derivatives. The IR, PMR, and mass spectra of the synthesized compounds are presented.

It has been previously shown [1] that the bromination of 4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (I) with N-bromosuccinimide (NBS) leads to substitution of the hydrogen atoms of the methyl group, as a result of which 4-bromomethyl and 4-dibromomethyl derivatives were isolated.

The present research was devoted to the chlorination of 4-methyl-8-methoxy-1,5-benzodiazepin-2-one (II) and quantum-chemical calculations of 4-methyl-2,3-dihydro-1,5-benzodiazepin-2-ones (I-VI) in the case of homolytic halogenation. The calculations were made by the CNDO/2 method with the standard set of parameters [2]. The experimental geometry of the molecule [3] constituted the foundation of the calculations. The standard values of the bond lengths and angles were used for all of the substituents.

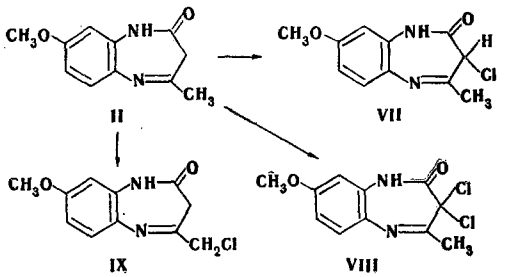


I R=H; II R=8-OCH_3; III R=7-CH_3; IV R=8-CH_3; V R=7-Cl; VI R=8-Cl

The activities of the methyl and methylene groups in radical substitution were compared. The f_R values proposed by Fukui and co-workers [4] served as the indexes:

$$f_R = (C_H^{UO})^2 + (C_H{}^{LV})^2$$

where C_H^{UO} and C_H^{LV} are the corresponding contributions of the 1S AO of the hydrogen atoms of a given group to the upper occupied (UO) and lower vacant (LV) molecular orbitals (MO). On the basis of the data obtained (Table 1) it may be assumed that the tendency for substitution



II VII IX VIII

Dnepropetrovsk Institute of Chemical Technology, Dnepropetrovsk 320640. Dnepropetrovsk State University, Dnepropetrovsk 320625. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1272-1274, September, 1981. Original article submitted September, 11, 1980.

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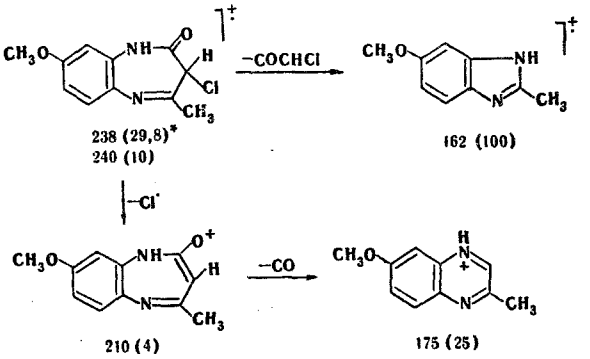
TABLE 1. Activities of the Methyl and Methylene Groups in Radical Substitution

Compound	$f_{R}^{12}{}_{13}$	$f_{R}^{14}{}_{16}^{15}$
I	0,0106	0,0125
II	0,0054	0,0042
III	0,0094	0,0106
IV	0,0098	0,0118
V	0,0090	0,0100
VI	0,0071	0,0094

at the methyl group should be retained for the majority of the examined compounds. In the case of benzodiazepinone II the calculations predict primary orientation of the halogen at the methylene group. In fact, we demonstrated that the chlorination of this diazepinone with N-chlorosuccinimide leads, in conformity with theory, to 3-chloro-4-methyl-8-methoxy-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VII).

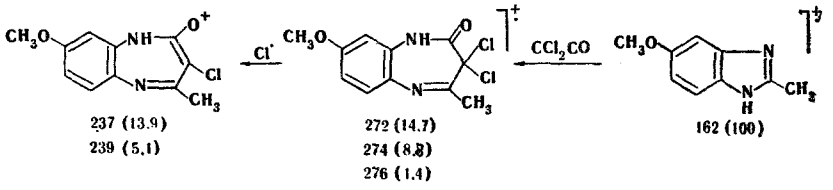
Bands of stretching vibrations of free and associated groups at 3180-3360 cm^{-1} and strong adsorption bands of amide and azomethine groups at 1675 cm^{-1} and 1640 cm^{-1} are observed in the IR spectrum of this compound. Thus it is not the N-chloroamide.

Signals of methyl and methoxy groups at 2.5 and 3.69 ppm, as well as a broad singlet of a methylidyne proton of the diazepine ring, are observed, in addition to a multiplet of aromatic protons at 7.12-8.02 ppm, in the PMR spectrum of chlorodiazepinone VII. The maximum peak in the mass spectrum is the peak of $[M - CHClCO]^+$ ions; this is characteristic for 1,5-benzodiazepin-2-one systems [5]. The successive splitting out of a chlorine atom and a CO molecule occurs simultaneously:



The chlorination of diazepinone II with 2 moles of N-chlorosuccinimide leads to 3,3-dichloro-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VIII).

The PMR spectrum does not contain signals of methylene or methylidyne protons. The maximum peak in the mass spectrum of diazepinone VIII is the peak of ions formed as a result of splitting out of a molecule of dichloroketene:



The chlorination of the diazepinone with sulfuryl chloride is accompanied by substitution of the hydrogen atoms of the methyl group and the formation of 4-chloromethyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IX). Signals of two nonequivalent methylene groups at 4.43 ($3-CH_2$) and 5.73 ppm ($4-CH_2Cl$) are observed in the PMR spectrum of this compound. The mass spectrum contains low-intensity peaks of a molecular ion, the fragmentation of

*These are the m/z values (the intensities of the peaks in percent are given in parentheses).

which is accompanied by the successive splitting out of a chlorine atom and a ketene molecule. Thus in the case of diazepinone II chlorination with sulfuryl chloride leads to substitution of a hydrogen atom of the methyl group rather than the methylene group.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in trifluoroacetic acid were recorded with a Tesla-80 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were obtained with a modified MKh-1303 spectrometer at an ionizing-electron energy of 50 eV. The course of the reactions and the purity of the products were monitored by means of thin-layer chromatography (TLC) on Silufol in a benzene–ethyl acetate system (7:3).

3-Chloro-4-methyl-8-methoxy-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VII). A 1.02-g (0.005 mole) sample of diazepinone II was refluxed with 0.67 g (0.005 mole) of N-chlorosuccinimide in 30 ml of CCl_4 for 2 h, after which the mixture was cooled, and the precipitated succinimide was removed by filtration. The solvent was removed from the filtrate by vacuum distillation to give 0.87 g (73%) of a yellow substance with mp 136-137°C (from CCl_4) and R_f 0.38. PMR spectrum: 5.24 (2H, s, 3-H), 2.5 (3H, s, C–CH_3), 3.69 (3H, s, OCH_3), and 7.12-8.20 ppm (3H, m, aromatic protons). Mass spectrum, m/z (relative intensity, %): 240 (10.1), 239 (4.1), 238 (29.8), 210 (3.6), 204 (3.6), 195 (4.6), 176 (4.1), 175 (24.7), 173 (5.2), 163 (13.5), 162 (100), 161 (17.1), 160 (13.8), 159 (5.7), 149 (5.9), 148 (9.8), 147 (70.8), 146 (3.6), 145 (3.1), 134 (3.3), 133 (8.8). 132 (22.9), 131 (8.3). Found: Cl 14.7; N 11.5%. $C_{11}H_{11}ClN_2O_2$. Calculated: Cl 14.9; N 11.7%.

3,3-Dichloro-4-methyl-8-methoxy-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VIII). A 1.02-g (0.005 mole) sample of diazepinone II and 1.033 g (0.1 mole) of N-chlorosuccinimide were refluxed in 30 ml of CCl_4 for 1 h, after which the mixture was worked up to give 0.71 g (52%) of a substance with mp 150-151°C (from CCl_4) and R_f 0.63. PMR spectrum: 3.06 (3H, s, CH_3), 3.73 (3H, s, OCH_3), and 6.69-7.96 ppm (3H, m, aromatic protons). Mass spectrum, m/z (relative intensity, %): 276 (1.6), 274 (8.8), 272 (14.7), 239 (5.1), 237 (13.9), 211 (7.7), 210 (5.1), 209 (20.5), 208 (6.9), 198 (6.2), 196 (21.3), 194 (11.0), 189 (7.7), 174 (18.7), 173 (29.4), 166 (17.2), 163 (14.7), 162 (100.0), 161 (14.3), 159 (12.8), 158 (6.6), 148 (8.4), 147 (85.2), 131 (12.8), 130 (12.1). Found: Cl 26.18; N 10.1%. $C_{11}H_{10}Cl_2N_2O_2$. Calculated: Cl 26.0%; N 10.2%.

4-Chloromethyl-8-methoxy-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IX). A solution of 0.331 g (2.5 mmole) sample of sulfuryl chloride in 3 ml of acetic acid was added dropwise to a stirred mixture of 0.51 g (2.5 mmole) of the diazepinone in 15 ml of glacial acetic acid, and the mixture was stirred for 3 h. Workup gave 0.51 g (87%) of a white crystalline substance with mp 238°C (from acetic acid) and R_f 0.24 that was soluble in hot acetic acid and DMF. PMR spectrum: 4.43 (2H, s, 3-H), 5.73 (2H, s, CH_2Cl), 6.01 (3H, s, OCH_3), and 9.02-10.01 ppm (3H, m, aromatic protons). Mass spectrum, m/z (relative intensity, %): 240 (0.3), 238 (0.7), 204 (10.6), 203 (78.2), 190 (4.0), 189 (2.3), 175 (3.4), 174 (11.5), 172 (2.6), 164 (12.8), 161 (100), 160 (53.3), 159 (8.6), 158 (4.5), 148 (8.8), 147 (4.7), 146 (95.5), 145 (15.1), 144 (8.0), 143 (3.1), 135 (5.1), 134 (11.5), 133 (20), 132 (22.2), 131 (177.7), 130 (5.4). Found: Cl 14.2; N 11.3%. $C_{11}H_{11}ClN_2O_2$. Calculated: Cl 14.6; N 11.7%.

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