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SYNTHESIS OF 4-PYRIDYL-2,3-DIHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES

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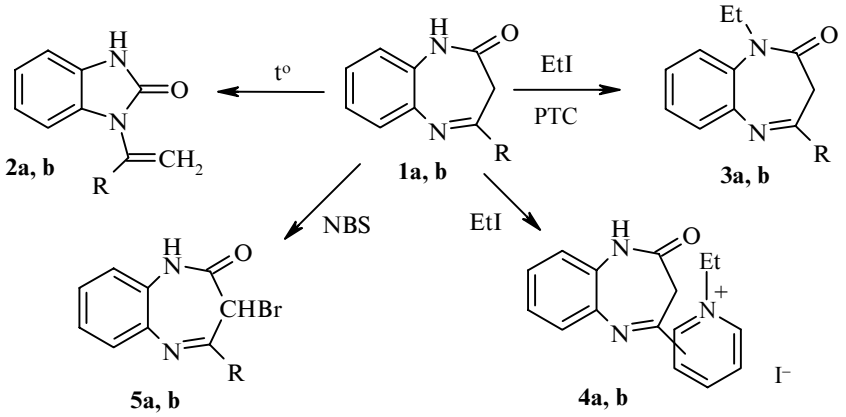
4-Pyridyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones were obtained by the condensation of ethyl nicotinoyl- or isonicotinoylacetates with o-phenylenediamine. Alkylation of the pyridylbenzodiazepinones with ethyl iodide under phase-transfer catalysis conditions occurred at the amide nitrogen of the heterocycle, whereas in nitromethane it occurred at the nitrogen of the pyridine substituent. Bromination with N-bromosuccinimide occurred at position 3 of the heterocycle. Pyridyldibenzodiazepinones underwent thermal rearrangement to derivatives of vinylbenzimidazole.

Keywords: 1,5-benzodiazepin-2-ones, alkylation, bromination, synthesis.

Benzodiazepine and pyridine rings are the part of the structure of a series of medicinals [1]. With the objective of studying the reactivity of 1,5-benzodiazepinones containing a heterocyclic substituent, we have prepared 4-(3-pyridyl)- and 4-(4-pyridyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-ones **1a,b**, which are of interest both as biologically active substances and as substances for theoretical study.

The reaction of ethyl nicotinoylacetate with aromatic amines is known [2]. The authors described the reaction products as 4,5-dihydro derivatives of 1,5-benzodiazepinone.



1-3, **5a** R = 3-pyridyl, **b** 4-pyridyl; **4a** -3-pyridinio-, **b** -4-pyridinio-

The ^{1}H NMR spectra of compounds **1a** and **1b** contain a singlet for one amide hydrogen at 10.62 ppm and a singlet for the methylene protons of the diazepine ring in the region of 3.5 ppm. Signals for the protons of the pyridine ring and the fused benzene ring also appear (Tables 1 and 2).

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TABLE 1. ^{1}H NMR Spectra (DMSO-d_6) of Compounds **1a-5a**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)								
	NH (1H, s)	3-H	Ar		Protons of the pyridine substituent				Other groups
			3H, m	1H, d	2'-H (1H, s)	4'-H (1H, d)	5'-H (1H, dd)	6'-H (1H, d, *J*= 5)	
1a	10.62	3.56 (2H, s)	7.18-7.35	7.67 (*J* = 7)	9.23	8.40 (*J* = 8)	7.55 (J_1 = 4.5, J_2 = 7.8)	8.75	
2a	11.14		6.95-7.15	6.73 (*J* = 7.8)	8.60	7.70 (*J* = 8)	7.39 (J_1 = 4.5, J_2 = 8)	8.56	5.66 (1H, s, =CH_2); 6.32 (1H, s, =CH_2)
3a		3.21 (1H, d, *J* = 14); 4.21 (1H, d, *J* = 14)	7.42-7.60	7.67 (*J* = 7.67)	9.34	8.62 (*J* = 9)	7.69 (J_1 = 5, J_2 = 8)	8.75	3.93 (1H, m, N–$\underline{CH_2}$–CH_3); 4.25 (1H, m, N–$\underline{CH_2}$–CH_3); 1.15 (3H, m, N–CH_2–$\underline{CH_3}$)
4a	10.79	3.71 (2H, s)	7.23-7.43	7.49 (*J* = 7.49)	9.68	9.22 (*J* = 8)	8.30 (J_1 = 6, J_2 = 8)	9.11	4.75 (2H, dd, J_1 = 8, J_2 = 13, N–$\underline{CH_2}$–CH_3); 1.60 (3H, m, N–$CH_2\underline{CH_3}$)
5a	11.26	6.13 (1H, s, CH–Br)	7.20-7.38	7.55 (*J* = 7.55)	9.68	9.22 (*J* = 8)	8.30 (J_1 = 6, J_2 = 8)	9.11	

TABLE 2. ^{1}H NMR Spectra (DMSO-d_6) of Compounds **1b-5b**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)						
	NH (1H, s)	3-H	Ar		Protons of the pyridine substituent		Other groups
			3H, m	1H, d	2'-, 6'-H (2H, d)	3'-, 5'-H (2H, d)	
1b	10.63	3.53 (2H, s)	7.21-7.36	7.44 (*J* = 7.5)	8.76 (*J* = 6.3)	7.95 (*J* = 6.3)	—
2b	11.17	—	6.75-7.12	6.71 (*J* = 7.5)	8.57 (*J* = 6)	7.32 (*J* = 6)	5.79 (1H, s, = CH_2); 6.42 (1H, s, = CH_2)
3b	—	3.00 (1H, d, *J* =14); 4.11 (1H, d, *J* = 14)	7.32-7.46	7.61 (*J* = 7)	8.78 (*J* = 6)	7.98 (*J* = 6.3)	3.79 (1H, m, N–$\underline{CH_2}$–CH_3) ; 4.05 (1H, m, N–$\underline{CH_2}$–CH_3); 0.99 (3H, m, N–CH_2–$\underline{CH_3}$)
4b	10.85	3.69 (2H, s)	7.25-7.45	7.54 (*J* = 7.5)	9.25 (*J* = 6)	8.66 (*J* = 6.3)	4.71 (2H, dd, J_1 = 8, J_2 = 15, N–$\underline{CH_2}$–CH_3); 1.58 (3H, m, N–CH_2–$\underline{CH_3}$)
5b	11.30	6.09 (1H, s, CH–Br)	7.25-7.42	7.53 (*J* = 7.5)	8.78 (*J* = 6)	7.97 (*J* = 6.3)	—

TABLE 3. Characteristics of the Compounds Synthesized

Compound*	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}			Yield, %
		C	H	N		NH	C=N, C=C	C=O	
1a	$C_{14}H_{11}N_3O$	70.78 / 70.89	4.58 / 4.64	17.63 / 17.72	217-218	3200-3070	1610, 1590	1670	85
2a	$C_{14}H_{11}N_3O$	70.21 / 70.89	4.42 / 4.64	17.44 / 17.72	163-164	3280-3050	1625, 1600	1715	48
3a	$C_{16}H_{15}N_3O$	72.15 / 72.45	5.42 / 5.66	15.42 / 15.85	70-71	—	1615, 1575	1675	67
4a	$C_{16}H_{16}IN_3O$	48.48 / 48.98	3.90 / 4.08	10.18 / 10.71	225-227	3125-3075	1634, 1608	1676	74
5a	$C_{14}H_{10}BrN_3O$	52.84 / 53.16	3.02 / 3.16	12.89 / 13.29	>260 (dec.)	3320-3200	1610, 1580	1675	80
1b	$C_{14}H_{11}N_3O$	70.68 / 70.89	4.32 / 4.64	17.34 / 17.72	207-208	3200-3050	1610, 1580	1668	82
2b	$C_{14}H_{11}N_3O$	70.28 / 70.89	4.35 / 4.64	17.45 / 17.72	120-122	3280-3100	1620, 1600	1710	32
3b	$C_{16}H_{15}N_3O$	72.22 / 72.45	5.26 / 5.66	15.63 / 15.85	111-112	—	1610, 1595	1685	72
4b	$C_{16}H_{16}IN_3O$	48.52 / 48.98	3.80 / 4.08	10.83 / 10.21	220-222	3145-3070	1632, 1600	1670	60
5b	$C_{14}H_{10}BrN_3O$	52.90 / 53.16	3.02 / 3.16	13.10 / 13.29	>220 (dec.)	3280-3100	1620, 1590	1670	88

* Found, %: Br 24.86 (**5a**), 25.12 (**5b**). Calculated, %: Br 25.32.

Chromatographic monitoring of the course of the reaction showed that formation of the pyridylbenzodiazepinones **1a,b** is accompanied by rearrangement of the benzodiazepine ring into a benzimidazole ring, which is known for a series of 1,5-benzodiazepines [3]. Rearrangement of compound **2b** is complicated by polymerization at the vinylpyridine unit. The ^{1}H NMR spectra of benzimidazolones **2**, in distinction from those of the benzodiazepinones **1**, contain signals of the vinyl protons as singlets at 5.66 and 6.30 ppm (**2a**) and at 6.23 and 6.42 ppm (**2b**).

Alkylation of 1,5-benzodiazepin-2-ones may lead to alkylation at positions 1 and 3 of the heterocycle, or at the oxygen atom of the carbonyl group [4], or at the nitrogen atom of the pyridine ring [5], depending on ratio of the reagents and the structure of the alkyl halide. Alkylation of the benzodiazepin-2-ones **1** was studied using ethyl iodide in nitromethane or under phase-transfer catalytic conditions (tetrabutylammonium bromide–50% NaOH solution–benzene). We found that alkylation in nitromethane with a 1:2 ratio of diazepine to ethyl iodide occurred at the nitrogen atom of the pyridine ring with formation of compounds **4**. The absorptions of the NH and CO groups were retained in the IR spectra of the products, while in the ^{1}H NMR spectra the signals of the N-ethyl substituent on the pyridine ring appeared as two signals: a quartet for the methylene protons and a triplet for the methyl protons. Alkylation under phase transfer catalysis conditions gave alkylation at the amide nitrogen of the heterocycle. The NH absorption was absent from the IR spectra. In distinction from the unsubstituted compounds and the products alkylated at the pyridine nitrogen, in the ^{1}H NMR spectra of the $N_{(1)}$-alkyl substituted derivatives of 1,5-benzodiazepinones the methylene protons of the 3H heterocycle remained inequivalent and appeared as two doublets, which can be explained by the conformational characteristics of the 1,5-benzodiazepine structure [4, 6].

Bromination of the benzodiazepinones **1** with molecular bromine or N-bromosuccinimide occurred regioselectively at position 3 of the heterocycle to give the 3-bromo derivatives **5**, in the ^{1}H NMR spectra of which there is a singlet signal of the methyne proton in the 6.00-6.20 ppm range, while the signals of the methylene protons are disappeared.

According to the results of pharmacological studies compounds **1a** and **3a** have marked anticonvulsive and tranquilizing activities.

EXPERIMENTAL

The course of reactions and the purity of the compounds synthesized were monitored by chromatography on Silufol UV-254 plates. IR spectra (KBr disks) were recorded on a Specord IR-75 spectrometer. ^{1}H NMR spectra (DMSO-d_6) were recorded on a Varian VXR-300 (300 MHz) machine.

4-Pyridyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (1). Ethyl nicotinoyl- or isonicotinoylacetate (2.32 g, 12 mmol) in xylene (20 ml) was added dropwise to a boiling mixture of *o*-phenylenediamine (1.08 g, 10 mmol) in xylene (80 ml). The reaction mixture was boiled for 45 min. Benzoyldiazepinone **1** was filtered from the cooled mixture and crystallized from nitromethane.

Thermal Rearrangement of 4-Pyridyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (2). Compound **1** (0.60 g, 2.5 mmol) was heated at 180-190°C for 15-20 min. The cooled melt was washed with hot acetone. The solid residue was chromatographically pure benzodiazepine **2a**. To separate compound **2b**, the acetone-insoluble residue was chromatographed on a silica gel column with 1:2 ethanol–ethyl acetate eluent. Compound **2b** (0.19 g) and a mixture of the products of polymerization of benzimidazolone **2b** (0.24 g) were separated.

1-Ethyl-4-pyridyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (3). A mixture of diazepinone **1** (0.50 g, 2.1 mmol), ethyl iodide (0.33 g, 2.1 mmol), tetrabutylammonium bromide (0.032 g), NaOH (3 ml, 50% solution), and benzene (10 ml) were stirred at 60-65°C until the organic layer became clear. The benzene layer was separated, washed with water, dried with $MgSO_4$, the solvent evaporated, and the residue recrystallized from hexane.

Iodides of 4-(N-Ethylpyridinio)-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (4). Diazepinone **1** (0.6 g, 2.5 mmol) and ethyl iodide (0.8 g, 5 mmol) in nitromethane (30 ml) was boiled. The mixture was cooled, the residue filtered off, washed with ethanol, and crystallized from nitromethane.

3-Bromo-4-pyridyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (5). A solution of compound **1** (0.32 g, 1.35 mmol) and bromosuccinimide (0.32 g, 1.8 mmol) was heated for 3 h, the succinimide was filtered off, and the solvent was evaporated. The residue was washed with ammonia solution and ethanol and recrystallized from CCl_4.

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