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BROMINATION OF SUBSTITUTED 5H-IMIDAZO[1,2-*b*]-1,2,4-TRIAZEPIN-4-ONES AND -THIONES

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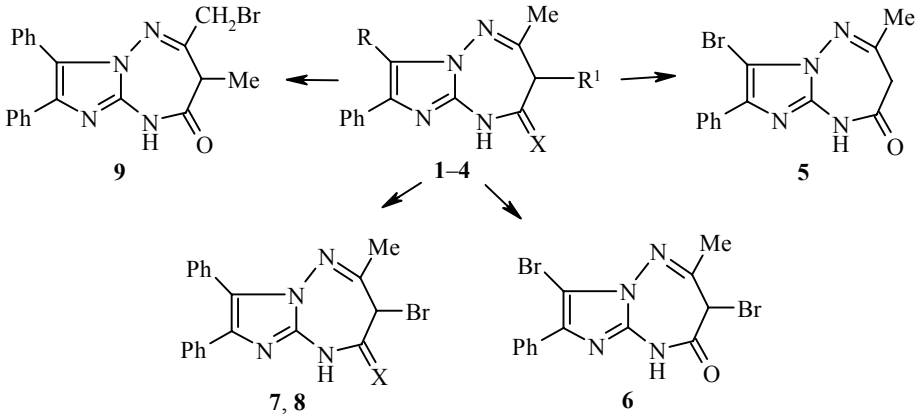
The reactions of substituted 5H-imidazo[1,2-b]-1,2,4-triazepin-4-ones and -thiones with bromine and N-bromosuccinimide have been studied. Derivatives of 3- and 8-bromo-, 3,8-dibromoimidazo[1,2-b]-1,2,4-triazepine and 5H-2-bromomethyl-3-methyl-7,8-diphenylimidazo[1,2-b]-1,2,4-triazepin-4-one are formed, depending on the degree of substitution, the nature of the brominating agent, and the reaction conditions.

Keywords: 5H-imidazo[1,2-*b*]-1,2,4-triazepineone and -thione, bromination.

In a continuation of the reactivity studies of derivatives of imidazo[1,2-*b*]-1,2,4-triazepines [1-3], the reactions of di-, tri- and tetra-substituted 5H-imidazo[1,2-*b*]-1,2,4-triazepine-4-one(thione) **1-4** with bromine and N-bromosuccinimide (NBS) have been studied. The direction of the bromination of monophenyl-substituted compound **1** was found to depend on the nature of the brominating agent, the solvent, the ratio of the reagents, and temperature. Only 8-bromoimidazotriazepine **5** (Table 1) was isolated when equimolar amounts of compound **1** and NBS were heated in carbon tetrachloride to 60°C. The signal of the 8-H proton is absent from the ^{1}H NMR spectrum of compound **5** but the signals of the imine, methylene, methyl, and phenyl protons appear as in the spectrum of starting material **1** at 11.62 (1H, s, NH), 3.64 (2H, s, CH_2), 2.28 (3H, s, CH_3) and 7.73 (5H, m, H arom.) respectively.



1 R = R^1 = H; **2**, **3** R = Ph, R^1 = H; **4** R = Ph, R^1 = Me; **1**, **2**, **4**, **7** X = O; **3**, **8** X = S

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The mass spectrum of compound **5** contains two molecular ion peaks of equal intensity which indicates the presence of a single bromine atom in the molecule. Fragmentation of M^+ is typical of imidazotriazepinones [2-4] and includes the processes $[M - CH_3CN]^+ - \Phi$ and $[\Phi - CHCO]^+ - \Phi_2$. The absence of the bromine atom in the ions $\Phi - \Phi_2$ together with the formation of the charged fragments $[PhC(NH)=CBr]^+$ and $[PhC\equiv C\text{-}Br]^+$ with *m/z* 196, 194 and 182, 180 confirms the presence of the bromine atom at $C_{(8)}$.

The selectivity of the process decreased when the reaction temperature was raised to 80°C, both 8-bromo- and 3,8-dibromo-substituted compounds **5** and **6** being formed, with the yield of 8-bromo derivative predominating (Table 1). Doubling the quantity of NBS changed the proportions of the products in favor of 3,8-dibromo-substituted compound **6**, while replacing of CCl_4 by benzene completely excluded the formation of 8-bromoimidazotriazepine **5**.

Reaction of compound **1** with bromine in acetic acid at room temperature led to predominant formation of 3,8-dibromo derivative **6**, while bromination in DMF at heating gave only 8-bromoimidazotriazepine **5** (Table 1).

The ^{1}H NMR spectrum of 3,8-dibromoimidazotriazepine **6**, like that of its monosubstituted analog **5**, contained signals for protons of the imino, methyl, and phenyl groups at 12.02, 2.43, and 7.60 ppm respectively, but in place of the signals of the protons of the methylene group a singlet for the proton of the methyne group appeared at 5.74 ppm. This shows that the second bromine atom is at $C_{(3)}$ in the bicyclic molecule **6**. The direction of bromination of compound **2**, in which there is phenyl substituent at $C_{(8)}$, does not depend on the nature of the brominating agent, the solvent, or the reaction temperature, but proceeds with formation of the 3-bromoimidazotriazepineone **7** [1].

Reaction of thione **3** with bromine in acetic acid at 20-25°C or with NBS in boiling CCl_4 gave 5H-3-bromo-2-methyl-7,8-diphenylimidazo[1,2-*b*]-1,2,4-triazepin-4-thione (**8**). The same compound was obtained from the reaction of bromoimidazotriazepine **7** with P_2S_5 in boiling pyridine.

The following signals appeared in the ^{1}H NMR spectrum of compound **8**: 11.78 (1H, s, NH); 5.63 (1H, s, CH); 2.34 (3H, s, CH_3); 7.81 ppm (10H, m, H arom.).

The bromination of the bicyclic compound **4**, in which the reactive positions 3 and 8 are blocked by methyl and phenyl substituents, occurs quite differently. When compound **4** was boiled with NBS in CCl_4 5H-2-bromomethyl-3-methyl-7,8-diphenylimidazo[1,2-*b*]-1,2,4-triazepin-4-one (**9**) was obtained.

TABLE 1. Conditions and Results of Bromination of Compound **1**

Method	Brominating agent (proportions of starting materials, mol)	Solvent	Reaction temperature, °C	Reaction time, h	Yield of products, %	
					5	**6**
A	NBS (1 : 1)	CCl_4	55-60	4	63*	—
B	NBS (1 : 1)	CCl_4	80	3	35*	10
C	NBS (1 : 1)	Benzene	80	3	42*	8
D	NBS (1 : 2)	CCl_4	80	4	8	41
E	NBS (1 : 2)	Benzene	80	4	—	55
F	Br_2 (1 : 2)	CH_3COOH	20-25	5	12	42
G	Br_2 (1 : 1)	DMF	65-70	4	—	32*
H	Br_2 (1 : 2)	DMF	65-70	4	—	52
I	Br_2 (1 : 3)	DMF	65-70	4	—	58

* Starting material **1** was also isolated from the reaction mixture: 20 (A), 15 (B), 8 (C), and 10% (G).

TABLE 2. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f	Yield, % (method)
		C	H	Br	N			
5*	$C_{13}H_{11}BrN_4O$	48.69 / 48.64	4.12 / 4.04	25.10 / 24.89	17.70 / 17.45	194-195	0.62	63 (A)
6	$C_{13}H_{10}Br_2N_4O$	38.96 / 39.23	2.41 / 2.53	40.25 / 40.15	14.21 / 14.07	178-180	0.69	58 (I)
7	$C_{19}H_{15}BrN_4O$	57.83 / 57.74	4.02 / 3.83	20.39 / 20.22	13.95 / 14.17	221-222*[2]	0.63	88 (A) 79 (B)
8	$C_{19}H_{15}BrN_4O$	55.78 / 55.48	3.72 / 3.68	19.56 / 19.43	13.89 / 13.62	236-237	0.53	60 (A) 48 (B) 50 (C)
9	$C_{20}H_{17}BrN_4O$	58.81 / 58.69	4.33 / 4.19	19.72 / 19.52	13.79 / 13.69	207-208	0.66	42

* Compound **5** was crystallized from methanol, **6** from propanol-2, **7** and **8** from acetic acid, and **9** from 2-methylpropanol-1.
*[2] Lit. m.p. 220-222°C [1].

The mass spectrum of compound **9** contains M^+ peaks with *m/z* 410 and 408 (1:1 intensity ratio) which, along with peaks for the ions $[M - Br]^+$, $[Br]^+$, and $[HBr]^+$ with *m/z* 329, 81 and 79, 82 and 80, indicates the presence of a single bromine atom in the molecule. The presence of a signal for the ion $[M - BrCH_2CN]^+$ with *m/z* 289 in the mass spectrum of compound **9**, and the absence of a peak for the ion $[M - CH_3CN]^+$ in the case of compounds with unsubstituted methyl group at $C_{(2)}$ [2, 3], is direct confirmation of its structure as 2-bromomethyl-substituted imidazotriazepineone **9**.

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker WH-90 apparatus. Mass spectra were recorded with a Varian MAT 311A instrument under standard conditions. Purity of the compounds prepared was monitored by TLC on Silufol strips with solvent system of 2:1 toluene–propanol-2. Column chromatography was carried out with column (40 × 2.5 cm) filled with L 100/160 silica gel and using 2:1 toluene–propanol-2 as eluent. Results of bromination of compound **1** are given in Table 1 and the characteristics of compounds **5-9** – in Table 2.

Bromination of 5H-2-Methyl-7-phenylimidazo[1,2-*b*]-1,2,4-triazepin-4-one (1). Methods A-E. NBS (2 or 4 mmol) was added to solution of triazepine **1** (0.48 g, 2 mmol) in an organic solvent (10-15 ml) and the mixture was heated. After cooling the precipitate of compound **5** was filtered off, washed with ether, and dried. In reactions using methods B-D the precipitate was chromatographed on a column. Bromoimidazotriazepine **5** was obtained from the first colorless fraction with R_f 0.62 after removal of the solvent, recrystallization and drying. Dibromide **6** was obtained from the second yellow fraction after removal of the solvent, recrystallization and drying. From the synthesis by method E the precipitate of compound **6** obtained after cooling the mixture was filtered off, washed with ether and dried.

Methods F-I. Mixture of compound **1** (1.2 g, 5 mmol) and bromine (5, 10, or 15 mmol) was heated in an organic solvent (10 ml) or kept in acetic acid (10 ml) at room temperature. Treatment was as in method E. In the case of method F, the reaction mixture was poured into water (50 ml), neutralized with sodium acetate, the precipitate of compounds **5** and **6** was filtered off, washed with water, dried, and chromatographed as described for methods B-D. Mass spectrum of compound **5**, *m/z* (I_{rel}, %): M^+ 320 (26), 318 (27); Φ – 279 (16), 277 (15);

Φ – 251 (12), 249 (12); 240 (17), 239 (14); $Φ_2$ – 238 (4), 236 (13), 196 (11), 194 (12), 182 (10), 180 (9), 161 (20), 149 (14), 144 (10), 136 (15), 129 (30), 117 (14), 104 (50), 103 (16), 102 (12), 89 (13), 88 (99), 87 (13), 77 (27), 58 (100).

5H-3-Bromo-2-methyl-7,8-diphenylimidazo[1,2-*b*]-1,2,4-triazepin-4-one (7). A. Bromine (0.48 g, 3 mmol) was added in three portions to solution of compound **2** (0.64 g, 2 mmol) in acetic acid (5 ml) at 25°C. The solution was stirred for 1 h at 40°C, then poured into water (100 ml). The yellow precipitate was filtered off, washed with water and dried.

B. Solution of compound **2** (0.64 g, 2 mmol) and NBS (0.36 g, 2 mmol) in carbon tetrachloride (10 ml) was boiled for 10 h. After cooling, the precipitate of compound **7** was filtered off, washed with ether, and dried.

5H-3-Bromo-2-methyl-7,8-diphenylimidazo[1,2-*b*]-1,2,4-triazepin-4-thione (8). A. Solution of bromine (0.4 g, 2.5 mmol) in acetic acid (5 ml) was added dropwise to solution of thione **3** [2] (0.66 g, 2 mmol) in acetic acid (10 ml) and the mixture was stirred for 1 h at 20-22°C. The precipitate which formed was filtered off, washed with acetone, and dried.

B. Mixture of compound **3** (0.33 g 1 mmol), NBS (0.36 g, 2 mmol), and CCl_4 (10 ml) was boiled for 4 h. After cooling the precipitate was filtered off, washed with ether, and dried.

C. Mixture of compound **7** (0.4 g, 1 mmol), P_2S_5 (0.34 g, 1.5 mmol) and anhydrous pyridine (10 ml) was boiled for 3 h. The reaction mixture was cooled, the precipitate was filtered off, washed with ethanol, and dried.

5H-2-Bromomethyl-3-methyl-7,8-diphenylimidazo[1,2-*b*]-1,2,4-triazepin-4-one (9). NBS (0.36 g, 2 mmol) was added to solution of imidazotriazepineone **4** (0.66 g, 2 mmol) in CCl_4 (15 ml) and the mixture was boiled for 8 h. The reaction mixture was cooled, the precipitate was filtered off, washed with ether, and dried. Mass spectrum, *m/z* (I_{rel}, %): M^+ 410 (4), 408 (13); 329 (27), 289 (25), 261 (10), 260 (12), 234 (37), 219 (7), 218 (6), 193 (53), 178 (14), 136 (48), 82 (96), 81 (34), 80 (100), 79 (36), 77 (33).

REFERENCES

1. V. P. Kruglenko, N. S. Patalakha, P. V. Kurapov, N. A. Klyuev, V. A. Idzikovskii, I. I. Grandberg, and M. V. Povstyanoi, *Khim. Geterotsikl. Soedin.,* 694 (1985).
2. V. P. Kruglenko, V. A. Idzikovskii, N. A. Klyuev, and M. V. Povstyanoi, *Khim. Geterotsikl. Soedin.,* 386 (1988).
3. V. P. Kruglenko, V. A. Idzikovskii, N. N. Kobets, and M. V. Povstyanoi, *Khim. Geterotsikl. Soedin.,* 234 (1990).