ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 4, pp. 697–700. © Pleiades Publishing, Ltd., 2019.
Russian Text © The Authors(s), 2019, published in Zhurnal Obshchei Khimii, 2019, Vol. 89, No. 4, pp. 561–565.

Reaction of 1-Allyl(methallyl)theobromine with Halogens

K. Yu. Petrova[a]*, D. G. Kim[a], O. S. Eltsov[b], and T. D. Eremenko[a]

[a] *National Research University (NPU), pr. Lenina 76, Chelyabinsk, 454080 Russia*
**e-mail: osheko_kseniya@mail.ru*

[b] *Ural Federal University, Yekaterinburg, Russia*

Received September 6, 2018; revised September 16, 2018; accepted September 17, 2018

Abstract—The reactions of bromine and iodine with 1-allyltheobromine and 1-methallyltheobromine were studied. Depending on the nature of the halogen and the initial theobromine, the reaction can lead to the formation of the adducts at the double bond, oxazolopurines or complex compounds.

Keywords: theobromine, 1-methallyltheobromine, oxazolopurine, allyltheobromine

DOI: 10.1134/S1070363219040091

Theobromine derivatives are known to possess antihypoxic activity [1]. At the same time, there are no data on oxazolopurinium species, which may have high biological activity.

Aiming to obtain new fused oxazolopurinium derivatives, we studied the reactions of 1-allyltheobromine **1a** and 1-methallyltheobromine **1b** with bromine and iodine.

Previously, synthesis of compound **1a** has been performed by alkylation of theobromine with allyl bromide in DMF or isopropyl alcohol in the presence of a base (*i*-BuONa, NaOH or K_2CO_3) [2–6]. We obtained theobromine **1a** in the presence of K_2CO_3 in DMF. The ^{1}H NMR data and melting point of compound **1a** coincide closely with those reported earlier [2].

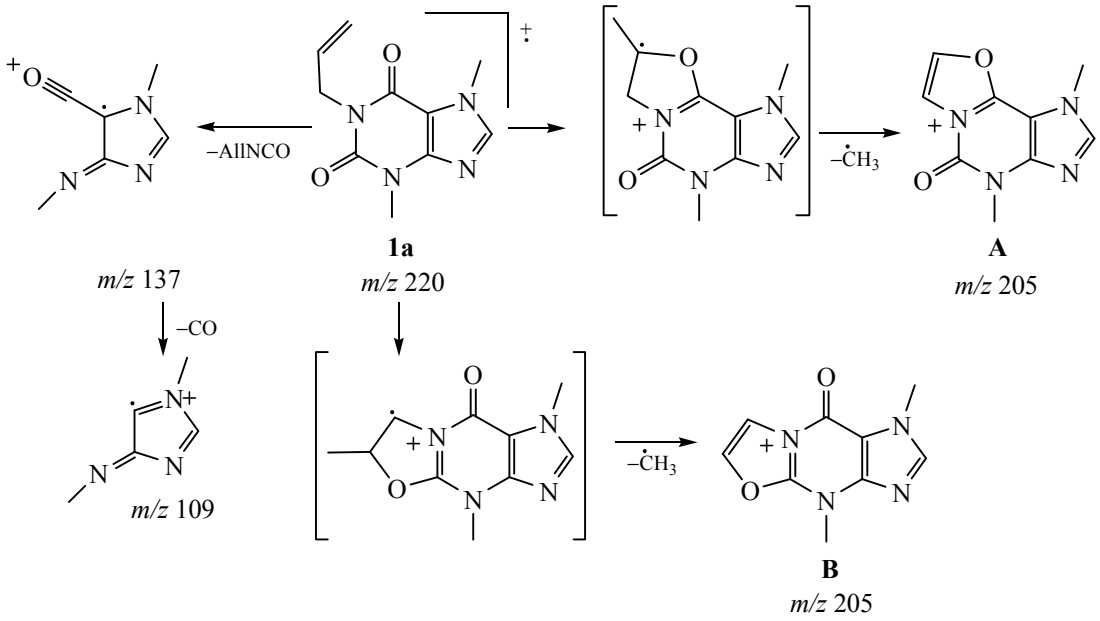
The mass spectrum of allyltheobromine **1a** contains the molecular ion $[M]^{+\bullet}$ peak with an intensity of 82%, and a peak with *m*/*z* 205 caused by the detachment of the methyl radical, which has a maximum intensity (Scheme 1). In our opinion, a high signal intensity indicates the formation of stable tricyclic systems **A** or **B**. For allyltheobromine **1a** fragmentation, elimination of allyl isocyanate and further liberation of CO are characteristic (peaks with *m*/*z* 137 and 109, respectively).

Methallyltheobromine **1b** was obtained for the first time by alkylation of theobromine with methallyl chloride in DMF in the presence of anhydrous potassium carbonate (Scheme 2).

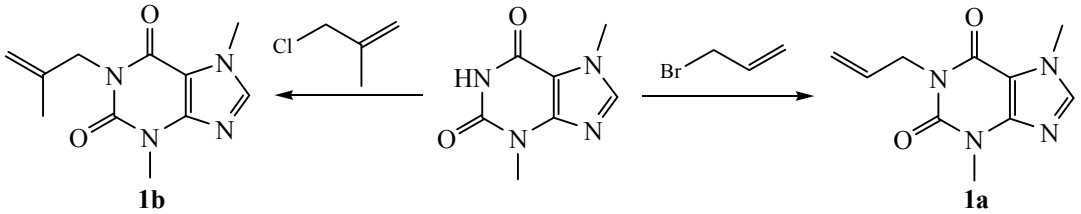
The reactions of allyltheobromines **1a** and **1b** with bromine can proceed in different ways: the halogenation followed by cyclization into [1,3]oxazolo[2,3-*i*]purinium systems or by the addition of bromine to the double bond. It was found that the reaction of theobromine **1a** with bromine in chloroform leads to the formation of 1-(2,3-dibromopropyl)theobromine **2** (Scheme 3). The ^{1}H NMR spectrum of compound **2** contains two multiplets of CH_2Br group in the 3.95–4.05 ppm region; the signals of NCH_2 group are recorded at 4.25 and 4.43 ppm. The proton of CHBr moiety appears at 4.68 ppm, which closely matches the signals of similar protons in *N*-(2,3-dibromopropyl)isatin [7].

The reaction of methallyltheobromine **1b** with bromine in acetic acid and dichloromethane afforded a mixture of two isomers, namely 6-(bromomethyl)-1,4,6-trimethyl-9-oxo-3a,4,6,7,9,9a-hexahydro-1*H*-oxazolo[3,2-*a*]purinium **3** and 8-(bromomethyl)-1,4,8-trimethyl-5-oxo-3a,4,5,7,8,9b-hexahydro-1*H*-oxazolo-[2,3-*i*]purinium **4** bromides in the ratio of 1 : 0.63 in acetic acid and 1 : 0.95 in dichloromethane (Scheme 4). The ^{1}H NMR spectra of bromides **3** and **4** are very close, and the H^8 proton signal is shifted to a weak field with respect to the initial compound **1b** (7.88 → 8.45–8.80 ppm), which is due to the appearance of a positive charge in the system. In the case of a linear structure **3**, the proton signal of the imidazole ring is in a weaker field than the signal of the same proton in the case of **4**.

Scheme 1.



Scheme 2.

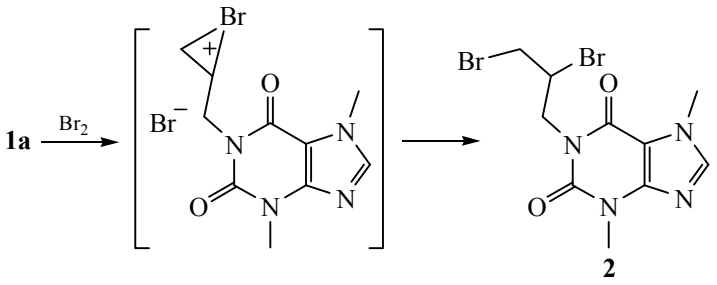


After the separation of bromides **3** and **4**, in the solution of acetic acid the product of the bromine addition at the double bond, 1-(2,3-dibromo-2-methylpropyl)theobromine **5**, was found (Scheme 4). As in the case of adduct **2**, in the ^{1}H NMR spectrum of compound **5**, the H^8 proton appears as a singlet in the same region as in the case of the starting **1b**.

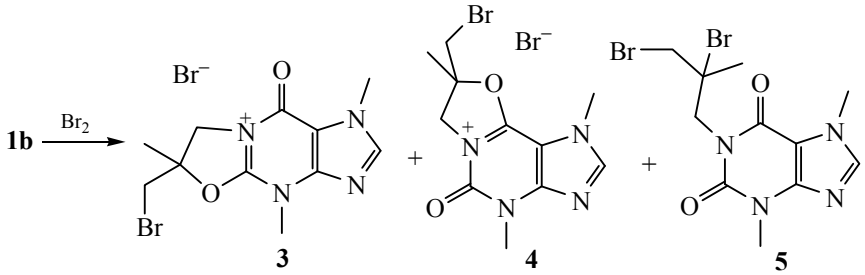
During the reaction of theobromine **1a** with iodine, a complex of iodine with 1-allyltheobromine **6** was formed (Scheme 5), which was isolated as a stable dark powdery substance. The ^{1}H NMR spectrum of complex **6** contains the signals of allyl group.

Methallyltheobromine **1b** reacts with iodine differently: as a result of the reaction, 6-(iodomethyl)-1,4,6-trimethyl-9-oxo-3a,4,6,7,9,9a-hexahydro-1*H*-oxazolo[3,2-*a*]purinium triiodide powder was isolated. When reacting with sodium iodide in acetone, it was converted to 6-(iodomethyl)-1,4,6-trimethyl-9-oxo-3a,4,6,7,9,9a-hexahydro-1*H*-oxazolo[3,2-*a*]purinium iodide **7** (Scheme 7). In the ^{1}H NMR spectrum, the

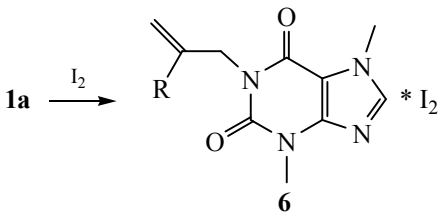
Scheme 3.



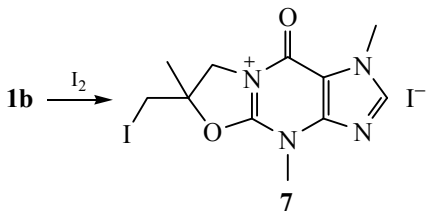
Scheme 4.



Scheme 5.



Scheme 6.



proton of imidazole ring appears at 8.75 ppm, which indicates the formation of a linear oxazolopurinium system.

In conclusion, bromine reacts with 1-allyltheobromine to form the adduct at the double bond. In the case of 1-methallyltheobromine, a mixture of oxazolopurines and 1-(2,3-dibromo-2-methylpropyl)theobromine was obtained. The reaction of 1-allyltheobromine with iodine leads to the formation of a complex, and methallyltheobromine reacts with iodine to furnish linear oxazolopurine.

EXPERIMENTAL

^{1}H NMR spectra (400 MHz) were registered on a Bruker AVANCE II instrument from DMSO-d_6 solutions relative to internal TMS. Mass spectrum was registered on a GCMS-QP2010 Ultra, Shimadzu gas chromatography mass spectrometer (EI, 70 eV).

1-Allyltheobromine (1a) was synthesized according to the procedure described in [5]. Yield 80%, white powder, mp 147–148°C (mp 142–143°C [2], 143°C [6]). Mass spectrum, *m/z* (I_{rel}, %): 220 (82.5) $[M]^+$, 219 (20.0) $[M - H]^+$, 205 (100) $[M - CH_3]^+$, 203 (20.0) $[M - OH]^+$, 191 (7.5), 175 (5.0), 165 (5.0), 150 (7.4), 138 (15.0), 137 (6.4) $[M - CH_2{=}CHCH_2NCO]^{\bullet+}$, 136 (12.5) $[M - CH_2{=}CHCH_2NCO - H]^+$, 109 (37.5) $[M - CH_2{=}CHCH_2NCO - CO]^+$, 82 (24.5), 70 (13.5), 67 (37.0), 56 (9.9), 55 (24.4), 42 (22.5), 40 (25).

1-Methallylteobromine (1b). To a solution of 360 mg (2 mmol) of theobromine in 10 mL of DMF was added 276 mg (2 mmol) of anhydrous potassium carbonate, and the mixture was heated on a water bath for 30 min. A solution of 0.19 mL (2 mmol) of methallyl chloride in 1 mL of DMF was added to the mixture. The resulting mixture was heated on a water bath for 5 h. The precipitate was filtered off, the filtrate was evaporated, the obtained residue was washed with water and dried. Yield 384 mg (82%), gray powder, mp 68–72°C. ^{1}H NMR spectrum, δ, ppm: 1.76 s (3H, CH_3), 3.39 s (3H, N^3CH_3), 3.94 s (3H, N^7CH_3), 4.39 s (2H, NCH_2), 4.59 s (1H, CH_2), 4.75 s (1H, CH_2), 7.88 s (1H, H^8). Found, %: C 56.42; H 5.99;N 23.90. $C_{11}H_{14}N_4O_2$. Calculated, %: C 56.40; H 6.02; N 23.92. *M* 234.25.

1-(2,3-Dibromopropyl)theobromine (2). To a solution of 0.052 mL (1 mmol) of bromine in 5 mL of chloroform was added 0.110 g (0.5 mmol) of 1-allyltheobromine. After 48 h the solvent was evaporated. Yield 0.137 g (72%), oil. ^{1}H NMR spectrum, δ, ppm: 3.41 s (3H, N^3CH_3), 3.89 s (3H, N^7CH_3), 3.95 m and 4.02 m (2H, CH_2Br), 4.44 m and 4.27 m (2H, NCH_2), 4.69 m (1H, CHBr), 8.07 s (1H, H^8). Found, %: C 31.57; H 3.17; N 14.77. $C_{10}H_{12}Br_2N_4O_2$. Calculated, %: C 31.60; H 3.18; N 14.74. *M* 380.04.

Reaction of 1-methallylthebromine with bromine. *a*. To a solution of 0.052 mL (1 mmol) of bromine in 5 mL of acetic acid was added 0.118 g (0.5 mmol) of

1-methallyltheobromine. After 48 h the precipitate was filtered off. The filtrate was evaporated, the oily residue is 1-(2,3-dibromo-2-methylpropyl)theobromine. The precipitate was treated with acetone and filtered to give a mixture of 0.069 g (yield 35%) of 6-(bromomethyl)-1,4,6-trimethyl-9-oxo-3a,4,6,7,9,9a-hexahydro-1*H*-oxazolo[3,2-*a*]purinium bromide and 8-(bromomethyl)-1,4,8-trimethyl-5-oxo-3a,4,5,7,8,9b-hexahydro-1*H*-oxazolo[2,3-*i*]purinium bromide in a ratio of 1.57 : 1.

b. To a solution of 0.052 mL (1 mmol) of bromine in 5 mL of dichloromethane was added 0.118 g (0.5 mmol) of 1-methallyltheobromine. After 48 h the formed precipitate was filtered off, dried, then treated with acetone and filtered to give a mixture of 0.138 g (70% yield) of 6-(bromomethyl)-1,4,6-trimethyl-9-oxo-3a,4,6,7,9,9a-hexahydro-1*H*-oxazolo[3,2-*a*]purinium bromide and 8-(bromomethyl)-1,4,8-trimethyl-5-oxo-3a,4,5,7,8,9b-hexahydro-1*H*-oxazolo[2,3-*i*]purinium bromide in a ratio of 1 : 0.95.

6-(Bromomethyl)-1,4,6-trimethyl-9-oxo-3a,4,6,7,9,9a-hexahydro-1*H*-oxazolo[3,2-*a*]purinium bromide (3). ^{1}H NMR spectrum, δ, ppm: 1.91 s (3H, N^6CH_3), 3.62 s (3H, N^4CH_3), 3.94 s (3H, N^1CH_3), 4.15 m and 4.22 m (2H, CH_2Br), 4.19 m (2H, NCH_2), 8.79 s (1H, H^2).

8-(Bromomethyl)-1,4,8-trimethyl-5-oxo-3a,4,5,7,8,9b-hexahydro-1*H*-oxazolo[2,3-*i*]purinium bromide (4). ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, N^8CH_3), 3.85 s (3H, N^4CH_3), 4.02 s (3H, N^1CH_3), 4.38 m and 4.45 m (2H, CH_2Br), 4.41 m (2H, NCH_2), 8.47 s (1H, H^2).

1-(2,3-Dibromo-2-methylpropyl)theobromine (5). Yield 0.077 g (39%, method *a*). ^{1}H NMR spectrum, δ, ppm: 1.21 s (3H, CH_3), 3.48 s (3H, N^3CH_3), 3.94 s (3H, N^7CH_3), 3.46 s (2H, CH_2Br), 4.13–4.15 m (2H, NCH_2), 7.94 s (1H, H^8). Found, %: C 33.51; H 3.59; N 14.19. $C_{11}H_{14}Br_2N_4O_2$. Calculated, %: C 33.53; H 3.58; N 14.22. *M* 394.06.

6-(Iodomethyl)-1,4,6-trimethyl-9-oxo-3a,4,6,7,9,9a-hexahydro-1*H*-oxazolo[3,2-*a*]purinium iodide (7). To a solution of 254 mg (1 mmol) of iodine in 5 mL of chloroform (acetic acid) was added 0.5 mmol of 1-methallyltheobromine. After 48 h the resulting dark brown precipitate of 6-(iodomethyl)-1,4,6-trimethyl-9-oxo-3a,4,6,7,9,9a-hexahydro-1*H*-oxazolo[3,2-*a*]purinium triiodide was filtered off, dried, then dissolved in acetone. To the solution was added NaI, and the resulting pale yellow precipitate was filtered off. Yield 0.146 g (60%), mp 97–98°C. ^{1}H NMR spectrum, δ, ppm: 1.96 s (3H, N^6CH_3), 3.65 s (3H, N^4CH_3), 3.95 s (3H, N^1CH_3), 3.40 m and 3.76 m (2H, NCH_2), 4.42 m (2H, CH_2Br), 8.75 s (1H, H^2).

FUNDING

This work was financially supported by the Government of the Russian Federation (Decree no. 211, March 16, 2013, agreement no. 02.A03.21.0011) and the Ministry of Education and Science of the Russian Federation as part of the governmental task (no. 4.9665.2017/8.9).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Zlatkov, A., Peikov, P., Rodriguez-Alvarez, J., Danchev, N., Nikolova, I., and Mitkov, J., *Eur. J. Med. Chem*., 2000, vol. 35, no. 10, p. 941. doi 10.1016/s0223-5234(00)01172-7
2. Hung-Kun, L. and Fen-Tair, L., *J. Chin. Chem. Soc*., 2012, vol. 59, no. 3, p. 394. doi 10.1002/jccs.201100565
3. USA Patent 94/00674, 1993.
4. Madyastha, K.M. and Sridhar, G.R., *J. Chem. Soc. Perkin Trans. 1*, 1999, no. 6, p. 677. doi 10.1039/a900089e
5. Lysakowska, M., Balzarini, J., and Piotrowska, D.G., *Arch. Pharm*., 2014, vol. 347, no. 5, p. 341. doi 10.1002/ardp.201300382
6. Daly, J.W., Padgett, W.L., and Shamim, M.T., *J. Med. Chem*., 1986, vol. 29, no. 7, p. 1305. doi 10.1021/jm00157a035
7. Ukrainets, I.V., Bereznyakova, N.L., Gorokhova, O.V., and Shishkina, S.V., *Chem. Heterocycl. Compd*., 2009, vol. 45, no. 10, p. 1241. doi 10.1007/s10593-010-0413-5