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Transformations of 2-Alkoxy-6-chloro- and 6-Alkoxy-2-chloro-7-methylpurines Under the Action of Methyl Iodide

by A. Kowalska and A. Maślankiewicz*

Department of Organic Chemistry, Silesian School of Medicine, Jagiellońska 4, 41-200 Sosnowiec, Poland

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2-Alkoxy-6-chloro-7-methylpurines **3** were prepared by 6-chloro-dealkoxylation of 2,6-dialkoxy-7-methylpurines **4**. Reactions of alkoxy-chloro-7-methylpurines **2** and **3** with methyl iodide led as N-9 methylation and as N-3 methylation to give *N*-methyl purinium salts **9** and **11** from purine **2** or **6** and **7** from purine **3**. The formation of purinium salts was accompanied by 6-iodo-dechlorination leading from **3** to 6-iodopurinium salt **5** and by alkyl iodide elimination leading to hypoxanthine **10**.

Key words: 7,9-dialkylpurinium salts, chloropurines, dialkoxypurines, *N*-alkylation of purines, oxopurines

Purinium salts are of great interest for functionalization of purines including Hilbert-Johnson reaction [1] and transglycosylation [2]. The latter could be applied to the preparation of anti-viral drugs *Acyclovir* and *Gancyclovir* [3]. There were also reports concerning biological activity of purinium salt against adenocarcinoma in mice [4], moderate anticytomegalovirus activity *in vitro* [4], and the effect on pig brain ATPase [5]. Some 2-R,R′,*N*-6-methoxy-7,9-dimethylpurinium salts (R = R′ = CH_3, R = H and R′ = CH_3, R = R′ = H), *i.e.* heteromines A, B, C as well as some 7,9-dimethylguaninium salts have been isolated from *Heterostemma browni* Hay (Asclepiadaceae) [6,7]. Heteromines are cytotoxic to several cancer lines [7].

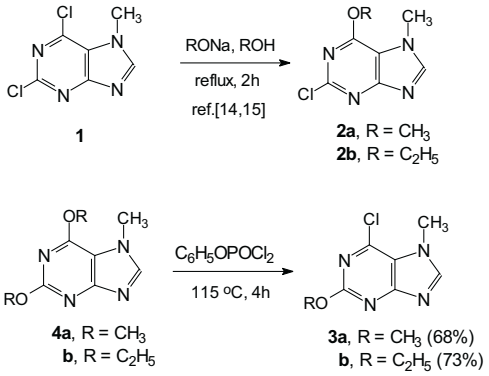
N-Alkylpurinium salts are most often obtained by the alkylation of purines [8–10]. Treatment of adenine bearing five chemically non-equivalent nitrogen atoms with alkylating agent may lead to five types of ammonium salts [4]. However, in the case of purine bases, the reactivity of nitrogen atoms toward alkylating agent usually falls in the following order: N-7 ~N-9 > N-3 > N-1 [11,12]. In the previous paper we described the behaviour of 2,6-dialkoxy-7-methylpurines **4** toward alkylating agents [13]. This paper describes studies of 2-alkoxy-6-chloro- and 6-alkoxy-2-chloro -7-methylpurines **2** and **3** reactions with methyl iodide. The chloropurinium salts were expected to offer greater possibilities of functionalizing purines than the alkoxypurinium salts prepared previously [13].

* Author for correspondence.

RESULTS AND DISCUSSION

2-Chloro-6-alkoxy-methylpurines **2** can be easily prepared according to a described procedure [14,15] of 6-alkoxy-dechlorination of 2,6-dichloro-7-methylpurine **1** with appropriate sodium alkoxide. In order to prepare isomeric 6-chloro-2-alkoxy-7-methylpurines **3**, 2,6-dialkoxy-7-methylpurines **4** were treated at 20–120°C with phosphorus oxychloride/DMF system. The reaction also took place at the 6 position to give 6-chloropurines **3** with 8–14% yield. Significant improvement (up to 73%) in the transformation of **4** to **3** was achieved by using phenyl-dichlorophosphate as a chlorination agent.

Scheme 1

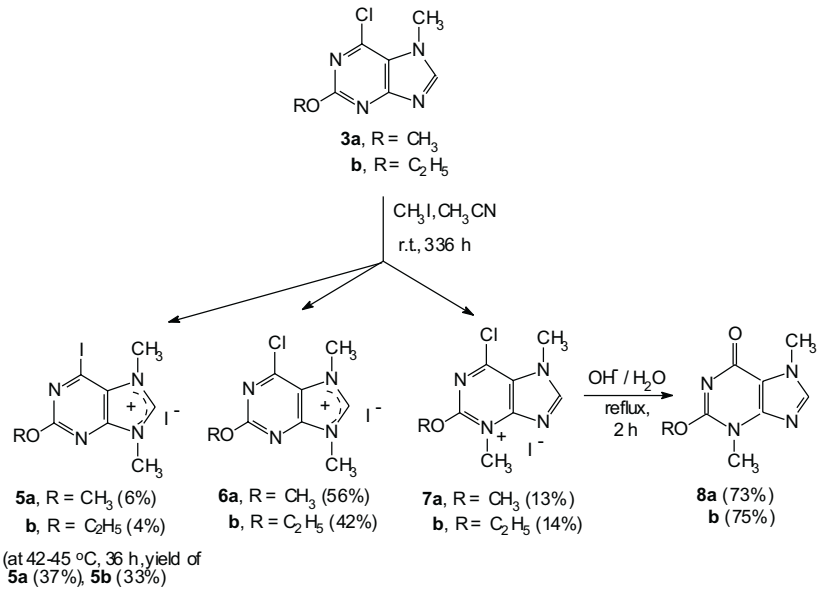


The alkylation of **4** with alkyl iodides takes place at N-9 and at N-3 [13]. From stereoelectronic reason, including X-ray study of **4a** [16], compound **3** seems to be more similar to **4** than compound **2**. The reaction of methyl iodide with **3** under experimental conditions (acetonitrile, r.t., 336 h, precipitation with ether) elaborated previously for compounds **4** [13] (Scheme 2) gave a mixture of salts **6** and **5** (N-9 methylation products) and salt **7** (N-3 methylation product) separated by column chromatography. At a higher temperature (42–45°C) substantial amounts of 6-iodopurinium salts **5** (up to 37%) were obtained. The crucial data for the structural assignment of salts **6** and **5** come from ^{1}H NMR spectra. As compared to the starting alkoxy-7-methylpurines **2**, the presence of new *N*-methyl group was observed Also, as in the case of 7,9-dialkylpurinium salts [13] the singlet of H-8 proton in purines **2** and **3** was shifted by $\Delta\delta$ = 1.73–3.22 ppm up to the value of δ = 9.77–11.20 ppm in 7,9-dimethylpurinium salts **9**, **11** and **6**, **5**. The same tendency was observed in ^{1}H NMR spectra of the inosine, guanosine, xanthosine and hypoxanthine derivatives compared with data for their 7,9-dialkylpurinium salts or betaines [17].

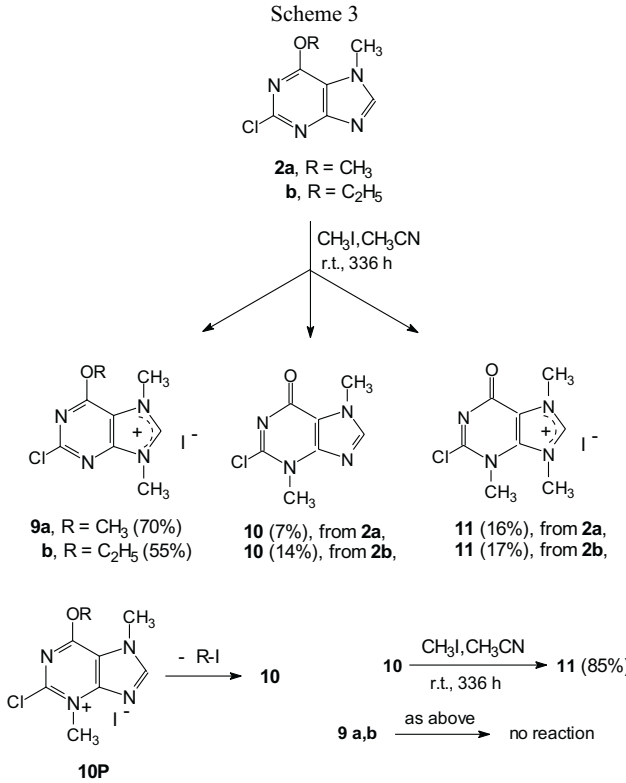
The alkylation of α- and γ-chloroazines with methyl iodide proceeded often with an exchange of chloro-substituent for iodo-one and led to the α- or γ-iodo-*N*-methylazinium salts [18]. In spite of this, potentiometric titration of aqueous solution of **6** and **7** with silver nitrate [19] indicates the iodide nature of chloropurinium salts **6** and **7**. The structure assignment of **7** as N-3 methylation product of **3** was supported by hydrolysis of **7** to the known 2-alkoxytheobromines **8** [20–21]. The methylation of

2 was performed analogously as that of **3**. It led to the mixture of purinium salts **9** and **11** as well as to 2-chloro-theobromine **10** (see Scheme 3). The formation of **10** may be

Scheme 2



Scheme 3



rationalized in terms of elimination of alkyl iodide from the initially formed N-3 purinium salt **10P** and formation of hypoxanthine **10**, as this type of transformation was usually observed in the course of Hilbert-Johnson reaction [1]. In order to learn the reaction sequence leading to **11** we studied the methylation of **9** and **10**. Whereas no reaction of **9** with methyl iodide was observed, the reaction of **10** afforded **11** (85%). It means that compound **11** was formed following the reaction sequence: **2** → [**10P**] → **10** → **11**. Thus, the ratio of primarily formed N-9 : N-3 methylation products could be deduced from the ratio of **9** to (the sum of **10** and **11**).

CONCLUSIONS

From four nitrogen atoms in purines **2** and **3** only N-9 and N-3 ones act as nucleophiles in the reaction with methyl iodide forming N-9 and N-3 methylpurinium salts, respectively. Taking into account the ratios of N-9 to N-3 methylation products for purines **2a**,**b** (3.0 or 1.8) *versus* those for purines **3a**,**b** (4.8 or 3.3) one can conclude that the orientation in N-9 / N-3 methylation reaction is affected by higher sterical interaction of bulkier 2-alkoxy group in **3** than 2-chloro one in purine **2**.

EXPERIMENTAL

Melting points were determined in open capillary tubes using Boetius melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker MSL 300 and a UNITY plus-300 spectrometers at 300 MHz using deuteriochloroform or dimethylsulfoxide-d_6 with tetramethylsilane as the internal standard. EI MS spectra were run on a LKB 9000S spectrometer at 15 eV. FAB MS spectra were recorded on a Finnigan MAT 95 spectrometer (Cs^+, 13 keV, 3-nitrobenzyl alcohol as a matrix). Thin layer chromatography was performed on silica gel 60_{254}F plates (Merck) using a solution of chloroform - methanol (9:1) as an eluent.

2-Alkoxy-6-chloro-7-methylpurine (3): A mixture of 2,6-dialkoxy-7-methylpurine **4** (10 mmol) and phenyl-dichlorophosphate (15 ccm) was stirred for 4 h at 115°C (oil bath). It was then cooled to r.t. and cautiously poured on 120 g of ice and neutralized with solid potassium carbonate at 0–5°C up to pH ~7. The mixture was extracted with chloroform (3 × 15 ccm). The extracts were combined and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue was recrystallized from ethanol to give 2-alkoxy-6-chloro-7-methylpurine **3**.

6-Chloro-2-methoxy-7-methylpurine (3a): M.p. 156–8°C (yield 68%). ^{1}H NMR ($CDCl_3$), δ: 4.06 (s, 3H, CH_3-N), 4.15 (s, 3H, CH_3-O), 8.04 (s, 1H, H-8). EI MS (70 eV), m/z = 198 (M^+, 100). *Anal.* Calcd. for $C_7H_7ClN_4O$ (198.61): C 42.33 , H 3.55, Cl 17.85 , N 28.21. Found: C 42.51 , H 3.70, Cl 17.55 , N 28.08.

6-Chloro-2-ethoxy-7-methylpurine (3b): M.p.179–181°C (yield 73%). ^{1}H NMR ($CDCl_3$), δ: 1.45 (t, 3H, *J* = 7.1 Hz, $C\underline{H}_3CH_2$), 4.09 (s, 3H, CH_3-N), 4.51 (q, 2H, *J* = 7.1 Hz, $CH_3C\underline{H}_2$), 8.05 (s, 1H, H-8). EI MS (70 eV), m/z = 212 (M^+, 83), 184 (M- C_2H_4, 100). *Anal.* Calcd. for $C_8H_9ClN_4O$ (212.63): C 45.19 , H 4.27, Cl 16.67, N 26.35. Found: C 44.98 , H 4.45, Cl 16.90, N 26.06.

The reaction of methyl iodide with alkoxy-chloro-7-methylpurines (2 or 3). A mixture of alkoxy-chloro-purine **2** or **3** (10 mmol), acetonitrile (50 ccm) and methyl iodide (1.24 ccm, 20 mmol) was stirred at r.t. for 14 days (or at 42–45°C for 36 h). The mixture was cooled to r.t., diluted with 150 ccm of anhydrous ether and left in refigerator at 4°C over night. The solid was filtered off, dissolved in minimal volume of anhydrous methanol (8–10 ccm) and precipitated again with anhydrous ether (25–30 ccm). The product mixture was filtered off and dried under vacuum. It was separated by column chromatography on silica gel (100–200 mesh) using a mixture of chloroform/ethanol 99:1, v/v to give salts **9** and **11** from **2** and salts **6**, **7** and **5** from **3**. For analytical purposes the salts were recrystallized from anhydrous methanol.

The first filtrate was concentrated to dryness, the residue was extracted with hot chloroform. The extract was dried over anhydrous sodium sulfate and the solvent was removed to give 2-chloro-3,7-dimethylhypoxanthine **10**. It was recrystallized from water to give material with m.p. 252–4°C, ref. [20] m.p. 251–3°C.

6-Iodo-2-methoxy-7,9-dimethylpurinium iodide (5a): M.p.190–193°C (yield 37%). ^{1}H NMR ($CDCl_3$), δ: 4.17 (s, 3H, CH_3-N-7), 4.45 (s, 3H, CH_3-N-9), 4.20 (s, 3H, CH_3-O), 11.20 (s, 1H, H-8). MS-FAB (m/z): 305 (M^+,100). *Anal.* Calcd. for $C_8H_{10}I_2N_4O$ (432.00): C 22.24, H 2.33, I 58.75, N 12.97. Found: C 21.98, H 2.42, N 12.86.

6-Iodo-2-ethoxy-7,9-dimethylpurinium iodide (5b): M.p. 242–245°C (yield 33%). ^{1}H NMR ($CDCl_3$): δ = 1.49 (t, 3H, J = 7.1 Hz, $C\underline{H}_3CH_2$), 4.46 (q, 2H, J = 7.1 Hz, $CH_3C\underline{H}_2$), 4.18 (s, 3H, CH_3-N-7), 4.43 (s, 3H, CH_3-N-9), 11.02 (s, 1H, H-8). MS-FAB, (m/z): 319 (M^+, 76), 154 (100). *Anal. Cald.* $C_9H_{12}I_2N_4O$ (446.02): C 24.24, H 2.71, I 56.90, N 12.56; *Found* C 24.04, H 2.80, N 12.29.

6-Chloro-2-methoxy-7,9-dimethylpurinium iodide (6a): M.p. 124–126°C (yield 56%). ^{1}H NMR ($CDCl_3$), δ: 4.14 (s, 3H, CH_3-N-7), 4.44 (s, 3H, CH_3-N-9), 4.18 (s, 3H, CH_3-O), 9.77 (s, 1H, H-8). MS-FAB (m/z): 213 (M^+,100). *Anal.* Calcd. for $C_8H_{10}ClIN_4O$ (340.55): C 28.22, H 2.96, Cl 10.41, I 37.26, N 16.45. Found: C 28.34, H 3.06, N 16.53.

6-Chloro-2-ethoxy-7,9-dimethylpurinium iodide (6b): M.p. 176–178°C (yield 42%). ^{1}H NMR ($CDCl_3$), δ: 1.47 (t, 3H, *J* = 7.1, $C\underline{H}_3CH_2$), 4.56 (q, 2H, *J* = 7.1, $CH_3C\underline{H}_2$), 4.16 (s, 3H, CH_3-N-7), 4.42 (s, 3H, CH_3-N-9), 9.81 (s, 1H, H-8). MS-FAB, (m/z): 227 (M^+, 100). *Anal.* Calcd. for $C_9H_{12}ClIN_4O$ (354.57): C 30.49, H 3.41, Cl 10.00, I 35.79, N 15.80. Found: C 30.80, H 3.53, N 15.61.

6-Chloro-2-methoxy-3,9-dimethylpurinium iodide (7a): M.p. 171–173°C (yield 13%). ^{1}H NMR ($CDCl_3$), δ: 3.97 (s, 3H, CH_3-N-7), 3.60 (s, 3H, CH_3-N-3), 4.06 (s, 3H, CH_3-O), 7.99 (s, 1H, H-8). MS-FAB (m/z): 213 (M^+,100). *Anal.* Calcd. for $C_8H_{10}ClIN_4O$ (340.55): C 28.22, H 2.96, Cl 10.41, I 37.26, N 16.45. Found: C 28.21, H 2.96, N 16.19.

6-Chloro-2-ethoxy-3,9-dimethylpurinium iodide (7b): M.p. 216–218°C (yield 14%). ^{1}H NMR ($CDCl_3$), δ: 1.51 (t, 3H, *J* = 7.1, $C\underline{H}_3CH_2$), 4.60 (q, 2H, *J* = 7.1, $CH_3C\underline{H}_2$), 3.97 (s, 3H, CH_3-N-7), 3.60 (s, 3H, CH_3-N-3), 8.00 (s, 1H, H-8). MS-FAB, (m/z): 227 (M^+, 75), 154 (100). *Anal.* Calcd. for $C_9H_{12}ClIN_4O$ (354.57): C 30.49, H 3.41, Cl 10.00, I 35.79, N 15.80. Found: C 30.26, H 3.32, N 15.99.

2-Chloro-6-methoxy-7,9-dimethylpurinium iodide (9a): M.p. 216–217°C (yield 70%). ^{1}H NMR ($CDCl_3$), δ: 4.19 (s, 3H, CH_3-N-7), 4.37 (s, 3H, CH_3-N-9), 4.29 (s, 3H, CH_3-O), 11.17 (s, 1H, H-8). MS-FAB, (m/z): 213 (M^+, 100). *Anal.* Calcd. for $C_8H_{10}ClIN_4O$ (340.55): C 28.22 , H 2.96, Cl 10.41, I 37.26, N 16.45. Found: C 28.26, H 3.00, N 16.21.

2-Chloro-6-ethoxy-7,9-dimethylpurinium iodide (9b): M.p. 103–105°C (yield 55%). ^{1}H NMR ($CDCl_3$), δ: 1.53 (t, 3H, *J* = 7.1, $C\underline{H}_3CH_2$), 4.74 (q, 2H, *J* = 7.1, $CH_3C\underline{H}_2$), 4.18 (s, 3H, CH_3-N-7), 4.36 (s, 3H, CH_3-N-9), 11.02 (s, 1H, H-8). MS-FAB, (m/z): 227 (M^+, 100). *Anal.* Calcd. for $C_9H_{12}ClIN_4O$ (354.57) : C 30.49, H 3.41, Cl 10.00, I 35.79, N 15.80. Found: C 29.92, H 3.31, N 15.48.

2-Chloro-3,7,9-trimethyl-6-oxo-3,6-dihydropurinium iodide (11): M.p. 130–132°C (yield 16–17%). ^{1}H NMR ($CDCl_3$), δ: 4.12 (s, 3H, CH_3-N-7), 4.35 (s, 3H, CH_3-N-9), 3.79 (s, 3H, CH_3-N-3), 10.82 (s, 1H, H-8). FAB MS, m/z = 213 (M^+, 100). *Anal.* Calcd. for $C_8H_{10}ClIN_4O$ (340.55): C 28.22, H 2.96, Cl 10.41, I 37.26, N 16.45. Found: C 28.08, H 2.95, N 16.28.

Hydrolysis of purinium iodide (7). A solution of purinium iodide **7** (2 mmol) in 2 ccm of 1 N aqueous sodium hydroxide was boiled for 2 h. The mixture was cooled down to r.t. and neutralized with acetic acid. The mixture was extracted with chloroform (3 × 10 ccm). The extracts were combined and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue was recrystallized from ethyl acetate to give 2-alkoxy-3,7-dimethyl-6-oxo-3,6-dihydropurine **8**, (yield 73–75%). M.p. of **8a** = 179–180°C, ref. [20] m.p. 180°C. M.p. of **8b** = 148–150°C, ref. [21] m.p. 149–151°C.

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