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REGIOSELECTIVE *N*- AND *O*-ALKYLATION OF 3*H*-[1,2,3]TRIAZOLO-[4,5-*d*]PYRIMIDINE-5,7(4*H*,6*H*)-DIONES (8-AZAXANTHINES) AND TRANSFORMATION OF 3-ALKYL DERIVATIVES INTO 1-ALKYL ISOMERS

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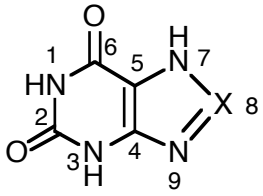
Abstract – The alkylation on the pyrimidine ring of 3-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**1**) with an equimolecular amount of alkylating agent in the presence of anhydrous potassium carbonate in aprotic solvents under heating took place only at the 4-position. The similar alkylation on the triazole ring of 6-methyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**4**) with an equivalent alkylating reagent happened simultaneously at the 1- and 2-positions with the priority at the 2-position. On the other hand, the alkylation of 3,6-disubstituted derivatives (**12a-d**) at room temperature led to the 5-*O*-alkylation (**14a-e**) accompanied with the 4-*N*-alkylation (**3a**, **13a-d**), but at high temperature only the 4-*N*-alkylation occurred. The 3,4,6-tri-substituted derivatives (**3a**, **13d**) underwent transformation with excess alkylating agents at high temperature leading to the formation of 1,4,6-tri-substituted derivatives (**7**, **15**) with elimination of the 3-substituent in the same manner as xanthine.

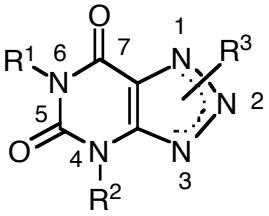
Naturally occurring, modified, and substituted purines and xanthines (I) have been synthesized and subjected to close scrutiny by scientists seeking to establish structure-biological activity relashionships. Some of these are found to possess wide biological activities such as antiviral[1-6] and anti-tumor activities[3, 4, 6-10] as well as xanthine oxidase inhibitory activities.[11, 12] Structural alternations of xanthine have

resulted in several potent antagonists in biological systems,[13-18] *e.g.* caffeine and theophylline exhibit a variety of pharmacological actions[18] including antiasthmatic, diuretic, respiratory stimulant, central stimulant, cardiac stimulant, and analgesic adjuvant activities. A variety of analogues of xanthine with different substituents at the different positions have been assessed for potency and selectivity as antagonists at adenosine receptors.[13-18] Hence, the alkylation of xanthine has been studied intensively,[14, 19-23] but the chemistry of 8-azaxanthine (II) has remained largely unexplored area in spite of their biological significance.[24-26]

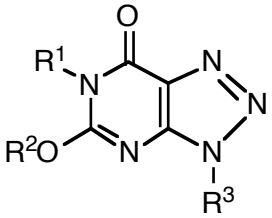
The limited but encouraging success of clinical treatment[27-31] for neoplastic diseases in man or other animals by certain purine derivatives and related compounds has prompted us to synthesize purine derivatives and their analogues and to study their biological activity. As part of our program directed toward evaluation of novel xanthine oxidase inhibitory activities,[32-35] the syntheses of modified purines were of interest. We communicate here the reliable synthesis of substituted 1*H*-, 2*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (8-azaxanthines) (III) and the transformation of the 3-alkyl derivatives into 1-alkyl isomers, and the first study of their regioselective *O*- (IV) and *N*-alkylation (III) in comparison with xanthine in view of evaluating the positional basis for biological activity.



X = CH: **xanthine (I)**
X = N: **8-azaxanthine (II)**

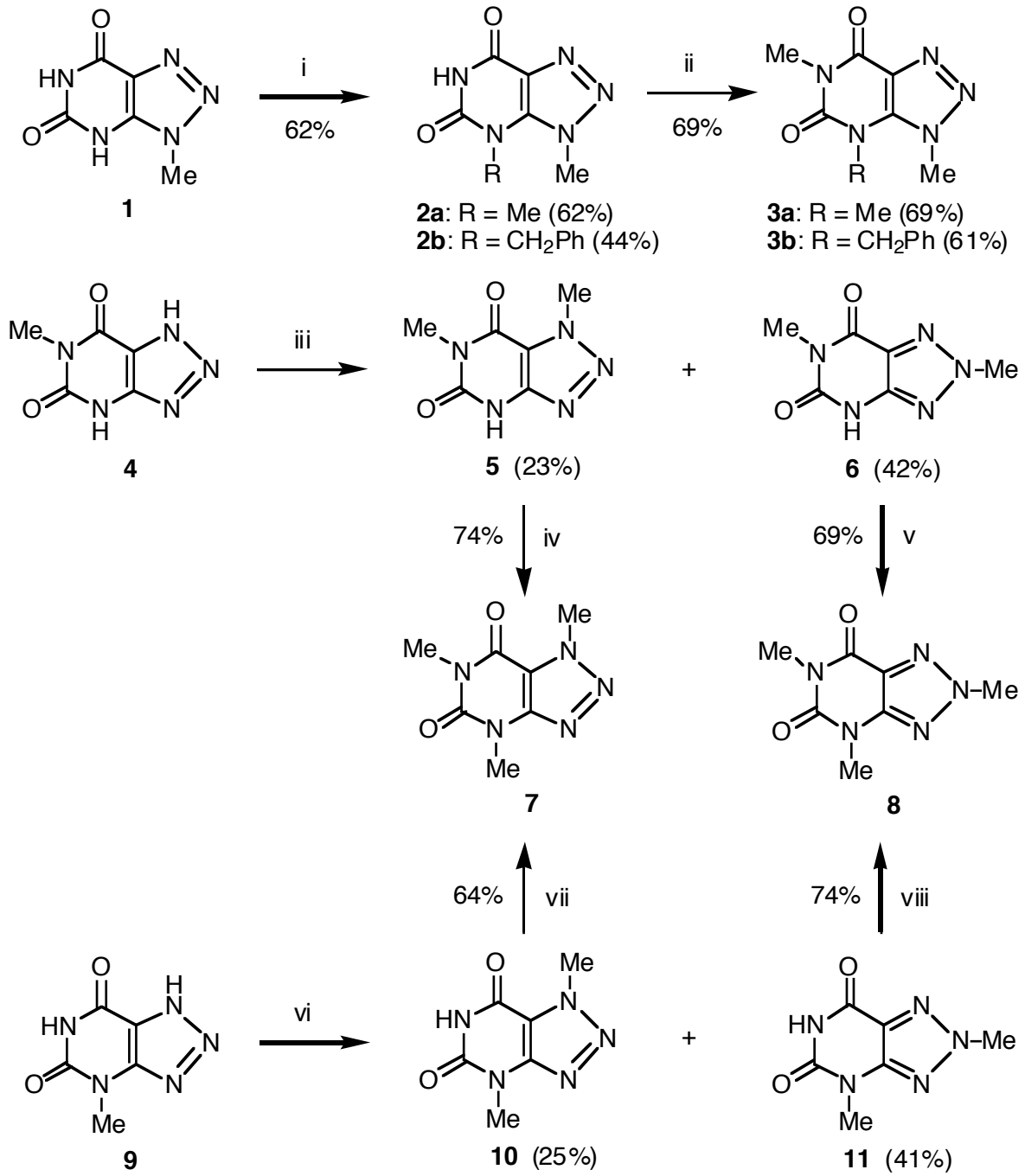


(III)



(IV)

Since the convenient synthesis of 8-azaxanthines reported by Pfleiderer, *et al.*[36] in 1965, those many derivatives have been prepared. However, the regioselective alkylation on 8-azaxanthine has not been clarified completely yet. We revealed now not only the regioselective *N*-alkylation but also new *O*-alkylation on 8-azaxanthines. The desired 1*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**1**, **4**, **9**, and **12**) were synthesized according to the previously outlined procedure.[36] Namely, cyclization of the appropriate 5,6-diaminouracils leading to the formation of substituted 8-azaxanthines (**1**, **4**, **9**, and **12**) was accomplished by treating with nitrous acid at room temperature in good yield. When 3-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**1**) was treated with an equivalent methyl iodide or benzyl bromide in the presence of anhydrous potassium carbonate in dry *N*,*N*-dimethylformamide at boiling temperature afforded only the 3,4-dialkyl derivatives (**2a**; 62% yield) and

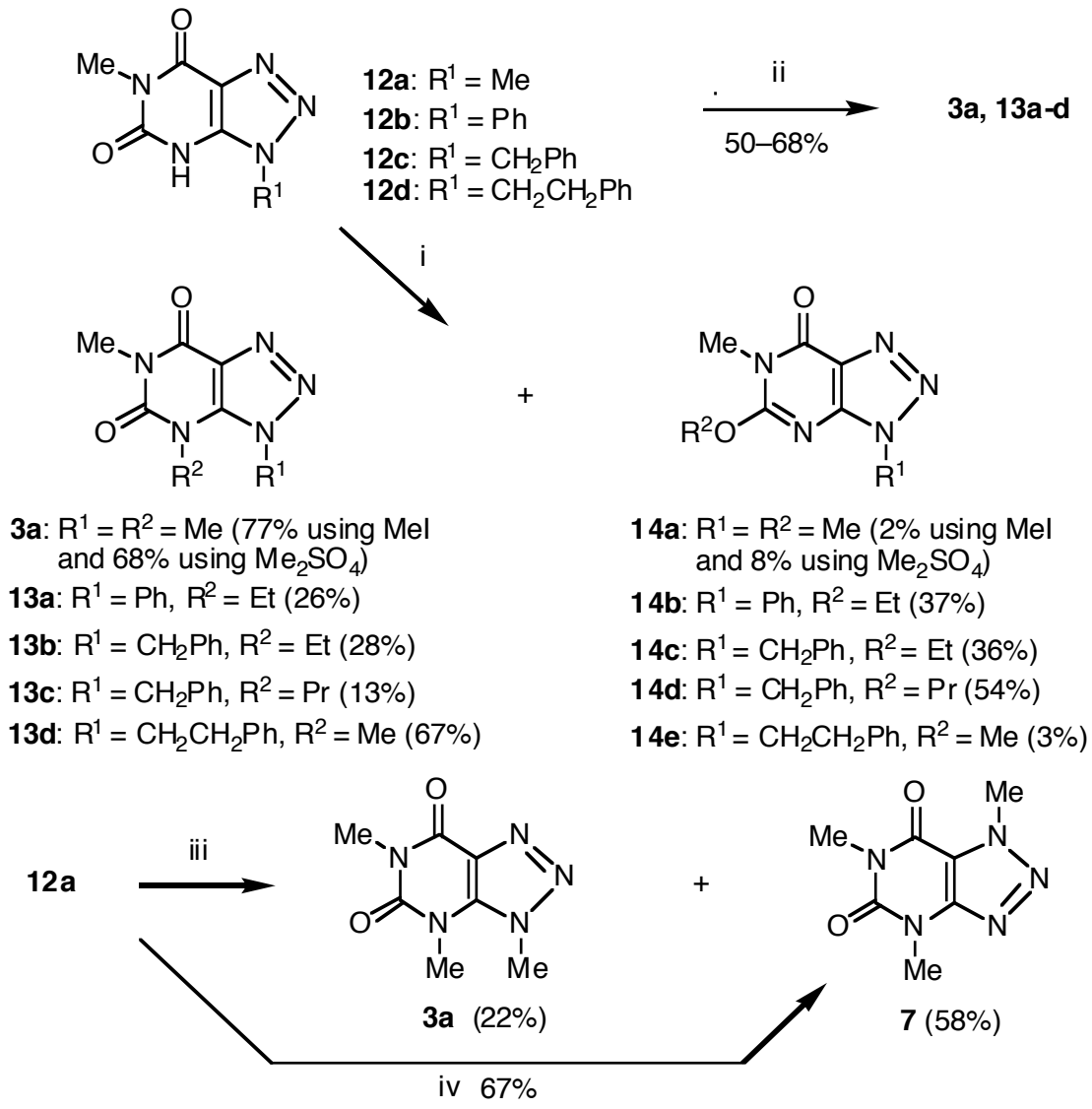


Scheme 1 *Reagents and conditions*: i, MeI or $PhCH_2Br$ (1equiv.), K_2CO_3, DMF, reflux; ii, MeI, K_2CO_3, DMF, reflux; iii, MeI (1equiv.), K_2CO_3, DMF, reflux; iv, MeI, K_2CO_3, DMF, rt; v, MeI, K_2CO_3, DMF, rt; vi, MeI (1equiv.), K_2CO_3, DMF, reflux; vii, MeI, K_2CO_3, DMF, reflux; viii, MeI, K_2CO_3, DMF, reflux.

(**2b**; 44% yield; mp 257–259 °C), respectively (Scheme 1). The alkylation of the 3-methyl derivative (**1**) took place not at the 6-position but at the 4-position in spite of steric repulsion between the substituents at the 3-position and the 4-position. The ^{1}H-NMR spectrum of **2a** showed a singlet signal at δ 3.60 assigned to methyl protons of the 4-position, which was quite similar to other 4-*N*-methylated derivatives (δ 3.3–3.8). Hence, it is obvious that the electrophilic substitution reaction on the pyrimidine ring of

[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones happens more preferentially at the 4-position than the 6-position. Similarly the methylation of 6-methyl derivative (**4**) with an equimolecular methyl iodide in *N*,*N*-dimethylformamide at boiling temperature resulted in the formation of two regioisomers of 1,6-dimethyl-1*H*- (**5**; 23% yield,) and 2,6-dimethyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**6**; 42% yield). The same methylation of 4-methyl derivative (**9**) also led to two regioisomers of 1,4-dimethyl-1*H*- (**10**; 25% yield) and 2,4-dimethyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**11**; 41% yield). Therefore, it is clear that the methylation of 8-azaxanthine with an equivalent reagent takes place not on the pyrimidine ring but only on the triazole ring. Moreover, the alkylation on the triazole ring always took place simultaneously at the 1- and 2-positions without at the 3-position and the alkylation at the 2-position got priority over at the 1-position. ^{1}H-NMR spectra of the methylated products provided a sufficient evidence for methylation on the triazole ring. That is, the chemical shifts for all *N*-C*H*$_3$ protons attached to the triazole ring usually appear at δ 4.0–4.4, whereas for *N*-C*H*$_3$ protons attached to the pyrimidine ring these appear at δ 3.2–3.8. We observed the chemical shift in the former region (δ 4.0–4.3) for the newly appeared *N*-C*H*$_3$ protons attributable to a methyl group on the triazole ring. The di-*N*-alkyl derivatives (**2a**,**b**, **5**, **6**, **10**, and **11**) were converted smoothly into the corresponding tri-*N*-alkyl derivatives (**3a**,**b**, **7**, and **8**) with appropriate alkyl halides in *N*,*N*-dimethylformamide at room temperature or at reflux temperature. All compounds[37] except for **2b** were identical to the authentic samples[36] prepared by another method.

A superior and rather novel alkylation on 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones was accomplished in simple way, which led to the 5-*O*-alkylation along with 4-*N*-alkylation (Scheme 2). The *O*-alkylation of xanthines and 8-azaxanthines was not claimed previously by anyone. Thus treatment of 3,6-disubstituted derivatives (**12a**-**d**) with excess an appropriate alkyl halide or dimethyl sulfate in the presence of potassium carbonate in *N*,*N*-dimethylformamide at room temperature gave the corresponding mixture of the 4-*N*-alkylated (**3a**, **13a-d**) and 5-*O*-alkylated isomers (**14a-e**) (i). The ratio of yields between these two regioisomers was highly affected by size of both the alkylating agents and the 3-substituents. The 5-*O*-alkylation took place in preference to the 4-*N*-alkylation due to the steric repulsion between the bulkyer alkylating agents and 3-substituents, and the opposite result was achieved in the less steric repulsion. For example, when 3,6-dimethyl derivative (**12a**) was treated with methyl iodide at room temperature, the *O*-methylation (**14a**)[38] of 2% took place with 77% *N*-methylation (**3a**), whereas the same methylation with dimethyl sulfate yielded the *O*-methylated compound and *N*-methylated cpmpound in 8% and 68%, respectively. The ethylation of 6-methyl-3-phenyl derivative (**12b**) with ethyl iodide also contributed clarification of the more steric effect giving the *O*-ethyl derivative (**14b**) and *N*-ethyl isomer (**13a**) in 37% and 26% yield, respectively. The effect of greatest steric repulsion in the propylation of 3-benzyl-6-methyl derivative (**12c**), which afforded a mixture of the



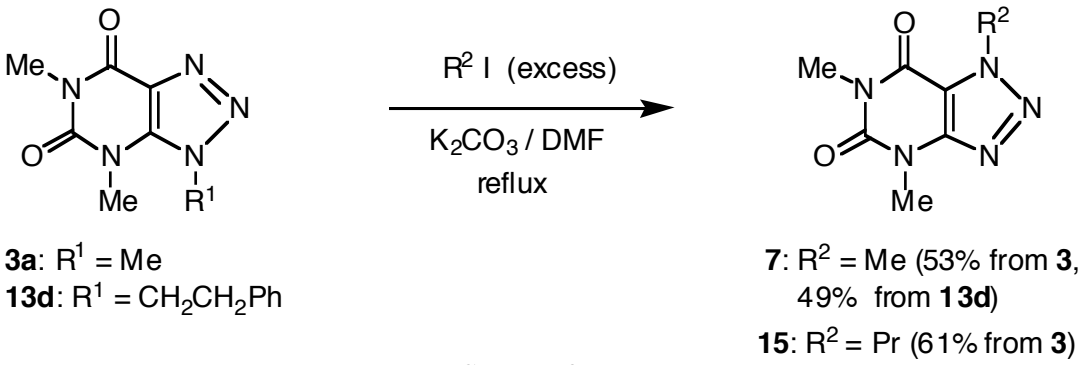
Scheme 2 *Reagents and conditions*: i, R^2I or $(R^2O)_2SO_2$, K_2CO_3, DMF, rt; ii, R^2I (1equiv.), K_2CO_3, DMF, reflux; iii, MeI (4 equiv.), K_2CO_3, DMF, reflux; iv, MeI (excess, dropwise), K_2CO_3, DMF, reflux.

O-propyl derivative (**14d**, 54% yield) and *N*-propyl isomer (**13c**, 13% yield), was observed. In contrast to the room temperature, at heating temperature with an equivalent alkyl halide only the 4-*N*-alkylation happened, *e.g*. the compounds (**12a-d**) gave the corresponding products (**3a**, **13a-d**) in 50–68% yields (ii). However, in the case of the reaction of **12a** with excess alkyl halide at heating under reflux, the transformation of alkyl group at the 3-position into the 1-position took place principally in single step. For example, heating compound (**12a**) with four equivalent methyl iodide in *N*,*N*-dimethylformamide at boiling temperature afforded a mixture of compound (**3a**; 22% yield) and compound (**7**; 58% yield) (iii). The same reaction with more excess methyl iodide (*ca*. 10 eq, added dropwise) at boiling temperature gave only the compound (**7**) in 67% yield (iv). The formation of only the 4-*N*-alkylated products (**3a**, **13a-d**) with an equivalent alkylating agent at high temperature can be explained by the following fact. That is to say, the adequate energy is supplied to overcome the steric repulsion to afford only the

comparatively more stable *N*-alkylated products. All new compounds (**12b**,**d**, **13a-d**, and **14b-e**) exhibited satisfactory elemental combustion analyses and spectral data consistent with structures indicated. The IR,[39] ^{1}H-NMR,[40] ^{13}C-NMR[41] and UV[42] spectra of the *O*-alkyl and *N*-alkyl isomers provided clear evidence for discrimination and identification of these products. Usually the IR spectra for 8-azaxanthines show two maximum absorption bands in the regions of 1660–1700 and 1715–1750 cm^{-1} due to the 5-CO and 7-CO groups, respectively. In the case of the *O*-alkylated derivatives, the absorption bands based on the 5-CO in the region of 1660–1700 cm^{-1} disappeared. This clearly indicated the disappearance of the 5-oxo group due to the formation of 5-*O*-alkyl derivatives. Moreover, the ^{1}H-NMR spectra displayed significant evidence showing the chemical shift for 5-*O*-C*H* protons (δ 4.04–4.61 for compounds **14a-e**) in the more down field than that of 4-*N*-C*H* protons (δ 3.41–3.98 for compounds **3a**, **13a-d**) due to the inductive effect. It is also noteworthy that the chemical shift for the methyl/methylene group attached to the 3-position of 4-*N*-alkylated products appeared in the more down field as compared with the compound having no substituent at the 4-position, *e.g.* δ 4.35 (3-CH_3 for compound **3a**) and δ 4.82–5.81 (3-CH_2 for compound **13b-d**), due to the steric repulsion with the 4-substituent. On the contrary, these values at the 3-position for the 5-*O*-alkylated products appeared in the upper field of δ 4.14 (3-CH_3 for compound **14a**) and δ 4.67–5.59 (3-CH_2 for compound **14c-e**), because the 5-*O*-alkyl group and 3-substitent are too far away to cause interaction. The UV spectra of the 3,4,6-trisubstituted derivatives (**3a**, **13a-d**) showed two maximum absorption bands at 240–243 and 256–257 nm, whereas the *O*-alkylated derivatives (**14a-e**) exhibited only the one band at 250–263 nm. We measured the ^{13}C NMR spectra of compounds (**3a**, **7**, **8** and **14a**). Chemical shift assigned to the carbon of the methyl group attached to the oxygen was appeared in the more down field (δ 56.63 for compound **14a**) than that of the methyl group (δ 28.21–42.98 for compounds **3a**, **7**, **8**) attached to the nitrogen due to the inductive effect. Thus, by comparison of several spectral data we distinguished and established the 5-*O*-alkylation along with the 4-*N*-alkylation for 8-azaxanthines.

We mentioned in the above paragraph that the methylation of 3,6-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**12a**) with excess methyl iodide at heating temperature involved some transformation of the 3-methyl derivative (**3a**) into the 1-methyl isomer (**7**) (iii and iv). Therefore, it should be noted that the alkylation demeanour of xanthine and 8-azaxanthine has some similarities. Usually the alkylation[19-23] on the imidazole ring of xanthine takes place at the 7-postion, but not at the 9-position. Beside, in 1976 Yoneda and Nagamatsu[19] were reported the first transformation of 9-substituted xanthines into the 7-substituted xanthines with excess of alkylating agents in aprotic solvent under heating *via* the formation of quaternary xanthinium derivatives alkylated at the 7-position and 9-position followed by elimination of the 9-substituent. Herein we also successfully performed the similar transformation of 3-alkyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (8-azaxanthines) into

their 1-alkyl derivatives as shown in Scheme 3. For example, heating the 3,4,6-trimethyl derivative (**3a**) with excess methyl iodide and propyl iodide in the presence of potassium carbonate in *N*,*N*-dimethylformamide at boiling temperature resulted in the formation of the 1,4,6-trimethyl (**7**) and 4,6-dimethyl-1-propyl derivative (**15**) in 53% and 61% yield, respectively, with the elimination of the 3-methyl group. Similarly, compound (**13d**) with excess methyl iodide afforded the 1,4,6-trimethyl (**7**) in 49% yield with loss of the phenethyl group at the 3-position. On heating of the 3,4,6-trialkyl derivative (**3a**) itself without alkyl halide in *N*,*N*-dimethylformamide, no corresponding transformation was observed. Therefore, a simple thermal transformation was excluded. This necessity of extra alkylating agent suggests that the transformation is accompanied by alkylation at the 1-position of the 3-alkylated triazole moiety, formation of the quaternary salt, and elimination of alkyl group at the 3-position like xanthine to afford the corresponding 1-alkylated derivatives.



3a: R^1 = Me
13d: R^1 = CH_2CH_2Ph

7: R^2 = Me (53% from **3**, 49% from **13d**)
15: R^2 = Pr (61% from **3**)

Scheme 3

Thus, this can be concluded that the direction of the electrophilic substitution toward 1*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (8-azaxanthines) suggests an important information on the electronic and inductive effects and steric repulsion of the alkyl groups at various positions. The triazole ring contains a single 'tautomeric' hydrogen atom and the alkylation in aprotic solvents suggests that the proton locates not as the 3-*N*H but as the 1-*N*H and 2-*N*H tautomers. Beside, the 4-*N*H proton also remains as the 4-*N*H and 5-*O*H tautomers. The transformation of the 3-alkylated derivatives into the 1-alkylted isomers is facile like xanthine with excess alkyl halide under heating conditions. An order can be made for alkylation at different positions according to the priority as follows: *N*2 > *N*1 > *N*4 > *N*6. Since xanthine and 8-azaxanthine have a great deal of coincidence in structure as well as affinity toward electrophile, so this can be expected that the positional alternation of 8-azaxanthine will result in potent biological activity. Further syntheses and biological activities of 8-azaxanthine analogs are in progress, and will be reported in detail shortly.

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37. *^{1}H-NMR spectral data in $CDCl_3$ [C] or $(CD_3)_2SO$ [D].* For **1** *[D]* : 3.98 (3H, s, CH_3), 11.11 (1H, s, 6-NH), 12.33 (1H, br s, 4-NH). For **2a** *[D]*: 3.60 (3H, s, 4-NCH_3), 4.27 (3H, s, 3-NCH_3), 11.51 (1H, s, NH). For **2b** *[D]*: 3.95 (3H, s, NCH_3), 5.40 (2H, s, NCH_2), 7.21–7.36 (5H, m, Ph-*H*), 11.65 (1H, s, NH). For **3a** *[C]*: 3.44 (3H, s, 6-NCH_3), 3.79 (3H, s, 4-NCH_3), 4.35 (3H, s, 3-NH). For **3b** *[D]*: 3.38 (3H, s, 6-NCH_3), 4.05 (3H, s, 3-NCH_3), 5.50 (2H, s, NCH_2), 7.34–7.46 (5H, m, Ph-*H*). For **4** *[D]* : 3.24 (3H, s, CH_3), 12.11 (1H, br s, 4-NH), 15.75 (1H, br s, 3-NH). For **5** *[D]* : 3.20 (3H, s, 6-NCH_3), 4.25 (3H, s, 1-NCH_3), 12.33 (1H, s, NH). For **6** *[D]* : 3.20 (3H, s, 6-NCH_3), 4.23 (3H, s, 2-NCH_3), 12.17 (1H, s, NH). For **7** *[C]* : 3.42 (3H, s, 6-NCH_3), 3.67 (3H, s, 4-NCH_3), 4.37 (3H, s, 1-NCH_3). For **8** *[C]* : 3.44 (3H, s, 6-NCH_3), 3.56 (3H, s, 4-NCH_3), 4.28 (3H, s, 2-NCH_3). For **9** *[D]* : 3.40 (3H, s, CH_3), 11.37 (1H, s, 6-NH), 15.65 (1H, br s, 3-NH). For **10** *[D]* : 3.45 (3H, s, 4-NCH_3), 4.26 (3H, s, 1-NCH_3), 11.59 (1H, s, NH). For **11** *[D]* : 3.33 (3H, s, 4-NCH_3), 4.25 (3H, s, 2-NCH_3), 11.47 (1H, s, NH).
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39. *Infrared spectral data* [ν_{max}(Nujol)/cm^{-1} (CO)]: **3a**: 1720, 1680; **13a**: 1725, 1680; **13b**: 1720, 1670; **13c**: 1720, 1680; **13d**: 1725, 1670; **14a**: 1710; **14b**: 1720; **14c**: 1720; **14d**: 1720; **14e**: 1710.

40. *^{1}H-NMR spectral data in $CDCl_3$.* For **13a**: 0.99 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.47 (3H, s, NCH_3), 3.74 (2H, q, *J* = 6.9 Hz, 4-NCH_2), 7.51–7.55 (2H, m Ph-*m*H), 7.61–7.69 (3H, m, Ph-*o,p*H). For **13b**: 1.19 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.42 (3H, s, NCH_3), 3.98 (2H, q, *J* = 7.2 Hz, 4-NCH_2), 5.81 (2H, s, 3-NCH_2) 7.07–7.10 (2H, m Ph-*m*H), 7.36–7.40 (3H, m, Ph-*o,p*H). For **13c**: 0.93 (3H, t, *J* = 7.8 Hz, CH_2CH_3), 1.59 (2H, sextet, *J* = 7.8 Hz, CH_2CH_2), 3.42 (3H, s, NCH_3), 3.84 (2H, t, *J* = 8.1 Hz, 4-NCH_2), 5.79 (2H, s, 3-NCH_2) 7.05–7.08 (2H, m Ph-*m*H), 7.37–7.42 (3H, m, Ph-*o,p*H). For **13d**: 3.30 (2H, t, *J* = 6.6 Hz, CH_2CH_3), 3.36 (3H, s, 6-NCH_3), 3.41 (3H, s, 4-NCH_3), 4.82 (2H, t, *J* = 6.9 Hz, NCH_2), 7.0–7.03 (2H, m Ph-*m*H), 7.26–7.30 (3H, m, Ph-*o,p*H). For **14a**: 3.50 (3H, s, 6-NCH_3), 4.09 (3H, s, 5-OCH_3), 4.14 (3H, s, 3-NCH_3). For **14b**: 1.51 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.55 (3H, s, NCH_3), 4.61 (2H, q, *J* = 7.2 Hz, OCH_2), 7.43–7.48 (1H, m Ph-*p*H), 7.53–7.59 (2H, m, Ph-*m*H), 8.09–8.12 (2H, m, Ph-*o*H). For **14c**: 1.47 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.48 (3H, s, NCH_3), 4.56 (2H, q, *J* = 7.2 Hz, OCH_2), 5.59 (2H, s, NCH_2), 7.32–7.39 (5H, m Ph-*H*). For **14d**: 1.07 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 1.86 (2H, sextet, *J* = 6.6 Hz, OCH_2CH_2), 3.49 (3H, s, NCH_3), 4.45 (2H, t, *J* = 6.6 Hz, OCH_2), 5.59 (2H, s, NCH_2), 7.32–7.39 (5H, m Ph-*H*). For **14e**: 3.29 (2H, t, *J* = 7.2 Hz, $PhCH_2$), 3.47 (3H, s, NCH_3), 4.04 (3H, s, OCH_2), 4.67 (2H, t, *J* = 7.2 Hz, NCH_2), 7.12–7.15 (2H, m Ph-*m*H), 7.23–7.28 (3H, m, Ph-*o,p*H).

41. *^{13}C-NMR spectral data in $CDCl_3$.* For **3a**: 28.32 (6-NCH_3), 30.95 (4-NCH_3), 36.54 (3-NCH_3), 124.83 (7a-*C*), 140.31(3a-*C*), 150.38 (7-*C*), 156.96 (5-*C*). For **7**: 28.34 (6-NCH_3), 30.28 (4-NCH_3), 37.17 (1-NCH_3), 113.14 (7a-*C*), 150.29 (3a-*C*), 150.91 (7-*C*), 153.64 (5-*C*). For **8**: 28.45 (6-NCH_3), 30.90 (4-NCH_3), 42.98 (2-NCH_3), 125.10 (7a-*C*), 149.61(3a-*C*), 151.20 (7-*C*), 156.14 (5-*C*). For **14a**: 28.21 (6-NCH_3), 32.53 (3-NCH_3), 56.63 (5-OCH_3), 126.02 (7a-*C*), 147.41(3a-*C*), 155.64 (7-*C*), 157.28 (5-*C*).

42. *Ultraviolet spectral data* [λ_{max}/nm (log ε) in EtOH]: **3a**: 240 (4.06), 257 (4.08); **13a**: 243 (4.18), 256 (4.21); **13b**: 242 (4.20), 256 (4.22); **13c**: 242 (4.21), 256 (4.23); **13d**: 242 (4.12), 257 (4.17); **14a**: 250 (4.18); **14b**: 263 (4.36); **14c**: 252 (4.26); **14d**: 252 (4.27); **14e**: 252 (4.35).