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Reactions of 8,9-Dihydroxanthines with Acetylenic Compounds. Formation of Heteropropellanes

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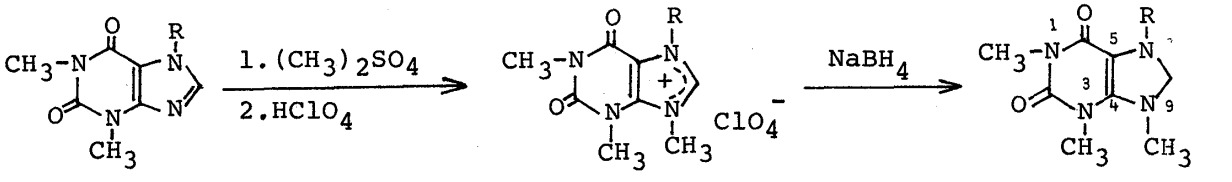
Reactions of 7-substituted 1,3,9-trimethyl-8,9-dihydroxanthines (**3**) with dimethyl acetylenedicarboxylate afforded heteropropellanes (**5**) in good yields. The reactions with methyl propiolate afforded pyrimidodiazepines (**7**) as well as propellanes (**6**) when the xanthines have small substituents at the 7 position. The mechanisms of formation of the products are also discussed.

Keywords——8,9-dihydroxanthine; heteropropellane; pyrimidodiazepine; long-range coupling; NOE experiment; dimethyl acetylenedicarboxylate; methyl propiolate; cycloaddition

Xanthine derivatives are widely distributed as natural products[1] and are used as medicines such as diuretics, central nervous system stimulants and inhibitors of cyclic adenosine monophosphate (c-AMP) phosphodiesterase.[2] However, only a few reactions of the dihydroderivatives of the skeleton are described in the literature. El'tsov and Muravich-Alexander[3] and Hecht *et al.*[4] reported some reactions of an 8,9-dihydroxanthine (**3a**); The imidazoline moiety of 8,9-dihydroxanthines was shown to be electron rich, and therefore, reactions with electrophiles such as activated acetylenic compounds would be expected. In this paper we wish to report on the ring transformation reaction of 1,3,7,9-tetraalkyl-8,9-dihydroxanthines.[5]

7-Substituted 1,3,9-trimethyl-8,9-dihydroxanthines (**3**) were synthesized by a modification of the reported method.[3] 7-Alkyl-1,3-dimethylxanthines were methylated with methyl tosylate or dimethyl sulfate[6] followed by treatment with perchloric acid to give 7-substituted 1,3,9-trimethylxanthinium perchlorates (**2a**,[4] **2b**,[7] and **2c**[8]) in good yields. Although El'tsov and Muravich-Alexander reported that the reaction of the perchlorate (**2a**) with KBH_4 or



1a : R=CH_3
1b : R=C_2H_5
1c : R= $CH_2C_6H_5$

2a–c

3a–c

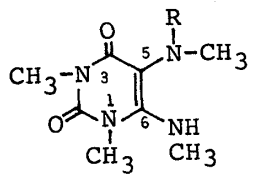


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Chart 1

TABLE I. 7-Alkyl-1,3,9-trimethylxanthinium Perchlorates (**2a—d**)

Compd.	R	mp (°C)	Recryst. solvent (Appearance)	Yield (%)	^{1}H-NMR (DMSO-d_6)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
2a	CH_3[4]	198	EtOH (Colorless prisms)	81	3.25, 3.71, 4.05, 4.13 (each 3H, each s, N–CH_3), 9.23 (1H, s, C-8–H)				
2b	C_2H_5[7]	145—146	EtOH (Colorless prisms)	89	1.47 (3H, t, J=7.2 Hz, N–$CH_2\underline{CH_3}$), 3.25, 3.71, 4.12 (each 3H, each s, N–CH_3), 4.45 (2H, q, J=7.2 Hz, N–CH_2), 9.27 (1H, s, C-8–H)	$C_{10}H_{15}ClN_4O_6$	37.22 (37.36	4.68 4.55	17.36 17.60)
2c	$CH_2C_6H_5$[8]	>300	H_2O (Colorless needles)	92	3.20, 3.68, 4.11 (each 3H, each s, 3×N–CH_3), 5.66 (2H, s, N-7–CH_2), 7.36 (5H, s, arom H), 9.41 (1H, s, C-8–H)	$C_{15}H_{17}ClN_4O_6$	46.82 (46.92	4.45 4.34	14.56 14.62)
2d	CH_3 (N-9–CD_3)	202—204	EtOH (Colorless powder)	85	3.25, 3.71, 4.04 (each 3H, each s, 3×N–CH_3), 9.21 (1H, s, C-8–H)				

TABLE II. 7-Alkyl-1,3,9-trimethyl-8,9-dihydroxanthines (**3a—d**)

Compd.	R	Yield (%)	^{1}H-NMR ($CDCl_3$)	MS m/z
3a	CH_3[3]	Quant.	2.71, 2.95, 3.31, 3.47 (each 3H, each s, 4×N–CH_3), 4.36 (2H, s, C-8–CH_2)	210 (M^+), 209
3b	C_2H_5	Quant.	1.09 (3H, t, J=7.2 Hz, N-7–$CH_2\underline{CH_3}$), 2.96, 3.28, 3.46 (each 3H, each s, 3×N–CH_3), 3.02 (2H, q, J=7.2 Hz, N-7–CH_2), 4.44 (2H, s, C-8–CH_2)	224 (M^+), 223
3c	$CH_2C_6H_5$	Quant.	2.55, 3.33, 3.35 (each 3H, each s, 3×N–CH_3), 4.13 (2H, s, N-7–CH_2), 4.36 (2H, s, C-8–CH_2), 7.25 (5H, s, arom H)	286 (M^+), 285
3d	CH_3 (N-9–CD_3)	98	2.68, 3.27, 3.46 (each 3H, each s, 3×N–CH_3), 4.35 (2H, s, C-8–CH_2)	213 (M^+), 212

$NaBH_4$ at room temperature gave **3a** together with 1,3-dimethyl-5-(dimethylamino)-6-(methylamino)uracil (**4**, R=methyl) as a by product,[3] the $NaBH_4$ reduction of **2** under ice-cooling gave only **3** in good yield and **4** was not detected by proton nuclear magnetic resoannce (^{1}H-NMR) spectroscopy or thin-layer chromatography (TLC)[9] (Tables I and II).

Reactions with Dimethyl Acetylenedicarboxylate

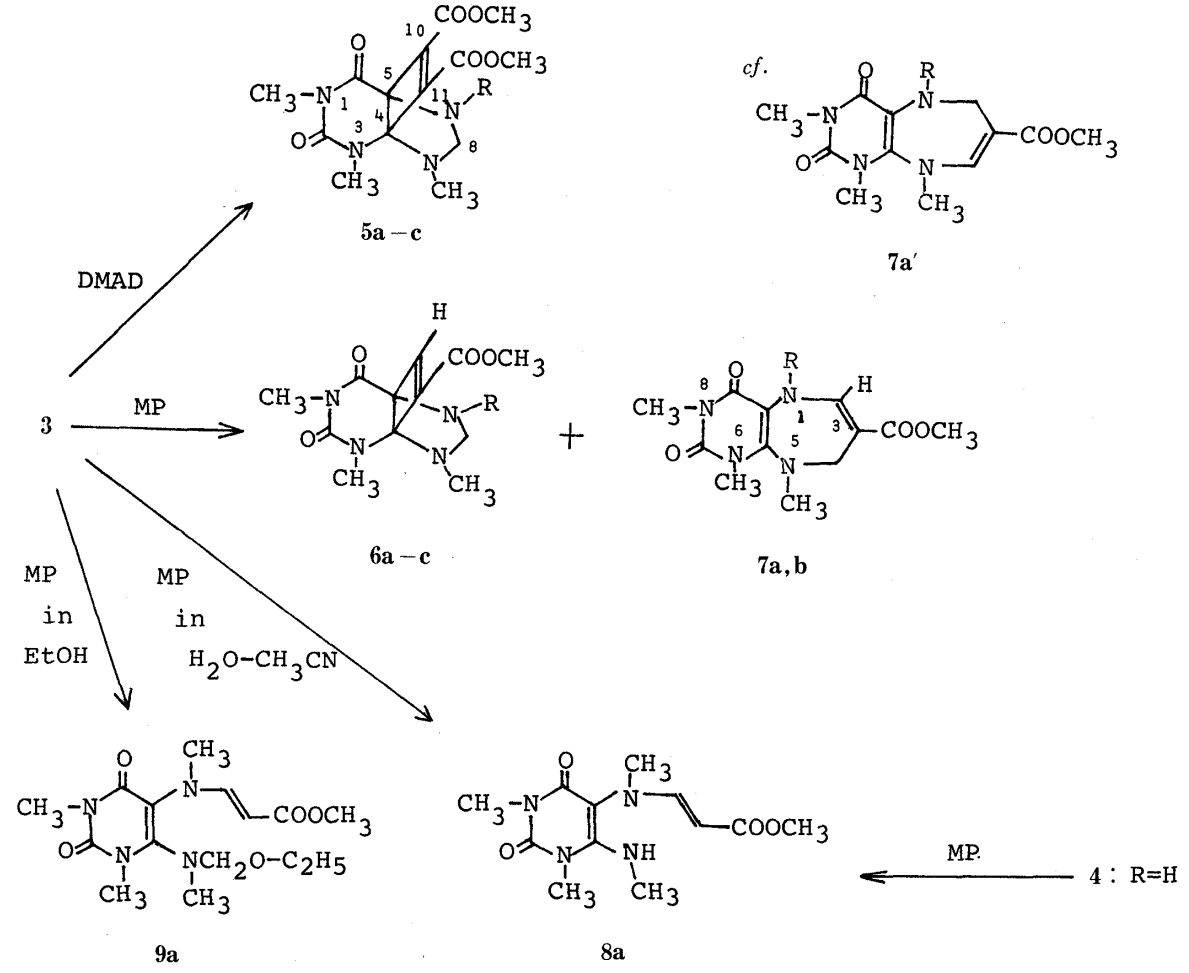
The reaction of **3a** with dimethyl acetylenedicarboxylate (DMAD) was carried out in acetonitrile to give a crystalline product (**5a**) in 76% yield. The product was proved to be the 1 : 1 adduct of **3a** and DMAD on the basis of the mass spectrum (MS) and elemental analyses. The structure of **5a** was determined by the inspection of the NMR spectra. In the ^{1}H-NMR spectrum the signals of the C-8 methylene protons were observed at δ 3.31 and 4.02 with geminal coupling (J=7.0 Hz). Furthermore in the carbon-13 (^{13}C-)NMR spectrum, signals of quaternary carbons were observed at δ 83.0 and 71.8, which were assigned to bridgehead

carbons (C-4 and C-5). Methylene carbon and two sp^2 carbons were observed at δ 77.0 (C-8), 141.6 and 142.4, respectively. Under non-decoupling conditions, long range couplings between C-8 methylene carbon and N-7 or N-9 methyl carbons were observed (J=4.2 and 2.8 Hz respectively). These spectral data revealed the existence of a CH_3–N–CH_2–N–CH_3 moiety. Thus, the structure of **5a** was established as 4,5-(bismethoxycarbonyletheno)-1,3,7,9-tetramethyl-4,5,8,9-tetrahydropurine-2,6-dione. The higher shift of one (δ 4.02) of the C-8 methylene protons can be explained in terms of the shielding effect of the C-10–C-11 double bond. Similarly, the reactions of **3b**, **c** with DMAD afforded propellanes (**5b**, **c**) in 47.7 and 35.6% yields, respectively.

Very recently, Poje *et al.* reported a propellane type derivative of uric acid, 9-acetyl-4,5-(1-methoxyethylidenedioxy)-4,5-dihydrouric acid.[10]

Reaction with Methyl Propiolate

The reaction of **3a** with methyl propiolate (MP) afforded the propellane (**6a**) in only 25%



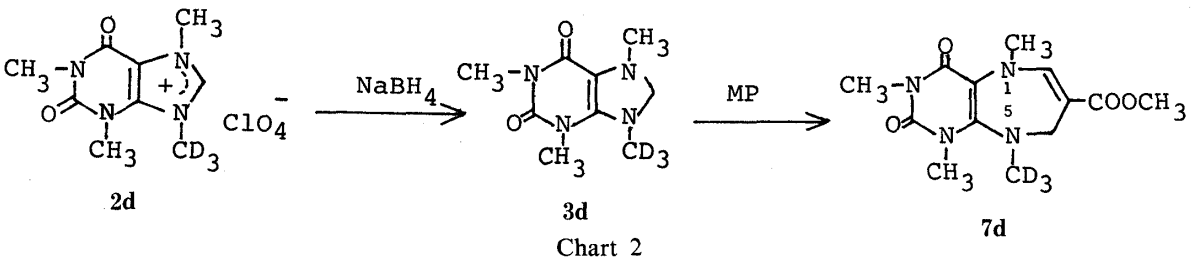


Chart 2

TABLE III. Reactions of 8,9-Dihydroxanthines (**3a**—**c**) with Acetylenes or Acids

Run	Dihydro-xanthine	Acetylene	Time (d)	Solvent	Products (%)	Note
1	**3a**	DMAD	1	CH_3CN	**5a** (76)	
2	**3a**	DMAD	2	Benzene	**5a** (21)	
3	**3a**	DMAD	1	CH_3CN	**5a** (70)	In the dark
4	**3a**	DMAD	2	Benzene	**5a** (25)	In the presence of 2,6-di-*tert*-butyl-*p*-cresol
5	**3b**	DMAD	0.5	CH_3CN	**5b** (47.7)	
6	**3c**	DMAD	2	CH_3CN	**5c** (35.6)	
7	**3a**	MP	2	CH_3CN	**6a** (25), **7a** (25)	
8	**3b**	MP	2	CH_3CN	**6b** (31), **7b** (20)	
9	**3c**	MP	2	CH_3CN	**6c** (40)	
10	**3a**	MP	1	CH_2Cl_2	**7a** (7), **4** (20), **3a** (18)[a]	BF_3–Et_2O 0.2 eq
11	**3a**	MP	1	CH_2Cl_2	**7a** (10), **4** (40), **3a** (37)[a]	BF_3–Et_2O 1.0 eq
12	**3a**	MP	1	CH_3CN	**7a** (9), **8a** (42)	With H_2O
13	**3a**	MP	0.2	C_2H_5OH	**9a** (88.8)	
14	**3a**	—	1	CH_2Cl_2	**4** (50), **3a** (45)[a]	CF_3COOH 1 eq
15	**3a**	—	0.5	CH_2Cl_2	**4** (50), **3a** (40)[a]	BF_3–Et_2O 1 eq
16	**3a**	—	1	CH_2Cl_2	**4** (25), **3a** (20)[a]	BF_3–Et_2O 0.2 eq

a) Compound **2a** was isolated as **3a** after treatment with $NaBH_4$.

yield and another type of 1 : 1 adduct (**7a**) in 25% yield. In the ^{1}H-NMR of the adduct (**7a**), one methylene signal and an olefinic signal with allyl coupling to each other were observed at δ 3.84 and 7.41, respectively. In the ^{13}C-NMR, the signals at δ 51.1, 97.8 and 145.9 were assigned to C-4, C-3 and C-2 carbons, respectively. From these data the structure of **7** was considered to be pyrimido[4,5-*b*][1,4]diazepine skeleton. However, two isomeric structures, **7a** and **7a'**, had to be considered. We first made the NMR assignment of the N-1 and N-5 methyl groups of **7a**. Compound **7d** having a trideuteriomethyl group at position 5 was synthesized from **1a** by treatment with hexadeuteriodimethyl sulfate followed by $NaBH_4$ reduction and then reaction with MP (Chart 2). The 1-N-methyl (δ 3.32) and 5-N-methyl (δ 2.68) groups of **7a** could be clearly assigned by comparison of the ^{1}H-NMR spectra of **7a** and **7d**. Next nuclear Overhauser effect (NOE) measurements were made.[11] When the 1-N-methyl group was irradiated, the intensity of the olefinic proton (δ 7.41) was increased by about 20%. On the other hand, when methylene protons (δ 3.84) were irradiated, the intensity of the N-5-methyl group signal (δ 2.68) was increased by about 18%. From these results, the structure of the ring-enlarged product was confirmed to be **7a**, not **7a'**.

In Diels–Alder type reactions, Lewis acids are known to act as a catalyst to increase the reactivity and/or to improve the stereoselectivity and regioselectivity. However, the reaction of **3a** with MP in the presence of Lewis acids[12] gave no propellane (**6a**) but only a small amount of **7a**. Furthermore, the reaction with acids (CF_3COOH or BF_3) gave **4** and at the same time **3a** was recovered from the water layer after treatment with $NaBH_4$. As these two products were obtained in the same yields, the formation mechanism might be as follows. Lewis acids first coordinate to the C-6 carbonyl group and the ring opened intermediate **13** is formed. The remaining **3a** supplies hydride ion to **13** to give **14**, and finally **4** and **2a** are formed. The acids thus only accelerated the disproportionation of the dihydroxanthines.

Discussion

The results of the reactions of **3a**—**c** with activated acetylenic compounds (DMAD and MP) are summerized in Table III.

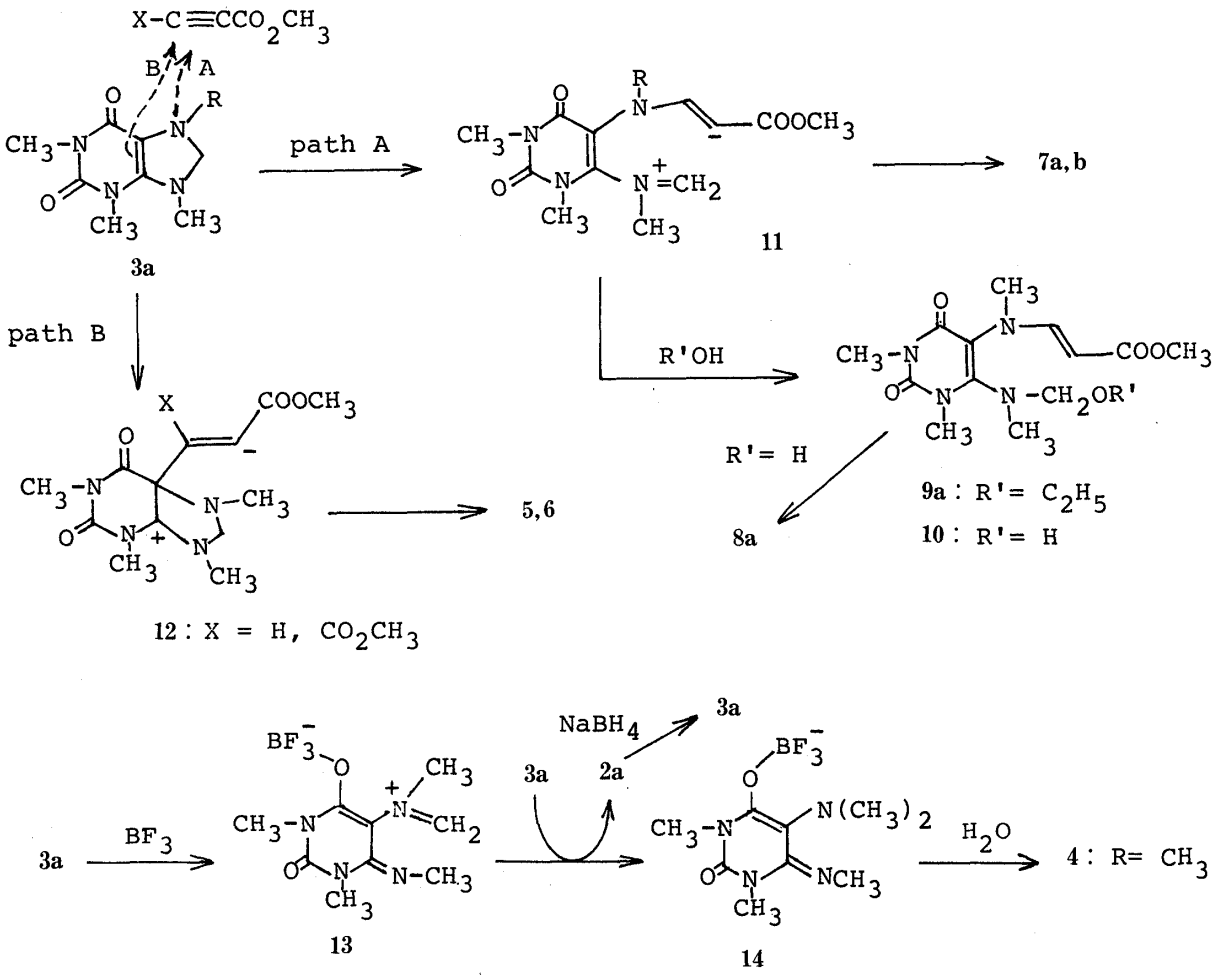


Chart 3

To clarify the reaction mechanism, several reactions were investigated. In the presence of 10 eq of water, the reaction of **3a** with MP gave **8a** as a main product (run 12). Compound **8a** was speculated to be a 6-(methylamino)uracil derivative from the typical NMR signal of the 6-methylamino group (doublet at δ 2.95, J=6.0 Hz). The structure of **8a** was confirmed by direct comparison of **8a** with an authentic sample prepared from **4** (R=H), which was obtained from 5-bromo-6-(methylamino)-1,3-dimethyluracil[13] and methylamine. The reaction in dry ethanol afforded the 6-*N*-(ethoxymethylene)-5-*N*-(methylamino)uracil derivative (**9a**) in 88.8% yield.[14] From these results, the reaction was considered to have been initiated by the attack of electrophiles at N-7 position and then the imidazoline ring was cleaved, followed by intramolecular cyclization to give **7** (path A). In the presence of water or ethanol the intermediate **11** was trapped to give hetero acetals (**9a**, **10**). Compound **9a** could be isolated (mp 68—70 °C) but **10** was hydrolyzed to **8a** (Chart 3).

Acetylenic compounds react with the C5–C6 double bond of uracils[15] and olefins add to dihydroxanthines[16] through a photo-allowed 2+2 cycloaddition reaction. The following experiments were carried out to clarify the reaction course of the present reactions. Yields of propellanes were decreased in non-polar solvents such as benzene. The reaction in the dark (run 3) or with 2,6-di-*tert*-butyl-*p*-cresol as a radical scavenger (run 4) proceeded with unchanged yield of **5a**.[17]

On the basis of these results, the propellanes (**5**, **6**) were produced not by photo or radical reactions but through an ionic mechanism. That is, as shown in Chart 3, the formation of propellanes proceeded stepwise *via* electrophilic attack of the enaminone double bond on

TABLE IV. Spectral Data for Propellanes (**5**—**6**) and Pyrimidodiazepines (**7**)

Compd.	mp (°C) (Recryst. solv.)	^{1}H-NMR ($CDCl_3$) δ ppm	MS *m/z*	Analysis (%) Calcd (Found) C	H	N
5a	110 (Et_2O)	2.53, 2.67, 3.24, 3.27 (4 × N–CH_3), 3.31 (1H, d, J=7.0 Hz, C-8–H), 3.86, 3.92 (3H × 2, each s, 2 × OCH_3), 4.02 (1H, d, J=7.0 Hz, C-8–H) ^{13}C-NMR 28.7, 32.3, 34.9, 37.2 (4 × NCH_3), 53.1 (2 × OCH_3), 71.8 (C-5), 77.0 (C-8), 83.0 (C-4), 141.6, 142.4 (C-10, 11), 152.1 (C-2), 161.7, 162.6 (2 × CO), 165.8 (C-6)	351 (M^+-1), 210 (base)	51.13 (50.96	5.72 5.71	15.90 15.89)
5b	Oil	1.09 (3H, t, J=7.2 Hz, $\underline{CH_3}CH_2$), 2.56, 3.22, 3.27 (each 3H, each s, 3 × N–CH_3), 3.15—3.80 (3H, m, CH_2, C-8–H), 4.24 (1H, d, J=7.0 Hz, C-8–H), 3.86 (3H × 2, each s, 2 × OCH_3)	365 (M^+-1), 224 (base)	High-resolution MS Calcd for $C_{16}H_{22}N_4O_6$ 366.1538; Found 366.1513		
5c	Oil	2.48, 3.27, 3.27 (3H × 3, each s, 3 × NCH_3), 3.15—3.85 (3H, m, C-8–H_2, benzyl H), 3.86, 3.90 (3H × 2, each s, 2 × OCH_3), 4.98 (1H, J= 13.0 Hz, benzyl H), 7.28 (5H, br s, arom H)	428 (M^+), 427 (M^+-1), 286, 195 (base)	High-resolution MS Calcd for $C_{21}H_{24}N_4O_6$ 428.1683; Found 428.1695		
6a	93—95 (Et_2O)	2.51, 2.57, 3.19, 3.33 (3 × N–CH_3), 3.11 (1H, d, J=6.6 Hz, C-8–H), 3.80 (3H, s, OCH_3), 3.98 (1H, d, J=6.6 Hz, C-8–H), 7.13 (1H, s, olefinic H)	293 (M^+-1), 210 (base)	53.05 (52.86	6.16 6.19	19.03 19.16)
6b	Oil	1.09 (3H, t, J=6.0 Hz, N–$CH_2\underline{CH_3}$), 2.53, 3.18, 3.32 (3 × N–CH_3), 3.00—3.40 (2H, N–CH_2), 3.03 (1H, d, J=6.0 Hz, C-8–H), 3.81 (3H, s, OCH_3), 4.16 (1H, d, J=6.0 Hz, C-8–H), 7.12 (1H, s, C-10–H)	307 (M^+-1), 214 (base)	High-resolution MS Calcd for $C_{14}H_{20}N_4O_4$ 308.1455; Found 308.1452		
6c	122—124 (Et_2O)	2.47, 3.24, 3.31 (3 × N–CH_3), 3.04 (1H, d, J=6.6 Hz, C-8–H), 3.80 (3H, s, OCH_3), 3.82 (1H, d, J=6.6 Hz, C-8–H), 3.46, 4.78 (1H, 1H, each d, J=13.2 Hz, N-7–CH_2), 7.12 (1H, s, olefinic H), 7.28 (5H, s, arom H) ^{13}C-NMR 28.3, 32.0, 36.8 (3 × NCH_3), 52.8 (NCH_2), 52.1 (OCH_3), 69.4 (C-5), 74.4 (C-8), 82.9 (C-4), 128.4, 128.5, 137.8 (arom C), 141.2 (C-11), 143.1 (C-10), 150.9 (C-2), 160.9 (C-6), 166.5 (CO)	370 (M^+-1), 286 (base)	61.61 (61.58	5.99 6.09	15.13 15.14)
7a	136 (Et_2O)	2.68, 3.32, 3.32, 3.45 (3 × NCH_3), 3.84 (2H, br s, C-4–CH_2), 3.69 (3H, s, OCH_3), 7.41 (1H, s, C-2–H) ^{13}C-NMR 28.5, 29.8, 37.8, 43.1 (4 × NCH_3), 51.1 (C-4), 52.6 (OCH_3), 97.8 (C-3), 117.7 (C-9a), 145.9 (C-2), 150.8 (C-5a), 151.9 (C-7), 159.9 (CO), 168.1 (C-9)	294 (M^+), 209 (base)	53.05 (53.08	6.16 6.21	19.03 19.09)
7b	146—148 (Et_2O)	1.18 (3H, t, J=6.6 Hz, N–CH_2), 2.69, 3.32, 3.45 (3 × NCH_3), 3.68 (3H, s, OCH_3), 3.85 (2H, br s, C-4–CH_2), 7.50 (1H, s, C-2–H)	308 (M^+, base)	54.54 (54.73	6.56 6.57	18.17 18.34)
7d	138—139 (Et_2O)	3.34, 3.34, 3.46 (3 × NCH_3), 3.69 (3H, s, OCH_3), 3.86 (2H, br s, C-4–CH_2), 7.43 (1H, s, C-2–H)	297 (M^+), 212 (base)	High-resolution MS Calcd for $C_{13}H_{15}D_3N_5O_4$ 297.1518; Found 297.1518		

DMAD or MP. From the mechanistic considerations, the regiochemistry at C-10–C-11 of **6a** was deduced to be as shown in Chart 2. Furthermore, the structures of **6** were confirmed by comparison of the chemical shifts of N-9-CH_3 (the highest field signals among the N–CH_3 groups) and N-7-CH_3. Although the differences of chemical shifts of N-9-CH_3 between **5a—c** and **6a—c** were within 0.03 ppm, the difference of that of N-7-CH_3 between **5a** (δ 2.67) and **6a** (δ 2.57) was 0.1 ppm. This is attributable to the shielding effect of the CO_2CH_3 group at C-10 on N-7-CH_3.

When **3b** and **3c**, having N-7 substituents larger than a methyl group, reacted with MP, the yields of propellanes (**6**) were increased and those of the ring enlarged products (**7**) were decreased: in the case of **3c**, no pyrimidodiazepine (**7c**) was obtained (Table III). These observations can be explained by the speculation that the attack at N-7 (path A) was sterically hindered in the case of **3b** and **3c** and attack occurred preferentially at the C-5 position (path B) to give propellanes (**6b, c**). It is not clear at present why the reaction of **3a** and MP in protic solvents such as H_2O–CH_3CN or EtOH afforded **8a** or **9a**, not **5** or **6**.

Experimental

Melting points were determined on a Yanagimoto micro-hot stage apparatus and are uncorrected. TLC was performed with Merck precoated Silica gel 60 PF_{254} plates. Preparative TLC was done with the same commercial product, 20×20 cm, with a thickness of about 0.5 mm. ^{1}H-NMR spectra were measured on a Hitachi R20-B spectrometer at 60 MHz and chemical shifts are expressed relative to tetramethylsilane as an internal standard. ^{13}C-NMR spectra were taken at 90 MHz with a JEOL FX-90 spectrometer. MS were determined on a JEOL D-300 machine.

General Procedure for the Syntheses of 7-Substituted 1,3,9-Trimethylxanthinium Perchlorates (2a—c)——Dimethyl sulfate (2 eq) was added to a solution of a 7-substituted 1,3-dimethylxanthine (1 eq) in nitrobenzene at 90—100 °C over 1 h and the mixture was stirred for 24 h at that temperature. After cooling of the reaction mixture, excess ethyl ether was added and the solvent was decanted off. The residue was washed with ether several times then with hot acetone, and the solid was filtered off. A 70% perchloric acid (1.2 eq) was slowly added to an alcohol solution of the above solid and the mixture was stirred for 6 h at room temperature. The crystals were collected and recrystallized from ethanol to give 7-alkyl- or 7-benzyl-1,3,9-trimethylxanthinium perchlorate (**2a—c**) (Table I).

General Procedure for the Syntheses of 7-Substituted 1,3,9-Trimethyl-8,9-dihydroxanthines (3a—c)——Sodium borohydride (4.0 eq) was slowly added to an aqueous (20 eq) solution of **2a—c** under ice-cooling. The mixture was stirred at that temperature for 1 h then at room temperature for 1 h, and was finally extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and evaporated to give **3a—c** in almost quantitative yields (Table II).

General Procedure for the Reaction of 7-Substituted 1,3,9-Trimethyl-8,9-dihydroxanthines with Acetylenic Compounds——Acetylenic ester (1.5 eq) was added to a solution of **3a—d** in a solvent at room temperature under N_2. The mixture was evaporated and the residual oil or solid was separated by silica gel column chromatography (benzene–acetone was used as the eluent) and purified by recrystallization from the appropriate solvent, as shown in Tables III and IV.

General Procedure for the Reaction of 3a with Lewis Acids——A solution of **3a** and 1.5 eq of Lewis acid was stirred under N_2 at room temperature for 0.5—1 d. Then 10% aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica gel (acetone–benzene as the eluent), 1,3-Dimethyl-5-(dimethylamino)-6-(methylamino)uracil was obtained and recrystallized from Et_2O. Colorless prisms mp 104—105 °C (mp was not given in ref. 3). *Anal.* Calcd for $C_9H_{16}N_4O_2$: C, 50.93; H, 7.60; N, 26.40. Found: C, 50.82; H, 7.64; N, 26.48. ^{1}H-NMR ($CDCl_3$) δ: 2.68 [6H, s, $N(CH_3)_2$], 2.86 (3H, d, J=6.0 Hz, $N(CH_3)$), 3.29, 3.42 [(3H, 3H, each s, 2×$N(CH_3)_2$], 5.50—6.60 (1H, br, NH). MS m/z: 212 (M^+).

$NaBH_4$ was added to the aqueous layer under ice-cooling and the mixture was stirred for 2 h. The solution was treated as noted above in the general procedure for the syntheses of **3**, and 1,3,7,9-tetramethyl-8,9-dihydroxanthine (**3a**) was obtained.

5-[(*trans*-2-Methoxycarbonylvinyl)methylamino]-6-(methylamino)-1,3-dimethyluracil (8a)——A solution of 1,3-dimethyl-5-bromo-6-(methylamino)uracil[13] (5.0 g) and then 30% methylamine in MeOH (10 ml) was refluxed for 15 min and then evaporated. The residue was extracted (CH_2Cl_2) and the extract was dried ($MgSO_4$). 1,3-Dimethyl-4,5-bis(methylamino)uracil[13] (**4**, R=H) was obtained as crystals. 2.98 g (75%).

A solution of **4** (R=H, 0.4 g) and methyl propiolate (0.26 g) in dry CH_3CN (16 ml) was stirred for 2 d at room temperature under N_2. Evaporation of the solvent and TLC separation of the residue gave 0.205 g of **8a** (36%) as an oil and 0.225 g of recovered **4**. The spectral data of **8a** were identical with those of the product obtained from the reaction of **3a** with MP in the presence of 10 eq of H_2O. ^{1}H-NMR δ: 2.95 (3H, d, J=6.0 Hz, $NHCH_3$), 3.06, 3.30, 3.45

(each 3H, each s, 3 × N–CH_3), 3.62 (3H, s, OCH_3), 4.62 (1H, d, J = 13.2 Hz, olefinic H), 4.90—5.20 (1H, br, NH), 7.42 (1H, d, J = 13.2 Hz, olefinic H), MS m/z: 282 (M^+), 209 (base). High-resolution MS m/z: Calcd for $C_{12}H_{18}N_4O_4$: 282.1298. Found: 282.1295.

Reaction of 3a with MP in Ethanol——A solution of **3a** (0.500 g, 2.379 mM) and 0.345 g of MP in ethanol (10 ml) was stirred at room temperature for 4.5 h. The solvent was evaporated off and the residue was chromatographed on silica gel (acetone : benzene = 1 : 8 as the eluent). Crystalline **9a** was obtained (719 mg, 88.8%). Colorless prisms (ethyl acetate). mp 68—70 °C. *Anal.* calcd for $C_{15}H_{24}N_4O_5$: C, 52.95; H, 7.10; N, 16.46. Found: C, 52.72; H, 7.03; N, 16.37. NMR ($CDCl_3$) δ: 1.22 (3H, t, J = 7.0 Hz, $C\underline{H}_3CH_2$), 2.86 (3H, s, 6-N–CH_3), 3.05, 3.32, 3.42 (each 3H, each s, 3 × NCH_3), 3.62 (3H, s, OCH_3), 3.34 (2H, q, J = 7.0 Hz, $C\underline{H}_2CH_3$), 4.36 (2H, s, CH_2O), 4.68, 7.35 (each 1H, each d, J = 13.0 Hz, olefinic H).

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