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Studies on Xanthine Derivatives. II.¹⁾ Synthesis of 1,2,3,7-Tetrahydro-6H-purin-6-ones from Xanthine Hydrolyzates

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Intramolecular cyclization of caffeidine homologues (**2a** and **2b**) in the presence of ethanolic hydrogen chloride gave 9-oxo-1H-pyrrolo[1,2-a]purine (**4a**) and 11-oxo-1H-azepino[1,2-a]purine (**4b**) derivatives, both containing a 1,2,3,7-tetrahydro-6H-purin-6-one ring system. Purine ring system compounds, 2-monosubstituted (**7**) and 2,2-disubstituted (**8**) 1,2,3,7-tetrahydro-6H-purin-6-ones, were synthesized by intermolecular cyclization between caffeidine and aldehydes (**5**) or ketones (**6**) in the presence of acid catalysts. Pyrolysis of 4,7,8,9,9a,11-hexahydro-1,4,9a-trimethyl-5,11-dioxo-1H,5H-imidazo[4,5-f]pyrrolo[2,1-b][1,3,5]-oxadiazocine hydrochloride (**9**·HCl) derived from a urea derivative (**3a**) afforded **4a** and 1,4-dimethyl-4,5-dihydro-5,7-dioxo-1H,7H-imidazo[4,5-d][1,3]oxazine (**11**). Many of these compounds (**4**, **7** and **8**) showed relaxing activity against KCl-induced contraction of arterial strips isolated from the rabbit mesenterium, and potent activity was observed in the case of **7l**.

Keywords—1,2,3,7-tetrahydro-6H-purin-6-one; caffeidine; caffeidine homologue; intramolecular cyclization; intermolecular cyclization; ethanolic hydrogen chloride; acid catalyst; pyrolysis; relaxing effect on KCl-induced vasocontraction

The purine ring system is present in nucleic acid bases such as adenine and guanine and in alkaloids such as hypoxanthine and xanthine, and it plays important roles in biological systems. Many investigators have attempted to synthesize various purine derivatives because of their biological importance. In the synthesis of purines, aminoimidazoles having a carbamoyl group adjacent to an amino group give purine rings on cyclization with one-carbon units such as formate ester, carbonate ester and guanidine, and these purine rings have an *sp*² carbon atom at the 2-position.²⁾ However, few reports have appeared on the synthesis of the 1,2,3,7-tetrahydro-6H-purin-6-one ring system. Such a synthetic process has been reported only in the desulfurization of 2-thiotheophylline by Raney Ni³⁾ and in the reduction of 1,3-dimethyl-8-phenylhypoxanthinium iodide by NaBH₄,⁴⁾ but these methods are not usually applied to the synthesis of highly substituted ring systems such as 4,4a,5,6,7,8-hexahydro-1,4,4a-trimethyl-10-oxo-1H-pyrido[1,2-a]purine reported by us previously.¹⁾ Thus, it seemed interesting to study the synthesis of 1,2,3,7-tetrahydro-6H-purin-6-ones to examine their pharmacological activities. The structural relation between xanthines and the above compounds is similar to that between phenobarbital and primidone,⁵⁾ which have a xanthine partial structure and are used as anticonvulsive agents; the former compounds have a C=O group at the 2-position, whereas the latter compounds are reduced derivatives (—CH₂—) of the former. The correlations between structure and pharmacological activity in these ring systems are expected to be similar to those in the case of the anti-convulsive agents. It is also expected that compounds having this ring system may show some of the pharmacological activities of xanthine. Thus, we have synthesized various purine derivatives containing this ring system.

The present paper deals with the synthesis of fused purine derivatives (**4**) formed by intramolecular cyclization of caffeidine homologues (**2**) having an oxoalkyl group, and the synthesis of purine compounds (**7**, **8**) derived from intermolecular cyclization between caffeidine (**2d**) and carbonyl compounds (**5**, **6**). Attempts to synthesize other types of fused purine derivatives containing a 1,3,6,7-tetrahydro-2*H*-purin-2-one ring system are also discussed. Furthermore, some pharmacological activities of the above compounds (**4**, **7** and **8**) are reported.

Hydrolysis of 1,3,7-trisubstituted xanthines (**1a—c**)⁶⁾ in aqueous alkaline solution gave 3-methyl-5-methylamino-*N*-oxoalkyl-4-imidazolcarboxamides (**2a—c**) and 3-methyl-5-(3-oxoalkyl-1-methylureido)-4-imidazolcarboxylic acids (**3a—c**), which were used as starting materials in the present study (Chart 1). Another starting material, caffeidine (**2d**), was obtained from caffeine (**1d**) by Hoskinson's method.⁷⁾ The structures of **2** and **3** were assigned on the basis of elemental analysis and spectral data (Tables II, III and IV).

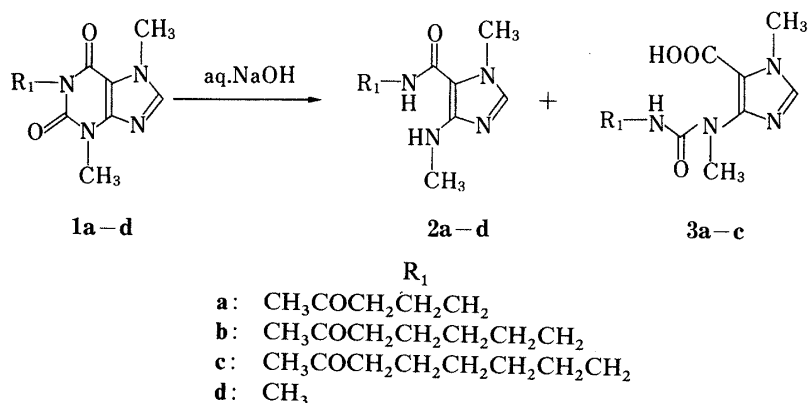


Chart 1

In the previous paper, we reported that the treatment of 3-methyl-5-methylamino-*N*-(5-oxohexyl)-4-imidazolcarboxamide in the presence of ethanolic hydrogen chloride gave 10-oxo-1*H*-pyrido[1,2-*a*]purine derivatives.¹⁾ This result indicates that the 4-amino group and 5-carbamoyl group of caffeidine or caffeidine homologues undergo cyclization with a suitable carbonyl compound to form the purine ring system. Initially, we attempted intramolecular cyclization of caffeidine homologues having a 4-oxopentyl (**2a**), 6-oxoheptyl (**2b**) or 7-oxooctyl (**2c**) group in order to develop the synthesis of fused purine derivatives (**4**) (Chart 2). When **2a** and **2b** were left at room temperature in the presence of ethanolic hydrogen chloride for 1—6 d, the hydrochlorides of **4a** and **4b** were obtained in yields of 38% and 28%, respectively. The elemental analysis and mass spectrum (MS) ($M^+ - \text{HCl}$ m/z : 220) of **4a**·HCl established the molecular formula of **4a** as $\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}$, which indicated that the reaction of **2a** to **4a** had proceeded with elimination of water. The infrared (IR) spectrum showed no absorption bands corresponding to the two NH groups and a ketone CO group of **2a**. In the proton nuclear magnetic resonance (^1H -NMR) spectrum, a 3H singlet signal due to a tertiary methyl group was newly observed at δ 1.35. Thus, **4a** was assigned as intramolecularly cyclized 4,4a,5,6,7,9-hexahydro-1,4,4a-trimethyl-9-oxo-1*H*-pyrrolo[1,2-*a*]purine. Similarly, the structure of **4b** was determined as the 11-oxo-1*H*-azepino[1,2-*a*]purine derivative from the analytical and spectral data. However, similar treatment of **2c** did not cause cyclization but resulted in recovery of **2c**. This result was assumed to be due to valency angle strain in the eight-membered ring which was expected to fuse to the purine ring.

Next, we performed the synthesis of purine ring system compounds (**7**, **8**) by intermolecular cyclization of caffeidine (**2d**) with various carbonyl compounds (**5** and **6**) (Charts 3 and 4). Treatment of **2d** with a large excess of 90% acetaldehyde (**5a**) in the presence of

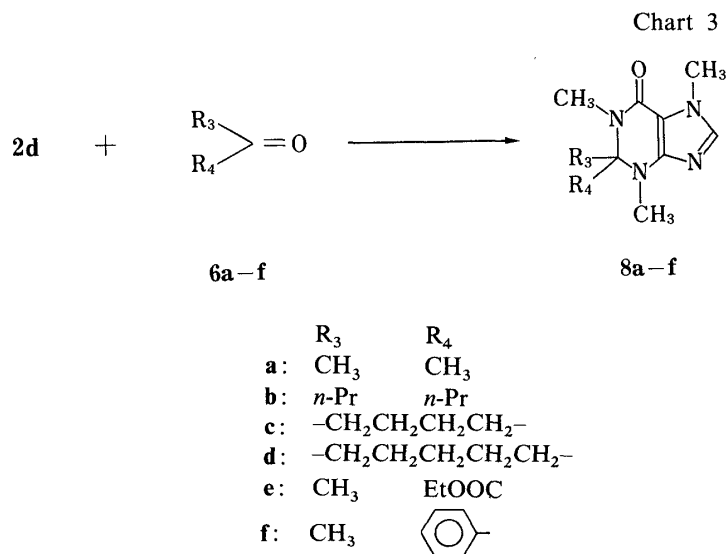
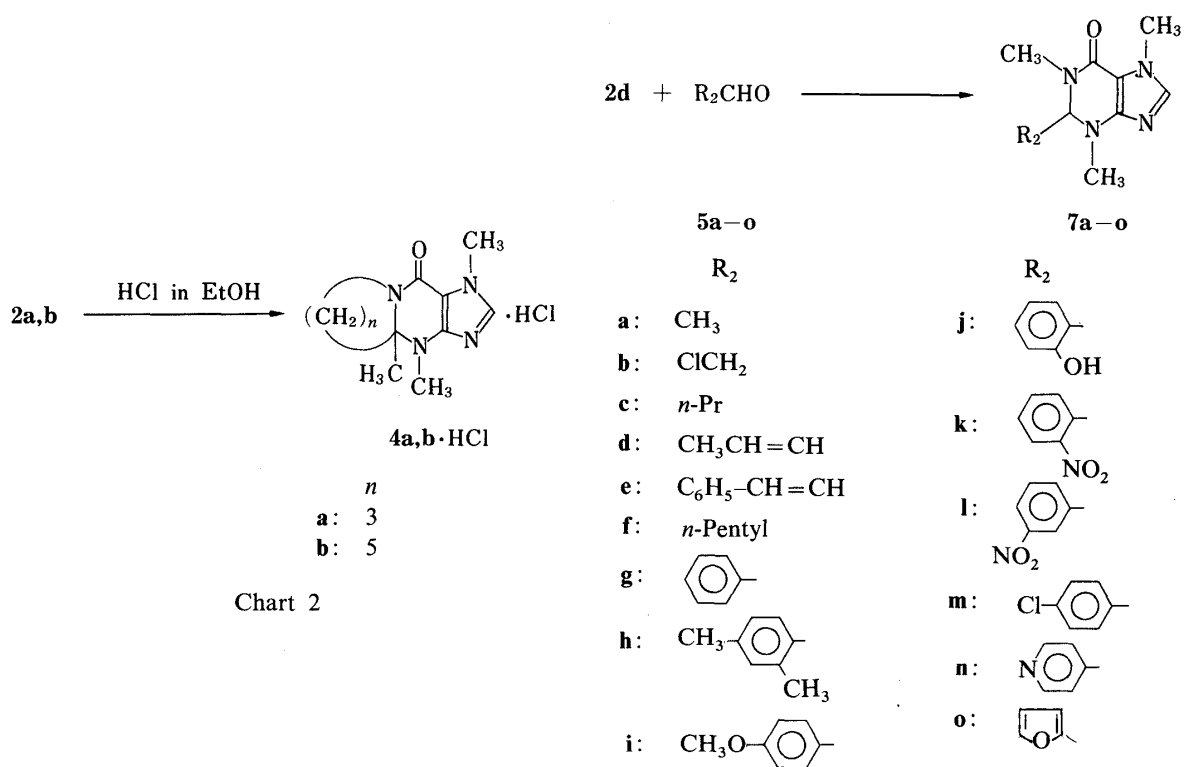


TABLE I. Reaction Conditions for Caffeidine (2d) with Cyclohexanone (6d)

Method	Catalyst (Amount)	2d (mmol)	6d (mmol)	Solvent	Refluxed time (h)	Yield of 8d (%)
A	PPA, (catalytic amount) P ₂ O ₅ (0.2 g)	3	9.6	CHCl ₃	3	13
B	HCl (excess against 2d)	3	9.6	EtOH	4	Trace
C	<i>o</i> -Nitrobenzoic acid (1.5 mol ratio against 2d)	3	9.6	C ₆ H ₆ ^{a)}	3	71
D	AcOH (large excess against 2d)	3	9.6	C ₆ H ₆ ^{a)}	16	39

a) Water is removed by means of a water separator.

ethanolic hydrogen chloride under reflux for 4 h furnished **7a**·HCl in a low yield (22%). The elemental analysis and MS ($M^+ - \text{HCl}$ m/z : 194) established the molecular formula of **7a** as $\text{C}_9\text{H}_{14}\text{N}_4\text{O}$. The IR spectrum showed no absorption bands corresponding to the two NH groups of **2d**. In the ^1H -NMR spectrum, the presence of a 3H doublet signal at δ 1.40 and a 1H quartet signal at δ 5.04 linked to each other with a coupling constant of 8 Hz suggested the presence of a methylnitrogen group adjacent to two nitrogen atoms. From these data, the structure of **7a** was characterized as 1,2,3,7-tetrahydro-1,2,3,7-tetramethyl-6H-purin-6-one. The hydrochloride of **7a** was mostly hydrolyzed to **2d** under reflux in H_2O for 1.5 h. Improvement of the yield was achieved by employing P_2O_5 as the dehydrating agent under mild reaction conditions: heating of **2d** with **5a** in CHCl_3 containing P_2O_5 in the presence of a catalytic amount of polyphosphoric acid (PPA) gave rise to **7a** in a yield of 61%. The treatment of **2d** with aliphatic aldehydes (**5b–f**), aromatic aldehydes (**5g–m**) and heteroaromatic aldehydes (**5n, o**) under similar conditions afforded 2-monosubstituted 1,2,3,7-tetrahydro-1,3,7-trimethyl-6H-purin-6-ones (**7b–o**) in fairly good yields (Table V). The structures of **7b–o** were assigned on the basis of analytical and spectral data. In the MS of **7**, all the base ion peaks appeared at m/z 179, reflecting elimination at the 2-position (Table V). Treatment of **2d** with cyclohexanone (**6d**) under similar conditions to those described for the aldehydes afforded 1,2,3,7-tetrahydro-1,3,7-trimethyl-6H-purin-6-one-2-spirocyclohexane (**8d**), though in a low yield (13%). This low yield seemed due to lower reactivity and greater steric hindrance with the ketone than with the aldehyde. In order to improve the yield of **8d**, various reaction conditions were examined (Table I). Compound **8d** was not formed in the catalytic reaction using polyphosphoric acid ethyl ester or boron trifluoride etherate, which indicated that the cyclization to **8d** was proton-catalyzed. Use of HCl (method b) inhibited the cyclization due to precipitates of **2d**·HCl. Compound **8d** was obtained in a larger yield by catalysis with *o*-nitrobenzoic acid (method C) than with AcOH (method D). The in-

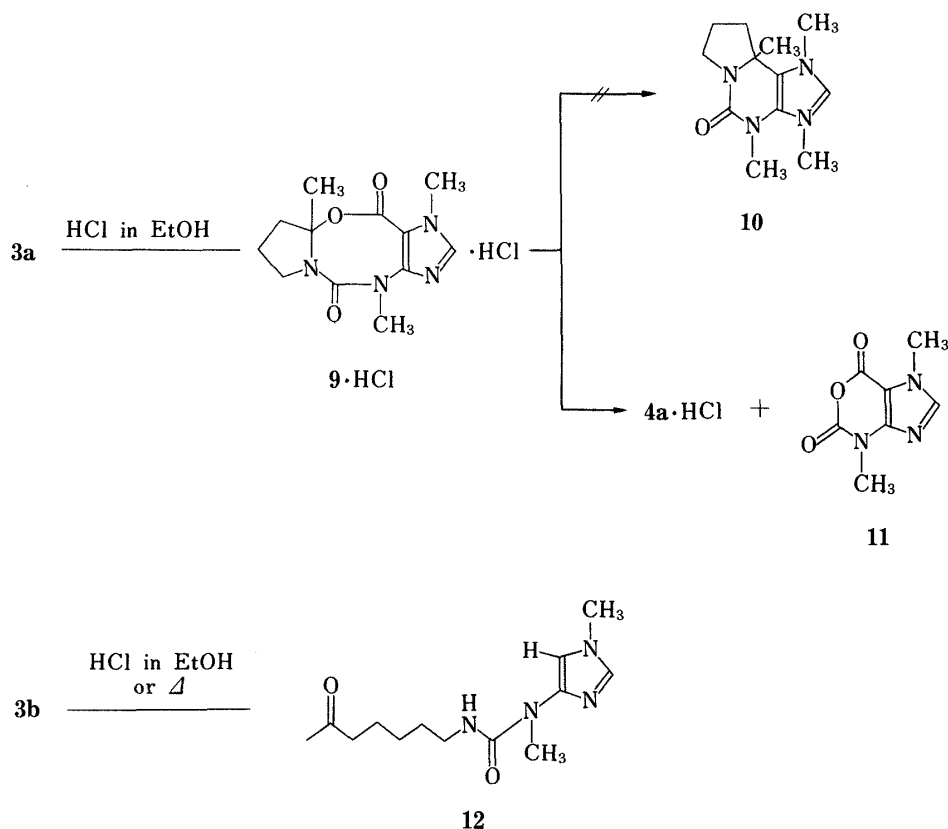


Chart 5

termolecular cyclization of **2d** with ketones (**6b—f**) under the same conditions as used in method C gave 2,2-disubstituted 1,2,3,7-tetrahydro-1,3,7-trimethyl-6*H*-purin-6-ones (**8b—f**) in fairly good yields. However, the reaction of **2d** with acetone (**6a**) by this method did not proceed. Thus, **2d** was refluxed in acetone for 4 h in the presence of ethanolic hydrogen chloride to afford **8a**, though the yield was poor. On the other hand, **2d** did not react with benzophenone or *d*-camphor, presumably because of the bulkiness of the ketones. The structures of **8** were assigned on the basis of analytical and spectral data. In the MS of **8**, the typical base ion peaks formed by elimination at the 2-position were observed (Table VII).

As mentioned above, the procedure reported here proved to be more useful for the synthesis of highly substituted 1,2,3,7-tetrahydro-6*H*-purin-6-ones than the methods reported so far.^{3,4)}

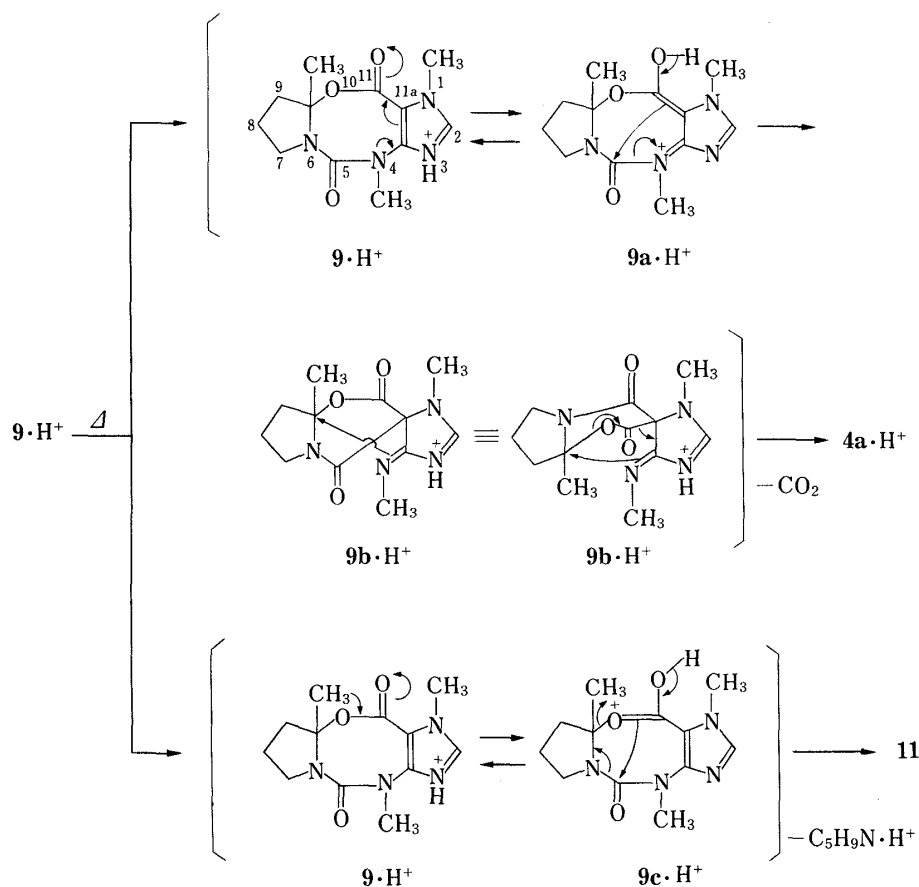


Chart 6

The urea derivatives (**3**) are readily obtainable, so we attempted the synthesis of fused purine derivatives containing the 1,3,6,7-tetrahydro-2*H*-purin-2-one ring system (type **10**), which was isomeric to 1,2,3,7-tetrahydro-6*H*-purin-6-one (type **4**). We applied a reaction analogous to that reported previously¹⁾ to **3a** or **3b**. Intramolecular cyclization of **3a** in the presence of ethanolic hydrogen chloride at room temperature gave the 5,11-dioxo-1*H*,5*H*-imidazo[4,5-*f*]pyrrolo[2,1-*b*][1,3,5]oxadiazocine derivative ($9 \cdot HCl$) in 72% yield. In fast atom bombardment mass spectrum (FAB-MS), $9 \cdot HCl$ showed a quasi-molecular ion peak of the base moiety (MH^+) at m/z 265. In the 1H -NMR spectrum, a 3H singlet signal due to the methyl group at the 9a-position appeared at δ 1.76. In the IR spectrum, $9 \cdot HCl$ showed lactone group absorptions at 1720, 1220 and 1190 cm^{-1} , and the NH, CO and carboxylic OH absorption bands disappeared. These spectral data as well as elemental analysis supported the

structural assignment of **9**. When **9**·HCl was fused at 185–200 °C, the expected compound (**10**) could not be detected, but two compounds, the hydrochloride of **4a** and a crystalline product (**11**) were obtained in poor yields (16% and 6.9%, respectively). The former compound was identified by IR spectrophotometry. The elemental analysis and MS (M^+ m/z : 181) of the latter established the molecular formula as $C_7H_7N_3O_3$. In the IR spectrum, the presence of an anhydride group was indicated by CO absorption bands at 1790 and 1740 cm^{-1} . The 1H -NMR spectrum showed a 3H singlet signal at δ 3.94 and a 1H singlet signal at δ 7.62, which indicated the presence of a 4,5-disubstituted 1-methylimidazole partial structure in **11**. A 3H singlet signal observed at δ 3.56 was shifted downfield by *ca.* 0.3 ppm from that of **3a**. The presence of this signal, as well as the IR spectral data, supported the presence of an anhydride group. These spectral data characterized the structure of **11** as 1,4-dimethyl-4,5-dihydro-5,7-dioxo-1*H*,7*H*-imidazo[4,5-*d*][1,3]oxazine. On the basis of these structural determinations, plausible reaction mechanisms are indicated in Chart 6. Pyrolytic activation of **9** into enol forms (**9a** and **9c**) leads to the formation of **4a** and **11**: in one of the enol forms (**9a**) the CO group is connected with the 11a-position to form a spiro compound (**9b**) (this could not be isolated), which is then decarboxylated into a ring-transformed compound (**4a**); the other enol (**9c**) forms an anhydride group between the 5-position and 10-position by elimination of the pyrrole ring to give **11**. Since the yield of **4a** was twice that of **11** or more, the formation of **9a** and **9c** may be a controlling factor in these reactions. On the other hand, similar treatment of **3b** resulted in decarboxylation to give *N*-[4-(1-methylimidazolyl)]-*N*-methyl-*N'*-(6-oxoheptyl)urea (**12**). This compound (**12**) was also obtained by pyrolysis of **3b**.

Pentoxifylline and propentofylline, both of which are pharmacologically active xanthines, have potent vasodilative activities. We examined some of **4**, **7** and **8** for vasodilative activity in terms of the relaxing effect on KCl-induced vasoconstriction using the mesenteric artery of rabbits and the effect on the blood flow in the rabbit cerebral cortex by the hydrogen clearance technique. Hardly any effect was observed in the latter case. On the other hand, the activity of **7l** was as potent as that of papaverine (ED_{50} : 63 μM) in the former test, and **4a**, **7f**, **7g**, **7j**, **7m**, and **8a–d** also showed slight activity (Table IX). Further studies are in progress in the hope of finding more potent purine ring compounds.

Experimental

All melting points are uncorrected. IR spectra were measured with a Hitachi 285 spectrometer. Mass spectra were taken with a JEOL JMS-01SG or JEOL JMS-DX300 mass spectrometer. 1H -NMR spectra were recorded with a JEOL JNM-MH-100 or JEOL JMN-Fx90Q spectrometer using TMS or DSS as an internal standard. Chemical shifts were given in δ values (ppm) and the abbreviations of signal patterns are: s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet, br=broad. All organic extracts were dried over anhydrous Na_2SO_4 . Column chromatography was done on silica gel (Wakogel C-200).

General Procedure for Preparation of 3-Methyl-5-methylamino-*N*-oxoalkyl-4-imidazolcarboxamide Picrates (2·Picrate) and 3-Methyl-5-(3-oxoalkyl-1-methylureido)-4-imidazolcarboxylic Acids (3)—A solution of **1** (0.02 mol) in 2*N* NaOH (300 ml) was refluxed for 1 h and extracted with $CHCl_3$. The extract was evaporated *in vacuo* to afford a residue, which was converted after column chromatography (**2a**, **2b** and **2c** were eluted with 10:1, 20:1 and 10:1 mixtures of $CHCl_3$ –EtOH, respectively) into the corresponding picrate using Et_2O –picric acid. The salt was recrystallized from Et_2O –EtOH to afford 2·picrate.

After extraction with $CHCl_3$, the aqueous layer was neutralized with conc. HCl and evaporated to dryness *in vacuo* to afford a residue, which was extracted with EtOH. The insoluble material was removed by filtration and the filtrate was evaporated *in vacuo* to afford a residue. The residue was passed through a column of Dowex 50W $\times$ 8 (H^+ form) with EtOH– H_2O (3:2) and the eluate was evaporated *in vacuo* to afford an oil, which was recrystallized from Et_2O –EtOH to give **3**.

General Procedure for Preparation of 4,4a,5,6,7,9-Hexahydro-1,4,4a-trimethyl-9-oxo-1*H*-pyrrolo[1,2-*a*]purine Hydrochloride (4a·HCl) and 4,4a,5,6,7,8,9,11-Octahydro-1,4,4a-trimethyl-11-oxo-1*H*-azepino[1,2-*a*]purine Hydrochloride (4b·HCl)—Excess ethanolic hydrogen chloride was added to a solution of **2** (3 mmol) in abs. EtOH (10 ml).

TABLE II. Physicochemical Data for Caffeidine Homologues (2) and Urea Derivatives (3)

Compd. No.	mp (°C)	Appearance	Formula	MS (m/z)	Analysis (%) Found (Calcd)			Yield (%)
					C	H	N	
2a ·picrate	203—205 (dec.)	Yellow needles	C ₁₁ H ₁₈ N ₄ O ₂ · C ₆ H ₃ N ₃ O ₇	238 (M ⁺ —picric acid), 229 138 (B) ^{a)}	43.73 (43.69)	4.51 (4.53)	20.97 (20.98)	31
2b ·picrate	145—146 (dec.)	Yellow needles	C ₁₃ H ₂₂ N ₄ O ₂ · C ₆ H ₃ N ₃ O ₇	266 (M ⁺ —picric acid), 229 138 (B)	45.85 (46.06)	5.09 (5.09)	19.52 (19.79)	18
2c ·picrate	121—122 (dec.)	Yellow needles	C ₁₄ H ₂₄ N ₄ O ₂ · C ₆ H ₃ N ₃ O ₇	280 (M ⁺ —picric acid), 229 138 (B)	47.09 (47.15)	5.33 (5.34)	19.15 (19.24)	21
3a	127—128 (dec.)	Colorless needles	C ₁₂ H ₁₈ N ₄ O ₄	283 (MH ⁺) ^{b)}	51.14 (51.06)	6.30 (6.43)	20.05 (19.85)	17
3b	124—125 (dec.)	Colorless needles	C ₁₄ H ₂₂ N ₄ O ₄	311 (MH ⁺) ^{b)}	54.31 (54.18)	7.07 (7.14)	17.95 (18.05)	19
3c	127—128 (dec.)	Colorless needles	C ₁₅ H ₂₄ N ₄ O ₄	325 (MH ⁺) ^{b)}	55.28 (55.54)	7.55 (7.46)	17.18 (17.27)	20

a) Base peak. b) Measured by FAB-MS.

The solution was allowed to stand at room temperature for 1—6 d and then evaporated *in vacuo*. The residue was neutralized with aq. NaHCO₃ and the mixture was extracted with CHCl₃. The extract was evaporated *in vacuo* to afford an oil, which was converted after column chromatography (4a and 4b were eluted with 25:1 and 20:1 mixtures of CHCl₃—EtOH, respectively) into the corresponding hydrochloride using Et₂O—HCl. The salt was recrystallized from Et₂O—EtOH to afford colorless needles of 4·HCl.

4a·HCl: Yield 0.29 g (38%). mp 223—225 °C. *Anal.* Calcd for C₁₁H₁₇ClN₄O: C, 51.46; H, 6.67; N, 21.82. Found: C, 51.41; H, 6.70; N, 21.72. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2550, 2250 (N⁺H), 1655 (NCO). ¹H-NMR (DMSO-*d*₆) δ : 1.35 (3H, s, CH₃-C-4a), 1.80—2.32 (4H, m, C-5-H + C-6-H), 2.95 (3H, s, CH₃-N-4), 3.46 (2H, t, *J* = 7 Hz, C-7-H), 3.85 (3H, s, CH₃-N-1), 8.49 (1H, s, C-2-H). MS *m/z*: 220 (M⁺—HCl), 205 (base peak).

4b·HCl: Yield 0.21 g (28%). mp 188—190 °C. *Anal.* Calcd for C₁₃H₂₁ClN₄O: C, 54.83; H, 7.43; N, 19.67. Found: C, 54.78; H, 7.60; N, 19.54. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2670, 2450 (N⁺H), 1660 (NCO). ¹H-NMR (DMSO-*d*₆) δ : 1.05—2.05, 2.20—2.44 (7H, m, 1H, m, C-5-H + C-6-H + C-7-H + C-8-H), 2.70—3.10 (1H, m, C-9-H), 2.96 (3H, s, CH₃-N-4), 3.87 (3H, s, CH₃-N-1), 4.16—4.48 (1H, m, C-9-H), 8.60 (1H, s, C-2-H). MS *m/z*: 248 (M⁺—HCl), 233 (base peak).

1,2,3,7-Tetrahydro-1,2,3,7-tetramethyl-6H-purin-6-one Hydrochloride (7a·HCl)—Excess ethanolic hydrogen chloride was added to a solution of **2d** (1.0 g, 6 mmol) and 90% acetaldehyde (3 ml) in EtOH (30 ml). The mixture was heated at 60 °C for 3 h and evaporated *in vacuo*. The residue was neutralized with aq. NaHCO₃ and the mixture was extracted with CHCl₃. The extract was evaporated *in vacuo* to afford an oil, which was converted, after column chromatography with CHCl₃—EtOH (25:1), into the corresponding hydrochloride by Et₂O—HCl treatment. The salt was recrystallized from Et₂O—EtOH to afford **7a**·HCl. Yield 0.31 g (22%).

Hydrolysis of 7a·HCl—A solution of **7a**·HCl (0.2 g, 0.87 mmol) in H₂O (10 ml) was refluxed for 1.5 h and neutralized with NaHCO₃. The mixture was extracted with CHCl₃ and the extract was evaporated *in vacuo*. The residue was purified by column chromatography using CHCl₃—EtOH (10:1) as the eluent to afford 0.07 g (48%) of **2d**, which was identified by ¹H-NMR spectrometry.

General Procedure for Preparation of 2-Monosubstituted-1,2,3,7-tetrahydro-1,3,7-trimethyl-6H-purin-6-ones (7)—PPA (catalytic amount) and P₂O₅ (0.2 g) were added to a solution of **2d** (0.5 g, 3 mmol) and **5** (excess amount) in dry CHCl₃ (10 ml) and the mixture was refluxed for 2—3.5 h. The reaction mixture was washed with aq. NaHCO₃ and evaporated *in vacuo*. The residue was purified by column chromatography using CHCl₃—EtOH as the eluent to afford **7**, which was directly recrystallized or converted into the corresponding hydrochloride or picrate using Et₂O—HCl or EtOH—picric acid.

1,2,2,3,7-Pentamethyl-1,2,3,7-tetrahydro-6H-purin-6-one (8a)—Excess ethanolic hydrogen chloride was added to a solution of **2d** (1 g) in acetone (**6a**) (20 ml). The solution was refluxed for 6 h and evaporated *in vacuo*. The residue was neutralized with aq. NaHCO₃ and the mixture was extracted with CHCl₃. The extract was evaporated *in vacuo* to give a residue, which was purified by column chromatography using CHCl₃—EtOH (20:1) as the eluent to afford **8a**.

1,2,3,7-Tetrahydro-1,3,7-trimethyl-6H-purin-6-one-2-spirocyclohexane (8d)—Method A: PPA (catalytic

TABLE III. ^1H -NMR and IR Spectral Data for Caffeine Homologues (2)

Compd. No.	¹ H-NMR (δ) ^{a)}					IR (cm ⁻¹) ^{b)}						
	N ₃ -CH ₃ (s)	C ₂ -H (s)	C ₅ -NCH ₃ (s)	CH ₃ CO (s)	C ₄ -Sub.	NH	CONH	N ⁺ H	CO	CON		
					-(CH ₂) _n - CONH						Aromatic proton	
2a·picrate	3.90	8.68	2.88	2.10	1.70 (2H, m, CH ₂), 2.50 (2H, t, J=7 Hz, COCH ₂), 3.22 (2H, q, J=7 Hz, CH ₂ N)	3430	3380	2600—2300	1700	1670		
2b·picrate	3.84	8.58	2.82	2.06	1.10—1.68 (6H, m, CH ₂ × 3), 2.40 (2H, t, J=8 Hz, COCH ₂), 3.16 (2H, q, J=8 Hz, CH ₂ N)	3460	3350	2600—2300	1705	1670		
2c·picrate	3.85	8.65	2.84	2.06	1.10—1.64 (8H, m, CH ₂ × 4), 2.40 (2H, t, J=8 Hz, COCH ₂), 3.20 (2H, q, J=8 Hz, CH ₂ N)	3460	3380	2600—2400	1700	1670		

a) ^1H -NMR spectra were measured in DMSO- d_6 . b) IR spectra were measured by the KBr disc method.

TABLE IV. ¹H-NMR and IR Spectral Data for Urea Derivatives (3)

Compd. No.	¹ H-NMR (δ) ^{a)}					IR (cm ⁻¹) ^{b)}					
	CH ₃ CO (s)	Oxoalkyl group -(CH ₂) _n -	NCH ₃ (s)	Imidazole ring		NH	COOH (br s)	COOH	NH	CO COOH	CON
				N ₃ -CH ₃ (s)	C ₂ -H (s)						
3a	2.12	1.76 (2H, m, CH ₂), 2.50 (2H, t, J=8 Hz, CH ₂ CO), 3.24 (2H, m, CH ₂ N)	3.24	3.90	7.50	5.64 (t, J=4 Hz)	12.30	3380 2500—2300	3260	1705	1640
3b	2.12	1.00—1.80 (6H, m, CH ₂ × 3), 2.40 (2H, t, J=7 Hz, CH ₂ CO), 3.20 (2H, m, CH ₂ N)	3.32	3.92	7.48	5.52 (t, J=4 Hz)	10.64	3380 2600—2400	3320	1720	1650
3c	2.12	1.08—1.62 (8H, m, CH ₂ × 4), 2.41 (2H, t, J=8 Hz, CH ₂ CO), 3.19 (2H, m, CH ₂ N)	3.23	3.91	7.51	5.44 (t, J=4 Hz)	10.54	3390 2600—2400	3280	1710	1640

a) ¹H-NMR spectra were measured in CDCl₃. b) IR spectra were measured by the KBr disc method.

TABLE V. Physicochemical Data for 2-Monosubstituted-1,2,3,7-tetrahydro-1,3,7-trimethyl-6*H*-purin-6-ones (7)

Compd. No.	mp (°C)	Appearance (Recryst. solvent)	Formula	MS (<i>m/z</i>)	Analysis (%) Found (Calcd)			Yield (%)
					C	H	N	
7a ·HCl	189—193	Colorless needles (EtOH–Et ₂ O)	C ₉ H ₁₄ N ₄ O·HCl	194 (M ⁺ – HCl) 179 (B) ^{a)}	46.61 (46.86)	6.68 (6.55)	24.12 (24.29)	61
7b ·HCl	181—184	Colorless needles (EtOH–Et ₂ O)	C ₉ H ₁₃ ClN ₄ O·HCl	228 (M ⁺ – HCl) 179 (B)	40.73 (40.77)	5.34 (5.32)	21.11 (21.13)	46
7c ·HCl	153—156	Colorless needles (EtOH–Et ₂ O)	C ₁₁ H ₁₈ N ₄ O·HCl	222 (M ⁺ – HCl) 179 (B)	50.97 (51.06)	7.61 (7.40)	21.71 (21.65)	65
7d ·picrate (dec.)	149—150	Yellow needles (EtOH–Et ₂ O)	C ₁₁ H ₁₆ N ₄ O· C ₆ H ₃ N ₃ O ₇	220 (M ⁺ – picric acid), 229 179 (B)	45.44 (45.44)	4.31 (4.26)	21.72 (21.82)	22
7e ·picrate (dec.)	156—157	Yellow needles (EtOH–Et ₂ O)	C ₁₆ H ₁₈ N ₄ O· C ₆ H ₃ N ₃ O ₇	282 (M ⁺ – picric acid), 229 179 (B)	51.65 (51.67)	4.09 (4.14)	19.07 (19.17)	61
7f ·HCl	146—149	Colorless needles (EtOH–Et ₂ O)	C ₁₃ H ₂₂ N ₄ O·HCl	250 (M ⁺ – HCl) 179 (B)	54.42 (54.44)	8.28 (8.08)	19.54 (19.53)	55
7g ·HCl	164—166	Colorless needles (EtOH)	C ₁₄ H ₁₆ N ₄ O·HCl	284 (M ⁺ – HCl) 179 (B)	57.34 (57.44)	5.87 (5.85)	19.29 (19.14)	70
7h ·HCl	184—188	Colorless needles (EtOH–Et ₂ O)	C ₁₆ H ₂₀ N ₄ O·HCl	256 (M ⁺ – HCl) 179 (B)	59.88 (59.90)	6.71 (6.60)	17.47 (17.46)	63
7i ·HCl	184—187	Colorless needles (EtOH–Et ₂ O)	C ₁₅ H ₁₈ N ₄ O ₂ ·HCl	286 (M ⁺ – HCl) 179 (B)	55.57 (55.81)	5.97 (5.93)	17.52 (17.36)	91
7j	219—220	Colorless needles (CHCl ₃ –Et ₂ O)	C ₁₄ H ₁₆ N ₄ O ₂	272 (M ⁺) 179 (B)	61.75 (61.75)	5.92 (5.92)	20.65 (20.57)	62
7k	121—122	Yellow needles (Et ₂ O)	C ₁₄ H ₁₅ N ₅ O ₃	301 (M ⁺) 179 (B)	55.58 (55.81)	5.00 (5.02)	23.11 (23.24)	86
7l	157—158	Yellow needles (EtOH–petr. ether)	C ₁₄ H ₁₅ N ₅ O ₃	301 (M ⁺) 179 (B)	55.63 (55.81)	4.96 (5.02)	23.01 (23.24)	82
7m ·HCl	189—192	Colorless needles (EtOH–Et ₂ O)	C ₁₄ H ₁₅ ClN ₄ O· HCl	290 (M ⁺ – HCl) 179 (B)	51.16 (51.39)	4.99 (4.93)	17.38 (17.12)	62
7n ·2HCl	184—187	Colorless needles (MeOH–Et ₂ O)	C ₁₃ H ₁₅ N ₅ O·2HCl	257 (M ⁺ – 2HCl) 179 (B)	47.24 (47.29)	5.26 (5.19)	21.34 (21.21)	68
7o ·HCl	115—116	Colorless needles (EtOH–Et ₂ O)	C ₁₂ H ₁₄ N ₄ O ₂ ·HCl	246 (M ⁺ – HCl) 179 (B)	50.71 (50.98)	5.30 (5.35)	19.60 (19.82)	68

a) Base peak.

amount) and P₂O₅ (0.2 g) were added to a solution of **2d** (0.5 g) and **6d** (1 ml, 9.6 mmol) in dry CHCl₃ (10 ml) and the mixture was refluxed for 4 h. The reaction mixture was washed with aq. NaHCO₃ and evaporated *in vacuo* to give a residue, which was purified by column chromatography using AcOEt–MeOH (25:2) as the eluent to afford **8d**.

Method B: Excess ethanolic hydrogen chloride was added to a solution of **2d** (0.5 g) and **6d** (1 ml) in EtOH (10 ml) until **2d**·HCl precipitated out. The suspension was refluxed for 4 h and evaporated *in vacuo*. The residue was neutralized with aq. NaHCO₃ and the mixture was extracted with CHCl₃. The extract was evaporated *in vacuo* to give a residue, which was purified in the same manner as in method A to afford **8d**.

Method C: A solution of **2d** (0.5 g), **6d** (1 ml) and *o*-nitrobenzoic acid (0.75 g, 4.5 mmol) in C₆H₆ (30 ml) was refluxed for 3 h, with removal of water by means of a water separator. The reaction mixture was washed with aq. NaHCO₃ and evaporated *in vacuo* to give an oil, which was purified in the same manner as in method A to afford **8d**.

Method D: A solution of **2d** (0.5 g), **6d** and AcOH (1 ml) in C₆H₆ (30 ml) was refluxed for 4 h, with removal of water by means of a water separator. The reaction mixture was evaporated *in vacuo* to give a residue, which was purified in the same manner as in method A to afford **8d**.

2,2-Disubstituted-1,2,3,7-tetrahydro-1,3,7-trimethyl-6*H*-purin-6-ones (8b, c, e, f)—A solution of **2d** (0.5 g), **6** (b,

TABLE VI. ¹H-NMR and IR Spectral Data for 2-Monosubstituted-1,2,3,7-tetrahydro-1,3,7-trimethyl-6*H*-purin-6-ones (7)

Compd.	¹ H-NMR (δ)						IR (cm ⁻¹) ^d
	No.	N ₁ -CH ₃ (s)	N ₃ -CH ₃ (s)	N ₇ -CH ₃ (s)	C ₂ -H	C ₈ -H (s)	
					C ₂ -Substituted group	Aromatic proton	
7a ·HCl ^a		3.17	3.00	3.96	5.04 (q, <i>J</i> = 8 Hz)	8.33	1.40 (3H, d, <i>J</i> = 8 Hz, CH ₃) 2500 (br) (N ⁺ H) 1650 (CON)
7b ·HCl ^b		3.19	2.99	3.95	5.25 (t, <i>J</i> = 7 Hz)	8.67	3.95 (2H, d, <i>J</i> = 7 Hz, CH ₂ Cl) 2450 (br) (N ⁺ H) 1650 (CON)
7c ·HCl ^a		3.16	3.05	4.00	4.78 (t, <i>J</i> = 8 Hz)	8.40	0.92 (3H, t, <i>J</i> = 8 Hz, CH ₃), 1.20–2.00 (4H, m, CH ₂ × 2) 2700, 2450 (br) (N ⁺ H) 1160 (CON)
7d ·picrate ^b		2.86	2.79	3.85	5.06 (d, <i>J</i> = 9 Hz)	8.40	1.69 (3H, d, <i>J</i> = 5 Hz, CH ₃), 5.44–6.08 (2H, m, CH=CH) 2700 (br) (N ⁺ H) 1660 (CON)
7e ·picrate ^b		2.94	2.87	3.88	5.32 (d, <i>J</i> = 7 Hz)	8.42	6.44 (1H, dd, <i>J</i> = 18, 7 Hz, C ₂ -CH=), 6.73 (1H, d, <i>J</i> = 18 Hz, CH=C-C ₂), 7.20–7.70 (5H, m, Ph) 2700 (br) (N ⁺ H) 1670 (CON)
7f ·HCl ^a		3.15	3.04	3.94	4.95 (t, <i>J</i> = 7 Hz)	8.37	0.86 (3H, t, <i>J</i> = 8 Hz, CH ₃), 1.30 (6H, m, CH ₂ × 3), 1.83 (2H, m, C ₂ -CH ₂) 2450 (br) (N ⁺ H) 1670 (CON)
7g ·HCl ^a		3.15	3.02	4.04	6.00 (s)	8.42	7.51 (5H, s, Ph) 2500 (br) (N ⁺ H) 1660 (CON)
7h ·HCl ^a		2.93	2.79	4.04	5.07 (s)	8.38	2.31 (3H, s, CH ₃) 2.44 (3H, s, CH ₃) 2500, 2250 (br) (N ⁺ H) 1660 (CON)

7i ·HCl ^{a)}	3.10	2.98	3.86	5.94 (s)	8.41	4.09 (3H, s, OCH ₃), 7.13 (2H, d, <i>J</i> =9 Hz, Ph-H ₂ , H ₆), 7.43 (2H, d, <i>J</i> =9 Hz, Ph-H ₃ , H ₅)	2500, 2260 (br) (N ⁺ H) 1670 (CON)
7j ^{c)}	2.89	2.81	3.86	5.94 (s)	7.24	6.44—7.28 (4H, m, Ph-H ₃ , H ₄ , H ₅ , H ₆)	3200—2300 (OH) 1650 (CON)
7k ^{c)}	3.08	2.96	3.85	6.23 (s)	7.18	9.27 (1H, br s, OH) 7.35—7.56 (3H, m, Ph-H ₄ , H ₅ , H ₆), 7.78 (1H, dd, <i>J</i> =7, 2 Hz, Ph-H ₃)	1650 (CON)
7l ^{c)}	3.01	2.98	3.87	5.51 (s)	7.21	7.52 (1H, t, <i>J</i> =9 Hz, Ph-H ₅) 7.73 (1H, d, <i>J</i> =9 Hz, Ph-H ₆) 8.20 (1H, d, <i>J</i> =9 Hz, Ph-H ₄) 8.24 (1H, s, Ph-H ₂)	1640 (CON)
7m ·HCl ^{c)}	3.08	2.97	3.97	5.96 (s)	8.30	7.45 (4H, s, Ph-H ₂ , H ₅ , H ₆)	2450, 2200 (br) (N ⁺ H) 1670 (CON)
7n ·HCl ^{b)}	3.11	3.01	3.83	6.26 (s)	8.01	7.88 (2H, d, <i>J</i> =6 Hz, Py-H ₃ , H ₅), 8.86 (2H, d, <i>J</i> =6 Hz, Py-H ₂ , H ₆)	2300 (br) (N ⁺ H) 1680 (CON)
7o ·HCl ^{b)}	3.08	2.89	3.90	6.09 (s)	8.59	6.43 (2H, m, fura-H ₃ , H ₄) 7.68 (1H, s, fura-H ₅)	2450, 2150 (br) (N ⁺ H) 1640 (CON)

a) ¹H-NMR spectra were measured in D₂O. b) ¹H-NMR spectra were measured in DMSO-*d*₆. c) ¹H-NMR spectra were measured in CDCl₃. d) IR spectra were measured by the KBr disc method.

TABLE VII. Physicochemical Data for 2,2-Disubstituted-1,2,3,7-tetrahydro-1,3,7-trimethyl-6*H*-purin-6-ones (**8**)

Compd. No.	mp (°C)	Appearance (Recryst. solvent)	Formula	MS (<i>m/z</i>)	Analysis (%) Found (Calcd)			Yield (%)
					C	H	N	
8a	115—116	Colorless plates (Et ₂ O)	C ₁₀ H ₁₆ N ₄ O	208 (M ⁺) 193 (B) ^{a)}	57.54 (57.67)	7.83 7.74	26.82 26.90)	22
8b ·HCl	199—203	Colorless needles (Et ₂ O–EtOH)	C ₁₄ H ₂₄ N ₄ O·HCl	264 (M ⁺ – HCl) 221 (B)	55.60 (55.90)	8.33 8.38	18.46 18.62)	51
8c	108—109	Colorless needles (Et ₂ O)	C ₁₂ H ₁₈ N ₄ O	234 (M ⁺) 205 (B)	61.38 (61.52)	7.87 7.74	24.11 23.91)	63
8d	156—157	Colorless needles (AcOEt–Et ₂ O)	C ₁₃ H ₂₀ N ₄ O	248 (M ⁺) 205 (B)	62.84 (62.88)	8.24 8.12	22.56 22.56)	71
8e ·HCl	185—188	Colorless needles (Et ₂ O–EtOH)	C ₁₂ H ₁₈ N ₄ O ₃ ·HCl	267 (MH ⁺ – HCl) ^{b)} 193 (B)	47.43 (47.61)	6.33 6.33	18.29 18.51)	72
8f ·HCl	182—186	Colorless needles (Et ₂ O–EtOH)	C ₁₅ H ₁₈ N ₄ O·HCl	270 (M ⁺ – HCl) 255 (B)	58.70 (58.73)	6.23 6.24	18.29 18.26)	80

a) Base peak. b) Measured by FAB-MS.

TABLE VIII. ¹H-NMR and IR Spectral Data for 2,2-Disubstituted-1,2,3,7-tetrahydro-1,3,7-trimethyl-6*H*-purin-6-ones (**8**)

Compd. No.	¹ H-NMR (δ)					IR (cm ⁻¹) ^{c)}
	N ₁ -CH ₃ (s)	N ₃ -CH ₃ (s)	N ₇ -CH ₃ (s)	C ₈ -H (s)	C ₂ -Substituted group	
8a ^{a)}	2.98	2.96	3.87	7.13	1.49 (6H, s, CH ₃ × 2)	1640 (CON)
8b ·HCl ^{b)}	3.01	2.95	3.93	8.23	0.92 (6H, t, <i>J</i> = 7 Hz, CH ₃ × 2) 1.10—2.02 (8H, m, CH ₂ × 4)	2700, 2450 (br) (N ⁺ H) 1660 (CON)
8c ^{a)}	3.00	2.82	3.88	7.24	1.60—2.30 (8H, m, CH ₂ × 4)	1640 (CON)
8d ^{a)}	2.98	2.71	3.89	7.27	1.30—1.90 (8H, m, CH ₂ × 4) 2.10—2.30 (2H, m, CH ₂)	1650 (CON)
8e ·HCl ^{b)}	3.20	3.11	3.96	8.39	1.19 (3H, t, <i>J</i> = 7 Hz, CH ₃) 1.99 (3H, s, CH ₃) 4.21 (2H, q, <i>J</i> = 7 Hz, CH ₂)	2150, 2450 (br) (N ⁺ H) 1740 (CO), 1660 (CON), 1010 (C–O–CO)
8f ·HCl ^{a)}	2.85	2.54	4.17	9.16	1.88 (3H, s, CH ₃) 7.51 (5H, m, Ph)	2650 (br) (N ⁺ H) 1660 (CON)

a) ¹H-NMR spectra were measured in CDCl₃. b) ¹H-NMR spectra were measured in D₂O. c) IR spectra were measured by the KBr disc method.

c, e, f; excess amount) and *o*-nitrobenzoic acid (0.75 g) in C₆H₆ (30 ml) was refluxed for 3—18 h, with removal of water by means of a water separator. The reaction mixture was washed with aq. NaHCO₃ and evaporated *in vacuo*. The residue was purified by column chromatography using CHCl₃–EtOH as the eluent to afford **8**, which was directly recrystallized or converted into the corresponding hydrochloride.

4,7,8,9,9a,11-Hexahydro-1,4,9a-trimethyl-5,11-dioxo-1*H*,5*H*-imidazo[4,5-*f*]pyrrolo[2,1-*b*][1,3,5]oxadiazocine Hydrochloride (9·HCl)—Excess ethanolic hydrogen chloride was added to a solution of **3a** (0.6 g, 2 mmol) in abs. EtOH (5 ml). The solution was left at room temperature overnight. The precipitated crystals were recrystallized from EtOH to afford 0.43 g (72%) of 9·HCl as colorless needles. mp 168—169 °C (dec.). Anal. Calcd for C₁₂H₁₇ClN₄O₃: C, 47.93; H, 5.70; N, 18.63. Found: C, 48.09; H, 5.93; N, 18.51. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 2830—2250 (≡N⁺H), 1720 (OCO), 1680 (CON), 1220, 1190 (OCO). ¹H-NMR (CD₃OD) δ: 1.76 (3H, s, CH₃–C-9a), 2.05—2.78 (4H, m, C-8-H + C-9-H), 3.43 (3H, s, CH₃–N-4), 3.64 (2H, t, *J* = 6 Hz, C-7-H), 4.04 (3H, s, CH₃–N-1), 9.16 (1H, s, C-2-H). FAB-MS *m/z*: 265 (MH⁺ – HCl).

Pyrolysis of 9·HCl—Heating of 9·HCl (1.2 g, 4 mmol) at 180—190 °C for 20 min gave a brown oil. The oil was purified by column chromatography using CHCl₃–EtOH (19:1) as the eluent. The first fraction afforded 0.05 g

TABLE IX. Relaxing Effect of Fused Purine Derivatives (4) and 1,2,3,7-Tetrahydro-6H-purin-6-ones (7, 8)

	Compd. No.									
	4a	7f	7g	7j	7k	7m	8a	8b	8c	8d
Relaxing effect vs. papaverine ^{a)} (%)	5	27	22	28	37	20	35	33	35	37

a) Expressed as % of papaverine-induced relaxation.

(6.9%) of 1,4-dimethyl-4,5-dihydro-5,7-dioxo-1H,7H-imidazo[4,5-d][1,3]oxazine (11) as colorless needles (from Et₂O). mp 185—187 °C. *Anal.* Calcd for C₇H₇N₃O₃: C, 46.41; H, 3.89; N, 23.20. Found: C, 46.44; H, 3.94; N, 23.30. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1790, 1740 (CO). ¹H-NMR (CDCl₃) δ : 3.56 (3H, s, CH₃-N-4), 3.94 (3H, s, CH₃-N-1), 7.62 (1H, s, C-2-H). MS *m/z*: 181 (M⁺), 137 (M⁺ - CO₂), 109 (base peak).

The second fraction was evaporated *in vacuo* to give an oil, which was converted into the hydrochloride of 4a by Et₂O-HCl treatment. Yield 0.16 g (16%). The salt was identified by IR spectrophotometry.

N-[4-(1-Methylimidazolyl)]-N-methyl-N'-(6-oxoheptyl)urea Picrate (12·Picrate)—a) Excess ethanolic hydrogen chloride was added to a solution of 3b (0.2 g, 0.65 mmol) in abs. EtOH (5 ml). Then the solution was left at room temperature for 5 d and evaporated *in vacuo*. The residue was neutralized with aq. NaHCO₃ and the mixture was extracted with CHCl₃. The extract was evaporated *in vacuo* to afford an oil, which was converted, after column chromatography with CHCl₃-EtOH (20: 1), into the picrate of 12 as yellow prisms (from Et₂O-EtOH). Yield 0.15 g (47%). mp 90—91 °C. *Anal.* Calcd for C₁₉H₂₅N₇O₉: C, 46.06; H, 5.09; N, 19.79. Found: C, 45.97; H, 5.09; N, 19.77. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3390 (CONH), 1710 (CO), 1650 (CON). ¹H-NMR (DMSO-*d*₆) δ : 1.08—1.64 (6H, m, CH₂CH₂CH₂CH₂CH₂), 2.06 (3H, s, CH₃CO), 2.39 (2H, t, *J* = 7 Hz, CH₃COCH₂), 3.04 (2H, t, *J* = 7 Hz, CH₂NH), 3.12 (3H, s, CH₃NH), 3.76 (3H, s, CH₃-N-1), 7.00 (1H, br s, NHCO), 7.32 (1H, d, *J* = 2 Hz, imidazole 5-H), 8.48 (2H, s, aromatic H), 8.64 (1H, d, *J* = 2 Hz, imidazole 2-H). MS *m/z*: 266 (M⁺ - picric acid).

b) Compound 3b (0.15 g, 0.48 mmol) was heated at 130—135 °C for 40 min and changed into a brown oil. The oil was purified in the same manner as described in the preceding paragraph to afford the picrate of 12. Yield 0.07 g (29%).

Relaxing Effect on KCl-Induced Vasocontraction—Male albino rabbits were killed by air embolism. The superior mesenteric artery was removed and cut into helical strips of 0.5 × 15 mm. Each vascular strip was vertically suspended in a 20 ml organ bath filled with physiological saline solution (PSS) the temperature of which was maintained at 37 °C. The composition of the PSS was, in millimolar concentrations, NaCl, 115; KCl, 4.7; CaCl₂·2H₂O, 2.5; MgCl₂·6H₂O, 1.2; NaHCO₃, 25; KH₂PO₄, 1.2; and dextrose, 10.0. A mixture of O₂ and CO₂ (19: 1) was constantly bubbled through the PSS in the organ bath. The mechanical activity was recorded isometrically by means of a force-displacement transducer (Nihon Kohden, TB-612T). An initial resting tension of 1 g was applied to the arterial strip. Before initiation of the experiments, the strips were allowed to equilibrate for 1 h in the PSS, during which the bathing solution was replaced every 15 min with fresh PSS. In all experiments, pre-contraction was produced twice by the addition of KCl (final concentration of KCl in the bath was 54.7 mM), before a dose-response curve was determined. After the vascular strip had attained a submaximal steady-state level of tone in the presence of 20 mM KCl, increasing cumulative doses of a test compound were added to the bath to obtain cumulative dose-relaxation curves for 4a, 4b, 7a—c, 7f, 7g, 7i—o and 8a—f. Papaverine at a concentration of 100 μM was added at the end of each experiment and the relaxation induced by papaverine was taken as 100%. The response of the strip to each compound was calculated as a percentage of the maximum relaxation and the ED₅₀ values were read from a plot of percent relaxation vs. log concentration of the compounds. The results are summarized in Table IX. The ED₅₀ value for 7i was 63 μM.

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