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Summary

It has been found that the Friedel-Crafts reaction of 3-iodoanisole with acetyl chloride yielded, contrary to Oki's report, four products, 2′-hydroxy-4′-iodo-, 2′-iodo-4′-hydroxy, 2′-iodo-4′-methoxy-, and 2′-methoxy-4′-iodoacetophenone.

The Ullmann condensation of 2′-iodo-4′-methoxyacetophenone with methyl 2-bromo- or 2-iodo-veratrate, followed by hydrolysis, gave, in a poor yield, 2′-acetyl-5,5′6-trimethoxy-2-biphenylcarboxylic acid which was characterized as its oxime as well as its methyl ester.

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186. Takanobu Itai[*1] and Genzō Itō[*2] : Potential Anti-Cancer Agents. VII.[1] Azido-purine Derivatives.

(*National Institute of Hygienic Sciences*[*1] *and Shōwa Pharmaceutical College*[*2])

As 6-azidopurine[2] and 7-azidomethyl-8-chlorotheophylline[3] have been known to show anti-cancer action, an attempt was made to synthesize some azido derivatives of purine for screening their action. Starting from 2,6-dichloro-7-methylpurine (I) and 2,6,8-trichloro-7-methylpurine (II), the former had been synthesized from theobromine with phosphorus oxychloride,[4] and the latter with phosphorus oxychloride and phosphorus pentachloride.[5] Azido group was produced by an usual approach, that is, chloro group was changed to hydrazino group by heating with hydrazine, and then by the reaction with nitrous acid to azide group. In order to prove their structure, these azido derivatives were reduced to amino derivatives and compared with amino derivatives already known in literatures. If not, amino derivatives were synthesized from corresponding chloro derivatives by heating with ammonia.

Fischer[6] had already reported 6-hydrazinopurine by heating 6-chloro-compound with anhydrous hydrazine, and Montgomery[7] also studied 2- and 6-derivatives examining the reactivity of chlorine atom.

In the experiments of this series, at first, (I) and (II) were converted to 2-chloro-6-ethoxy-7-methylpurine[4] (III), 2,6-dichloro-8-ethoxy-7-methylpurine[8] (IV), and 2-chloro-6,8-diethoxy-7-methylpurine[4] (V). By heating (I), (II), (III), (IV), and (V) with 80%

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1) Y. Itai, T. Nakashima : Part VI. Submitted to this Bulletin.
2) Ciba Foundation Symposium, Chem. and Biol. of Purines, 8 (1957).
3) T. Itai, S. Kamiya : unpublished.
4) E. Fischer : Ber., **30**, 2402 (1897).
5) *Idem* : *Ibid.*, **28**, 2480 (1895).
6) *Idem* : *Ibid.*, **31**, 104 (1899).
7) J.A. Montogomery, L.B. Holum : J. Am. Chem. Soc., **79**, 2187 (1957).
8) E. Fischer : Ber., **30**, 1847 (1897).

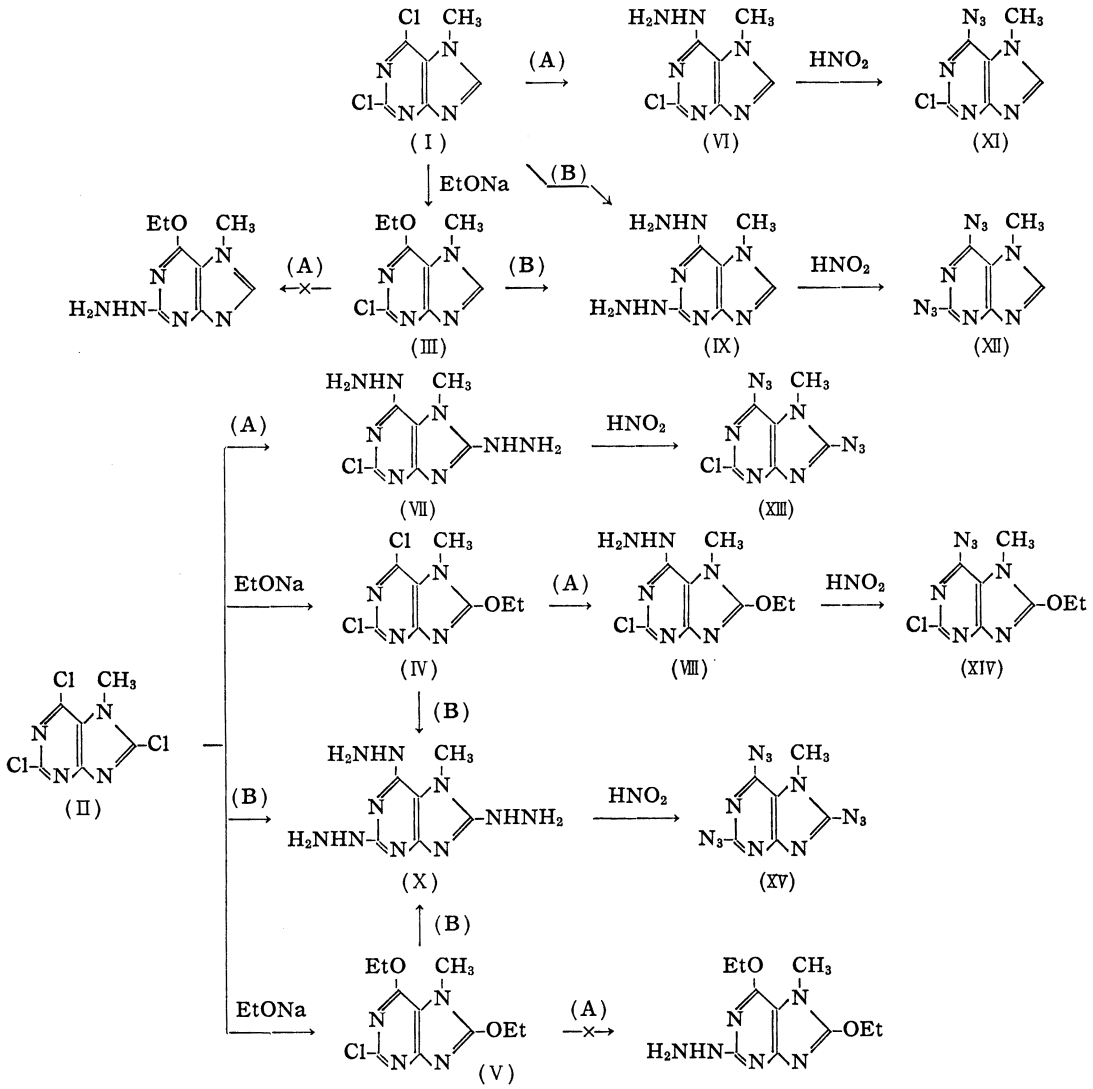
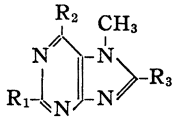


Table I. 7-Methylpurine Hydrazino Derivatives



Compd. No.	Substituents R_1	R_2	R_3	Crystalline form	m.p. (°C) (decomp.)	Yield (%)
(VI)	Cl	$NHNH_2$	H	needles	200	70
(VII)	Cl	$NHNH_2$	$NHNH_2$	needles[a)]	198	70
(VIII)	Cl	$NHNH_2$	EtO	needles	207	60
(IX)	$NHNH_2$	$NHNH_2$	H	needles	258~260	80 (from (I)) 77 (from (III))
(X)	$NHNH_2$	$NHNH_2$	$NHNH_2$	needles	260~262	95 (from (II)) 52 (from (IV)) 41 (from (V))

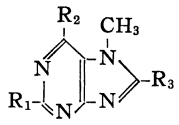
a) Hydrochloride.

ethanolic hydrazinehydrate solution on a water bath, 2-chloro-6-hydrazino-7-methylpurine (VI), 2-chloro-6,8-dihydrazino-7-methylpurine (VII), and 2-chloro-6-hydrazino-8-ethoxy-7-methylpurine (VIII) were produced. But (III) and (V) did not react at all, owing to the inactivity of 2-chloro- and 6-ethoxy-groups.

Next, they were boiled with 80% hydrazine hydrate, and 2,6-dihydrazino-7-methylpurine (IX) was obtained from (I) and (III), 2,6,8-trihydrazino-7-methylpurine (X) from (II), (IV) and (V), respectively. At this condition, chlorine atom at 2-position and ethoxy groups at 6- and 8-position were all substituted by hydrazine. The results are shown in Table I.

These hydrazino-compounds were reacted with sodium nitrite in the presence of hydrochloric acid, as generally known. The products were recrystallized from diluted ethanol, which are listed in Table II. They exploded violently on melting point determination.

Table II. 7-Methylpurine Azide Derivatives

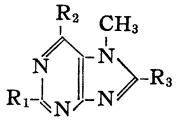


Compd. No.	Substituents			Crystalline form	m.p. (°C) (decomp.)	Yield (%)	Infrared absorption ($-N=N^+=N^-$) (in KBr, cm^{-1})
	R_1	R_2	R_3				
(XI)	Cl	N_3	H	needles	190~191	82	2145, 2220
(XII)	N_3	N_3	H	needles	175~180	83	2140, 2175, 2220
(XIII)	Cl	N_3	N_3	needles	190~195	50	2145, 2175, 2215
(XIV)	Cl	N_3	EtO	needles	160~163	81	2120, 2140
(XV)	N_3	N_3	N_3	needles	155	44	2110, 2135, 2175, 2225
(XVI)	8-azidotheobromine			scales	170~180	50	2085, 2145, 2200

These azido-derivatives were led to corresponding amino-derivatives by catalytic hydrogenation over 10% palladium-charcoal. As one mole of nitrogen evolved in this reaction, the volume of gas in eudiometer did not reduce. Then, it was necessary to change the gas in the reaction flask every 5 minutes, and by this, reduction was completed after 30 minutes, and the amino-derivatives are obtained in good yields. The results are tabulated in Table III. In this reaction, chlorine atom at 2-position was not replaced by hydrogen.[9]

The amino-compounds, thus obtained, coincided entirely with amino-compounds[6,10]

Table III. 7-Methylpurine Amino Derivatives



Compd. No.	Substituent			Crystalline form	m.p. (°C) (decomp.)	Yield (from azido-compd.) (%)
	R_1	R_2	R_3			
(XVII)	Cl	NH_2	H	needles	284	89
(XVIII)	NH_2	NH_2	H	needles	360	95
(XIX)	Cl	NH_2	NH_2	needles	311~312	63
(XX)	Cl	NH_2	EtO	needles	242~243	99
(XXI)	NH_2	NH_2	NH_2	plates	335~340	58
(XXII)	8-aminotheobromine			needles	near 400	57

9) S.R. Breshears, *et al.* : J. Am. Chem. Soc., **81**, 379 (1959).
10) Boehringer, Soehne : D.R.P., 164425.

synthesized by heating corresponding chloro-compounds with ammonia by mixed melting points determination and their infrared spectra, except (XXI).

(XX) was hydrolyzed to 8-hydroxy compound, which was shown to be identical with 2-chloro-6-amino-7-methyl-8-hydroxypurine[11] (XXIII), obtained by amination of 2,6-dichloro-7-methyl-8-hydroxypurine. In this connection, though (II) could be led to (XIX) in a good yield (70%) by heating with 28% ammonia in a sealed tube at 170~180° for 7 hours, (XXI) was never obtained.

As these azido groups were located adjacent to nitrogen atoms in rings, it was presumed that tetrazole rings might be formed.[12] But, all of their infrared spectra have strong absorption bands near 2140 cm^{-1}, characteristic to an azido group.[13] With this fact together with the results from hydrogenation of azido-compounds, it might be thought that the rings existed as $-N=N^+=N^-$, and did not form tetrazole rings.

(XI) was found to be carcinostatic and bacteriostatic, and (XIV) and (XVI) were slightly carcinostatic, in the screening tests *in vitro*, which were performed in the Department of Microbiology, National Institute of Hygienic Sciences.

Experimental

Preparation of Hydrazino Compounds——Among the hydrazino-compounds listed in Table I, (VI), (VII) and (VIII) were prepared by A-method, and (IX) and (X) were prepared by B-method.

A-method——To a solution of 500 mg. of (I) suspended in 200 ml. of 95% EtOH, 1.5 ml. of 80% $NH_2NH_2 \cdot H_2O$ was added and the mixture was refluxed on a steam bath for 1 hr. After cool, the residue was filtered, washed with EtOH and was recrystallized from 50% MeOH to colorless needles. Then the filtrate was evaporated which gave the same residue. Total yield, 340 mg. (70%).

B-Method——A mixture of 500 mg. of (I) and 30 ml. of 80% $NH_2NH_2 \cdot H_2O$ was refluxed in an oil bath for 1 hr. After cool the residue was filtered and washed with H_2O, EtOH and $CHCl_3$. Yield, 380 mg. (80%). Colorless needles (from 50% MeOH), m.p. 258~260°(decomp.).

Preparation of Azido Compounds——All of the compounds listed in Table II were prepared from 7-methylpurine hydrazino derivatives by a method similar to the synthesis of (XI) from (VI).

2-Chloro-6-azido-7-methylpurine (XI)——To a solution of 150 mg. of (VI) dissolved in 15 ml. of 3% HCl, a solution of 55 mg. of $NaNO_2$ dissolved in 3 ml. of H_2O was added dropwise with cooling at 0°. After standing for 30 min., the solution was neutralized with $NaHCO_3$. The residue was filtered and washed with H_2O. The crude product was recrystallized from 50% EtOH after treatment with charcoal to give colorless needles. Yield, 130 mg. (82%), m.p. 190~191° (explosive).

Table IV. Analytical Data of Azido-Compounds

Compd. No.	Formula	Calcd. (%)			Found (%)		
		C	H	N	C	H	N
(XI)	$C_6H_4N_7Cl$	34.38	1.92	46.78	35.43	1.82	47.36
(XII)	$C_7H_4N_{10}$	33.33	1.87	64.80	34.16	1.94	64.76
(XIII)	$C_6H_3N_{10}Cl$	28.75	1.21	55.89	30.26	1.27	55.97
(XIV)	$C_8H_8ON_7Cl$	37.88	3.18	38.66	38.06	3.17	38.69
(XV)	$C_6H_3N_{13}$	28.02	1.18	70.81	29.03	0.98	71.13
(XVI)	$C_7H_7O_2N_7$	38.01	3.19	44.33	38.06	3.10	44.62

Reduction of Azido Compounds——All of the compounds listed in Table III were prepared from 7-methylpurine-azido derivatives listed in Table II by the catalytic reduction over 10% Pd-C, and the method of reduction was same to method of the following synthesis of (XVII).

2-Chloro-6-amino-7-methylpurine (XVII)——A mixture of 200 mg. of (XI) in 60 ml. of 95% EtOH was hydrogenated over 100 mg. of 10% Pd-C for 30 min. opening a cock of flask every 5 min. After removal of the catalyst by filtration, EtOH was evaporated to dryness. The residue was recrystallized from H_2O to colorless needles, m.p. 284°(decomp.). Yield, 155 mg. (89%).

11) E. Fisher: Ber., **31**, 109 (1898).
12) J. A. Johnson, *et al.*: J. Am. Chem. Soc., **80**, 700 (1958).
13) S. R. Breshears, *et al.*: *Ibid.*, **81**, 379 (1959).

Table V. Analytical Nitrogen Data of Amino-Compounds

Compd. No.	Formula	Calcd. (%) N	Found (%) N
(XVII)	$C_6H_6N_5Cl$	38.15	38.22
(XVIII)	$C_6H_8N_6$	51.20	51.19
(XIX)	$C_6H_7N_6Cl$	42.31	43.15
(XX)	$C_8H_{10}ON_5Cl$	30.77	30.67
(XXI)	$C_6H_9N_7$	54.72	54.76
(XXII)	$C_7H_9O_2N_5 \cdot HCl$	30.24	30.26

2-Chloro-6,8-diamino-7-methylpurine (XIX) from 2,6,8-Trichloro-7-methylpurine (II)——A mixture of 300 mg. of (II) and 15 ml. of 28% NH_4OH was heated in a sealed glass tube at 170~180° for 7 hr. After cool colorless needles obtained, were washed with H_2O and $CHCl_3$ and recrystallized from H_2O to a pure sample, m.p. 311~312°(decomp.). Yield, 180 mg. (71%). *Anal.* Calcd. for $C_6H_7N_6Cl$: N, 42.31. Found : N, 43.18.

2-Chloro-6-amino-7-methyl-8-hydroxypurine (XXIII) from 2-Chloro-6-amino-7-methyl-8-ethoxypurine (XX)——A mixture of 140 mg. of (XX) and 3 ml. of conc. HCl was heated on a steam bath for 5 min. To the mixture 20 ml. of H_2O was added and the residue was filtered and washed with 2% HCl and H_2O. The residue was dissolved in 10% NH_4OH, the solution was filtered and evaporated to expel NH_3. Then colorless plates were obtained, m.p. 355°(decomp.). Yield, 103 mg. (77%). *Anal.* Calcd. for $C_6H_6ON_5Cl \cdot H_2O$: N, 32.18. Found : N, 31.74.

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Summary

Azido derivatives of 7-methylpurine were synthesized from 2,6-dichloro-7-methylpurine (I) and 2,6,8-trichloro-7-methylpurine (II), and they were catalytically reduced to corresponding amino derivatives. From the results, it might be thought that the azido groups on purines existed as $-N=N^+=N^-$ and did not form tetrazole ring.

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