Notes

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Hidetaka Yuki,*2 Torahiko Kishikawa, Yasuo Tohira, and Kazuhiro Watanabe: Synthesis of Purine and Pyrimidine Derivatives of Arsonic Acid.

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In the previous paper,[1] it has been demonstrated that some sulfhydryl reagents acted as antiviral agents, but arsanilic acid and phenylarsine oxide were both inactive against the Adenovirus type 5 regardless of the considerable reaction rate of the latter with an SH-group of methyl N-acethyl cysteinate.

There are, however, several papers dealing with the antiviral activity of arsenicals,[2~4] and Peters[5] suggested that arsenicals would be worthy of consideration as antiviral agents. In the present study, in order to find more effective antiviral arsenicals, purine and pyrimidine derivatives have been prepared, which might act as antimetabolite in addition to the arsenical function.

To prepare the above-mentioned compounds, 2-amino-4,6-dichloropyrimidine was treated with arsanilic acid at the presence of hydrochloric acid as a catalyst according to a reported method[6] to give N-(2-amino-4-chloro-6-pyrimidinyl)arsanilic acid (I), but another chlorine could not be replaced even in the presence of excess of arsanilic acid. This chlorine did not react with sodium ethoxide at the boiling point of the alcohol either, but was reacted with sodium alkoxides of higher boiling point such as butanol or ethyleneglycol to afford (II) and (III). However, because of a strong electron attracting effect of 5-nitro group, both chlorine atoms of 4,6-dichloro-5-nitropyrimidine (IV and V) were easily replaced with arsanilic acid. In the case of 2,4,6-trichloro-5-nitropyrimidine (V), one of three chlorine atoms has remained unchanged, which was assumed to be that of position 2 by analogy with the high reactivity of chlorine atoms at position 4 and 6 of (IV). 5-Amino-4,6-dichloropyrimidine also reacted with one molar of arsanilic acid to afford N-(5-amino-4-chloro-6-pyrimidinyl)arsanilic acid (VIII) remaining the second chlorine unchanged, but once it has been cyclized to *p*-(6-chloro-9*H*-purin-9-yl)benzenearsonic acid (IX) the chlorine atom regained the activity and was easily replaced by primary and secondary amines. Replacement by aliphatic amine was accomplished in excess of that, and replacement by aromatic amine required presence of hydrochloric acid as a catalyst. Reaction with formic acid afforded hydroxy compound (XXII), and reaction with sodium methoxide and phenoxide gave the corresponding methoxy-(XXIII), and phenoxy-compound (XXIV). 6-Chloropurine was also reacted with arsanilic acid to yield N-(6-purinyl)arsanilic acid (XXV).

Most compounds prepared had to be purified by reprecipitation from alkaline solution by addition of hydrochloric acid because of their insolubility in water and organic

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1) Hidetaka Yuki, *et al.*: This Bulletin, **14**, 139 (1966).
2) Monroe D. Eaton, *et al.*: Proc. Soc. Exptl. Biol. Med., **71**, 508(1949).
3) M. Sasatani: Ann. Paediat, Japan, **5**, 1112 (1959).
4) *Idem*: *Ibid.*, **5**, 573 (1959).
5) R. A. Peters: Health Hyg., **15**, 122 (1952).
6) Paymond J. Andres, *et al.*: J. Am. Chem. Soc., **67**, 946 (1945).

solvents, and showed higher decomposition points than 250° as is seen in the Table 1. Repeated attempts to reduce these arsonic acids to the corresponding arsenoxides were unsuccessful.

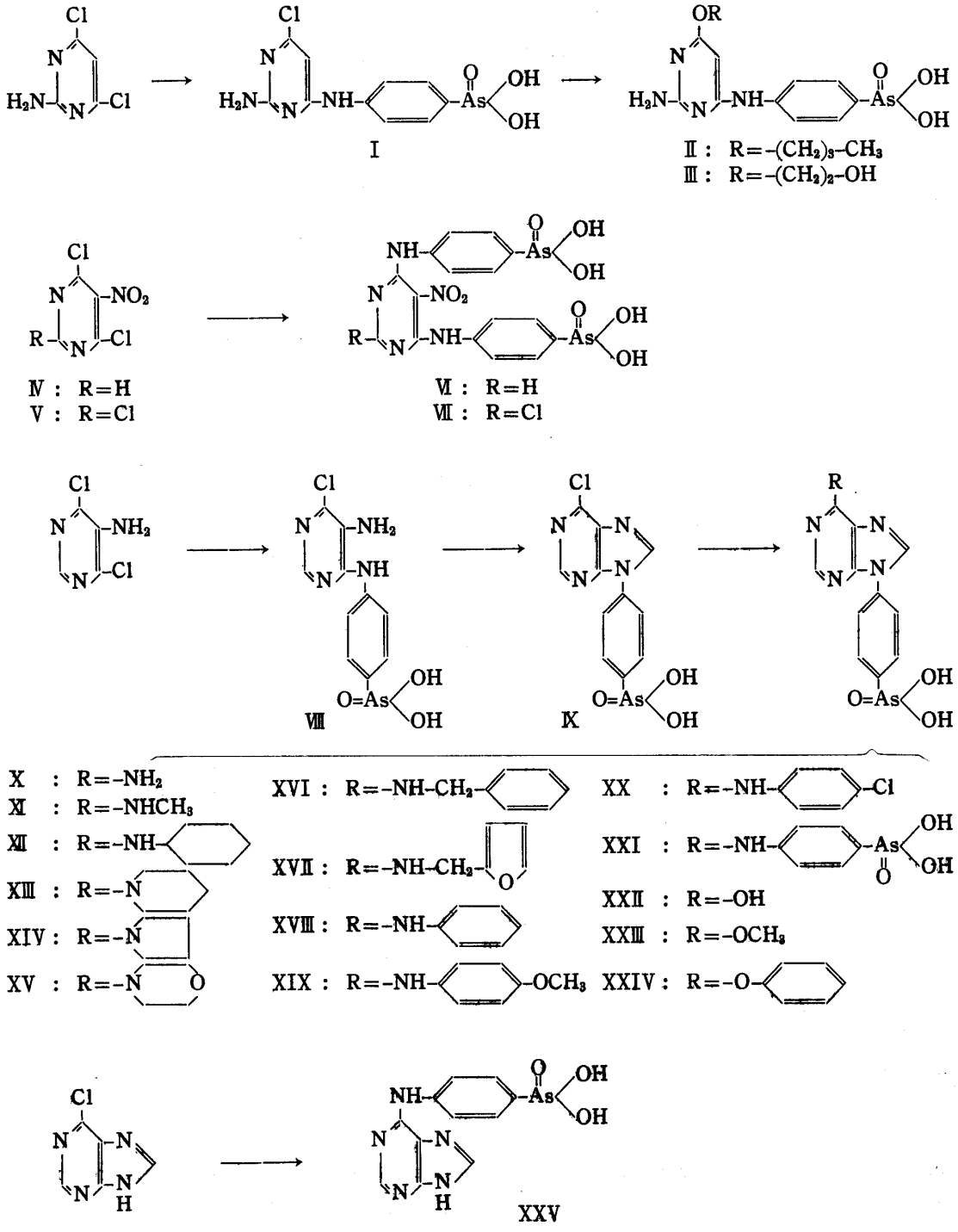

Chart 1.

In a preliminary experiment on a paper disc agar difusion method, compound (XXIII) was found to be active against Newcastle disease virus. Antibacterial and antitumor activity were all negative.

Table I. Purine and Pyrimidine Derivatives of Arsonic Acid

Compounds	m.p. (°C)	Purification	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
II	175 (dp.)	EtOH–H_2O	$C_{14}H_{19}O_4N_4As \cdot 2H_2O$	40.18	5.99	13.40	40.01	6.00	13.33
III	>250	H_2O	$C_{12}H_{15}O_5N_4As_2 \cdot H_2O$	37.10	4.38	14.43	36.98	4.46	14.33
VI	>250	RP[a]	$C_{16}H_{15}O_8N_5As$	34.55	2.69	12.58	34.10	2.82	12.33
VII	>250	RP	$C_{16}H_{14}O_8N_5ClAs$	32.50	2.38	11.86	32.77	2.87	11.92
VIII	253~255 (dp.)	RP	$C_{10}H_{10}O_3N_4ClAs$	34.83	2.90	16.25	35.09	3.00	16.32
IX	>250	RP	$C_{11}H_8O_3N_4ClAs$	37.29	2.25	15.80	37.88	2.85	16.08
X	>250	RP	$C_{11}H_{10}O_3N_5As$	39.42	2.98	20.90	39.52	3.31	20.80
XI	>250	RP	$C_{12}H_{12}O_3N_5As$	41.20	3.91	20.11	41.10	3.91	20.81
XII	>250	RP	$C_{17}H_{20}O_3N_5As$	49.06	4.80	16.78	48.77	4.89	16.77
XIII	>250	RP	$C_{16}H_{18}O_3N_5As$	47.67	4.46	17.37	48.02	4.78	17.50
XIV	>250	RP	$C_{15}H_{16}O_3N_5As$	46.30	4.11	17.99	46.04	4.37	18.14
XV	>250	RP	$C_{15}H_{16}O_4N_5As$	44.5	3.95	17.28	44.70	4.30	17.44
XVI	>250	RP	$C_{18}H_{16}O_3N_5As$	50.90	3.76	16.48	51.22	4.15	16.34
XVII	>250	RP	$C_{16}H_{14}O_4N_5As$	46.30	3.38	16.86	45.96	3.28	16.24
XVIII	>250	RP	$C_{17}H_{14}O_3N_5As$	49.67	3.41	17.03	49.99	3.48	17.25
XIX	>250	RP	$C_{18}H_{16}O_4N_5As$	49.00	3.63	15.88	49.03	3.89	16.13
XX	>250	RP	$C_{17}H_{13}O_3N_5ClAs \cdot H_2O$	44.04	3.24	15.10	44.13	3.81	15.65
XXI	>250	RP	$C_{17}H_{15}O_6N_5As_2 \cdot 2H_2O$	35.75	3.33	12.25	36.01	3.19	12.19
XXII	>250	H_2O	$C_{11}H_9O_4N_4As$	39.35	2.67	16.72	39.63	3.24	16.74
XXIII	>250	CH_3OH–H_2O	$C_{12}H_{11}O_4N_4As$	41.10	3.14	16.00	41.10	3.71	15.89
XXIV	>250	RP	$C_{17}H_{13}O_4N_4As$	49.55	3.15	13.59	49.42	3.15	13.69
XXV	>250	RP	$C_{11}H_{10}O_3N_5As$	39.55	2.69	20.95	39.88	2.73	21.08

a) Reprecipitated from NH_4OH or $NaHCO_3$ soln. by addition of HCl.

Experimental

N-(2-amino-6-butoxy-4-pyrimidinyl)arsanilic Acid (II)——Metalic sodium (0.2 g.) was dissolved in 5 ml. of MeOH. To the solution was added 10 ml. of BuOH, and the solvent was distilled off. Forty ml. of BuOH and 1 g. of (I) were added to the residue, and the mixture was heated in a sealed tube at 180° for 1 hr. After cool, the mixture was extracted with 50 ml. of 5% NaOH soln. and the extract was neutralized with AcOH. Crystals separated were recrystallized from aq. EtOH. Yield, 0.8 g.

N-[2-Amino-6-(2-hydroxyethoxy)-4-pyrimidinyl]arsanilic Acid (III)——One gram of (I) was dissolved in a warm ethylenglycol (8 ml.) containing 0.35 g. of NaOH, and the mixture was heated at 170° for 30 mins. After cool, the mixture was poured into 60 ml. of water, and neutralized with AcOH to precipitate (III). Yield, 0.8 g.

N,N'-(5-Nitro-4,6-pyrimidinyl)diarsanilic Acid (VI)——A mixture of 50 ml. of water, 50 ml. of acetone, 2.2 g. of arsanilic acid, 1.5 g. of (IV), and 0.85 ml. of conc. HCl was refluxed for 30 mins. A yellow precipitate was collected and purified by reprecipitation. Yield, 2.5 g.

N,N'-(2-Chloro-5-nitro-4,6-pyrimidinyl)diarsanilic Acid (VII)——A mixture of 0.25 g. of (V), 0.8 g. of arsanilic acid, 10 ml. of water, 10 ml. of acetone and 0.2 ml. of conc. HCl was refluxed for 10 mins. A yellow precipitate formed was collected and purified by reprecipitation. Yield, 0.5 g.

N-(5-Amino-6-chloro-4-pyrimidinyl)arsanilic Acid (VIII)——A mixture of 16 ml. of water, 0.25 ml. of conc. HCl, 1.6 g. of arsanilic acid, and 1 g. of 5-amino-4,6-dichloropyrimidine was refluxed for 5 hr. The precipitate formed was collected and purified by reprecipitation. Yield, 1.7 g.

***p*-(6-Chloro-9*H*-purin-9-yl)benzenearsonic Acid (IX)**——A mixture of 90 ml. of ethyl orthoformate, 90 ml. of Ac_2O, and 18 g. of (VIII) was refluxed for 1.5 hr., and the solvent was concentrated under a reduced pressure. Water was added to the residue, and precipitate formed was collected. Yield, 17 g.

Preparation of (X) and (XI)——Two grams of (IX) was added to 25 ml. of EtOH soln. containing excess NH_3 or CH_3NH_2, and the mixture was heated in a sealed tube at 140° for 3 hr. After cool, neutralization with dil. HCl precipitated (X) or (XI).

Preparation of (XII, XV, XVI and XVII)——A mixture of 1 g. of (IX), 2 ml. of the corresponding amine, and 20 ml. of methyl cellosolve was refluxed for 2 hr. After cool, dil. HCl was added to precipitate the product. Yield, 0.8~1.0 g.

Preparation of (XIII) and (XIV)——A mixture of 1 g. of (IX) and 5 ml. of piperidine or pyrrolidine was refluxed for 1 hr., and the excess amine was distilled off under a reduced pressure. The residue was dissolved in water and precipitated by addition of dil. HCl. Yield, 0.6 g.

Preparation of (XVIII, XIX, XX, and XXI)——A mixture of 1 g. of (IX), 0.7 g. of the corresponding amine, 0.5 ml. of conc. HCl and 20 ml. of H_2O was refluxed for 30~60 min. After cool, precipitate was collected and purified by reprecipitation. Yield, 0.7~1.3 g.

***p*-(6-Hydroxy-9*H*-purin-9-yl)benzenearsanilic Acid (XXII)**——A mixture of 0.5 g. of (IX) and 15 ml. of 90% formic acid was refluxed for 1 hr. The excess formic acid was distilled off under a reduced pressure. The residue was dissolved in NaOH soln., and precipitated by addition of dil. HCl. Yield, 0.3 g.

***p*-(6-Methoxy-9*H*-purin-9-yl)benzenearsonic Acid (XXIII)**——Sodium hydroxide (0.5 g.) and (IX) (1.0 g.) were dissolved in 40 ml. of MeOH, and the mixture was refluxed for 1 hr. The reaction mixture was evaporated to dryness, and the residue was dissolved by addition of 10 ml. of water. Neutralization with dil. HCl precipitated 0.6 g. of (XXIII).

***p*-(6-Phenoxy-9*H*-purin-9-yl)benzenearsonic Acid (XXIV)**——A mixture of (IX) (0.8 g.), phenol (0.4 g.), and NaOH (0.3 g.) in 7 ml. of water was refluxed for 4 hr. After cool, addition of dil. HCl precipitated (XXIV). Yield, 0.5 g.

N-(Purin-6-yl)arsanilic Acid (XXV)——A mixture of arsanilic acid (0.7 g.), 6-chloropurine (0.5 g.), and conc. HCl (0.2 ml.) in 25 ml. of water was refluxed for 20 min. Precipitate formed was collected and purified. Yield, 0.2 g.

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Tokuji Suzuki and Yuichi Tanimura : A Mehtod for Determining Hydrolytic Rate Constants of Succinylcholine Chloride with Analog Computation.

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The degradation of succinylcholine chloride in aqueous solution followed a two-step sequence, succinylcholinechloride (SCC) → succinylmonocholine chloride (SmCC) → succinic acid.[1] The kinetics of this pathway could be interpreted on the basis of consecutive first-order reactions.[2,3] Both the quantitative ion exchange chromatography and the colorimetry of the ferric-hydroxamic acid complex derivatives of the choline esters by Hestrin's method[4] were used to determine concentration of each of the two esters, SCC and SmCC, at any time in buffer solutions.[5] The rate constants (k_1) of the first reaction were calculated from the slopes of the plots of the logarithms of the concentrations of SCC against time at various pH and temperatures, and the rate constants (k_2) of the second reaction were measured independently using SmCC under the same conditions.

An absorbance (E_T) of degrading SCC solution at any time by the colorimetry is shown as follows :

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1) M. P. Earles, *et al.* : J. Pharm. Pharmacology, **6**, 773 (1954).
2) T. Suzuki : This Bulletin, **10**, 912 (1962).
3) *Idem* : *Ibid.*, **10**, 1017 (1962).
4) S. Hestrin : J. Biol. Chem., **180**, 249 (1949).
5) H. Nogami, T. Suzuki : This Bulletin, **9**, 646 (1961).