2,3,4-collidine 1-oxides could not be measured because of their great hygroscopic character. The samples were redistilled under a reduced pressure before use.

Ultraviolet Absorption Spectra—The absorption spectra were determined using a Shimazu Spectrophotometer type QB-50, with quartz cells of 10-mm. optical depth, in the region of 225~320 mμ. Density measurements were never made at intervals of more than 2 mμ, while in the neighbourhood of maxima the interval was decreased to 0.5 mμ. Solvent water was purified by repeated distillation, and ether and ethanol were carefully purified by the usual procedures. The concentrations of the solutions were 0.05 *mM*. The temperature was at 20°±2°.

Summary

The ultraviolet absorption spectra of pyridine 1-oxide and nine kinds of methylpyridine 1-oxide were measured in ether and in 95%, 50%, and 10% ethanol. The methyl group in the α-position exhibits a hypsochromic effect and in the β- or γ-position a bathochromic effect. These spectral results and physical constants of methlpyridine 1-oxides suggest the presence of a weak hydrogen bond between the oxygen atom and the hydrogen atom of the α-methyl group.

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91. Tadakazu Tsuji: Researches on Chemotherapeutic Drugs against Viruses. XVII.* Synthesis and Antiviral Properties of Urazoles and Related Compounds.

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It was found by Toyoshima[1] in the screening tests of enzyme-inhibitors on influenza viruses that both sodium azide and melamine exerted a weak inhibitory activity against the influenza A virus. Later several benzimidazole derivatives were reported to possess weak inhibitory activities on the influenza A virus.[2]

On the basis of these findings, a number of heterocyclic compounds containing nitrogen and related compounds were synthesized and examined as to their antiviral activities. This paper describes the synthesis and antiviral activities of 4-alkylphenylurazoles, dialkylphenylureas, 4-alkylurazoles, acylurazoles, 1-substituted biureas, and 1,6-disubstituted biureas.

Synthesis of Urazole and Related Compounds Several of the known five- and six-membered ring compounds, as illustrated in Table VI, were prepared and screened as to their activities against the Nakayama strain of *Encephalitis japonica* and PR-8 strain of influenza A virus. In these preliminary examinations, urazole and 4-phenylurazole among the above compounds were found to possess a weak activity against the virus. Consequently, urazole and its related compounds were taken up in the search for antiviral drugs.

4-Alkylphenylurazole is not known yet, but its parent compound, 4-phenylurazole was synthesized by Thiele[3] and by Arndt,[4] along with diphenylurea as a by-product, on

* T. Ueda, S. Toyoshima: Researches on Chemotherapeutic Drugs against Viruses. XVII. Part XVI: This Bulletin, **1**, 379(1953).

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1) S. Toyoshima, *et al.*: Papers read at the Annual Meeting of the Pharmaceutical Society of Japan (1954).

2) I. Tamm, K. Folkers, C. H. Shunk, F. L. Horsfall: J. Exptl. Med., **98**, 245(1953); *Ibid.*, **99**, 227 (1954).

3) Thiele, Stange: Ann., **283**, 45(1894).

4) F. Arndt, L. Löwe, A. Tarlan-Akõn: C. A., **42**, 8190(1948).

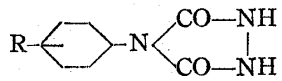
fusion of aniline hydrochloride and biurea at 220° for four hours.

According to this method, 4-alkylphenylurazoles were synthesized by the thermal reaction of alkylaniline hydrochloride and biurea, and dialkylphenylureas were obtained as by-products in this synthetic reaction. In the above case, it was found that diarylurea is exclusively obtained by using the free amine in place of the amine hydrochloride, while neither 4-alkylphenylurazole nor dialkylphenylurea is obtained by employing an amine sulfate.

These urazole derivatives were found to be obtained generally in poor yields, particularly 4-*p*-hexyl- and 4-*p*-octylphenylurazoles. 4-*p*-Decylphenylurazole was not obtained by this reaction and di-*p*-decylphenylurea was the only product. The thermal reaction was observed to begin above 190° and gave an almost constant poor yields in the range of 200~220°. Therefore, it may be said that the reaction for 4-alkylphenylurazole proceeds with difficulty and the yield decreases as the carbon number of the alkyl in alkylaniline increases.

Among 4-alkylurazoles, only 4-methylurazole has been synthesized by Arndt, *et al.* by the thermal reaction of 1,6-dimethylbiurea.[4] However, this method was not suitable for the synthesis of 4-alkylurazole because of its poor yield and lack of available material. Thus, from the analogy of 4-alkylurazole to 4-alkylphenylurazole, the reaction employed in the synthesis of 4-alkylphenylurazoles was attempted with alkylamine hydrochloride and biurea. It was thereby found that the 4-alkylurazoles were formed similarly by such a reaction. It was also observed that the reaction afforded 4-alkylurazoles in a good yield and was not accompanied by any by-products. Since the solubilities of the resulting 4-alkylphenyl- and 4-alkyl-urazoles varied with lengthening of the alkyl group, the method of isolation and purification of these urazoles could be controlled by consideration of their solubilities. These synthesized compounds are summarized in Tables I, II; and III.

Among acylurazoles, 1,2-diacetylurazole has already been synthesized by boiling urazole with acetic anhydride.[5] The same compound was also obtained in a good yield

TABLE I. 4-Alkylphenylurazoles 

No.	R	Compound	m.p. °C	Solubility in H_2O	Solubility in EtOH
I	*o*-CH_3	4-*o*-Tolylurazole	206~207	Sol.	Freely sol.
II	*p*-CH_3	4-*p*-Tolylurazole	243~244	〃	〃
III	*p*-C_2H_5	4-*p*-Ethylphenylurazole	241~242	Sparingly sol.	Sol.
IV	*p*-C_3H_7	4-*p*-Propylphenylurazole	228~230	〃	〃
V	*p*-C_4H_9	4-*p*-Butylphenylurazole	194~195	〃	〃
VI	*p*-C_6H_{13}	4-*p*-Hexylphenylurazole	156~158	〃	〃
VII	*p*-C_8H_{17}	4-*p*-Octylphenylurazole	143~144.5	〃	〃

TABLE II. Dialkylphenylureas 

No.	R	Compound	m.p. °C
Ia	*o*-CH_3	Di-*o*-tolylurea	245~246
IIa	*p*-CH_3	Di-*p*-tolylurea	259~260
IIIa	*p*-C_2H_5	Di-*p*-ethylphenylurea	216~217
IVa	*p*-C_3H_7	Di-*p*-propylphenylurea	204~205.5
Va	*p*-C_4H_9	Di-*p*-butylphenylurea	186~187
VIa	*p*-C_6H_{13}	Di-*p*-hexylphenylurea	184~185
VIIa	*p*-C_8H_{17}	Di-*p*-octylphenylurea	170~172
VIIIa	*p*-$C_{10}H_{21}$	Di-*p*-decylphenylurea	165~166

5) Cuneo: Chem. Zentr., 1898. I, 39.

Table III. 4-Alkylurazoles R—N(CO—NH / CO—NH)

No.	R	Compound	m.p. °C	Solubility in H_2O	Solubility in EtOH
IX	CH_3	4-Methylurazole	232~233	Sol.	Freely sol.
X	C_2H_5	4-Ethylurazole	195~196	〃	〃
XI	n-C_3H_7	4-Propylurazole	168~169.5	〃	Sol.
XII	n-C_4H_9	4-Butylurazole	167~168	〃	〃
XIII	n-C_6H_{13}	4-Hexylurazole	143~145	Sparingly sol.	〃
XIV	n-C_8H_{17}	4-Octylurazole	138~139	〃	〃
XV	n-$C_{10}H_{21}$	4-Decylurazole	137~138	〃	〃
XVI	n-$C_{12}H_{25}$	4-Dodecylurazole	133~135	〃	〃
XVII	n-$C_{14}H_{29}$	4-Tetradecylurazole	131~132	〃	〃
XVIII	n-$C_{16}H_{33}$	4-Hexadecylurazole	128~129	〃	〃
XIX	n-$C_{18}H_{37}$	4-Octadecylurazole	120~121	〃	〃
XX	$C_6H_5CH_2$-	4-Benzylurazole	182~183.5	〃	〃

by heating urazole with acetyl chloride in acetic acid medium. Diacylurazole was considered to be generally obtainable by this method. However, the resulting compound from urazole and caproyl chloride in acetic acid medium was not the anticipated 1,2-dicaproylurazole, but 1-caproylurazole. Other acylurazoles will be reported with their antiviral properties in the near future.

Both 1-alkyl- and 1-aryl-biureas are unknown. Among the related compounds, only thiobiurea had been synthesized by reacting thiosemicarbazide with potassium cyanate,[6] as well as by combining free semicarbazide with aryl isocyanate.[7] On application of this reaction in the present case, 1-aryl- and 1-alkyl-biureas were synthesized by combining 1-substituted semicarbazide with potassium cyanate in acetic acid medium, as well as by combining free semicarbazide with aryl or alkyl isocyanate, according to the following formulae :

$$R—NH—CO—NH—NH_2 + KNCO + H_2O \longrightarrow R—NH—CO—NH—NH—CO—NH_2 + KOH$$
$$NH_2—CO—NH—NH_2 + RNCO \longrightarrow R—NH—CO—NH—NH—CO—NH_2$$

Several 1,6-dialkylbiureas had already been synthesized from isocyanate and hydrazine hydrate[4]. According to this method, diundecylbiurea was obtained from undecyl isocyanate and hydrazine hydrate. These acylurazoles and -biureas obtained are summarized in Tables IV and V.

Table IV. Acylurazoles

No.	Structural formula	Compound
XXI	$CH_3CO—N(—CO)(—CO—N—CO)>NH$	1,2-Diacetylurazole
XXII	$C_5H_{11}CO—N(—CO)(—HN—CO)>NH$	1-Caproylurazole

Table V. Biurea compounds

No.	Structural formula	Compound
XXIII	 -NHCONHNHCONH$_2$	1-Phenylbiurea
XXIV	 -NHCONHNHCONH$_2$	1-*o*-Tolylbiurea
XXV	n-$C_{11}H_{23}$-NHCONHNHCONH$_2$	1-Undecylbiurea
XXVI	n-$C_{13}H_{27}$-NHCONHNHCONH$_2$	1-Tridecylbiurea
XXVII	n-$C_{11}H_{23}$-NHCONH / n-$C_{11}H_{23}$-NHCONH	1,6-Diundecylbiurea

6) M. Ohta, H. Koyama : J. Pharm. Soc. Japan, **72**, 1533(1952).
7) F. Arndt, E. Milde, F. Tschenscher : Ber., **55**, 341(1922).

The relationship between urazole and biurea is now discussed. As described above, 4-substituted urazole, in general, was formed by the thermal reaction of an amine with biurea, according to the following:

$$R{-}NH_2 + NH_2{-}CO{-}NH{-}NH{-}CO{-}NH_2 \longrightarrow R{-}N\begin{matrix}CO{-}NH\\ \quad\quad|\\ CO{-}NH\end{matrix} + 2NH_3$$

where R could be alkyl or aryl.

In contrast with this synthetic process, 4-methylurazole was obtained by Arndt, *et al.*[4] in a poor yield from 1,6-dimethylbiurea, as follows:

$$CH_3{-}NH{-}CO{-}NH{-}NH{-}CO{-}NH{-}CH_3 \longrightarrow CH_3{-}N\begin{matrix}CO{-}NH\\ \quad\quad|\\ CO{-}NH\end{matrix}$$

This reaction was considered unsuitable because of its poor yield.

In connection with this reaction, it was made clear that 4-arylurazole could be obtained in a poor yield by directly heating biurea, as follows:

$$\varphi{-}NH{-}CO{-}NH{-}NH{-}CO{-}NH_2 \longrightarrow \varphi{-}N\begin{matrix}CO{-}NH\\ \quad\quad|\\ CO{-}NH\end{matrix}$$

From these findings, it may be said that 4-substituted urazoles can, in general, be synthesized by either the thermal reaction of amine and biurea or of 1-substituted biurea as well as 1,6-disubstituted biurea.

Antiviral activities Several triazine derivatives related to melamine were examined as to their antiviral activities *in vivo* on the Nakayama strain of Japanese encephalitis virus, in embryonated eggs on the PR-8 strain, and *in vivo* on the PR-8 strain and FM-1 strain of influenza A virus.

1) Tests *in vivo* on the Nakayama Strain—Each virus dilution was inoculated intranasally into groups of mice, and six hours later, solution of the compound was injected intravenously into the above mice with each dose described in the table. These treated mice were observed during subsequent 2 weeks and the chemotherapeutic effects of those compounds were determined by the survival ratio. Results are given in Table VI, in which the numerator represents the number of mice that survived, the denominator the total number injected.

2) Tests in Embryonated Eggs—PR-8 Strain (LD_{50} corresponding to 10^{-6}) was employed for the tests. 0.1 cc. of each virus dilution was inoculated into the allantois of embryonated egg (five eggs for the test of one group), which had previously been incubated at 37° for 9~10 days. One hour later, 0.1 cc. of each solution (1 mg./cc. of distilled water) was injected into the allantois. The presence of demonstrable hemagglutination in the allantoic fluid collected from the egg after 48 hours' incubation at 37°, was used as the criterion of the infection. Results are given in the table by the hemagglutination titer.

3) Tests *in vivo* on the PR-8 and FM-1 Strains of Influenza A Virus—Mouse lung infected with the virus was employed for the tests. Dilution of infective mouse lung was prepared with inactivated serum-Lush's solution and 3 drops of each virus dilution was inoculated by the intranasal inoculation technique under ether anesthesia into mice (ca. 10 g. body weight). After 2 hours, aqueous solutions of each compound were injected intravenously into the above mice. These treated mice were observed during seven days and the chemotherapeutic effects of the compounds were determined by the syndrome development percentage with CCA Test.[8] Results are given in Tables VI and VII, in which the numerator represents the number of non-syndrome developed mice, the denominator represents the total number injected.

8) Zark: J. Immunol., **49**, 88(1944).

TABLE VI. Antiviral Effects *in vivo* on the Nakayama Strain of *Encephalitis japonica*

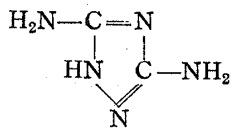
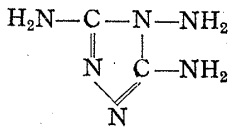
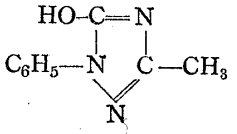
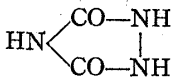
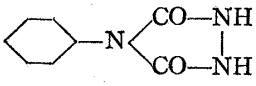
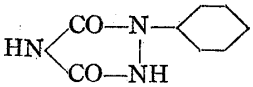
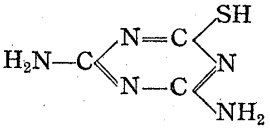
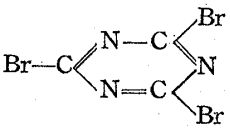
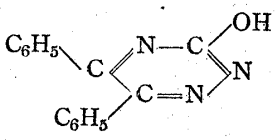
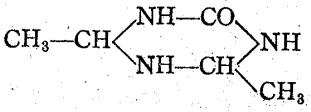
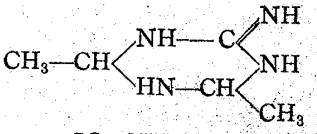
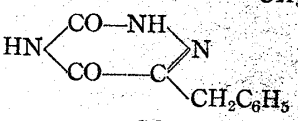
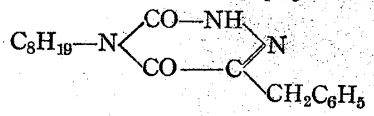
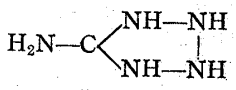
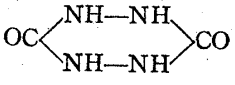
No.	Structural Formula	Compound	Dose (mg./kg.)	Virus dilution 10^{-2}	10^{-3}	10^{-4}	LD_{50}
T_1		Guanazole	150	0/8	2/8	0/8	$>10^{-4.33}$
T_2		Guanazine	150	0/10	0/9	0/9	$>10^{-4.5}$
T_3		1-Phenyl-3-methyl-5-hydroxy-1,2,4-triazole	150	0/10	0/6	5/10	$10^{-4.0}$
T_4		Urazole	150	0/10	3/11	6/13	$>10^{-3.85}$
T_5		4-Phenylurazole	200	0/10	0/10	2/10	$>10^{-4.38}$
T_6		1-Phenylurazole	—	—	—	—	—
T_7		Thiammeline	25	0/10	0/10	4/10	$>10^{-4.17}$
T_8		Cyanur bromide	150	0/6	0/10	2/6	$>10^{-4.25}$
T_9		5,6-Diphenyl-3-hydroxy-1,2,4-triazine	150	0/5	1/6	1/5	$>10^{-4.25}$
T_{10}		4-Oxo-2,6-dimethyl hexahydro-1,3,5-triazine	150	0/10	0/10	3/10	$<10^{-4.28}$
T_{11}		4-Imino-2,6-dimethyl hexahydro-1,3,5-triazine	150	0/10	0/8	3/6	$10^{-4.0}$
T_{12}		3,5-Dioxo-6-benzyl tetrahydro-1,2,4-triazine	75	0/10	1/10	3/10	$>10^{-4.21}$
T_{13}		3,5-Dioxo-4-octyl-6-benzyltetrahydro-1,2,4-triazine	75	0/10	2/10	5/10	$10^{-3.8}$
T_{14}		5-Aminotetrazole	—	—	—	—	—
T_{15}		*p*-Urazine	—	—	—	—	—
Control			—	0/10	0/10	3/10	$>10^{-4.28}$

TABLE VII. Antiviral Effects in Embryonated Eggs on the PR-8 Strain and *in vivo* on PR-8 and FM-1 Strains of Influenza A Virus

No.	Virus dilution in embryonated eggs			Dose (mg./kg.)	Virus dilution *in vivo* on the PR-8 strain			Virus dilution *in vivo* on the FM-1 strain		
	10^{-2}	10^{-3}	10^{-4}		10^{-2}	10^{-3}	LD_{50}	10^{-2}	10^{-3}	LD_{50}
T_1	320	80	0	—	—	—	—	—	—	—
T_4	40	40	20	150	1/10	0/10	$>10^{-3.45}$	1/10	3/8	$>10^{-3.1}$
T_5	—	0	0	200	2/9	4/10	$>10^{-3.0}$	0/10	2/10	$>10^{-3.38}$
T_6	—	320	320	—	—	—	—	—	—	—
T_7	80	20	0	25	1/9	1/7	$>10^{-3.25}$	1/9	0/9	$>10^{-3.44}$
T_8	320	640	—	—	—	—	—	—	—	—
T_9	40	0	0	150	1/7	2/10	$>10^{-3.31}$	2/8	0/10	$>10^{-3.4}$
T_{10}	—	320	1280	—	—	—	—	—	—	—
T_{11}	—	320	320	—	—	—	—	—	—	—
T_{14}	320	320	—	—	—	—	—	—	—	—
T_{15}	320	1280	1280	—	—	—	—	—	—	—
Control	640	1280	1280	—	0/10	1/7	$>10^{-3.42}$	0/10	0/7	$>10^{-3.5}$

TABLE VIII. Antiviral Effects *in vivo* on the Nakayama Strain of *Encephalitis japonica*

No.	Dose(mg./kg.)	Virus dilution 10^{-2}	10^{-3}	10^{-4}	LD_{50}
I	200	0/10	0/10	5/11	$>10^{-4.08}$
III	150	1/10	0/10	6/10	$10^{-3.76}$
IV	150	1/8	0/10	3/11	$>10^{-4.25}$
V	150	0/10	0/9	2/11	$>10^{-4.39}$
VI	75	0/10	1/10	5/10	$10^{-3.92}$
VII	150	0/9	1/10	5/10	$10^{-3.92}$
XI	75	0/10	1/10	0/10	$>10^{-4.45}$
XII	75	0/10	2/10	3/10	$>10^{-4.14}$
XIII	75	0/10	1/10	5/10	$10^{-3.92}$
XV	75	0/10	0/10	5/10	$10^{-4.0}$
XVII	75	0/10	0/10	1/10	$>10^{-4.44}$
XVIII	75	0/10	1/10	3/10	$>10^{-4.21}$
XIX	75	0/10	2/10	6/10	$10^{-3.6}$
XX	75	0/10	2/10	6/10	$10^{-3.6}$
XXI	75	0/10	3/10	3/10	$>10^{-4.07}$
XXII	75	0/10	0/10	4/10	$>10^{-4.17}$
XXIV	75	0/10	2/10	4/10	$>10^{-4.0}$
Control	—	0/10	0/10	3/10	$>10^{-4.28}$

TABLE IX. Antiviral Effects *in vivo* on PR-8 and FM-1 Strains of Influenza A Virus

Compound	Dose(mg./kg.)	Virus dilution PR-8 10^{-2}	PR-8 10^{-3}	PR-8 LD_{50}	FM-1 10^{-2}	FM-1 10^{-3}	FM-1 LD_{50}
I	200	0/10	1/9	$>10^{-3.44}$	0/9	0/9	$>10^{-3.5}$
II	100	1/10	3/9	$>10^{-3.17}$	0/10	0/10	$>10^{-3.5}$
IX	100	1/9	2/9	$>10^{-3.29}$	0/10	1/10	$>10^{-3.44}$
X	100	0/7	1/10	$>10^{-3.44}$	0/9	1/10	$>10^{-3.44}$
Control	—	0/12	0/10	$>10^{-3.5}$	0/9	0/10	$>10^{-3.5}$

From Tables VI and VII, it may be noted that urazole (T_4), 4-phenylurazole (T_5), and 3,5-dioxo-4-octyl-6-benzyltetrahydro-1,2,4-triazine (T_{13}) showed weak activity on the Nakayama strain, thiammeline (T_7), 5,6-diphenyl-3-hydroxy-1,2,4-triazine (T_9), and 4-phenylurazole (T_5) exerted weak activity on the PR-8 strain, and urazole (T_4) possessed a weak activity against the FM-1 strain.

Urazole and biurea derivatives described above were examined as to their antiviral activities *in vivo* on the Nakayama strain, the PR-8 strain, and FM-1 strain. The results are shown in Tables VIII and IX, from which it may be said that of the 4-alkylphenyl- and 4-alkyl-urazoles, the compounds possessing long carbon chains exerted weak activities on the Nakayama strain, even though activities were too weak to compare with that of PANS-No. 610.[9] Acylurazole and biurea derivatives did not show any activity against the virus and only 4-*p*-tolylurazole showed weak activity against the PR-8 strain.

All biurea derivatives except *o*-tolylbiurea, could not be tested as to their antiviral properties because of their small solubility.

As described above, a few of the substituted urazoles and biureas showed weak activity, approximately equal to that of PANS-No. 25, on the Nakayama strain and effects *in vivo* weaker than carbamic esters of hydroxyquinoline[10] on the PR-8 strain. However, urazole derivatives of other types are of interest on seeking more effective antiviral drugs, since it was made clear by these studies that several substituted urazoles possessed antiviral properties.

Experimental

3,5-Dioxo-4-octyl-6-benzyltetrahydro-1,2,4-triazine (T_{13})—A solution of 4.8 g. of octyl bromide in 8 cc. of 90% EtOH was added into a solution of 5.1 g. of 3,5-dioxo-6-benzyltetrahydro-1,2,4-triazine in 1.4 g. of KOH and 30 cc. of 90% EtOH, heated on a water bath for 20 hrs. under reflux. After the solvent was removed, the residue was washed with water, dissolved in ether, filtered, and dried over anhyd. Na_2SO_4. The solvent was removed, and the residual crystals were recrystallized from EtOH to colorless needles, m.p. 98~100°. Yield, 4.7 g. *Anal.* Calcd. for $C_{18}H_{25}O_2N_3$: N, 13.33. Found: N, 13.16.

4-Substituted Urazole—General procedure: A mixture of 0.02 *M* amine hydrochloride and the equimol. amount of biurea was heated with stirring at 210~220°(oil bath temp.) for 4~5 hrs. The reaction mixture was purified by one of the following four methods, in accordance with the solubility of the urazole compound.

A) The reaction mixture was treated with hot water, and separated into an aqeuous layer (a) and an insoluble residue (b).

(a) The aqueous layer was cooled, filtered, and evaporated to dryness. The residue was dissolved in a small amount of dil. NH_4OH, filtered, and the filtrate was acidified with HCl. The precipitated urazole was recrystallized from water.

(b) The residue, dialkylphenylurea, was recrystallized from AcOH.

B) The reaction mixture was washed with hot water, dried, and treated with hot MeOH and the methanol solution (a) and insoluble residue (b) were treated as follows:

(a) The solvent was distilled off, the residue was dissolved in a small amount of dil. NH_4OH, filtered, and the filtrate was acidified with HCl. The precipitated urazole was recrystallized from MeOH.

(b) The residue, dialkylphenylurea, was recrystallized from AcOH.

C) The reaction mixture was washed with hot water, dried, and treated with hot MeOH and the MeOH solution (a) and insoluble residue (b) were treated as follows:

(a) The solvent was removed, the residue was dissolved in ether, filtered, and the solvent removed. The residual urazole, was recrystallized from MeOH.

(b) The residue, dialkylphenylurea, was recrystallized from AcOH.

D) and E) Procedures followed the method (Aa) and (Ba), respectively, but not treated with NH_4OH.

4-*o*-Tolylurazole (I)—Prepd. by method (Aa) to colorless needles, m.p. 206~207°. Yield, 0.3 g.

9) T. Ueda, S. Toyoshima, T. Wachi: This Bulletin, **1**, 379(1953).
10) T. Ueda, *et al.*: This Bulletin, **1**, 375(1953).

Anal. Calcd. for $C_9H_9O_2N_3$: N, 22.00. Found : N, 22.62.

Di-*o*-tolylurea (Ia)—Prepd. by method (Ab) to colorless needles, m.p. 245~246°(literature, 250°). Yield, 0.7 g. *Anal.* Calcd. for $C_{15}H_{16}ON_2$: N, 11.67. Found : N, 11.76.

4-*p*-Tolylurazole (II)—Prepd. by method (Aa) to colorless prisms, m.p. 243~244°. Yield, 0.2 g. *Anal.* Calcd. for $C_9H_9O_2N_3$: N, 22.00. Found : N, 20.93.

Di-*p*-tolylurea (IIa)—Prepd. by method (Ab) to colorless needles, m.p. 259~260°(literature, 260°). Yield, 1.3 g. *Anal.* Calcd. for $C_{15}H_{16}ON_2$: N, 11.67. Found : N, 11.35.

4-*p*-Ethylphenylurazole (III)—Prepd. by method (Aa) to colorless prisms, m.p. 241~243°. Yield, 0.6 g. *Anal.* Calcd. for $C_{10}H_{11}O_2N_3$: N, 20.50. Found : N, 20.33.

Di-*p*-ethylphenylurea (IIIa)—Prepd. by method (Ab) to colorless needles, m.p. 216~217°. Yield, 0.8 g. *Anal.* Calcd. for $C_{17}H_{20}ON_2$: N, 10.45. Found : N, 10.43.

4-*p*-Propylphenylurazole (IV)—Prepd. by method (Aa) to colorless prisms, m.p. 228~230°. Yield, 0.6 g. *Anal.* Calcd. for $C_{11}H_{13}O_2N_3$: C, 60.24; H, 5.98; N, 19.19. Found : C, 60.44; H, 5.89; N, 19.41.

Di-*p*-propylphenylurea (IVa)—Prepd. by method (Ab) to colorless needles, m.p. 204~205.5°. Yield, 0.5 g. *Anal.* Calcd. for $C_{19}H_{24}ON_2$: N, 9.45. Found : N, 9.07.

4-*p*-butylphenylurazole (V)—Prepd. by method (Ba) to colorless prisms, m.p. 194~195°. Yield, 0.5 g. *Anal.* Calcd. for $C_{12}H_{15}O_2N_3$: N, 18.03. Found : N, 17.94.

Di-*p*-butylphenylurea (Va)—Prepd. by method (Bb) to colorless needles, m.p. 186~187°. Yield, 0.8 g. *Anal.* Calcd. for $C_{21}H_{28}ON_2$: N, 8.64. Found : N, 8.51.

4-*p*-Hexylphenylurazole (VI)—Prepd. by method (Ca) to colorless prisms, m.p. 156~158°. Yield, 0.1 g. *Anal.* Calcd. for $C_{14}H_{19}O_2N_3$: N, 16.09. Found : N, 15.75.

Di-*p*-hexylphenylurea (VIa)—Prepd. by method (Cb) to colorless plates, m.p. 184~185°. Yield, 0.6 g. *Anal.* Calcd. for $C_{25}H_{36}ON_2$: N, 7.37. Found : N, 7.58.

4-*p*-Octylphenylurazole (VII)—Prepd. by method (Ca) to colorless plates, m.p. 143~144.5°. Yield, 0.4 g. *Anal.* Calcd. for $C_{16}H_{23}O_2N_3$: N, 14.53. Found : N, 14.43.

Di-*p*-octylphenylurea (VIIa)—Prepd. by method (Cb) to colorless plates, m.p. 171~172°. Yield, 1.1 g. *Anal.* Calcd. for $C_{29}H_{44}ON_2$: N, 6.42. Found : N, 6.52.

Di-*p*-decylphenylurea (VIIIa)—Prepd. by method (Cb) to colorless plates, m.p. 165~166°. Yield, 0.9 g. *Anal.* Calcd. for $C_{33}H_{52}ON_2$: N, 5.69. Found : N, 5.59.

4-Methylurazole (IX)—Prepd. by method (D) to colorless plates, m.p. 232~233°(literature, 233°). Yield, 0.8 g. *Anal.* Calcd. for $C_3H_5O_2N_3$: N, 36.52. Found : N, 36.95.

4-Ethylurazole (X)—Prepd. by method (D) to colorless plates, m.p. 195~196°. Yield, 1 g. *Anal.* Calcd. for $C_4H_7O_2N_3$: C, 37.19; H, 5.47; N, 32.56. Found : C, 37.44; H, 5.55; N, 32.57.

4-Propylurazole (XI)—Prepd. by method (D) to colorless prisms, m.p. 168~169.5°. Yield, 1 g. *Anal.* Calcd. for $C_5H_9O_2N_3$: N, 29.37. Found : N, 29.41.

4-Butylurazole (XII)—Prepd. by method (D) to colorless prisms, m.p. 167~168°. Yield, 1.2 g. *Anal.* Calcd. for $C_6H_{11}O_2N_3$: N, 26.75. Found : N, 26.81.

4-Hexylurazole (XIII)—Prepd. by method (E) to colorless prisms, m.p. 143~145°. Yield, 1.4 g. *Anal.* Calcd. for $C_8H_{15}O_2N_3$: N, 22.70. Found : N, 22.70.

4-Octylurazole (XIV)—Prepd. by method (E) to colorless prisms, m.p. 138~139°. Yield, 1.4 g. *Anal.* Calcd. for $C_{10}H_{19}O_2N_3$: C, 56.29; H, 8.98; N, 19.71. Found : C, 56.46; H, 8.88; N, 19.81.

4-Decylurazole (XVI)—Prepd. by method (E) to colorless prisms, m.p. 137~138°. Yield, 1.1 g. *Anal.* Calcd. for $C_{12}H_{23}O_2N_3$: N, 17.42. Found : N, 17.46.

4-Dodecylurazole (XVI)—Prepd. by method (E) to colorless prisms, m.p. 133~135°. Yield, 1.3 g. *Anal.* Calcd. for $C_{14}H_{27}O_2N_3$: N, 15.61. Found : N, 15.40.

4-Tetradecylurazole (XVII)—Prepd. by method (E) to colorless prisms, m.p. 131~132°. Yield, 1.4 g. *Anal.* Calcd. for $C_{16}H_{31}O_2N_3$: N, 14.14. Found : N, 13.94.

4-Hexadecylurazole (XVIII)—Prepd. by method (E) to colorless prisms, m.p. 128~129°. Yield, 1.4 g. *Anal.* Calcd. for $C_{18}H_{35}O_2N_3$: N, 12.92. Found : N, 12.09.

4-Octadecylurazole (XIX)—Prepd. by method (E) to colorless prisms, m.p. 120~121°. Yield, 1.6 g. *Anal.* Calcd. for $C_{20}H_{39}O_2N_3$: N, 11.89. Found : N, 11.82.

4-Benzylurazole (XX)—Prepd. by method (E) to colorless needles, m.p. 182~183.5°. Yield, 1.4 g. *Anal.* Calcd. for $C_9H_9O_2N_3$: N, 22.00. Found : N, 22.57.

1,2-Diacetylurazole (XXI)—A solution of 2 g. of urazole and 9.4 g. of AcCl in 8 cc. AcOH was warmed on a water bath for 1 hr. After cooling, the solvent was distilled off under a diminished pressure. The residual crystals were recrystallized from EtOH to colorless plates, m.p. 206~207°, not depressed when admixed with the sample obtained by Cuneo[5]. Yield, almost quantitative. *Anal.* Calcd. for $C_6H_7O_4N_3$: N, 22.71. Found : N, 22.46.

1-Caproylurazole (XXII)—Obtained in a similar way as above, from a solution of 2.1 g. of urazole, 17.5 g. of caproyl chloride, and 19.5 g. AcOH, to colorless needles, m.p. 186~188°. Yield, 1.4 g. *Anal.* Calcd. for $C_8H_{13}O_3N_3$: N, 21.10. Found : N, 22.11. This substance was not subjected to change

by hydrolysis.

1-Substituted Biureas—General procedures: a) 1.8 g. of KCNO was slowly added with stirring into a mixture of 0.02*M* 1-arylsemicarbazide hydrochloride, 30 cc. of water, 1.1 g. Na_2CO_3, and 1.2 g. AcOH. After standing over night, the reaction mixture was filtered, washed with water, and purified from AcOH.

b) 0.02*M* aryl or alkyl isocyanate was added dropwise, under cooling with efficient stirring, into a solution of semicarbazide, obtained from a paste of 2.23 g. of semicarbazide hydrochloride with water, 1.1 g. of Na_2CO_3, and 5~10 cc. MeOH. The resulting mixture was filtered and the by-product was dissolved off by boiling in MeOH. The undissolved residue was recrystallized from AcOH.

1-Phenylbiurea (XXIII)—Prepd. by method (a) to colorless prisms, m.p. 232~234°. Yield, 3 g. *Anal.* Calcd. for $C_8H_{10}O_2N_4$: N, 28.87. Found: N, 28.60.

This was also obtained by method (b) to colorless prisms, m.p. 233~234°, not depressed when admixed with the sample obtained above. Yield, 3.1 g. *Anal.* Calcd. for $C_8H_{10}O_2N_4$: N, 28.87. Found: N, 28.35. This only dissolved in hot AcOH.

1-*o*-Tolylbiurea (XXIV)—Prepd. by method (a) to colorless plates, m.p. 206~207°. Yield, 3.4 g. *Anal.* Calcd. for $C_9H_{12}O_2N_4$: N, 26.92. Found: N, 26.57. This dissolved in hot MeOH and AcOH.

1-Undecylbiurea (XXV)—Prepd. by method (b) to colorless needles, m.p. 230~231°. Yield, 1.9 g. *Anal.* Calcd. for $C_{13}H_{28}O_2N_4$: N, 20.58. Found: N, 20.00. This only dissolved in hot AcOH.

1-Tridecylbiurea (XXVI)—Prepd. by method (b) to colorless needles, m.p. 224~226°. Yield, 1.2 g. *Anal.* Calcd. for $C_{15}H_{32}O_2N_4$: N, 18.66. Found: N, 17.87. This only dissolved in hot AcOH.

1,6-Diundecylbiurea (XXVII)—3.9 g. of undecyl isocyanate was added dropwise under cooling with stirring into a mixture of excess of hydrazine hydrate and 5 cc. of ether. The reaction mixture was filtered and diundecylurea dissolved off by treating with hot MeOH. The residue was purified from AcOH to colorless crystals, m.p. 232~233°. Yield, 1.9 g. *Anal.* Calcd. for $C_{24}H_{30}O_2N_4$: N, 13.79. Found: N, 13.67. This only dissolved in hot AcOH.

4-Phenylurazole (XXVIII)—1 g. of 1-phenylbiurea was heated at 220° for 4 hrs. After cooling, the residue was recrystallized from water to colorless prisms, m.p. 202~203°, not depressed on admixture with the sample prepared by Thiele[5]. *Anal.* Calcd. for $C_8H_7O_2N_3$: N, 23.73. Found: N, 23.18.

4-*o*-Tolylurazole (XXIX)—This was obtained in a similar way as above as colorless prisms, m.p. 206~207°, not depressed when admixed with the sample (I). *Anal.* Calcd. for $C_9H_9O_2N_3$: N, 22.00. Found: N, 20.89.

Summary

Several triazine compounds, alkylphenylurazoles, alkylurazoles, acylurazoles, and biureas were synthesized and examined as to their antiviral activities.

By fusing of 4-alkylphenylamine hydrochloride with biurea, 4-alkylphenylurazoles were obtained together with dialkylphenylureas as by-products. In the same way 4-alkylurazoles were also obtained. In the latter reaction it was found that no side-reaction had occurred and the yield was good. 1,2-Diacetylurazole was obtained from urazole and acetyl chloride, and 1-caproylurazole was obtained in the same way. 1-Substituted biureas were obtained by combining 1-substituted semicarbazide with aryl or alkyl isocyanates. 1,6-Diundecylbiurea was obtained by the usual method.

These compounds thus obtained did not exert remarkable effect on the Nakayama strain of *Encephalitis japonica*, and the PR-8 strain and FM-1 strain of influenza A virus.

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