indebted to Dr. F. Uchimaru for gas chromatography, and to Mr. B. Kurihara and Miss K. Hanawa for elemental analyses.

Summary

Pyrolysis of androstane derivatives which contain 17β-hydroxy-17α-methyl grouping was shown to afford three kinds of dehydration products : 17-methyl-Δ^{16}, 17-methylene, and 17,17-dimethyl-18-nor-Δ^{13}-compounds. The last compound was formed by a Wagner-Meerwein type rearrangement.

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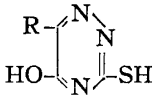
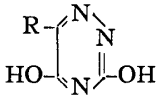
15. Takeo Ueda and Mitsuru Furukawa : Syntheses and Antiviral Effects of 3-Amino-6-alkyl-*as*-triazin-5-ol Derivatives.

(*Pharmaceutical Institute, Keio-Gijuku University*[*1])

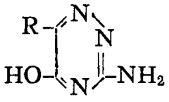
As described in the previous report,[1] our group found that several compounds of 3-mercapto-6-alkyl-*as*-triazin-5-ol (I) and 6-alkyl-*as*-triazin-3,5-diol (II) showed antiviral activities against the PR-8 strain of influenza virus.



I



II



III

From the view of the relationship between the antiviral activity and the structure of these series, it is suggested that the simultaneous existence of alkyl groups of optimum carbon length and hydroxyl or mercapto group might be necessary for the generation of antiviral activity.

On the other hand, 3-amino-*as*-triazine is known to inhibit the biosyntheses of riboflavine,[2] adenine, histidine,[3] chlorophyll[4] etc. and antagonize the activities of tyrosinase, lactoperoxidase, carboxylic acid peroxidase etc.[5] Particularly, it is of interest that this agent inhibits the incorporation of phosphate in the process of nucleic acid biosynthesis.[6] This fact suggests that this agent might be worthy to be screened as an inhibitor of virus nucleic acid synthesis. Such the action of this agent may be due to the existence of amino group at 3-position of *as*-triazine ring. This assumption prompted the authors to conceive an idea to replace hydroxyl or mercapto group at 3-position in the series of I and II with amino group.

Thus, compounds of 3-amino-6-alkyl-*as*-triazin-5-ol (III) were synthesized and examined as to their antiviral activity.

This report is concerned with the synthesis and antiviral activity of 3-amino-6-alkyl-*as*-triazin-5-ol.

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1) T. Ueda, I. Nakata : Yakugaku Zasshi, **80**, 1068 (1960).
2) K. A. Sund, H. N. Little : Science, **132**, 622 (1960).
3) F. W. Weyter, H. P. Broquist : Biochim. et Biophys. Acta, **40**, 567 (1960).
4) H. T. Pyform, D. Appleman, W. G. Heim : Plant Physiol, **32**, 674 (1957).
5) P. Castelfranco : Biochim. et Biophys. Acta, **41**, 485 (1960).
6) D. J. Wort, B. C. Loughman : Can. J. Botany, **39**, 339 (1961).

Any compound of this series has not been revealed in any literature, to date.

The authors synthesized, with success, these compounds referred from the synthetic method of 3-mercapto-6-alkyl-*as*-triazin-5-ol.[7] The whole process is shown in Chart 1.

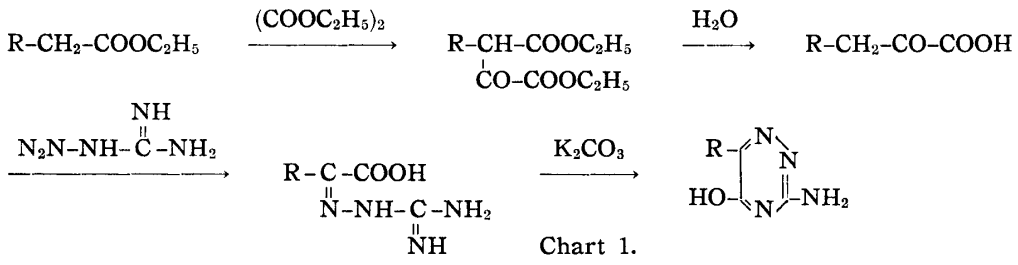


Chart 1.

Ethyl aliphatic carboxylate was employed as the starting material, from which diethyl α-oxalylcarboxylate was prepared by the method of Adickes.[8] Diethyl α-oxalylcarboxylate thus obtained was converted to α-oxocarboxylic acid by the hydrolysis with hydrochloric acid, in which the method of Adickes was observed unapplicable to the syntheses of the higher homologs. The hydrolysis of them, however, was found successful in conducting under more drastic condition, increasing the concentration of hydrochloric acid in the hydrolysor. After the purification of these α-oxocarboxylic acids by taking up with alkaline solution and reprecipitation with hydrochloric acid, it was condensed with aminoguanidine to afford the corresponding amidinohydrazone. These compounds synthesized are listed in Table I.

Table I. R-C(=N-NH-C(=NH)-NH$_2$)-COOH

R	m.p. (°C)	Yield	Formula	Anal. N (%) Calcd.	Found
CH_3	248	92	$C_4H_8O_2N_4$	38.87	38.82
C_2H_5	307	95	$C_5H_{10}O_2N_4$	35.43	35.45
C_3H_7	301	86	$C_6H_{12}O_2N_4$	32.54	32.33
C_4H_9	235～236	88	$C_7H_{14}O_2N_4$	30.06	29.77
C_5H_{11}	298～299	52	$C_8H_{16}O_2N_4$	27.98	27.86
C_7H_{15}	288～289	48	$C_{10}H_{20}O_2N_4$	24.54	24.81

The compounds of amidinohydrazone were converted to the objective compounds of 3-amino-6-alkyl-*as*-triazin-5-ol by the treatment with potassium carbonate in aqueous solution. This reaction was observed to proceed, with ease, in a small addition of ethanol, when the higher homologs of amidinohydrazone were insoluble in aqueous solution of potassium carbonate. Table II indicates the compounds of 3-amino-6-alkyl-*as*-triazin-5-ol synthesized.

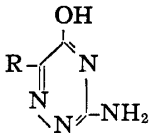
Analogously, the conversion of amidinohydrazone of α-oxocarboxilic ester to 3-amino-6-alkyl-*as*-triazin-5-ol, in which the reaction involved the hydrolysis and ring closure was attempted under the similar condition as that for amidinohydrazones of α-ketocarboxylic acid. However, the objective compounds were unobtainable by this process presumably because of the failure of the effective hydrolysis.

Among compounds of 3-amino-6-alkyl-*as*-triazin-5-ol, there should exist the following four structures due to the possible tautomerism.

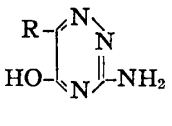
7) R.B. Barlow, A.D. Welch : J. Am. Chem. Soc., **78**, 1258 (1956); S. Rossi : Gazz. Chim. Ital., **83**, 133 (1953).

8) F. Adickes, G. Andresen : Ann., **555**, 41 (1949).

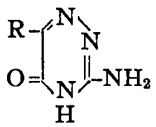
Table II.



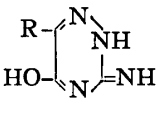
R	m.p. (°C)	Yield	Formula	Anal. N (%) Calcd.	Found
CH_3	>300	81	$C_4H_6ON_4$	44.43	44.58
C_2H_5	316	78	$C_5H_8ON_4$	39.98	40.09
C_3H_7	305	85	$C_6H_{10}ON_4$	36.34	36.42
C_4H_9	310~311	83	$C_7H_{12}ON_4$	33.31	33.44
C_5H_{11}	291~292	86	$C_8H_{14}ON_4$	30.75	30.46
C_7H_{15}	289~290	88	$C_{10}H_{18}ON_4$	26.65	26.92
C_9H_{19}	274~275	79	$C_{12}H_{22}ON_4$	23.51	23.37



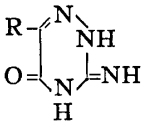
IIIa



IIIb



IIIc



IIId

It is of interest to reveal the possible existence of the tautomers in the ground state. Infrared absorptions of these compounds exhibited the existence of absorption assigned to carbonyl group at near 1660 cm^{-1}, but not any absorption assigned to hydroxyl group at any region, as can be seen in Fig. 1.

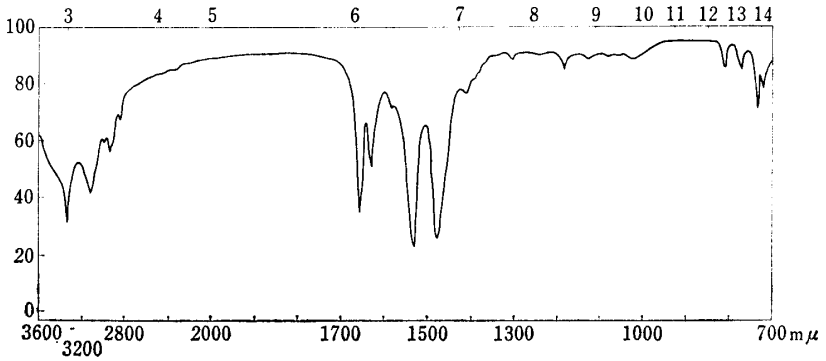


Fig. 1. Infrared Spectra of 3-Amino-6-ethyl-*as*-triazin-5-ol (KBr)

Hydroxyl group at 5-position is, therefore, assumed to exist in keto form. Regarding the infrared spectrum of 3-amino-*as*-triazine, it is reported by Mason[9] that the amino group at 3-position shows two bands at 3533 and 3420 cm^{-1}. If the amino group at 3-position exists as primary amine in 3-amino-6-alkyl-*as*-triazin-5-ol, the similar two bands are presumably expected in these region. However, such a band corresponding to amino form were not observed, but a single band in the 3360 cm^{-1} region was observed, as shown in Table III. This fact shows the evidence for the existence of the imino group

Table III. Absorption Bands of 3-Amino-6-alkyl-*as*-triazin-5-ol

IR ν_{max}^{KBr} cm^{-1}	CH_3	C_2H_5	C_3H_7	C_4H_9	C_5H_{11}	C_7H_{15}
C=O	1659	1661	1661	1661	1660	1662
NH	3346	3344	3346	3345	3346	3345

9) S.F. Mason: J. Chem. Soc., **1958**, 3619.

rather than the amino group. From these results, in the ground state 3-amino-6-alkyl-*as*-triazin-5-ol derivatives should be assumed to possess the structure such as the formula (IIIa) among the possible tautomers.

The compounds of amidinohydrazone of α-oxocarboxylic acid and 3-amino-6-alkyl-*as*-triazin-5-ol derivatives were tested as to their activity on PR-8 strain of influenza A virus and K-2211 strain of common cold virus according to the method described in the previous paper.[10] The result of these tests indicated that only amidinohydrazone of 2-oxovaleric acid was found a significantly effective on common cold virus.

Experimental

α-Oxocarboxylic Acids——These compouds were prepared in accordance with the method of Adickes.

General Procedure for Synthesis of Amidinohydrazone of α-Oxocarboxylic Acid——To a solution of 0.01 mole of aminoguanidine hydrochloride in 20 ml. of H_2O, 0.015 mole of AcONa and 0.01 mole of α-oxocarboxylic acid were added with stirring under heating. When α-ketocarboxylic acid was difficult to dissolve, a suitable amount of EtOH was added into the reaction solution to make completely clear. After warming for 30 min., the reaction solution was allowed to stand overnight. The resulting precipitates were collected by suction and recrystallized from H_2O or dil. EtOH. Analytical data of the compounds obtained thus are summarized in Table I.

General Procedure for Synthesis of 3-Amino-6-alkyl-*as*-triazin-5-ol——To a solution of 0.015 mole of K_2CO_3 in 30 ml. of H_2O, 0.01 mole of amidinohydrazone of α-oxocarboxylic acid was added to reflux for 2 to 5 hr. during the evaporation of CO_2. After cooling, the solution was neutralized with AcOH. The resulting precipitates were collected by filtration, washed by H_2O and recrystallized from H_2O or dil. EtOH. Analytical data of the compounds obtained are shown in Table II.

Summary

The thirteen compounds of amidinohydrazone of α-oxocarboxylic acid and 3-amino-6-alkyl-*as*-triazin-5-ol were synthesized and tested as to their antiviral activity. Only amidinohydrazone of 2-oxovaleric acid was found effective on common cold virus.

Also, it was revealed that the possible existence of the tautomers of 3-amino-6-alkyl-*as*-triazin-5-ol in the ground state should be in form of keto and imino.

(Received September 12, 1963)

10) T. Ueda, S. Toyoshima, T. Tsuji, Y. Seto : Keio J. Med., **10**, 257 (1961); T. Ueda, S. Toyoshima, T. Tsuji, Y. Seto, J. Nomoto : Antibiotics & Chemotherapy, **12**, 330 (1962).