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Studies on Antitumor Substances. VII.[1] Reaction of N-Amidino-O-alkylisourea with Some Carboxylic Esters

Seigoro Hayashi, Mitsuru Furukawa, Junko Yamamoto, and Yoko Nishizima

Faculty of Pharmaceutical Sciences, Kumamoto University[2]

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The reaction of N–amidino–O–alkylisourea with some carboxylic esters was attempted. Condensation with diethyl oxalate in alcohol gave alkyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate through the formation of the five membered–ring intermediate. Alkyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate was easily converted into the coresponding amide with a variety of amines. Condensation with ethyl acetoacetate gave 6–methyl–2–alkoxyamidino–4–pyrimidinol and 4–amino–2–alkoxy–6–acetomethyl–*s*–triazine. Condensation with ethyl cyanoacetate afforded only 4–amino–2–alkoxy–6–cyanomethyl–*s*–triazine, but not any expected pyrimidinol. Condensation with ethyl chloroacetate gave 4–amino–2–alkoxy–6–chloromethyl–*s*–triazine, which was converted into 4–amino–2–alkoxy–6–substituted amino–*s*–triazine with a variety of amines.

In the previous paper,[3] it was reported that 2,4–diamino–6–substituted–*s*–triazine derivatives exerted a weak inhibitory effect on Ehrlich ascites carcinoma with CAP method. For the purpose of finding antitumor drugs having superior effectiveness in the series of these compounds, new triazine derivatives possesing a variety of substituent groups were synthesized. This paper is concerned with the syntheses of 4–amino–2–alkoxy–6–substituted–*s*–triazine derivatives.

Up to the present time, a number of *s*–triazine derivatives have been prepared by the reaction of biguanide derivatives with carboxylic acids,[4] carboxylic esters,[5–7] carboxamides,[8] lactones[9] and so forth. Besides, the new synthetic route of *s*–triazine derivatives through the intermediate formation of dioxoimidazolidinylidene guanidine derivatives from biguanide derivatives as starting materials was found by the authors as described in the previous papers.[10] In order to expand this method toward the syntheses of 4–amino–2–alkoxy–6–substituted–*s*–triazine derivatives, the reactions between N–amidino–O–alkylisoureas possesing the same structural moiety as biguanides and several carboxylic esters, such as diethyl oxalate, ethyl acetoacetate, ethyl cyanoacetate and ethyl chloroacetate, were attempted in the present time.

Reaction of N-Amidino-O-alkylisourea with Diethyl Oxalate

These ring closure reactions have been generally carried out using a alkaline catalyst. However, N–amidino–O–alkylisourea (I) was found to react immediately with alkaline to

1) Part VI: *Chem. Pharm. Bull.* (Tokyo), **15**, 1310 (1967).
2) Location: *Kuhonji Oe–machi, Kumamoto.*
3) S. Hayashi, M. Furukawa, J. Yamamoto, Y. Nishizima, E. Sannomiya, and H. Ueki, *Kumamoto Pharm. Bull.*, **7**, 7 (1966).
4) Austrian Patent 168063 (1951) [*C.A.*, **47**, 8097 (1953)].
5) C.G. Overberger, F.G. Michelotti, and P.M. Carabateas, *J. Am. Chem. Soc.*, **79**, 941 (1957).
6) S.L. Shapiro, V.A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 5064 (1957).
7) S.L. Shapiro, V.A. Parrino, and L. Freedman, *J. Org. Chem.*, **25**, 379, 384 (1960).
8) C.G. Overberger and S.L. Shapiro, *J. Am. Chem. Soc.*, **76**, 93 (1954).
9) J.T. Thurston and D.W. Kaiser, U.S. Patent 2309680 (1943) [*C.A.*, **37**, 3769 (1943)].
10) M. Furukawa and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 596 (1963).

afford cyanoguanidine (II), as shown in Chart 1, so that the reactions with several carboxylic esters were carried out without any alkaline catalyst.

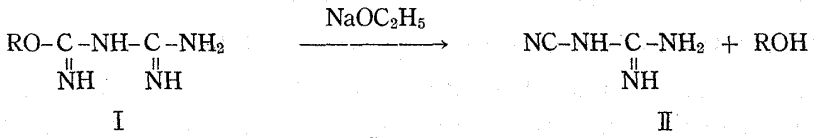


Chart 1

Thus, ethyl 4–amino–2–alkoxy–6–substituted–*s*–triazine derivatives were obtained in approximate 50% yields by refluxing N–amidino–O–alkylisourea with diethyl oxalate in ethanol. In this connection, in the reaction of biguanide derivatives (III) with diethyl oxalate, five–membered ring compounds (IV) could be intermediately isolated under milder condition, from which ethyl 4,6–diamino–*s*–triazine–2–carboxylates (V) were derived in good yields, as shown in Chart 2. In the case of N–amidino–O–alkylisourea, however, the similar

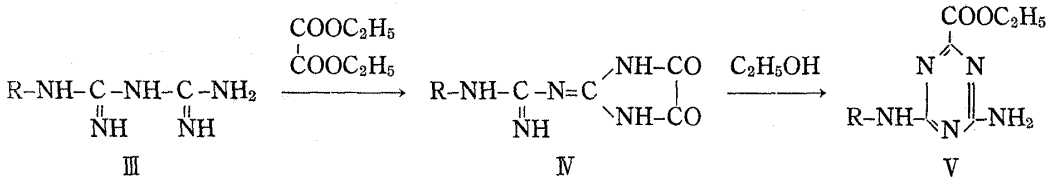


Chart 2

intermediate product was not able to isolate in any degree. Therefore, it was not confirmed that the reaction proceeded through the intermediate as above. On the other hand, it was found that the reaction of N–amidino–O–alkylisourea (VI) with diethyl oxalate afforded ethyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate (VIII) by refluxing in absolute ethanol, while methyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate (IX) by refluxing in absolute methanol. This finding suggested that an ester exchange took place in the course of the reaction. To ascertain this assumption, the reaction between ethyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate (VIII) and methanol was examined under the same condition and any amount of methyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate (IX) was not found in the reaction mixture. From this fact, it was inferred that the intermediate products might be produced prior to the formation of triazine derivatives as well as the reaction of biguanides with diethyl oxalate and the resulting intermediates might give rise to methyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate (IX) and ethyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate (VIII) by reacting with methanol and ethanol respectively, as shown in Chart 3. These

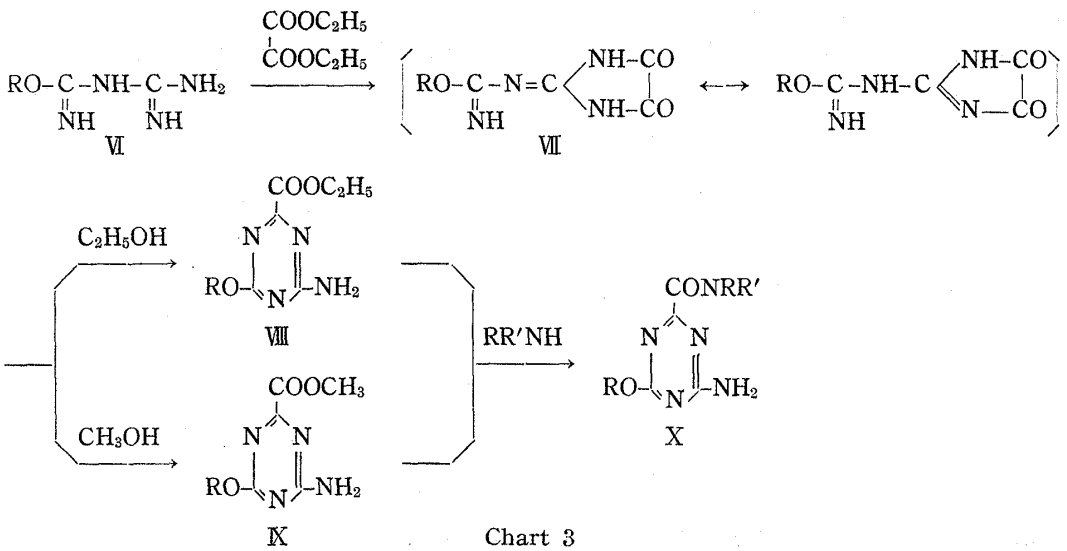


Chart 3

methyl and ethyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylates reacted easily with various amines, such as diethanolamine, piperidine, morpholine and hydrazine, to afford the corresponding amides (X) by refluxing in absolute ethanol.

Reaction of N-Amidino-O-alkylisourea with Ethyl Acetoacetate

In the reaction of N–amidino–O–alkylisourea with ethyl acetoacetate, there should be two possible courses of the reaction, pyrimidine or triazine formation, due to the tendency that N–amidino–O–alkylisourea might react with the carbonyl moiety or the carboxyl moiety in ethyl acetoacetate, as shown in Chart 4.

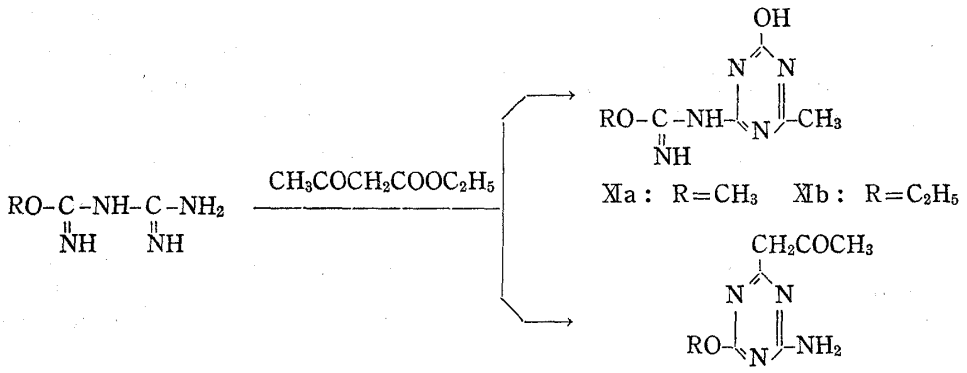


Chart 4

In this connection, it was reported by the author[11] that arylbiguanides reacted with ethyl acetoacetate in the absence of a catalyst to afford only 6–methyl–2–arylamino–4–pyrimidinols without giving any *s*–triazine type compounds expected. However, when N–amidino–O–methylisourea was submitted to react with ethyl acetoacetate in ethanol, the expected two products (XIa), (XIIa) were obtained in almost same degree in yield, while N–amidino–O–ethylisourea reacted with ethyl acetoacetate to afford the corresponding two products (XIb), (XIIb) at the rate of three to one. These two products were readily separated by the difference of their solubilities in ethanol and identified by the infrared absorption spectra measurement.

Reaction of N-Amidino-O-alkylisourea with Ethyl Cyanoacetate

In the reaction of N–amidino–O–alkylisourea with ethyl cyanoacetate, there should be two possible courses of the reaction similar to the case of the reaction with ethyl acetoacetate, because of the existence of the two functional groups, cyano and carbonyl group, in ethyl cyanoacetate.

However, when N–amidino–O–alkylisourea was treated with the equivalent amount of ethyl cyanoacetate in absolute ethanol at room temperature for five days, only a kind of

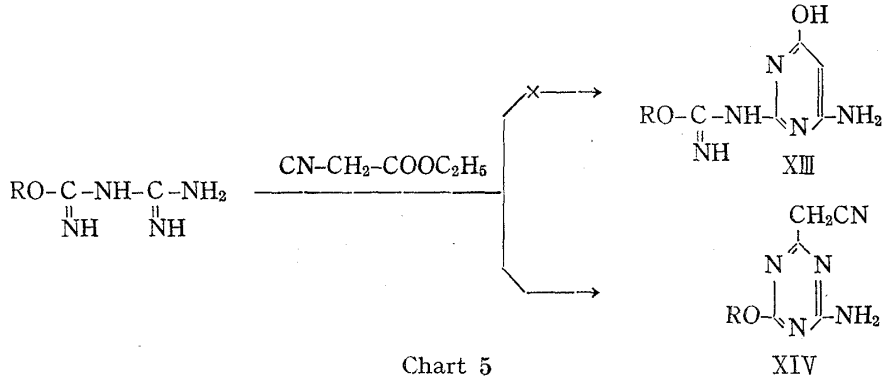
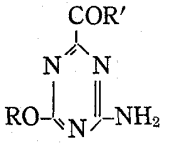
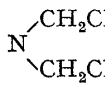
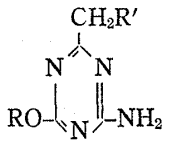
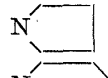
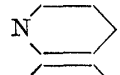
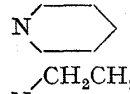
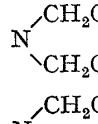
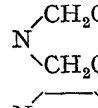
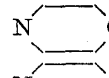
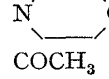
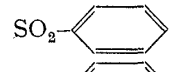
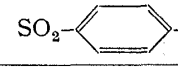


Chart 5

11) M. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1215 (1962).

Table I

Compd. No.	R	R′	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
											
I	CH_3	OC_2H_5	94	138—139	$C_7H_{10}O_3N_4$	42.42	5.08	28.27	41.97	4.92	27.42
II	C_2H_5	OCH_3	45	123—124	$C_7H_{10}O_3N_4$	42.42	5.08	28.27	42.44	4.98	28.73
III	C_2H_5	OC_2H_5	49	139—140	$C_8H_{12}O_3N_4$	45.26	5.74	26.39	45.72	5.85	26.01
IV	CH_3	$NHNH_2$	89	233—234	$C_5H_8O_2N_6$	34.48	4.63	45.63	35.05	4.81	45.15
V	C_2H_5	$NHNH_2$	78	182—183	$C_6H_{10}O_2N_6$	36.36	5.08	42.40	36.39	5.43	42.62
VI	CH_3	$NHCH_2CH_2OH$	81	174—176	$C_7H_{11}O_3N_5$	39.44	5.25	32.84	39.94	5.25	32.68
VII	C_2H_5	$NHCH_2CH_2OH$	44	163—164	$C_8H_{13}O_3N_5$	42.29	5.77	30.82	42.84	5.95	30.85
VIII	CH_3		94	163—164	$C_9H_{15}O_4N_5$	42.02	5.87	27.22	41.79	5.86	27.15
IX	C_2H_5		52	155—156	$C_{10}H_{17}O_4N_5$	44.27	6.32	25.82	44.29	6.28	25.93
											
X	CH_3	Cl	26	162—163	$C_5H_7ON_4Cl$	34.39	4.04	32.09	34.76	4.31	32.34
XI	C_2H_5	Cl	27	139—140	$C_6H_9ON_4Cl$	38.21	4.80	29.69	37.83	4.72	29.40
XII	CH_3	CN	18	206—207	$C_6H_7ON_5$	44.84	4.27	42.40	44.85	4.59	42.47
XIII	C_2H_5	CN	22	140—141	$C_7H_9ON_5$	46.92	5.06	40.74	46.47	4.92	40.52
XIV	CH_3		52	152—153	$C_9H_{15}ON_5$	51.65	7.22	33.47	51.64	7.16	33.53
XV	C_2H_5		56	117—118	$C_{10}H_{17}ON_5$	53.79	7.67	31.36	53.58	7.80	31.08
XVI	CH_3		98	156—157	$C_{10}H_{17}ON_5$	53.79	7.67	31.36	53.73	7.94	30.85
XVII	C_2H_5		80	121—122	$C_{11}H_{19}ON_5$	55.70	8.07	29.51	56.05	8.19	29.35
XVIII	CH_3		70	126—127	$C_9H_{17}O_3N_5$	44.43	7.04	28.78	44.26	7.19	28.64
XIX	C_2H_5		68	132—133	$C_{10}H_{19}O_3N_5$	46.68	7.44	27.22	46.76	7.48	27.12
XX	CH_3		96	170—171	$C_9H_{15}O_2N_5$	47.99	6.71	31.09	47.85	6.70	30.97
XXI	C_2H_5		69	116—118	$C_{10}H_{17}O_2N_5$	50.19	7.16	29.27	49.91	7.05	29.03
XXII	CH_3	$COCH_3$	39	195—196	$C_7H_{10}O_2N_4$	46.15	5.53	30.75	46.57	5.54	30.22
XXIII	C_2H_5	$COCH_3$	26	209—210	$C_8H_{12}O_2N_4$	48.97	6.21	28.54	49.71	6.31	28.31
XXIV	C_2H_5		58	160—161	$C_{12}H_{14}O_3N_4S$	48.97	4.79	19.03	49.44	4.89	19.40
XXV	C_2H_5		54	178—179	$C_{13}H_{16}O_3N_4S$	50.63	5.23	18.23	50.83	5.42	17.75

crystalline product was obtained in approxymate 20% yield accompanying the tar formation. The infrared spectra of these compounds showed the absorption assigned to cyano group near 2350 cm^{-1}. Therefore, these compounds should be 4–amino–2–alkoxy–6–cyanomethyl–*s*–triazine (XIV), but not 6–amino–2–alkoxyamidino–4–pyrimidinol (XIII) as shown in Chart 5.

Reaction of N-Amidino-O-alkylisourea with Ethyl Chloroacetate

It was known that biguanide derivatives reacted with ethyl chloroacetate to give 2,4–diamino–6–chloromethyl–*s*–triazine derivatives in the presence of alkaline catalyst. In the same way, 4–amino–2–alkoxy–6–chloromethyl–*s*–triazine derivatives (XV) were obtained by the reaction of N–amidino–O–alkylisourea with ethyl chloroacetate in low yields.

These chloromethyl–*s*–triazine derivatives (XV) obtained were easily aminated by refluxing in absolute ethanol with two moles of several amines, such as ethanolamine, diethanolamine, piperidine and morpholine, as shown in Chart 6.

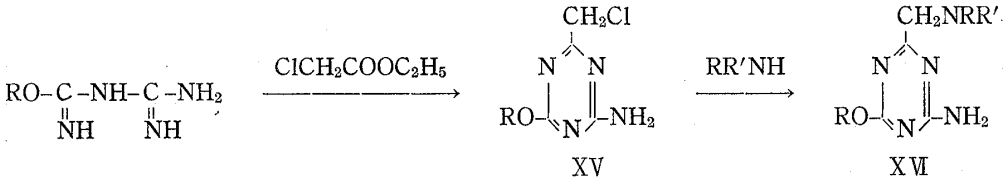


Chart 6

The whole compounds obtained by these several reactions are listed in Table I.

The antitumor and pharmacological effects of these compounds will be described in the other paper.

Experimental

N-Amidino-O-alkylisourea Hydrochloride——It was prepared from dicyandiamide and alcohol by Kawano method.[12]

Alkyl 4-Amino-6-alkoxy-*s*-triazine-2-carboxylate (I)—(III)——A solution of 0.02 mole of N–amidino–O–alkylisourea hydrochloride in 30 cc of anhyd. alcohol was treated with an alcoholic sodium alkoxide solution prepared by dissolving 0.02 mole of metalic Na in a suitable amount of anhyd. alcohol and the resulting precipitates were filtered off. To the filtrate was added 0.02 mole of diethyl oxalate. The solution was heated for 24 hr under reflux and then concentrated. The resulting precipitates deposited on cooling were collected by suction and recrystallized from EtOH as colorless prisms.

4-Amino-6-alkoxy-*s*-triazine-2-carboxamide (VI)—(IX)——A solution of 0.01 mole of alkyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate and 0.01 mole of amine in 5 cc of anhyd. EtOH was refluxed for 5 hr. After the completion of the reaction, the precipitates deposited on cooling were collected by filtration and recrystallized from EtOH as colorless prisms.

4-Amino-6-alkoxy-*s*-triazine-2-carboxyhydrazide (IV)—(V)——To a solution of 0.01 mole of ethyl 4–amino–6–alkoxy–*s*–triazine–2–carboxylate in 10 cc of anhyd. EtOH was added with stirring 0.01 mole of hydrazine hydrate at room temperature. The resulting precipitates were collected by suction, washed with EtOH and recrystallized from EtOH as colorless prisms or needles.

4-Amino-2-alkoxy-6-chloromethyl-*s*-triazine (X), (XI)——A solution of 0.1 mole of N–amidino–O–alkylisourea hydrochloride in 80 ml of anhyd. EtOH was treated with an ethanolic NaOEt solution prepared by dissolving 0.1 mole of metalic Na in a small amount of anhyd. EtOH and the resulting precipitates were removed by filtration. To the filtrate was added with shaking 0.1 mole of ethyl chloroacetate on cooling. After standing overnight, the resulting precipitates were recrystallized from EtOH as colorless needles.

4-Amino-2-alkoxy-6-substituted-amino-*s*-triazine (XIV)—(XXI)——To a solution of 0.01 mole of 4–amino–2–alkoxy–6–chloromethyl–*s*–triazine in 5 cc of anhyd. EtOH was added 0.02 mole of amine. After refluxing for 2 to 5 hr, the solution was concentrated. The precipitates deposited on cooling were collected by suction and recrystallized from EtOH as colorless prisms.

4-Amino-2-alkoxy-6-cyanomethyl-*s*-triazine (XII), (XIII)——A solution of 0.02 mole of N–amidino–O–alkylisourea hydrochloride in 30 ml of anhyd. EtOH was treated with an ethanolic NaOEt solution prepared by dissolving 0.02 mole of metalic Na in a small amount of anhyd. EtOH and the resulting precipitates were removed by filtration. To the filtrate was added 0.02 mole of ethyl cyanoacetate. After standing

12) K. Kawano, *Kyushu Kogyo Daigaku Kenkyu Hokoku* (Japan), **12**, 69 (1962).

for 5 days at room temperature, the precipitates deposited were collected by suction and washed with ether. Recrystallization from EtOH gave colorless prisms.

Reaction of N-Amidino-O-methylisourea with Ethyl Acetoacetate——A solution of 4.58 g of N-amidino-O-methylisourea hydrochloride in 30 ml of anhyd. EtOH was treated with an ethanolic NaOEt solution prepared by dissolving 0.69 g of metalic Na and the precipitates deposited were removed by filtration. To the filtrate was added 3.90 g of ethyl acetoacetate. After refluxing for 5 hr, the resulting precipitates were collected by suction and recrystallized from a large volume of EtOH as colorless prisms of 6-methyl-2-methoxyamidino-4-pyrimidinol, mp 187—188°, yield 2.25 g. *Anal.* Calcd. for $C_7H_{10}O_2N_4$: C, 46.15; H, 5.53; N, 30.75. Found: C, 46.48; H, 5.58; N, 30.56.

Concentrating of the filtrate gave colorless prisms of 4-amino-2-methoxy-6-acetomethyl-*s*-triazine (XXII), mp 195—196°, yield 2.10 g.

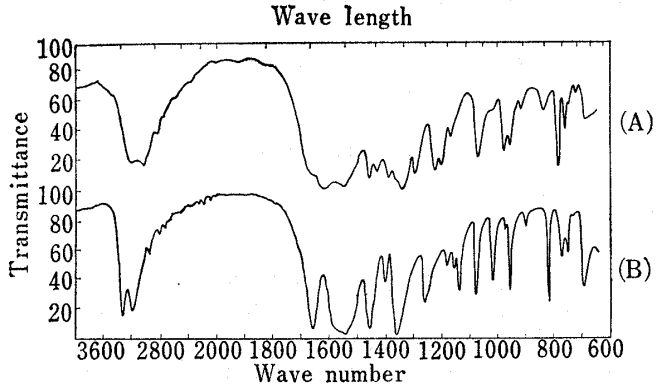


Fig. 1. Infrared Absorption Spectra of 6-Methyl-2-methoxyamidino-4-pyrimidinol (A) and 4-Amino-2-methoxy-6-acetomethyl-*s*-triazine (B)

IR spectra of these compounds are shown in Fig. 1.

Reaction of N-Amidino-O-ethylisourea with Ethyl Acetoacetate——Treatment of N-amidino-O-ethylisourea with ethyl acetoacetate by the same method as described above gave colorless prisms of 6-methyl-2-ethoxyamidino-4-pyrimidinol, mp 144—145°, yield 64.0%. *Anal.* Calcd. for $C_8H_{12}O_2N_4$: C, 48.97; H, 6.21; N, 28.54. Found: C, 49.62; H, 6.36; N, 28.31, and colorless prisms of 4-amino-2-ethoxy-6-acetomethyl-*s*-triazine (XXIII), mp 209—210°, yield 25.5%.

4-Amino-2-ethoxy-6-benzenesulfonylmethyl-*s*-triazine (XXIV)——To a solution of 0.50 g of 4-amino-2-ethoxy-6-chloromethyl-*s*-triazine (XI) in 10 ml of anhyd. EtOH was suspended 0.54 g of powdered sodium benzenethiosulfonate. The reaction mixture was heated with stirring for 24 hr under reflux and then concentrated. The resulting precipitates were collected by suction and recrystallized from EtOH as colorless needles, mp 160—161°, yield 0.45 g.

4-Amino-2-ethoxy-6-(*p*-toluenesulfonyl)methyl-*s*-triazine (XXV)——It was obtained from 5.0 g of 4-amino-2-ethoxy-6-chloromethyl-*s*-triazine (XI) and 5.6 g of sodium *p*-toluenethiosulfonate by the same procedure as described above, as yellow colums, mp 178—179°, yield 4.4 g.

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