Anal. Calcd. for $C_{15}H_{27}NS_2$: C, 63.10; H, 9.53; mercaptan sulfur, 11.23. Found:[B] C, 63.40; H, 9.60; mercaptan sulfur,[17] 10.9.

1-Phthalimidohexanone-2.—Potassium phthalimide (2.0 g.) and 1.4 g. of 1-chlorohexanone-2 were mixed with 15 cc. of 95% ethanol, and the mixture refluxed for seventy minutes. The solution was decanted from the grainy deposit of potassium chloride, evaporated nearly to dryness, and the residue extracted twice with petroleum ether (b. p. 30–40°). Cooling the extracts in the refrigerator caused 0.36 g. (15%) of white needles, m. p. 63–65°, to separate. Recrystallization raised the melting point to 69–69.5°.

Anal. Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16. Found:[C] C, 69.02; H, 6.13.

This compound was also prepared (in 29% yield) by heating 1-chlorohexanone-2 and a slight excess of potassium phthalimide without solvent at 120–130° for half an hour.

(17) Mercaptan sulfur analysis through courtesy of Dr. W. C. MacTavish, New York University.

1-Phthalimidoheptanone-2.—By the method described above, there was obtained a 13% yield of this derivative which, after recrystallization from petroleum ether (b. p. 40–60°), melted at 62.5–63.5°.

Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 69.41; H, 6.61. Found:[C] C, 69.19; H, 6.44.

Summary

1. α-Chloroketones have been obtained in moderate yield by the reaction of alkylcadmium compounds with chloroacetyl chloride and α-chloropropionyl chloride.

2. The data obtained emphasize the lesser nucleophilic reactivity of organocadmium as compared to organozinc compounds.

3. The preparation of two 4-alkyl-2-mercaptothiazoles is described.

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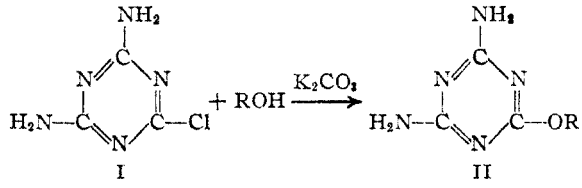
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

Alkoxy-*s*-Triazines

BY JOHN CONTROULIS[1] AND C. K. BANKS

In a previous study of the reaction of 2-chloro-4,6-diamino-*s*-triazine (I) with arylarsonic acids,[1a] the reaction between *p*-hydroxybenzenearsonic acid and I was attempted. The first medium employed was dilute hydrochloric acid but the only product isolated was ammeline, 2-hydroxy-4,6-diamino-*s*-triazine. When this same reaction was carried out in dry cellosolve with an equivalent of potassium carbonate, an unexpected product was obtained. Instead of the phenolic hydroxyl group of the benzenearsonic acid taking part in the reaction, the hydroxyl group of the cellosolve reacted with the triazine (I) yielding 2-β-ethoxyethoxy-4,6-diamino-*s*-triazine as indicated in the type reaction



The arsonic acid was recovered unchanged.

Due to the pharmacological properties exhibited by the triazine arsenicals,[1a] it was thought advisable to prepare a series of compounds of the same type as II. The extent of the interaction of I with various alcohols in the presence of potassium carbonate was unsatisfactory both with respect to the yield of product and the time of reaction. The conditions of the classical Williamson reaction were then employed and found to be suitable. The sodium alcoholate was prepared in an excess of the alcohol and then the chloro-triazine was added. Refluxing this mixture for one to five hours was sufficient to obtain complete reaction. In an instance where an excess of the alcohol was not available, a second procedure was employed wherein an equivalent of the alcohol dissolved in xylene was treated with sodium. When the metal had dissolved, the halide was added and refluxing effected to cause the elimination of sodium chloride. The same products were also obtained when alcoholic suspensions of halotriazines were saturated with dry hydrogen chloride. However, the products obtained by this method were purified with greater difficulty.

Of the various types of alcohols employed it was found that the *iso*- and *sec*-alkyl alcohols took part in the reaction as readily as the primary alcohols. However, no ether type product was obtained from the action of the halotriazine on sodium *t*-butylate. This was also the case with the sodium derivatives of benzhydrol, fluorenol, xanthydrol and menthol. Whether or not this phenomenon was due to steric influence was not determined.

Table I lists the compounds prepared and their physical constants. 2-Ethoxy-4,6-diamino-*s*-triazine was prepared by Hofmann[2] by the action of ammonia on the triethyl ester of cyanuric acid. The melting point he observed was 190–200°, the considerable range probably being due to the presence of ammeline, which has a high decomposition point. The occurrence of this impurity in the crude alkoxy-triazines listed in this paper caused an elevation of the melting points of these

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(1a) Banks, Gruhzit, Tillitson and Controulis, THIS JOURNAL, **66**, 1771 (1944).

(2) Hofmann, *Ber.*, **19**, 2080 (1886).

TABLE I

2-R-4,6-Diamino-s-triazine	Recrystallized from	M. p., °C.	Yield, %	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
R = Methoxy	Dioxane	229–230	81	34.04	34.03	4.96	4.73
Ethoxy[2]	Water	182	72	38.71	38.87	5.81	6.04
n-Propoxy	Water	182–183	88	42.60	42.50	6.51	6.59
i-Propoxy	Water	172	78	42.60	42.77	6.51	6.31
n-Butoxy	Water	174–175	75	45.90	46.03	7.10	6.80
i-Butoxy	Dioxane-water	186	93	45.90	46.09	7.10	7.13
s-Butoxy	Dioxane	173–174	50	45.90	45.94	7.10	6.96
n-Pentoxy	Ethanol-water	147	28	48.73	48.87	7.61	7.72
n-Hexoxy	Dioxane-water	152	58	51.18	51.47	8.06	7.76
n-Heptoxy	Dioxane-water	139	63	53.33	53.38	8.44	8.03
n-Octoxy	Benzene	122–124	46	55.23	55.15	8.79	8.45
n-Nonoxy	Xylene	115	41	56.92	57.00	9.09	9.17
n-Decoxy	Benzene	121–123	29	58.42	58.17	9.36	9.50
Allyloxy	Ethanol	181–182	82	43.10	42.80	5.38	5.46
β-Ethoxyethoxy	Water	155–156	33	42.70	42.38	6.13	6.08
β-Phenoxyethoxy	Ethanol	184–185	77	53.49	53.62	5.26	5.06
Cyclohexoxy	Dioxane-water	209	53	51.70	51.69	7.77	7.61
Benzyloxy	Ethanol-xylene	187	65	55.32	55.59	5.07	5.12
β-N,N-Dimethylaminoethoxy	Ethanol-water	122	37	42.45	42.59	7.07	7.09
γ-N,N-Diethylaminopropoxy	Acetone-water	147	38	50.00	50.13	8.33	8.53
β-Morpholinoethoxy	Water	211–212	46	45.01	44.97	6.66	6.84
Isopropylthio	Ethanol-water	190	68	38.91	39.16	5.95	5.52
2-Ethoxy-4,6-di(monoisopropanolamino)-*s*-triazine	Water	119–120	49	48.70	48.80	7.75	8.14
2-Ethoxy-4-monoisopropanolamino-6-amino-*s*-triazine	Water	140–142	83	45.01	45.02	7.04	7.14
2-N-Butoxy-4-monoisopropanolamino-6-amino-*s*-triazine	Ethanol-water	131	87	49.82	49.93	7.89	8.29

[a] The analyses were performed by A. W. Spang, microanalyst of these Laboratories.

compounds. Upon recrystallization of the impure material, leading to the removal of the ammeline, consistently lower melting points were obtained. Satisfactory results were never obtained from either the Dumas or the Kjeldahl nitrogen determinations, even when special catalysts were employed.

For pharmacological purposes, two variations on the type of compounds prepared in this series were made. 2-Isopropylthio-4,6-diamino-*s*-triazine was prepared to compare the activity of the oxygen linkage with that of the sulfur linkage. The other variation was the preparation of 2-alkoxy-4-hydroxy-alkylamino-6-amino-*s*-triazines and a 2-alkoxy-4,6-bis-(hydroxyalkylamino)-*s*-triazine. These compounds were prepared according to the Williamson reaction using the appropriately substituted halide.

Some pharmacological properties of the alkoxy-*s*-triazines were determined by Dr. E. R. Loew, Margaret Kaiser and Mona Anderson of these laboratories. The most interesting property of the compounds was their ability to alleviate histamine shock in guinea pigs. The activity of the compounds as compared with that of aminophylline is listed in Table II. The toxicity of the ethers as determined in white mice is also included in the table. Examination of the data shows that the potency of the compounds at first increases with molecular weight and then decreases. The peak lies in the vicinity of the propyl and butyl derivatives. Perhaps the activity of the cyclohexyl ether may be explained on the basis of similarity in length of the molecule to that of the propyl and butyl ethers. The anti-histamine effect of 2-isopropylthio-4,6-diamino-*s*-triazine is about the same as that of the oxygen analog. Substitutions of the amino groups in the four and six positions on the ring did not appreciably alter the activity of the unsubstituted compounds.

Experimental

The alcohols were obtained from Eastman Kodak Company or were reagent-grade shelf chemicals. All were dried over anhydrous magnesium sulfate sixteen to twenty-four hours prior to use.

General Procedure.—Sodium (0.1 mole) was added to 100 ml. of the dry alcohol in a three-necked flask equipped with a condenser and mercury-sealed mechanical stirrer. With the higher molecular weight alcohols, gentle refluxing was necessary to effect solution of the metal. When the last trace of sodium disappeared, the halotriazine[1b] (0.1 mole) was added with continued stirring. Refluxing was continued until the appearance of the suspended solid changed from that of the amorphous halide to that of the crystalline sodium chloride. The mixture was then filtered hot and the filtrate chilled to 5–10°. This usually caused crystallization of the ether in a fairly pure state. The filter-cake, consisting largely or wholly of sodium chloride, was slurried in 100 ml. of water to recover any unreacted halide or product which may have separated from the hot reaction mixture. In the case of the more soluble ethers,

TABLE II

2-R-4,6-Diamino-*s*-triazine	LD-50, mg./kg. I. P., white mice	Histamine-shocked[a] guinea pigs, survival (50%), mg./kg.	Relative anti-histamine activity[b]	Relative toxicity[b]	Comparative index
Aminophylline	260	50	1	1.0	1
R = Methoxy-	500	50	1	0.5	2
Ethoxy-	500	25	2	0.5	4
n-Propoxy-	520	12.5	4	0.5	8
i-Propoxy-	360	12.5	4	0.7	6
i-Propylthio-		12.5	4		
n-Butoxy	220	25	2	1.2	2
i-Butoxy-	340	12.5	4	0.8	5
s-Butoxy-	410	12.5	4	0.6	7
n-Pentoxy-	130	25	2	2.0	1
n-Hexoxy-	120	18	3	2.3	1
n-Heptoxy-	55	>50	..	...	.
n-Octoxy-	45	>25	..	...	..
n-Nonoxy-	120	>50	..	...	..
Allyloxy-	..	25	2	...	..
β-Ethoxyethoxy-	>1000	50	1	<0.3	>3
β-Phenoxyethoxy-	..	>50	..	...	..
Cyclohexoxy-	240	12.5	4	1.1	4
Benzyloxy-	..	>25	..	...	..
β-N,N-Dimethylaminoethoxy-	..	>25	..	...	..
γ-N,N-Diethylaminopropoxy-	..	>100	..	...	..
β-Morpholinoethoxy-	>1000	>100	..	...	..
2-Ethoxy-4,6-di-(monoisopropanolamino)-*s*-triazine	930	25	2	0.3	6
2-N-Butoxy-4-monoisopropanolamino-6-amino-*s*-triazine	420	12.5	4	0.6	7

[a] The histamine-induced shock method is that reported by Dr. E. R. Loew, *et al.*, *J. Pharmacol.*, **83**, 120 (1945). [b] Compared to aminophylline.

the filtrate from the reaction mixture was concentrated to obtain a maximum yield. The crude ethers were recrystallized from various solvents to purify the compounds. All were white crystalline solids when analytically pure.

2-γ-N,N-Diethylaminopropoxy-4,6-diamino-*s*-triazine. Sodium (0.1 mole) was added to 0.12 mole of γ-diethylaminopropanol dissolved in 100 ml. of xylene. One-tenth mole of the triazine halide was added to the mixture of the precipitated sodium alcoholate and solvent. A much longer refluxing time was necessary to effect homogeneity of the suspended material by this method. The product separated, even from the hot solvent, so that the filter-cake obtained upon filtration of the hot reaction mixture was warmed with 100 ml. of water, filtered and the solid remaining on the filter-plate recrystallized from an acetone–water mixture. The xylene filtrate was concentrated *in vacuo* and the residual solid recrystallized in the same fashion.

2-Isopropylthio-4,6-diamino-*s*-triazine.—Isopropyl mercaptan (0.07 mole) was dissolved in 7 ml. 10 *N* sodium hydroxide solution in 100 ml. of water. 2-Chloro-4,6-diamino-*s*-triazine (0.07 mole) was added and the mixture refluxed for sixteen hours. Solution occurred and when the colorless reaction mixture was cooled, a white crystalline solid separated. This was recrystallized from 15% ethyl alcohol.

Summary

A number of new alkoxy-*s*-triazines were prepared by an adaptation of the Williamson reaction. These compounds are of interest because of their ability to prevent deaths of histamine-shocked guinea pigs.

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