The Synthesis and the Reactions of 2, 4, 6-Tri-(ω-hydroxyalkyl)-1, 3, 5-triazines

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The present study will deal with the synthesis and the reactions of 2, 4, 6-tri-(ω-hydroxyalkyl)-1, 3, 5-triazines. The formation of the triazines was found in the cours of an experiment to prepare *N*-unsubstituted cyclic iminoethers, which had been expected to afford polyamides by the 1, 4-addition type ring-opening polymerization,[1-4] by treating their hydrochlorides with triethylamine.

The hydrochlorides of cyclic iminoethers (I) were prepared from the corresponding ω-cyanohydrines by the action of hydrogen chloride (Table I). The hydrochlorides decomposed to give the corresponding ring-opening products, ω-chloroalkylamides (II), in high yields when they were heated above their melting points (Table II).

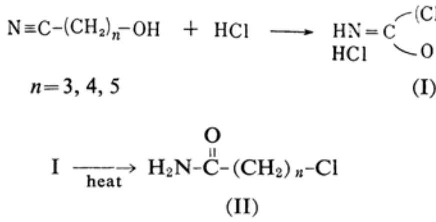
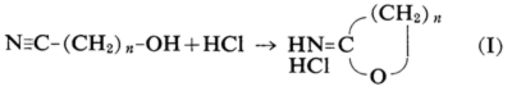


TABLE I

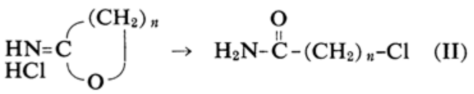


n	Yield %	M. p. [lit.] °C	Formula		C	H	N	Cl
3	95	103—105 [95a)]	C_4H_8ClNO	Found	38.65	6.25	11.60	29.41
				Calcd.	39.51	6.62	11.53	29.50
4	90	128—129	$C_5H_{10}ClNO$	Found	44.57	7.64	10.42	26.15
				Calcd.	44.62	7.48	10.41	26.20
5	85	143—144	$C_6H_{12}ClNO$	Found	48.11	8.25	9.55	
				Calcd.	48.23	8.08	9.37	

(Analysis, %: C, H, N, Cl)

a) K. S. Topchiev and M. L. Kirmalova, *Doklady Akad. Nauk S. S. S. R.*, **63**, 281 (1948); *Chem. Abstr.*, **43**, 2579e.

TABLE II



n	yield %	M. p. [lit.] °C	Formula		C	H	N
3	95	97 [90.4—90.7a)]	C_4H_8ClNO	Found	39.25	6.50	11.65
				Calcd.	39.51	6.62	11.53
4	80	78 [78—79b)]	$C_5H_{10}ClNO$	Found	44.76	7.58	10.55
				Calcd.	44.62	7.48	10.41
5	95	102	$C_6H_{12}ClNO$	Found	48.34	7.93	9.58
				Calcd.	48.23	8.08	9.37

(Analysis, %: C, H, N)

a) M. Berthet, *Bull. classe sci. Acad. roy. Belg.*, **27**, 212 (1941); *Chem. Abstr.*, **37**, 3400^7.
b) A. N. Nesmeyanow and L. I. Zakharkin, *Izvest. Akad. Nauk S. S. S. R., Otdel. Kim. Nauk*, **1953**, 988; *Chem. Abstr.*, **49**, 2298c.

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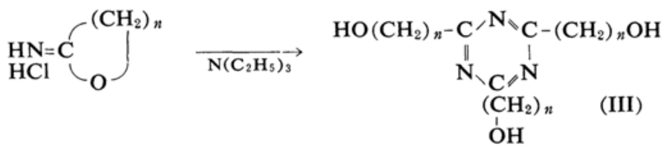
[1] T. Mukaiyama, T. Fujisawa, H. Nohira and T. Hyugaji, *J. Org. Chem.*, **27**, 3337 (1962).

[2] T. Mukaiyama and K. Sato, This Bulletin, **36**, 99 (1963).

[3] T. Fujisawa, Y. Tamura and T. Mukaiyama, ibid., **37**, 793 (1964).

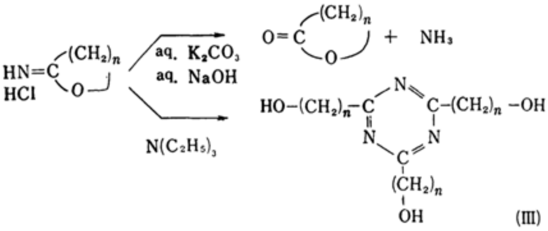
[4] H. Nohira, Y. Nishikawa and T. Mukaiyama, ibid., **37**, 797 (1964).

TABLE III



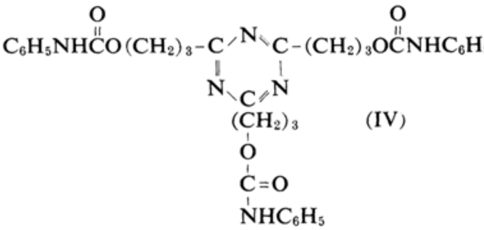
n	Yield %	B. p. °C(mmHg)	Formula		Analysis, % C	H	N	IR absorption ν_{max}, cm^{-1}	UV absorption λ_{max}, mμ(log ε)
3	53	196—198(0.1)	$C_{12}H_{21}N_3O_3$	Found Calcd.	56.65 56.45	8.08 8.29	16.62 16.46	3350(s, broad), 2925(m), 2850(m), 1545(vs), 1060(s)	259(2.85)
4	70	207—209(0.04)	$C_{15}H_{27}N_3O_3$	Found Calcd.	59.84 60.58	8.15 9.15	14.88 14.13	3340(s, broad), 2925(s), 2855(s), 1543(vs), 1065(s)	260(2.88)
5	50	218—221(0.01)	$C_{18}H_{33}N_3O_3$	Found Calcd.	63.48 63.68	9.88 9.80	12.49 12.39	3350(s, broad), 2930(s), 2860(s), 1542(vs), 1065(s)	259(2.82)

Several attempts to prepare free cyclic iminoethers from the hydrochlorides were made according to the ordinary procedures. When the hydrochlorides were treated with an aqueous solution of potassium carbonate or sodium hydroxide, they were mainly hydrolyzed to give the corresponding lactones and ammonia; free cyclic iminoethers could not be isolated. On the other hand, when the hydrochlorides were treated with anhydrous triethylamine, viscous liquids with a high boiling point resulted. The infrared spectra of these liquids showed strong absorptions at 3350 (OH), 1060 (CH_2-OH) and 1545 cm^{-1} (*sym*-triazine ring). Further examinations by means of elementary analyses, ultraviolet spectra and the determination of molecular weight confirmed their structures to be 2, 4, 6-tri-(ω-hydroxyalkyl)-1, 3, 5-triazines (III). From the hydrochlorides of the five-, the six- and the seven-membered cyclic iminoethers, the corresponding *sym*-triazines were obtained in fairly good yields, as Table III shows.



A crystalline derivative (IV) was obtained from the reaction of 2,4,6-tri-(γ-hydroxypropyl)-1, 3, 5-triazine and three equivalent moles of phenylisocyanate:

III + $3C_6H_5$-NCO →
$n=3$



The similar triazine formation reaction of iminoethers reported by Cramer et al.[5] has been developed by Schaefer and Peters[6] into a convenient synthetic method for the preparation of 2, 4, 6-trisubstituted-1, 3, 5-triazines. A possible mechanism of these trimerization reactions of the iminoethers has been proposed by Schaefer and Peters. It does not seem unlikely that the cyclic iminoethers which are formed from their hydrochlorides trimerized by essentially the same mechanism. However, one of the significant features in the trimerization reaction of the cyclic iminoethers is that the cyclic iminoethers trimerize more easily than typical non-cyclic iminoethers. This seems to be attributable to the ring strain of the cyclic systems.

In conclusion, it has now been found that the *N*-unsubstituted cyclic iminoethers tend to trimerize more easily in such a fashion as to give *sym*-triazines, rather than to polymerize so as to give polyamides by the 1, 4-addition-type ring-opening polymerization. As a result, a convenient synthetic method for the preparation of ω-hydroxyalkyl-derivatives of *sym*-triazine has been established.

Next, further study was carried out of the reaction of the 2, 4, 6-tri-(ω-hydroxyalkyl)-1, 3, 5-triazines thus obtained.

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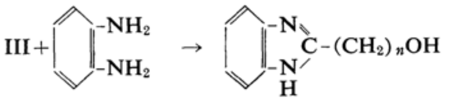
[5] F. Cramer, K. Pawelzik and J. Kupper, *Angew. Chem.*, **68**, 649 (1956).

[6] F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

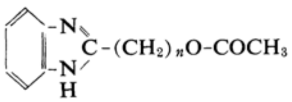
TABLE IV

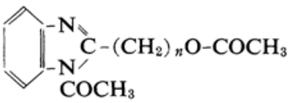


(V)

n	Yield %	M. p. °C	Crystn. Solvent	Formula		Analysis, % C	H	N
3	85	160—161[163[a]]	THF	$C_{10}H_{12}N_2O$	Found	67.90	7.01	16.11
					Calcd.	68.16	6.86	15.90
4	79	164—165	THF	$C_{11}H_{14}N_2O$	Found	69.25	7.24	14.98
					Calcd.	69.44	7.42	14.73
5	55	106	EA	$C_{12}H_{16}N_2O$	Found	70.45	8.17	13.98
					Calcd.	70.56	7.90	13.72

THF=tetrahydrofuran, EA=ethyl acetate

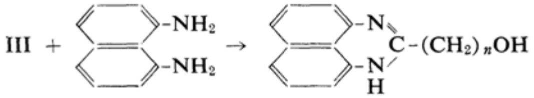




n	M. p. °C	Formula		Analysis, % C	H	N	M. p. °C	Formula		Analysis, % C	H	N
3	88—89	$C_{12}H_{14}N_2O_2$	F.	66.27	6.74	12.87						
			C.	66.03	6.47	12.84						
4	95—97	$C_{13}H_{16}N_2O_2$	F.	66.84	7.25	12.08	68—69	$C_{15}H_{18}N_2O_3$	F.	65.71	6.70	10.20
			C.	67.22	6.94	12.06			C.	65.67	6.61	10.21
5							78—79	$C_{16}H_{20}N_2O_3$	F.	66.25	6.76	9.90
									C.	66.64	6.99	9.72

a) W. Reppe, et al., *Ann.*, **596**, 158 (1955).

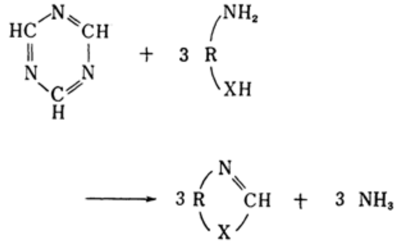
TABLE V



(VI)

n	Yield %	M. p. °C	Crystn. solvent	Formula		Analysis, % C	H	N
3	34	145—146	Dioxane	$C_{14}H_{14}N_2O$	Found	73.48	6.86	11.81
					Calcd.	74.31	6.24	12.38
4	45	157—158	THF	$C_{15}H_{16}N_2O$	Found	75.17	6.90	11.71
					Calcd.	74.97	6.71	11.66
5	60	185—187	Dioxane	$C_{16}H_{18}N_2O$	Found	75.35	7.27	10.89
					Calcd.	75.56	7.13	11.02

Crundmann⁷⁾ has suggested a convenient synthesis of various heterocyclic compounds by the use of unsubstituted *sym*-triazine, as is shown in the following general equation:



X= -NH-, -O-, -S-

The same investigator and Kreuzberger⁸⁾ have reported that this type of ring cleavage is not applicable to 2, 4, 6-trisubstituted-1, 3, 5-triazines; for example, 2, 4, 6-trimethyl-1, 3, 5-triazine does not react with aniline up to 200°C. In the present investigation, however, it has been found that the above-mentioned 2, 4, 6-tri-(ω-hydroxyalkyl)-1, 3, 5-triazines react with diamines when the reactions are carried out above 200°C. That is, when III was heated with three equivalent moles of *o*-phenylenediamine at 220-230°C in a nitrogen atmosphere, the evolution of ammonia was observed, and

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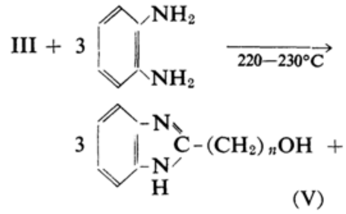
7) C. Grundmann, *Angew. Chem.*, **75**, 393 (1963).

8) C. Grundmann and A. Kreuzberger, *J. Am. Chem. Soc.*, **77**, 6559 (1955).

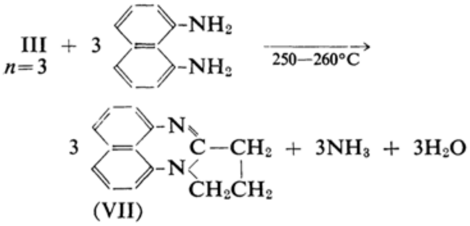
2-(ω-hydroxyalkyl) benzimidazoles (V) were obtained in good yields (Table IV).


(V)

In a similar fashion, III reacted with 1,8-naphthylenediamine to give 2-(ω-hydroxyalkyl)-perimidines (VI) (Table V).


(VI)

At higher temperatures, 250—260°C, however, azolidino[1,2-a]perimidine (VII), a dehydrated product of VI ($n=3$), was obtained by the reaction of 2,4,6-tri-(γ-hydroxypropyl)-1,3,5-triazine (III, $n=3$) with 1,8-naphthylenediamine.


(VII)

Experimental

Trimethylen Cyanohydrin.—This compound was prepared by the reaction of trimethylene chlorohydrin and potassium cyanide in a mixed solvent of ethanol and water;[9] b. p. 107—108°C (11 mmHg); yield, 30%.

Tetramethylene Cyanohydrin. — The reported method,[10] which is essentially analogous to the above reaction, gave the cyanohydrin in poor yields only (5—10%). An improved method is given as follows. A mixture of tetramethylene chlorohydrin (22 g., 0.2 mol.), potassium cyanide (33 g., 0.5 mol.), glycerol (50 ml.) and water (25 ml.) was heated while being mechanically stirred at 100—110°C for 15 min. After it had cooled, the mixture was extracted four times with 50 ml. portion of tetrahydrofuran. The extract was then dried over anhydrous magnesium sulfate, and the solvent was subsequently removed. The residue was distilled under reduced pressure; b. p. 86—88°C (0.5 mmHg); yield, 7.0 g. (35%).

When the distillation was carried out without extracting soon after the reaction was complete, another liquid (b. p. 65—66°C) was obtained. This liquid was identified as tetrahydrofuran by comparing its infrared spectrum with that of an authentic specimen. The formation of this liquid can be explained in terms of the cyclization of the chlorohydrin used, with the loss of hydrogen chloride. The yield of this by-product amounted to almost 30%. This seems to be one of the main factors lowering the yield of the tetramethylene cyanohydrin.

Pentamethylene Cyanohydrin.—This compound was prepared from pentamethylene chlorohydrin and potassium cyanide by method analogous to that described above; b. p. 97—98°C (3 mmHg); yield, 83%.

Hydrochloride of 2-Iminotetrahydrofuran (I, *n*=3).—Dry hydrogen chloride was passed into a solution of 8.5 g. of trimethylene cyanohydrin in 300 ml. of dry ether maintained at 10—15°C with external cooling. The flask was tightly stoppered and allowed to stand at room temperature for 2 days. The crystals were then collected and washed with dry ether; yield, 11.5 g (Table I).

Similarly, hydrochloride of 2-iminotetrahydropyrane (I, $n=4$) was prepared from tetramethylene cyanohydrin and hydrogen chloride. In this case, however, it was necessary to carry the reaction out in a more dilute (1.5—2.0%) ethereal soultion.

Hydrochloride of 2-Iminooxepan (I, *n*=5).—Dry hydrogen chloride was passed into a solution of 4.5 g. of pentamethylene cyanohydrin in 150 ml. of dry ether and 80 ml. of dry, glycol acetal-free dioxane with external cooling. The reaction mixture was allowed to stand at room temperature for 4 days, and then refluxed for 3 hr. The solvent was subsequently removed under reduced pressure. The crystals were washed with cold and dry dioxane and successively with dry ether; yield, 5.1 g. (Table I).

ω-Chloroalkyl Amides (II).—These compounds were obtained from the corresponding hydrochlorides of cyclic iminoethers (I) by heating them at 150—160°C for about 5 min. or by refluxing them in toluene. They were then recrystallized from ligroin or ligroin-benzene (Table II).

2,4,6-Tri-(γ-hydroxypropyl)-1,3,5-triazine (III, *n*=3).—In a 200 ml. flask, 9.6 g. (0.08 mol.) of hydrochloride of 2-iminotetrahydrofuran (II, $n=3$), 16.0 g. of triethylamine and 80 ml. of absolute tetrahydrofuran were placed, and then the flask was tightly closed with a stopper. It was allowed to stand at room temperature with intermittent shaking for 3 days. After the precipitate of the hydrochloride of triethylamine had been filtered off, the solvent and the excess triethylamine were removed by distillation. The residual viscous liquid was distilled under reduced pressure; b. p. 196—198°C (0.1 mmHg), yield, 3.6 g. (53%).

Similarly, 2,4,6-tri-(δ-hydroxybutyl)-1,3,5-triazine (III, $n=4$) and 2,4,6-tri-(ε-hydroxypentyl)-1,3,5-triazine (III, $n=5$) were obtained from the corresponding hydrochlorides of cyclic iminoethers.

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9) G. Aksnes and J. E. Prue, *J. Chem. Soc.*, **1959**, 103.

10) C. C. Price, G. A. Cypher and I. V. Krishnamurti, *J. Am. Chem. Soc.*, **74**, 2987 (1952).

Their yields, boiling points, analyses and infrared and ultraviolet absorptions are summarized in Table III.

2, 4, 6-Tri-[γ-(phenylaminocarboxy) propyl]-1,3,5-triazine (IV).—To a solution of 0.5 g. of 2, 4, 6-tri-(γ-hydroxypropyl)-1, 3, 5-triazine in 10 ml. of tetrahydrofuran, 0.7 g. of phenylisocyanate was added. After the mixture had been allowed to stand for 2 days, the solvent was evaporated and the precipitate was recrystallized from 95% ethanol. Yield, 1.1 g. (92%) ; m. p. 124—125°C.

Found : C, 64.00, H, 6.03 ; N, 14.45, Calcd. for $C_{33}H_{36}N_6O_6$: C, 64.69, H, 5.92 ; N, 13.72%.

The Reaction of 2, 4, 6-Tri-(ω-hydroxyalkyl)-1, 3, 5-triazine with *o*-Phenylenediamine or 1, 8-Naphthylenediamine.—A general procedure employed was as follows. A triazine (III) was heated with three equivalent moles of *o*-phenylenediamine or 1, 8-naphthylenediamine in a nitrogen atomsphere in an oil bath maintained at 220—230°C. After a while, the evolution of ammonia gas began ; the heating was continued until the evolution of gas had ceased (15—60 min.). The reaction mixture was then washed with ether, and the precipitate was recrystallized from a suitable solvent, as is shown in Tables IV and V.

O-Acetyl-derivatives of V were obtained from the reaction of V and 1.2 equivalent moles of acetic anhydride in pyridine at room temperature.

O-, *N*-Diacetyl-derivatives of V were obtained from the reaction of V and 2.5 equivalent moles of acetic anhydride in pyridine at 100°C.

Azolidino[1, 2-a]perimidine (VII).—A mixture of 0.5 g. of 2,4,6-tri-(γ-hydroxypropyl)-1,3,5-triazine (III, $n=3$) and 0.7 g. of 1, 8-naphthylenediamine was heated in a nitrogen atmosphere at 250—260°C for one hour. The reaction mixture was then washed with ether, and the precipitate was recrystallized from tetrahydrofuran. Yield, 0.5 g. (34%) ; m. p. 143—144°C.

Found : C, 80.30, H, 6.87; N, 13.71, Calcd. for $C_{14}H_{12}N_2$: C, 80.74, H, 5.81 ; N, 13.45%.

Summary

2, 4, 6-Tri-(ω - hydroxyalkyl) - 1, 3, 5 - triazines have been prepared by the reaction of hydrochlorides of cyclic iminoethers, such as 2-iminotetrahydrofuran, 2-iminotetrahydropyrane or 2-iminooxepan, with triethylamine. The reactions of the triazines with *o*-phenylenediamine or 1, 8-naphthylenediamine to give 2-(ω-hydroxyalkyl) benzimidazoles or 2-(ω-hydroxyalkyl) perimidines have also been described.

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