Hydrochloric acid was added to bring the *p*H to 5.5. The mixture was shaken on a rotary shaker for 16 hr., at which time the *p*H was adjusted to 3.0 with HCl, and the mixture was agitated for an additional 48 hr. The product accumulated as a precipitate in the aqueous phase, and was filtered without phase separation. The tetracycline-urea compound was dried *in vacuo* at 50°, weight 7.80 g. (90% from organic extract), assay 938 μg./mg. as tetracycline hydrochloride.

Anal. Calcd. for $C_{23}H_{30}N_4O_{10}$: C, 52.80; H, 5.75; N, 10.72. Found: C, 52.85; H, 5.68; N, 10.70.

Determination of solubilities. An unweighed portion of the tetracycline derivative was suspended in the solvent and placed on a rotary shaker for two hours at room temperature, the undissolved material filtered, and the filtrate assayed spectrophotometrically.

Determination of distribution coefficients. Samples were dissolved in *p*H 2.5/0.25*M* sodium dihydrogen phosphate buffer (previously equilibrated against the organic phase) at a final concentration of 50 μg./ml. and equilibrated with a mixture of 80% chloroform-20% butanol (10 ml. of each phase). Each phase was assayed spectrophotometrically after thirty inversions. The distribution coefficient for tetracycline urea compound was 0.14 (organic phase/aqueous phase), for tetracycline base, 0.13.

Fractionation of mixtures of tetracycline and 7-chlorotetracycline. Mixtures containing 7-chlorotetracycline neutral and tetracycline neutral were prepared, and 5.0 g. of the crystal mixture was slurried in 100 ml. of saturated aqueous urea solution. After one hour of shaking the undissolved material was filtered and analyzed.

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[CONTRIBUTION FROM THE ROHM & HAAS CO.]

Preparation of α-Hydroxyguanamines from Cyanohydrins

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Lactonitrile, a typical cyanohydrin, was not stable in an attempted base-catalyzed condensation with dicyandiamide to an α-hydroxyguanamine. The acid-catalyzed condensation of cyanohydrins with vinyl ethers gave α-cyanoacetals, I, which were stable in this condensation. Acid-catalyzed hydrolysis of the resulting diaminotriazines, II, gave the desired α-hydroxyguanamines, III (2,4-diamino-*s*-triazine-6-alkanols). A homologous formal, 2,4-diamino-6-ethoxymethoxymethyl-*s*-triazine, was either recovered quantitatively or converted to resins under comparable conditions.

The base-catalyzed reaction of dicyandiamide with nitriles[1] is usually one of the best methods of synthesizing guanamines (2,4-diamino-6-alkyl-*s*-triazines). However, when a cyanohydrin, such as lactonitrile, was used in the method, no hydroxyguanamine was obtained. It was probable that reversion of the cyanohydrin to the aldehyde and HCN occurred with subsequent base-catalyzed polymerization reactions.

The desired α-hydroxyguanamines[2] (III) were therefore prepared by a sequence of reactions (Fig. 1) involving in the first step the stabilization of the cyanohydrins to basic conditions, in the form of their addition products to various vinyl ethers. The convenience and high yields of this reaction sequence provide a practical and general synthesis for this series of compounds. It is illustrated in the accompanying table and in the experimental section for cyanohydrins from three aldehydes (formaldehyde, acetaldehyde, and benzaldehyde) and two ketones (acetone and cyclohexanone). The only previous synthesis (for lactoguanamine)[3] was from a corresponding α-hydroxy-

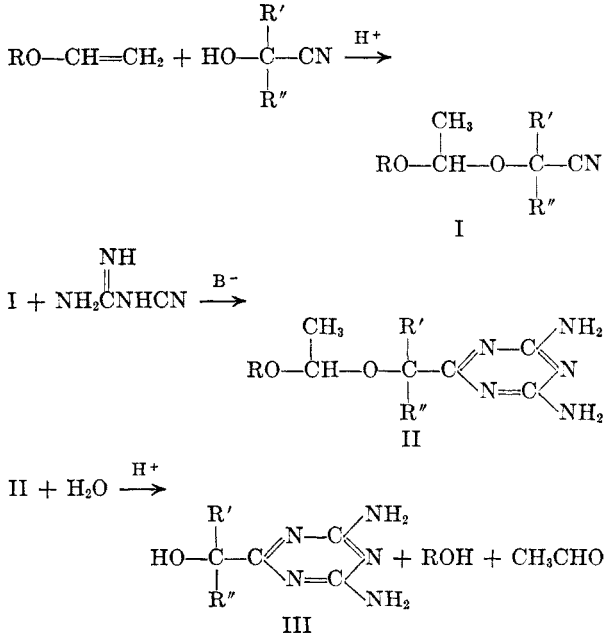

Figure 1

(1) (a) W. Zerweck and W. Brunner, U. S. Patent 2,302,163; *Chem. Abstr.*, **37**, 2016 (1943); (b) J. K. Simons, U. S. Patent 2,532,519; *Chem. Abstr.*, **45**, 3429 (1951).

(2) The non-systematic term "guanamine" will be used in the discussion section. Compounds III are named after the corresponding hydroxyacids, thus: glycologuanamine (R, = R′ = H), α-hydroxyisobutyroguanamine (R′ = R″ = CH_3), etc.

(3) J. T. Thurston, U. S. Patent 2,394,526 (1946); *Chem. Abstr.*, **40**, 5776 (1946).

TABLE I

CYANOACETALS (I)

Compound	R	R′	R″	Yield, %	B.P., °C.	Mm.	n_D^{25}	Empirical Formula	% N Calcd.	% N Found
Ia	n-C_4H_9	H	H	91	52–56	1.0	1.4147	$C_8H_{15}NO_2$	8.9	9.1
Ib	C_2H_5	CH_3	H	76	64–70	13	—	$C_7H_{13}NO_2$	9.8	10.1
Ic	n-C_4H_9	CH_3	H	74	90–94	17	1.4070	$C_9H_{17}NO_2$	8.2	8.2
Id	C_2H_5	CH_3	CH_3	77	69–71	14	1.4070	$C_8H_{15}NO_2$	8.9	9.2
Ie	n-C_4H_9	CH_3	CH_3	76	97–103	18	1.4135	$C_{10}H_{19}NO_2$	7.6	7.6
If	C_2H_5	—$(CH_2)_5$— [a]		87	70–75	0.9	1.4470	$C_{11}H_{19}NO_2$	7.1	7.3
Ig	C_2H_5	C_6H_5	H	72	Not distilled [b]			$C_{12}H_{15}NO_2$	10.5	9.7 [b]

[a] Derived from cyclohexanone. [b] Stripped at 40° at 20 mm. to remove low-boiling components.

TABLE II

α-(ALKOXYETHOXY)GUANAMINES (II)

Compound	R	R′	R″	Yield, %	M.P., °C.	Empirical Formula	% N Calcd.	% N Found
IIa	n-C_4H_9	H	H	85	153	$C_{10}H_{19}N_5O_2$	29.0	28.9
IIb	C_2H_5	CH_3	H	66	169–172	$C_9H_{17}N_5O_2$	30.8	30.8
IIc	n-C_4H_9	CH_3	H	71	165–169	$C_{11}H_{21}N_5O_2$	27.4	27.4
IId	C_2H_5	CH_3	CH_3	86	170	$C_{10}H_{19}N_5O_2$	29.0	29.0
IIe	n-C_4H_9	CH_3	CH_3	78	130–132	$C_{12}H_{23}N_5O_2$	26.0	25.6
IIf	C_2H_5	—$(CH_2)_5$— [a]		85	220–222	$C_{13}H_{23}N_5O_2$	24.9	24.8
IIg	C_2H_5	C_6H_5	H	74	189–192	$C_{14}H_{19}N_5O_2$	24.2	24.5

[a] Derived from cyclohexanone.

TABLE III

α-HYDROXYGUANAMINES (III)

Compound	R′	R″	Yield, %	M.P., °C.	Empirical Formula	% N Calcd.	% N Found
IIIa	H	H	93	286–288	$C_4H_7N_5O$	49.6	48.9
IIIb	CH_3	H	76	254 [a]	$C_4H_9N_5O$	45.2	45.0
IIIc	CH_3	CH_3	97	165–167	$C_6H_{11}N_5O$	41.4	40.8
IIId	—$(CH_2)_5$— [b]		91	209	$C_9H_{15}N_5O$	33.5	33.3
IIIe	C_6H_5	H	91	182–190	$C_{10}H_{11}N_5O$	31.0	30.7

[a] Yield of crude product, m.p. 226–230°, was 98%. The product was recrystallized from water. Reported m.p.[3] is 254°. [b] Derived from cyclohexanone.

ester and biguanide, two reagents which are usually difficult to obtain.

The preparation of α-cyanoacetals (I) from cyanohydrins and vinyl ethers has been reported.[4] All of them obtained in our work (Table I) were distillable liquids with the exception of Ig prepared from benzaldehyde and ethyl vinyl ether (1-α-cyanobenzyloxy-1-ethoxyethane). When the compounds I were refluxed in alcohol solution with dicyandiamide and potassium hydroxide, and the reaction mixture was cooled, the α-(alkoxyethoxy)-guanamines (II, Table II) precipitated. Undistilled I could be used, although the presence of cyanohydrin in it caused the reaction mixture to become quite dark. This color, probably due to HCN polymer, was easily removed from the solid products by washing them with water.

The hydrolysis of the guanamine acetals (II) to the α-hydroxyguanamines (III, Table III) occurred in very dilute acid solutions. For example, an aqueous suspension of 2,4-diamino-6-(1-n-butoxyethoxymethyl)-s-triazine (IIa) was hydrolyzed to glycologuanamine in one hour in the presence of 2 mole % of hydrochloric acid. In most experiments, an equivalent of acid was added. This helped to dissolve II, as their hydrochlorides, particularly in the case of the higher members of the series. The α-hydroxyguanamines were easily recovered by adding an equivalent of base.

The successful hydrolysis of II and isolation of III in the presence of the basic diaminotriazine ring apparently depends substantially on the assistance provided by the methyl group on the central acetal carbon atom to the formation of intermediate carbonium ions.[5] The homologous formal, 2,4-diamino-6-ethoxymethoxymethyl-s-triazine[6] (IV), was prepared from ethoxymethoxyacetonitrile.

(4) B. Tchoubar, *Compt. rend.*, **237**, 1006 (1953).

(5) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 244.

(6) W. F. Gresham, U. S. Patent **2,491,658**; *Chem. Abstr.*, **44**, 3538 (1950).

$$C_4H_9OCHOCH_2Tr \qquad C_2H_5OCH_2OCH_2Tr$$
$$\begin{matrix}|\\ CH_3\end{matrix}$$
IIa IV
(Tr = diaminotriazine residue)

Unlike IIa under similar conditions, IV was recovered in quantitative amounts from an attempted hydrolysis in the presence of 2 mole % of hydrochloric acid. In the presence of an equivalent of hydrochloric acid, a gummy solid was obtained in low yield. It had a wide melting range and was resinous in character. It was assumed to be the product of the reaction of glycologuanamine with formaldehyde split out in the hydrolysis, since this reaction is commonly used in the preparation of guanamine aminoplast resins. The choice of the vinyl ether reaction to protect the cyanohydrin was therefore a fortunate one.

The α-hydroxyguanamines display the customary reactions of the diamino-*s*-triazines. In particular, they can be used as the raw materials for a series of resins, based on their reaction with formaldehyde.[3]

EXPERIMENTAL

Acetone cyanohydrin and lactonitrile were commercial products, freshly distilled before use. The commercial 70% aqueous solution of glycolonitrile was stripped using a water aspirator, until removal of water was substantially complete. Mandelonitrile[7] and cyclohexanone cyanohydrin[8] were prepared by the base-catalyzed reaction of HCN with benzaldehyde and cyclohexanone, respectively. The preparative steps were fairly uniform, and will be illustrated below with several examples of each.

Cyanoacetals, I: 1-n-butoxy-1-(cyanomethoxy)ethane (Ia). Commercial (70%) glycolonitrile (81.5 g., 1 mole) was heated on a steam bath at 20 mm. vacuum until the water was substantially removed. To the hot concentrate was added *n*-butyl vinyl ether (100 g., 1 mole) over a period of about 2 hr. at 95°. The acid catalyst present in the commercial glycolonitrile was sufficient to bring about the reaction. The crude product was distilled *in vacuo* through a 4-inch Vigreux column to give 143.5 g. (91%) of colorless liquid, b.p. 52–56°/1 mm.

1-(1'-Cyanocyclohexoxy)-1-ethoxyethane (If). Cyclohexanone cyanohydrin (125 g., 1 mole) was acidified with 3 drops of 5% HCl and heated to 50°. Ethyl vinyl ether was then added over a period of 2 hr. at such a rate as to maintain the temperature between 50 and 75° and to avoid undue refluxing of the low-boiling ether. The reaction mixture was then heated at 90° for 2 hr. and finally distilled through a 6-inch Vigreux column *in vacuo*, to give 172 g. (87%) of colorless liquid, b.p. 70–75°/0.9 mm.

α-Alkoxyethoxyguanamines [2,4-diamino-6-(1-alkoxyethoxyalkyl)-s-triazines], II: 2,4-diamino-6-(1-n-butoxyethoxymethyl)-s-triazine (IIa). A mixture was made of 1-butoxy-1-(cyanomethoxy)ethane, Ia (157 g., 1 mole), dicyandiamide (106 g., 1.25 mole) and isopropyl alcohol (400 ml.). The mixture was brought to reflux and to it was added a solution of potassium hydroxide (16.5 g., 0.25 mole) in isopropyl alcohol (300 ml.) dropwise over a period of 1 hr. The mixture was refluxed for a period of 16 hr., cooled in an ice bath, and filtered. The precipitate was slurried twice with 500-ml. portions of hot water. The product was then dried at 70° to yield 204.5 g. (85%), m.p. 148–150°. Drying at 70° *in vacuo* raised the melting point to 153°. This general procedure was used for all preparations.

α-Hydroxyguanamines (2,4-diamino-s-triazine-6-alkanols), III: glycologuanamine (IIIa). A mixture of 2,4-diamino-6-(1-*n*-butoxyethoxymethyl)-*s*-triazine, IIa (12 g., 0.05 mole), 50 ml. of water and 5 ml. of concentrated hydrochloric acid was heated on the steam bath for 2.5 hr. The mixture became clear. A solution of sodium hydroxide (4 g.) in 30 ml. of water was then added, and the mixture was chilled and filtered. The residue (6.5 g., 93%), m.p. 286–288° was recrystallized from water without change in melting point.

2,4-Diamino-6-(1-hydroxycyclohexyl)-s-triazine (IIId). A mixture of 2,4-diamino-6-[1-(ethoxyethoxy)cyclohexyl]-*s*-triazine, IIf (28.1 g., 0.1 mole), concentrated hydrochloric acid (10.2 g.) and 150 ml. water was heated for 2 hr. on the steam bath. To the resulting hot solution was added a solution of sodium hydroxide (4 g.) in 25 ml. water. The mixture was cooled in an ice bath and filtered and washed with water. After oven drying at 85°, there was obtained 19 g. (91%), m.p. 209°.

Attempted direct preparation of lactoguanamine. A mixture of lactonitrile (14.2 g., 0.2 m.), dicyandiamide (21 g., 0.25 m.) and isopropyl alcohol (75 ml.) was brought to reflux and to it was added a solution of potassium hydroxide (2.8 g., 0.05 m.) in isopropyl alcohol (50 ml.) over a period of 1.5 hr. The mixture was refluxed with stirring for 20 hr. When the resulting dark-brown mixture was cooled to 0° and filtered, only a small amount of recovered dicyandiamide was obtained. No lactoguanamine could be isolated.

2,4-Diamino-6-ethoxymethoxymethyl-s-triazine[9] (IV). To a mixture of ethoxymethoxyacetonitrile[6] (7 g., 0.06 m.), dicyandiamide (6.1 g., 0.07 m.) and isopropyl alcohol (25 ml.) at reflux was added a solution of 85% potassium hydroxide (0.08 g., 0.012 m.) in isopropyl alcohol (15 ml.), over a period of 20 min. The reaction was refluxed for 16 hr., cooled to 0°, and filtered. The crude product was recrystallized from water, using charcoal, to give 7 g. (58%) of slightly tan crystals, m.p. 179–181°. The reported m.p.[6] is 177.5–178.5°.

Comparative experiments on the hydrolysis of 2,4-diamino-6-(1-n-butoxyethoxymethyl)-s-triazine (IIa) *and 2,4-diamino-6-ethoxymethoxymethyl-s-triazine* (IV). Suspensions of 0.005 mole of each guanamine in 10 ml. of 0.01*N* hydrochloric acid were gently refluxed for 1 hr. They were cooled and to them was added one ml. of 0.1*N* sodium hydroxide. They were heated to boiling and immediately cooled in an ice bath. From the reaction of IIa, there was obtained 0.65 g. (93%) of glycologuanamine, m.p. 283–286°. IV was recovered quantitatively.

When the reaction was repeated with IV (0.005 mole) in 10 ml. of 0.1*N* hydrochloric acid, only a small amount of oil separated after the addition of sodium hydroxide. The oil was not identified.

When the reaction was repeated with IV (0.005 mole) and 10% hydrochloric acid (0.0044 mole), there was recovered 0.39 g. of a yellow, resinous solid which melted with decomposition from 190–285°, and which could not be purified by crystallization from hot water in the manner ordinarily successful for glycologuanamine.

PHILADELPHIA, PA.

(7) A. Albert, *Ber.*, **49**, 1383 (1916).
(8) A. J. Ultee, *Rec. trav. chim.*, **28**, 1 (1909).
(9) The preparation was originally described using piperidine as a catalyst (ref. 6).