[CONTRIBUTION FROM THE ROHM AND HAAS CO.]

Substituted α-(N-Alkylmelamino)-guanamines[1]

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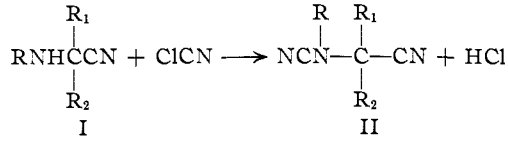
Reaction of α-(N-alkylamino)-nitriles with cyanogen chloride in the presence of a suitable acceptor for by-product hydrogen chloride furnishes a general method for the preparation of a series of N-alkyl-N-α-cyanoalkylcyanamides. By further reaction of these compounds with two moles of dicyandiamide, there are usually produced corresponding bis-4,6-diamino-1,3,5-triazines, which are substituted α-(N-alkylmelamino)-guanamines. The latter reaction is affected to some extent by the structural features of the intermediate cyanoalkylcyanamides.

During his investigation of the reaction of cyanogen bromide with tertiary amines, von Braun[2] prepared the lower members of a series of N-alkyl-N-cyanomethylcyanamides, $RN(CN)CH_2CN$. The method is limited and not very satisfactory. The direct cyanation of the appropriate α-(N-alkylamino)-nitrile (I) with a cyanogen halide, in the presence of a suitable acceptor for the by-product halogen halide, furnished a very general method for the preparation of N-alkyl-N-α-cyanoalkylcyanamides (II)



I II

aminonitrile was used as acceptor. This method gave good yields but this was tempered by some decomposition during recovery of the aminonitrile from its hydrochloride. In aqueous and solvent–aqueous systems, potassium carbonate was used in molar equivalents to neutralize the hydrogen chloride. Considering the instability of both reactants to aqueous base, yields were remarkably good. It was possible to use the crude aminonitrile in many reactions.

Only two cases resulted in failure. N-Phenylaminoacetonitrile failed to react, presumably because cyanomethylation lowered the basicity of an already weak amine. α-N-Cyclohexylaminoisobutyronitrile also failed to react. In this case, failure is ascribed to the accumulation of blocking groups on the α-carbon atom, since N-cyclohexylaminoacetonitrile gave a cyanamide in high yield.

TABLE I

N-ALKYL-N-(α-CYANOALKYL)-CYANAMIDES NC—N(R)—C(R₁)(R₂)—CN

R	R₁	R₂	Empirical formula	Yield, %	Method of reaction[a]	B.p., °C.	B.p., Mm.	$n^{25}D$	d^{25}_{25}	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	H	H	$C_4H_5N_3$	80	A[b]	147–148	13[b]	1.4449	1.0504	44.2	44.0
CH_3	C_2H_5	H	$C_6H_9N_3$	96	B	100	1.6	1.4400	0.9768	34.1	33.6
CH_3	CH_3	CH_3	$C_6H_9N_3$	89	A	73	0.5	1.4376	.9766	34.1	34.1
CH_3	C_2H_5	CH_3	$C_7H_{11}N_3$	52	C	80–81	.8	1.4465	.9718	30.6	30.7
n-C_4H_9	H	H	$C_7H_{11}N_3$	94	C	118	.6	1.4481	.9631	30.6	30.5
$(CH_3)_3C$	H	H	$C_7H_{11}N_3$	86	C	129–134	1.7	1.4506	.9742	30.6	30.4
CH_2=$CHCH_2$	CH_3	CH_3	$C_8H_{11}N_3$	78	A	137–138	16	1.4575	.9741	28.2	27.7
n-C_4H_9	CH_3	H	$C_8H_{13}N_3$	86	C	111–112	1.1	1.4419	.9427	27.8	27.5
CH_3	$-(CH_2)_5-$		$C_9H_{13}N_3$	74	C	106–107	0.7	1.4792	1.0326	25.7	25.3
Cyclohexyl	H	H	$C_9H_{13}N_3$	81	B	140–150	1.0	1.4839	1.0397	25.7	25.4
n-C_4H_9	CH_3	CH_3	$C_9H_{15}N_3$	55	C	96	1.0	1.4451	0.9299	25.4	25.3
n-C_4H_9	C_2H_5	CH_3	$C_{10}H_{17}N_3$	70	C	98	0.8	1.4471	.9277	23.4	23.4
n-C_8H_{17}	H	H	$C_{11}H_{19}N_3$	71	B	154–165	1.5	1.4534	.9277	21.7	21.7
C_8H_{17}[c]	H	H	$C_{11}H_{19}N_3$	78	B	144–145	1.0	1.4546	.9284	21.7	21.1
C_8H_{17}[d]	H	H	$C_{11}H_{19}N_3$	66	C	131–134[e]	0.7	1.4647	.9505	21.8	21.6
CH_3	C_8H_{17}[f]	H	$C_{12}H_{21}N_3$	87	B	133–140	1.5	1.4519	.9255	20.3	19.5
C_9H_{19}[g]	H	H	$C_{12}H_{21}N_3$	82	B	141–149	1.1	1.4545	.9170	20.3	19.8

[a] For explanation, see Experimental section. [b] von Braun[2] reports b.p. 150–151° at 12 mm. Method B was unsuccessful, probably because of the instability of the product to alkaline medium. [c] 2-Ethylhexyl group. [d] 1,1,3,3-Tetramethylbutyl group. [e] Recrystallized from ethanol, m.p. 34.5–35.° [f] 2,4,4-Trimethylpentyl group. [g] 3,5,5-Trimethylhexyl group.

A series of α-(N-alkylamino)-nitriles has been prepared, and is described in a separate note.[3] Their reaction with cyanogen chloride gave good yields in both solvent and aqueous systems (Table I). In organic solvents, an extra mole of the

The N-alkyl-N-α-cyanoalkylcyanamides are distillable liquids which are quite stable. Decomposition during distillation is encountered only in the higher members of the series. An important and interesting feature of their chemistry is the variation of their reactivity with structure. N-Methyl-N-cyanomethylcyanamide is abnormally

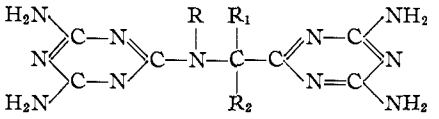
(1) Given at the 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March 16, 1953.

(2) J. von Braun, *Ber.*, **40**, 3933 (1907).

(3) L. J. Exner, L. S. Luskin and P. L. deBenneville, THIS JOURNAL, **75**, Oct. 5 (1953).

TABLE II

PREPARATION OF BIS-TRIAZINES

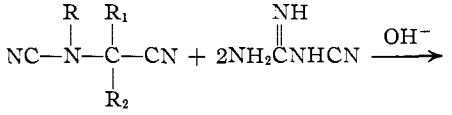


R	R_1	R_2	Reflux, hours	Yield, %	Empirical formula	Nitrogen, % Calcd.	Found	M.p., °C.
CH_3	CH_3	H	8	43[a]	$C_9H_{15}N_{11}$	55.6	55.1	>300
CH_3	CH_3	CH_3	20	74	$C_{10}H_{17}N_{11}$	52.9	52.7	>300
CH_3	C_2H_5	H	24	58[b]	$C_{10}H_{17}N_{11}$	52.9	52.9	255–260
n-C_4H_9	CH_3	H	2	49	$C_{12}H_{21}N_{11}$	48.2	47.1	200–202
n-C_4H_9	CH_3	CH_3	6.5	47[c]	$C_{13}H_{23}N_{11}$	46.2	45.9	271–272
n-C_4H_9	C_2H_5	CH_3	48	27	$C_{14}H_{25}N_{11}$	44.4	44.2	>290
CH_3	C_8H_{17}[d]	H	22	53[d]	$C_{16}H_{29}N_{11}$	31.0	40.2	256–258
—C_8H_{17}[e]	CH_3	CH_3	12	35[a]	$C_{17}H_{31}N_{11}$	39.5	39.6	246

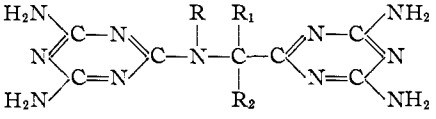
[a] In these cases, the triazines were prepared from crude N-alkyl-N-cyanoalkylcyanamides. [b] After 4 hours reflux period in isopropyl alcohol, a 96% yield of mono-triazine was isolated. This product melted at 232–234°. Calcd. for $C_8H_{13}N_7$, N, 47.3. Found: N, 47.2. The mono-triazine was then combined with fresh dicyandiamide and catalyst, and converted to the bis-triazine by an additional reflux period of 24 hours in methyl cellosolve. [c] A small yield (14%) of predominantly mono-triazine was also isolated. [d] C_8H_{17} was the 2,4,4-trimethylpentyl group. A small yield (5%) of predominantly mono-triazine was isolated. [e] 2-Ethylhexyl group.

unstable to hydrolysis with 2 *N* sodium hydroxide, reacting vigorously at room temperature. On the other hand, N-methyl-N-α-cyanoisopropylcyanamide shows the expected stability of the cyanamide group, being hydrolyzed rather slowly at steam-bath temperatures. This difference is an important factor in the further utilization of these products as intermediates for the preparation of bis-4,6-diamino-1,3,5-triazines.

This new series of bis-4,6-diamino-1,3,5-triazines was prepared by the base-catalyzed reaction of those N-alkyl-N-α-cyanoalkylcyanamides which had at least one alkyl group on the α-carbon atom (II, R_1 = alkyl, R_2 = alkyl or H) with two moles of dicyandiamide. This general reaction for the



II



III

preparation of triazines[4] is most successfully carried out in a solution of an alcohol such as isopropyl alcohol, *n*-butyl alcohol, methyl cellosolve, etc., at reflux, in the presence of about 20 mole per cent. of a suitable alkali such as potassium hydroxide. Because of its sensitivity to base, N-methyl-N-cyanomethylcyanamide gave only a tarry product. However, introduction of only one methyl group on the α-carbon atom stabilized the molecule to a sufficient extent to allow it to participate in this reaction. Within the above limits, it was therefore possible to prepare a series of these bis-triazines, which are substituted α-(N-alkylmelamino)-guanamines (III). These products are useful intermediates in the preparation of triazine–formaldehyde resins. Data on a number of preparations are listed in Table II.

The importance of structural relationships is shown by the data on compounds derived from *n*-butylamine (III, R = *n*-butyl). The increasing reflux period necessary to obtain the bis-triazine as R_2 is increased from H to CH_3 to C_2H_5(R_1 = CH_3) is indicative of the severe effect of α-carbon atom substitution. The difference in rate was in fact visible in the speed with which the insoluble bis-triazine precipitated from the reaction mixture. Increasing chain length on the α-carbon atom beyond CH_3 seems to decrease the reactivity of one of the –CN groups. The bis-triazine III, R = R_1 = R_2 = CH_3, was always the major product of reaction, even with a deficiency of dicyandiamide, indicating the –CN groups to be approximately equivalent. However, the presence of the larger ethyl group brought about a stepwise reaction, so that the mono-triazine could be isolated in high yield, and this then could be converted to the bis-triazine III, R = CH_3, R_1 = H, R_2 = C_2H_5.

In our experiments, no pure bis-triazine could be isolated from the reaction of N-alkyl-N-cyanomethylcyanamides with dicyandiamide. For the most part, as described for the N-methyl derivative, a high proportion of tars was formed, and solid products if isolated, did not approach the proper composition. In the one case of N-1,1,3,3-tetramethylbutyl-N-cyanomethylcyanamide, stabilization toward the reaction mixture was apparently effected by the large, bulky tertiary alkyl group. The product, however, was only a mono-triazine. This was also the result of the reaction of N-methyl-N-1-cyano-1-cyclohexylcyanamide, a similarly bulky molecule, with dicyandiamide. Unfortunately, in all of the cases where mono-triazines were isolated, it has not been possible to prove definitely which of the –CN groups took part in the reaction with dicyandiamide.

Experimental

α-(N-Alkylamino)-nitriles were prepared by standard methods.[3] Cyanogen chloride was prepared by a modification of the method of Price and Green,[5] and was used either as the distilled solid or as a solution in benzene or toluene, being in either case analyzed for purity by standard methods. The toluene solution was handled as a normal liquid

(4) (a) W. Zerweck and W. Brunner, U. S. Patent 2,302,162; *C. A.*, **37**, 2016 (1943); (b) J. K. Simons, U. S. Patent 2,532,519; *C. A.*, **45**, 3429 (1951); (c) D. W. Kaiser, U. S. Patent 2,567,847; *C. A.*, **46**, 2587 (1952).

(5) T. Price and S. Green, *J. Soc. Chem. Ind.*, **39**, 108 (1920).

reactant. The solid was added by distillation over the reaction mixture. Stirring and a condenser cooled by ice-water were used in all reactions. Three methods of reaction were used, as shown in the following examples. All appear to be about equivalent.

Method A. N-Methyl-N-cyanomethylcyanamide.—To a solution of sarcosine nitrile (28.6 g., 0.4 mole) in 100 ml. of benzene was added cyanogen chloride (13 g., 0.2 mole on a purity basis) as a gas over a period of 20 minutes at 5–10°. After stirring for one hour at room temperature, the reaction mixture was filtered to yield 23 g. of sarcosine nitrile hydrochloride. The benzene solution was distilled through a 25-cm. Vigreux column to yield 15.1 g. (80%) of product boiling at 147–148° at 13 mm.

Method B. N-Methyl-N-α-cyanopropylcyanamide.—To a mixture of α-N-methylaminobutyronitrile (74.4 g., 0.75 mole) and anhydrous potassium carbonate (51.8 g., 0.375 mole) suspended in 150 ml. of benzene and 37.5 ml. of water was added cyanogen chloride (49.5 g., 0.75 mole on a purity basis) as a gas over a period of one-half hour at 10–25°. After stirring for one-half hour, the mixture was filtered and the benzene layer separated and distilled. There was obtained 88.6 g. (96%) of the product as a colorless liquid distilling at 100° at 1.6 mm.

Method C. N-*n*-Butyl-N-cyanomethylcyanamide.—To a solution of cyanogen chloride (32.2 g., 0.5 mole on a purity basis) in 50 ml. of benzene was added a solution of N-*n*-butylaminoacetonitrile (56.1 g., 0.5 mole) in 100 ml. of benzene over a period of 25 minutes at 20–30°. The hydrochloride of the aminonitrile precipitated during reaction. To this mixture was added a solution of anhydrous potassium carbonate (34.5 g., 0.25 mole) in 35 ml. of water over a 15-minute period at 20–25°. After stirring for one-half hour, the mixture was filtered and the benzene layer distilled to yield 64.7 g. (94%) of the product as a colorless oil boiling at 118° at 0.6 mm.

The preparation of bis-4,6-diamino-1,3,5-triazines is illustrated by the following preparations:

α-(N-Methylmelamino)-isobutyroguanamine (III, R = R_1 = R_2 = CH_3).—To a well-stirred suspension of N-methyl-N-(α-cyanoisopropyl)-cyanamide (36.9 g., 0.3 mole) and dicyandiamide (55.4 g., 0.66 mole) in 65 ml. of isopropyl alcohol at reflux, was added over a 10-minute period a solution of potassium hydroxide (9.9 g., 0.15 mole on a purity basis) in 150 ml. of isopropyl alcohol. Almost all of the solids went into solution, and toward the end of addition precipitation began. After a 20-hour reflux period, the mixture was cooled and filtered. The solid product was washed twice with 250-ml. portions of water at 70° to remove unreacted dicyandiamide, refiltered and dried to give 64.5 g. (74%) of the colorless high-melting product.

α-(N-Methylmelamino)-butyroguanamine.—To a mixture of N-methyl-N-α-cyanopropylcyanamide (61.6 g., 0.5 mole), dicyandiamide (92.5 g., 1.1 moles) and 240 ml. of isopropyl alcohol was added at reflux a solution of potassium hydroxide (16.5 g., 0.25 mole on a purity basis) in 270 ml. of isopropyl alcohol over a period of 50 minutes. After a 4.5-hour reflux period, the cooled product was filtered off and washed with 1500 ml. of hot methanol. The colorless solid weighed 99 g. (96%) and corresponded in analysis to the mono-triazine (see Table II, footnote *b*). A mixture of this mono-triazine (41.4 g., 0.2 mole) and dicyandiamide (18.5 g., 0.22 mole) in 96 ml. of methyl cellosolve was brought to reflux (115°) and to it was added a solution of potassium hydroxide (6.6 g., 0.1 mole on a purity basis) in 90 ml. of methyl cellosolve. After 24 hours reflux, the solid material, which was mainly dicyandiamide, was filtered from the cold solution and the methyl cellosolve stripped off under reduced pressure. The residue was washed with 250 ml. of water at 65° and filtered to yield 33.7 g. of the bis-triazine melting at 255–260°.

Mono-triazines.—(1) From N-1,1,3,3-tetramethylbutyl-N-cyanomethylcyanamide: The reaction of this cyanamide with dicyandiamide, carried out in similar fashion to the preparation of α-(N-methylmelamino)-isobutyroguanamine, gave an 86% yield of light tan solid, m.p. 199–201°. *Anal.* Calcd. for $C_{13}H_{23}N_7$: N, 38.2. Found: N, 38.5. (2) From N-methyl-N-1-cyano-1-cyclohexylcyanamide: The reaction of this cyanamide gave an 83% yield of colorless solid, m.p. 257–258°. *Anal.* Calcd. for $C_{11}H_{17}N_7$: N, 39.7. Found: N, 39.3.

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PHILADELPHIA 37, PENNA.

[CONTRIBUTION FROM THE WYETH INSTITUTE OF APPLIED BIOCHEMISTRY]

Fluorine-containing Barbituric Acids[1]

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Ethyl 3-fluoropropyl diethylmalonate and its allyl and isoamyl analogs, also ethyl 5-fluorodiethylmalonate and its allyl and isoamyl analogs, were obtained by the interaction of the sodio derivatives of the respective malonic esters with 1-bromo-3-fluoropropane and 1-chloro-5-fluoropentane in ethanol. These new esters were treated with urea in an ethanolic solution of sodium ethoxide to secure the corresponding barbituric acids. Attempts to alkylate various sodio alkylmalonic esters with α- or β-fluoroalkyl halides in ethanol or toluene were incomplete because of difficulties encountered in the purification of the products.

Of the halogen-containing barbituric acids described previously, none contain fluorine and only those with halogen in the relatively inert position on a double bond have proved sufficiently useful to be adopted as drugs for clinical use.[2-4] Since the inertness of the halogen thus appears to be a factor in the utility of these compounds, we were interested to examine some barbiturates containing a fluorine–carbon bond, since the halogen is known to be relatively inert and firmly bound in compounds of the fluoro-hydrocarbon type.[5]

The new fluorine-containing barbituric acids prepared during the course of this work were specifically 5-alkyl-5-(ω-fluoroalkyl) derivatives of barbituric acid. They are as follows: 5-ethyl-5-(3′-fluoropropyl)-barbituric acid, 5-allyl-5-(3′-fluoropropyl)-barbituric acid, 5-isoamyl-5-(3′-fluoropropyl)-barbituric acid, 5-ethyl-5-(5′-fluoro-*n*-amyl)-barbituric acid, 5-allyl-5-(5′-fluoro-*n*-amyl)-barbituric acid, and 5-isoamyl-5-(5′-fluoro-*n*-amyl)-barbituric acid. These compounds were prepared by treating the required alkyl-(ω-fluoroalkyl)-malonic

(1) Presented at the Miniature Meeting of the Philadelphia Section of the American Chemical Society, January 29, 1953.

(2) G. S. Skinner, THIS JOURNAL, **59**, 322 (1937).

(3) G. S. Skinner and J. B. Bicking, *ibid.*, **72**, 1140 (1950).

(4) Jenkins and Hartung, "Chemistry of Organic Medicinal Products," Second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 553.

(5) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. 1A, Elsevier Publishing Co., New York, N. Y., 1951, p. 556.