[CONTRIBUTION FROM THE RESEARCH DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

CHEMISTRY OF DICYANDIAMIDE. II. PREPARATION AND HYDROLYSIS OF ACYLDICYANDIAMIDES

P. ADAMS, D. W. KAISER, D. E. NAGY, G. A. PETERS, R. L. SPERRY,[1] AND J. T. THURSTON

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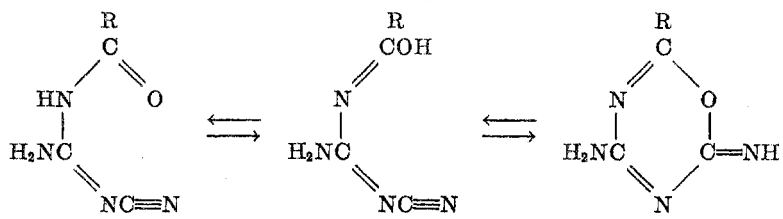
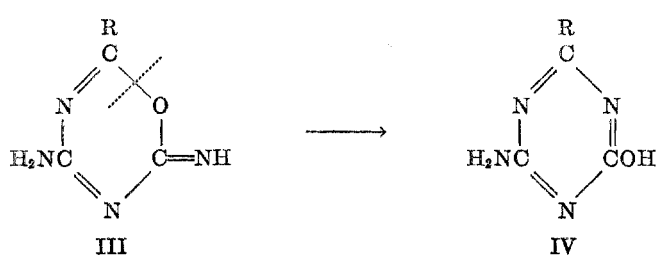
In a previous paper the reaction of dicyandiamide with chlorocarbonates was discussed (1). Expansion of the reaction to include acyl chlorides and anhydrides produced acyldicyandiamides which on the basis of past discussion (1) can be represented by structure I. Certain anomalous reactions of acyldicyandiamides, however, were suggestive of the presence of cyclic structure III which could be formed by tautomeric shifts.



I II III

Evidence of II was demonstrated by intensification of the color of ferric chloride with aqueous solutions of certain of the acyldicyandiamides, such as acetyldicyandiamide. Infrared examination could not confirm the presence of III, inasmuch as cyano absorption was present. However, equilibrium to produce a small quantity of III, which in certain reactions was the reactive intermediate, seemed likely. One reaction presented in this paper which was indicative of the existence of cyclic structure III was the molecular rearrangement of acyldicyandiamides to guanides (2-substituted-4-hydroxy-6-amino-*s*-triazines, IV). Heat alone produced the change but amine salts catalyzed the reaction.



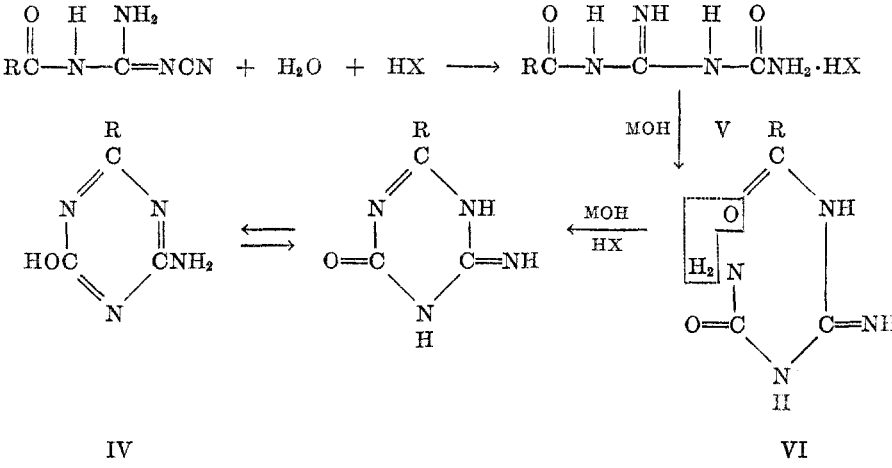
III IV

Regardless of structural isomerization, the identity of the acyldicyandiamides prepared in the present work was firmly established by complete analyses and reactions. Several so-called acyldicyandiamides have been described in a patent (2). These compounds were prepared by heating dicyandiamide, in the absence

[1] Present address, Page Testing Lab., P.O. Box 461, Ventura, Calif.

of a base, with an acyl chloride in a high-boiling solvent such as chlorobenzene. An example given in the patent was repeated. Reaction occurred but the nature of the product was such that no definite material could be characterized.

The acyldicyandiamides could be hydrolyzed with acids to acylguanylurea

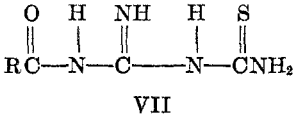


IV VI

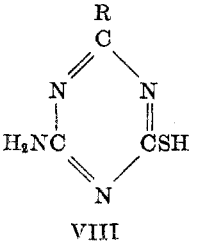
salts (V). An equivalent of alkali or excess ammonia precipitated the less soluble free base (VI) which could also be cyclized to a guanide (IV) by effecting solution with a second equivalent of caustic, followed by acidification.

This cyclization of an acylguanylurea was not new. Ostrogovich (3) had previously prepared acetyguanylurea hydrochloride by acetylation of a guanylurea salt. All his attempts to isolate acetylguanylurea by treatment of the hydrochloride with one equivalent of a variety of bases were unsuccessful. Spontaneous cyclization of the free base to acetoguanide occurred invariably. However, in the present work it was found possible to isolate the free base. This unexpected result was perhaps due to the use of a more concentrated solution than that used by Ostrogovich (3) who gave no details regarding his concentrations.

Addition of hydrogen sulfide to acyldicyandiamides gave the expected acylguanylthioureas (VII). Treatment of one of the acylguanylthioureas with caus-



VII

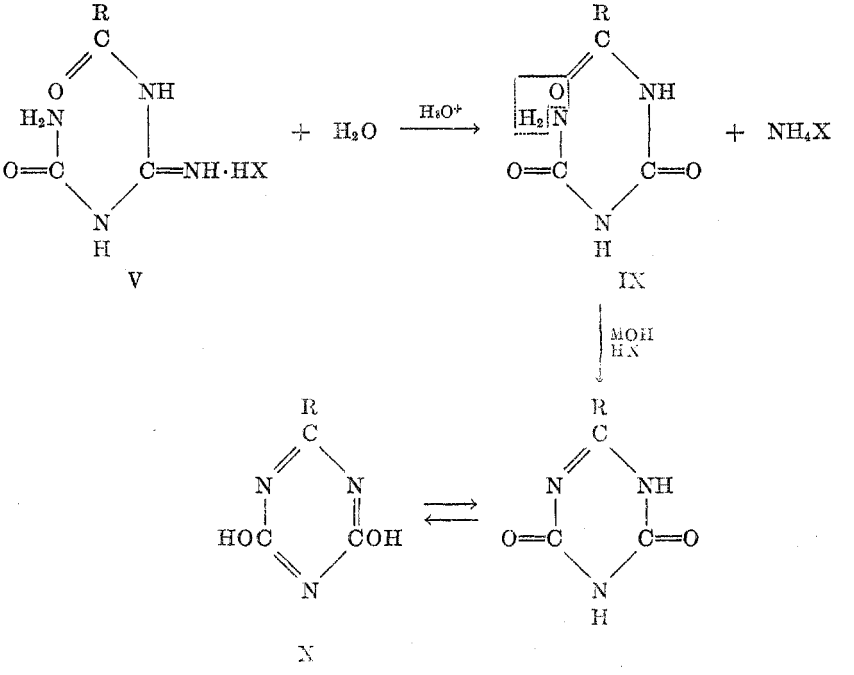


VIII

tic yielded a guanide (IV) rather than the expected thioguanide (VIII). Since thioguanides are stable to alkali under the conditions employed (4), the acylguanylthiourea apparently suffered hydrolysis before or during cyclization.

Further acid hydrolysis of acylguanylurea salts (V) gave acylbiurets (IX).

This reaction was unexpected since biuret cannot be prepared by acid hydrolysis of guanylurea salts; instead cleavage occurs and guanidine salts are formed (5). Confirmation of the course of hydrolysis was obtained by cyclization of one of the acylbiurets by caustic to a guanamide [2-substituted-4,6-dihydroxy-*s*-triazine (X)]. This reaction had previously been examined by Ostrogovich (6).



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EXPERIMENTAL[2]

I. PREPARATION OF ACYLDICYANDIAMIDES

Method A. This modification in general gave higher yields but required a powerful stirring motor. A stainless steel beaker equipped with a Masonite board cover with holes through which the stirrer shaft, thermometer, and dropping-funnel could be inserted was superior to a flask for any but very small runs. A mixture, employing a general ratio of 1.25 moles of dicyandiamide, 2.0 moles of 85% potassium hydroxide pellets, and 900 ml. of acetone was vigorously stirred at 10° for an hour. During this time the pellets disintegrated and the dicyandiamide lost its crystalline appearance. The resulting amorphous appearing solid probably contained an appreciable quantity of potassium dicyandiamide. It was advisable during this and the subsequent period of addition of acylating agent to interrupt stirring occasionally and explore the mixture with a heavy glass rod to dislodge any material caking to the walls and bottom of the beaker. The temperature was lowered and maintained at 0–5° during addition of 1.0 mole of the acylating agent. After addition the slurry was diluted with three to four times its volume of water. The resulting solution was acidified, generally with an excess of acetic acid, and the colorless precipitate of acyldicyandiamide was filtered washed with water, and air-dried.

[2] All melting points are uncorrected.

Method B. This variation was easier to manipulate and employed an easily stirred two-phase system. The lower layer contained water, caustic, and dicyandiamide; the upper acetone. Either sodium or potassium hydroxides were satisfactory, although the latter was generally used since somewhat higher yields were realized. The ratio of reagents was the same as in Method *A* except that while the total volume of reaction media was 900 ml., 400 ml. of this was water. After solution of the alkali in the water, the dicyandiamide was added, followed by the acetone. The essentially clear, two-layer system was then maintained below 5° while the acylating agent was added. The reaction mixture was worked up as described under Method *A*.

General. Sodium hydroxide was not satisfactory for Method *A*. Yields do not necessarily represent the maximum since certain acylations were not studied extensively. The crude products were generally quite pure and were used in subsequent reactions. Only small portions were recrystallized for analytical purposes and crystallization was carried out rapidly to minimize rearrangement to the guanide. After crystallization the acyldicyandiamides were obtained in the form of colorless plates with the exception of acetyl and benzoyl compounds which were fine powders. Table I records the individual preparations.

Reaction of dicyandiamide with lauroyl chloride in chlorobenzene. The procedure given in Example 1 of a U. S. patent (2) was followed. A stirred suspension of 60 g. (0.71 mole) of dicyandiamide in 200 g. of chlorobenzene was heated to an internal temperature of 70°. After the gradual addition of 77 g. (0.35 mole) of lauroyl chloride in 50 g. of chlorobenzene, the temperature was slowly raised to 120°. At 100° hydrogen chloride was evolved and at 120° the mixture became orange and frothed considerably for a short time. Heating and stirring at 120° were continued for 24 hours. The chlorobenzene was removed by steam-distillation and the reddish-orange, slightly sticky solid was filtered, washed with water, and ground in a mortar with a concentrated sodium carbonate solution. Filtration, washing with boiling water, and drying in an oven at 50° gave 111 g. of orange solid, m.p. 134–171°. According to the patent (2) this material was lauroyldicyandiamide for which was recorded the m.p. 132–138°. For purification (not described in the patent), 100 g. of the solid was dissolved in hot toluene. The dark brown solution was treated unsuccessfully with decolorizing charcoal and the filtrate was diluted to about twice its volume with acetone. An amorphous solid separated which, after washing with acetone and air-drying, weighed 76 g. Drying caused the outer surfaces of the lumps to become dark brown and resinous, as if sintered. A portion of the unsintered yellow-brown solid melted over a range of 150–175°. Since the material was obviously a complex mixture it was not studied further.

II. PREPARATION OF ACYLGUANYLUREAS

General. The hydrolyses were carried out with a slight excess of 4–10% hydrochloric acid. The reagents were mixed and heated to reflux. Hydrolysis was generally slightly exothermic and rapid, a clear solution being obtained when reflux occurred. Heating was continued several minutes longer and on cooling the acylguanylurea hydrochloride generally crystallized. The less soluble free base was obtained by addition of excess ammonia or an equivalent of caustic. The colorless products were filtered, dried, and recrystallized from various solvents. Crystallization was best carried out rapidly to prevent decomposition and in several instances the free bases were converted to the more stable nitrate salts which were recrystallized for analysis. Table II lists the individual preparations.

Hydrolysis of benzoyldicyandiamide with various acids is recorded in Table III. These benzoylguanylurea salts were not analyzed but were converted to the free base which was identified by fusion with a previously prepared sample of benzoylguanylurea.

When an alkaline hydrolysis of benzoyldicyandiamide was carried out a 66.5% recovery of benzoic acid was obtained.

III. PREPARATION OF ACYLGUANYLTHIOUREAS

Lauroylguanylthiourea hydrochloride. Hydrogen sulfide was bubbled into a solution of 30.0 g. (0.11 mole) of lauroyldicyandiamide in 300 ml. of ethanol at 50–60° for four hours.

TABLE I

PREPARATION OF ACYLDICYANDIAMIDES

ACYLATING AGENT	METHOD	ACYLDICYANDIAMIDE	CRUDE YIELD, %	SOLVENT FOR PURIFICATION	M.P., °C.	FORMULA	ANALYSES					
							Calc'd			Found		
							C	H	N	C	H	N
Acetic anhydride	A	Acetyl[a, b]	72	Water	240[c]	$C_4H_6N_4O$	38.10	4.76	44.44	38.24	4.90	44.50
Propionic anhydride	B	Propionyl[a]	47.5	Ethanol	179–180[c]	$C_5H_8N_4O$	42.86	5.75	39.98	42.89	5.94	39.88
n-Butyryl chloride	B	*n*-Butyryl	56.5	Ethanol	184–185[c]	$C_6H_{10}N_4O$	46.74	6.53	36.34	46.79	6.72	36.32
n-Caproyl chloride	B	*n*-Caproyl[b]	63.6	Ethanol	179–180	$C_8H_{14}N_4O$	52.75	7.69	30.77	52.95	7.62	30.88
Lauroyl chloride	A	Lauroyl	51	Methyl ethyl ketone	168–169	$C_{14}H_{26}N_4O$	63.12	9.77	21.05	63.13	9.80	21.18
Benzoyl chloride	A	Benzoyl[b]	89	Methanol-Cellosolve, 1:1	205[c]	$C_9H_8N_4O$	57.44	4.25	29.79	57.53[d]	4.35	29.80

[a] An aqueous solution gave intensification of color with ferric chloride solution. [b] Infrared spectra showed strong absorption in the 2200 $cm.^{-1}$ region which is characteristic of this type nitrile group. [c] Immersed in a preheated bath. [d] Van Slyke determination.

Slow addition of concentrated hydrochloric acid, with cooling, to the yellow solution precipitated 22.0 g. (64.3% yield) of product. Two recrystallizations from acetone which contained a trace of hydrochloric acid gave light yellow crystals, m.p. 156–157°.

Anal. Calc'd for $C_{14}H_{27}N_3OS \cdot HCl$: C, 49.91; 8.68; N, 16.63; S, 9.49.
Found: C, 50.09; H, 8.80; N, 16.61; S, 9.32.

Benzoylguanylthiourea. A slurry of 94.0 g. (0.50 mole) of benzoyldicyandiamide in 1 l. of ethanol was treated with a slow stream of hydrogen sulfide for nine hours. The mixture became yellow, slightly warm, and as reaction proceeded orange crystals formed. The insoluble portion was removed and the filtrate diluted with water to recover additional prod-

TABLE II

PREPARATION OF ACYLGUANYLUREAS

GUANYLUREA	CRUDE YIELD, %	SOLVENT FOR PURIFICATION	M.P., °C,	FORMULA	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
Acetyl[a, b]	40	—[c]	165[d]	$C_4H_8N_4O_2$	33.33	5.56	38.89	33.15	5.70	38.95
Propionyl	77	Methanol	158–159[e]	$C_5H_{10}N_4O_2 \cdot HNO_3$	27.15	5.01	31.67	27.13	5.02	31.81
Butyryl	78	Acetone	159–160[f]	$C_6H_{12}N_4O_2 \cdot HNO_3$	30.64	5.57	29.78	30.63	5.50	29.87
Caproyl	88	Ethyl acetate	157–158[g]	$C_8H_{16}N_4O_2 \cdot HNO_3$	36.50	6.51	26.61	36.38	6.43	26.60
Lauroyl	100	Ethanol	132–133	$C_{14}H_{28}N_4O_2$	59.15	9.86	19.71	59.35	9.84	19.64
Benzoyl	97.2	Butanol	187–188	$C_9H_{10}N_4O_2$	52.42	4.89	27.17	52.61	4.99	27.15

[a] A 10% solution of acetylguanylurea hydrochloride was treated with an equivalent of concentrated ammonia solution. [b] Hydrochloride previously reported (3). [c] Not recrystallized. [d] Immersed in a preheated bath. [e] The free base was not isolated. [f] Melting point of free base 124–125°. [g] Melting point of free base 172–173°.

TABLE III

HYDROLYSIS OF BENZOYLDICYANDIAMIDE WITH VARIOUS ACIDS

BENZOYLGUANYLUREA SALT	M.P., °C. OF SALT	YIELD, %
p-Toluenesulfonate	185–186	90
Nitrate	179–180	83.2
Monochloroacetate	155–157	98.5
Formate	133–135	85.5

uct. The total yield was 97 g. (87.5%). After two recrystallizations from methanol, yellow crystals melting at 174–176° were obtained.

Anal. Calc'd for $C_9H_{10}N_4OS$: C, 48.65; H, 4.50; N, 25.23; S, 14.41.
Found: C, 48.65; H, 4.68; N, 25.11; S, 14.24.

IV. PREPARATION OF GUANIDES

A. From acyldicyandiamides. When solutions of acyldicyandiamides were heated, rearrangement to the less soluble guanide occurred. In general 50% aqueous Cellosolve solutions were employed. With the lower members of the series the guanide separated from the refluxing solution but with the higher members the hot solutions were poured into water to recover the product. In Table IV the conditions employed with heat alone are recorded.

In Table V are compared the catalytic influence of amine salts on the conversion of benzoyldicyandiamide to benzoguanide. Free bases were also effective but they were un-

TABLE IV

MOLECULAR REARRANGEMENT OF ACYLDICYANDIAMIDES TO GUANIDES BY HEAT

GUANIDE	TIME OF HEATING, min.	CRUDE YIELD, %	SOLVENT FOR PURIFICATION	M.P., °C.	FORMULA	ANALYSES					
						Calc'd			Found		
						C	H	N	C	H	N
Aceto[a]	60	68	—	Infusible	$C_4H_6N_4O$	38.10	4.76	44.44	38.07[b]	4.89	44.44
Propio	15	93	Water	265[c]	$C_5H_8N_4O$	42.86	5.75	39.98	42.86	5.73	39.91
Butyro	30	60	25% aqueous Cellosolve	262–264[d]	$C_6H_{10}N_4O$	46.74	6.53	36.34	46.74	6.40	36.37
Capro	240	64.5	Ethanol:water:Cellosolve, 4:1:1	253–254	$C_8H_{14}N_4O$	52.75	7.69	30.77	52.59	7.78	30.82
Lauro	30	100	Ethanol:Cellosolve, 1:1	229–230	$C_{14}H_{26}N_4O$	63.12	9.77	21.05	62.95	9.66	20.93

[a] First prepared by Nencki (8). [b] Van Slyke determination. [c] Literature value 277–278° (7). [d] Literature value 274–275° (7).

doubtedly transformed into salts by combination with the acidic acyldicyandiamide. In these listed experiments, 9.4 g. (0.05 mole) of benzoyldicyandiamide in 200 ml. of 37.5%

TABLE V

CATALYTIC REARRANGEMENT OF BENZOYLDICYANDIAMIDE TO BENZOGUANIDE

CATALYST	TIME FOR SOLID TO APPEAR, min.	TOTAL TIME OF REFLUX, min.	YIELD, %
None	60	70	60.5
Aniline hydrochloride, 1.0 g.	5	10	64.0
Aniline sulfate, 1.0 g.	5	10	74.5
p-Phenetidine hydrochloride, 1.0 g.	5	10	71.5
Ammonium nitrate, 1.0 g.	10	15	66.0
Conc'd ammonia soln., 2 ml.	17	22	60.0
n-Butylamine, 0.50 g.	4	9	74.0
n-Butylamine sulfate, 1.0 g.	8	18	68.0
n-Butylamine salicylate, 1.0 g.	3.5	8.5	84.0
n-Butylamine acetate, 1.3 g.	3.5	8.5	84.0

TABLE VI

CONVERSION OF ACYLGUANYLUREAS TO GUANIDES WITH CAUSTIC

GUANIDE	CRUDE YIELD, %	M.P., °C.
Propio[a, b]	90.6	265[c]
Butyro[a, b]	94.2	262–264[d]
Capro[a]	99	253–254
Lauro	91	299–230
Benzo	99	325[e]

[a] Guanylurea salt and two equivalents of caustic employed. [b] Solution allowed to stand at room temperature. [c] Literature value 277–278° (7). [d] Literature value 274–275° (7). [e] Literature value 323–324° (7).

TABLE VII

CONVERSION OF BENZOYLGUANYLUREA TO BENZOGUANIDE WITH DIFFERENT BASES

BASE	SOLVENT	TIME OF HEATING, min.	YIELD, %	M.P., °C.
Monoethanolamine	50% Cellosolve	5	65	321[a]
Potassium bicarbonate	16.5% Cellosolve	30	98	322
Sodium butoxide	Butanol	10	87.5	323
Calcium hydroxide	25% Cellosolve	60	82	322
Ammonia	60% Cellosolve	5	25.6	323
Pyridine	Cellosolve	10	0	—

[a] Literature value 323–324° (7).

Cellosolve, which gave complete solution at reflux, was employed. The recovered samples of benzoguanide were quite pure and all melted at 323° ± 2°; literature value 323–324° (7).

B. From acylguanylureas. General. The conversion of the acylguanylurea to the guanide was accomplished by dissolving the guanylurea in a small excess of sodium hydroxide solution (5–15%). In several instances a guanylurea salt was treated with two equivalents of alkali. The solution was either heated to boiling for several minutes, cooled and acidified

TABLE VIII

PREPARATION OF ACYLBIURETS

STARTING MATERIAL	ACID	TIME OF HEATING, hrs.	CRUDE YIELD, %	SOLVENT FOR PURIFICATION	M.P., °C.	FORMULA	ANALYSES					
							Calc'd			Found		
							C	H	N	C	H	N
Acetyldicyandiamide ...	Phosphoric	1	27.6[a]	Water	193–194[b]	$C_4H_7N_3O_3$			28.96			28.97
Lauroyldicyandiamide..	Hydrochloric	2	65.4	80% Ethanol	155–157	$C_{14}H_{27}N_3O_3$	58.94	9.47	14.73	59.00	9.19	14.84
Benzoyldicyandiamide..	Hydrochloric	1	67.6	Cellosolve	220[c]	$C_9H_9N_3O_3$	52.12	4.34	20.29	52.09	4.33	20.32
Benzoyldicyandiamide..	Sulfuric	1	72.5		220							
Benzoyldicyandiamide..	Nitric	1	77.4		220							
Benzoyldicyandiamide..	Sulfamic	2	67.6		220							
Benzoylguanylurea hydrochloride.....	—	1	65.2		220							

[a] Product isolated by storing solution in a refrigerator overnight during which time crystallization occurred. [b] Literature value 193–193.5° (9). [c] Literature values vary from a low of 215–216° (10) to a high of 233° (11).

with excess acetic acid, or allowed to stand overnight at room temperature before acidification. The products were recrystallized and identified by mixture melting points with authentic samples. Table VI records the details of the preparations.

In Table VII conversion of benzoylguanylurea to benzoguanide by the use of different bases is shown. In these experiments the guanylurea and a slight excess of the base were heated for varying periods of time and the resulting solution was cooled and acidified with acetic acid. The yields and melting points are those of the crude products.

C. From an acylguanylthiourea. The yellow solution obtained by the addition of 0.6 g. of benzoylguanylthiourea to 10 ml. of a 10% sodium hydroxide solution was allowed to stand overnight at room temperature. On the following morning the flask contained a solid mass of colorless crystals which dissolved on addition of more water. When acetic acid was added hydrogen sulfide was evolved and a colorless precipitate formed. A sodium fusion was negative for sulfur and the compound, m.p. 325–326°, was identified as benzoguanide by fusion with an authentic sample. The yield was 0.45 g. (90%).

V. PREPARATION OF ACYLBIURETS AND BENZOGUANAMIDE

General. In these experiments the more readily available acyldicyandiamide was employed rather than the acylguanylurea salt. The water-insoluble dicyandiamide was heated to reflux with a small excess of the mineral acid. As in the preparation of the acylguanylureas, an exothermic reaction accompanied by complete solution occurred. Continued heating caused the less soluble acylbiuret to separate; after cooling this substance was isolated by filtration. In one experiment benzoylguanylurea hydrochloride was isolated and dried. When an aqueous solution of this salt was heated, the biuret was obtained. This demonstrated that it was the intermediate guanylurea salt which underwent further hydrolysis and that an excess of acid was not necessary to catalyze the reaction. Details of the hydrolyses are tabulated in Table VIII.

Benzoguanamide. The cyclization followed the general procedure of Ostrogovich (6). A 5.0-g. (0.025 mole) sample of benzoylbiuret was dissolved in 100 ml. of water which contained 3.0 g. of 86% potassium hydroxide. Acidification two hours later with acetic acid gave a colorless precipitate. The dried solid weighed 4.6 g. (98% yield) and after recrystallization from hot water the material melted at 287–288°.

Anal. Calc'd for $C_9H_7N_3O_2$: C, 57.14; H, 3.70; N, 22.22.
Found: C, 57.08; H, 3.91; N, 22.04.

SUMMARY

The preparation and certain reactions of acyldicyandiamides have been presented. The reactions studied included molecular rearrangement, hydrolysis, and addition of hydrogen sulfide.

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REFERENCES

(1) KAISER AND THURSTON, *J. Org. Chem.*, **17**, 185 (1952).
(2) BINDLER AND SCHLÄPFER, U. S. Patent 2,324,354 (1943).
(3) OSTROGOVICH, *Gazz. chim. ital.*, **39**, I, 540 (1909); *Chem. Abstr.*, **5**, 684 (1911).
(4) OSTROGOVICH AND GALEA, *Atti accad. Lincei*, **11**, 1108 (1930); *Chem. Abstr.*, **25**, 1531 (1931).
(5) German Patent 267,380; *Frdl.*, **11**, 139 (1912–1914).
(6) OSTROGOVICH, *Bul. soc. stiinte Cluj.*, **4**, 521 (1929); *Chem. Abstr.*, **24**, 2120 (1930).
(7) OSTROGOVICH AND GALEA, *Gazz. chim. ital.*, **65**, 349, 357 (1935); *Chem. Zentr.*, II, 3241 (1935).
(8) NENCKI, *Ber.*, **9**, 232 (1876).
(9) OSTROGOVICH, *Ann.*, **291**, 377 (1896).
(10) WALTHER AND WLODKOWSKI, *J. prakt. Chem.*, [2] **59**, 266 (1899).
(11) HILL AND DEGNAN, *J. Am. Chem. Soc.*, **62**, 1595 (1940).