2-Methylthio-2-imidazoline Hydrochloride.—A mixture of 209.5 g. (2.05 moles) of ethylenethiourea, 120 ml. (2.36 moles) of methyl chloride, and 250 ml. of methanol was heated in a stainless steel bomb at 100° for 3 hr. The reaction mixture was filtered to obtain 196 g. of material melting at 166–169°. The filtrate was diluted with ether to obtain an additional 92.5 g. of product, m.p. 161–166°. Total yield was 288.5 g. (92%).

Anal. Calcd. for $C_4H_9ClN_2S$: C, 31.47; H, 5.94; N, 18.35. Found: C, 31.29; H, 6.05; N, 18.11.

Preparation of Guanidines.—The following are generalized procedures.

Method A.[4]—Equimolar amounts of the amine and 2-methyl-2-thiopseudourea sulfate in water, or the amine and 2-methyl-2-thiopseudourea hydriodide[13] in ethanol, were heated under reflux for 2 hr. or allowed to stand at room temperature overnight. In most cases one equivalent of acid was added; the solution was stripped, and the solid was recrystallized from an appropriate solvent.

Method B.—Equimolar amounts of the amine and cyanamide in water were heated under reflux for 6 hr. Acid was added and the solution was worked up in the manner described for method A.

Method C.—The method is essentially that of Raiford and Daddow.[14] When the reaction was run in benzene, however, it was heated under reflux for 30 hr. If the amine was low boiling, the reaction was carried out in a bomb and an excess of the amine was used as the solvent.

Method D.—The procedure was based on the one described by Scott, O'Donovan, and Reilly,[15] using ethanol as the solvent.

1-[2-(2-Piperidyl)-ethyl]guanidine Sulfate.—A solution of 20.4 g. (0.078 mole) of 1-[2-(2-pyridyl)-ethyl]-guanidine sulfate (Table III, 32) in 150 ml. of water was hydrogenated over 5% rhodium on alumina at 2.8 kg./cm.^{2} Uptake was complete in 3 hr. The catalyst was removed and the solution was taken to dryness. The residue was recrystallized from aqueous ethanol to give 20.7 g. (88%) of white, crystalline solid (Table III, 33).

Acknowledgments.—The pharmacological activity of these compounds was investigated by Dr. John Schmidt, Dr. Hollis Schoepke, Mr. Leo Wiemeler, and Mr. Charles Shannon of the Pharmacology Department, Abbott Laboratories. We are grateful to them for permission to use their data. Analytical data were provided by Mr. Elmer Shelberg, Mr. Orville Kolsto, and staff of the Abbott Microanalytical Laboratory. The catalytic hydrogenations and other pressure reactions were carried out by Mr. Morris Freifelder and Mr. George Stone.

We also wish to thank the following individuals for preparing one or more of the intermediate compounds required during the course of this work: Mr. William Chan, Mr. Robert Hallas, Mr. Carl Nordeen, Miss Evelyn Schuber, Mr. Norman Springer, and Mr. Robert Stein.

(13) A. Lespagnol, E. Cuingnet, and M. Debaert, *Bull. Soc. Chim. France*, 387 (1960).

(14) L. C. Raiford and W. T. Daddow, *J. Am. Chem. Soc.*, **53**, 1552 (1931).

(15) F. L. Scott, D. G. O'Donovan, and J. Reilly, *ibid.*, **75**, 4053 (1953).

Studies on Methylglyoxal Bis(guanylhydrazone)[1] Analogs. I. Homologs of Methylglyoxal Bis(guanylhydrazone)[2]

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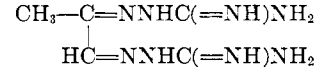
Investigation of different methods leading to the synthesis of alkylglyoxals was conducted. The method used in the preparation of ethylglyoxal *via* 2-butyne-1,4-diol is of only limited applicability. The reaction of Grignard reagents with dialkoxyacetylpiperidine provides the most convenient route to alkylglyoxals. The procedure utilizing ethyl diethoxyacetoacetate gives substituted glyoxals in relatively good yield. Use of dichloromethyl alkyl ketones as precursors is limited because of the poor yields of the dichloroketones. The preparation of all the theoretically possible methylated aminoguanidines bearing a free N-amino group has been studied. Condensation of these substituted aminoguanidines with methylglyoxal, together with the condensation of aminoguanidine with alkyl glyoxals, furnish all the necessary compounds for the phase I (homologs) study in the methylglyoxal bis(guanylhydrazone) series.

A recent report indicated that methylglyoxal bis(guanylhydrazone)[1] (I), prepared by Freedlander and French,[3] produced the first significant remissions in

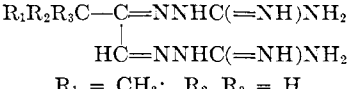


I

adult acute myelocytic leukemia.[4] This drug, however, is quite toxic.[5] These facts necessitated a systematic synthesis and investigation of compounds related to I in an attempt to prepare derivatives with better therapeutic indices. Studies on the synthesis of various compounds related to I have thus been undertaken.

The synthesis of the homologs of I can be divided into two areas: (1) homologs of the methylglyoxal moiety, and (2) homologs of the guanylhydrazone moiety.

Area 1—Homologs of the Methylglyoxal Moiety.—This area includes compounds in which the hydrogen atom(s) of the methyl group in I is (are) replaced by an alkyl group(s)



II.	$R_1 = CH_3$; $R_2, R_3 = H$
III.	$R_1, R_2 = CH_3$; $R_3 = H$
IV.	$R_1, R_2, R_3 = CH_3$
V.	$R_1 = CH_3(CH_2)_2$; $R_2, R_3 = H$
VI.	$R_1 = CH_3(CH_2)_3$; $R_2, R_3 = H$
VII.	$R_1 = CH_3(CH_2)_4$; $R_2, R_3 = H$
VIII.	$R_1 = CH_3(CH_2)_{14}$; $R_2, R_3 = H$

Although selenium dioxide is an outstanding agent

(1) The "Chemical Abstracts" name for this compound is 1,1'-[(methyl)-ethanediylidenedinitrilo]diguanidine.

(2) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service Contract SA-43-ph-3025.

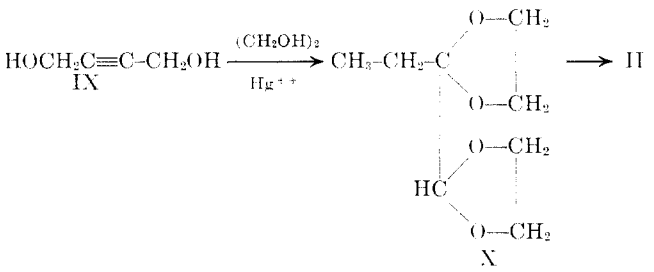
(3) B. L. Freedlander and F. A. French, *Cancer Research*, **18**, 360 (1958).

(4) F. Freireich and E. Frei, III, *Proc. Am. Assoc. Cancer Res.*, **3**, 319 (1962).

(5) (a) W. Regelson, O. Selawry, and J. F. Holland, *Proc. Am. Assoc. Cancer Res.*, **3**, 352 (1962); (b) M. E. Tidball and D. P. Rall, *ibid.*, **3**, 367 (1962).

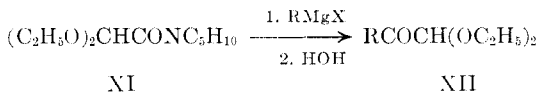
for the preparation of 1,2-dicarbonyl intermediates, the resulting condensation products would be contaminated by *traces* of selenium which is very toxic and difficult to remove. Consequently, for medicinal studies, other routes leading to the synthesis of alkyl glyoxals have been investigated.

Reaction of 2-butyne-1,4-diol (IX) and ethylene glycol in the presence of mercuric chloride gave ethylglyoxal bis(ethyleneglycolacetal)[6] (X). Hydrolysis of



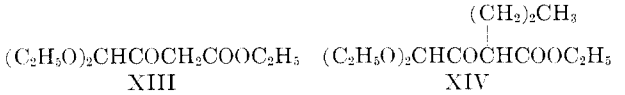
X in the presence of aminoguanidine sulfate gave ethylglyoxal bis(guanylhydrazone) sulfate.

A convenient method for the preparation of α-ketoacetals (XII) was first described by Wohl and Lange.[7]



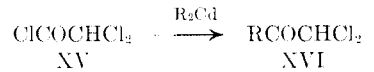
The method involves the reaction of Grignard reagents with dialkoxyacetylpiperidine (XI). Accordingly, 2-keto-3-methylbutyraldehyde diethylacetal [XII, R = $(CH_3)_2CH$],[8] 3,3-dimethyl-2-keto-butyraldehyde diethylacetal [XII, R = $(CH_3)_3C$],[9] and 2-ketoöctadecylaldehyde diethylacetal [XII, R = $CH_3(CH_2)_{15}$] were prepared by this method. Treatment of each of the ketoacetals with aminoguanidine in the presence of acid gave the corresponding guanylhydrazone derivatives (III, IV, VIII).

Another relatively convenient and quite versatile method for the synthesis of ketoacetals involves the use of ethyl γ-diethoxyacetoacetate (XIII) prepared from dichloroacetic acid by the method of Dakin and Dudley.[10] The sodium salt of XIII was treated with bromopropane to give the corresponding propyl derivative (XIV). Base hydrolysis of XIV yielded butyl-



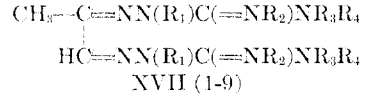
glyoxal diethylacetal, which reacted readily with aminoguanidine sulfate in acid to form the butyl analog (V) of I. This method, while being somewhat more involved than that of Wohl and Lange,[7] has the distinct advantage of not being limited to the preparation of only those compounds which require Grignard reagents as intermediates.

In view of the reported ease of preparation of the dioxime of ethylglyoxal by the reaction of hydroxylamine and α-dichloromethyl ethyl ketone,[11] an analogous procedure was utilized for the preparation of compounds VI and VII. The dichloromethyl alkyl ketones in both cases were prepared by a reaction similar to that described by Bunnett and Tarbell for the preparation of α-chloroketones.[12] Utilization of dichloroacetyl chloride (XV) instead of chloroacetyl chloride gave the desired dichloromethyl alkyl ketone (XVI, R = C_5H_{11}, C_6H_{13}), which yielded the appropriate guanylhydrazone compounds (VI and VII) with aminoguanidine.



All the primary and secondary substituted bis(guanylhydrazone) compounds in area 1 possess a characteristic ultraviolet absorption maximum at 283 mμ at *p*H 1. Replacement of all hydrogen atoms of the CH_3 group by three methyl groups caused a bathochromic shift of this maximum to 300 mμ.

Area 2—Homologs of the Guanylhydrazone Moiety.—This area includes compounds in which the hydrogen atoms in the guanylhydrazone portion are replaced by methyl groups.



Theoretically, the arrangement of methyl groups in the guanylhydrazone moiety gives rise to nine possible homologs.

*two mono*substituted derivatives:

XVIII-1. R_1, R_2, R_3 = H; R_4 = CH_3
XVIII-2. R_1 = CH_3; R_2, R_3, R_4 = H

*three di*substituted derivatives:

XVIII-3. R_1, R_2 = H; R_3, R_4 = CH_3
XVIII-4. R_1, R_3 = H; R_2, R_4 = CH_3
XVIII-5. R_2, R_3 = H; R_1, R_4 = CH_3

*three tri*substituted derivatives:

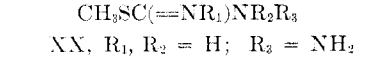
XVIII-6. R_1 = H; R_2, R_3, R_4 = CH_3
XVIII-7. R_2 = H; R_1, R_3, R_4 = CH_3
XVIII-8. R_3 = H; R_1, R_2, R_4 = CH_3

and *one tetra*substituted derivative:

XVIII-9. R_1, R_2, R_3, R_4 = CH_3

In addition, a closely related *tetra*substituted compound $H_2NN{=}C[N(CH_3)_2]_2$ (XIX) should also be included in this area.

Compounds XVIII-1[13] and XVIII-3 were prepared by treating S-methylthiosemicarbazide[14] (XX) with methylamine and dimethylamine, respectively. Compound XVIII-2[15] was prepared by the reaction of methylhydrazine with S-methylisothiourea (XXI).



XX, R_1, R_2 = H; R_3 = NH_2
XXI, R_1, R_2, R_3 = H
XXII, R_1, R_2 = H; R_3 = CH_3
XXIII, R_1, R_2 = CH_3; R_3 = H
XXIV, R_1 = H; R_2, R_3 = CH_3
XXV, R_1, R_2, R_3 = CH_3

(6) W. Reppe and H. J. Pistor, *Ann. Chem.*, **596**, 50 (1955).
(7) A. Wohl and M. Lange, *Ber.*, **41**, 3612 (1908).
(8) H. D. Dakin and H. W. Dudley, *J. Biol. Chem.*, **18**, 29 (1914).
(9) J. B. Wright, *J. Am. Chem. Soc.*, **77**, 4884 (1955).
(10) H. D. Dakin and H. W. Dudley, *J. Chem. Soc.*, **105**, 2453 (1914).
(11) E. E. Blaise, *Compt. rend.*, **155**, 1252 (1912).
(12) J. F. Bunnett and D. S. Tarbell, *J. Am. Chem. Soc.*, **67**, 1944 (1945).
(13) G. W. Kirsten and G. B. L. Smith, *ibid.*, **58**, 800 (1936).
(14) M. Freund and T. Paradies, *Ber.*, **34**, 3114 (1901).
(15) G. H. Green and G. B. L. Smith, *J. Am. Chem. Soc.*, **72**, 874 (1950).

TABLE I

PRELIMINARY TESTING RESULTS OF AREA 1 COMPOUNDS

$R_1R_2R_3C—C{=}N—NH—C({=}NH)NH_2$

$HC{=}N—NH—C({=}NH)NH_2$ (attached to the C above)

R_1	R_2	R_3	Tumor system	Dose (IP) (mg./kg./day)	Survivors	Wt. diff.	T/C (%)	Slope	ED_{50}
CH_3	H	H	LE[a]	60.0	5/6	−1.5	110		
			DL[b]	12.5	6/6	0.0	100		
			SA[c]	12.5	6/6	−1.7	76		
			CA[d]	12.5	10/10	−0.2	135		
			KB[e]					—	1.0 × 1
								−0.20	2.2 × 1
								−0.96	3.0 × 10
CH_3	CH_3	H	LE	30.0	6/6	−0.5	105		
CH_3	CH_3	CH_3	LE	15.0	6/6	−0.5	105		
$CH_3(CH_2)_2$	H	H	LE	30.0	6/6	−0.3	103		
			KB					−0.65	1.8 × 10
$CH_3(CH_2)_3$	H	H	LE	15.0	6/6	−2.5	98		
			KB					−0.54	1.3 × 10
$CH_3(CH_2)_4$	H	H	LE	60.0	4/6	−1.2	109		
			KB					−0.56	6.6 × 1
$CH_3(CH_2)_{14}$	H	H	LE	60.0	6/6	0.1	110		

[a] LE = Lymphoid leukemia 1210. [b] DL = Dunning leukemia (solid). [c] SA = Sarcoma 180. [d] CA = Adenocarcinoma 755. [e] KB = Tissue culture (cell line).

Methylhydrazine converted N,S-dimethylthiourea (XXII) into XVIII-5. A common intermediate for XVIII-4[16,17] and XVIII-8, N,N′-S-trimethylisothiourea (XXIII), was prepared from methyl isothiocyanate.[18] Treatment of XXXIII with hydrazine and methylhydrazine yielded the desired products.

N,N-Dimethylthiourea,[19,20] prepared by a method analogous to the preparation of N,N-dimethylselenourea[21] by using hydrogen sulfide rather than hydrogen selenide, was methylated readily to yield N,N,S-trimethylisothiourea hydroiodide (XXIV). Methylhydrazine then converted XXIV to XVIII-7.

Treatment of N,N,N′,S-tetramethylisothiouronium iodide[22] (XXV) with hydrazine and methylhydrazine gave XVIII-6[17] and XVIII-9, respectively.

Condensation of these substituted aminoguanidines with methylglyoxal gave the desired compounds (XVII, 1-9) in this area. Many of these compounds and their intermediates are very hygroscopic, and they tend to form hydrates or alcoholates with the environmental solvents. Hence, some of the products were extremely difficult to purify.

The preparation of compound XIX was first investigated *via* the reduction of N,N,N′,N′-tetramethyl-N″-nitroguanidine (XXVII); the latter was prepared from the nitration of N,N,N′,N′-tetramethylguanidine.[20]

$Z{=}C[N(CH_3)]_2$

XXVI. Z = NH
XXVII. Z = NNO_2
XXVIII. Z = S

$CH_3SC{=}N^+(CH_3)_2 \cdot I^-$ with $N(CH_3)_2$ on the C

XXIX

Various attempted reductions of XXVII, however, failed to yield any identifiable products.

Methylation of N,N,N′,N′-tetramethylthiourea (XXVIII)[23] readily gave N,N,N′,N′,S-pentamethylisothiouronium iodide (XXIX),[24] which was treated with hydrazine to yield compound XIX. The desired condensation product XXX was obtained from XIX and methylglyoxal.

$CH_3C{=}NN{=}C[N(CH_3)_2]_2$

$HC{=}NN{=}C[N(CH_3)_2]_2$

XXX

Preliminary biological evaluations[25] of these compounds have revealed that compound II in tissue culture studies has an ED_{50} (the dose that causes a 50% inhibition of growth) of 2.2 μg./ml. (slope: −0.20).[26] (See Tables I and II.)

Experimental[27]

1,1′-(Ethylethanediylidenedinitrilo)diguanidine Sulfate (II).—To a suspension of 50.0 g. (0.36 mole) of aminoguanidine bicarbonate in 80 ml. of water was added dropwise 19.6 g. (0.20 mole) of sulfuric acid (prediluted as a 50% aqueous solution). The resulting mixture was warmed on the steam bath for 30 min. and filtered into a 250-ml. erlenmeyer flask equipped with a reflux condenser. Ethylglyoxal diethyleneglycolacetal,[6] 31.3 g. (0.18 mole), was added and the resultant two phase system was refluxed with stirring. After 3 hr., a considerable amount of white solid had formed. Refluxing then was discontinued and the reaction mixture stirred at room temperature for 2 days. The solid was filtered and washed successively with small amounts of warm water, absolute ethanol and dry ether. The product was dried

(16) R. A. Henry and G. B. L. Smith, *J. Am. Chem. Soc.*, **73**, 1858 (1951).

(17) D. B. Murphy and J. P. Picard, *J. Org. Chem.*, **19**, 1807 (1954).

(18) M. Schenck, *Arch. Pharm.*, **249**, 478 (1911).

(19) Reported by O. Wallach, *Ber.*, **32**, 1872 (1899), without preparative details.

(20) M. Schenck and F. v. Graevenitz, *Z. physiol. Chem.*, **141**, 132 (1924).

(21) F. Bennett and R. Zingaro, *Org. Syn.*, **36**, 23 (1956).

(22) A Reference, L. C. Anderson and N. V. Seeger, *J. Am. Chem. Soc.*, **71**, 340 (1949), was cited in ref. 17. A careful examination of both papers, however, failed to reveal the description of this compound.

(23) O. Billeter, *Ber.*, **43**, 1857 (1910).

(24) H. Lecher and C. Heuck, *Ann.*, **438**, 169 (1924).

(25) Testing work was carried out by Contract Screeners of CCNSC.

(26) The slope as given is the difference in response for a one-log difference in dose, the response being the ratio of the growth of the test sample to that of the untreated control.

(27) All melting points (corrected) were taken on a Thomas–Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2, and the infrared spectra were taken with a Perkin-Elmer Infracord.

TABLE II

PRELIMINARY TESTING RESULTS OF AREA 2 COMPOUNDS

$CH_3C(=NN(R_1)C(=NR_2)NR_3)R_4$

$HC(=NN(R_1)C(=NR_2)NR_3)R_4$

R_1	R_2	R_3	R_4	Tumor system	Dose (IP) (mg./kg./day)	Survivors	Wt. diff.	T/C (%)	Slope	ED_{50}
H	H	H	CH_3	LE	240	6/6	−0.5	110		
				SA	100	6/6	0.5	101		
				CA	50	10/10	−2.1	100		
				KB					−0.50	5.3×10
CH_3	H	H	H	LE	960	6/6	−0.6	113		
				SA	200	6/6	0.6	84		
				CA	100	6/6	1.2	98		
				KB					−0.55	1.0×10
H	H	CH_3	CH_3	LE	760	6/6	−0.3	112		
				SA	100	6/6	0.6	93		
				CA	100	6/6	1.2	50		
				KB					−1.02	2.8×10
CH_3	H	H	CH_3	LE	120	6/6	0.0	113		
				WA[a]	100	6/6	2.0	128		
H	CH_3	CH_3	CH_3	LE	30	6/6	−1.5	106		

[a] WA = Walker 256 (subcutaneous).

overnight at room temperature *in vacuo* then an overnight exposure to air to yield 50.0 g. (88.5%) m.p. 243–244° dec.; $\lambda_{max}^{pH\ 1}$ 283 mμ (ε 44,900); $\lambda_{max}^{pH\ 7}$ 284 mμ (ε 34,900).

Anal. Calcd. for $C_6H_{14}N_8 \cdot H_2SO_4 \cdot H_2O$: C, 22.9; H, 5.77; N, 35.6. Found: C, 23.0; H, 5.98; N, 35.5.

2-Keto-3-methylbutyraldehyde Diethylacetal.—To a stirred, cooled (5°) solution of isopropylmagnesium bromide, prepared from 61.5 g. (0.50 mole) of isopropyl bromide and 12.2 g. (0.50 mole) of magnesium, was added 54.0 g. (0.25 mole) of diethoxyacetylpiperidine.[7] As the stirred reaction mixture slowly warmed up, the gum which had formed initially gradually gave way to a white solid. The reaction mixture was refluxed and stirred for 3 hr. followed by overnight stirring at room temperature. The reaction mixture was then treated with a concd. solution of ammonium chloride, maintaining the temperature at about 20°. The ethereal layer was decanted and the aqueous phase was extracted with ether. The combined ethereal solution was dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the residue fractionated. The main fraction was collected at 69–72° (8-9 mm.) [lit.[8] b.p. 75–77° (10-12 mm.)], $n^{26}D$ 1.4085. The yield of the colorless liquid was 30.6 g. (70%).

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.0; H, 10.4. Found: C, 61.4; H, 10.4.

2-Ketooctadecylaldehyde Diethylacetal was prepared in a manner similar to that described for the isopropyl compound. The reaction mixture was refluxed for 10 hr. Volatile components in the ether phase boiling up to 127° (0.75 mm.) were removed. The residue, *ca.* 50 g., was used as such for the preparation of the bis(guanylhydrazone).

1,1′-(Isopropylethanediylidenedinitrilo)diguanidine Sulfate (III).—To a solution of 0.36 mole of aminoguanidine sulfate in 100 ml. of water was added 30.6 g. (0.18 mole) of isopropylglyoxal diethylacetal in 80 ml. of ethanol. The stirred reaction mixture was refluxed for 2 hr. and stirred at room temperature for 2 days. The white solid which had formed was isolated by filtration, washed with water, ethanol, and dry ether. The product was dried at 25° (1 mm.) for 3 hr. to yield 47.5 g. (79%) as the sesquihydrate, m.p. 214–215°, $\lambda_{max}^{pH\ 1\ and\ 7}$ 283 mμ (ε 21,200).

Anal. Calcd. for $C_7H_{16}N_8 \cdot H_2SO_4 \cdot 1.5H_2O$: C, 24.9; H, 6.25; N, 33.3. Found: C, 24.8; H, 6.37; N, 33.7.

1,1-(*tert*-Butylethanediylidenedinitrilo)diguanidine Sulfate (IV) was prepared in a manner similar to the above procedure, from *t*-butylglyoxal diethylacetal.[9] The reaction afforded 31.1 g. (70%) of product as its monohydrate, m.p. 214–215°; $\lambda_{max}^{pH\ 1}$ 300 mμ (ε 11,300); $\lambda_{max}^{pH\ 7}$ 305 mμ (ε 11,300); $\lambda_{max}^{pH\ 11}$ 318 mμ (ε 16,750).

Anal. Calcd. for $C_8H_{18}N_4 \cdot H_2SO_4 \cdot H_2O$: C, 28.0; H, 6.48; N, 32.7. Found: C, 27.7; H, 6.66; N, 32.5.

1,1′-(Cetylethanediylidenedinitrilo)diguanidine Sulfate (VIII) was similarly prepared from 2-ketooctadecylaldehyde diethylacetal. The waxy product melted at 241–243° with decomposition; $\lambda_{max}^{pH\ 1\ and\ 7}$ 283 mμ (ε 26,400).

Anal. Calcd. for $C_{20}H_{42}N_8 \cdot H_2SO_4 \cdot 2H_2O$: C, 45.5; H, 9.16; N, 21.2. Found: C, 45.5; H, 9.16; N, 21.2.

Ethyl γ-Diethoxyacetoacetate[10] **(XIII).**—This compound was prepared from ethyl diethoxyacetate[28] and ethyl acetate according to the procedure of Johnson and Mikeska.[29] The yield of the colorless liquid was 59%; b.p. 103–106° (3.1–3.4 mm.); $n^{25}D$ 1.4250.

Ethyl γ-Diethoxy-α-propylacetoacetate (XIV).—To 43.6 g. (0.20 mole) of XIII in 150 ml. of dry ether was added portionwise 4.6 g. (0.20 g.-atom) of sodium. After the vigorous reaction had subsided and all the sodium had reacted, 24.6 g. (0.20 mole) of bromopropane was added and the resulting solution stirred at room temperature overnight. The reaction mixture then was refluxed for 3 hr. and cooled. To the reaction mixture there was then added 200 ml. of absolute ethanol and 5 g. of potassium iodide. After the ether was removed by distillation, the mixture was refluxed for 1 day, at which time an appreciable quantity of solid had separated and the *p*H of the reaction mixture was about 7. The ethanol was evaporated *in vacuo* and the residue taken up with water and extracted several times with ether. The combined ethereal extracts were dried over anhydrous sodium sulfate and evaporated. Fractional distillation of the residue gave 38.0 g. (73% yield) of XIV, b.p. 80–83° (0.23 mm.), $n^{26}D$ 1.4270.

Anal. Calcd. for $C_{13}H_{26}O_5$: C, 60.0; H, 9.29. Found: C, 60.3; H, 9.13.

1,1′-(Butylethanediylidenedinitrilo)diguanidine (V).—To a solution of 38.0 g. (0.14 mole) of XIV in 80 ml. of methanol was added 9 g. of potassium hydroxide in 80 ml. of water. The resulting mixture was refluxed for 2 hr., cooled, and extracted with ether. The ethereal extract was dried and evaporated and the residual liquid distilled fractionally to yield 11.6 g. (42%) of **2-ketocaproic aldehyde diethylacetal,** b.p. 86–89° (8 mm.); $n^{24}D$ = 1.4150. This ketoacetal was treated with aminoguanidine sulfate in the usual manner to give a 76% yield of V, m.p. 261° dec.; $\lambda_{max}^{pH\ 1}$ 283 mμ (ε 39,800); $\lambda_{max}^{pH\ 7}$ 284 mμ (ε 34,000); $\lambda_{max}^{pH\ 11}$ 328 mμ (ε 31,900).

Anal. Calcd. for $C_5H_{18}N_8 \cdot H_2SO_4 \cdot H_2O$: C, 28.0; H, 6.48; N, 32.7. Found: C, 28.1; H, 6.39; N, 32.8.

1,1-Dichloro-2-heptanone (XVI, R = C_5H_{11}).—To a cold, stirred amyl Grignard reagent, prepared from 151 g. (1 mole) of amyl bromide and 24.3 g. (1 g.-atom) of magnesium, was added 97.1 g. (0.53 mole) of anhydrous cadmium chloride. The reaction mixture was refluxed for 45 min. and the ether was removed by distillation. Approximately 100 ml. of benzene was added and the distillation was continued for a short time longer to ensure the complete removal of ether. About 600 ml. of benzene

(28) R. B. Moffett, *Org. Syn.*, **35**, 59 (1959).

(29) T. B. Johnson and L. A. Mikeska, *J. Am. Chem. Soc.*, **41**, 810 (1919).

was added and the reaction mixture cooled to 3°. Dichloroacetyl chloride, 147 g. (1 mole), in 50 ml. of benzene then was added slowly (5 min.). The temperature of the reaction mixture began to rise quickly to *ca.* 50°. After cooling to room temperature the reaction mixture was stirred overnight, then hydrolyzed with ice and dilute sulfuric acid. The benzene layer was separated and the aqueous portion extracted with benzene. The combined benzene phase was washed successively with water, sodium bicarbonate solution, and water, then filtered through anhydrous sodium sulfate. Evaporation of benzene and fractionation of the residual liquid gave 1,1-dichloro-2-heptanone in 72.6 g. (40%) yield, b.p. 85–92° (15 mm.), $n^{24}D$ 1.4515.

Anal. Calcd. for $C_7H_{12}Cl_2O$: C, 46.0; H, 6.61. Found: C, 46.6; H, 6.76.

1,1′-(Amylethanediylidenedinitrilo)diguanidine (VI).—Freshly prepared 1,1-dichloro-2-heptanone, 21.0 g. (0.11 mole), in 20 ml. of ethanol was warmed with 0.22 mole of aminoguanidine sulfate in 40 ml. of water on a steam bath for 30 min. The reaction mixture was then stirred overnight at room temperature and the solid product was filtered and washed successively with water, ethanol, and ether. The yield of VI was 21.0 g. (54%), m.p. 266° dec.; $\lambda_{max}^{pH\ 1}$ 283 mμ (ε 38,100); $\lambda_{max}^{pH\ 7}$ 283 mμ (ε 35,240).

Anal. Calcd. for $C_9H_{20}N_8 \cdot H_2SO_4 \cdot H_2O$: C, 30.3; H, 6.79; N, 31.4. Found: C, 30.3; H, 6.54; N, 31.2.

1,1′-(Hexylethanediylidenedinitrilo)diguanidine Sulfate (VII) was prepared in a manner similar to VI from 1,1-dichloro-2-octanone (prepared in 43% yield from hexylmagnesium bromide, cadmium chloride and dichloroacetyl chloride, b.p. 115–122° (21 mm.), $n^{25}D$ 1.4540) in 65% yield, m.p. 260° dec.; $\lambda_{max}^{pH\ 1}$ 283 mμ (ε 40,000); $\lambda_{max}^{pH\ 7}$ 284 mμ (ε 35,150); $\lambda_{max}^{pH\ 11}$ 328 mμ (ε 32,550).

Anal. Calcd. for $C_{10}H_{22}N_8 \cdot H_2SO_4 \cdot H_2O$: C, 32.4; H, 7.07; N, 30.3. Found: C, 32.6; H, 7.06; N, 30.3.

1,1′-(Methylethanediylidenedinitrilo)-bis(3-methyl)guanidine Sulfate (XVII-1).—To a solution of 20.0 g. (0.15 mole) of 3-amino-1-methyl-guanidine sulfate[13] in 100 ml. of water was added with stirring 13.2 g. of a 43.2% solution of methylglyoxal. The mixture was stirred for 24 hr. The white solid which formed was filtered, then washed successively with water, ethanol, and ether. The product was dried at 56° (1 mm.) for 3 hr. to yield 22.5 g. (94%) of XVII-1, m.p. 246–249° dec.; $\lambda_{max}^{pH\ 1}$ 286 mμ (ε 40,300); $\lambda_{max}^{pH\ 7}$ 283 mμ (ε 37,700).

Anal. Calcd. for $C_7H_{16}N_8 \cdot H_2SO_4 \cdot H_2O$: C, 25.6; H, 6.14; N, 34.1. Found: C, 25.4; H, 6.02; N, 34.3.

1,1′-(Methylethanediylidenedinitrilo)-bis(1-methyl)guanidine Sulfate (XVII-2).—A slurry of 75.0 g. (0.54 mole) of 1-amino-1-methyl-guanidine sulfate[15] in 60 ml. of water was stirred manually while there was added dropwise 46.5 g. (0.27 mole) of a 43% solution of methylglyoxal in water. The reaction mixture was stirred intermittently for several hours and then left to stand overnight. Approximately 100 ml. of cold water was added and the remaining solid isolated by filtration. The solid was washed well with 50 ml. of cold water, two 50-ml. quantities of absolute ethanol, and finally 150 ml. of dry ether (no attempt was made to recover material from the washings). After being dried at 25° (1 mm.) for 3 hr. and then exposed to air for several days, the product weighed 54.0 g. (52% yield); the solid decomposes slowly above 216°; $\lambda_{max}^{pH\ 1}$ 270 mμ (ε 22,200); $\lambda_{max}^{pH\ 7}$ 270 mμ (ε 21,000).

Anal. Calcd. for $C_7H_{16}N_8 \cdot H_2SO_4 \cdot 4H_2O$: C, 22.20; H, 6.86; N, 29.3. Found: C, 22.3; H, 7.00; N, 29.4.

1,1-Dimethyl-3-aminoguanidine Sulfate.—This compound was made from S-methylthiosemicarbazide and dimethylamine in a manner similar to that described for the preparation of 1-methyl-3-aminoguanidine sulfate.[13] The intermediate 1,1-dimethyl-3-aminoguanidine hydroiodide, m.p. 182–185°, was converted to the sulfate, m.p. 225.5° dec., by means of silver sulfate.

1,1′-(Methylethanediylidenedinitrilo)-bis(3,3-dimethyl)guanidine Sulfate (XVII-3).—This product was prepared in 68% yield from methylglyoxal and 1,1-dimethyl-3-aminoguanidine sulfate according to the procedure previously described for XVII 1, m.p. 232–234° dec. The product was exposed to the atmosphere for 12 hr. before being analyzed; $\lambda_{max}^{pH\ 1}$ 288 mμ (ε 41,600); $\lambda_{max}^{pH\ 7}$ 290 mμ (ε 29,400).

Anal. Calcd. for $C_9H_{20}N_8 \cdot H_2SO_4 \cdot 3H_2O$: C, 27.5; H, 7.19; N, 28.6. Found: C, 27.2; H, 6.92; N, 28.7.

1,1′-(Methylethanediylidenedinitrilo)-bis(2,3-dimethyl)guanidine Hydroiodide (XVII-4).—A suspension of 40.0 g. (0.17 mole) of 3-amino-1,2-dimethyl-guanidine hydroiodide[16] in 200 ml. of absolute methyl alcohol and 14.0 g. (0.085 mole) of a 43% aqueous solution of methylglyoxal was stirred at room temperature overnight. The solid then was isolated by filtration and washed with cold water, absolute ethanol, and dry ether. After recrystallization from methyl alcohol, the product, which was obtained in 64% yield (29.5 g.), m.p. 268–269° dec., had $\lambda_{max}^{pH\ 1}$ 226 mμ (ε 33,900) and 286 mμ (ε 33,900); $\lambda_{max}^{pH\ 11}$ 338 mμ (ε 33,300).

Anal. Calcd. for $C_9H_{20}N_8 \cdot 2HI \cdot H_2O \cdot CH_3OH$: C, 22.0; H, 5.16; N, 20.5; I, 46.5. Found: C, 21.8; H, 5.35; N, 20.5; I, 46.8.

1,3-Dimethyl-3-aminoguanidine Sulfate.—Methylthiourea (2.0 moles) was treated with dimethyl sulfate (1.0 mole) according to the procedure[30] used for the preparation of S-methylisothiouronium sulfate. The product, a viscous liquid, was treated with methylhydrazine (2.0 moles) in anhydrous methanol at reflux temperature until the evolution of methyl mercaptan ceased. After evaporation of the solvent, recrystallization of the remaining solid from ethanol and ether gave 120 g. (78% yield) of the product, m.p. 194.5° dec.

Anal. Calcd. for $C_3H_{10}N_4 \cdot {}^1/_2H_2SO_4 \cdot H_2O$: C, 21.3; H, 7.10. Found: C, 21.7; H, 7.38.

1,1′-(Methylethanediylidenedinitrilo)-bis(1,3-dimethyl)guanidine Sulfate (XVII-5).—3-Amino-1,3-dimethylguanidine sulfate, 22.6 g. (0.15 mole), was suspended in 20 ml. of anhydrous methanol and 11.7 g. (0.075 mole) of a 43% solution of methylglyoxal in water was added. The reaction mixture was slowly stirred at room temperature for 2 hr. Volatile components of the reaction mixture then were evaporated on a flash evaporator. The oil remaining was taken up in methyl alcohol and treated with Norit. Evaporation of the methyl alcohol and three azeotropic distillations with benzene on the flash evaporator yielded 17.0 g. (61% yield) of a tan, *very* hygroscopic solid which melted slowly over 60° and decomposed at 100°; $\lambda_{max}^{pH\ 1}$ 279 mμ; $\lambda_{max}^{pH\ 7}$ 296 mμ.

Anal. Calcd. for $C_9H_{20}N_8 \cdot H_2SO_4 \cdot CH_3OH \cdot 2H_2O$: C, 29.6; H, 7.40; N, 27.5. Found: C, 30.2; H, 7.47; N, 27.2.

1,1′-(Methylethanediylidenedinitrilo)-bis(2,3,3-trimethyl)guanidine Dihydroiodide (XVII-6).—To a solution of 24.4 g. (0.1 mole) of 3-amino-1,1,2-trimethylguanidine iodide[17] in 50 ml. of anhydrous methanol was added 8.4 g. (0.05 mole) of a 43% solution of methylglyoxal in water. The reactants were stirred for 16 hr. after which the reaction mixture was concentrated. The solid was washed with a minimum amount of absolute ethanol and then dry ether. After drying for 12 hr. at 60° the product weighed 23.0 g. (88% yield), m.p. 212–213° dec.; $\lambda_{max}^{pH\ 1}$ 292 mμ (ε 39,800), 225 mμ (ε 34,500).

Anal. Calcd. for $C_{11}H_{24}N_8 \cdot 2HI$: C, 25.2; H, 4.96; N, 21.1. Found: C, 25.6; H, 5.22; N, 21.0.

N,N-Dimethylthiourea.—A stream of hydrogen sulfide was bubbled through a stirred solution of 111 g. of dimethylcyanamide[19] in 225 ml. of concd. ammonium hydroxide and 75 ml. of water at 20–30° for 4 hr. The reaction mixture was then cooled to 5° and the precipitated solid was filtered and air dried to give 87 g. (84% yield) of the product, m.p. 164–167° (recrystallized from ethanol); lit. m.p. 158–159°,[19] m.p. 164°.[20]

Anal. Calcd. for $C_3H_8N_2S$: N, 26.9. Found: N, 26.7.

N,N,S-Trimethylisothiourea Hydroiodide.—To a suspension of 21 g. (0.2 mole) of N,N-dimethylthiourea in 200 ml. of methanol was added through a condenser, with stirring, 29 g. (0.2 mole) of methyl iodide. The suspension gradually became clear during the process of the addition but no heat was produced. The reaction mixture was allowed to stir at room temperature overnight and heated gradually to reflux (6 hr.). Excess solvent then was evaporated and the residue slowly solidified. The crude product was recrystallized from a mixture of methanol and ethyl acetate to give 45 g. (92% yield) of white rhombic crystals, m.p. 100–101°.

Anal. Calcd. for $C_4H_{11}IN_2S$: C, 19.5; H, 4.5; N, 11.4. Found: C, 19.8; H, 4.62; N, 11.1.

1,1′-(Methylethanediylenedinitrilo)-bis(1,3,3-trimethyl)guanidine Sulfate (XVII-7).—A mixture of 33.4 g. (0.13 mole) of N,N,S-trimethylisothiourea hydroiodide and 6.0 g. (0.13 mole) of methylhydrazine in 200 ml. of absolute ethanol was refluxed until the methyl mercaptan odor could no longer be detected (approximately 3–4 hr.). The solution was cooled in an ice bath and 29.6 g. of a 58% solution of hydrogen iodide (0.13 mole) was added. To the mixture was added 11.7 g. of a 43% aqueous solution of methylglyoxal (0.07 mole) and the solution was stirred overnight at room temperature. The reaction mixture was then evaporated under reduced pressure and the viscous reddish brown oil was taken up in ethanol and excess silver sulfate (0.20 mole) was added. After 2 hr. with occasional shaking the reac-

(30) P. R. Shildneck and W. Windus "Organic Syntheses," Collective Vol. II, John Wiley and Sons, New York, 1943, p. 411.

tion mixture was filtered and the filtrate treated 3 times with charcoal. The amber colored solution then was evaporated azeotropically with absolute ethanol to give 3.5 g. of a yellow solid. The solid was washed successively with absolute ethanol and ether. It was extracted with anhydrous methanol. The methanol-soluble fraction was evaporated to yield a yellow solid, m.p. 237° dec.; $\lambda_{max}^{pH\ 1}$ 290 mμ (ε 49,000); $\lambda_{max}^{pH\ 7}$ 290 mμ (ε 36,500).

Anal. Calcd. for $C_{11}H_{24}N_8 \cdot 2H_2SO_4 \cdot 2H_2O$: C, 26.4; H, 6.40; N, 22.4; S, 12.8. Found: C, 26.5; H, 6.41; N, 22.2; S, 12.5.

1-Amino-1,2,3-trimethylguanidine Hydroiodide.—N,N′,S-Trimethylisothiourea hydroiodide,[15] 54.7 g. (0.22 mole), was suspended in 100 ml. absolute ethanol, and 11.5 g. (0.25 mole) of methylhydrazine in 50 ml. of absolute ethanol was added during a period of 30 min. The reaction mixture was refluxed until no more methyl mercaptan was evolved (about 25 hr.). The reaction mixture was concentrated to give a white gum. The gum was triturated with a minimum amount of absolute ethanol to give 15.1 g. (28% yield) of a white solid, m.p. 304–316° dec., which was used without purification.[31]

1,1′-(Methylethanediylidenedinitrilo)-bis(1,2,3-trimethyl)-guanidine Sulfate (XVII-8).—To a stirred suspension of 14.5 g. (0.06 mole) of 1-amino-1,2,3-trimethylguanidine hydroiodide in 50 ml. of absolute ethanol was added 5.0 g. of a 43% solution of methylglyoxal in water. The reaction mixture was stirred at room temperature overnight. Silver sulfate, 9.3 g. (0.03 mole), was added to the red solution and the mixture stirred for 1 hr. The reaction mixture was filtered and the red filtrate treated with charcoal several times until the red coloration had been removed. The solution now was evaporated on a flash evaporator to yield a tan oil. The oil was taken up in absolute ethanol and to this was added ethyl acetate until a very small quantity of a solid separated. On isolation the product was found to be very hygroscopic; $\lambda_{max}^{pH\ 1\ and\ 7}$ 278 mμ (ε 31,000); m.p. 293° dec (darkening about 186°).

Anal. Calcd. for $C_{11}H_{24}N_8 \cdot H_2SO_4 \cdot C_2H_5OH \cdot 2H_2O$: C, 34.8; H, 8.05; N, 25.0; S, 7.15. Found: C, 34.6; H, 8.31; N, 25.1; S, 7.35.

N-Amino-N,N′,N″,N″-tetramethylguanidine Sulfate.—To a stirred solution of 52.0 g. (0.20 mole) of N,N,N′,S-tetramethylisothiouronium iodide[22] in 150 ml. of water was added 31.1 g. (0.10 mole) of silver sulfate with initial cooling. The reaction mixture was stirred at room temperature for 2.5 hr. and filtered. The filtrate was evaporated under reduced pressure to yield a viscous oil, which could not be induced to solidify under 1 mm. of pressure at room temperature for several hours.

The oil now was suspended in 150 ml. of absolute ethanol and, with stirring, 18.4 g. (0.40 mole) of methylhydrazine was added. Stirring was continued for 18 hr. at room temperature after which the solution was concentrated *in vacuo*. A gray, tacky solid was obtained which was used for the next experiment without further purification.

1,1′-(Methylethanediylidenedinitrilo)bis(1,2,3,3-tetramethyl)-guanidine (XVII-9).—The product from the preceding reaction was added to 250 ml. of anhydrous ethanol and 16.7 g. of 43% (0.1 mole) methylglyoxal was added. The solution was stirred at room temperature for 3 hr. during which time it turned progressively dark red. The reaction mixture (maximum ultraviolet absorption, 288 mμ) was concentrated under reduced pressure and the residue taken up in absolute ethanol. To the ethanolic solution was added ethyl acetate until the solution became turbid. On standing, a hygroscopic solid separated which gave the maximum absorption at 288 mμ but was too hygroscopic to be analyzed.

(31) This compound has also been prepared and isolated as a picrate of its benzalhydrazone derivative by W. R. McBride, W. G. Finnegan, and R. A. Henry, *J. Org. Chem.*, **22**, 152 (1957).

N,N,N′,N′-Tetramethylguanidine Nitrate.—Careful addition of dilute nitric acid (0.5 mole) of 57.5 g. (0.5 mole) of N,N,N′,N′-tetramethylguanidine[20] and evaporation gave 64 g. (72% yield) of the nitrate, m.p. 85–88°. Recrystallization from a mixture of butanol and ether gave white, hygroscopic crystals, m.p. 87–88°. The infrared spectrum of this compound possessed a characteristic N–H stretching at 3400 cm.$^{-1}$ and nitrate vibration at 825 cm.$^{-1}$.

Anal. Calcd. for $C_5H_{13}N_3 \cdot HNO_3 \cdot 0.5H_2O$: C, 32.2; H, 8.0; N, 30.0. Found: C, 32.6; H, 7.5; N, 30.3.

N,N,N′,N′-Tetramethyl-N″-nitroguanidine (XXVII).—To 300 ml. of concd. sulfuric acid cooled to −5° was added 122 g. of the tetramethylguanidine nitrate. The solution was kept below 0° for 90 min., poured onto ice, and neutralized to *p*H 7 with ammonia. The aqueous solution then was extracted with chloroform. Evaporation of the chloroform extract afforded 100 g. (92%) of tetramethylnitroguanidine, m.p. 80–82°. Recrystallization from ethyl acetate and heptane and recrystallization from benzene gave large, white, rhombic crystals, m.p. 86–87°. An infrared spectrum of the product showed no band in the N–H stretching region but did indicate a –N–NO_2 band at 1250 cm.$^{-1}$.

Anal. Calcd. for $C_5H_{12}N_4O_2$: C, 37.5; H, 7.5; N, 35.0. Found: C, 37.4; H, 7.43; N, 34.9.

N,N,N′,N′-Tetramethyl-N″-aminoguanidine (XIX).—To a stirred suspension of 55.0 g. (0.20 mole) of N,N,N′,N′,S-pentamethylisothiouronium iodide, prepared in quantitative yield according to the method of Lecher and Heuck,[21] in 300 ml. of absolute ethanol was added 9.6 g. (0.30 mole) of 97% hydrazine. The reaction mixture was stirred at room temperature overnight during which time some solid separated. The solid was filtered, washed with small amounts of ethanol and ether and dried *in vacuo* to give 12 g. of white solid, m.p. 118–119.5°. The filtrate was evaporated to dryness under reduced pressure and the residue was recrystallized from absolute ethanol to yield 34.4 g. of white solid, m.p. 118–120°. The infrared absorption spectra for these two solid products were identical. The combined yield of XIX was 90%.

Anal. Calcd. for $C_5H_{13}N_3 \cdot HI$: C, 23.2; H, 5.82; N, 21.7; I, 49.3. Found: C, 23.1; H, 5.88; N, 21.5; I, 49.2.

1,1′-(Methylethanediylidenedinitrilo)bis(2,2,3,3-tetramethyl)-guanidine (XXX).—To 25.8 g. (0.10 mole) of XIX in 300 ml. of absolute ethanol (partially soluble) was added, with stirring, 8.4 g. of 43% (0.05 mole) solution of methylglyoxal. All the solid dissolved after the addition. The solution was stirred overnight at room temperature. A light yellow solid, which gradually formed, was filtered and washed with ethanol, then ether. It weighed 7 g. after being dried *in vacuo*, m.p. 275–276° dec. Additional product was formed from the filtrate on continued stirring. The total yield was 17.5 g. (61%). After recrystallization from ethanol the product melted at 285–286° dec.; $\lambda_{max}^{pH\ 1}$ 225 mμ (ε 37,000), 297 mμ (ε 43,300); $\lambda_{max}^{pH\ 7}$ 225 mμ (ε 37,000), 297 mμ (ε 38,700).

Anal. Calcd. for $C_{13}H_{28}N_8 \cdot 2HI \cdot H_2O$: C, 27.4; H, 5.65; N, 19.6; I, 44.5. Found: C, 27.6; H, 5.50; N, 19.5; I, 44.4.

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