Synthesis of Unsymmetrically Substituted Malonamidines

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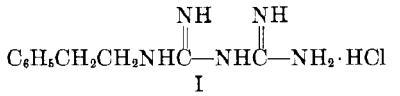
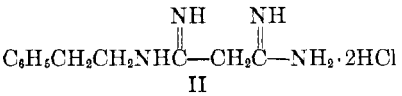
Unsymmetrically substituted malonamidines have been synthesized by a stepwise route which should be of general applicability. Ethyl cyanoacetimidate hydrochloride (VI) derived from malononitrile formed 2-cyano-N-phenethylacetamidine hydrochloride (VII) when treated with phenethylamine. Transformation of VII to ethyl N-phenethylamidinoacetimidate dihydrochloride (IX) was followed by reaction with ammonia to yield N-phenethylmalonamidine dihydrochloride (II). The parallel dependence of the ultraviolet spectra of biguanides and malonamidines on pH is discussed.

Phenethylbiguanide hydrochloride (I) is a clinically effective agent for the oral treatment of some types of diabetes.[1] A search for new, related systems has directed us to the synthesis of an isosteric compound, phenethylmalonamidine dihydrochloride (II). Al-



I



II

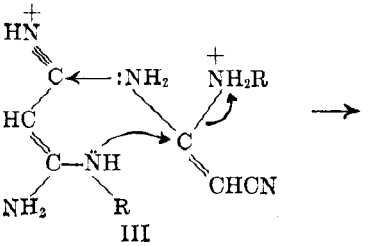
though II failed to display hypoglycemic activity, the stepwise path employed for its preparation should be of interest as a general synthetic route to unsymmetrically substituted malonamidines.

Malonamidines are a little studied class of compounds; only malonamidine[2] itself and several N,N'' symmetrically substituted derivatives[3] have been described in the literature.

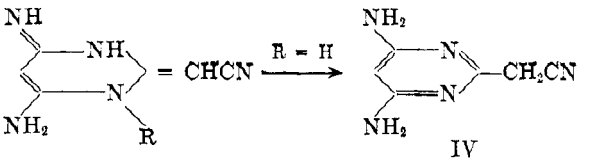
Our initial experiments directed toward the synthesis of unsymmetrical malonamidines were predicated upon the reaction of diethyl malonimidate dihydrochloride[2] with limited amounts of the requisite amines. Under these conditions, however, only symmetrically substituted products were isolated.

Attention was next directed toward a stepwise sequence by way of a substituted cyanoacetamidine hydrochloride. Although McElvain and Tate[4] had shown that cyanoacetamidine hydrochloride (III, R = H) spontaneously self-condenses to a pyrimidine (IV), the introduction of an N-alkyl substituent would prevent the final aromatization reaction and might, therefore, inhibit self-condensation[5] (col. 2).

Malononitrile (V) was converted to ethyl cyanoacetimidate hydrochloride (VI) as described by Cook, *et al.*[6] The preparation of cyano-N-phenethylacetamidine hydrochloride (VII) from VI proved to be extremely sensitive to experimental conditions. When phenethylamine was allowed to react with VI at room temperature in ethanol, ethyl cyano-N-phenethylacetimidate (VIII) was obtained. If heat was employed during solvent removal, variable amounts of the



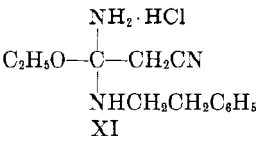
III



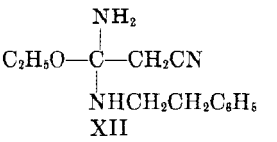
IV

desired amidine VII were isolated. When commerical sodium methoxide (one equivalent) was added to the reaction mixture, VII was sometimes isolated, but a reproducible procedure could not be developed (p. 309).

A more satisfactory method was developed from the assumption that under acidic conditions the initially formed amine–imidate adduct XI would lose ammonia



XI



XII

or phenethylamine more rapidly than ethanol to yield the starting imidate VI or the new imidate VIII. Under basic conditions, however, the uncharged adduct XII might be expected to eliminate ethoxide rather than the more basic amide anion, and lead to the formation of the amidine VII.[7] Based on these considerations, the imidate hydrochloride VI and phenethylamine were allowed to react in the presence of one equivalent of triethylamine in dioxane. The use of ethanol as the solvent was avoided to overcome a possible mass action effect. Under these conditions, the amidine VII was produced consistently.

The reaction of VII with anhydrous hydrogen chloride and one equivalent of ethanol in ether provided

(1) G. Ungar, L. Freedman, and S. L. Shapiro, *Proc. Soc. Exptl. Biol. Med.*, **95**, 190 (1957).

(2) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 574 (1943).

(3) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **80**, 2185 (1958); P. Oxley and W. F. Short, *J. Chem. Soc.*, 449 (1949); E. Richter and E. C. Taylor, *J. Am. Chem. Soc.*, **78**, 5848 (1956).

(4) S. M. McElvain and B. E. Tate, *ibid.*, **73**, 2761 (1961).

(5) We wish to thank Dr. E. Cohen for bringing this point to our attention.

(6) A. H. Cook, G. Harris, and A. L. Levy, *J. Chem. Soc.*, 3227 (1949).

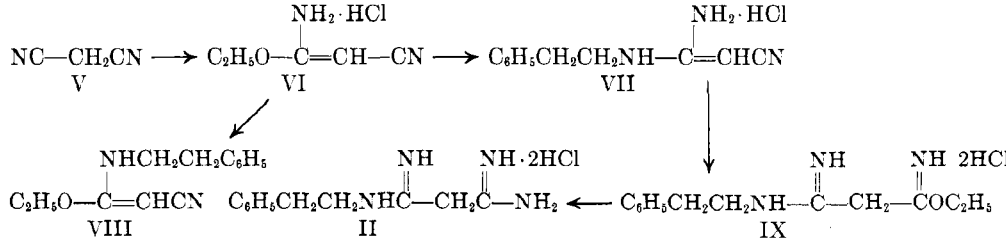
(7) A similar argument has been proposed[8] to explain the results of tracer experiments on the mechanism of amide hydrolysis.[9] Under basic conditions, the original O^{18} label of the amide was lost to the solvent. This was interpreted as evidence for the collapse of a "tetrahedral intermediate" to starting amide (hence, preference for loss of OH^- rather than NH_2^-). During acidic hydrolysis, exchange did not occur (hence, NH_3 elimination is faster than H_2O loss).

(8) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Book Co., Inc., 1962, p. 139.

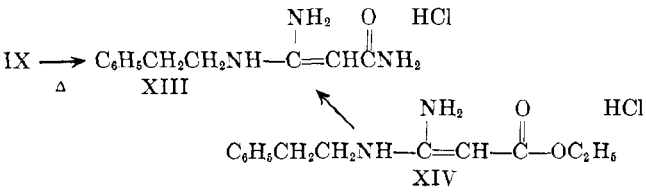
(9) M. L. Bender and R. D. Ginger, *J. Am. Chem. Soc.*, **77**, 348 (1955).

(10) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

(11) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).



ethyl N-phenethylamidinoacetimidate dihydrochloride (IX). The structure of IX was confirmed by pyrolysis[10] to N-phenethylamidinoacetamide hydrochloride (XIII). The identity of XIII was established by independent synthesis. Thus, ethyl ethoxycarbonylacetimidate hydrochloride[11] and phenethylamine gave



ethyl N-phenethylamidinoacetate hydrochloride (XIV), which yielded XIII by the action of ammonia.

The conversion of IX to N-phenethylmalonamidine dihydrochloride (II) with ammonia proceeded smoothly. Similarly, methylamine gave N-methyl-N''-phenethylmalonamidine dihydrochloride.

The ultraviolet spectra of phenethylbiguanide hydrochloride (I) and phenethylmalonamidine dihydrochloride (II) exhibit a strikingly parallel pH dependence (Table I). In strongly acidic media, the spectra of both compounds display only end absorption in addition to weak aromatic bands. As the acidity decreases, maxima develop. In strongly basic media, these peaks disappear, and end absorption is again observed.[12]

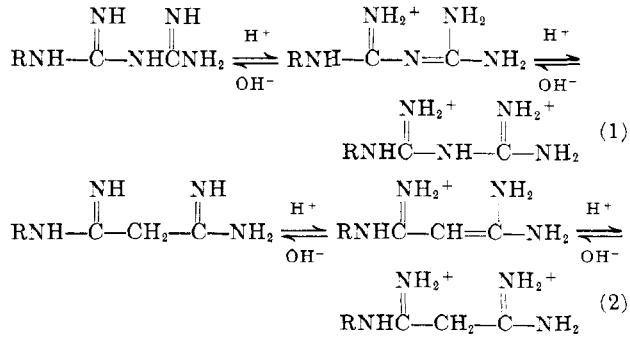
TABLE I

ULTRAVIOLET MAXIMA FOR PHENETHYLBIGUANIDE AND PHENETHYLMALONAMIDINE

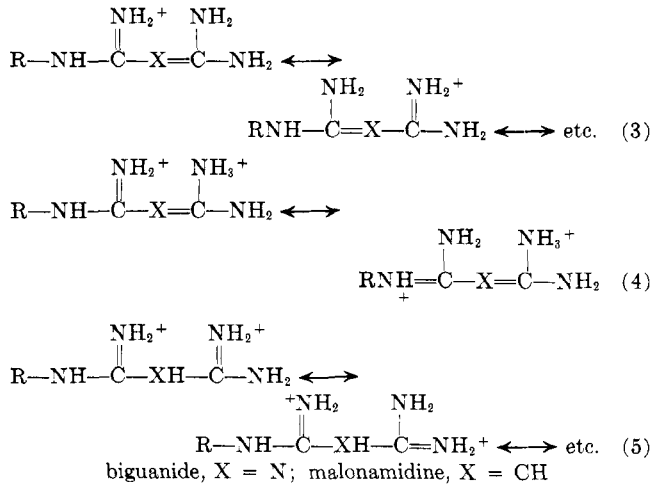
Solvent[a]	λ_{max}, mμ (ε)	
	I	II
0.01 *N* HCl	End absorption	End absorption
0.001 *N* HCl	237 (sh)	End absorption
Solvent (neat)	236 (18,100)	288 (2490)
0.0001 *N* NH_3	236 (18,100)	288 (25,500)
0.1 *N* NH_3	236 (17,500)	288 (17,900)
1 *N* NH_3	236 (15,600)	288 (9140)
0.01 *N* *i*-PrONa	End absorption, 235 (sh)	End absorption

[a] Spectra were determined on $10^{-4}M$ solutions of I and II. Solutions were prepared with standard anhydrous acid or base in isopropyl alcohol.

These observations are best interpreted by equilibria between dication, monocation, and free base having the structures given in eq. 1 and 2.[13] The conjugated chromophores of the monocations are destroyed by protonation on the central atoms (N in I, C in II) to yield the nonconjugated dications. Unexpectedly, the free bases appear to exist largely as the nonconjugated tautomers, although the appearance of a weak shoulder in the spectrum of phenethylbiguanide base suggests the presence of a small amount of conjugated tautomer at equilibrium.



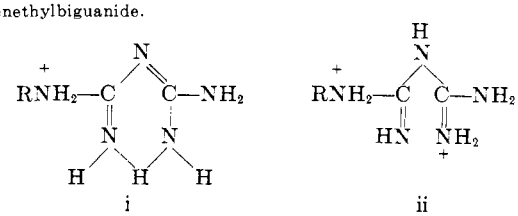
In classical terms, the preference for the conjugated systems of the monocations is clear; the positive charge can be distributed over the four terminal nitrogen atoms in both the biguanide and the malonamidine (eq. 3). On the other hand, in the conjugated forms of the dications, only one positive charge can be stabilized by delocalization (eq. 4), while the nonconjugated structures for the dications (eq. 5) permit distribution of both positive charges. Therefore, the nonconjugated tautomers should be favored. In the free bases, resonance stabilization must be provided by contributors



biguanide, X = N; malonamidine, X = CH

(12) The pH dependent spectral changes are all reversible; the possibility of destruction of the compounds under basic conditions is, therefore, precluded. When the 0.01 *N* *i*-PrONa solution of phenethylbiguanide hydrochloride was acidified, base line instability, probably caused by accumulation of sodium chloride, rendered the spectrum unreliable. However, reversibility was confirmed by spectra determined on the free base (see Experimental).

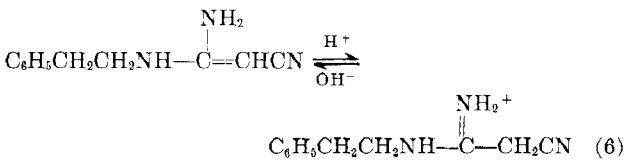
(13) The structures included in the equilibria are preferred over those advanced by Shapiro, *et al.*,[14] for the monocation (i) and the dication (ii) of phenethylbiguanide.



(14) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 2220 (1959).

in which charge separation develops and is, therefore, probably less important than in the protonated forms. This permits no ready prediction for the position of equilibrium of the biguanide free bases, and indeed the energy difference between the two forms is probably quite small. However, the malonamidine free bases have the same forces favoring the "nonenolized" forms as obtain in simple enol–ketone equilibria: namely, the electron promotion energy of enolization, which is apparently sufficiently high to counteract the additional delocalization in the "enol" form.[15]

The ultraviolet spectrum of the cyanoacetamidine hydrochloride IX is also pH dependent. In acidic medium only end absorption appears; in basic solution a maximum develops. These observations are accommodated by equilibrium 6, in which the conjugated system of the base is destroyed by carbon protonation.



(6)

Experimental[17]

2-Cyano-N-phenethylacetamidine Hydrochloride (VII). A.—To a solution of 0.57 g. (0.01 mole) of sodium methoxide in 20 ml. of anhydrous ethanol was added with stirring 1.5 g. (0.01 mole) of ethyl cyanoacetimidate hydrochloride.[6] The mixture was filtered, and 1.2 g. (0.01 mole) of phenethylamine was added to the filtrate. The solution was stirred at room temperature for 30 min. and was concentrated under reduced pressure to a yellow liquid. Acidification with a benzene–hydrogen chloride solution and concentration under reduced pressure gave a yellow gum, which formed a colorless solid upon trituration with ether. Recrystallization from ethanol–ether and then from isopropyl alcohol left 0.62 g. (28%) of colorless microcrystals, m.p. 155–156°. These results were not consistently reproducible. An analytical sample, m.p. 155–156°, was obtained after an additional recrystallization from isopropyl alcohol.

The ultraviolet spectrum exhibits λ_{max} 258 mμ (ε 10,900) in 0.1 *N* sodium hydroxide, end absorption in water.

Anal. Calcd. for $C_{11}H_{13}N_3 \cdot HCl$: C, 59.06; H, 6.27; N, 18.79; Cl, 15.88. Found: C, 59.15; H, 6.17; N, 19.02; Cl, 15.67.

B.—A solution of 6.0 g. (0.04 mole) of ethyl cyanoacetimidate hydrochloride and 4.8 g. (0.04 mole) of phenethylamine in 80 ml. of ethanol was stirred at room temperature for 30 min. and then concentrated under reduced pressure in a 60° bath to a tacky tan solid. Two recrystallizations from isopropyl alcohol afforded 2.2 g. (25%) of colorless crystals, m.p. 155–156°. The melting point was not depressed upon admixture with a sample of 2-cyano-N-phenethylacetamidine hydrochloride described before. These results were not consistently reproducible.

C.—To a solution of 12 g. (0.10 mole) of phenethylamine and 11 g. (0.11 mole) of triethylamine in 200 ml. of dioxane was added with stirring 15 g. (0.10 mole) of ethyl cyanoacetimidate hydrochloride. After 2 hr. at room temperature, the mixture was filtered. The filtrate was concentrated under reduced pressure to a viscous brown liquid, which was suspended in chloroform and acidified with a benzene–hydrogen chloride solution. The supernatant liquid was decanted. Two recrystallizations of the tacky solid residue afforded 4.9 g. (22%) of colorless crystals, m.p. 155–156.5°. The melting point was not depressed upon admixture with authentic 2-cyano-N-phenethylacetamidine hydrochloride. Under these conditions, yields of 20 to 25% were obtained consistently.

Ethyl N-Phenethylamidinoacetimidate Dihydrochloride (IX).—A mixture of 2.05 g. (9.2 mmoles) of 2-cyano-N-phenethylacetamidine hydrochloride, 0.44 g. (9.5 mmoles) of dry ethanol, and 200 ml. of dry ether was saturated with anhydrous hydrogen chloride at 0° with vigorous stirring. The mixture was stirred at room temperature for 20 hr., and the white solid was collected. The product, colorless crystals, m.p. 135° (dec., gas evolution followed by resolidification) amounted to 2.3 g. (81%).

The ultraviolet spectrum exhibits λ_{max} 281 mμ (ε 7700) in methanol solution.

Anal. Calcd. for $C_{13}H_{19}N_3O \cdot 2HCl$: C, 50.98; H, 6.86; N, 13.73; Cl, 23.20. Found: C, 50.68; H, 6.99; N, 14.11; Cl, 23.07.

N-Phenethylmalonamidine Dihydrochloride (II).—A mixture of 1.0 g. (3.3 mmoles) of ethyl N-phenethylamidinoacetimidate dihydrochloride and 100 ml. of isopropyl alcohol containing 3.3 mmoles of ammonia was stirred at room temperature for 2 hr., and the solvent was removed under reduced pressure. Recrystallization of the white solid residue from isopropyl alcohol afforded 0.40 g. (44%) of colorless crystals, m.p. 228–230° dec. Three additional recrystallizations gave colorless prisms, m.p. 231–231.5° dec.

Anal. Calcd. for $C_{11}H_{16}N_4 \cdot 2HCl$: C, 47.65; H, 6.50; N, 20.22; Cl, 25.63. Found: C, 47.48; H, 6.55; N, 19.94; Cl, 25.64.

N-Methyl-N''-phenethylmalonamidine Dihydrochloride.—A solution of 2.0 g. (6.5 mmoles) of ethyl N-phenethylamidinoacetimidate dihydrochloride in 200 ml. of isopropyl alcohol containing 6.5 mmoles of methylamine was stirred at room temperature for 2 hr. The precipitate which separated amounted to 1.3 g. (68%) of colorless plates, m.p. 284–286° dec. Recrystallization from methanol provided the analytical sample, m.p. 284–286° dec.

Anal. Calcd. for $C_{12}H_{18}N_4 \cdot 2HCl$: C, 49.48; H, 6.87; N, 19.24; Cl, 24.00. Found: C, 49.48; H, 7.05; N, 18.95; Cl, 24.53.

Ethyl 2-Cyano-N-phenethylacetimidate (VIII).—To a solution of 4.8 g. (0.04 mole) of phenethylamine in 80 ml. of anhydrous ethanol was added 6.0 g. (0.04 mole) of ethyl cyanoacetimidate hydrochloride.[6] The mixture was stirred at room temperature for 30 min. and then concentrated at room temperature under reduced pressure to a white solid. Recrystallization from isopropyl alcohol afforded 4.5 g. (51%) of colorless crystals, m.p. 70–71°. Two recrystallizations from ethanol provided the analytical sample, m.p. 70–72°.

The ultraviolet spectrum exhibits λ_{max} 256 mμ (ε 22,400) in methanol.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95; OC_2H_5, 20.80. Found: C, 72.18; H, 7.33; N, 13.16; OC_2H_5, 19.90.

Pyrolysis of Ethyl N-Phenethylamidinoacetimidate Dihydrochloride.—Ethyl N-phenethylamidinoacetimidate dihydrochloride, 313 mg. (1.0 mmole), was heated at 150–160° for 15 min. Crystallization of the resulting yellow glass from isopropyl alcohol yielded 89 mg. (37%) of colorless needles, m.p. 166–168°. The melting point was not depressed upon admixture with a sample of N-phenethylamidinoacetamide hydrochloride (XIII) prepared as described later.

Ethyl N-Phenethylamidinoacetate Hydrochloride (XIV).—A mixture of 19.6 g. (0.1 mole) of ethyl ethoxycarbonylacetimidate hydrochloride,[11] λ_{max} 260 mμ (ε 10,000) in 0.1 *N* methanolic sodium methoxide, in 75 ml. of anhydrous ethanol was treated with 5.4 g. (0.095 mole) of sodium methoxide in 25 ml. of ethanol, and the resulting mixture was filtered. To the filtrate was added 12.2 g. (0.1 mole) of phenethylamine. The solution was stirred at room temperature for 3 hr., acidified with ethanolic hydrogen chloride, and concentrated under reduced pressure to a tacky white solid. Two recrystallizations from ethanol afforded 5.2 g.

(15) A molecular orbital explanation for the sites of protonation of biguanides and malonamidines was considered. LCAO-MO calculations for each possible tautomer of the free bases, monocations, and dications were developed, by means of Streitweiser's suggested parameters[16] modified for the specific properties of the atoms in the molecules. The calculated energies were then adjusted to take into account the electron promotion energies involved in "enolization" of the malonamidine derivatives (estimated from the keto-enol equilibrium constant of acetone and LCAO-MO calculations on a simple enamine). While the calculated energies predict qualitatively the positions of the protons in malonamidine, biguanide, and the dications of malonamidine and biguanide, they are ambiguous for biguanide monocation and misleading with respect to malonamidine monocation. The failure to predict the protonation positions in the monocations probably results from the failure of the calculations to take adequate account of stabilization due to delocalization of the positive charge.

(16) A. Streitweiser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 135.

(17) Melting points were taken in capillary tubes in a Hershberg apparatus and are uncorrected. Ultraviolet spectra were determined with a Cary 11 spectrophotometer.

(19%) of colorless prisms, m.p. 129.5–132°. Two additional recrystallizations from isopropyl alcohol gave the analytical sample, m.p. 134.5–135.5°.

The ultraviolet spectrum exhibits λ_{max} 271 mμ (ε 41,000) in 0.1 *N* methanolic sodium methoxide.

Anal. Calcd. for $C_{13}H_{18}N_2O_2 \cdot HCl$: C, 57.67; H, 7.02; N, 10.35; Cl, 13.12. Found: C, 57.64; H, 7.18; N, 10.15; Cl, 13.30.

N-Phenethylamidinoacetamide Hydrochloride (XIII).—A solution of 1.4 g. (5.0 mmoles) of ethyl N-phenethylamidinoacetate hydrochloride in 75 ml. of saturated ammoniacal ethanol was stirred at room temperature for 4 days and then concentrated under reduced pressure to a viscous oil, which slowly crystallized. Recrystallization from isopropyl alcohol afforded 0.6 g. (50%) of colorless needles, m.p. 168.5–169.5°. An additional recrystallization gave the analytical sample, m.p. 169.5–170.5°.

The ultraviolet spectrum exhibits λ_{max} 276 mμ (ε 10,000) in 0.1 *N* methanolic sodium methoxide.

Anal. Calcd. for $C_{11}H_{15}N_3O \cdot HCl$: C, 54.66; H, 6.63; N, 17.39; Cl, 14.70. Found: C, 54.57; H, 6.73; N, 17.38; Cl, 14.57.

N,N″-Diphenethylmalonamidine Dihydrochloride.—To a solution of 0.25 g. (0.011 g.-atom) of sodium in 15 ml. of anhydrous ethanol was added 2.5 g. (0.011 mole) of diethylmalonimidate dihydrochloride[2] and 1.3 g. (0.011 mole) of phenethylamine. The mixture was heated under reflux for 2.5 hr. and filtered. The filtrate was acidified with concentrated hydrochloric acid and concentrated under reduced pressure to an oily yellow solid. Recrystallization from water afforded 1.0 g. (48%) of colorless plates, m.p. 311–313° dec.

Anal. Calcd. for $C_{19}H_{24}N_4 \cdot 2HCl$: C, 59.84; H, 6.82; N, 14.70; Cl, 18.64. Found: C, 59.70; H, 6.93; N, 14.43; Cl, 18.47.

N,N′,N″,N‴-Tetraphenethylmalonamidine Dihydrochloride and Hydrochloride.—A solution of 4.6 g. (0.02 mole) of diethylmalonimidate dihydrochloride,[2] 12.0 g. (0.099 mole) of phenethylamine, and 0.099 mole of ammonia in 300 ml. of anhydrous ethanol was stirred at room temperature for 5 days. The solution was concentrated under reduced pressure to about 75 ml., and the white precipitate (5.3 g.) which separated was collected. This solid was partially dissolved in hot ethanol. The insoluble colorless crystals, m.p. 308–311° dec., amounted to 3.3 g. (43%). The melting point was not depressed upon admixture with authentic N,N″-diphenethylmalonamidine dihydrochloride. The ethanol-soluble fraction was recovered by concentration of the solution to dryness. Recrystallization of the solid residue from acetone, followed by recrystallization from isopropyl alcohol, afforded 0.05 g. (0.4%) of N,N′,N″,N‴-tetraphenethylmalonamidine dihydrochloride as colorless needles, m.p. 193–194°.

Anal. Calcd. for $C_{35}H_{40}N_4 \cdot 2HCl$: C, 71.31; H, 7.13; N, 9.51; Cl, 12.05. Found: C, 71.16; H, 7.31; N, 9.38; Cl, 12.12.

Concentration of the remainder of the original reaction solution under reduced pressure left oily crystals. Two recrystallizations from isopropyl alcohol afforded 1.6 g. (14%) of N,N′,N″,N‴-tetraphenethylmalonamidine hydrochloride as long colorless prisms, m.p. 155–156°. Two more recrystallizations gave the analytical sample, m.p. 157.5–158°.

Anal. Calcd. for $C_{35}H_{40}N_4 \cdot HCl$: C, 76.02; H, 7.42; N, 10.14; Cl, 6.43. Found: C, 75.71; H, 7.53; N, 10.15; Cl, 6.49.

The ultraviolet spectrum of N,N′,N″,N‴-tetraphenethylmalonamidine hydrochloride exhibits λ_{max}^{MeOH} 308 mμ (ε 21,200).

The monohydrochloride was converted to the dihydrochloride with ethanolic hydrogen chloride.

Phenethylbiguanide.—A solution of 2.30 g. (0.10 g.-atom) of sodium in 500 ml. of anhydrous ethanol was prepared, and 24.15 g. (0.10 mole) of phenethylbiguanide hydrochloride was added at room temperature with stirring. After 1 hr., the mixture was filtered, and the filtrate was concentrated to a colorless oil which crystallized on standing. Two recrystallizations from ethanol and three from acetonitrile afforded colorless prisms, m.p. 94–95°.

Anal. Calcd. for $C_{10}H_{15}N_5$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.21; H, 7.22; N, 34.07.

The ultraviolet spectrum exhibits λ_{max} 236 mμ (ε 17,100) in 10^{-5} *N* methanolic hydrochloric acid, 233 (ε 1410) in water, 235 μ (sh) in 0.04 *N* methanolic sodium methoxide, 232 (sh) in acetonitrile or dioxane.

Acknowledgment.—We wish to thank Mr. L. M. Brancone and associates for the analytical data and Mr. W. Fulmor and associates for ultraviolet spectra

Synthesis of Azoxy Compounds from Nitrosohydroxylamine Tosylates[1]

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A convenient synthesis of azoxy compounds from organonitrosohydroxylamine tosylates, R—N(→O)=N—OTs, and Grignard reagents is outlined. Displacement on sulfur, with the expulsion of nitrosohydroxylamine anion and the formation of sulfones, predominated when the nitrosohydroxylamine tosylates were exposed to nucleophiles such as phenyllithium, alkoxides, and phenoxides. The azoxy ether structure, R—N(→O)=N—OR′, is assigned to the stable alkylation products of organonitrosohydroxylamines.

Unsymmetrical azoxy compounds usually are obtained by oxidation of an unsymmetrical azo compound,[2,3] by condensation of a nitroso compound and an hydroxylamine[4,5] or by selective substitution on an aromatic azoxy compound.[5,6] The first two methods often give a mixture of isomers.

More selective methods, such as the oxidation of indazole oxides[7] or the reaction of Grignard reagents, and the stable alkylation products of organonitrosohydroxylamines[8] also are reported.

An attractive approach to a general synthesis of azoxy compounds would be one where the R—N(→O)=N— group possessed a substituent capable of easy displace-

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(2) See C.-S. Hahn and H. H. Jaffé [*J. Am. Chem. Soc.*, **84**, 949 (1962)] for references and a table of properties of substituted azoxybenzenes.

(3) Oxidation of hydrazones has produced many azoxy compounds: B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **27**, 413 (1962).

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