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A Facile Synthesis of Piperazines from Primary Amines (I)

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A general procedure is described for converting primary amines to *N*-substituted piperazines. Reaction of an amine with an *N*-substituted iminodiacetic acid anhydride (V) yields an iminodiacetic acid monoamide (VI) which closes to a 2,6-piperazinedione (VII) upon treatment with acetic anhydride. The diones are reduced to piperazines with borane-THF. Fourteen examples of this process, using twelve aliphatic or aromatic amines and three iminodiacetic acids, are presented. Yields of piperazines, based upon starting amine, ranged from 21 to 52%. The procedure is rapid and no purification problems were encountered. Alternate methods for preparing the 2,6-piperazinedione intermediates are discussed.

During a synthetic program directed toward potential antimalarial agents, it was necessary to prepare several 1,4-disubstituted piperazines from a primary aromatic amine. The procedures of Prelog (2) and Pollard (3), utilizing bis(2-haloethyl)amines and bis(2-hydroxyethyl)amines respectively, have been widely used to effect this conversion, but both proved inadequate in the present case and another was sought. Reduction of a 2,6-piperazinedione (*e.g.*, II), wherein R₄ and its attached nitrogen are provided by the primary amine, appeared *a priori* to be an attractive alternate possibility. The additional five atoms of the piperazine ring would thus be provided by an iminodiacetic acid moiety (*e.g.*, Ia), several of which (*N*-unsubstituted, *N*-methyl, and *N*-benzyl) are commercially available. Examination of the literature revealed three examples of lithium aluminum hydride reductions of such diones to piperazines (4-6) although, in each case, the goal of the work was not the incorporation of a primary amine into the ring.

Chase and Downs (4) used this procedure to prepare isotopically labeled 1-methylpiperazine (IIIa) by reduction of 4-methylpiperazine-2,6-dione (IIa). The dione was obtained by fusion of *N*-methyliminodiacetic acid (Ia) with urea. More recently, Cignarella (5) prepared *cis*-2,6-dimethylpiperazine (IIIb) by a similar reduction of 1-benzyl-*cis*-3,5-dimethyl-2,6-piperazinedione (IIb) followed by removal of the benzyl group by catalytic hydrogenolysis. In this case, the dione was obtained by thermal ring closure of the iminodiacetic acid monoethyl ester monobenzylamide (Ib). Both papers report excellent yields. Roderick, Platte, and Pollard (6), however, found that a similar sequence (Ic → IIc → IIIc) leading to 2-phenylpiperazine (IIIc) gave poor yields and they abandoned it. A patent has been granted (7) for a procedure involving alkylation of the *N*-sodio derivative of IIa followed by lithium aluminum hydride reduction of the resulting 1,4-disubstituted dione.

To apply this route to substituted piperazines, an

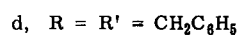
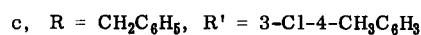
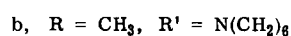
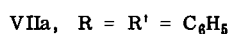
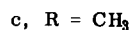
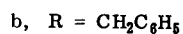
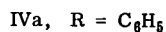
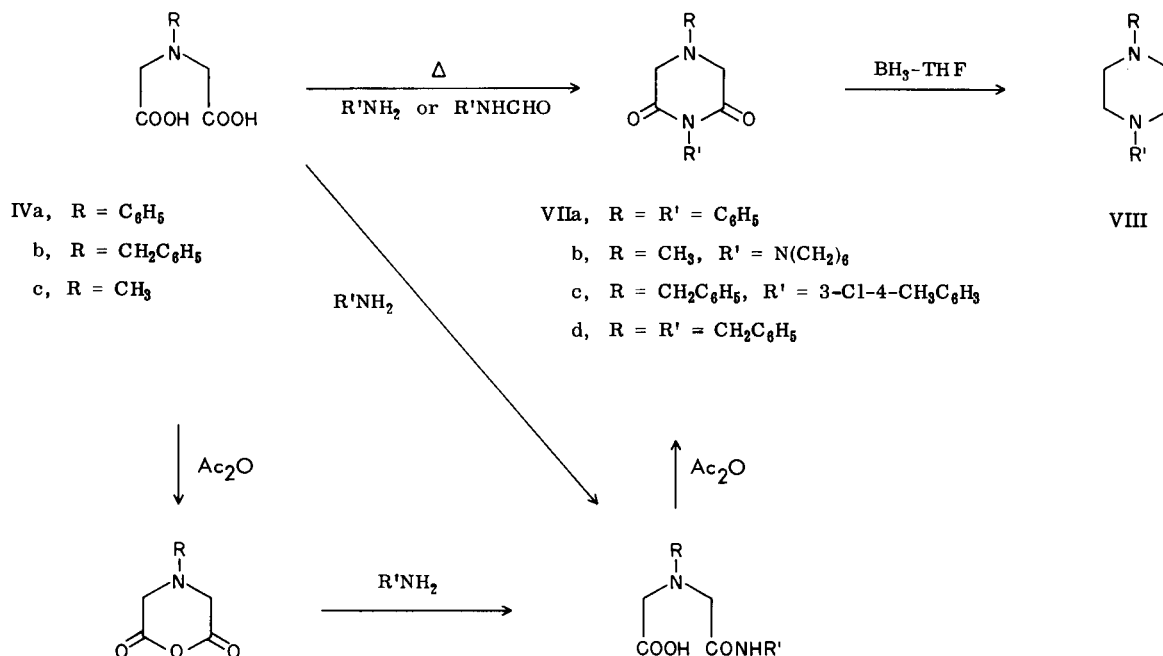
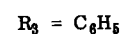
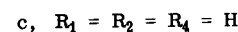
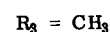
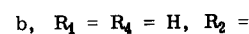
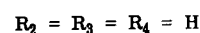
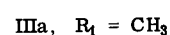
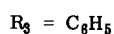
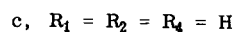
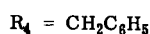
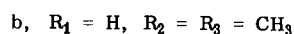
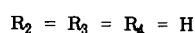
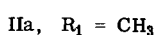
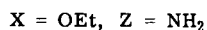
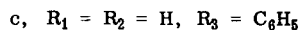
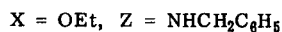
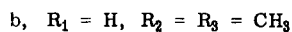
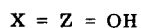
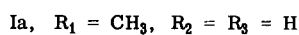
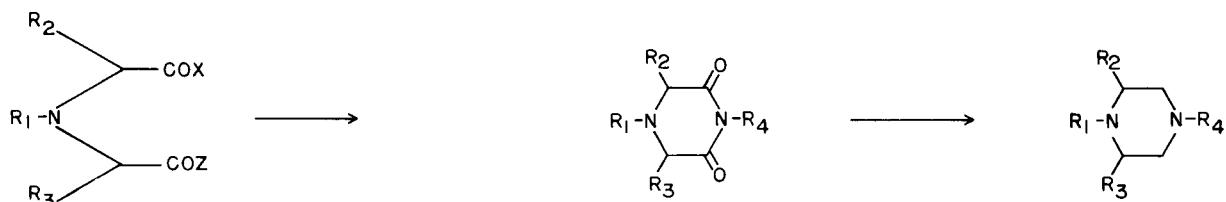
efficient method of preparing the 2,6-diones from primary amines is necessary. In addition to the examples already mentioned, Bischoff and Hausdorfer (8) accomplished this transformation in unstated yield by fusion of the *N*-phenyliminodiacetic acid (IVa) with aniline to give *N*-phenyliminodiacetic acid monoanilide (VIa). Acetic anhydride treatment of the monoanilide gave 1,4-diphenyl-2,6-piperazinedione (VIIa). These workers also reported that *N*-phenyliminodiacetic acid (IVa) could be cyclized to the anhydride (Va) by treatment with acetic anhydride (9). When allowed to react with aniline at 150°, the anhydride opened to give the already known monoanilide (VIa). The patent literature reports that the 2,6-diones can be prepared by fusion of iminodiacetic acids with *N*-formyl derivatives of primary amines (10).

Preliminary evaluation of the various possible routes from IV to VII indicated that the most generally reliable was via anhydride V and monoamide VI. Although the longest sequence in terms of number of steps, it proved quite convenient procedurally and the transformation from primary amine to *N*-substituted piperazine was accomplished readily and rapidly. As the overall sequence appeared to have practical potential as a general synthetic method, its scope was investigated by employing various combinations of three *N*-substituted iminodiacetic acids and twelve primary aromatic or aliphatic amines.

Surprisingly, the only anhydride of an *N*-substituted iminodiacetic acid that was found in the literature was the *N*-phenyl derivative of Bischoff and Hausdorfer (9,11). *N*-Benzyl and *N*-methyliminodiacetic acids (IVb and IVc) also readily formed anhydrides (Vb and Vc) when refluxed briefly (5-30 minutes) in acetic anhydride. The rate of anhydride formation appeared to be governed by the solubility of the acids in the reaction medium, the *N*-benzyl and *N*-phenyl derivatives dissolving more rapidly than the *N*-methyl. The cyclic anhydrides were not stable to heat and prolonged refluxing produced

progressively darker reaction mixtures containing tarry byproducts. When powdered before use, the *N*-methyl acid reacted much more rapidly. The *N*-benzyl and *N*-methyl cyclic anhydrides were isolated by removal of excess acetic anhydride *in vacuo* at 100° and were used without purification. The *N*-phenyl anhydride (9) is a more stable crystalline compound which can be readily stored. A sample

of *N*-methyliminodiacetic acid anhydride (Vc), isolated by gas-liquid chromatography, gave a good microanalysis and had an infrared spectrum little different from that of the crude product employed in the synthetic experiments. The *N*-benzyl anhydride (Vb) was insufficiently stable to survive either gas-liquid chromatography or low pressure distillation and was not characterized beyond its



VIII

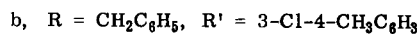
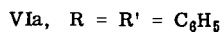
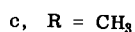
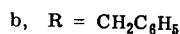
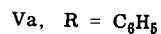


TABLE I
Percent Yields of Intermediates and Final Products in the Preparation of
N,N'-disubstituted Piperazines from Primary Amines and *N*-substituted Iminodiacetic Acids

Example	Amine	Iminodiacetic Acid <i>N</i> -substituent	Monoamide (VI)	Dione (VII)	Piperazine (VIII)	Over-all
			% Yield			
A	Aniline	CH ₃	82	77	64	40
B	Aniline	CH ₂ C ₆ H ₅	75	48	58	21
C	3-chloro- <i>p</i> -toluidine	CH ₃	83	77	69	44
D	3-chloro- <i>p</i> -toluidine	CH ₂ C ₆ H ₅	(a)	62 (b)	51	32
E	3-chloro- <i>p</i> -toluidine	C ₆ H ₅	84	69	60	35
F	3-nitroaniline	CH ₂ C ₆ H ₅	87	82	72	51
G	3-amino-6-methylbiphenyl	CH ₃	82	72	66	39
H	3-amino-6-methylbiphenyl	CH ₂ C ₆ H ₅	94	63	59	35
I	3-aminopyridine	CH ₂ C ₆ H ₅	91	80	71	52
J	4,4'-diaminodiphenylmethane	CH ₃	89	67	49	29
K	benzylamine	CH ₂ C ₆ H ₅	{ 61 (a)	{ 45 56 (c)	{ 54 85	{ 30 31
L	benzylamine	C ₆ H ₅	(a)	37 (c)	40	25
M	isopropylamine	CH ₃	79	79	60	34
N	<i>N</i> -aminomopiperidine	CH ₃	79	75	-	-
O	<i>t</i> -butylamine	CH ₃	100	0 (d)	-	-
P	2-aminothiazole	CH ₃	0 (e)	-	-	-

(a) Not isolated. (b) By fusion of *N*-formyl-3-chloro-*p*-toluidine and *N*-benzyliminodiacetic acid. (c) Combined yield over two steps. (d) The monoamide decomposed during the ring closure reaction. (e) 2-Aminothiazole failed to react with *N*-methyliminodiacetic acid anhydride under the standard reaction conditions.

TABLE II

Time (minutes)	Yield (%)	
	VIIc	VIIId
30	27	29
60	50	35
120	58	41
180	62	53
360	57	33

infrared spectrum. When exposed to the atmosphere, the *N*-methyl and *N*-benzyl anhydrides soon became cloudy and solids precipitated out after a short time. This behavior was not specifically investigated, but was assumed to be due to hydrolysis back to the starting iminodiacetic acids. The presence of tertiary amino groups in these molecules would be expected to markedly accelerate such a hydrolysis.

The conversion of a cyclic anhydride to an iminodiacetic acid monoamide (VI) was effected by treatment of a solution of the anhydride with one equivalent of a primary amine. Benzene, the usual solvent for the reaction, was convenient because the monoamide products were nearly always insoluble and precipitated from solution as they formed. The exothermic reaction occurred immediately at room temperature. The products were usually crystalline solids which were isolated in 80–90% yield by simple filtration. When crystalline products were not obtained, the solvent was removed *in vacuo* and the subsequent acetic anhydride ring closure step was performed on the residue. A few of the iminodiacetic acid monoamides were characterized by microanalyses but the majority were cyclized to 2,6-piperazinediones (VII) without further purification. One of the primary amines to which this synthesis was applied, 2-aminothiazole, failed to react cleanly with a cyclic anhydride and no product was isolated.

Ring closure of the iminodiacetic acid monoamides to 2,6-piperazinediones was effected by heating them for a few minutes with acetic anhydride. Removal of the excess anhydride by volatilization *in vacuo* left the crude diones which were typically recrystallized once from methanol to give pure products in about 70% yield. The few liquid diones were distilled at reduced pressure.

Although lithium aluminum hydride had already been established as a suitable reagent for the reduction of the diones to piperazines (4, 5), the use of borane-THF for this purpose appeared to offer some advantages, such as simpler workup and more functional group selectivity. Brown and Heim (12) reported the use of borane-THF for the efficient reduction of amides to amines but did not apply it to imides. Our reduction proceeded smoothly via a modification of Brown's procedure to give yields of piperazines averaging about 60%. The reaction usually did not appear to be quite complete, in spite of prolonged reflux times and a large excess of borane-THF, since some carbonyl containing contaminants were present in the crude products.

This problem was also reported with the lithium aluminum hydride reduction of the 3-phenyl-2,6-piperazinedione of Roderick, *et. al.*, (6). In practice, this difficulty was circumvented by incorporating an acidic hydrolysis of the crude product as part of the workup of the reduction step. This served to convert unreduced amide byproducts to amino acids which remained in solution when the hydrolysis mixture was made alkaline. The piperazine products thus precipitated were usually oils which could be isolated in a pure state either as crystalline oxalic acid salts or by distillation.

In one case, borane-THF reduction did not produce the expected piperazine and it was found necessary to employ lithium aluminum hydride. The use of borane-THF on 1-(*N*-homopiperidyl)-4-methyl-2,6-piperazinedione (VIIb) apparently resulted in cleavage of the N-N bond and only low boiling products were encountered.

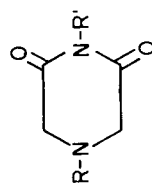
Table I summarizes the sixteen examples to which this synthetic procedure was applied. Percent yields are given for each step and for the overall conversion of primary amine to piperazine. The average overall yield was 36%, ranging from 21 to 52%.

In most cases, the complete procedure was carried out only once and never more than twice. The scale utilized for this study was typically 10 to 50 mmoles of starting amine. A somewhat larger scale was more convenient when liquid dione intermediates were encountered, as in examples M and N, since distillative purification was necessary. Oxalate salts were used to isolate and characterize the piperazines in about half of the examples to eliminate the necessity of distilling relatively small quantities of the frequently oily free bases. Distillation, as used in examples I, M, and N, would probably be the preferred method of isolation for nearly all of the piperazines if the synthesis were carried out on a larger scale.

Brief studies were carried out on alternate methods of converting the starting primary amine to the 2,6-piperazinedione. In two cases, direct fusion of *N*-benzyliminodiacetic acid with the primary amine at 200° gave moderate yields of the dione. In this way diones VIIc and VIIId were prepared in 49 and 34% yield respectively. This method failed, however, when applied to *m*-nitroaniline and 3-amino-pyridine using *N*-benzyl and *N*-methyliminodiacetic acids, respectively.

One attempt was made to reduce the number of manipulative steps required to go from the iminodiacetic acid to the dione. The amount of acetic anhydride used to convert IVb to its anhydride (Vb) was reduced to the theoretical one equivalent and 3-chloro-*p*-toluidine was added directly to the cooled reaction mixture, which presumably contained only Vb and acetic acid. The amine was followed, after a few minutes, by another equivalent of acetic anhydride to cyclize the intermediate monoamide (VIb). Although a simpler procedure resulted from these modifications, only a 29% yield of dione VIIc was obtained.

TABLE III
2,6-Piperazinediones



Example	R	R'	Mp or Bp °C	Recryst. Solvent	Empirical Formula	Calcd. % C H	Found % C H
A	CH ₃	C ₆ H ₅	127-129	MeOH	C ₁₁ H ₁₂ N ₂ O ₂	64.7 5.93	64.8 5.75
B	CH ₂ C ₆ H ₅	C ₆ H ₅	127-128.5	heptane, C ₆ H ₆	C ₁₇ H ₁₆ N ₂ O ₂	72.8 5.75	73.0 5.76
C	CH ₃	3-Cl-4-CH ₃ C ₆ H ₃	116-118	MeOH, EtOAc	C ₁₂ H ₁₃ ClN ₂ O ₂	57.0 5.18	57.2 4.95
D	CH ₂ C ₆ H ₅	3-Cl-4-CH ₃ C ₆ H ₃	180-183	MeOH	C ₁₈ H ₁₇ ClN ₂ O ₂	65.7 5.21	65.6 4.88
E	C ₆ H ₅	3-Cl-4-CH ₃ C ₆ H ₃	168-172	EtOH	C ₁₇ H ₁₅ ClN ₂ O ₂	64.8 4.80	65.0 4.82
F	CH ₂ C ₆ H ₅	3-NO ₂ C ₆ H ₄	146-147.5	EtOAc	C ₁₇ H ₁₅ N ₂ O ₄	62.8 4.65	62.9 4.50
G	CH ₃	3-(C ₆ H ₅)-4-CH ₃ C ₆ H ₃	119.5-121.5	MeOH	C ₁₈ H ₁₈ N ₂ O ₂	73.4 6.16	73.5 5.75
H	CH ₂ C ₆ H ₅	3-(C ₆ H ₅)-4-CH ₃ C ₆ H ₃	107-108.5	MeOH	C ₂₄ H ₂₂ N ₂ O ₂	77.8 5.99	73.4 6.00
I	CH ₂ C ₆ H ₅	3-pyridyl	141-143	MeOH, EtOAc	C ₁₆ H ₁₅ N ₃ O ₂	68.3 5.38	68.3 5.31
J	CH ₃		215-220	EtOH	C ₂₃ H ₂₄ N ₄ O ₄	65.7 5.75	65.4 5.67
K	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅	55.5-57.5	MeOH	C ₁₈ H ₁₈ N ₂ O ₂	73.5 6.17	73.8 6.14
L	C ₆ H ₅	CH ₂ C ₆ H ₅	105-107	MeOH	C ₁₇ H ₁₆ N ₂ O ₂	72.8 5.75	73.2 5.66
M	CH ₃	CH(CH ₃) ₂	91-97/3.0 mm	-	C ₈ H ₁₄ N ₂ O ₂	56.4 (a) 8.29	56.4 8.05
N	CH ₃	N(CH ₂) ₆	140-143/0.6 mm	-	C ₁₁ H ₁₉ N ₃ O ₂	58.7 8.50	58.5 8.35

(a) Analytical specimen collected by gas-liquid chromatography (Column: 2' x 3/8" 15% Apiezon L on Chromosorb W-HMDS. Conditions: 168°, 100 ml. He/minute. Retention time: 3.2 minutes).

The use of *N*-formylamines to prepare 2,6-piperazinediones by fusion with iminodiacetic acids was also investigated by a short series of experiments. The *N*-formyl derivatives of benzylamine and 3-chloro-*p*-toluidine were heated at 190° with equimolar amounts of *N*-benzyliminodiacetic acid for varying periods. The yields of diones VIIc and VIId thus obtained, after a standard workup procedure, are reported in Table II. Under these conditions peak yields were obtained in both cases at three hours and fell off after that. Higher yields could no doubt have been obtained if the formamide were not the limiting reagent and could be used in excess. This was the case in the patent procedures previously cited (10).

In summary, the described procedure provides a general route from primary amines to *N,N'*-disubstituted piperazines where the second *N*-substituent is provided by an *N*-substituted iminodiacetic acid. It may be applied to both aromatic and aliphatic amines and to bis-amines (e.g., example J). The piperazine product may be *N,N'*-diaryl, *N,N'*-dialkyl, or *N*-aryl-*N'*-alkyl substituted. It is useful in cases where other functional groups, such as tertiary amines, would make the use of an alkylating procedure (2,3) questionable. The procedure also is not limited to carbon substituents on the piperazine nitrogen. For example, the piperazine ring prepared in example N is also part of a tetrasubstituted hydrazine moiety. As has been demonstrated by others (4,5) the method may be applied to cases where 3- and/or 5-substituted piperazines are desired. *N*-Monosubstituted piperazines bearing only the single *N*-substituent of the original primary amine may be obtained by use of *N*-benzyliminodiacetic acid in the process. The benzyl group of the resulting product can then be removed by catalytic hydrogenolysis (5,13). The method is limited mainly by the reduction step which excludes substituents in the diones sensitive to borane or lithium aluminum hydride. The failure of *t*-butylamine and 2-aminothiazole (Examples O and P) represent potential limitations in applicable amine types, although modification of reaction conditions or use of other routes to the dione might circumvent the problems encountered with these amines.

Other *N*-substituted iminodiacetic acids may be prepared by alkylation of primary aliphatic amines (4,14) or *N*-arylglycines (8,15) with chloroacetic acid.

Tables III and IV provide preparative and characterization data for new 2,6-piperazinediones and piperazines prepared in this work. The 2,6-piperazinediones were also characterized by their infrared spectra. Their most diagnostic feature was the split carbonyl absorption at 5.70-5.77 μ (weak) and 5.89-5.98 μ (strong) associated with the cyclic imide. The structures of many of the piperazines of Table IV were confirmed by their NMR spectra. These data are presented in the experimental section.

EXPERIMENTAL (19)

All starting materials except *N*-phenyliminodiacetic acid and 3-amino-6-methylbiphenyl were commercially available and were used as obtained from the supplier.

Iminodiacetic Acid Monoamides. General Procedure.

The *N*-methyl and *N*-benzyliminodiacetic acid anhydrides were prepared by refluxing the iminodiacetic acids in five times their weight of acetic anhydride until essentially all had dissolved (5-30 minutes). The excess acetic anhydride and acetic acid were removed under reduced pressure at 100° until a nearly constant weight of residue remained (usually slightly more than theoretical). The brown oily residue of cyclic anhydride was taken up in benzene (10-20% solution) and, if necessary, the solution was filtered through glass wool. When *N*-methyliminodiacetic acid was used, a few small lumps frequently failed to dissolve. The benzene solution was then treated at room temperature with an equivalent of primary amine, usually as a 10-25% solution in benzene. In all cases except 2-aminothiazole, the mixture warmed spontaneously at once. The reaction mixture was usually further warmed very briefly on the steam bath (2-3 minutes). At this point or upon cooling, the crystalline monoamide precipitated from solution in examples C, G, I, M, and O. In examples A, B, F, H, and N, the products oiled out but were readily induced to crystallize by vigorous stirring and cooling. In example J (*N*-benzyliminodiacetic acid anhydride and benzylamine) the monoamide was soluble in benzene and partially oiled out upon addition of a little ether. Crystallization occurred after overnight storage at 0°. Two equivalents of *N*-methyliminodiacetic acid anhydride were used per equivalent of 4,4'-diaminodiphenylmethane in example J and the reaction was carried out in dimethylformamide instead of benzene. The *bis*-amide crystallized spontaneously from solution.

N-Phenyliminodiacetic acid anhydride was prepared from *N*-phenyliminodiacetic acid (15e) according to the literature procedure (9). Acetone, rather than benzene, was used to dissolve this anhydride (better solubility) and the amines were introduced in benzene solution. In example L (benzylamine) the monoamide was soluble in the acetone-benzene reaction medium and could not be induced to crystallize. In example E, the second use of *N*-phenyliminodiacetic acid anhydride, the monoamide crystallized readily from solution.

The crystalline monoamides were filtered off, washed with a little of the reaction solvent, and dried. In all cases, they were converted to 2,6-piperazinediones without further purification. In examples B and G the monoamide structures were confirmed by microanalysis.

N'-Phenyl-*N*-benzyliminodiacetic Acid Monoamide (Example B).

This compound, prepared by the general procedure, was recrystallized from aqueous ethanol for analysis, m.p. 138.5-139.5°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.4; H, 6.08. Found: C, 68.2; H, 5.97.

N'-(2-Methyl-5-biphenyl)-*N*-methyliminodiacetic Acid Monoamide (Example G).

This compound was obtained as a monohydrate, m.p. 203-206°, upon recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{16}H_{20}N_2O_3 \cdot H_2O$: C, 65.4; H, 6.72. Found: C, 65.6, 65.4; H, 6.57, 6.43.

N-Methyliminodiacetic Acid Anhydride (Vc).

An analytical specimen was obtained by preparative gas-liquid chromatography of the material used for synthetic work. (Column: 600 x 9 mm, 15% Apiezon L on Chromosorb W-HMDS. Conditions: 147°, 75 ml. He/min. Ret. time: 3.7 minutes). The colorless liquid obtained after one passage through the column was analyzed. Infrared spectrum: λ max (film), 3.40, 3.60, 5.48 (strong), 5.62 (strong), 6.88, 7.50, 7.80, 7.90, 8.26, 9.0 (strong, broad), 9.62, 10.50 (strong), 10.76, 12.06, 12.31 μ .

Anal. Calcd. for $C_5H_7NO_3$: C, 46.5; H, 5.46. Found: C, 46.3; H, 5.52.

2,6-Piperazinediones from Iminodiacetic Acid Monoamides. General Procedure.

The isolated monoamides were heated at reflux in five times their weight of acetic anhydride for approximately 5 minutes after they had dissolved. A total of 10 minutes heating usually sufficed except for the highly insoluble *bis*-amide of example J, which required 20 minutes. The excess acetic anhydride and acetic acid were removed under reduced pressure at 100° and the residue was purified by an appropriate method. In examples A, C, D, E, F, I, and J, the crude dione residues were crystalline and were recrystallized from a suitable

solvent. The crude diones in examples B, G, H, K, and L were syrups or glasses but readily crystallized from solution. A single vacuum distillation effectively purified the diones of examples M and N, which were liquids at room temperature. Table III summarizes data on the 2,6-piperazinediones.

1,4-Disubstituted Piperazines. General Procedure.

A solution (5-20%) of the 1,4-disubstituted-2,6-piperazinedione in anhydrous tetrahydrofuran (THF) was added dropwise over 5-30 minutes (depending on the scale of the experiment) to 3-4 molar equivalents of 1 M borane in THF (Metal Hydrides Incorporated, Beverly, Massachusetts). The mixture was stirred and cooled in an ice bath during the addition. After completion of the addition, the mixture, which sometimes contained a white precipitate, was refluxed for 2 hours. During the heating up to reflux period, a moderately vigorous exothermic reaction occurred on the larger scale runs when the internal temperature had risen to ca. 40-50°. Considerable gas was evolved during this period, presumably the excess borane. The cooled reaction mixture was treated carefully with ca. 15 molar equivalents (based on dione) of 6N hydrochloric acid and was then heated for 1 hour on the steam bath. The solvent boiled off during the first few minutes of heating. The addition of the hydrochloric acid had to be done with care, initially, due to vigorous evolution of hydrogen. The mixture was cooled and treated with excess ammonium hydroxide to precipitate the product. Oils were isolated by extraction with ether and solids by filtration. Thin-layer chromatography of the crude products (silica gel, methanol) usually indicated only minor contaminants. Vacuum distillation, oxalate salt formation or recrystallization was used to effect final purification.

Oxalate salts were prepared by addition of a warm acetone solution (ca. 10%) of one molar equivalent of oxalic acid to 10-20% acetone solutions (warm) of the crude piperazines. The products crystallized immediately upon mixing, or after brief cooling, and were washed with acetone. A dark color often developed soon after mixing the nearly colorless solutions, but the acetone wash removed most of this from the crystalline salts.

1-Methyl-4-(1-homopiperidyl)piperazine (Example N) by Lithium Aluminum Hydride Reduction.

A solution of 9.8 g. (43.5 mmoles) of 1-methyl-4-(1-homopiperidyl)-piperazine-3,5-dione in 50 ml. of tetrahydrofuran was added dropwise with stirring to an ice-cooled mixture of 6.6 g. (174 mmoles) of lithium aluminum hydride in 75 ml. of tetrahydrofuran. After the addition was complete, the mixture was refluxed for 2 hours and, while cooling, was carefully treated dropwise with water until the gray color of the salts became white. The mixture was filtered and the salts were thoroughly washed with more tetrahydrofuran. The residue (8.0 g.), after removal of solvent *in vacuo*, was distilled at reduced pressure (6 mm). The product (5.2 g., 60%) was collected at 125-127°. This material gave slightly low analytical values for carbon (0.6%) and the analytical sample was collected by preparative gas-liquid chromatography (Column: 6" x 3/8" 15% DC 550 on Chromosorb W. Conditions: 195°, 300 ml. He/min. Retention time: 5.2 minutes).

NMR Spectra.

Compounds listed refer to Table IV. Spectra were taken on the free bases and, unless otherwise specified, in carbon tetrachloride with tetramethylsilane as internal reference.

1-Methyl-4-phenylpiperazine (Example A).

Data: τ 2.8-3.0 (multiplet, 2H, *m*-ArH), 3.2-3.4 (multiplet, 3H, *o*,*p*-ArH), 6.93 (irregular triplet, 4H, ArNCH₂), 7.60 (irregular triplet, 4H, CH₂NCH₂), 7.80 (singlet, 3H, NCH₃).

1-Benzyl-4-phenylpiperazine (Example B).

Data: τ 2.65-3.02 (multiplet, 7H, ArH), 3.18-3.42 (multiplet, 3H, *o*,*p*-NArH), 6.54 (singlet, 2H, ArCH₂N), 6.80-6.98 (multiplet, 4H, ArNCH₂), 7.40-7.56 (multiplet, 4H, ArCH₂NCH₂).

1-Benzyl-4-(3-chloro-*p*-tolyl)piperazine (Example D).

Data: τ 2.80 (narrow multiplet, 5H, C₆H₅), 3.07 (doublet, 1H in 5-position of toluidine ring, J_O = 8 cps), 3.26 (doublet, 1H in 2-position of toluidine ring, J_M = 2.5 cps), 3.46 (quartet, 1H in 6-position of toluidine ring, J_O = 8 cps, J_M = 2.5 cps), 6.55 (singlet, 2H, ArCH₂N), 6.85-7.04 (multiplet, 4H, ArCH₂NCH₂), 7.88 (singlet, 3H, ArCH₃).

1-Phenyl-4-(3-chloro-*p*-tolyl)piperazine (Example E).

Data: τ 2.65-3.45 (multiplet, 8H, ArH), 6.10 (singlet, 8H, NCH₂), 7.75 (singlet, 3H, ArCH₃).

1-Methyl-4-(3-phenyl-*p*-tolyl)piperazine (Example G).

Data: τ 2.6-3.1 (multiplet, 6H, ArH), 3.30-3.44 (multiplet, 2H, *o*-NArH), 6.86-7.06 (multiplet, 4H, ArNCH₂), 7.50-7.70 (multiplet, 4H, CH₂NCH₂), 7.83 (singlet, 3H, NCH₃), 7.94 (singlet, 3H, ArCH₃).

1-Benzyl-4-(3-phenyl-*p*-tolyl)piperazine (Example H).

Data: τ 2.60-2.95 (multiplet, 10H, C₆H₅), 3.00-3.12 (multiplet, 1H, *m*-NArH), 3.30-3.50 (multiplet, 2H, *o*-NArH), 6.57 (singlet, 2H, ArCH₂N), 6.85-7.05 (multiplet, 4H, ArNCH₂), 7.43-7.64 (multiplet, 4H, ArCH₂NCH₂), 7.92 (singlet, 3H, ArCH₃).

1-Benzyl-4-(3-pyridyl)piperazine (Example I).

Data: τ 1.80-1.90 (multiplet, 1H, 6-position of pyridine ring), 2.00-2.12 (multiplet, 1H, 2-position of pyridine ring), 2.80 (singlet, 5H, C₆H₅), 3.00-3.10 (multiplet, 2H, 4 and 5 positions of pyridine ring), 6.54 (singlet, 2H, ArCH₂N), 6.80-6.95 (multiplet, 4H, ArNCH₂), 7.40-7.55 (multiplet, 4H, ArCH₂NCH₂).

4,4'-Bis(1-methyl-4-piperazinyl)diphenylmethane (Example J) (CDCl₃).

Data: τ 2.98 (skewed doublet, 4H, *m*-NArH, J = 9 cps), 3.22 (skewed doublet, 4H *o*-NArH, J = 9 cps), 6.23 (singlet, 2H, ArCH₂Ar), 6.78-6.96 (multiplet, 8H, ArNCH₂), 7.36-7.54 (multiplet, 8H, CH₂NCH₂), 7.70 (singlet, 6H, NCH₃).

1-Methyl-4-isopropylpiperazine (Example M).

Data: τ 7.46 (heptet, J = 6 cps, NCH(CH₃)₂, partially obscured), 7.26-7.82 (multiplet, including heptet, 9H, NCH(CH₃)₂, NCH₂), 7.90 (singlet, 3H, NCH₃), 9.04 (doublet, 6H, J = 6 cps, CHCH₃).

1-Methyl-4-(*N*-homopiperidyl)piperazine (Example N).

Data: τ 7.2-7.5 (multiplet, 8H, CH₂NNCH₂), 7.60-7.80 (multiplet, 4H, CH₂NCH₂), 7.90 (singlet, 3H, NCH₃), 8.48 (slightly broadened singlet, 8H, NCH₂CH₂).

Preparation of 2,6-Piperazinediones by Fusion of *N*-Benzyliminodiacetic Acid with Primary Amines. 1-(3-Chloro-*p*-tolyl)-4-benzyl-2,6-piperazinedione (VIIc).

A mixture of 2.23 g. (10 mmoles) of *N*-benzyliminodiacetic acid and 1.42 g. (10 mmoles) 3-chloro-*p*-toluidine was heated at 200° for 0.5 hour in an oil bath. The initially pasty mass soon liquified and bubbled moderately. Gas evolution had essentially ceased after 0.5 hour. The mixture was cooled and boiled with 20-25 ml. of methanol while lumps were broken up with a stirring rod. A finely divided crystalline suspension of product replaced the initial amorphous melt. The suspension was cooled and filtered and the product was washed with methanol. The yield of almost colorless product, m.p. 178-182°, was 1.60 g. (49%). Data for the analytical specimen are in Table III.

1,4-Dibenzyl-2,6-piperazinedione (VIIId).

A mixture of 1.12 g. (5.0 mmoles) of *N*-benzyliminodiacetic acid and 0.55 ml. (0.54 g., 5.0 mmoles) of benzylamine was heated at 200° for 1 hour. It was initially stirred by hand until homogeneous (ca. 5 minutes). The reaction mixture was cooled and dissolved in 12 ml. of methanol. Cooling to 0° and seeding caused precipitation of 0.51 g. (34%) of crystalline product. It was collected by filtration, washed with cold methanol, and dried, m.p. 55-56.5°. Data for the analytical specimen are in Table III.

When 3-aminopyridine and 3-nitroaniline were treated under the same conditions with *N*-methyliminodiacetic acid and *N*-benzyliminodiacetic acid, respectively, very dark melts were obtained from which no crystalline products could be isolated.

Preparation of 2,6-Piperazinediones by Fusion of *N*-Benzyliminodiacetic Acid with *N*-Formyl Amines. 1-(3-Chloro-*p*-tolyl)-4-benzyl-2,6-piperazinedione (VIIc).

A mixture of 2.23 g. (10 mmoles) of *N*-benzyliminodiacetic acid and 1.69 g. (10 mmoles) *N*-formyl-3-chloro-*p*-toluidine in a 15-cm. test tube was heated at 190° in an oil bath for varying periods (Table II). The mixture was stirred by hand for a few minutes at the beginning of the heating period until it became homogeneous. A gentle stream of nitrogen was passed into the tube during the reaction to aid in removal of the evolved water and formic acid. After the heating period the melt was swirled, while cooling under the tap, to evenly coat the inside of the reaction tube and thus facilitate its dissolution in methanol. The glassy reaction product was boiled with 15 ml. of methanol while it was being scraped with a stirring rod to hasten its conversion to a finely divided crystalline suspension. When all amorphous material was gone, the mixture was cooled in ice and filtered. The precipitate of product was washed with a little cold methanol and, air dried. All samples thus prepared melted between 177 and 183°

(indicating satisfactory purity) except that obtained from the 360 minute run. It had a darker color and melted at 170-178°.

The *N*-formyl-3-chloro-*p*-toluidine used in these experiments was prepared by heating a mixture of 10.0 g. (71 mmoles) of 3-chloro-*p*-toluidine and 50 ml. of 90% formic acid for 0.5 hour at 100°. After excess formic acid had been thoroughly removed *in vacuo* at 100°, the residue of product crystallized upon slight cooling. The yield was 12.3 g. (theoretical amount, 12.0 g.). It was used without further purification, m.p. 90-95°, lit. m.p. (20) 97-97.5°.

1,4-Dibenzyl-2,6-piperazinedione (VIIId).

The reactions of this series of experiments were performed in the same manner as the preceding series, using *N*-benzylformamide instead of *N*-formyl-3-chloro-*p*-toluidine. The cooled reaction mixture was dissolved in 15 ml. of hot methanol and, after filtration, the solution was chilled in ice and seeded. The crystalline, nearly colorless precipitate was collected by filtration, washed with a little cold methanol, and air dried. All samples except that from the 360-minute run melted within 1° of the melting point of the analytical sample (m.p. 53-54°).

The *N*-benzylformamide was prepared by heating an equimolar mixture of benzylamine and 90% formic acid at 150° for 1 hour under reduced pressure (aspirator). The residue crystallized readily upon cooling (m.p. 56-58°) and was used without further purification, lit. m.p. (21), 59.8-60.4°.

3-Amino-6-methylbiphenyl.

2-Methyl-5-nitrobiphenyl (87.3 g., 0.41 mole) in 350 ml. of warm (ca. 50°) ethanol was hydrogenated with Raney nickel in a low pressure Parr apparatus. Uptake of hydrogen was 108% of theoretical when absorption ceased after 5 hours. The catalyst was filtered off and the solvent was removed *in vacuo*. Distillation of the residue gave 62.3 g. (87%) of product boiling at 128-131° at 0.1 mm. An analytical sample was obtained by gas phase chromatography under the conditions used for 2-methyl-5-nitrobiphenyl. Retention time: 3 minutes.

Anal. Calcd. for C₁₃H₁₃N: C, 85.21; H, 7.15. Found: C, 85.01; H, 7.04.

2-Methyl-5-nitrobiphenyl.

A refluxing mixture of 150 g. (0.99 mole) of 2-methyl-5-nitroaniline in 3,600 ml. of benzene was treated over 45 minutes with 150 ml. (135 g., 1.31 moles) of freshly prepared butyl nitrite. Gentle nitrogen evolution began almost immediately, and a total of 23.9 l. was evolved over 17 hours, mostly during the first 6 hours (theoretical, 24.4 l.). The excess benzene was distilled off at atmospheric pressure, and the viscous residue was distilled at reduced pressure. After a forerun of 15.6 g. (boiling range 80-150°, 2.5-0.8 mm), the product was collected at 150-158° and 0.8-0.6 mm. The product partially crystallized in the condenser, and a hot air blower was used to aid transfer to the receiver, yield, 87.3 g. (41%). This material was used without further purification.

In a similar experiment, product recrystallized from methanol three times melted at 75.5-76.5°. The analytical specimen was obtained by gas phase chromatography (Column: 2' x 1/4" 7% SE 30 on Gas-Pak F 40-60. Conditions: 50 ml. He/minute, column temperature, 200°; retention time, 8 minutes).

NMR data (chloroform): τ 1.9 (2H, multiplet, *o*-NO₂ArH), 2.65 (6 protons, narrow multiplet, ArH), 7.66 (3H, singlet, ArCH₃).

Anal. Calcd. for C₁₃H₁₁NO₂: C, 73.20; H, 5.22. Found: C, 72.70; H, 5.28.

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