84.5°, lit.[17] m.p. 88–89°. Hydrolysis of the ester in 2 *N* hydrochloric acid afforded (±)-XII, m.p. and m.m.p. 56–57°. Identical results were obtained by subjection of (+)-XI to this sequence.

(+)-1-Methyl-3-acetoxy-3-benzoylpiperidine (XIII).—To 10 ml. of acetic anhydride was added 3.29 g. (15 mmoles) of (+)-XII, $[\alpha]^{27}D$ (absolute ethanol) +10.9° (*c* 5.25). After refluxing for 1 hr. the solution was cooled and poured into 100 ml. of 0.2 *N* hydrochloric acid. The aqueous layer was extracted with ether. The ether layers were discarded. The aqueous layer was treated with excess saturated sodium bicarbonate and extracted with petroleum ether. The organic phase was dried over sodium sulfate, treated with carbon, filtered through sintered glass, and evaporated to a final volume of about 15 ml. On cooling, 2.60 g. (10 mmoles, 67%) of XIII was obtained: m.p. 66–67°, $[\alpha]^{25}D$ (absolute ethanol) +34.7° (*c* 10.56), $[\alpha]^{25}D$ (0.5 *N* hydrochloric acid) +72.3° (*c* 11.14).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.78; H, 7.41; N, 5.44.

Hydrolysis of (+)-1-Methyl-3-acetoxy-3-benzoylpiperidine (XIII).—After refluxing a solution of 1.31 g. (5 mmoles) of the ester in 25 ml. of 2 *N* hydrochloric acid for 24 hr. and cooling, the reaction mixture was poured into a saturated solution of sodium bicarbonate and extracted with petroleum ether. The extract was dried over sodium sulfate, decolorized with carbon, filtered through sintered glass, evaporated to a final volume of about 10 ml. on the steam bath, and cooled to give 0.92 g. (4.2 mmoles, 84%) of (+)-XII: m.p. 72.5–73°, $[\alpha]^{25}D$ (absolute ethanol) +10.9° (*c* 5.00); lit.[7] m.p. 72.5–73°.

To 1.31 g. (5 mmoles) of the ester in 10 ml. of 5% alcoholic potassium hydroxide was added 10 ml. of water. After refluxing for 1 hr. the mixture was diluted with 100 ml. of water and worked up as above to give 0.98 g. (4.5 mmoles, 90%) of (+)-XII, m.p. 72.5–73°, $[\alpha]^{25}D$ (absolute ethanol) +10.9° (*c* 5.00).

(+)-1-Methyl-3-methoxy-3-benzoylpiperidine [(+)-XIV].—To 20 ml. of freshly prepared anhydrous *t*-butyl alcohol was added 1.0 g. (25.6 mg.-atoms) of freshly cut potassium shavings. When the potassium was consumed, the mixture was cooled to room temperature. To this was added a solution of 3.07 g. (14 mmoles) of (+)-XII, $[\alpha]^{26}D$ (absolute ethanol) + 10.9° (*c* 5.30), in 30 ml. of anhydrous ethyl ether. To the solution, cooled in an acetone–Dry Ice bath, was introduced a solution of 4.66 g. (25 mmoles) of methyl *p*-toluenesulfonate in anhydrous ethyl ether. The mixture was stirred for 3 hr. and then poured over ice, acidified to pH 3 with concentrated hydrochloric acid, and extracted first with chloroform and then with petroleum ether. The extracts were discarded. The aqueous portion was made basic with sodium hydroxide solution and extracted with petroleum ether. The combined extracts were dried over sodium sulfate, treated with carbon, filtered through sintered glass, and evaporated on the steam table to give an oil which was distilled under reduced pressure (0.1 mm.). The distillate was dissolved in ethanol and treated with anhydrous hydrochloric acid. On cooling there was obtained 1.35 g. (5 mmoles, 36%) of a dextrorotatory material, m.p. 268–269° dec., $[\alpha]^{22}D$ (water) +42.7° (*c* 1.227), which exhibited a carbonyl band (1667 $cm.^{-1}$) but no hydroxyl band in the infrared spectrum. Good yields of the pure salt were obtained in subsequent runs in which distillation was omitted.

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; Cl, 13.14; N, 5.19. Found: C, 61.95; H, 7.44; Cl, 13.42; N, 5.50.

The free amine, b.p. 106–109° (0.9 mm.), isolated from an analytically pure sample of the salt, exhibited an $[\alpha]^{27}D$ (absolute ethanol) of +10.0° (*c* 8.00). The observed rotation of a 2.00% solution of (+)-XIV in 2 *N* hydrochloric acid was constant at +1.71 ± 0.01° for 48 hr. at 25°.

Acknowledgment.—We are indebted to Dr. H. Fales and Miss Katherine Warren of the National Institutes of Health for the rotatory dispersion measurements, to Mr. J. Lyons for his expert technical assistance, and to both Bristol Laboratories and the Schering Corporation for funds which made possible the acquisition of a Zeiss polarimeter.

(17) R. E. Lyle and G. H. Warner, *J. Med. Pharm. Chem.*, **3**, 597 (1961).

Epoxy Ethers. XX.[1] Synthesis of Diamines, Morpholines, and Piperazines

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Epoxy ether Ia was converted to 1,2-diamine III by reaction with excess methylamine and subsequent reduction of the intermediate imine IIb. Epoxy ethers Ia and b were converted *via* reaction with aziridine to the corresponding α-amino ketones IVa and b. Treatment of IVa with butylamine, followed by reduction, produced diamine VI. Amino ketones IVa and b were also converted, *via* their corresponding carbinols, to morpholines IXa and b by acid treatments. Epoxy ether Ia was converted to hydroxymorpholines Xa and b by reaction with the appropriate ethanolamine. Epoxy ethers Ia, c, and d reacted with ethylenediamine forming tetrahydropyrazines XIIa, c, and d, which were readily reduced to their corresponding piperazines.

The treatment of epoxy ethers with secondary amines has been shown to produce α-amino ketones in high yield.[1] This present work reports illustrative reactions of epoxy ethers with primary amines, ethylenimine, ethanolamines, and ethylenediamine to demonstrate the utility of these reactions in the synthesis of diamines, morpholines, hydroxymorpholines, and piperazines, respectively.

1,2-Diamines.—Numerous methods for the preparation of substituted ethylenediamines are recorded in the chemical and patent literature. However, for those ethylenediamines with unsymmetrical carbon skeletons few syntheses have been recorded. One such synthesis[3] used the reaction of a β-chloramine with a second amine. Such a reaction could well proceed through an ethyleniminium ion[4] which could be opened by attack of the second amine at the two different carbon atoms of the intermediate to give two isomeric products. Thus, the β-chloramine starting material is not ideal for either synthesis or structure proof. The utility of an epoxy ether starting material results from the stepwise and directional incorporation of amines into molecules of unsymmetrical carbon skeleton.

Two successive treatments[5] of epoxy ether Ia with methylamine at and above 150° formed the α-iminoamine IIb, which was isolated in 68% yield. Imino-

(1) Paper XIX of this series: C. L. Stevens and C. H. Chang, *J. Org. Chem.*, **27**, 4392 (1962).

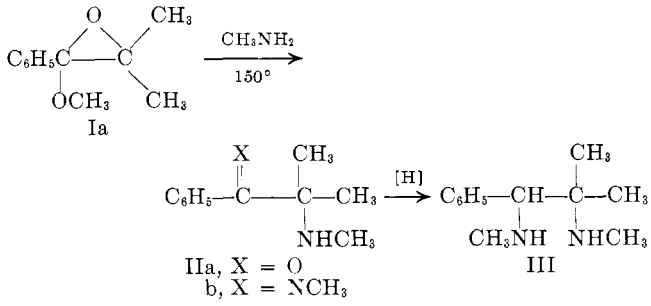
(2) (a) Parke, Davis and Co. Postdoctorate Research Fellow, Jan., 1959, to Jan., 1960. (b) Abstracted in part from the Ph.D. Dissertation of K. G. Taylor and the M.S. Thesis of A. L. Schy, Wayne State University, 1963.

(3) Roche Products Ltd., British Patent 729003 (April 27, 1955).

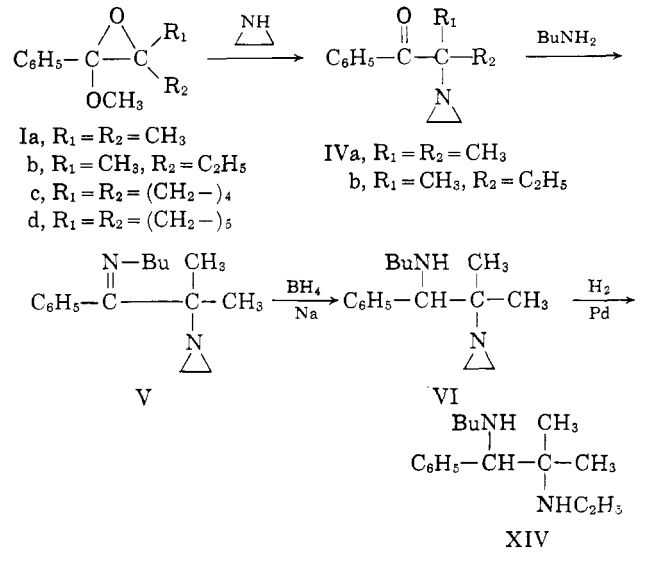
(4) R. C. Fuson and C. Zirkle, *J. Am. Chem. Soc.*, **70**, 2760 (1948).

(5) Successive treatments were necessary to convert all of the intermediate α-amino ketone, IIa, to the imine.

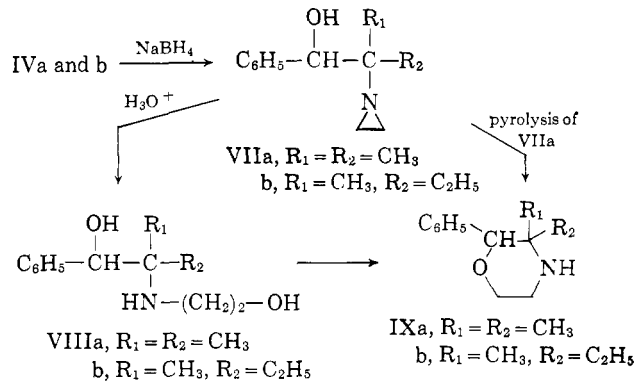
amine IIb displayed a strong C=N band at 6.07 μ in its infrared spectrum and was hydrolyzed in dilute acid solution to the known α-amino ketone IIa,[6] thereby confirming the structure. Chemical or catalytic reduction of IIb produced diamine III in over 90% yields.



The reaction of epoxy ether Ia with ethylenimine at 150° produced α-amino ketone IVa in 89% yield. However, amino ketone IVa reacted sluggishly with primary amines, presumably because of increased steric hindrance of its carbonyl group. Thus, three successive treatments with butylamine were required to produce only a moderate yield, 39%, of iminoamine V. Sodium borohydride reduction converted V to diamine VI in 90% yield. The infrared spectrum of VI exhibited a band at 6.77 μ indicative of the C–H absorption of the ethylenimine ring.[7] Confirmation that the aziridine ring was still intact in diamine VI was provided by the catalytic hydrogenation of that compound.[8] Thus, 1 mole equiv. of hydrogen was absorbed and a new diamine, XIV, was isolated in 68% yield.



Morpholines.—Amino ketone IVa proved to be a versatile intermediate. Reduction with sodium borohydride afforded the corresponding carbinol VIIa in high yield. Amino alcohol VIIa was then converted to morpholine IXa by several techniques. Conversion of VIIa to diol VIIIa was best effected by heating VIIa in 1 *N* perchloric acid or by refluxing the perchlorate salt in water.[9] Diol VIIIa was then converted to morpholine IXa following the methods of Knorr,[10] which involved heating the diol at 150° in 12 *N* hydrochloric acid or treatment with concentrated sulfuric acid at 5°. The yields of morpholine IXa were 76 and 93%, respectively. Heating amino alcohol VIIa in 50% perchloric acid converted it directly to morpholine IXa in 82% yield, thereby eliminating the isolation of the intermediate diol VIIIa.[11] A dry pyrolysis of the perchlorate salt of VIIa also converted it to morpholine IXa, most likely *via* an intramolecular aziridine ring opening by the adjacent hydroxyl group.[12] The structural confirmation of IXa is discussed later. In a manner similar to the preparation of VIIa, amino alcohol VIIb was synthesized and converted, *via* the corresponding diol VIIIb, to morpholine IXb by the sulfuric acid procedure of Knorr.[13] Yields above 70% were obtained in all steps.



Hydroxymorpholines.—The reaction of epoxy ethers with ethanolamines posed the interesting question of a competition between the hydroxyl group and the amino group in reaction with the epoxy ether. The acid-catalyzed reaction of alcohols with epoxy ethers often is very rapid.[14] However, since alcohol is formed during the reaction of epoxy ethers with amines, the high yields of α-amino ketones obtained from those reactions[15] gave a preliminary indication that the amine group of the ethanolamine would react with the epoxy ether in preference to the alcohol group. Indeed, N-methylethanolamine reacted with epoxy ether Ia and produced 2-phenyl-3,3,4-trimethylmorpholin-2-ol (Xb) in 94% yield. The structure of Xb was confirmed by independent synthesis from amino ketone IIb and ethylene oxide. Hydroxymorpholine Xa was prepared from the epoxy ether and ethanolamine in only 26% yield. However, it was found that α-aziridinyl ketone IVa could be converted to Xa in high yield by treatment with 12 *N* hydrochloric acid for extended periods of time. The hemiketal ring of Xa and b was stable to acid hydrolysis and catalytic hydrogenation. On lithium aluminum hydride reduction, however, the hemiketal group reacted and the potential carbonyl group was reduced, thus producing diol XIV. Treat-

(6) C. Mannich and H. Budde, *Arch. Pharm.*, **271**, 51 (1933).

(7) H. Thompson and W. Cave, *Trans. Faraday Soc.*, **47**, 951 (1951).

(8) M. Kharasch and H. Priestly [*J. Am. Chem. Soc.*, **61**, 3425 (1939)] reported the hydrogenation of an ethylenimine to an ethylamine.

(9) When dilute hydrochloric acid was used under similar conditions, the corresponding β-chloramine was isolated in 84% yield.

(10) L. Knorr, *Ber.*, **22**, 2084 (1889); *ibid.*, **30**, 918 (1897).

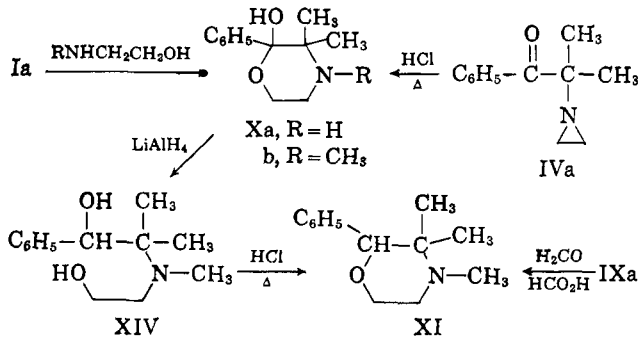
(11) That diol VIIIa probably was an intermediate was demonstrated by converting it to IXa under identical reaction conditions, in 95% yield.

(12) Since water was used early in the work-up, diol VIIIa was subjected to work-up conditions. However, it was recovered unchanged, thereby eliminating it as a precursor of IXa in this instance.

(13) Unsuccessful attempts were made at various stages to separate the diastereomers formed when amino ketone IVb was reduced.

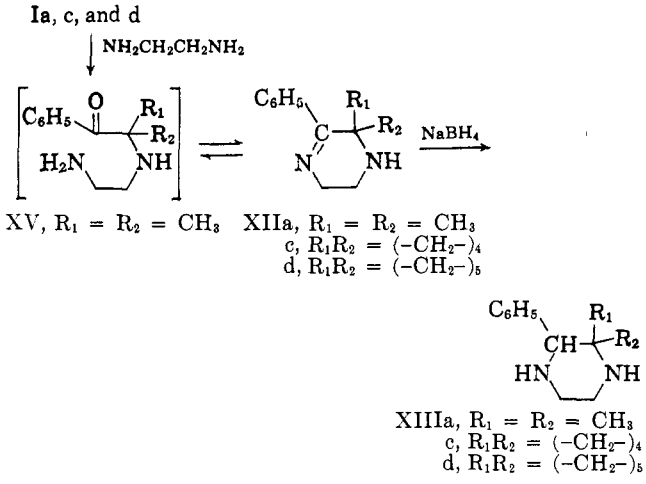
(14) See, for example, C. L. Stevens, R. L. McLean, and A. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 2276 (1958).

(15) Epoxy ether–amine reactions, however, are conducted using excess amine.



ment of diol XIV with the hydrochloric acid procedure of Knorr[10] converted it to morpholine XI in 75% yield. Morpholine IXa was then related structurally to XI by N-methylation.

Piperazines.—In contrast to the reaction with ethanolamine, Ia reacted smoothly with ethylenediamine and afforded 2-phenyl-3,3-dimethyl-3,4,5,6-tetrahydropyrazine (XIIa) in 91% yield.[16a,b,17] The reaction was carried out in refluxing toluene and the water, as it was formed, was thus azeotropically distilled from the reaction mixture to drive the equilibrium between



the intermediate α-(β-aminoethylamino) ketone (XV) and XIIa to the right and thus prevent possible dimerizations and polymerizations. Subsequent experiments showed that this technique was unnecessary. The high temperature required for the reaction of epoxy ether Id required the use of an autoclave. Even in this closed system, the pyrazine XIId was isolated in 63% yield. Ethanol, a good solvent for nucleophilic opening of epoxides,[18] was also suitable as a solvent for the reaction of epoxy ether Ic. Thus, pyrazine XIIc was prepared in 71% yield. All three tetrahydropyrazines were reduced with sodium borohydride to their respective piperazines in high yield. The piperazines were most conveniently isolated as their dihydrochloride salts.

(16) Earlier reports dealing with this class of pyrazines: (a) J. G. Aston, D. Ailman, C. Scheuermann, and J. Koch, *J. Am. Chem. Soc.*, **56**, 1163 (1934); (b) L. T. Plante, W. G. Lloyd, C. Schilling, and L. Clapp, *J. Org. Chem.*, **21**, 82 (1956).

(17) A short paper reporting the structural verification and some reactions of this compound has been submitted to *The Journal of Organic Chemistry*.

(18) W. Horne and R. Shriner, *J. Am. Chem. Soc.*, **54**, 2925 (1932).

Experimental

All melting points are uncorrected; analyses were performed by Alfred Bernhardt Microanalytical Laboratories, Mülheim, Germany; infrared spectra were obtained on a Baird Associates recording spectrophotometer and Beckman IR-4, and ultraviolet spectra on a Cary 14 spectrophotometer. Amine hydrochlorides were prepared by addin a saturated isopropyl alcohol–hydrogen chloride solution to an ethereal solution of the amine, unless otherwise noted.

α-N-Methyl-β-methylimino-α,α-dimethylphenethylamine (IIb).—A solution of 20 g. (0.11 mole) of epoxy ether Ia[19] in 35.5 g. (0.93 mole) of monomethylamine was heated in a stainless steel autoclave at 200° for 24 hr. Volatile components were then evaporated *in vacuo*, and the residual oil was redissolved in excess methylamine and reheated at 150° for 12 hr. Evaporation of volatile components left a liquid which was distilled through a Vigreux column *in vacuo*. The main fraction afforded a pale yellow liquid: 14.2 g. (68%); b.p. 69–73° (0.75 mm.); $n^{25}D$ 1.5191; d^{25}_4 0.965; infrared spectrum (μ), 3.05 (NH), 6.07 (C=N), 7.29, and 7.39 (CH_3—C—CH_3). An ultraviolet spectrum showed only end absorption.

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53. Found: C, 75.88; H, 9.45.

A solution of 5.0 g. (0.026 mole) of the Schiff base (IIb) in 15 ml. of 6 *N* hydrochloric acid was heated on a steam bath for 1 hr. The solution was neutralized with 10% sodium hydroxide solution and washed with three 25-ml. portions of ether. After drying (potassium carbonate), the ether was evaporated *in vacuo;* the residual liquid was fractionally distilled through a Vigreux column *in vacuo*. The main fraction yielded 4.1 g. (87%) of IIa, a pale yellow liquid: b.p. 70–71° (0.3 mm.); $n^{25}D$ 1.5246; infrared spectrum (μ), 3.03 (NH), 5.93 (C=O), 7.26, and 7.36 (CH_3—C—CH_3).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.53; H, 8.49; N, 7.98.

A hydrochloride salt was precipitated from an ethereal solution of 0.1 g. of the amino ketone by the addition of a saturated solution of hydrogen chloride in isopropyl alcohol. Recrystallization from methanol–ether afforded 0.12 g. (96%) of white crystals, m.p. 212–213° (lit.[6] m.p. 215°)

N^1,N^2,2-Trimethyl-1-phenyl-1,2-propanediamine (III). **A.**—A solution of 5.4 g. (0.028 mole) of imine IIb in 50 ml. of absolute ethanol was cooled and swirled with 1.06 g. (0.028 mole) of sodium borohydride. After the initial vigorous reaction subsided, the reaction was left at room temperature overnight. The reaction was made strongly acidic with 6 *N* hydrochloric acid and washed with ether. After basification, the aqueous solution was washed with ether and the combined ether extracts were dried. Evaporation of the ether left a pale yellow liquid which was fractionally distilled *in vacuo*. The main fraction yielded 5.0 g. (92%) of a colorless liquid: b.p. 49–53° (0.03 mm.); $n^{27}D$ 1.5150; d^{25}_4 0.959; infrared spectrum (μ), 3.05 (NH), 7.25, and 7.35 (CH_3-C-CH_3).

Anal. Calcd. for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48. Found: C, 75.17; H, 10.46.

A dihydrochloride salt was prepared and recrystallized from methanol–ether to give white crystals: m.p. 249–250°; pK'_a 5.1 and 9.9 (H_2O).; ultraviolet spectrum, $\lambda^{H_2O}_{max}$ 267 mμ (ε 270), 261 (347), 256 (297), and 251 (213).

Anal. Calcd. for $C_{12}H_{22}Cl_2N_2$: C, 54.34; H, 8.36. Found: C, 54.51; H, 8.66.

A dibenzamide was prepared in 50% yield from the dihydrochloride, benzoyl chloride, and triethylamine in benzene. Recrystallization from ethanol–water afforded white needles, m.p. 146–147°.

Anal. Calcd. for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05; N, 6.99. Found: C, 78.02; H, 6.84; N, 7.28.

B.—A solution of 2.3 g. (0.012 mole) of imine (IIb) in 20 ml. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature using 0.23 g. of platinum oxide as catalyst, 1 mole equiv. of hydrogen being absorbed over a 4-hr. period. The catalyst was removed by filtration, and the solvent was evaporated *in vacuo*. The residual liquid was flash distilled *in vacuo* to yield 2.2 g. (94%) of the colorless diamine, b.p. 47–48° (0.03 mm.), $n^{25}D$ 1.5160.

(19) C. L. Stevens and T. Coffield, *ibid.*, **80**, 1919 (1958).

A portion was converted to the dihydrochloride salt, m.p. 249–250°. Mixture melting point with the borohydride reduction product showed no depression.

2-(1-Aziridinyl)-2-methylpropiophenone (IVa).—A solution of 15.0 g. (0.084 mole) of epoxy ether (Ia) in 15 g. (0.36 mole) of ethylenimine was heated in a stainless steel autoclave at 150° for 15 hr. Excess ethylenimine was evaporated *in vacuo* (hood) leaving yellow liquid which was fractionally distilled *in vacuo* through a Vigreux column. The main fraction yielded 14.1 g. (89%) of a colorless liquid: b.p. 65–67° (0.15 mm.); $n^{25}D$ 1.5290; d^{25}_4 0.988; infrared spectrum (μ), 5.94 (C=O), 6.80 ($N<\begin{smallmatrix}CH_2\\|\\CH_2\end{smallmatrix}$), 7.25, and 7.35 ($CH_3$—C—$CH_3$); ultraviolet spectrum, λ_{max}^{EtOH} 243 mμ (ϵ 8200).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.91; H, 7.87; N, 7.55.

1-β-n-Butylimino-α,α-dimethylphenethyl)aziridine (V).—A solution of 10.0 g. (0.053 mole) of amino ketone (IVa) in 15 ml. of *n*-butylamine was heated at 150° in a stainless steel autoclave for 12 hr. The reaction mixture was poured over a column of potassium hydroxide pellets, the column was washed with additional *n*-butylamine, and the solution was reheated in the autoclave for another 12 hr. This procedure was repeated twice again and then worked up by evaporating the butylamine and fractionally distilling the residual liquid. The fraction distilling at 60–64° (0.05 mm.) yielded 5.82 g. of starting ketone, identified by its infrared spectrum. The fraction distilling at 77–80° (0.06 mm.) yielded 2.13 g. (16.5%) of the desired iminoamine: $n^{25}D$ 1.5096; d^{25}_4 0.959; infrared spectrum, 6.03 (C=N), 6.78 ($\overline{N—CH_2—CH_2}$), 7.24, and 7.34 (CH_3—C—CH_3). An ultraviolet spectrum showed only end absorption. Based on recovered starting material, the yield was 39%.

Anal. Calcd. for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.47. Found: C, 78.40; H, 9.68; N, 11.55.

Preparation of 1-(β-Butylamino-α,α-dimethylphenethyl)aziridine (VI).—A solution of 2.4 g. (0.01 mole) of imine (V) in 20 ml. of absolute ethanol was swirled with 0.38 g. (0.01 mole) of sodium borohydride and left to stand at room temperature for 48 hr. The reaction was then poured into water and the oily layer which separated was extracted with ether. After drying (potassium carbonate), the ether was evaporated *in vacuo* and the residual liquid was subjected to vacuum distillation. The main fraction yielded 2.2 g. (90%) of a colorless liquid: b.p. 83–85° (0.07 mm.); $n^{25}D$ 1.5090; d^{25}_4 0.949; infrared spectrum (μ, $CHCl_3$), 3.03 (NH), 6.75 ($\overline{N—CH_2—CH_2}$), 7.24, and 7.33 (*gem*-dimethyl); ultraviolet spectrum, λ_{max}^{EtOH} 264 mμ (ϵ 139), 259 (214), and 252 (211).

Anal. Calcd. for $C_{16}H_{26}N_2$: C, 77.99; H, 10.64; N, 11.37. Found: C, 78.17; H, 10.58; N, 11.24.

Preparation of N^1-Butyl-N^2-ethyl-1-phenyl-2-methyl-1,2-propanediamine Dihydrobromide (XIV).—A solution of 0.74 g. (0.003 mole) of diamine (VI) in 40 ml. of absolute ethanol was hydrogenated at atmospheric pressure employing 0.1 g. of 10% palladium on carbon as catalyst. After 1 hr., 91% of 1 mole equiv. of hydrogen had been absorbed and no further uptake was evidenced. The catalyst was removed by filtration over Celite, the ethanol was evaporated *in vacuo*, and the oily residue was dissolved in dilute hydrochloric acid. The acid solution was washed with ether and made basic with solid potassium hydroxide. The basic solution was washed with ether and the combined ether extracts were dried (potassium carbonate). The product was precipitated as the dihydrobromide salt by passing gaseous hydrogen bromide over the ethereal solution. Recrystallization from methanol–ether afforded 0.84 g. (68%) of small white crystals, m.p. 209–211° dec. Recrystallization of a portion from methanol–ether gave an analytical sample, m.p. 213–215° dec., pK'_a 3.75 and 10.0 (50% methanol).

Anal. Calcd. for $C_{16}H_{20}Br_2N_2$: C, 46.85; H, 7.37; N, 6.83. Found: C, 46.87; H, 7.35; N, 6.96.

A portion was converted to the corresponding free base for an infrared spectrum (μ, $CHCl_3$): 3.05 (NH), 7.22, and 7.32 (*gem*-dimethyl and ethyl methyl).

1-Phenyl-2-(1-aziridinyl)-2-methylpropanol (VIIa).—A solution of 10.0 g. (0.053 mole) of amino ketone IVa in 100 ml. of methanol was swirled during the gradual addition of 1.0 g. (0.026 mole) of sodium borohydride. Cooling was necessary during the addition. After standing for 6 hr. the methanol was evaporated *in vacuo* and 100 ml. of water was added. The amino alcohol was collected by filtration and dried to yield 9.1 g. (90%) of white crystals, m.p. 96–97°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.54; H, 8.70; N, 7.36.

The **picrate** of VIIa, m.p. 128–129°, was prepared in 87% yield in benzene.

Anal. Calcd. for $C_{18}H_{20}N_4O_8$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.67; H, 4.82; N, 13.11.

The **perchlorate** salt of VIIa was prepared in 84% yield by the addition of 1 equiv. of 71% perchloric acid to an ethereal solution of VIIa followed by vigorous scratching. Recrystallization from ethanol–ether–petroleum ether (b.p. 30–60°) yielded white crystals, m.p. 109–110°.

Anal. Calcd. for $C_{12}H_{18}ClNO_5$: C, 49.40; H, 6.22; Cl, 12.16. Found: C, 49.58; H, 6.42; Cl, 12.05.

2-Phenyl-3,3-dimethylmorpholine (IXa). A.—A solution of 1.63 g. (0.0078 mole) of diol VIIIa hydrochloride in 30 ml. of 12 *N* hydrochloric acid was heated at 140° for 10 hr. in a sealed tube. After dilution with 30 ml. of water, the reaction was made basic with dilute sodium hydroxide solution and washed with three portions of ether. After drying the combined ether extracts, the ether was reduced in volume and the hydrochloride salt was precipitated in the usual fashion. Recrystallization from ethanol–ether afforded 1.3 g. (73%) of white crystals, m.p. 269–270° dec., pK'_a 8.1 (50% methanol).

Anal. Calcd. for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.18; H, 7.74; N, 6.03.

B.—A solution of 1.0 g. (0.0048 mole) of VIIIa in 10 ml. of concentrated sulfuric acid was allowed to stand at 5° for 2 hr. After pouring on ice, the reaction mixture was neutralized and extracted with ether. The hydrochloride salt, 1.02 g. (93%), was isolated as above, m.p. 267–269° dec. A mixture melting point with that prepared by procedure A was undepressed.

C.—A solution of VIIIa (0.50 g., 0.0024 mole) in 20 ml. of 50% perchloric acid was heated on a steam bath for 12 hr. Work-up as before afforded 0.52 g. (95%) of the morpholine hydrochloride, m.p. 266–268° dec. A mixture melting point with a sample prepared by procedure A was undepressed.

D.—A solution of 2.0 g. (0.01 mole) of amino alcohol IVa in 20 ml. of 50% perchloric acid was heated on a steam bath for 24 hr. The usual work-up provided 1.95 g. (82%) of the morpholine hydrochloride, m.p. 263–265° dec.

E.—A sealed tube containing 0.50 g. (0.0017 mole) of the perchlorate salt of VIIa was heated at 130° for 1.5 hr. Isolation of the product as the hydrochloride salt afforded 0.32 g. (82%) of morpholine IXa hydrochloride, m.p. 263–265° dec.

The **picrate** of IXa, prepared in benzene solution, melted at 228–229° dec. after recrystallization from methanol.

Anal. Calcd. for $C_{18}H_{20}N_4O_8$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.32; H, 4.76; N, 13.44.

2-(1-Aziridinyl)-2-methylbutyrophenone (IVb).—A solution of 30.0 g. (0.156 mole) of epoxy ether Ib[20] in 60 ml. of ethylenimine was heated at 250° for 12 hr. and at 150° for an additional 10 hr. in a stainless steel autoclave. After evaporation of excess ethyleneimine (hood), the residual liquid was distilled *in vacuo* through a short Vigreux column. The fraction boiling 101–103° (0.9 mm.) yielded 21.8 g. (78%) of the desired α-amino ketone: $n^{25}D$ 1.5295, ultraviolet spectrum (ethanol), λ_{max} 242 mμ (ϵ 8700).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.58; H, 8.58.

1-Phenyl-2-(1-aziridinyl)-2-methylbutanol (VIIb).—A solution of 5.0 g. (0.025 mole) of amino ketone IVb in 200 ml. of methanol was swirled with 1.0 g. (0.026 mole) of sodium borohydride and allowed to stand at room temperature for 2 hr. After evaporation of the methanol *in vacuo*, water was added and the resulting mixture was washed three times with ether. The combined ether extracts were dried (sodium sulfate) and the ether was then reduced to a small volume. After cooling overnight, 4.2 g. (84%) of white crystals were collected by filtration, m.p. 52–55°. A portion was recrystallized from petroleum ether (b.p. 30–60°) for analysis: m.p. 58–59°; ultraviolet spectrum (ethanol), λ_{max} 264 mμ (ϵ 146), 258 (192), 252 (153), and 247 (108).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.83. Found: C, 76.24; H, 9.33; N, 6.68.

Treatment of alcohol VIIIb with dry hydrogen chloride in ether converted it to the corresponding β-chloroamine hydrochlo-

(20) C. L. Stevens, R. D. Elliott, and B. L. Winch, *J. Am. Chem. Soc.*, **85**, 1464 (1963).

ride. Recrystallization from a small volume of absolute ethanol yielded white crystals, m.p. 208–209°.

Anal. Calcd. for $C_{13}H_{21}Cl_2NO$: C, 56.11; H, 7.61; N, 5.03. Found: C, 55.93; H, 7.52; N, 4.93.

1-Phenyl-2-(β-hydroxyethylamino)-2-methylbutanol (VIIIb) Hydrochloride.—A solution of 2.0 g. (0.0098 mole) of amino alcohol VIIb in 50 ml. of 1 *N* perchloric acid was heated on a steam bath for 10 hr. After an ether wash, the aqueous layer was made basic with solid sodium hydroxide and washed six times with ether. The combined ether extracts were dried (sodium sulfate) and reduced to about one-third volume. Addition of saturated isopropyl alcohol–hydrogen chloride solution precipitated the product as the oily hydrochloride salt which solidified on standing to yield 1.79 g. (71%) of white crystals, m.p. 145–150°. A portion was recrystallized from ethanol–ether for an analytical sample: m.p. 155–160°; ultraviolet spectrum (ethanol), λ_{max} 264 mμ (ε 155), 258 (194), 252 (147), and 247 (101); pK'_a 8.8 (50% methanol).

Anal. Calcd. for $C_{13}H_{22}ClNO_2$: C, 60.10; H, 8.54; N, 5.40. Found: C, 60.07; H, 8.40; N, 5.40.

The corresponding free base could be crystallized from pentane solution with cooling, m.p. 57–58°.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.97; H, 9.61; N, 6.40.

2-Phenyl-3-methyl-3-ethyl-morpholine (IXb) Hydrochloride.—A solution of 0.500 g. (0.0019 mole) of diol VIIIb hydrochloride in 5 ml. of concentrated sulfuric acid was kept at 0° for 2 hr. (ice bath) and then poured over 20 g. of ice. After neutralization with solid sodium hydroxide, the aqueous solution was washed with three 25-ml. portions of ether. The combined ether extracts were dried (sodium sulfate) and then concentrated to one-third volume. Addition of isopropyl alcohol–hydrogen chloride solution caused the precipitation of an oily hydrochloride, which crystallized on scratching to yield 0.38 g. (82%) of white crystals, m.p. 222–225°. Recrystallization of a portion from methanol–ether, with good recovery, provided an analytical sample: m.p. 230–231°; ultraviolet spectrum (ethanol), λ_{max} 267 mμ (ε 99), 263 (186), 261 (153), 257 (220), and 251 (161); pK'_a 7.95 (50% methanol).

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; N, 5.79. Found: C, 64.29; H, 8.47; N, 6.04.

The corresponding picrate, prepared from the free base and picric acid in benzene solution, melted at 202–204° after recrystallization from methanol–ether–pentane solution.

Anal. Calcd. for $C_{19}H_{23}N_4O_8$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.77; H, 5.29; N, 12.95.

2-Phenyl-3,3-dimethylmorpholin-2-ol (Xa). A.—A solution of 5.0 g. (0.028 mole) of epoxy ether Ia and 2.2 g. (0.036 mole) of ethanolamine in 15 ml. of dioxane (previously dried) was heated in a sealed tube at 105–110° for 23 hr. After evaporation (*in vacuo*) of the solvent and excess ethanolamine, the residue was crystallized from methylene chloride and petroleum ether, yielding 1.5 g. (26%) of white crystals, m.p. 127–129°. The infrared spectrum showed no absorption in the carbonyl region.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 69.53; H, 8.26; N, 6.75. Found: C, 69.69; H, 8.35; N, 6.88.

B.—A solution of 1.3 g. (0.0069 mole) of amino ketone IVa in 15 ml. of 4 *N* hydrochloric acid was heated at 140° (sealed tube) for 20 hr. After cooling, the reaction solution was made basic with sodium hydroxide solution and washed thoroughly with ether. After drying the combined ether extracts, the ether was evaporated *in vacuo* yielding a solid. Recrystallization from ether–petroleum ether gave 1.2 g. (85%) of hydroxymorpholine Xa, m.p. 125°. A mixture melting point with that prepared *via* the ethanolamine reaction was undepressed.

2-Phenyl-3,3,4-trimethylmorpholin-2-ol (Xb). A.—A sealed tube containing 5.0 g. (0.028 mole) of epoxy ether Ia and 20 g. (0.28 mole) of N-methylethanolamine was heated at 120° for 12 hr. After distillation of the excess amine (*in vacuo*), the residue was crystallized from petroleum ether. Recrystallization from the same solvent afforded 5.8 g. (94%) of white crystals, m.p. 103–105°.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.74; H, 8.85.

B.—A sealed tube containing 0.30 g. (0.017 mole) of α-amino ketone IIa and 3 ml. of ethylene oxide was heated at 120° for 8 hr. After evaporation of excess ethylene oxide, the residue was crystallized from petroleum ether. Recrystallization from the same solvent yielded 0.080 g. (21%) of white crystals, m.p. 102–104°. A mixture melting point with a sample prepared *via* the epoxy ether reaction was undepressed, and the infrared spectra of the two samples were identical.

1-Phenyl-2-(N-methyl-2-hydroxyethylamino)-α-methylpropanol (XIV).—A mixture containing 0.50 g. (0.0023 mole) of hydroxymorpholine Xb and 0.50 g. (0.013 mole) of lithium aluminum hydride in 50 ml. of tetrahydrofuran was refluxed with stirring for 5 hr. Excess hydride was decomposed with ethylacetate and water. After evaporation of the solvent, the residue was mixed with water and washed twice with ether. The combined ether extracts were dried and evaporated to give a residue which crystallized from ether–petroleum ether. Recrystallization from the same solvent mixture afforded 0.40 g. (80%) of white crystals, m.p. 57–58°.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.91; H, 9.48; N, 6.27. Found: C, 69.64; H, 9.54; N, 6.19.

2-Phenyl-3,3,4-trimethylmorpholine (XI). A.—A sealed tube containing 4.5 g. (0.02 mole) of diol XIV in 15 ml. of 12 *N* hydrochloric acid was heated at 145° for 12 hr. The reaction mixture was then diluted with water and washed with ether to remove any acid insoluble material. The aqueous solution was made basic with 10% sodium hydroxide solution and washed thoroughly with ether. The combined ether extracts were dried and evaporated. The residual oil was distilled *in vacuo*. The fraction boiling at 72–73° (0.1 mm.) was collected and yielded 3.0 g. (75%) of a colorless liquid, $n^{25}D$ 1.5275.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.32; N, 6.82. Found: C, 75.83; H, 9.47; N, 6.88.

A **methiodide** was prepared, m.p. 232–233°.

Anal. Calcd. for $C_{14}H_{22}INO$: C, 48.42; H, 6.39; I, 36.55. Found: C, 48.62; H, 6.46; I, 36.30.

A **hydrochloride** was prepared in the usual manner and was recrystallized from acetone–ether, m.p. 195–196°.

Anal. Calcd. for $C_{13}H_{20}ClNO$: Cl, 14.66. Found: Cl, 14.59.

B.—An aqueous solution containing 3.0 g. (0.013 mole) of IXa hydrochloride was neutralized and the free base isolated by extraction with ether. After the ether was evaporated, 25 ml. of 37% formalin solution and 25 ml. of 90% formic acid were added. The solution was heated on a steam bath for 24 hr., after which the solution was evaporated to an oil *in vacuo*. Concentrated hydrochloric acid (20 ml.) was added and the evaporation was repeated. Dilution with water, followed by basification and a thorough ether extraction, produced an ethereal solution containing the desired product. After drying, the product was precipitated as its hydrochloride salt in the usual fashion. Recrystallization from methanol–ether afforded white crystals, 1.25 g. (39%), m.p. 191–193°. A mixture melting point with that prepared *via* hydroxymorpholine Xb was undepressed.

5-Phenyl-1,4-diazospiro[5.5]undec-4-ene (XIId).—A solution of 9.6 g. (0.044 mole) of epoxy ether Id[21] and 2.7 g. (0.044 mole) of ethylenediamine in 10 ml. of toluene were heated at 150° for 16 hr. in a stainless steel bomb. Removal of solvent left a brown solid which was purified by sublimation at 60° (0.01 mm.). This afforded 6.3 g. (63%) of off-white crystals: m.p. 90–91°; ultraviolet spectrum, $\lambda_{max}^{C_2H_5OH}$ 263 mμ (ε 344) and 257 (426), infrared spectrum (μ, $CHCl_3$), 3.05 (broad, NH) and 6.09 (C=N).

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.94; H, 8.83; N, 12.27. Found: C, 78.67; H, 8.90; N, 12.05.

5-Phenyl-1,4-diazaspiro[5.5]undecane (XIIId) Dihydrochloride.—A solution of 0.23 g. (0.001 mole) of pyrazine XIId in 15 ml. of absolute ethanol was treated with 0.15 g. (0.004 mole) of sodium borohydride and allowed to stand at room temperature for 10 hr. The reaction was then poured into 50 ml. of 3 *N* hydrochloric acid and the acid layer was washed with ether. After basification with solid potassium hydroxide the aqueous layer was washed five times with chloroform. After the combined extracts were dried, the chloroform was removed *in vacuo* and replaced with dry ether. The product was precipitated as the dihydrochloride salt prepared in the usual manner. Recrystallization from methanol–ether afforded white crystals, 0.29 g. (97%), m.p. >300° dec. Further recrystallization of a portion from methanol–acetone provided an analytical sample: infrared spectrum (μ, KBr), 6.35 (NH_2); pK'_a 3.78 and 8.68 (50% methanol).

Anal. Calcd. for $C_{15}H_{24}Cl_2N_2$: C, 59.41; H, 7.98; N, 9.24. Found: C, 59.19; H, 8.03; N, 8.99.

The corresponding free base was purified by sublimation at 50° (0.1 mm.) and melted at 77–78°.

(21) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 618 (1952).

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.17. Found: C, 78.43; H, 9.89; N, 12.00.

10-Phenyl-6,9-diazaspiro[4.5]dec-9-ene (XIIc).—A solution of 2.5 g. (0.012 mole) of epoxy ether Ic[20] and 1.6 g. (0.027 mole) of ethylenediamine in 10 ml. of absolute ethanol was heated at reflux for 70 hr. Removal of solvents *in vacuo* yielded a pale yellow solid. Recrystallization from ether–petroleum ether afforded 1.57 g. of off-white crystals, m.p. 88–89°. The mother liquors were washed with dilute hydrochloric acid, the acid portion was made basic, and the organic product was extracted with chloroform. After drying, the chloroform was evaporated *in vacuo* leaving a yellow solid, which was purified by sublimation at 50° (0.1 m.) to yield an additional 0.27 g. of product, m.p. 85–86°. The total yield was 1.84 g. (71%). An analytical sample was prepared by recrystallization from ether–petroleum ether: m.p. 88.5–89.5°; infrared spectrum (μ, $CHCl_3$), 3.05 (broad, NH) and 6.10 (C=N).

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.47; H, 8.46; N, 13.08. Found: C, 78.51; H, 8.39; N, 12.88.

10-Phenyl-6,9-azaspiro[4.5]decane Dihydrochloride (XIIIc).—A solution of 0.37 g. (0.0017 mole) of pyrazine XIIc in 20 ml. of absolute ethanol was swirled with 0.19 g. (0.005 mole) of sodium borohydride and left to stand at room temperature for 8 hr. The mixture was then poured into 30 ml. of 2 *N* hydrochloric acid, and the acidic solution was washed with ether. The aqueous portion was made basic with solid potassium hydroxide and then washed with chloroform. After drying (sodium sulfate), the chloroform was removed *in vacuo* and replaced with dry ether. The product was precipitated as the dihydrochloride salt prepared in the usual manner. Recrystallization from methanol–ether afforded 0.35 g. (71%) of white crystals, m.p. 260° dec. A further recrystallization from methanol–acetone gave an analytical sample of the same decomposition point: infrared spectrum (μ, KBr), 6.30 (NH_2); pK'_a 3.74 and 8.85 (50% methanol).

Anal. Calcd. for $C_{14}H_{22}Cl_2N_2$: C, 58.12; H, 7.66; N, 9.68. Found: C, 57.87; H, 7.84; N, 9.52.

The corresponding free base was purified by recrystallization from petroleum ether and melted at 84–85°.

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.70; H, 9.32; N, 12.95. Found: C, 77.65; H, 9.34; N, 12.99.

A Study of the Aminophthalimidoacetic Acids[1]

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The 3- and 4-aminophthalimidoacetic acids and their methyl esters have been synthesized by hydrogenation of the corresponding nitro compounds, and the ultraviolet absorption spectra of these and of the aminophthalimides have been determined. The aminophthalimide moieties have absorption maxima at 385–389 mμ for the 3-isomer and 372–375 mμ for the 4-isomer, but show a substantial hypsochromic shift under basic conditions. The results are discussed in terms of structures of substituted phthalimides and the reactions of the imide group with aqueous base.

With the exception of the nitrophthalimides,[3] only brief studies have been made of the syntheses and properties of phthalimides monosubstituted on the aromatic ring, and very little of this work has been done with the potentially biologically interesting phthalimido acids. The reactions and other properties of the phthalimido acids with substituents on the phthalimide group are thus largely unknown. This paper describes the first of a series of projected explorations into the chemistry of such phthalimido acids.

The aminophthalimidoacetic acids were selected for initial study because of their possible interest as novel amino acids. Among the procedures which have been used for their synthesis, the phthalimidoacetic acids have been made from the phthalic anhydride and glycine either by fusion of the reactants,[4] or by reaction in refluxing toluene[5] or acetic acid.[6] The nitrophthalimidoacetic acids have also been made by the hydrolysis of the nitrophthalimidoacetonitriles.[7] We have been able to improve the synthesis of phthalimidoacetic acids by carrying out the reaction between the phthalic anhydride and glycine in refluxing nitrobenzene, which removes the limitation on the size of the run imposed by the fusion method, and requires a shorter reaction time than is the case with lower boiling solvents.

The unsubstituted aminophthalimides are conveniently prepared from the nitrophthalimides by the action of stannous chloride,[8] or by high-pressure hydrogenation on nickel.[9] Low-pressure hydrogenation on palladium was found in the present work to be very satisfactory for reducing the nitrophthalimidoacetic acids.

The most striking physical property of the aminophthalimides is their intense yellow color. This property is unexpected, considering that the chromophores in these molecules normally do not absorb sufficiently strongly at the longer wave lengths to convey visible color. On the other hand, the nitrophthalimides are nearly colorless, displaying only a pale ivory color instead of the light yellow usually characteristic of nitro compounds.

The ultraviolet absorption spectra of the nitro- and aminophthalimide derivatives and of some representative models were determined in neutral, acidic, and basic solutions. All of the 3-amino compounds showed a maximum at 383–389 mμ in neutral and acid solution, and, in most cases, a roughly equally strong band at 256–258 mμ. The 4-amino compounds showed absorption bands at shorter wave lengths, 368–375, and usually also at 252–260 mμ in neutral and acid solutions. The 4-amino compounds also showed a weaker band at 298–308 mμ. A summary of the ab-

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(2) Abstracted in part from the M.S. Thesis of P. C. Atkinson.

(3) For example: (a) P. P. T. Sah and T. S. Ma, *Ber.*, **65**, 1630 (1932); (b) J. W. Alexander and S. M. McElvain, *J. Am. Chem. Soc.*, **60**, 2285 (1938); (c) J. H. Billman and R. V. Cash, *ibid.*, **75**, 2499 (1953).

(4) (a) A. Reese, *Ann.*, **242**, 1 (1887); (b) J. H. Billman and W. F. Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948); (c) J. C. Sheehan and J. J. Ryan, *ibid.*, **73**, 4367 (1951); (d) L. H. Rombach and I. R. MacGregor, *J. Org. Chem.*, **19**, 428 (1954).

(5) A. K. Bose, F. Greer, and C. C. Price, *ibid.*, **23**, 1335 (1958).

(6) G. Vanags and A. Veinbergs, *Ber.*, **75B**, 1558 (1942).

(7) H. Stephen, *J. Chem. Soc.*, 871 (1931).

(8) (a) H. Kaufmann and A. Beissenger, *Ber.*, **36**, 2494 (1903); (b) M. T. Bogert and R. R. Renshaw, *J. Am. Chem. Soc.*, **30**, 1141 (1908); (c) M. T. Bogert and F. L. Jouard, *ibid.*, **31**, 488 (1909).

(9) H. J. Francis, Jr., M.S. Thesis, Pennsylvania State University, 1949, pp. 52, 55.