oxide catalyst. The crude diamine weighed 1.6 g. and had m.p. 134–135°. Two crystallizations from 50% ethanol gave 1.3 g. of shiny plates, m.p. 138–139°. The spectrum showed maxima at 226 (ϵ 29,800), 281 (ϵ 8,610), and 327 mμ (ϵ 5,270) and minima at 261 (ϵ 4,810), and 300 mμ (ϵ 3,400) with a shoulder at 239 mμ (ϵ 20,500).

Anal. Calc'd for $C_{13}H_{12}N_2$: C, 79.55; H, 6.26; N, 14.28. Found: C, 79.23; H, 6.26; N, 14.13.

4,5-Di(acetylamino)fluorene was prepared by acetylation of III with acetic anhydride in benzene. It crystallized from ethanol as white fluffy needles, m.p. 273°. The spectrum had maxima at 221 (ϵ 72,100), 243 (ϵ 46,700) and 275 mμ (ϵ 33,200) with minima at 241 (ϵ 46,300) and 260 mμ (ϵ 26,400).

Anal. Calc'd for $C_{17}H_{16}N_2O_2$: N, 10.00. Found: N, 9.68.

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The Preparation of 4-Amino-2-phenyl-2-butanol

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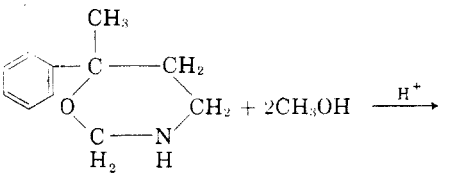
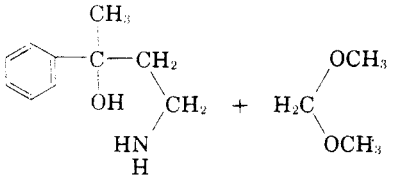
The preparation of 6-methyl-6-phenyltetrahydro-1,3-oxazine (I) from α-methylstyrene, formaldehyde, and ammonium chloride has been reported.[1,2] During investigations of this reaction involving the methanolysis previously described,[2] it was observed that prolongation or repetition of the methanol treatment resulted in cleavage of the oxazine ring. When 6-methyl-6-phenyltetrahydro-1,3-oxazine (I) was heated with one equivalent of hydrochloric acid and excess methanol[3] there was obtained 82%



I

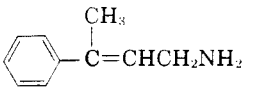


II

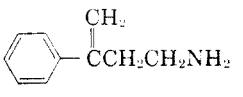
of 4-amino-2-phenyl-2-butanol (II). The reaction involves cleavage of the oxazine ring and elimination of formaldehyde by its conversion to methylal.

Other examples of the degradation of tetrahydro-1,3-oxazines have been reported by Urbanski and co-workers.[4,5] These investigators successfully cleaved and eliminated formaldehyde from 5-nitro-5-ethyltetrahydro-1,3-oxazine and 5-nitro-5-alkyl-3-benzyltetrahydro-1,3-oxazines using hydrochloric acid alone or diluted with alcohol. The corresponding amino alkanols were obtained. Cleavage of 6-methyl-6-aryltetrahydro-1,3-oxazines by hydrochloric acid alone, however, does not give the corresponding 3-amino alkanols. Ring closure takes place instead, to give the corresponding 4-aryl-4-piperidinols and 4-aryl-1,2,3,6-tetrahydropyridines.[2,6]

Dehydration of 4-amino-2-phenyl-2-butanol (II) to 3-phenyl-2-butenylamine (III) has been carried out using either hydrochloric acid or polyphosphoric acid. The structure of III was established by quantitative hydrogenation to 3-phenylbutylamine, which has been prepared previously by Tsukervanik and Grebenyuk[7] from β-phenylbutyronitrile, and by its spectra. The ultraviolet spectrum showed strong styrene-like conjugation. The alternative structure (IIIa) was eliminated by the infrared spectrum which showed only weak ab-



III



IIIa

sorption in the region of olefinic hydrogen wagging ($\sim$ 890 cm.$^{-1}$) and C=C stretching ($\sim$ 1625 cm.$^{-1}$). Further support for III was provided by methyl group absorption at $\sim$1370 cm.$^{-1}$ and by resemblance to the spectrum of 2-phenyl-2-butene.[8]

Acknowledgment. We wish to thank Dr. J. D. Stroupe and his staff for spectroscopic data and physical-chemical interpretation and Mr. C. W. Nash and his staff for analytical data reported.

EXPERIMENTAL[9]

4-Amino-2-phenyl-2-butanol (II). (*Method A*). *From 6-methyl-6-phenyltetrahydro-1,3-oxazine* (I). A mixture of 50 g. (0.28 mole) of 6-methyl-6-phenyltetrahydro-1,3-oxazine (I), 100 g. (3.13 moles) of methanol, and 28 g. (0.28 mole) of concentrated hydrochloric acid was heated at 72° for 6 hours and then to 95° during another hour while the methanol distilled off. The mixture was cooled, poured into

(1) Hartough, Dickert, and Meisel, U. S. Patent 2,647,117 (July 28, 1953); *Chem. Abstr.*, **48**, 8265 (1954).

(2) Schmidle and Mansfield, *J. Am. Chem. Soc.*, **78**, 1702 (1956).

(3) Subsequent to submission of this communication Hartough, Dickert, and Meisel reported the reaction of 6-phenyltetrahydro-1,3-oxazine with methanol and acid to give 3-amino-1-phenyl-1-propanol and methylal. Abstracts of Papers, First Regional Meeting Delaware Valley, American Chemical Society, Philadelphia, Pa., February 16, 1956.

(4) Hirst, Jones, Minahan, Ochynski, Thomas, and Urbanski, *J. Chem. Soc.*, 924 (1947).

(5) Gurne and Urbanski, *Bull. acad. polon. sci., Classe III*, **3**, 175 (1955); *Chem. Abstr.*, **49**, 13998 (1955).

(6) Schmidle and Mansfield, *J. Am. Chem. Soc.*, **78**, 425 (1956).

(7) Tsukervanik and Grebenyuk, *Doklady Akad. Nauk S.S.S.R.*, **76**, 223 (1951); *Chem. Abstr.*, **45**, 6904 (1951).

(8) Cram, *J. Am. Chem. Soc.*, **74**, 2137 (1952).

(9) All melting points are uncorrected.

500 ml. of water, extracted with toluene, and made basic with excess 50% sodium hydroxide. The amine was taken up in toluene, dried, and distilled to give 38 g. (82%) of 4-amino-2-phenyl-2-butanol (II), b.p. 105–115° (1.7 mm.). This crystallized and after recrystallization from heptane melted at 75–77°.

Anal. Calc'd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.84; H, 9.02; N, 8.43.

A *hydrochloride* was prepared and this melted at 142–143° after recrystallization from a 20:1 mixture of acetone and isopropyl alcohol.

Anal. Calc'd for $C_{10}H_{16}ClNO$: C, 59.54; H, 7.99; N, 6.94; Cl, 17.6. Found: C, 59.85; H, 8.17; N, 7.05; Cl, 17.5.

(*Method B*). *Directly from α-methylstyrene, formaldehyde, and ammonium chloride.* A stirred mixture of 108 g. (2.02 moles) of ammonium chloride, 334 g. (4.13 moles) of 37% aqueous formaldehyde, and 118 g. (1.00 mole) of α-methylstyrene was warmed to 60° and held at 60–61° by external cooling until the exothermic reaction subsided. Stirring was continued another ½ hour while the temperature fell to 40°. There was added 300 ml. of methanol, the mixture was stirred for ½ hour, and then was heated to 90° while the methanol distilled off. The methanol treatment was repeated twice and the mixture was poured into 1 l. of water, extracted with toluene, and made basic with excess 50% sodium hydroxide. The amine was taken up in toluene, dried, and distilled to give 102 g. (62%) of 4-amino-2-phenyl-2-butanol (II), b.p. 95–105° (0.65 mm.). This solidified and was recrystallized from heptane, m.p. 75–77°. The melting point of a mixture with the material from *Method A* was 75–77°.

3-Phenyl-2-butenylamine (III). *A. Using hydrochloric acid.* A mixture of 50 g. (0.30 mole) of 4-amino-2-phenyl-2-butanol (II) and 200 g. (1.0 mole) of 18.5% hydrochloric acid was stirred on a steam-bath for 4 hours, cooled, diluted with 300 ml. of water, and made basic with excess 50% sodium hydroxide solution. The amine was taken up in toluene, dried, and distilled to give 15 g. (34%) of 3-phenyl-2-butenylamine (III), b.p. 80–90° (1.0 mm.). There was also recovered 12 g. of unreacted II, b.p. 100–105° (1.0 mm.) which solidified and melted at 75–77° after recrystallization from heptane.

Anal. Calc'd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.76; H, 9.05; N, 9.34.

B. Using polyphosphoric acid (115% ortho-equivalent). To 50 g. (0.30 mole) of stirred 4-amino-2-phenyl-2-butanol was slowly added 100 g. of polyphosphoric acid, the exotherm being controlled by external cooling so that the temperature did not rise above 150°. The mixture was stirred 15–20 minutes at 125–150° and then for one hour while cooling took place. There was added 500 ml. of water and excess 50% sodium hydroxide solution. The amine was taken up in toluene, dried, and distilled to give 10 g. (23%) of 3-phenyl-2-butenylamine (III), b.p. 83–93° (1.6 mm.).

Anal. Calc'd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.70; H, 8.97; N, 9.59.

A *hydrochloride* was prepared which melted at 204–206° after recrystallization from a 20:1 mixture of acetone and isopropyl alcohol.

Anal. Calc'd for $C_{10}H_{14}ClN$: C, 65.39; H, 7.68; N, 7.63; Cl, 19.3. Found: C, 64.94; H, 7.69; N, 7.71; Cl, 19.4.

3-Phenylbutylamine. Quantitative hydrogenation of 3-phenyl-2-butenylamine (III) using a 5% palladium on alumina catalyst in 95% ethanol at atmospheric pressure required 0.99 *molar*-equivalent of hydrogen. A *picrate* prepared from the resulting solution of 3-phenylbutylamine melted at 137–139°. Tsukervanik and Grebenyuk[7] reported m.p. 138–139°.

Anal. Calc'd for $C_{16}H_{18}N_4O_7$: C, 50.79; H, 4.79; N, 14.81. Found: C, 50.41; H, 4.90; N, 14.59.

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Heterocyclic Sulfonamides as Carbonic Anhydrase Inhibitors. 2-Acylamido- and 2-Sulfonamido-1,3,4-thiadiazole-5-Sulfonamides

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The observation reported here that the 2-propionamido analog of 2-acetamido-1,3,4-thiadiazole-5-sulfonamide,[2,3,4] has appreciable *in vitro* carbonic anhydrase inhibitory activity led to the synthesis of other compounds of this type. A series of analogs was prepared, therefore, in which the 2-acetamido group in the parent compound was replaced by other 2-acylamido and by 2-sulfonamido groups. The compounds prepared and their relative *in vitro* activities are listed in Table I.

Ordinary, well-known reaction conditions for the acylation of amines were used throughout in the preparation of this series of 2-N-substituted aminothiadiazoles. The efficiency of the various techniques varied markedly over the series, however. Thus, the low-molecular-weight aliphatic acyl groups, formyl through propionyl, were introduced by heating 2-amino-1,3,4-thiadiazole-5-sulfonamide[3] with the corresponding acid anhydrides. The higher acyl analogs, butyryl through valeryl, could not be obtained by this procedure but were prepared by causing the corresponding acid chlorides to react with the aminothiadiazole in pyridine. Schotten-Baumann conditions were unsuccessful with these acid chlorides.

With the aromatic acyl and sulfonyl chlorides, exactly the opposite was true. The products could not be obtained in pyridine, but were obtained, usually in low yield, under conditions of the Schotten-Baumann reaction.

We are indebted to Dr. T. H. Maren and staff of the Pharmacological Research Department for the *in vitro* activities reported in Table I.

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(2) Diamox ® brand of Acetazolamide.

(3) Roblin and Clapp, *J. Am. Chem. Soc.*, **72**, 4890 (1950).

(4) Miller, Dessert, and Roblin, *J. Am. Chem. Soc.*, **72**, 4893 (1950).