and Brewster[9] in their studies on *ortho*-substituted diphenyl ethers.

The 11.6–14.3 μ region of the spectra (characteristic of the Si—C linkage) is equally complicated by aromatic absorption bands.

The absence of hydroxy absorptions in the 2.7–3.0 μ region of these spectra supports the fact that these derivatives are phenoxy-substituted silanes and not hydroxyphenyl-substituted silanes.

EXPERIMENTAL

General procedure. All reactions were carried out under a dry nitrogen atmosphere and the sequence of reactions was the following:

A molar solution of the phenol in tetrahydrofuran was prepared in a flask equipped with a stirring assembly, condenser, dropping funnel, and a nitrogen inlet. To the solution was added an equivalent molar quantity or slight excess of ethereal three molar methylmagnesium bromide. After a short reflux period, the appropriate chlorosilane, dimethyldichloro- or trimethylchlorosilane, was added.

The reaction mixture was then refluxed for a short time, cooled, diluted with benzene, toluene, or a hydrocarbon, concentrated to remove any unreacted chlorosilane and ethereal solvent, then filtered to remove the magnesium halides formed. The filtrate was then fractionated at reduced pressures.

Due to the almost identical boiling points of the phenols and their trimethylsilyl derivatives, these filtrates were treated with metallic sodium or methylmagnesium bromide in order to retain the phenol present during the distillation.

Phenoxytrimethylsilane (Ia). The yield of Ia from 94.1 g. (1 mole) of phenol, 1.29 moles of methylmagnesium bromide, and 1.43 moles of trimethylchlorosilane was 96.6 g. (58% yield): b.p. 110° (90 mm.); f.p. −55°; d_4^{25} 0.9209, n_D^{20} 1.4782. (Langer[1] lists b.p. 181.9–182.4; d_4^{25} 0.9209; n_D^{20} 1.4782.)

Anal. Calcd. for $C_9H_{14}SiO$: C, 65.01; H, 8.49; Si, 16.88. Found: C, 64.95; H, 8.44; Si, 16.92.

2,6-Dimethylphenoxytrimethylsilane (Ib). The yield of Ib from 122.2 g. (1 mole) of 2,6-dimethylphenol, 1.33 moles of methylmagnesium bromide, and 200 ml. (1.58 moles) of trimethylchlorosilane was 144.2 g. (74% yield): b.p. 120° (43 mm.); f.p. −44°; d_4^{25} 0.9228; n_D^{20} 1.4862.

Anal. Calcd. for $C_{11}H_{18}SiO$: C, 67.99; H, 9.34; Si, 14.44. Found: C, 68.25; H, 9.22; Si, 14.74.

2,6-Diisopropylphenoxytrimethylsilane (Ic). The yield of Ic from one mole quantities of 2,6-diisopropylphenol, methylmagnesium bromide, and trimethylchlorosilane was 184 g. (74% yield): b.p. 154° (50 mm.); f.p. −12.4°; d_4^{25} 0.9015; n_D^{20} 1.4838.

Anal. Calcd. for $C_{15}H_{26}SiO$: C, 71.94; H, 10.47; Si, 11.20. Found: C, 72.14; H, 10.46; Si, 11.30.

Diphenoxydimethylsilane (IIa). The yield of IIa from 226 g. (2.4 moles) of phenol, 800 ml. of 3*M* methylmagnesium bromide, and 154.9 g. (1.2 moles) of dimethyldichlorosilane was 234.3 g. (79.9% yield): b.p. 104–106° (0.8 mm.) and 93–94° (0.15 mm.); f.p. −23°; d_4^{25} 1.0599; n_D^{20} 1.5330. (George and Newkirk[2] list b.p. 206° (100 mm.); d_{20} 1.063; n_D^{20} 1.5335.)

Anal. Calcd. for $C_{14}H_{16}O_2Si$: C, 68.82; H, 6.60; Si, 11.48. Found: C, 68.92; H, 6.20; Si, 11.60.

Bis(2,6-dimethylphenoxy)dimethylsilane (IIb). The yield of IIb from 293.3 g. (2.4 moles) of 2,6-dimethylphenol, 2.4 moles of methylmagnesium bromide, and 159.9 g. (1.2 moles) of dimethyldichlorosilane was 288.7 g. (80.1% yield): b.p. 130–131° (0.2–0.3 mm.); m.p. 37–38°; n_D^{20} 1.5320 (supercooled).

Anal. Calcd. for $C_{18}H_{24}O_2Si$: C, 71.96; H, 8.05; Si, 9.34. Found: C, 71.91, 72.14; H, 7.99, 8.19; Si, 9.24, 9.11.

Bis(2,6-diisopropylphenoxy)dimethylsilane (IIc). The yield of IIc from 178.3 g. (1.0 mole) of 2,6-diisopropylphenol, 1.05 moles of methylmagnesium bromide, and 64.5 g. (0.50 mole) of dimethyldichlorosilane was 154.0 g. (74.7% yield) after recrystallizing from denatured ethanol: b.p. 142–146° (0.15 mm.); m.p. 89.0–89.5°.

Anal. Calcd. for $C_{22}H_{40}O_2Si$: C, 75.76; H, 9.77; Si, 6.80. Found: C, 76.10, 75.95; H, 9.71, 9.89; Si, 6.60, 6.52.

2,6-Diisopropylphenoxydimethylchlorosilane (IIIc). A solution of bromomagnesium-2,6-diisopropylphenoxide, prepared from 178.3 g. (1.0 mole) of 2,6-diisopropylphenol and 1.05 moles of methylmagnesium bromide in tetrahydrofuran, was added to a second solution of 258 g. (2.0 moles) of dimethyldichlorosilane in tetrahydrofuran. The yield of IIIc was 55.0 g. (20.3% yield): b.p. 66–67° (0.4–0.45 mm.); n_D^{20} 1.4925.

Anal. Calcd. for $C_{14}H_{23}OSiCl$: C, 62.08; H, 8.56; Si, 10.36; Cl, 13.09. Found: C, 61.76; H, 8.48; Si, 10.59; Cl, 13.58.

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(9) M. Dahlgard and R. Brewster, *J. Am. Chem. Soc.*, **80**, 5861 (1958).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KANSAS]

Reaction of Epoxides with 2-Aminobenzenethiol

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Reaction of ethylene oxide, cyclopentene oxide, and styrene oxide with 2-aminobenzenethiol anion has been found to give the corresponding 2-aminophenyl-2-hydroxyethyl sulfides. With styrene oxide, the product is a mixture of 2-aminophenyl-2-hydroxy-1-phenylethyl sulfide and 2-aminophenyl-2-hydroxy-2-phenylethyl sulfide. 2-Aminobenzene thiol in basic solution effects debromination of *trans*-1,2-dibromocyclohexane to give an almost quantitative yield of cyclohexene.

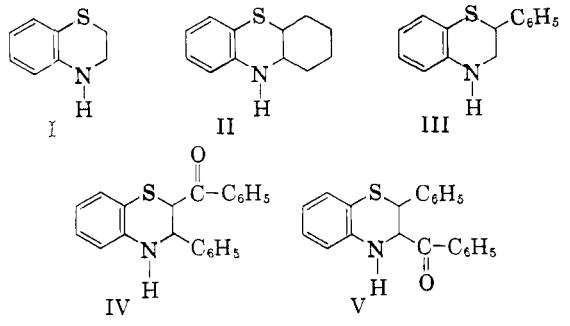
In 1949, Culvenor and co-workers[2] reported that the reaction of 2-aminobenzenethiol anion with ethylene oxide, cyclohexene oxide, styrene oxide, and benzoylphenylethylene oxide, respectively, afforded in every case the corresponding dihydrobenzo-1,4-thiazine [2,3-dihydrobenzo-1,4-thiazine

(1) Smith Kline and French Laboratories.

(1a) University of Kansas.

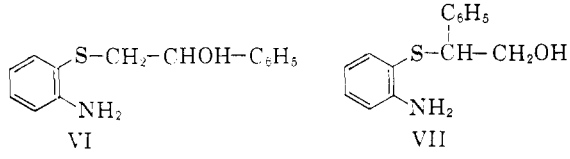
(2) C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 278 (1949).

(I), hexahydropheno-1,4-thiazine (II), 2-phenyl-2,3-dihydrobenzo-1,4-thiazine (III), or one of the two possible benzoylphenyl-2,3-dihydrobenzo-1,4-thiazines (IV and V)].



Ring closure presumably resulted from elimination of a molecule of water between the amino group of 2-aminobenzenethiol and the hydroxy group formed upon nucleophilic opening of the epoxide ring by the negatively charged sulfur.

Fusco and Palazzo[3] in 1951 extended this work. They likewise reported that the reaction of the anion of 2-aminobenzenethiol with ethylene oxide afforded I, which, they noted, however, underwent hydrolysis with ring opening to form a dibenzoyl derivative under Schotten-Baumann conditions and to form a coupled product with β-naphthol under typical coupling conditions. These authors reported further that with propylene oxide the product was 3-methyl-2,3-dihydrobenzo-1,4-thiazine but that with styrene oxide a mixture of III and 2-aminophenyl-2-hydroxy-2-phenylethyl sulfide (VI) was obtained.



Since then, other workers[4,5] have based dihydrobenzothiazine structure assignments on the work of Culvenor *et al.*[2]

As part of a continuing study on the opening of epoxide rings, we undertook to re-examine these reactions. It soon became apparent that reaction of 2-aminobenzenethiol anion with epoxides does not normally proceed with ring closure to the dihydrobenzothiazine. While our work was in progress, Fujii[6] demonstrated conclusively that the product of reaction of 2-aminobenzenethiol with ethylene oxide was the uncyclized 2-aminophenyl-2-hydroxyethyl sulfide, and not I, an authentic sample of which had been prepared by reaction of 2-aminobenzenethiol with ethylene bromide,[7] and more recently by the lithium aluminum hydride reduction of 2,3-dihydrobenzo-1,4-thiazin-3-one.[8] The confusion concerning the separate identity of I and of 2-aminophenyl-2-hydroxyethyl sulfide apparently arose from the chance circumstance that both compounds melt at exactly the same temperature (40°), as do also their phenylthiourea derivatives (129°).

More recently Hromatka and co-workers[9] have shown that the reaction of the anion of 2-aminobenzenethiol with cyclohexene oxide leads not to II, but to the uncyclized amino alcohol 2-aminophenyl-2-hydroxycyclohexyl sulfide. This group has since reported the synthesis of hexahydrophenothiazine-9-dioxide[10] and of hexahydrophenothiazine[11] itself.

Our work has confirmed the results of Fujii[6] and of Hromatka.[9] We have found, further, that 2-aminobenzenethiol anion reacts with cyclopentene oxide to form 2-aminophenyl-2-hydroxycyclopentyl sulfide and with styrene oxide to form a mixture of the uncyclized isomers 2-aminophenyl-2-hydroxy-2-phenylethyl sulfide (VI) and 2-aminophenyl - 2 - hydroxy - 1 - phenylethyl sulfide (VII), formed by opening of the epoxide ring at the primary and secondary carbon atoms, respectively. The ring-closed 2-phenyl-2,3-dihydrobenzo-1,4-thiazine (III), reported by Fusco,[3] was absent. VII is a solid, m.p. 105.0–106.5°, whereas VI is a liquid, m.p. of hydrochloride 175.5–177.0°.

The structures of VI and VII were established by means of analytical and infrared data and by desulfurization of VI to 2-phenylethanol or, through the use of freshly prepared W-6 Raney nickel catalyst, to a mixture of toluene and ethylbenzene.[12]

Authentic 2 - phenyl - 2,3 - dihydrobenzo-1,4-thiazine was prepared by the lithium aluminum hydride reduction of 2-phenyl-2,3-dihydrobenzo-1,4-thiazin-3-one, and its properties differed markedly from those of either VI or VII.

An attempt to prepare hexahydrophenothiazine by reaction of the anion of 2-aminobenzenethiol with *trans*-1,2-dibromocyclohexane gave only cyclohexene and 2,2′-diaminodiphenyldisulfide in

(3) R. Fusco and G. Palazzo, *Gazz. chim. ital.*, **81**, 735 (1951).

(4) G. Cauquil, H. Barrera, and R. Barrera, *Bull. soc. chim. France*, 1276 (1950).

(5) G. Cauquil and A. Casadevall, *Bull. soc. chim. France*, 768 (1955).

(6) K. Fujii, *J. Pharm. Soc. Japan*, **77**, 352 (1957); *Chem. Abstr.*, **51**, 12101 (1957).

(7) N. A. Langlet, *Bihang. till Svenska Vet.-Akad. Handlingar*, **22**II, 3 (1896); *Beilstein*, **27**, p. 34.

(8) J. C. Craig, W. P. Rogers, and G. P. Warwick, *Australian J. Chem.*, **8**, 252 (1955).

(9) O. Hromatka, M. Vaculny, H. Petrousek, and F. Goss, *Monatsh.*, **88**, 307 (1957).

(10) O. Hromatka, J. Augl, and K. Wiltschke, *Monatsh.*, **89**, 418 (1958).

(11) O. Hromatka, J. Augl, M. Vaculny, and H. Petrousek, *Monatsh.*, **89**, 517 (1958).

(12) J. A. Zderic, W. A. Bonner, and T. W. Greenlee, *J. Am. Chem. Soc.*, **79**, 1696 (1957), have shown that by treatment with very active Raney nickel 2-phenylethanol is converted into a mixture of toluene and ethylbenzene and 1-phenylethanol into ethylbenzene.

high yields. Preliminary experiments indicate that this reaction is fairly general for thiols and 1,2-dihaloalkanes. Further studies on this reaction are in progress.

EXPERIMENTAL

2-Aminophenyl-2-hydroxyethyl sulfide. Ethylene oxide (35 g., 0.79 mole) was added from a Dry Ice-jacketed dropping funnel to a stirred and cooled solution of 94 g. (0.75 mole) of 2-aminobenzenethiol and 42 g. (0.75 mole) of potassium hydroxide in 750 ml. of alcohol. After the addition was complete, the reaction mixture was warmed slowly, refluxed for 1 hr. and then concentrated under reduced pressure. The residue was distilled under reduced pressure to give 75 g. (66%) of colorless 2-aminophenyl-2-hydroxyethyl sulfide, b.p. 200–203° (20 mm.), m.p. after one recrystallization from ether–petroleum ether, 39.5–41.0°. Comparable results were obtained when ethylene chlorohydrin was used in place of ethylene oxide. The product was readily diazotized, and its infrared spectrum showed the bands for a primary amine and a hydroxyl group.

Anal. Calcd. for $C_8H_{11}NOS$: C, 56.8; H, 6.55; N, 8.28. Found: C, 57.1; H, 6.50; N, 8.23.

Admixture of the product with authentic 2,3-dihydrobenzo-1,4-thiazine, m.p. 39.0–40.8°, obtained by lithium aluminum hydride reduction of 2,3-dihydrobenzo-1,4-thiazin-3-one, synthesized according to Unger,[13] formed an oil.

The phenylthiourea derivative melted at 128.0–129.5° (reported[8] 127–128°) after recrystallization from alcohol. It depressed the melting point (128.3–129.1°) of the phenylthiourea derivative of authentic 3,4-dihydrobenzo-1,4-thiazine.

Anal. Calcd. for $C_{15}H_{16}N_2OS_2$: C, 59.2; H, 5.30. Found: C, 59.5; H, 5.42.

A dibenzoyl derivative, m.p. 82.5–84.0° after recrystallization from alcohol, was formed by the Schotten-Baumann procedure.

Anal. Calcd. for $C_{22}H_{19}NO_3S$: C, 70.0; H, 5.07. Found: C, 70.1; H, 5.16.

The acid tartrate salt melted at 127.0–128.3° after recrystallization from alcohol.

Anal. Calcd. for $C_{12}H_{17}NO_7S$: C, 45.1; H, 5.37. Found: C, 45.2; H, 5.34.

Reaction of 2-aminobenzenethiol with cyclopentene oxide. Cyclopentene oxide (8.4 g., 0.10 mole) was added dropwise to a stirred solution of 12.5 g. (0.10 mole) of 2-aminobenzenethiol and 5.6 g. (0.10 mole) of potassium hydroxide in 100 ml. of ethanol. The mixture was refluxed for 30 min., then cooled, and several volumes of water were added. The oil layer was separated, the water layer was extracted with two 150-ml. portions of ether, and the organic layers were combined and dried over magnesium sulfate. After removal of the ether, the residue was distilled to give 16.7 g. (80%) of a colorless solid, m.p. 74.5–75.2°, which on the basis of its analysis, the fact that its infrared spectrum showed two strong absorption maxima in the N—H and one in the O—H stretching region, and its ready formation of a diazonium salt, was assigned the structure 2-aminophenyl-2-hydroxycyclopentyl sulfide.

Anal. Calcd. for $C_{11}H_{15}NOS$: C, 63.1; H, 7.23; N, 6.69. Found: C, 63.4; H, 7.40; N, 6.64.

Treatment of the amino alcohol with *p*-nitrobenzoyl chloride in refluxing pyridine gave a mixture of the mono- and di-*p*-nitrobenzoates, m.p. 149.2–150.1° and 107.0–108.2°, respectively, which were separated chromatographically on an alumina column.

Anal. Calcd. for $C_{18}H_{18}N_2O_4S$: C, 60.3; H, 5.06; N, 7.82; S, 8.93. Found: C, 60.1; H, 5.04; N, 7.91; S, 9.06.

Anal. Calcd. for $C_{25}H_{21}N_3O_7S$: C, 59.2; H, 4.17; N, 8.28. Found: C, 59.4; H, 4.13; N, 8.40.

(13) O. Unger, *Ber.*, **30**, 607 (1897).

Reaction of 2-aminobenzenethiol with styrene oxide. Styrene oxide (30 g., 0.25 mole) was added dropwise with stirring over a 30-min. period to a solution of 31 g. (0.25 mole) of 2-aminobenzenethiol and 14.0 g. (0.25 mole) of potassium hydroxide in 250 ml. of ethanol. The solution was refluxed for 1 hr. and then concentrated to half its original volume. Several volumes of water were added, the oil layer separated, and the water layer extracted with two 125-ml. portions of ether. The combined organic layers were extracted with 250 ml. of 3*N* hydrochloric acid. The acid layer was cooled in an ice bath, and a hydrochloride salt gradually separated. This was removed by filtration and treated with 100 ml. of 10% sodium hydroxide solution and 150 ml. of ether. The ether solution was separated, dried over magnesium sulfate and the ether removed. Vacuum distillation of the residue afforded 23 g. (38%) of a heavy yellow oil, b.p. 192–197° (0.3 mm.), which was converted to the hydrochloride, m.p. 175.5–177.1° after recrystallization from alcohol.

Anal. Calcd. for $C_{14}H_{15}ClNOS$: C, 59.7; H, 5.7. Found: C, 59.7, 59.7; H, 6.0, 5.9.

The acid filtrate remaining after removal of the crystalline hydrochloride was made basic with sodium hydroxide and extracted with ether. The ether solution was dried over magnesium sulfate and the ether removed. The solid remaining was recrystallized from alcohol and afforded 18 g. (30%) of colorless needles, m.p. 104.6–105.5°.

Anal. Calcd. for $C_{14}H_{15}NOS$: C, 68.6; H, 6.16. Found: C, 68.6; H, 6.36.

Both products showed two strong infrared absorption peaks in the N—H and one in the O—H stretching region and both were readily diazotized. On the basis of its subsequent desulfurization to 2-phenylethanol and to a mixture of toluene and ethylbenzene, the solid isomer was assigned the structure 2-aminophenyl-2-hydroxyethyl-1-phenylethyl sulfide (VII). The liquid isomer is, accordingly, 2-aminophenyl-2-hydroxyethyl-2-phenylethyl sulfide (VI).

Treatment of VII with *p*-nitrobenzoyl chloride in refluxing pyridine afforded a mixture of the mono-*p*-nitrobenzoyl derivative, m.p. 109.5–110.6° after recrystallization from benzene-hexane, and the di-*p*-nitrobenzoate, m.p. 177.0–178.4° after recrystallization from benzene-hexane. The two *p*-nitrobenzoates were separated by chromatographic adsorption on alumina from a solution of 50% (by volume) of hexane and chloroform.

Anal. Calcd. for $C_{21}H_{18}N_2O_4S$: C, 64.0; H, 4.60; N, 7.10. Found: C, 64.2; H, 4.75; N, 6.92.

Anal. Calcd. for $C_{28}H_{21}N_3O_7S$: C, 61.9; H, 3.89; N, 7.73. Found: C, 62.0; H, 4.07; N, 7.53.

Desulfurization of 2-aminophenyl-2-hydroxy-1-phenylethyl sulfide. Seven grams of the solid isomer (m.p. 104.6–105.5°) formed in the reaction of 2-aminobenzenethiol with styrene oxide was refluxed for 4 hr. with 120 g. of Raney nickel and 200 ml. of 95% alcohol. The mixture was filtered, the solvent removed, and the residue taken up in ether and washed several times with dilute hydrochloric acid. The ether was removed and the remaining oil, b.p. 215–221° (748 mm.), distilled. The phenylurethane prepared directly from the distillate melted at 79.0–80.2° and did not depress the melting point (80.0–80.5°) of the phenylurethane of authentic 2-phenylethanol.

With freshly prepared W-6 Raney nickel the product was a mixture of toluene and ethylbenzene, analyzed by means of vapor phase chromatography.

2-Phenyl-2,3-dihydrobenzo-1,4-thiazine. To a slurry of 3 g. of lithium aluminum hydride in 200 ml. of ether was added a suspension in 250 ml. of ether of 13.2 g. of 2-phenyl-2,3-dihydrobenzo-1,4-thiazin-3-one, m.p. 205.0–206.5°, prepared by reaction of 2-aminobenzenethiol with D,L-2-chlorophenylacetic acid in ethanol according to the general method of Unger.[13] The mixture was heated under reflux for 24 hr. The complex was then decomposed with methanol, the resulting mixture was filtered, and the filtrate evaporated to dryness. The residue was leached with benzene and hexane added to the benzene solution. The solid product which

crystallized was recrystallized from benzene-hexane to yield 9.2 g. (74%) of 2-phenyl-2,3-dihydrobenzo-1,4-thiazine, m.p. 131.2–132.4°, depressed upon admixture with either VI or VII. The infrared spectrum of the product showed only one band in the N—H and none in the O—H stretching region.

Anal. Calcd. for $C_{14}H_{13}NS$: C, 74.0; H, 5.77. Found: C, 73.7; H, 5.98.

Reaction of 2-aminothiophenol with trans-1,2-dibromocyclohexane. To a cooled solution of 12.5 g. (0.10 mole) of 2-aminobenzenethiol and 5.60 g. (0.10 mole) of potassium hydroxide in 50 ml. of ethanol, 12.1 g. (0.050 mole) of *trans*-1,2-dibromocyclohexane in 50 ml. of ethanol was added dropwise with stirring. The mixture was heated under reflux for 1 hr. and the ethanol then removed by distillation.

The residue was washed with water and crystallized from ethanol to give 12.0 g. (96%) of 2,2′-diaaminodiphenyl disulfide, m.p. 90.8–91.5° (reported[14] 89–91°). The aqueous washes upon evaporation afforded 10.8 g. (91%) of potassium bromide.

The ethanol distillate was added to 750 ml. of water and twice extracted with 200-ml. portions of ether. The ether extracts were combined, washed with water, and dried over magnesium sulfate, and the ether was removed. Distillation of the residue yielded 4.0 g. (95%) of cyclohexene, b.p. 81–83°, identified as the 2,4-dinitrobenzenesulfenyl chloride adduct, m.p. 117.2–118.4° (reported[15] 117–118°).

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LAWRENCE, KAN.

(14) J. A. Gardner, British Patent **558,887**, Jan. 26, 1944; *Chem. Abstr.*, **40**, 7237 (1946).

(15) N. Kharasch and C. M. Buess, *J. Am. Chem. Soc.*, **71**, 2724 (1949).

[CONTRIBUTION FROM THE CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of Some Heterocyclic Derivatives of α-Keto Acids

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Hippuric acid was condensed with several alicyclic, aliphatic, and aromatic aldehydes to yield the corresponding 4-(substituted)-2-phenyl-2-oxazoline-5-ones. Using acid hydrolysis, several of these compounds were converted to the corresponding α-keto acid derivative. Cyclohexane- and cyclopentane-glyoxylic acids were condensed with *o*-phenylenediamine to form the corresponding 2-(cycloalkyl)-3-hydroxyquinoxalines, and the latter two keto acids were also allowed to react with 4,5,6-triaminopyrimidine to form the corresponding cycloalkyl-hydroxy-4-amino pteridine derivatives.

For the purpose of study of the biological properties of keto acids which are structurally related to certain naturally occurring keto acids, several derivatives have been prepared in this and a previous investigation.[2] The chemistry of certain of these keto acids was further examined to the extent of preparing the corresponding quinoxaline and pteridine derivatives.

2-Oxo-3-(3-cyclohexene)propionic acid, the keto acid analog corresponding to the leucine antagonist, 3-cyclohexenealanine,[3] was prepared by the interaction of 3-cyclohexene-1-carboxaldehyde with hippuric acid to form the corresponding 2-oxazoline-5-one derivative. Acid hydrolysis of the latter compound yielded the desired keto acid analogue.[4] In the preparation of 4-(3-cyclohexene-1-methylidene)-2-phenyl-2-oxazoline-5-one, the use of sodium acetate as the condensing agent gave a low yield of the intermediate; however, a much superior yield was obtained later by carrying out the reaction in tetrahydrofuran using lead acetate as the condensing agent.[5] Alkaline hydrolysis of the 2-oxazoline-5-one condensation product described above gave 2-benzamido-3-(3-cyclohexene)-acrylic acid. The sequence of these reactions is indicated in the accompanying equations.

The yield of the corresponding 2-oxazoline-5-one derivative through the above reaction is found to be much better in the case of aromatic aldehydes than in the case of aliphatic aldehydes and ketones[4]; however, using the appropriate conditions, cyclopentanone, which has been reported to fail to condense with hippuric acid,[5,6] has recently been converted to the desired derivative, 4-cyclopentylidene-2-phenyl-2-oxazoline-5-one,[2] although in poor yield. Using the above described preparative procedure, tiglic aldehyde was condensed with both hippuric acid and *N*-acetylglycine to yield

(1) Rosalie B. Hite pre-doctoral fellow 1957–1959.

(2) J. D. Fissekis, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, **81**, 2715 (1959).

(3) J. Edelson, C. G. Skinner, J. M. Ravel, and W. Shive, *Arch. Biochem. Biophys.*, **80**, 416 (1959).

(4) Patterned after the procedure of G. R. Ramage and J. L. Simonsen, *J. Chem. Soc.*, 532 (1935); and R. Neher, M. Spillman, L. H. Werner, A. Wettstein, and K. Miescher, *Helv. chim. Acta*, **29**, 1874 (1946).

(5) E. Baltazzi and R. Robinson, *Chem. & Ind. (London)*, **1954**, 191.

(6) V. Boekelheide and L. M. Schramm, *J. Org. Chem.*, **14**, 298 (1948).