unfavored as the increasing bulk of the R groups approaches that of the phenyl.

The increase in the strength of the hydrogen bond, as reflected in $\Delta\nu$,[13] from 35 in the *meso*-methyl to 50 cm.$^{-1}$ in *meso*-*n*-propyl is expected in light of previous observations that replacement by increasingly bulky alkyl groups on the carbons bearing the hydroxyl and phenyl reduces the O–C–C angle and brings the hydroxyls into closer proximity. This is in accord with the Thorpe–Ingold deformation hypothesis that says when steric repulsions increase one of the angles at a carbon atom, the opposite angle is decreased.[13,14]

While these observations support the conclusion that in this series simple intramolecular bonding between hydroxyls is occurring, it is impossible to eliminate completely the possibility of –OH to π bonding involving the electrons of the phenyl ring. The $\Delta\nu$'s obtained in this work are of the approximate order of magnitude as those observed for the –OH to π bonding in β-phenyl ethanols,[15] and the diols measured herein might be considered structural analogs of the β-phenyl ethanols with suitable changes in substitution on the α and β carbons.

The possibility of –OH to π bonding in the PhRC(OH)C(OH)RPh series has been tested by employing the known sensitivity of such bonding to the basicity of the acceptor.[15,16] A tighter hydrogen bond is obtained when electron release into the aromatic system is facilitated.

Synthesis and spectral examination of the *dl* forms of *p*-methyl and *p*-methoxyacetophenone pinacols gave $\Delta\nu$ values of 36 and 35 cm.$^{-1}$, respectively, and a strong intramolecular bonding peak. Since these values are in perfect agreement with the unsubstituted *dl*-acetophenone pinacol (see Table I), it appears that bonding between hydroxyls is favored.

The diols I, III, and V can be assigned the *dl*-configuration, and II, IV, and VI, the *meso*. In the case of I and II this is in agreement with the results obtained by Cram and Kopecky.[7]

Experimental

The bonding measurements were performed in these laboratories on a Perkin-Elmer 421 grating spectrophotometer and by P. von R. Schleyer of Princeton University on a Perkin-Elmer Model 21 spectrophotometer with lithium fluoride optics. All diols were examined as dilute solutions in spectral grade carbon tetrachloride according to standard procedures.

The diols were prepared according to the procedure in the references noted (see Table I) and recrystallized to constant melting point. With the exception of the high melting isomer of 4,5-diphenyl-4,5-octanediol (VI), all had melting points in agreement with those reported. Diol VI was obtained after several recrystallizations from 1:1 hexane–benzene as white microneedles of m.p. 128–129°, as reported.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.47; H, 8.88.

The *dl* isomer of 2,3-di-*p*-tolyl-2,3-butanediol was prepared as described by Backer, Stevens, and Van der Bij.[17] The configurational assignments provided by the authors, on the basis of relative oxidation rates with lead tetraacetate, are confirmed by the bonding study.

The *dl* isomer of 2,3-di-*p*-anisyl-2,3-butanediol was prepared by a method employing Cram's rule of asymmetric induction.[7] To an ice-cooled solution containing 0.40 mole of *p*-anisylmagnesium bromide in 700 cc. of anhydrous ether was added 0.10 mole of 2,3-butanedione in 20 cc. of ether. After addition was complete, the mixture was stirred 12 hr. and hydrolyzed with ice–ammonium chloride solution. The ethereal extracts were concentrated to an oil and steam distilled to remove unchanged diketone and other volatiles. The organic portion of the nonvolatiles was dried and chromatographed on alumina with hexane–benzene elutants. A total of 7.1 g. (23%) of the *dl*-diol was obtained, m.p. 122–123°, (lit.[18] m.p. 122–123°).

Acknowledgment.—Appreciation is expressed to Dr. P. von R. Schleyer, Princeton University, for confirming a portion of the bonding measurements and suggesting the possibility of –OH to π bonding and to Dr. Harold C. Beachell, this institution, for helpful discussions and interpretation.

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Preparation of 2-Bromopyrimidines

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Received January 28, 1963

Conversion of 2-amino- to 2-chloropyrimidines is usually effected by diazotization in concentrated hydrochloric acid. The yields by this procedure rarely exceed 30%.[2] Alternatively, the amine may be diazotized in the presence of sulfuric acid, giving the 2-hydroxy compound which subsequently is chlorinated with phosphorus oxychloride; the over-all yield in this process is likewise about 30%. In our own experience, application of the first method to 2-amino-4,5-diethoxypyrimidine gave the 2-chloro derivative in 38% yield.

We have observed that significantly better results can be obtained in the analogous preparation of 2-bromopyrimidines, by diazotization in hydrobromic acid after formation of a perbromide. This method, introduced by Craig[3] for application to 2-aminopyridines, seems not to have been used hitherto in the pyrimidine series. Thus, 2-amino-4,5-diethoxypyrimidine gave 2-bromo-4,5-diethoxypyrimidine in 79% yield, and 2-amino-4-chloro-5-ethoxypyrimidine gave 2-bromo-4-chloro-5-ethoxypyrimidine in 67% yield.

However, the utility of this reaction is circumscribed by the possibility of side reactions; in particular, it appears that the ease of electrophilic 5-bromination of the pyrimidine ring[4a] will limit the use of the Craig reaction to 5-substituted pyrimidines. From 2-amino-4-methoxypyrimidine the major product was 2-

(1) American Cyanamid Company, Bound Brook, N. J.

(2) (a) N. Sperber, D. Papa, E. Schwenk, M. Sherlock, and R. Fricano, *J. Am. Chem. Soc.*, **73**, 5752 (1951), reported a 52% yield of 2-chloropyrimidine from 2-aminopyrimidine; however, (b) I. C. Kogon, R. Minin, and C. G. Overberger, *Org. Syn.*, **35**, 34 (1955), obtained yields of only 26–27% in this same preparation; (c) K. L. Howard, U. S. Patent 2,477,409 (July 26, 1949), quotes only one yield, 26.8% in the conversion of 2-amino-5-chloropyrimidine to 2,5-dichloropyrimidine.

(3) L. C. Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934).

(4) (a) G. W. Kenner and Sir A. Todd in R. C. Elderfield, "Heterocyclic Compounds," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 290–295; (b) p. 301.

amino-4-methoxy-5-bromopyrimidine (25%), together with 2,5-dibromo-4-methoxypyrimidine (19%). Under the same conditions, the only product isolable from 2-aminopyrimidine itself was 2% of 2-amino-5-bromopyrimidine.[5]

The low yield of recognizable products in the latter case indicated that some side reaction other than ring bromination also was taking place. In a few other instances, such as 2-amino-4,5-di-*n*-propylpyrimidine and 2-amino-4-chloro-5-*n*-propylpyrimidine, the desired product was obtained in only about 10% yield. The principal products from these reactions, which could not be purified, were bromine-containing solids insoluble both in nonpolar solvents and in water. Since they showed no absorption maxima in the ultraviolet, it may be conjectured that degradation of the pyrimidine ring had occurred.

In all the bromopyrimidines described, the position of the bromine atoms was verified by attempted displacement with sodium methoxide. As is well known, halogen substituents in the 2-, 4-, and 6-positions undergo ready nucleophilic displacement, whereas those in position 5 are resistant to such attacks.[4b] In conformity with expectations, 2-amino-5-bromopyrimidine and 2-amino-4-methoxy-5-bromopyrimidine were recovered unchanged, and 2,5-dibromo-4-methoxypyrimidine underwent selective displacement of the 2-bromine atom to give 2,4-dimethoxy-5-bromopyrimidine. It may be worth noting that, in 2-bromo-4-chloro-5-ethoxypyrimidine, the 4-chloro substituent proved to be more susceptible to nucleophilic attack than the bromine in position 2. With one equivalent of sodium ethoxide, it was converted in 95% yield to 2-bromo-4,5-diethoxypyrimidine. (With excess sodium ethoxide, both halogen atoms were replaced, giving 95% of 2,4,5-triethoxypyrimidine.)

Experimental

2-Bromo-4,5-diethoxypyrimidine.—To a suspension of 20.2 g. (0.11 mole) of 2-amino-4,5-diethoxypyrimidine[6] in 55 ml. of 48% hydrobromic acid, 16.9 ml. (0.32 mole) of bromine was added at 0°, with stirring, over a period of 45 min. During this addition, the mixture became very thick, but subsequently thinned out again. A solution of 19.4 g. (0.28 mole) of sodium nitrite in 28 ml. of water was added, still at 0°, over a 30-min. period and the stirring was continued for an additional 30 min. The resulting dark solution was cooled to −10°, and 200 ml. of a 20% solution of sodium hydroxide was added until a permanent basic reaction was produced. Filtration yielded 21.5 g. (79.0%) of 2-bromo-4,5-diethoxypyrimidine as a pale yellow solid, m.p. 49°, which crystallized from pentane without change in melting point.

Anal. Calcd. for $C_8H_{11}BrN_2O_2$: C, 38.88; H, 4.49. Found: C, 38.61; H, 4.48.

The **hydrochloride**, prepared with ethereal hydrogen chloride, melted at 135°; after softening, 95°.

Anal. Calcd. for $C_8H_{12}BrClN_2O_2$: C, 33.88; H, 4.27. Found: C, 34.29; H, 4.45%.

2-Bromo-4-chloro-5-ethoxypyrimidine.—Under the same conditions, except that the product was isolated by extraction with methylene dichloride, 2-amino-4-chloro-5-ethoxypyrimidine[6] gave a 67% yield of 2-bromo-4-chloro-5-ethoxypyrimidine, m.p. 43–46°, after recrystallization from hexane.

Anal. Calcd. for $C_6H_6BrClN_2O_2$: C, 30.35; H, 2.55; N, 11.80. Found: C, 30.65; H, 2.57; N, 11.80.

2-Bromo-4-chloro-5-*n*-propylpyrimidine.—Diazotization of 2.8 g. (0.0163 mole) of 2-amino-4-chloro-5-*n*-propylpyrimidine (prepared *via* 5-*n*-propylisocytosine, m.p. 236°, by the method reported for 2-amino-4-chloro-5-methylpyrimidine[7]; m.p. 168°) and work-up in the same manner described gave, after concentration of the methylene dichloride extract, a residue which was extracted with pentane. Distillation of the pentane extract yielded 0.35 g. (9.3%) of 2-bromo-4-chloro-5-*n*-propylpyrimidine, b.p. 130° (18 mm.), $n^{22}D$ 1.5475.

Anal. Calcd. for $C_7H_8BrClN_2$: C, 35.69; H, 3.42. Found: C, 35.66; H, 3.74.

The pentane-insoluble residue was recrystallized several times from isopropyl alcohol, yielding 0.98 g. of a solid, m.p. 226–227°, which failed to give a good analysis.

2-Amino-4-methoxy-5-bromopyrimidine.—Twenty-five grams (0.2 mole) of 2-amino-4-methoxypyrimidine was subjected to the Craig bromination procedure, the reaction mixture was extracted with ether, and the extracts evaporated to dryness.

The residue was extracted with hot hexane, and the solution concentrated to a volume of 150 ml. A 10.0-g. sample (24.5%) of 2-amino-5-bromo-4-methoxypyrimidine, separated as pale yellow prisms, m.p. 118°; lit.[8] m.p. 125–126°.

Anal. Calcd. for $C_5H_6BrN_3O$: C, 29.43; H, 2.96; Br, 39.17; N, 20.59. Found: C, 29.58; H, 2.93; Br, 38.88; N, 20.12.

2,5-Dibromo-4-methoxypyrimidine.—The hexane mother liquor was washed with 10% aqueous hydrochloric acid (to remove remaining traces of starting material), then dried, and concentrated. A 10.4-g. sample (19.4%) of 2,5-dibromo-4-methoxypyrimidine crystallized as colorless needles, m.p. 85°.

Anal. Calcd. for $C_5H_4Br_2N_2O$: C, 22.41; H, 1.50; Br, 59.66. Found: C, 22.83; H, 1.50; Br, 59.72.

2-Amino-5-bromopyrimidine.—Treatment of 23.5 g. of 2-aminopyrimidine with bromine and nitrite in the same manner described gave, after ether extraction of the reaction mixture, a residue of 0.7 g. (1.7%) of 2-amino-5-bromopyrimidine as light yellow plates, m.p. 235° (after softening), which crystallized from methanol in long needles; lit. m.p. 242–244°[9] and 235–237°.[10]

Anal. Calcd. for $C_4H_4BrN_3$: C, 27.61; H, 2.32; Br, 45.93. Found: C, 27.33; H, 2.35; Br, 46.20.

Reaction of 2-Bromo-4-chloro-5-ethoxypyrimidine with Sodium Ethoxide. (A) 2-Bromo-4,5-diethoxypyrimidine.—A solution of 16.5 g. (0.0695 mole) of the pyrimidine in 50 ml. of ethanol was added at 0° to a solution of 1.6 g. (0.0695 g.-atom) of sodium in 50 ml. of ethanol. The mixture was heated under reflux for 2 hr., filtered, and concentrated *in vacuo*. To the residue a small amount of water was added and the mixture extracted with pentane. From the extract 16.3 g. (95% yield) of 2-bromo-4,5-diethoxypyrimidine, m.p. 48°, was obtained.

(B) 2,4,5-Triethoxypyrimidine.—In the same way, 22.9 g. (0.0965 mole) of the pyrimidine and 6.7 g. (0.29 g.-atom) of sodium in 150 ml. of ethanol gave 17.9 g. (95%) of 2,4,5-triethoxypyrimidine, as a pale yellow solid, m.p. 33–34°, b.p. 147° (15 mm.), solidifying to a colorless solid, m.p. 35.5°.

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.58; H, 7.60. Found: C, 56.81; H, 7.72.

The **hydrochloride**, prepared in ethereal hydrogen chloride solution, crystallized in clusters of needles, m.p. 104°.

Anal. Calcd. for $C_{10}H_{17}ClN_2O_3$: C, 48.28; H, 6.89; N, 11.27. Found: C, 48.32; H, 6.60; N, 11.13.

The same triethoxypyrimidine was obtained in 84% yield from 2-bromo-4,5-diethoxypyrimidine and sodium ethoxide.

5-Bromo-2,4-dimethoxypyrimidine.—A solution of 2.0 g. (0.00747 mole) of 2,5-dibromo-4-methoxypyrimidine and 0.44 g. of sodium methoxide in 50 ml. of methanol was heated under reflux for 16 hr., then evaporated to dryness. The residue was treated with water and extracted with methylene dichloride. The dried extract gave, on vacuum distillation, 0.8 g. (50%) of oil, b.p. 125° (17 mm.), which crystallized as colorless plates, m.p. 51–52°. Hilbert and Jansen[11] recorded the compound as prisms, m.p. 63–64°.

(5) After this work was completed D. D. Bly and M. G. Mellon reported [*J. Org. Chem.*, **27**, 2945 (1962)] conversion of 2-aminopyrimidine to 2-bromopyrimidine in a 26.6% yield by "reverse addition" diazotization. The scope of this method has not been established. It may be complementary in its application to the method described in the present paper.

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(11) G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **56**, 134 (1934).

Anal. Calcd. for $C_6H_7BrN_2O_2$: C, 32.89; H, 3.22; Br, 36.48. Found: C, 32.91; H, 3.15; Br, 36.49.

Acknowledgment.—The authors are grateful to Mr. Joseph Grodsky and Mr. Charles N. Harper for the elemental analyses.

Studies on Sphingolipids. VIII. Separation of the Diastereoisomeric Dihydrosphingosines. A Simplified Synthesis[1]

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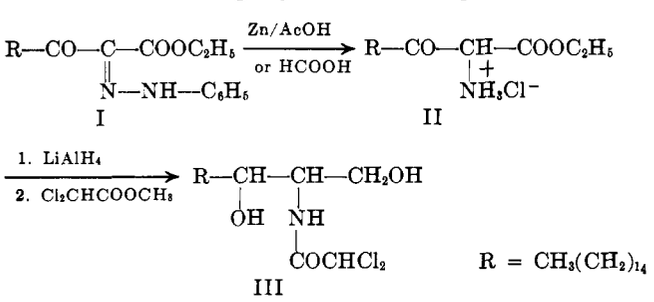
Received March 6, 1963

Most syntheses of dihydrosphingosine lead to a mixture of the two possible diastereoisomers,[2-6] whose separation is difficult to achieve. In the course of a recent investigation we observed that pure *erythro*-N-dichloroacetyldihydrosphingosine crystallized from the crude mixture and could thus be separated from its steric counterpart.

In a previous report[7] we described a synthesis of dihydrosphingosine which involved reductive acetylation of the phenylhydrazone I and a selective reduction of the resulting ethyl 2-acetamido-3-oxooctadecanoate with lithium aluminum hydride to give N-acetyldihydrosphingosine. While deacetylation proceeded satisfactorily when run on a relatively small scale, we experienced difficulties with the preparation of larger quantities of dihydrosphingosine, since considerable amounts of the amide resisted hydrolysis even after prolonged reaction.

Reduction of phenylhydrazones of type I with zinc and acetic acid usually is effected in the presence of acetic anhydride with formation of an acetamido group.[7-9] We have found that acetylation can be avoided by employing moist acetic acid, and we were able to isolate the keto ester II as the hydrochloride in 89% yield. The same result was achieved with formic acid at a slightly elevated temperature.



The crude mixture of isomers resulting from the reduction of the hydrochloride II with lithium aluminum hydride was treated directly with methyl dichloroacetate[10] and pure *erythro*-N-dichloroacetyldihydrosphingosine (III) was obtained after one crystallization. Mild alkaline hydrolysis afforded dihydrosphingosine.

The present synthesis offers a convenient method for the preparation of dihydrosphingosine in batches of ten to twenty grams.

Experimental

Ethyl 2-Amino-3-oxooctadecanoate Hydrochloride (II). (A) With Zinc Formic Acid.—To a vigorously stirred suspension of zinc powder (10 g.) in 98% formic acid (100 cc.) the phenylhydrazone I (8.56 g.) was added in portions, the temperature being maintained at 45–50°. After the addition was complete, the mixture was stirred for 20 min., cooled, and the zinc filtered off. The filtrate was poured into cold 2 *N* hydrochloric acid (100 cc.) and the product was filtered, washed with water, and dried. Crystallization from ten volumes of tetrahydrofuran yielded 6.7 g. (89%) of II, m.p. 126–128° (lit.[11] m.p. 114–116°).

Anal. Calcd. for $C_{20}H_{40}NO_3Cl$: C, 63.53; H, 10.64; Cl, 9.39; N, 3.70. Found: C, 63.30; H, 10.47; Cl, 9.27; N, 4.04.

(B) With Zinc–Acetic Acid.—A solution of the phenylhydrazone (8.56 g.) in 97% acetic acid (70 cc.) was added during 30 min. to a stirred suspension of zinc powder (10 g.) in 97% acetic acid (30 cc.), the temperature being maintained at 18–22° by external cooling. After stirring the colorless mixture for 15 min., the zinc was filtered off and the filtrate poured into cold 2 *N* hydrochloric acid (100 cc.). Crystallization from tetrahydrofuran yielded 6.5–6.7 g. of II, m.p. 126–128°.

***erythro*-N-Dichloroacetyldihydrosphingosine (III).**—A solution of the ester hydrochloride II (25 g.) in dry tetrahydrofuran (500 cc.) was added to a cold suspension of lithium aluminum hydride (10 g.) in dry tetrahydrofuran (250 cc.). After stirring at 40° for 1 hr., the mixture was cooled and the excess of lithium aluminum hydride decomposed by ethyl acetate (5 cc.). Sodium potassium tartrate solution (10%, 500 cc.) was then added, followed by 2 *N* sodium hydroxide solution (50 cc.), and saturated sodium chloride solution (100 cc.). The ethereal extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The solid residue (18 g.), melting at 60–70°, was dissolved in methyl dichloroacetate (200 cc.) and the solution heated in a boiling water bath for 2 hr. To the slightly cooled mixture petroleum ether (500 cc.) was added and the precipitated product was crystallized from methanol; yield 12 g. (45%); m.p. 142–144°.

Anal. Calcd. for $C_{20}H_{39}NO_3Cl_2$: C, 58.25; H, 9.53; N, 3.40; Cl, 17.20. Found: C, 58.50; H, 9.44; N, 3.63; Cl, 17.09.

Dihydrosphingosine.—N-Dichloroacetyldihydrosphingosine (4.12 g.) was dissolved with slight warming in methanol (360 cc.), *N* sodium hydroxide solution (40 cc.) was added, and the solution was left overnight at room temperature. *N* Acetic acid (40 cc.) was added and the solution was concentrated *in vacuo* until precipitation set in. Crystallization from chloroform gave 2.45 g. (82%), m.p. 85–86°.

(1) Supported in part by a grant from Samuel Rothberg of Peoria, Ill.
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The Aqueous Chemistry of Peroxychloroacetic Acid

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Received November 20, 1962

There are several reports in the literature concerning the *in situ* preparations of substituted peroxyacetic