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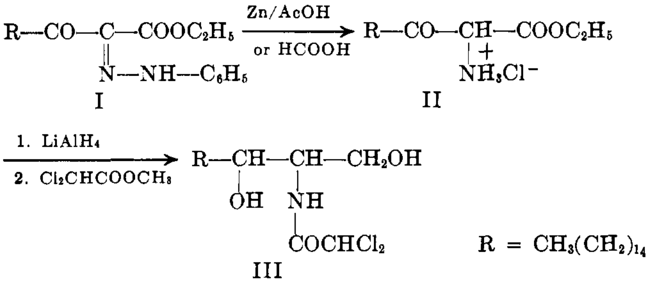
Most syntheses of dihydrosphingosine lead to a mixture of the two possible diastereoisomers,[2–6] whose separation is difficult to achieve. In the course of a recent investigation we observed that pure *erythro*-N-dichloroacetyldihydrosphingosine crystallized from the crude mixture and could thus be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



$$\underset{\text{I}}{\mathrm{R{-}CO{-}C({=}N{-}NH{-}C_6H_5){-}COOC_2H_5}} \xrightarrow[\text{or HCOOH}]{\text{Zn/AcOH}} \underset{\text{II}}{\mathrm{R{-}CO{-}CH(\overset{+}{N}H_3Cl^-){-}COOC_2H_5}}$$

$$\xrightarrow[\text{2. }Cl_2CHCOOCH_3]{\text{1. }LiAlH_4} \underset{\text{III}}{\mathrm{R{-}CH(OH){-}CH(NH{-}COCHCl_2){-}CH_2OH}} \qquad R = CH_3(CH_2)_{14}$$

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°.

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

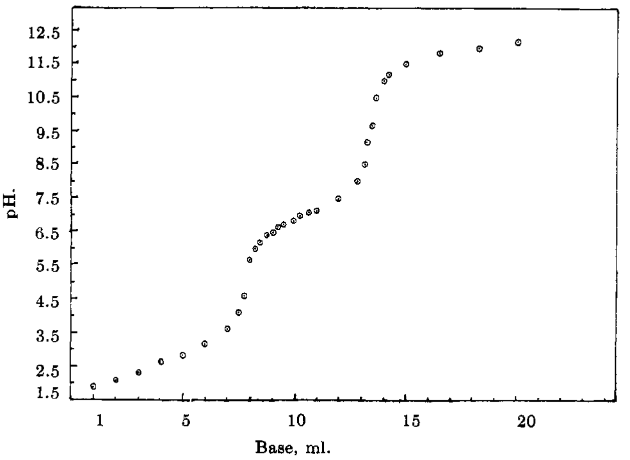

Fig. 1.—A typical basic titration curve for a sample of peroxychloroacetic acid, temp., 25°.

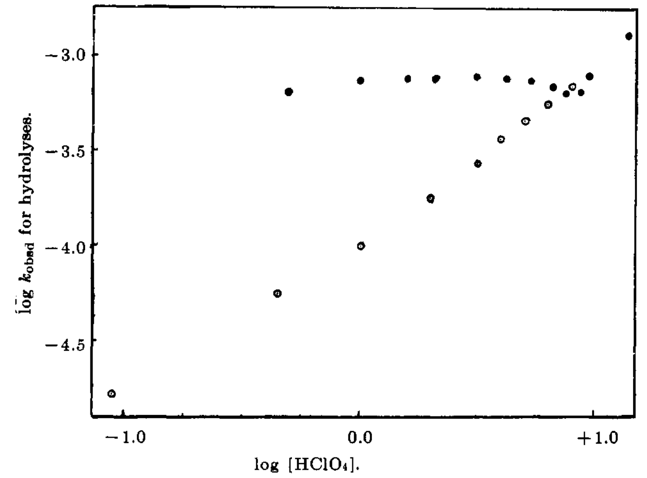

Fig. 2.—A plot of the log of the observed first-order rate constant in sec.$^{-1}$ for the hydrolysis of peroxyacetic acid and peroxychloroacetic acid *vs.* the log of the perchloric acid concentration: temp., 19.9°; ⊙, peroxyacetic acid; ●, peroxychloroacetic acid.

acids,[1] but there is available little reliable data concerning their isolation or their aqueous chemistry. In the case of peroxychloroacetic acid, most of these reports are found in the patent literature,[2] except for some early work by Panizzon.[3] He reported the preparation of peroxychloroacetic acid by its distillation (33–34° with decomposition at 3.5–4.0 mm.) from a mixture of chloroacetic anhydride and hydrogen peroxide in sulfuric acid. We have found it impossible to isolate any peroxy acid by this method. Our analysis[4] of the distillate with ceric and iodide ions showed all peroxide present to be hydrogen peroxide. This is consistent with the fact that the vapor pressure reported by Panizzon corresponds to that of hydrogen peroxide (lit.[5] 3.5–4.0 mm. at 33–34°).

Experimental

For the preparation of **peroxychloroacetic acid**, a modified version of the method of Panizzon[3] was used. Hydrogen peroxide (11.5 g. of 30% B&A reagent) was added dropwise over a period of 1 hr. to 70 g. of concentrated sulfuric acid which was immersed in an ice bath. Then 9.2 g. of chloroacetic anhydride (or 9.5 g. of chloroacetic acid) was added slowly and the resulting mixture stirred until all solid material was dissolved. The resulting clear solution was then allowed to stand for 24 hr. at room temperature after which it was extracted with three 30-ml. portions of anhydrous redistilled dichloromethane. The extracts were combined and the dichloromethane removed by evaporation under reduced pressure at 0°; precautions were taken to exclude moisture. A clear viscous liquid (3 to 4 ml.) remained after the removal of dichloromethane. Analysis[4] of the liquid showed it to contain 50–60% peroxychloroacetic acid, 1–5% hydrogen peroxide, and 40–50% chloroacetic acid. The per cent amount of the last compound was established from basic titration curves obtained using a Beckman Model G pH meter.

For the hydrolysis experiments 0.5 to 1 ml. of a freshly prepared sample of the last material was added to 50 ml. of perchloric acid solutions, varying in concentration from 0.1 to 11.6 *M*. These perchloric acid solutions were prepared by direct dilution of 72% perchloric acid (B&A reagent grade) with deionized water. The rates of hydrolysis were studied at 0, 25, and 35°, constant temperatures being maintained by means of ice and/or water baths. Care was exercised to eliminate possible errors due to trace metal-catalyzed decomposition.

Peroxyacetic acid was prepared by a method analogous to that used for the preparation of peroxychloroacetic acid, except that in this case the peroxy acid could be distilled from the reaction mixture under reduced pressure (30.5 ± 0.5° at 26 mm.). The distillate contained about 70% peroxyacetic acid, 25% acetic acid, and 5% hydrogen peroxide. In this case, as also in the case of peroxychloroacetic acid, the parent acid and the small amount of hydrogen peroxide were found to have little effect on the hydrolysis reaction, the kinetics of which are being reported now.

Measurements of the rate of oxidation of nitrosobenzene were carried out in 47% ethanol–water mixtures in a temperature-controlled Beckman DK-1 recording spectrophotometer with 1-cm. cells. These experiments were conducted under pseudo first-order conditions, 0.101 *M* nitrosobenzene being oxidized by 0.10–0.15 *M* peroxy acid.

Results and Discussion

Fig. 1 shows a typical curve of pH *vs.* milliliters of base added obtained for samples of peroxychloroacetic acid. Although active decomposition of the peroxy acid takes place at pH values near the pK_a, with rapid measurement a reproducible pK_a value of 7.2 was obtained. Thus peroxychloroacetic acid is the strongest peroxy acid known to exist in aqueous solution (with the possible exception of peroxyformic acid,[6] for which a pK_a value has been measured).

It may be pointed out that peroxy acids are known to undergo decomposition in aqueous solution by two pathways other than hydrolysis. These are (1) spontaneous decomposition in aqueous alkaline media[7,8] and (2) trace metal ion-catalyzed decomposition.[9,10] During the spontaneous decomposition of peroxyacetic acid, oxygen is evolved, while the trace metal ion-catalyzed decomposition is accompanied by the evolution of oxygen, carbon dioxide, and traces of carbon monoxide.[10] However, during the hydrolysis of peroxyacetic and peroxychloroacetic acid no gaseous products were ob-

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served, the only products produced being hydrogen peroxide and the parent acid. Conditions under which each of these three pathways could be studied for the decompositions of peroxyacetic and peroxychloroacetic acid were established. The results of the studies on the spontaneous decompositions and decompositions catalyzed by metal ions are the subjects of separate communications.[8,10]

In view of these facts, during the acid hydrolysis experiments both the kinetics of the disappearance of peroxy acid and the appearance of hydrogen peroxide were studied. No change in total peroxide content was noticed up to 90% reaction; *i.e.*, the rate of disappearance of peroxy acid corresponded exactly to the rate of formation of hydrogen peroxide. Therefore, acid hydrolysis was not accompanied either by decomposition to oxygen or by decomposition to oxygen and carbon dioxide. Both rates (peroxyacetic and peroxychloroacetic acids) appear to follow a first-order relationship (log concentration of peroxy acid *vs.* time gave a linear plot) to 90% reaction. The results now obtained for first-order rates of hydrolysis of the two peroxy acids as a function of the perchloric acid concentration are given in Fig. 2. The value 0.96×10^{-4} l./mole sec. for the second-order acid-catalyzed rate constant of peroxyacetic acid agrees with the value of 1.0×10^{-4} previously obtained by Bunton and co-workers.[11]

The rates of hydrolysis were measured at three temperatures (0, 24.8, and 35.3°); the rate constants are listed in Table I. The energies of activation (E_a) calculated from the rate constants given in Table I are 16.8 kcal./mole for the acid-catalyzed hydrolysis of peroxyacetic acid and 13.7 kcal./mole for the uncatalyzed hydrolysis of peroxychloroacetic acid. The entropies of activation (ΔS^*) are -22.6 cal./deg. mole and -29.3 cal./deg. mole in the same order.

Experiments to determine the effect of ionic strength upon the hydrolysis rate proved rather unsatisfactory, for the addition of sodium perchlorate led to a rapid decrease in total peroxide content. Most likely this resulted from addition of trace amounts of catalytic ions contained in the perchlorate salt.

The rates of hydrolysis of the two peroxy acids can be discussed in terms of the over-all rate law, rate = $k_O[\text{ROOH}] + k_H[\text{ROOH}][H_3O^+]$. From the apparent first-order dependence of the rate of hydrolysis of peroxyacetic acid on perchloric acid concentration, it is likely, as Bunton has pointed out, that the hydrolysis proceeds *via* nucleophilic attack by water on the unprotonated form. Nevertheless, the constant k_O must be less than 5×10^{-6} sec.$^{-1}$ and thus in 1 *M* acid the uncatalyzed rate amounts to less than 5% of the total rate of hydrolysis.

It is seen from Fig. 2 that, in the hydrolyses of the chloro substituted peroxy acid, the uncatalyzed rate is predominant over most of the acidity range, the value of k_O being 7×10^{-4} sec.$^{-1}$. Thus the uncatalyzed hydrolysis rate is much more significant than the acid-catalyzed hydrolysis over most of the acid range. However, at 8 *M* perchloric acid, the acid-catalyzed rate begins to contribute significantly to the over-all observed rate as demonstrated by the sharp increase in k_{obsd}. This behavior is not completely unexpected since the chlorine atom, while increasing the positive character of the carbonyl carbon, decreases the basicity of the carbonyl oxygen. Therefore, even though the protonated peroxychloroacetic acid is more susceptible to nucleophilic attack, its equilibrium concentration is much lower (relative to peroxyacetic acid under the same conditions), these two effects acting in opposition to each other. Tommila and Hinshelwood,[12] in their studies on the acid-catalyzed hydrolysis of benzoic acid esters, found that substituents on the benzene ring had virtually no influence on the rate of reaction; *i.e.*, k_H was found to be essentially the same for the variously substituted benzoic acid esters. Presumably the substituents exert electronic effects similar to those suggested for the chlorine atom in the peroxychloroacetic acid.

TABLE I

THE OBSERVED FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF PEROXYACETIC AND PEROXYCHLOROACETIC ACIDS AT VARIOUS TEMPERATURES AND AT VARIOUS CONCENTRATIONS OF PERCHLORIC ACID

Peroxyacetic acid $[HClO_4]$	k_{obs} (sec.$^{-1}$) 24.8°	35.3°	0°
0.10	1.56×10^{-5}	...	...
0.50	5.56×10^{-5}	...	...
1.00	9.65×10^{-5}	2.54×10^{-4}	...
2.00	1.78×10^{-4}	4.75×10^{-4}	...
3.00	2.65×10^{-4}	7.05×10^{-4}	...
4.00	3.42×10^{-4}	...	...
5.00	4.43×10^{-4}	...	2.96×10^{-5}
6.00	5.38×10^{-4}	...	3.43×10^{-5}
7.00	6.16×10^{-4}	...	4.82×10^{-5}
8.00	7.56×10^{-4}	...	...
Peroxychloroacetic acid			
0.50	5.85×10^{-4}	...	...
1.00	6.23×10^{-4}	1.33×10^{-3}	8.35×10^{-5}
1.50	6.84×10^{-4}	...	...
2.00	6.66×10^{-4}	1.58×10^{-3}	8.70×10^{-5}
3.00	7.24×10^{-4}	1.64×10^{-3}	8.70×10^{-5}
4.00	7.05×10^{-4}	1.70×10^{-3}	9.01×10^{-5}
5.00	6.90×10^{-4}	...	...
6.00	6.48×10^{-4}	...	...
7.00	6.65×10^{-4}	...	...
9.00	6.70×10^{-4}	...	...
10.0	8.35×10^{-4}	...	...
11.6	13×10^{-4} (initial rate)	...	...

In order to test the kinetic reactivity of peroxychloroacetic acid as an electrophile, the rate of oxidation of nitrosobenzene to nitrobenzene has been measured along with comparative data for two known peroxy acids. The second-order rate constants for the oxidation of nitrosobenzene at 30° were found to be 5.15×10^{-4}, 35×10^{-4}, and 167×10^{-4} l./mole sec. for peroxyacetic,[13] peroxymonosulfuric, and peroxychloroacetic acid, respectively.

The main disadvantages associated with this new peroxy acid appear to be the ease with which it is hydrolyzed into chloroacetic acid and hydrogen peroxide and its spontaneous decomposition[8] into chloroacetic acid and oxygen. The former is prevalent at all ranges of pH while the latter is significant near the pK_a

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of the peroxy acid. In the case of peroxychloroacetic acid both processes take place at a much greater rate than with peroxyacetic acid.

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2,3-Dihydro-4*H*-1,3-benzothiazinones-4

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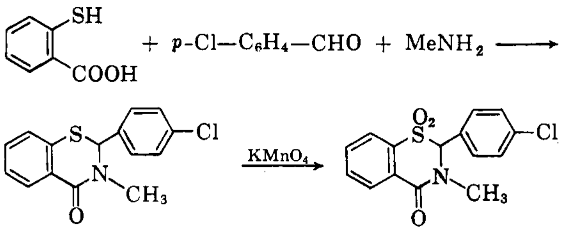
The only references to the synthesis of 4*H*-1,3-benzo thiazinones utilize the reaction of thiosalicylamide with aldehydes[1] or benzal chloride.[2]



We have found that 2-phenyl-3-alkyl-dihydrobenzothiazinones are readily prepared from thiosalicyclic acid, an aldehyde, and a primary amine in refluxing benzene. Oxidation by permanganate in acetic acid gives the sulfone.

When methylamine was replaced by 1,1-dimethylhydrazine or by aniline, the reaction failed.

Experimental[3]

2,3-Dihydro-3-methyl-2-(*p*-chlorophenyl)-4*H*-1,3-benzothiazinone-4.—*p*-Chlorobenzaldehyde (10.0 g., 0.071 mole) was mixed with 30 ml. of anhydrous benzene previously saturated with methylamine. After 5 min. the solution turned milky. The solution was refluxed and water was removed azeotropically; the theoretical amount of water was obtained in 1 hr. The solution was cooled, powdered thiosalicyclic acid (0.071 mole) was added, and reflux was continued until another equivalent of water was removed (several hours). After cooling, the solution was rinsed with dilute base, dried, and the solvent was then removed. The residual viscous oil soon crystallized. The solid was triturated with hexane then recrystallized from benzene–isopropyl ether (11.0 g., m.p. 123.5–124°).

Anal. Calcd. for $C_{15}H_{12}ClNOS$: C, 62.17; H, 4.17. Found: C, 62.17; H, 4.08.

2,3-Dihydro-3-methyl-2-(*p*-chlorophenyl)-4*H*-1,3-benzothiazin-4-one 1,1-dioxide.—An aqueous solution containing 8.3 g. (0.053 mole) potassium permanganate was added portionwise, with stirring, to a solution of 9.0 g. (0.031 mole) of the thiazinone in 90 ml. of acetic acid. Slight cooling was required to keep the temperature below 35°. The brown mixture containing a tan suspended solid was stirred an additional half hour and a small amount of sodium hydrosulfite was then added to decolorize the solution. The tan solid product was filtered and recrystallized from alcohol–acetone giving 5.5 g. of white crystals (m.p. 169–170°).

Anal. Calcd. for $C_{15}H_{12}ClNO_3S$: C, 55.99; H, 3.76. Found: C, 55.69; H, 3.87.

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[2] R. Boudet, *Bull. soc. chim. France*, 1518 (1955).

[3] All melting points are corrected. Analyses were performed by D Rolston and her staff of these laboratories.