[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Chemistry of Epoxy Compounds. IX.[2] Epoxidation of Oleamide and N-Substituted Oleamides with Peracetic Acid

BY EDWARD T. ROE, JOHN T. SCANLAN AND DANIEL SWERN

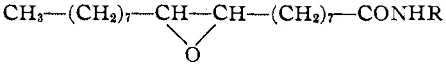
Previous papers in this series,[3,4] reported the epoxidation of mono-unsaturated fatty acids, esters and hydrocarbons, as well as oleyl alcohol and some triglycerides, with peracetic acid in acetic acid solution. In these papers, it was shown that, contrary to the generally accepted idea, peracetic acid in acetic acid solution could be employed for the preparation of oxirane (α-epoxy) compounds in good yield from unsaturated compounds. Thus, it was demonstrated that peracetic acid behaved in exactly the same manner as perbenzoic or monoperphthalic acid, although admittedly yields of oxirane compounds were sometimes lower than would be anticipated if the aromatic peracids had been employed. The ease with which an acetic acid solution of peracetic acid can be prepared from readily available starting materials,[3,5] however, makes it an attractive epoxidizing reagent.

This investigation was initiated for a dual purpose. First, we wished to demonstrate that long-chain unsaturated amides could be successfully epoxidized, thus adding to the classes of compounds epoxidizable by peracetic acid and further substantiating the hypothesis regarding the generality of this reaction.[3] Second, most of the long-chain amides which are commercially available and those which have been reported in the literature have relatively limited chemical reactivity, and we wished to prepare long-chain compounds which not only retained the amide group but also contained an extremely reactive functional group. The presence of the reactive oxirane group in a long-chain amide suggests many interesting reactions leading to the formation of potentially valuable products.

In this study, oleamide and N-substituted oleamides[6] have been converted to the corresponding 9,10-epoxystearamides in 30–90% yield by epoxidation with peracetic acid in acetic acid solution. The reaction proceeded smoothly and rapidly at 20–30° with a 20% molar excess of peracetic acid; approximately four hours reaction time was required. After an analysis indicated that no more peracetic acid was being consumed, the reaction mixtures were poured into cold water, and the crude epoxystearamides were separated by filtration and purified by recrystallization from organic solvents. The pure compounds were white, crystalline solids, insoluble in water and cold organic solvents, but readily soluble in hot organic solvents. The results are summarized in Table I.

TABLE I

CHARACTERISTICS OF 9,10-EPOXYSTEARAMIDES



$CH_3—(CH_2)_7—CH—CH—(CH_2)_7—CONHR$ (O bridging the two CH)

R	Crude amides			Purified amides									
	Yield, %	Oxirane oxygen,[a] %	M. p., °C.	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Oxirane oxygen,[a] % Calcd.	Oxirane oxygen,[a] % Found
Hydrogen	98	4.54	90.0–90.5	65[b]	94.0	72.7	72.7	11.9	11.5	4.71	4.54	5.38	5.28
Methyl	98	4.49	64.0–65.0	38[b]	65.5–66.0	73.3	73.3	12.0	12.3	4.50	4.43	5.14	5.20
n-Hexyl	98	3.53	62.0–63.5	53[b]	66.0–66.5	75.5	75.8	12.4	12.7	3.67	3.58	4.19	4.14
n-Decyl	99	3.21	73.0–73.5	89[c]	75.0–75.5	76.8	77.2	12.7	12.7	3.21	3.18	3.66	3.51
n-Dodecyl	98	2.80	75.5–76.0	45[b]	78.5–79.0	77.4	77.3	12.8	12.7	3.01	2.92	3.44	3.36
Phenyl	99	3.73	80.0–81.0	45[d]	83.0–83.5	77.2	77.1	10.5	10.3	3.75	3.75	4.28	4.28
2-Hydroxyethyl	97	4.20	79.0–80.0	59[e]	81.5–82.0	70.3	70.3	11.5	11.6	4.11	3.99	4.68	4.65
Acetyl	99	3.92	71.0–72.0	29[f]	74.0–75.0	70.8	70.8	11.0	11.0	4.12	4.07	4.71	4.51

[a] Determined by the method of Swern, Findley, Billen and Scanlan, *Anal. Chem.*, **19**, 414 (1947). [b] Crystallized two to four times from acetone, 7 to 10 ml./g., at 25°. [c] Crystallized as in [b]. Further crystallization from 95% ethanol, 3 ml./g. and 12 ml./g. at 25°, did not increase the purity as determined by the % oxirane oxygen. [d] Crystallized twice from petroleum naphtha, boiling range 63–70°, 5 ml./g. at 23°, and twice from acetone, 6 ml./g. at 25°. [e] Crystallized three times from 95% ethanol, 5 ml./g. at 0°. [f] Crystallized four times from acetone, 4 ml./g. at 0°, and twice from 95% ethanol, 2 ml./g. at 25°. Further crystallization from ethanol did not increase the purity as determined by the % oxirane oxygen.

Experimental

Materials Used.—Oleamide and N-substituted oleamides were prepared as described in an earlier paper.[6] Peracetic acid was prepared by the procedure of Findley, Swern and Scanlan.[3]

Epoxidation Techniques.—Since the epoxidation procedure is substantially the same for each of the amides, details will be given for the preparation of N-(*n*-hexyl)-

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[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

[2] For paper VIII of this series, see THIS JOURNAL, **71**, 1152 (1949).

[3] Findley, Swern and Scanlan, *ibid.*, **67**, 412 (1945).

[4] Swern, Billen and Scanlan, *ibid.*, **68**, 1504 (1946).

[5] Swern, *Chem. Rev.*, in press (1949).

[6] Roe, Scanlan and Swern, THIS JOURNAL, **71**, 2215 (1949).

9,10-epoxystearamide only. To a well-stirred solution of 18.3 g. (0.05 mole) of N-(*n*-hexyl)-oleamide[6] (iodine number, 69.3; m. p. 31.0–31.5°) in 10 ml. of glacial acetic acid at 20°, 55 ml. of approximately 1 *M* peracetic acid solution[3] (0.06 mole) was added within five minutes. The reaction temperature was maintained between 20 and 25° by external cooling, and a peroxide oxygen analysis was run at hourly intervals.[7] After about four hours, 85–90% of the calculated quantity of peracetic acid had been consumed, and the reaction mixture was then poured into about 500 ml. of ice-water. A granular solid precipitated, which was filtered off and washed with several portions of cold water. After being air-dried, the crude N-(*n*-hexyl)-9,10-epoxystearamide (purity, about 84%), m. p. 62–63.5°, weighed 18.6 g. Recrystallization to constant melting point from acetone at 25° resulted in a 53% yield of pure N-(*n*-hexyl)-9,10-epoxystearamide, m. p. 66.0–66.5°.

The quantity of glacial acetic acid required to dissolve 0.05 mole of the unsaturated amide varied with the amide employed, and was just sufficient to give a homogeneous solution at 20–25°. N-(*n*-Decyl)-oleamide required 840 ml. of glacial acetic acid. N-(*n*-Dodecyl)-oleamide was too insoluble in acetic acid at 20–25°; it was dissolved in 200 ml. of acetic acid at 30°, and the epoxidation reaction was conducted at that temperature. Higher temperatures should be avoided because of the increased rate of decomposition of peracetic acid and also because of the increased rate at which the oxirane ring is opened by acetic acid.

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Summary

Peracetic acid in acetic acid solution has been used to epoxidize some long-chain mono-unsaturated amides. 9,10-Epoxystearamide and a series of N-substituted 9,10-epoxystearamides have been prepared in 30–90% yield by the epoxidation of oleamide and N-substituted oleamides.

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[7] Wheeler, *Oil and Soap*, **9**, 89 (1932).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of 5-(1-Methoxypropyl)-5-alkyl (or 5-Phenyl) Hydantoins[1]

BY HENRY R. HENZE, GEORGE L. SUTHERLAND AND GEORGE W. BENZ

Recently, the synthesis has been reported[2] of a series of 5-alkyl (or 5-phenyl)-5-propoxymethylhydantoins which have been shown elsewhere[3] to possess considerable activity as anticonvulsants. In particular, the propoxymethyl and isopropoxymethyl derivatives were found to be worthy of intensive study, which, in turn, led to clinical testing of the latter.

Because of the desirable pharmacological activity exhibited by members of this series, it appeared to be desirable to prepare some related hydantoins, and especially the isomeric compound, 5-(1-methoxypropyl)-5-phenylhydantoin. The hydantoins, fifteen in number, were prepared from the corresponding alkyl (or phenyl) 1-methoxypropyl ketones[4] by means of the Bucherer procedure.[5]

Experimental

The Bucherer procedure,[5] in some instances with slight modification, was used to convert the ketones into the corresponding hydantoins. In general, the reactants were mixed in the proportions of one equivalent of ketone, 1.2–1.5 equivalent of sodium or potassium cyanide, and 3–5 equivalents of U. S. P. ammonium carbonate. The cyanide was dissolved in the minimal amount of water, and the solution was added to a solution of the ketone in five times its volume of ethyl alcohol. Water or alcohol were added, if needed, to produce a homogeneous solution in about 70% alcohol. After addition of the ammonium carbonate, the mixture was warmed at about 60° for from six to fifteen hours. In the case of the ketones containing either a 1-methylethyl, 1-methylbutyl, or 2-methylbutyl group, it was necessary to heat the reaction mixture in a pressure vessel at 100° for twelve hours.

The reaction mixtures were acidified with concentrated hydrochloric acid and chilled; solid material formed and was separated by filtration. Concentration of the mother liquors yielded additional products. In some cases, adequate purification was attained through repeated recrystallization from diluted alcohol. In other instances, it proved beneficial to dissolve the crude hydantoin in 10% sodium hydroxide solution and to reprecipitate the hydantoin by saturating the alkaline solution with carbon dioxide. Fifty per cent. alcohol–water, benzene, or benzene–dioxane served best for final recrystallization.

The phenyl hydantoin, after recrystallization from alcohol–water, and from benzene–dioxane, was dried for twenty-four hours at room temperature in a vacuum (about 30 inches) produced by an oil pump. The mass of white needles melted at 210–212°; analysis indicated mono-hydration of the hydantoin.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.28; Calcd. for $C_{13}H_{16}N_2O_3 \cdot H_2O$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.65; 58.73; H, 7.06, 7.13; N, 10.71, 10.65.

Although drying this material for twenty-four hours in a vacuum oven (30 inches) at 100° did not result in any change in the melting point, a loss of weight was observed.

Anal. Calcd. for $C_{13}H_{16}N_2O_3 \cdot H_2O$: H_2O, 6.76. Found: H_2O, 6.98.

The results of analyses of this anhydrous phenylhydantoin derivative, together with similar data for the other fourteen derivatives, may be found in Table I.

Through the courtesy of Parke, Davis and Co., five members of this series of 5-alkyl-5-(1-methoxypropyl)-hydantoins (namely, the ethyl, *s*-butyl, amyl, isoamyl and cyclohexyl) have been subjected to testing for activity as anticonvulsants. Although a slight degree of activity was found, the group appears to be markedly less active than is the alkoxymethyl series.

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[1] From the M.A. thesis of G. W. Benz, August, 1946, of G. and L. Sutherland, August, 1947.

[2] Henze, Melton and Forman, THIS JOURNAL, **70**, 2438 (1948).

[3] Merritt, Putnam and Bywater, *J. Pharmacol.*, **84**, 67 (1945).

[4] Henze, Benz and Sutherland, THIS JOURNAL, **71**, 2122 (1949).

[5] Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).