[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC RESEARCH, SCIENTIFIC DIVISION, THE WM. S. MERRELL CO.]

Some 2,3-Disubstituted Glycidamides and Related Compounds[1]

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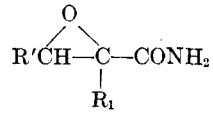
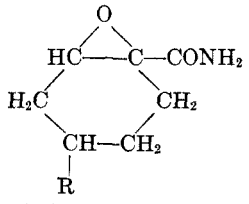
Several 2,3-disubstituted glycidamides have been prepared by the epoxidation of the unsaturated amides by means of monoperphthalic acid. The glycidamides containing alkyl groups of two to four carbon atoms show a useful degree of hypnotic or sedative action. A number of other related compounds prepared in the course of the work were also screened but showed little if any depressant action.

The sedative and hypnotic properties of many types of amides are well known. However, the depressant properties of analogs of glycidamide, I, have been studied but little. Billeter and coworkers[3] studied a group of 3-substituted and 3,3-disubstituted compounds. A large number of 3,3-disubstituted glycidamides have been prepared in our laboratories by B. R. Harriman.[4] Some of these were found to have a brief sedative action but of such slight degree as to be of little value.

We have now prepared a series of 2,3-disubstituted glycidamides, II, and two alicyclic epoxy amides, III:



I. R = R_1 = H
II. R = C_2H_5, C_3H_7, C_6H_5
R_1 = C_2H_5, C_3H_7, C_4H_9



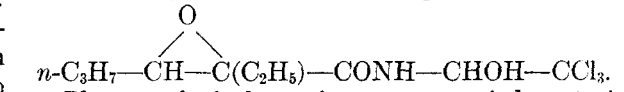
III. R = H, CH_3

These were prepared by the action of monoperphthalic acid on the unsaturated amide in anhydrous media. 2-Ethyl-3-propylglycidureide was prepared in the same way.

To determine the effect of a second amide group on the depressant activity, 2-carbamyl-3,3-diethylglycidamide (IV) was prepared. 2-Cyano-3-ethyl-2-pentenamide, from diethyl ketone and cyanoacetamide, was treated with alkaline hydrogen peroxide in acetone[5] to give IV directly in one step. While this particular reaction of an α-carbamyl-α,β-unsaturated nitrile appears not to have been previously reported, it is, of course, analogous to the preparation of α-phenyl glycidamides from α-phenyl-α,β-unsaturated nitriles.[6]

In connection with our study of the most interesting of the glycidamides reported here—2-ethyl-3-propylglycidamide (V)—it was desirable to have the 2,3-dihydroxy amide resulting from hydrolytic cleavage of the epoxy group. This epoxide proved to be surprisingly resistant to acid hydrolysis. After refluxing an acidified aqueous solution of the amide V for 48 hours, 20% unchanged amide was recovered and about a 50% yield of the desired product, 2,3-dihydroxy-2-ethylhexanamide, was obtained.

Finally, chloral was condensed with V. Numerous chloral derivatives of amides are reported in the literature, in which the products have the structure R—CONH-CHOH-CCl_3. However, in the case of the product from V, the chloral might possibly undergo reaction with the epoxide ring to give 2-trichloromethyl-4-ethyl-4-carbamyl-5-*n*-propyl-1,3-dioxolane. To prove that this was not the case and that the product did indeed have the structure resulting from condensation of chloral with the amide function, infrared spectra were used. 2-Ethylhexanamide[7] (VI) and its condensation product with chloral, *n*-C_4H_9-$CH(C_2H_5)$-CONH-CHOH-CCl_3[8] (VII), were prepared. The infrared spectra of V and VI showed the single absorption maximum at 1650–1670 $cm.^{-1}$, characteristic of *N*-unsubstituted amides, whereas the spectra from VII and the condensation product from V and chloral showed the twin maxima at 1665–1700 and 1500–1525 $cm.^{-1}$ characteristic of *N*-monosubstituted amides.[9] Thus, evidence was obtained that this product had the expected structure,



Pharmacological testing was carried out in rabbits, using the intravenous route of administration, or in rats, using the intraperitoneal route. All of the dialkyl-substituted glycidamides reported here show sedative or hypnotic activity in

(1) Presented in part before the Medicinal Chemistry Division at the 124th National Meeting of the American Chemical Society, Chicago, Sept. 6–11, 1953.

(2) Present address, Cutter Laboratories, Berkeley, California.

(3) (a) J. R. Billeter, Thesis, University of Paris, 1935. (b) E. Fourneau, J. R. Billeter, and D. Bovet, *J. Pharm. Chim.* **19**, 49 (1934).

(4) Unpublished work. Present address, Ansco, Binghamton, N. Y.

(5) B. Radziszewski, *Ber.* **18**, 355 (1885).

(6) J. V. Murray and J. B. Cloke, *J. Am. Chem. Soc.* **56**, 2749 (1934).

(7) F. F. Blicke and A. P. Centolella, *J. Am. Chem. Soc.* **60**, 2924 (1938).

(8) J. P. Larocca, J. M. Leonard, and W. E. Weaver, *J. Org. Chem.* **16**, 47 (1951).

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, 1954, pp. 180–185.

TABLE I

α,β-UNSATURATED AMIDES

$$R-CH=C(R^1)-CONH_2$$

R	R^1	M.P.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
C_2H_5	C_2H_5	75–90[a]	$C_7H_{13}NO$	66.09	65.70	10.30	10.01	11.01	10.80
n-C_3H_7	C_2H_5	67–68[b]	$C_8H_{15}NO$						
C_2H_5	n-C_3H_7	72–86[c]	$C_8H_{15}NO$						
n-C_3H_7	n-C_3H_7	55–65	$C_9H_{17}NO$	69.64	69.67	11.04	10.81	9.02	8.86
n-C_3H_7	n-C_4H_9	92–94[d]	$C_{10}H_{19}NO$	70.95	70.97	11.31	11.01	8.27	8.09
n-C_3H_7	n-C_4H_9	76–77[d]	$C_{10}H_{19}NO$	70.95	70.88	11.31	11.08	8.27	7.97
C_6H_5	C_2H_5	126.5–127[e]	$C_{11}H_{13}NO$						
$-CH_2CH_2CH_2CH_2-$		128–130[f]	$C_7H_{11}NO$						
$-CH_2CH(CH_3)CH_2CH_2-$		139.5–141[g]	$C_8H_{13}NO$						

[a] This material is apparently a mixture of *cis-trans* isomers; reported[12] m.p. 117°. [b] Reported[13] m.p. 67–68°. [c] A mixture of isomers; Macq[14] reports two isomers, melting at 89° and 115.5°. [d] Fractionally crystallized from petroleum ether (b.p. 40–60°). [e] Reported[17] m.p. 135–137°. [f] Reported[18] m.p. 129–130.5°. [g] Reported[19] m.p. 140°.

these animals with little or no toxicity. The other compounds reported here show little or no such activity. A detailed study of 2-ethyl-3-propylglycidamide has been published.[10] Clinically it is being used as a tranquillizing agent.

EXPERIMENTAL[11]

α,β-Unsaturated amides. The unsaturated amides from which the glycidamides were prepared are listed in Table I. These amides were prepared by one of three standard methods: 1) from the corresponding unsaturated acid by treatment of the acid with thionyl chloride, followed by treatment of the acid chloride with ammonia; 2) by heating the appropriate α-bromoamide with an excess of *N,N*-dimethylaniline for several hours at 130–140°; or 3) by hydrolysis of the corresponding α,β-unsaturated nitrile. The cyclohexene amides were prepared by method 3. 2-*n*-Propyl-2-pentenamide and the two isomeric 2-*n*-butyl-2-hexenamides were prepared by method 2, from 2-bromo-2-propylvaleramide[15] and 2-bromo-2-*n*-butylhexanamide,[16] respectively. The remaining unsaturated amides were prepared from the unsaturated acids. The acids were prepared in turn by dehydration and hydrolysis of β-hydroxy esters obtained from the Reformatsky reaction, or by oxidation of commercially available 2-ethyl-2-hexenaldehyde to give 2-ethyl-2-hexenoic acid.

The Reformatsky reaction of *n*-butyraldehyde with ethyl 2-bromovalerate gave *ethyl 2-n-propyl-3-hydroxycaproate,* b.p. 115–140°/18 mm., in 48% yield. Treatment of this ester with thionyl chloride and then with alcoholic potassium hydroxide gave *2-n-propyl-2-hexenoic acid,* b.p. 135–140°/15 mm., in 25% overall yield.

Anal. Calcd. for $C_9H_{16}O_2$: Neut. equiv. 156.2. Found: Neut. equiv. 155.5.

All of the remaining intermediates are known compounds. In the preparation of 4-methyl-1-cyclohexene-1-carboxamide,[19] the intermediate 1-cyano-4-methyl-1-cyclohexene was found to boil at 97–103°/34 mm., which is more in line with the anticipated boiling point than is the value of 98–100°/5 mm. previously reported.[19]

2,3-Disubstituted glycidamides. The unsaturated amide was dissolved in an ether solution of monoperphthalic acid[20] sufficient to provide about three moles of peracid per mole of unsaturated amide. A little anhydrous magnesium sulfate was added and the solution was stored in a refrigerator at 5°. The content of peracid was determined at intervals. The solution was allowed to stand until slightly more than the calculated amount of peracid had disappeared. Reaction time varied between 6 and 38 days. Water was added to destroy the excess peracid and the filtered solution was evaporated to dryness *in vacuo.* The residue was treated with chloroform, in which the desired glycidamide is soluble and the by-product phthalic acid is but slightly soluble. The chloroform extract was washed with dilute sodium bicarbonate solution to remove traces of phthalic acid, dried, and evaporated. The residue of crude glycidamide was recrystallized to constant melting point from petroleum ether (b.p. 75–90°). Yields of crude product were very good, but in some cases purification involved considerable loss.

Physical properties and yields of the glycidamides prepared are listed in Table II. The high- and low-melting isomers of 2-*n*-butyl-3-*n*-propylglycidamide were obtained from the high- and low-melting isomers of the unsaturated amides, respectively.

2-Ethyl-3-n-propylglycidureide. 2-Ethyl-2-hexenoic acid[21] was converted to the acid chloride, b.p. 89–92°/22 mm.,

(10) M. R. Warren, C. R. Thompson, and H. W. Werner, *J. Pharmacol. Exptl. Therap.* **96,** 209 (1949). Oxanamide is the generic name of 2-ethyl-3-*n*-propylglycidamide. Quiactin is the registered trade-mark of The Wm. S. Merrell Co. for its brand of oxanamide.

(11) Microanalyses by Micro-Tech Laboratories, Skokie, Ill. All melting and boiling points are uncorrected.

(12) H. Sutter, F. Rottmayr, and H. Porsch, *Ann.* **521,** 189 (1936).

(13) C. Mannich and E. Kniss, *Ber.* **74B,** 1637 (1941).

(14) A. Macq, *Bull. sci. acad. roy. Belg.* [5] **12,** 753 (1926).

(15) G. Fuchs, *Z. Angew. Chem.* **17,** 1508 (1904).

(16) M. Tiffeneau, *Bull. soc. Chim.* [4] **33,** 188 (1923).

(17) W. A. Lott and W. G. Christiansen, *J. Am. Pharm. Assoc.* **23,** 788 (1934).

(18) J. Kenner and R. L. Wain, *Ber.* **72B,** 456 (1939).

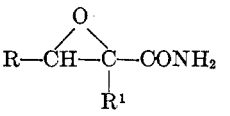
(19) M. Qudrat-i-Khuda and S. K. Ghosh, *J. Indian Chem. Soc.* **17,** 19 (1940).

(20) H. Böhme, *Org. Syntheses* **20,** 70 (1940). The batch size was doubled and only two ether extractions were used to give a more concentrated solution. Yields varied and the solution used contained from 0.20 to 0.52 mole of monoperphthalic acid per liter of ether solution.

(21) J. Lichtenberger and M. Naftali, *Bull. soc. Chim.* [5] **4,** 325 (1937).

TABLE II

2,3-DISUBSTITUTED GLYCIDAMIDES



R	R^1	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
C_2H_5	C_2H_5	6.5	91–93	$C_7H_{13}NO_2$	58.74	59.17	9.15	9.18	9.78	9.65
n-C_3H_7	C_2H_5	69	90–91	$C_8H_{15}NO_2$	61.13	60.96	9.62	9.59	8.91	8.80
C_2H_5	n-C_3H_7	43	99–100	$C_8H_{15}NO_2$	61.13	60.95	9.62	9.67	8.91	8.74
n-C_3H_7	n-C_3H_7	15	103.5–105	$C_9H_{17}NO_2$	63.11	63.22	10.01	9.98	8.18	7.96
n-C_3H_7	n-C_4H_9	30	93–95	$C_{10}H_{19}NO_2$	64.82	64.85	10.34	10.20	7.56	7.53
n-C_3H_7	n-C_4H_9	38	107–109	$C_{10}H_{19}NO_2$	64.82	64.57	10.34	10.03	7.56	7.37
C_6H_5	C_2H_5	—	144–150	$C_{11}H_{13}NO_2$	69.10	68.85	6.85	6.90	7.32	6.94
—$CH_2CH_2CH_2CH_2$—		50	107.5–108	$C_7H_{11}NO_2$	59.57	59.47	7.85	8.01	9.92	9.70
—CH_2—$CHCH_2CH_2$— (CH_3)		60	141.5–142	$C_8H_{13}NO_2$	61.93	62.15	8.44	8.44	9.03	8.92

which was heated with an excess of dry powdered urea for 6 hr. at 130–160°. The crude product was recrystallized from 50% aqueous ethanol and then from a 2:1 mixture of petroleum ether and absolute ethanol to give a 27% yield of *2-ethyl-2-hexenoylurea*, m.p. 151–153°.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.68; H, 8.74; N, 15.21. Found: C, 58.71; H, 8.59; N, 15.26.

This ureide was reported by Lott and Christiansen[17] but without melting point or analysis.

A solution of the unsaturated ureide with monoperphthalic acid in absolute ether and dioxane, kept at 5° for 21 days, gave a 48% yield of the glycidureide, m.p. 146–150°, after two recrystallizations from petroleum ether (b.p. 75–90°).

Anal. Calcd. for $C_9H_{16}N_2O_3$: C, 54.00; H, 8.06; N, 14.00. Found: C, 54.02; H, 7.79; N, 13.87.

2-Carbamyl-3,3-diethylglycidamide. Diethyl ketone and cyanoacetamide were condensed by the procedure of Cope *et al.*[22] to give *2-cyano-3-ethyl-2-pentenamide*, b.p. 115–116°/0.8 mm., m.p. 34–36°, in 45% yield.

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.91; H, 8.17; N, 18.58.

Twenty grams (0.131 mole) of this nitrile was treated with 200 ml. of 15% aqueous hydrogen peroxide and 50 ml. acetone. Slow addition of 10 ml. of 10% aqueous sodium carbonate solution caused a highly exothermic reaction, requiring ice cooling. After the mixture stood overnight at room temperature, the precipitate was collected, washed with water, and dried. The crude product weighed 22.3 g. (91% yield) and melted at 240–240.5°. The melting point was not changed by recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.05. Found: C, 51.83; H, 7.62; N, 15.01.

2,3-Dihydroxy-2-ethylhexanamide. A mixture of 20 g. of 2-ethyl-3-*n*-propylglycidamide, 5 drops of concd. sulfuric acid, and 50 ml. of water was refluxed for 48 hr. The water was removed *in vacuo* and the residue was recrystallized from a 6:1 mixture of petroleum ether (b.p. 75–90°) and absolute ethanol to give 11.2 g. of white needles, m.p. 110–112°. The analytical sample melted at 111–112° after another crystallization.

Anal. Calcd. for $C_8H_{17}NO_3$: C, 54.85; H, 9.78; N, 7.99. Found: C, 55.05; H, 9.55; N, 7.94.

From the filtrate of the original crystallization there was isolated 4 g. of unchanged glycidamide.

2-Ethyl-3-n-propyl-N-(1-hydroxy-2,2,2-trichloroethyl)glycidamide. A mixture of 31 g. (0.2 mole) of 2-ethyl-3-*n*-propylglycidamide and 44 g. (0.3 mole) of chloral was heated on a steam bath for 4 hr. The cooled solution was diluted with 100 ml. of ether and washed successively with water, sodium bisulfite solution, and water. The dried solution was evaporated and the viscous colorless oil remaining was put under a slight vacuum and seeded with a few crystals from an earlier preparation, whereupon the oil slowly crystallized. The crude material was recrystallized twice from petroleum ether (b.p. 30–60°) to give 11.5 g. (19% yield) of white crystals, m.p. 84.5–85.5°.

Anal. Calcd. for $C_{10}H_{16}Cl_3NO_3$: C, 39.42; H, 5.30. Found: C, 39.81; H, 5.52.

When the crude material was heated moderately under a vacuum of 0.2 mm. it decomposed into the starting amide and chloral.

Acknowledgment. The authors are indebted to Mr. Jay K. Seyler for technical assistance in a portion of this work and to Mr. William F. Boyd for the infrared spectra.

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(22) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.* **63**, 3452 (1941).