Syntheses of α-Keto Amides and Acids from Ethyl Alkylidenecyanoacetates[1]

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Ethyl alkylidenecyanoacetates (I) have been used as starting materials for the synthesis of α-keto acids. The key intermediates in this synthesis are epoxy amides (II) prepared from I and hydrogen peroxide. The epoxy amides were converted into the corresponding acids (III) by alkaline hydrolysis. Decarboxylation gave α-keto amides (IV); further, the amides (IV) were hydrolyzed to α-keto acids in good yield.

Ethyl alkylidenecyanoacetates were readily prepared from many carbonyl compounds by the Knoevenagel-Cope[2] reaction with ethyl cyanoacetate. It is well known that oxidation of the double bond adjacent to a cyano group with hydrogen peroxide results in the formation of an epoxy amide rather than an epoxy nitrile.[3,4] In the present study, the ethyl alkylidenecyanoacetate (I) was converted into the epoxy amide (II) by oxidation with hydrogen peroxide in the presence of an alkali such as sodium tungstate[5] or trisodium phosphate. The use of potassium carbonate as a catalyst gave a poor yield of II from I except in the case of ethyl cyclohexylidenecyanoacetate. The oxidations were carried out in ethanolic solution at an optimum temperature of 70–80°. After the peroxide had been consumed, the solvent was removed by distillation. In many cases the epoxy amides were isolated as viscous oils which solidified after standing overnight. Yields were from 50–80%.

The epoxy compounds (II) could be hydrolyzed in excellent yield to the corresponding acids (III) with alcoholic potassium hydroxide.

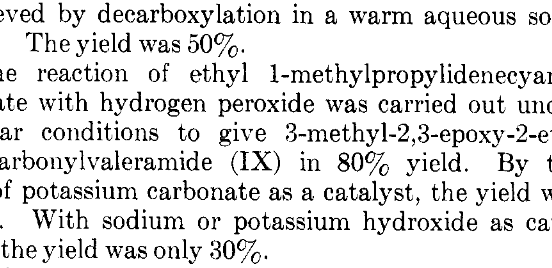
Decarboxylation of a glycidic acid is a well known synthetic method for the preparation of an aliphatic aldehyde.[6] In the present work, the epoxy acids were generally converted into resinous products by heating to the decomposition point. However, in the presence of a small amount of water, III smoothly gave α-keto amides (IV) on decarboxylation. Keto amides were hydrolyzed to α-keto acids in good yield.

The synthetic steps are shown in Chart I.

Payne[7] obtained 3-methyl-2,3-epoxy-2-ethoxycarbonylbutyramide (VI) in 37% yield by oxidation of ethyl isopropylidenecyanoacetate with 50% hydrogen peroxide under controlled pH conditions. In the present work, treatment of the same unsaturated nitrile with an excess of 30% hydrogen peroxide in the presence of sodium tungstate at 70–80° for one hour gave a 61% yield of VI. It could be hydrolyzed in 85% yield to 3-methyl-2,3-epoxy-2-carboxybutyramide (VII). Purification of VII by recrystallization from water was unsuitable since the resulting crystals always contained a small amount of decarboxylation product. It was best recrystallized from absolute ethanol. The compound gave mainly a resinous product when it was heated at 140–150°; in addition, a very small amount of colorless plates sublimed. The latter was assigned the keto amide structure (VIII) by infrared absorption and elementary analysis. The most efficient conversion of VII to 3-methyl-2-oxobutyramide (VIII) was achieved by decarboxylation in a warm aqueous solution. The yield was 50%.

The reaction of ethyl 1-methylpropylidenecyanoacetate with hydrogen peroxide was carried out under similar conditions to give 3-methyl-2,3-epoxy-2-ethoxycarbonylvaleramide (IX) in 80% yield. By the use of potassium carbonate as a catalyst, the yield was 40%. With sodium or potassium hydroxide as catalyst, the yield was only 30%.

This epoxy ester reacted with dry ammonia in ethanol to form 3-methyl-2,3-epoxy-2-carbamoylvaleramide (X).



IX
XXXIX

X, R = CH_3; R′ = C_2H_5
XL, R = H; R′ = i-C_3H_7

The conversion of the ester IX to 3-methyl-2,3-epoxy-2-carboxyvaleramide (XI) was effected by the usual alkaline hydrolysis. The yield was 86%. A 50% yield of 3-methyl-2-oxovaleramide (XII) was secured when the decarboxylation was carried out in water, acetic acid, or xylene solution. (See Table IV.) The hydrolysis of XII gave 3-methyl-2 oxovaleric acid (XIII) in good yield. XIII could also be prepared from XI by reaction with dilute hydrochloric acid. XII and XIII formed the corresponding oximes.

The epoxidation of ethyl cyclopentylidenecyanoacetate proceeded to the epoxy amide XXVII in 75% yield. Alkaline hydrolysis of the ethoxycarbonyl group and successive acidification with dilute hydrochloric acid at room temperature gave cyclopentaneglyoxylamide (XXVIII) directly without isolation of the corresponding epoxy acid. XXVIII was also hydrolyzed easily to the corresponding α-keto acid by dilute hydrochloric acid in excellent yield. Without isolating XXVIII, the over-all yield of cyclopentaneglyoxylic acid (XXIX) from XXVII was 60%.

Trisodium phosphate was used as catalyst in the epoxidation of ethyl benzylidenecyanoacetate. Sodium tungstate and potassium carbonate were unsuitable in this case. Other conditions and results in the formation of the α-keto acid (XLVIII) were similar to the preceding cases.

2,3-Epoxy-2-carboxypelargonamide (XLIV) gave no keto amide by the usual process. By heating the aqueous solution for a length of time, about 95% of the starting material was recovered. Meanwhile the epoxy amide (XLIV) was converted into 2-oxopelargon-

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(1) A brief report on a portion of this work has been published: M. Igarashi and H. Midorikawa, *Bull. Chem. Soc. Japan*, **34**, 1543 (1961).

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

(3) J. V. Murray and J. B. Cloke, *ibid.*, **56**, 2749 (1934).

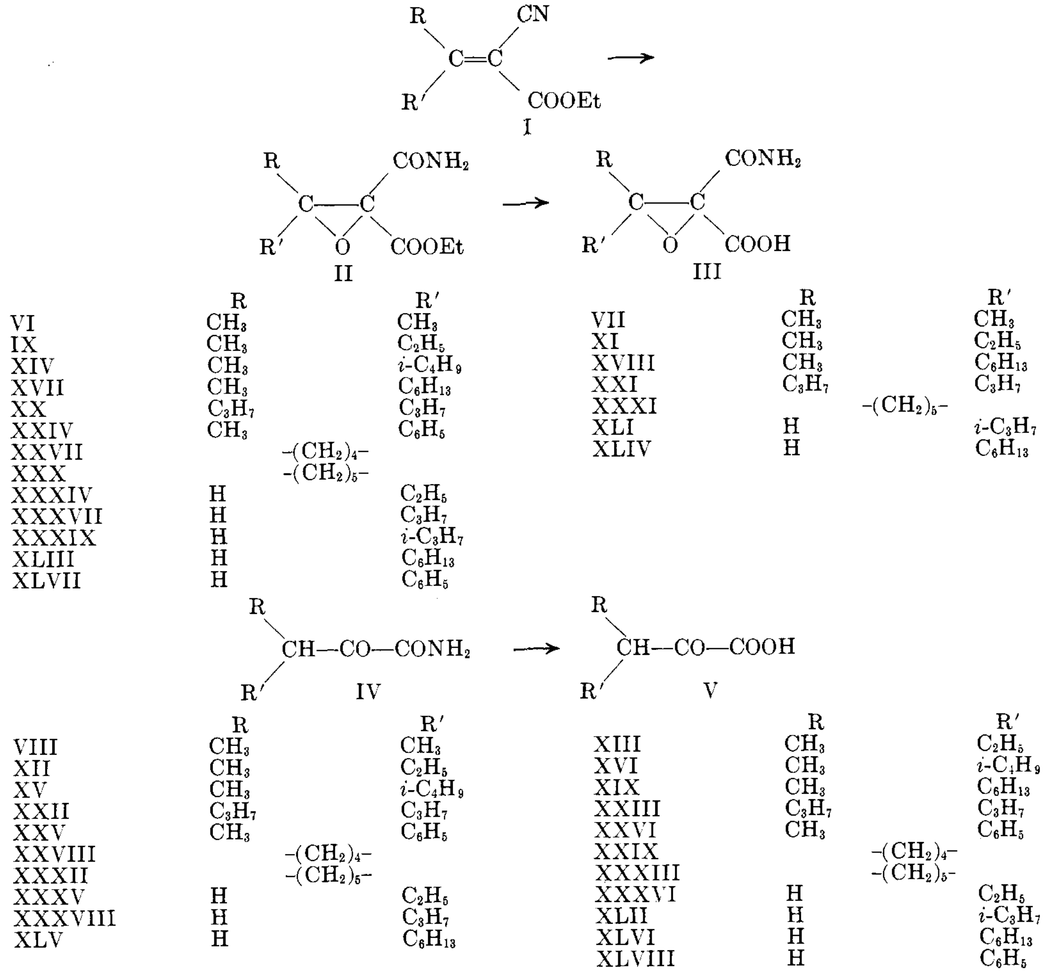
(4) E. C. Kornfeld, *et al.*, *ibid.*, **78**, 3087 (1956).

(5) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1959). The authors have shown that α,β-unsaturated acids such as crotonic acid and maleic acid are efficiently epoxidized with hydrogen peroxide using sodium tungstate as a catalyst at pH 4–5.5.

(6) M. S. Newman and B. J. Magerlein, *Org. Reactions*, **V**, 413 (1951).

(7) G. B. Payne, *J. Org. Chem.*, **26**, 663 (1961).

CHART I



	R	R′
VI	CH_3	CH_3
IX	CH_3	C_2H_5
XIV	CH_3	$i\text{-}C_4H_9$
XVII	CH_3	C_6H_{13}
XX	C_3H_7	C_3H_7
XXIV	CH_3	C_6H_5
XXVII	$-(CH_2)_4-$	
XXX	$-(CH_2)_5-$	
XXXIV	H	C_2H_5
XXXVII	H	C_3H_7
XXXIX	H	$i\text{-}C_3H_7$
XLIII	H	C_6H_{13}
XLVII	H	C_6H_5

	R	R′
VII	CH_3	CH_3
XI	CH_3	C_2H_5
XVIII	CH_3	C_6H_{13}
XXI	C_3H_7	C_3H_7
XXXI	$-(CH_2)_5-$	
XLI	H	$i\text{-}C_3H_7$
XLIV	H	C_6H_{13}

	R	R′
VIII	CH_3	CH_3
XII	CH_3	C_2H_5
XV	CH_3	$i\text{-}C_4H_9$
XXII	C_3H_7	C_3H_7
XXV	CH_3	C_6H_5
XXVIII	$-(CH_2)_4-$	
XXXII	$-(CH_2)_5-$	
XXXV	H	C_2H_5
XXXVIII	H	C_3H_7
XLV	H	C_6H_{13}

	R	R′
XIII	CH_3	C_2H_5
XVI	CH_3	$i\text{-}C_4H_9$
XIX	CH_3	C_6H_{13}
XXIII	C_3H_7	C_3H_7
XXVI	CH_3	C_6H_5
XXIX	$-(CH_2)_4-$	
XXXIII	$-(CH_2)_5-$	
XXXVI	H	C_2H_5
XLII	H	$i\text{-}C_3H_7$
XLVI	H	C_6H_{13}
XLVIII	H	C_6H_5

TABLE I

EPOXIDATION OF ETHYL ALKYLIDENECYANOACETATES

Epoxy compound	Ethyl alkylidenecyanoacetate	Yield, %[a]	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VI	Isopropylidene[b]	61 (A)	101[c]	$C_8H_{13}NO_4$	51.33	7.00	7.48	50.89	6.53	7.45
IX	1-Methylpropylidene[d]	80 (A), 40 (C), 30 (D)	77	$C_9H_{15}NO_4$	53.72	7.51	6.96	53.28	7.45	7.01
XIV	1,3-Dimethylbutylidene[d]	71 (A)	69 (b.p. 178–182°, 5 mm.)	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.37	8.01	6.15
XVII	1-Methylheptylidene[d]	64 (A)	88	$C_{13}H_{23}NO_4$	60.68	9.01	5.44	60.62	8.78	5.42
XX	1-Propylbutylidene[d]	50 (A)	99	$C_{12}H_{21}NO_4$	59.24	8.70	5.75	58.85	8.40	5.84
XXIV	1-Phenylethylidene[d]	70 (A)	91	$C_{13}H_{15}NO_4$	62.64	6.07	5.62	62.40	6.11	5.58
XXVII	Cyclopentylidene[e]	75 (A)	123	$C_{11}H_{15}NO_4$	56.32	7.09	6.57	55.99	6.83	6.53
XXX	Cyclohexylidene[d]	65 (A), 69 (C), 20 (D)	111	$C_{11}H_{17}NO_4$	58.13	7.54	6.16	58.23	7.45	6.07
XXXIV	Propylidene[f]	48 (A)	130–131	$C_8H_{13}NO_4$	51.33	7.00	7.48	51.45	6.93	7.48
XXXVII	*n*-Butylidene[g]	55 (A)	110–111	$C_9H_{15}NO_4$	53.72	7.51	6.96	53.20	7.09	7.07
XXXIX	Isobutylidene[g]	52 (A) 64 (B), 28 (C)	122	$C_9H_{15}NO_4$	53.72	7.51	6.96	53.35	7.38	7.16
XLIII	Heptylidene[h]	47 (A)	81–82	$C_{12}H_{21}NO_4$	59.24	8.70	5.76	59.13	8.40	5.75
XLVII	Benzilidene[i]	46 (B)	152–154	$C_{12}H_{13}NO_4$	61.27	5.57	5.96	61.27	5.40	5.91

[a] Capital letters refer to epoxidation methods designated by these letters in the Experimental section. [b] F. S. Prout, *J. Org. Chem.*, **18**, 928 (1953). [c] Lit.[7] 102–103°. [d] See ref. 2. [e] V. J. Harding and W. N. Haworth, *J. Chem. Soc.*, **97**, 486 (1910). [f] K. V. Anwers, *Ber.*, **56**, 1172 (1923). [g] F. D. Popp and A. Catala, *J. Org. Chem.*, **26**, 2738 (1961). [h] A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121**, 2741 (1922). [i] W. Baker and A. Lapworth, *ibid.*, **127**, 560 (1925).

amide (XLV) by heating at 130–140° in an oil bath. The crude keto amide turned a violet color with ferric chloride in an alcoholic solution, but it gave no discoloration after purification. Therefore, it is assumed that the decarboxylation of the epoxy amide is accompanied with the formation of a very small amount of β-keto amide as a by-product. The yield of XLV was 88%.

4-Methyl-2,3-epoxy-2-carboxyvaleramide (XLI) gave no 4-methyl-2-oxovaleramide, either by heating at the decomposition point (159°) or by warming it in the aqueous solution. By the former treatment a

TABLE II

HYDROLYSIS OF ETHYL 2,3-EPOXY-2-CARBAMOYLCARBOXYLATES

Epoxy acid	Yield, %[a]	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VII	85 (A)	133–134 dec.	$C_6H_9NO_4$	45.28	5.70	8.80	44.96	5.61	8.77
XI	86 (A), 70 (B)	140–141 dec.	$C_7H_{11}NO_4$	48.55	6.40	8.09	48.37	5.88	8.16
XVIII	84 (A)	108 dec.	$C_{11}H_{19}NO_4$	57.62	8.53		56.97	8.30	
XXI	57 (C)	117 dec.	$C_{10}H_{17}NO_4$	55.80	7.96		56.01	7.84	
XXXI	80 (A)	145 dec.	$C_9H_{13}NO_4$	54.26	6.58	7.03	54.31	6.50	7.02
XLI	92 (A)	159–160 dec.	$C_7H_{11}NO_4$	48.55	6.40	8.09	48.52	6.41	8.11
XLIV	85 (A)	118 dec.	$C_{10}H_{17}NO_4$	55.80	7.96	6.51	55.52	7.60	6.44

[a] Capital letters refer to hydrolysis methods designated by these letters in the Experimental section.

TABLE III

PREPARATION OF 2-OXOCARBOXYAMIDES FROM 2,3-EPOXY-2-CARBAMOYLCARBOXYLIC ACIDS

Keto amide	Yield, %[a]	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIII	50 (A)	112[b]	$C_5H_9NO_2$	52.16	7.88	12.17	51.89	7.77	11.99
Oxime		130–132	$C_5H_{10}N_2O_2$			21.53			21.54
XII	52 (A)	71	$C_6H_{11}NO_2$	55.79	8.58	10.85	55.81	8.59	10.85
Oxime		115–116	$C_6H_{12}N_2O_2$	49.98	8.39	19.43	50.18	7.82	19.39
XV	42[c]	143–145	$C_8H_{15}NO_2$	61.12	9.62	8.91	61.26	9.37	8.84
Oxime		103	$C_8H_{16}N_2O_2$			16.27			16.22
XXII	80 (A)	63	$C_9H_{17}NO_2$	63.13	10.00	8.18	62.84	9.49	8.20
XXV	64 (A)	116	$C_{10}H_{11}NO_2$	67.78	6.26	7.91	67.53	6.11	7.84
XXVIII	40[d]	134	$C_7H_{11}NO_2$	59.55	7.85	9.92	59.37	7.62	9.91
XXXII	48 (A)	120	$C_8H_{13}NO_2$	61.91	8.44	9.03	62.07	8.18	9.02
Oxime		177 dec.	$C_8H_{14}N_2O_2$			16.46			16.41
XXXV	53 (A), 82 (B)	105–106	$C_5H_9NO_2$	52.16	7.88	12.17	52.48	7.71	12.24
XXXVIII	47 (A)	87–88	$C_6H_{11}NO_2$	55.79	8.58	10.85	55.27	8.10	10.50
XLV	88 (B)	112[e]	$C_9H_{17}NO_2$	63.13	10.00	8.18	63.11	9.90	8.14
Oxime		134	$C_9H_{18}N_2O_2$			15.04			14.96

[a] Capital letters refer to decarboxylation methods designated by these letters in the Experimental section. [b] Lit. m.p. 109° [G. Barger and A. J. Ewins, *J. Chem. Soc.*, **97,** 284 (1910)]. [c] From 3,5-dimethyl-2,3-epoxy-2-carboxycaproamide hydrate (see Experimental). [d] From 2-ethoxycarbonyl-1-oxaspiro[2.4]heptane-2-carboxyamide (see Experimental). [e] Lit. m.p. 111° [J. Schreiber, *Compt. rend.*, **242,** 139 (1956)].

TABLE IV

DECARBOXYLATION OF 3-METHYL-2,3-EPOXY-2-CARBOXYVALERAMIDE (XI) IN VARIOUS SOLVENTS

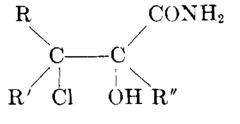
No.	Solvent	Heating time	Yield of XII, %
1	Water	2–3 min.	52
2	Acetic acid	2–3 min.	50
3	Ethanol	2–3 min.	Recovered
4	Benzene[a]	1 hr.	Trace
5	Toluene	10 min.	Trace
6	Toluene	5 hr.	47
7	Xylene	10 min.	48

[a] In suspension.

resinous product was obtained. On the other hand, the direct conversion of the epoxy amide XLI to 4-methyl-2-oxovaleric acid (XLII) in the presence of hydrochloric acid gave good results.

The epoxidation of ethyl butylidenecyanoacetate was also carried out by use of trisodium phosphate as a catalyst. The use of sodium tungstate as a catalyst lowered the yield from 55 to 40%.

In a few cases, oxirane ring-openings of epoxy amides were tried by treatment with concentrated hydrochloric acid. Chlorohydrins were formed but it was not confirmed which isomers were obtained.



XLIX, R = H; R′ = i-C_3H_7; R″ = COOH
L, R, R′ = -$(CH_2)_5$-; R″ = COOEt

These results are shown in Tables I–V.

Experimental

Epoxidation of Ethyl Alkylidenecyanoacetates. A.—Into a round-bottom flask equipped with thermometer and condenser was charged a solution of 0.05 mole of ethyl alkylidenecyanoacetate in 30–50 cc. of ethanol. To this was added 1.5 g. of sodium tungstate dihydrate and then 50 cc. of 30% hydrogen peroxide. A moderate exothermic reaction was held at 70–80° by warming on a water bath for 1–3 hr. After removal of the solvent, the residue was extracted by the use of chloroform or ether and the solvent evaporated. The oily residue solidified when it was allowed to stand at room temperature. The semisolid was washed with petroleum ether (b.p. 30–70°) to give colorless crystals of 2,3-epoxy-2-ethoxycarbonylcarboxyamide. The product was recrystallized prior to analysis.

The epoxidation of ethyl 1,3-dimethylbutylidenecyanoacetate was carried out according to the procedure already described. The ethereal extract was concentrated and distilled under reduced pressure. The fraction distilling at 178–182° (5 mm.) was collected. The distillate was dissolved in chloroform and then petroleum ether was added. When the solution was allowed to stand overnight in an icebox, a precipitate was formed. The precipitate was collected by suction filtration, and washed with petroleum ether. Recrystallization from chloroform–petroleum ether gave colorless microcrystals.

B.—The epoxidation was carried out as in A using 70 cc. of ethanol as solvent, 3.5 g. of trisodium phosphate dodecahydrate as catalyst, and 70 cc. of 30% hydrogen peroxide as oxidant. The separation of the product was carried out according to the procedure A.

TABLE V

SYNTHESIS OF 2-OXOCARBOXYLIC ACIDS

				Analyses, %					
				Calcd.			Found		
Keto acid	Yield, %[a]	B.p. (mm.), m.p., °C.	Formula	C	H	N	C	H	N
XIII	75 (A)	82–84 (18)[b] (m.p. 40)	$C_6H_{10}O_3$	55.37	7.75		55.01	7.59	
Oxime		164 dec.[c]	$C_6H_{11}NO_3$			9.65			9.51
XVI	80 (B)	104–110 (7)	$C_8H_{14}O_3$	60.74	8.92		60.04	8.69	
Oxime		132 dec.	$C_8H_{15}NO_3$			8.09			8.03
XIX	92 (A)	126–129 (8)[d]	$C_{10}H_{18}O_3$	64.49	9.74		63.97	9.41	
Oxime		90 dec.[e]	$C_{10}H_{19}NO_3$			6.96			6.71
XXIII	80 (B)	118–124 (7)	$C_9H_{16}O_3$	62.76	9.36		62.00	9.21	
Oxime		144 dec.	$C_9H_{17}NO_3$			7.48			7.33
XXVI	90 (B)	53	$C_{10}H_{10}O_3$	67.40	5.66		66.86	5.56	
Oxime		120 dec.	$C_{10}H_{11}NO_3$			7.25			7.02
XXIX	60 (A)[f]	54[g]	$C_7H_{10}O_3$	59.14	7.09		58.77	7.11	
Oxime		131 dec.	$C_7H_{11}NO_3$			8.91			8.92
XXXIII	98 (B)	50[h]	$C_8H_{12}O_3$	61.52	7.75		60.98	7.62	
Oxime		170	$C_8H_{13}NO_3$			8.18			8.18
XXXVI	83 (B)	61–63 (6)[i]	$C_5H_8O_3$						
Oxime		145 dec.[j]	$C_5H_9NO_3$			10.68			10.52
XLII	82 (A)	90–94 (20), (m.p. 10)[k]	$C_6H_{10}O_3$						
Oxime		148 dec.[l]	$C_6H_{11}NO_3$			9.65			9.42
XLVI	95 (B)	42[m]	$C_9H_{16}O_3$						
Oxime		97[n]	$C_9H_{17}NO_3$			7.48			7.20
XLVIII	47 (A)[o]	154–156 dec.[p]	$C_9H_8O_3$	65.85	4.91		65.48	4.91	
Oxime		173 dec.[q]	$C_9H_9NO_3$			7.82			7.51

[a] Capital letters refer to synthetic methods designated by these letters in the Experimental section. [b] Lit. b.p. 73° (10 mm.), m.p. 38–40°: A. Meister, *J. Biol. Chem.*, **190,** 269 (1951). [c] Lit. m.p. 164° dec.: L. Bouveault and R. Locquin, *Compt. rend.*, **141,** 115, (1905). [d] Lit. b.p. 124–125° (9 mm.): R. Locquin, *Bull. soc. chim. France*, [3] **31,** 1153 (1904). [e] Lit. m.p. 89–90° dec.: R. Locquin *ibid.*, [3] **31,** 1075 (1904). [f] Potassium salt of 2-carboxy-1-oxaspiro[2.4]heptane-2-carboxyamide (see Experimental) was treated by method A. [g] J. D. Fissekis, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, **81,** 2715 (1959), report m.p. 25–30° for this derivative. [h] Lit. m.p. 45–49°: D. D. E. Newman and L. N. Owen, *J. Chem. Soc.*, 4713 (1952). [i] Lit. b.p. 66° (6 mm.): F. Adickes and G. Andresen, *Ann.*, **555,** 41 (1944). [j] Lit. m.p. 145° dec.: K. E. Hamlin and W. H. Hartung, *J. Biol. Chem.*, **145,** 351 (1942). [k] Lit. b.p. 84° (15 mm.): J. Schreiber, *Ann. Chim.* (Paris), [12] **2,** 98 (1947). [l] Lit. m.p. 147° dec.: T. Uyemura, *Bull. Agr. Chem. Soc. Japan*, **15,** 353 (1939). [m] Lit.[i] m.p. 43–44°. [n] Lit.[i] m.p. 98–98.5°. [o] 3-Phenyl-2,3-epoxy-2-ethoxycarbonylpropionamide (XLVII) was treated with ethanolic potassium hydroxide, and then the potassium salt was treated by method A. [p] Lit. m.p. 156° dec.: M. Bergmann and A. Miekeley, *Ann.*, **458,** 40 (1927). [q] Lit. m.p. 173–174° dec.: Ch. Gränacher, *Helv. Chim. Acta.*, **5,** 610 (1922).

C.—To a flask equipped with stirrer, thermometer, and dropping funnel were charged 0.05 mole of ethyl alkylidenecyanoacetate, 10 cc. of 30% hydrogen peroxide, and 50–60 cc. of ethanol. Ten cubic centimeters of 4 *N* potassium carbonate was added dropwise to the mixture with stirring and cooling at 40–45°. After an additional 3 hr., the solvent was removed under reduced pressure. The reaction mixture, containing a precipitate, was diluted with water, chilled, and filtered to give the corresponding epoxy amide II.

D.—The process was carried out as in the foregoing method using 20 cc. of 15% hydrogen peroxide and 10 cc. of 4 *N* sodium hydroxide (or potassium hydroxide) at 30–35°. The reaction mixture was allowed to stand for 1 day at room temperature and then concentrated under vacuum. The residue was digested with ethanol to be separated into ethanol-soluble and insoluble parts. From the ethanol-soluble part, the corresponding epoxy amide II was obtained.

The ethanol-insoluble part was dissolved in water and acidified with dilute hydrochloric acid. The resulting precipitate was collected by filtration. Recrystallization from ethanol gave colorless microcrystals. This compound was identified as the corresponding 2,3-epoxy-2-carbamoylcarboxylic acid (III) by infrared spectrum and by the melting point.

By this method, 2-carboxy-1-oxaspiro[2.5]octane-2-carboxyamide (XXXI) was obtained in 12% yield from ethyl cyclohexylidenecyanoacetate. From ethyl 1-methylpropylidenecyanoacetate, XI was also obtained in a few per cent yield.

Hydrolysis of 2,3-Epoxy-2-ethoxycarbonylcarboxyamides. A.—To a three-necked flask equipped with a stirrer, dropping funnel, and thermometer was charged a solution of 2,3-epoxy-2-ethoxycarbonylcarboxyamide in ethanol, and ethanol containing an excess of potassium hydroxide was added dropwise under stirring at room temperature. After the mixture was allowed to stand overnight, the resulting white precipitate was separated by filtration, washed with ethanol, and dried. The potassium salt was again dissolved in a small amount of water, cooled in an ice bath, and neutralized with dilute hydrochloric acid. The resulting precipitate was collected by filtration, washed with a small amount of cold water, and dried. A sample was recrystallized from absolute ethanol or methanol prior to analysis.

B.—A mixture of 2,3-epoxy-2-ethoxycarbonylcarboxyamide and water containing an excess of sodium hydroxide was warmed on a water bath for about 1 hr. and allowed to cool to room temperature. The mixture was then treated with dilute hydrochloric acid and the resulting precipitate was collected by filtration.

C.—Hydrolysis of 3-propyl-2,3-epoxy-2-ethoxycarbonylcaproamide (XX) with ethanolic potassium hydroxide was carried out as before. (Treatment of the potassium salt with dilute hydrochloric acid gave only 3-propyl-2,3-epoxy-2-carboxycaproamide hydrate.) The barium salt was prepared from the potassium salt by the addition of barium chloride dissolved in hot water. A suspension of 3 g. of the barium salt and 1 g. of anhydrous magnesium sulfate in 30 cc. of ether was stirred at 0–5° and treated by adding the solution containing 0.6 g. of sulfuric acid in 3 cc. of ether in dropping form. The mixture was automatically stirred overnight at room temperature. After removal of barium sulfate by filtration, the filtrate was dried over magnesium sulfate and concentrated under vacuum to give 1.3 g. of 3-propyl-2,3-epoxy-2-carboxycaproamide (XXI), m.p. 117° dec.

Recrystallization of XXI from chloroform gave 3-propyl-2,3-epoxy-2-carboxycaproamide hydrate, m.p. 102° dec., which was dehydrated by heating at 70–80°.

Anal. Calcd. for $C_{10}H_{17}NO_4 \cdot H_2O$: C, 51.49; H, 8.21; N, 6.01. Found: C, 51.41; H, 7.81; N, 5.96.

3,5-Dimethyl-2,3-epoxy-2-carboxycaproamide Hydrate.—3,5-Dimethyl-2,3-epoxy-2-ethoxycarbonylcaproamide (XIV) was treated with alcoholic potassium hydroxide. The resulting potassium salt was dissolved in water and neutralized with dilute hydrochloric acid to give 3,5-dimethyl-2,3-epoxy-2-carboxycaproamide hydrate. The yield was 87%. Recrystallization from ether gave colorless microcrystals, m.p. 105° dec.

Anal. Calcd. for $C_9H_{15}NO_4 \cdot H_2O$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.49; H, 7.52; N, 6.41.

This compound was used for the following reaction without further dehydration.

3-Phenyl-2,3-epoxy-2-carboxybutyramide Hydrate.—Hydrolysis of 3-phenyl-2,3-epoxy-2-ethoxycarbonylbutyramide (XXIV) was carried out by method A. 3-Phenyl-2,3-epoxy-2-carboxybutyramide hydrate was obtained in 60% yield; m.p. 104° dec. (colorless needles from ether).

Anal. Calcd. for $C_{11}H_{11}NO_4 \cdot H_2O$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.01; H, 6.11; N, 5.58.

This was used without further treatment for the following preparation.

Decarboxylation of 2,3-Epoxy-2-carbamoylcarboxylic Acids. A.—The epoxy acid III was heated with a small amount of water for a short time and allowed to cool to room temperature. The reaction mixture containing precipitated product was filtered to give colorless plates of essentially pure 2-oxocarboxyamide (IV). A sample was recrystallized from water prior to analysis. The oxime was obtained by the usual way.

B.—2,3-Epoxy-2-carbamoylcarboxylic acid (III) was heated at 130–140° in an oil bath for 5–10 min. Here, carbon dioxide evolved. The product solidified after cooling. Recrystallization from ethanol or water afforded colorless plates of 2-oxocarboxyamide.

In the case of 2,3-epoxy-2-carboxypelargonamide (XLIV), the crude product gave a violet color with ferric chloride in ethanol whereas the pure substance gave no discoloration.

3,5-Dimethyl-2-oxocaproamide (XV).—3,5-Dimethyl-2,3-epoxy-2-carboxycaproamide hydrate was heated with water for 1.5 hr. The mixture was cooled and extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate, and then the ether was removed by distillation. Fractional distillation of the residue gave 3,5-dimethyl-2-oxocaproamide (XV), b.p. 122–130° (8 mm.), which solidified on standing in an ice bath, m.p. 138–143°. Recrystallization from ethanol gave colorless microcrystals, m.p. 143–145°.

Cyclopentaneglyoxylamide (XXVIII).—To a solution of 3 g. of 2-ethoxycarbonyl-1-oxaspiro[2.4]heptane-2-carboxyamide (XXVII) in ethanol, ethanolic potassium hydroxide was added at room temperature. A white crystalline precipitate formed during the addition. After the mixture had stood overnight, it was separated by filtration, washed with ethanol, and dried. The yield of the potassium salt was 2.8 g. (89%). The potassium salt was dissolved in water and neutralized with dilute hydrochloric acid. After standing overnight at room temperature, the resulting precipitate was collected by filtration. An additional amount of the product was obtained from the mother liquor by allowing it to stand for 2–3 days. The total yield was 0.8 g. (40% based on XXVII). Recrystallization from water gave colorless plates of cyclopentaneglyoxylamide.

Decarboxylation of 3-Methyl-2,3-epoxy-2-carboxyvaleramide (XI) in Various Solvents.—The decarboxylation of XI was carried out according to procedure A using water, acetic acid, ethanol, benzene, toluene, and xylene as solvent. The results are shown in Table IV.

Synthesis of 2-Oxocarboxylic Acids. A. From 2,3-Epoxy-2-carbamoylcarboxylic Acids.—The epoxy acid III was heated with an excess of dilute hydrochloric acid (1:1) for 1 hr. The solution was cooled and extracted by using three portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate, and then the solvent was removed by distillation. The fractional distillation under reduced pressure gave colorless liquid of 2-oxocarboxylic acid (V).

XLVIII was recrystallized from chloroform to give colorless plates, m.p. 154–156° dec.

B. From 2-Oxocarboxyamides.—The keto amide IV was treated with a slight excess of dilute hydrochloric acid and then extracted with ether. From the ethereal extract, 2-oxocarboxylic acid (V) was obtained by fractional distillation (or by recrystallization of the residue).

3-Methyl-2,3-epoxy-2-carbamoylvaleramide (X).—Reaction of a sample of 3-methyl-2,3-epoxy-2-ethoxycarbonylvaleramide (IX) with ammonia in alcohol at room temperature gave X, m.p. 237° dec.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03. Found: C, 48.79; H, 6.72.

4-Methyl-2,3-epoxy-2-carbamoylvaleramide (XL).—4-Methyl-2,3-epoxy-2-ethoxycarbonylvaleramide (XXXIX) was shaken 15 min. with concentrated aqueous ammonia. The solid dissolved, followed shortly thereafter by precipitation of the product XL, m.p. 181–182°.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.83; H, 6.48; N, 16.28.

Reaction of Epoxy Amide II with Concentrated Hydrochloric Acid.—A sample of 4-methyl-2,3-epoxy-2-ethoxycarbonylvaleramide (XXXIX) was dissolved in concentrated hydrochloric acid and allowed to stand at room temperature for 2 days. Recrystallization of the resulting precipitate gave prisms, m.p. 113–114° dec., having an analysis in substantial agreement for 4-methyl-3-hydroxy-2-chloro-2-carbamoylvaleric acid or its isomer, 4-methyl-3-chloro-2-hydroxy-2-carbamoylveric acid (XLIX, $R = C_2H_5$, $R' = H$).

Anal. Calcd. for $C_7H_{12}NO_4Cl$: C, 40.10; H, 5.76; N, 6.67; Cl, 16.91. Found: C, 40.57; H, 5.94; N, 6.48; Cl, 16.29.

A sample of 3-phenyl-2,3-epoxy-2-ethoxycarbonylpropionamide (XLVII) was shaken with concentrated hydrochloric acid at room temperature for a few minutes. The product, m.p. 169–172°, had an empirical formula in agreement with 3-phenyl-3-chloro-2-hydroxy-2-ethoxycarbonylpropionamid (L) or its isomer, 3-phenyl-3-hydroxy-2-chloro-2-ethoxycarbonylpropionamide.

Anal. Calcd. for $C_{12}H_{14}NO_4Cl$: C, 53.04; H, 5.19; Cl, 13.04. Found: C, 52.96; H, 4.94; Cl, 12.75.

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