[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Reactions of α-Ketols Derived from Tertiary Acetylenic Carbinols. III. The Preparation of 4-Methyl-4,5,5-trisubstituted-2-oxazolidinones[1]

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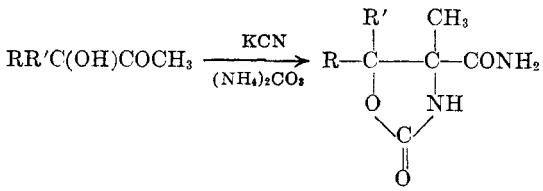
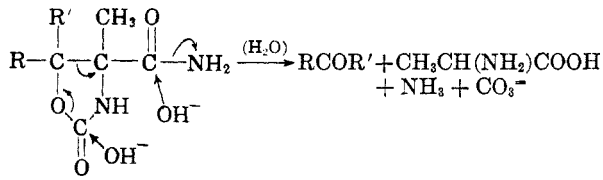
α-Ketols, $RR'C(OH)COCH_3$, react with potassium cyanide and ammonium carbonate in aqueous alcohol solution to produce 4-carbamyl-4-methyl-5,5-disubstituted-2-oxazolidinones, $RR'C(O{-}CO{-}NH{-}C(CH_3)CONH_2)$. Acid hydrolysis converts the latter to the corresponding 4-carboxylic acids in 65–80% yields. Alkaline hydrolysis proceeds by a reverse aldol type reaction producing ketones, RCOR', and alanine. Attempts to prepare α-amino-β-hydroxy acids by hydrolysis of the oxazolidinones were unsuccessful.

The reaction of potassium cyanide and ammonium carbonate with six α-ketols, $RR'C(OH)COCH_3$, obtained by hydration of the corresponding tertiary acetylenic carbinols, has been studied in connection with attempts to prepare α-amino-β-hydroxy acids *via* the intermediate hydantoins.[3] Crystalline products were readily obtained in good yield and they analyzed correctly in all instances for the expected hydantoin structures. Examination of these substances, particularly their behavior when subjected to hydrolysis, quickly revealed, however, that they are 4-carbamyl-4-methyl-5,5-disubstituted-2-oxazolidinones, formed according to the following equation.



Hydrolysis with hot 4–5*N* hydrochloric acid converted these substances to the corresponding 4-carboxylic acids. The latter could be reconverted to the starting materials by treatment with thionyl chloride and then with aqueous ammonia. Similarly, treatment of the acids with thionyl chloride followed by reaction with methanol produced methyl esters identical with those obtained by direct esterification. It is noteworthy that the oxazolidinone ring survives these reactions so well. This was not the case, however, when the 4-carbamyl compounds were hydrolyzed in alkaline media. In all such instances they were completely degraded, apparently by a reverse aldol type reaction as indicated below.



It is interesting to compare these results with those of Henze and Craig.[4] They treated benzoylcarbinyl acetate with potassium cyanide and ammonium carbonate in aqueous ethanol, obtaining 4-carbamyl-4-phenyl-2-oxazolidinone. Dilute hydrochloric acid hydrolysis of the latter produced the corresponding 4-carboxylic acid. Hydrolysis of both the amide and the acid, the former by dilute sodium hydroxide, the latter by either dilute alkali or 9*N* hydrochloric acid, led to the formation of α-amino-β-hydroxy-α-phenylpropionic acid. Apparently no cleavage was observed.

This contrasts with our results in which alkaline hydrolysis leads to complete degradation, and in which degradation has also been observed as a side reaction in the acidic hydrolysis of the 4-carbamyl compounds to the corresponding 4-carboxy compounds. In no case has it been possible to obtain the desired α-amino-β-hydroxy acids.

Preliminary work indicates that the α-ketol methyl ethers react in the expected manner with potassium cyanide and ammonium carbonate to produce hydantoins. In the one case studied, 3-phenyl-3-methoxy-2-butanone gave a 26% yield of 5-methyl-5-(α-methoxy-α-phenethyl)hydantoin.

The new compounds prepared are described in Table I.

EXPERIMENTAL

α-Ketols. 3-Methyl-3-hydroxy-2-butanone, 3-methyl-3-hydroxy-2-pentanone, 3-ethyl-3-hydroxy-2-pentanone, 1-acetylcyclohexanol, 3,5-dimethyl-3-hydroxy-2-hexanone, and 3-phenyl-3-hydroxy-2-butanone were prepared by hydration of *t*-acetylenic carbinols.[5] 3-Phenyl-3-methoxy-2-butanone was prepared as previously described.[6]

(1) Paper LXX on substituted acetylenes; previous paper, G. F. Hennion and E. J. Watson, *J. Org. Chem.*, **23**, 658 (1958).

(2) Eli Lilly Co. Fellow, 1955–1956. Abstracted from a portion of the Ph.D. Dissertation of F. X. O'S.

(3) K. Pfister *et al.*, *J. Am. Chem. Soc.*, **77**, 697 (1955); E. Ware, *Chem. Revs.*, **46**, 403 (1950).

(4) H. Henze and W. Craig, *J. Org. Chem.*, **10**, 16 (1945).

(5) G. F. Hennion and E. J. Watson, *J. Org. Chem.*, **23**, 656 (1958).

(6) G. F. Hennion and B. R. Fleck, *J. Am. Chem. Soc.*, **77**, 3253 (1955).

TABLE I

4-METHYL-4,5,5-TRISUBSTITUTED-2-OXAZOLIDINONES

RR′C(—O—CO—NH—)C(CH$_3$)—CO—X

Cpd.	R	R′	Yield, %	M. P., °C.[a]
		A. Amides (X = NH_2)		
I	CH_3	CH_3	34	208–209
II	CH_3	C_2H_5	31	224–226
III	C_2H_5	C_2H_5	72	175–177
IV	—CH_2—$(CH_2)_3$—CH_2—		79	253–254
V[b]	CH_3	i-C_4H_9	39	192–194
VI[b]	CH_3	i-C_4H_9	19	176–178
VII	CH_3	C_6H_5	24	222–224
		B. Acids (X = OH)		
VIII	CH_3	CH_3	74	206–207
IX	CH_3	C_2H_5	80	206–207
X	C_2H_5	C_2H_5	66	177–179
XI	—CH_2—$(CH_2)_3$—CH_2—		73	205–206
XII[c]	CH_3	i-C_4H_9	74	186–187
XIII[c]	CH_3	i-C_4H_9	69	195–196
XIV	CH_3	C_6H_5	72	198–199
		C. Esters (X = OCH_3)		
XV	CH_3	CH_3	58	99–100
XVI	—CH_2—$(CH_2)_3$—CH_2—		33	129–131
XVII	CH_3	i-C_4H_9	68	89–90

[a] All melting points are uncorrected. [b] Compounds V and VI are diastereoisomers. [c] Diastereoisomers, XII from V and XIII from VI.

TABLE II

IDENTIFICATION OF 4-METHYL-4,5,5-TRISUBSTITUTED-2-OXAZOLIDINONES

Compound	Name
I	4-Carbamyl-4,5,5-trimethyl-2-oxazolidinone
II	4-Carbamyl-4,5-dimethyl-5-ethyl-2-oxazolidinone
III	4-Carbamyl-4-methyl-5,5-diethyl-2-oxazolidinone
IV	4-Carbamyl-4-methyl-5,5-pentamethylene-2-oxazolidinone
V, VI	4-Carbamyl-4,5-dimethyl-5-isobutyl-2-oxazolidinone
VII	4-Carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone
VIII	4-Carboxy-4,5,5-trimethyl-2-oxazolidinone
IX	4-Carboxy-4,5-dimethyl-5-ethyl-2-oxazolidinone
X	4-Carboxy-4-methyl-5,5-diethyl-2-oxazolidinone
XI	4-Carboxy-4-methyl-5,5-pentamethylene-2-oxazolidinone
XII, XIII	4-Carboxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone
XIV	4-Carboxy-4,5-dimethyl-5-phenyl-2-oxazolidinone
XV	4-Carbomethoxy-4,5,5-trimethyl-2-oxazolidinone
XVI	4-Carbomethoxy-4-methyl-5,5-pentamethylene-2-oxazolidinone
XVII	4-Carbomethoxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone

Preparation of 4-carbamyl-4,5,5-trisubstituted-2-oxazolidinones. The procedure used was essentially that described by Henze[7] for the preparation of hydantoins from carbonyl compounds. In most cases the product readily crystallized from the cooled reaction mixture and was usually recrystallized from aqueous ethanol.

In a typical preparation, 108 g. (0.75 mole) of 3,5-dimethyl-3-hydroxy-2-hexanone, 65 g. (1 mole) of potassium cyanide, 288 g. (2.5 moles) of ammonium carbonate, and one liter of 50% ethyl alcohol were placed in a 2-liter 3-neck flask fitted with a thermometer and an air condenser. As a precaution against the evolution of hydrogen cyanide, a trap containing sodium hydroxide solution was connected to the top of the condenser and the reaction was run in the hood. The reaction mixture was maintained at 55–60° for 6 hr. and then allowed to cool overnight. The white crystalline product was filtered off, washed with 200 ml. of distilled water, and air dried. Two crystallizations from aqueous ethanol yielded 47.2 g. of 4-carbamyl-4,5-dimethyl-5-isobutyl-2-oxazolidinone (V), m.p. 192–194°. The filtrate and washings were combined and refrigerated overnight yielding another 16.1 g. of product, m.p. 192–194° after two crystallizations from aqueous ethanol. The total yield was 63.3 g. (39%).

The mother liquor then was concentrated by distillation to *ca.* one-third volume. A third crop of solid was obtained which, after crystallization from ethyl acetate, yielded 30 g. (19%) of the low melting diastereoisomer (VI), m.p. 176–178°.

Preparation of 4-carboxy-4,5,5-trisubstituted-2-oxazolidinones. These compounds were prepared by refluxing the 4-carbamyl-4,5,5-trisubstituted-2-oxazolidinones for 2 to 4 hr. in 4 to 5*N* hydrochloric acid. The product precipitated out upon cooling of the reaction mixture and was usually recrystallized from aqueous ethanol.

In a typical preparation, 10 g. (0.0426 mole) of 4-carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone was refluxed in 100 ml. of 5*N* hydrochloric acid for 3.5 hr. At the termination of reflux, a small amount of acetophenone, detectable as oily droplets in the reaction mixture, was steam distilled out. A 2,4-dinitrophenylhydrazone derivative was prepared, affording 2 g. of orange crystals, m.p. (corr.) 248.5–249.5° (lit.[8] m.p. 250°) after crystallization from ethyl alcohol–ethyl acetate. The formation of acetophenone indicates a small amount of side reaction involving ring cleavage similar to that observed in alkaline hydrolysis.

The reaction mother liquor, upon cooling, yielded 7.2 g. (72%) of 4-carboxy-4,5-dimethyl-5-phenyl-2-oxazolidinone (XIV) melting with decomposition at 198–199°. Crystallization from aqueous ethanol did not raise the melting point.

Conversion of 4-carboxy-4,5-dimethyl-5-phenyl-2-oxazolidinone to the corresponding 4-carbamyl compound. One gram of powdered 4-carboxy-4,5-dimethyl-5-phenyl-2-oxazolidinone (XIV) was refluxed with 5 ml. of thionyl chloride for 5 min. The hot solution then was added dropwise with shaking to 25 ml. of ice cold aqueous ammonia, producing a brown precipitate which was filtered off and dried. The product (0.8 g.) was crystallized twice from aqueous ethanol, the hot solutions being decolorized with activated charcoal (Norit A), yielding 4-carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone (VII), m.p. 222–224°. Mixture with the 4-carbamyl compound (VII) obtained from the α-ketol did not depress the melting point and the infrared spectra of the compounds obtained by both methods were identical.

Preparation of 4-carbomethoxy-4,5,5-trisubstituted-2-oxazolidinones. Method A. Direct esterification was accomplished by refluxing the acid with anhydrous methanol containing 3% dry hydrogen chloride. In a typical preparation, 5 g. of 4-carboxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone (XII) was refluxed for 9 hr. with 100 ml. of anhydrous methanol

(7) H. Henze *et al.*, *J. Am. Chem. Soc.*, **71**, 2220 (1949).

(8) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, New York, 3rd ed., p. 263.

TABLE III

ANALYTICAL DATA

Compound	Mol. Formula	Calcd. C	Calcd. H	Calcd. N	Obsd. C	Obsd. H	Obsd. N	Neut. Equiv. Calcd.	Neut. Equiv. Obsd.
I	$C_7H_{12}N_2O_3$	48.83	7.03		49.31	7.17			
II	$C_8H_{14}N_2O_3$	51.60	7.58		51.38	7.17			
III	$C_9H_{16}N_2O_3$	53.98	8.06	13.99	53.72	7.88	13.98		
IV	$C_{10}H_{16}N_2O_3$	56.58	7.60	13.20	56.32	7.86	13.08		
V	$C_{10}H_{18}N_2O_3$	56.05	8.47	13.08	56.01	8.40	13.20		
VI	$C_{10}H_{18}N_2O_3$	56.05	8.47	13.08	56.28	8.43	13.16		
VII	$C_{12}H_{14}N_2O_3$	61.52	6.02	11.96	61.89	6.07	11.40		
VIII	$C_7H_{11}NO_4$	48.55	6.40	8.09	48.42	6.67	8.00	173.2	174.1
IX	$C_8H_{13}NO_4$	51.33	7.00	7.48	51.69	7.18	7.26	187.2	188.3
X	$C_9H_{15}NO_4$	53.72	7.51	6.96	54.16	8.01	7.00	201.2	200.1
XI	$C_{10}H_{15}NO_4$	56.33	7.09	6.57	56.63	7.16	6.43	213.2	216.2
XII	$C_{10}H_{17}NO_4$	55.80	7.96	6.51	56.39	8.09	6.25	215.2	216.1
XIII	$C_{10}H_{17}NO_4$	55.80	7.96	6.51	56.05	8.19	6.38	215.2	215.9
XIV	$C_{12}H_{13}NO_4$	61.27	5.57	5.96	61.53	5.58	6.02	235.2	235.3
XV	$C_8H_{13}NO_4$	51.33	7.00	7.48	51.08	7.12	7.34		
XVI	$C_{11}H_{17}NO_4$	58.12	7.54	6.16	58.39	7.61	6.00		
XVII	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.82	8.53	6.02		

containing 3% dry hydrogen chloride. The mixture, after standing overnight, was concentrated by distillation *in vacuo* to a gummy residue. The residue was dissolved in 100 ml. of chloroform, filtered, and the filtrate dried overnight in the refrigerator with anhydrous sodium sulfate. The solution then was filtered and the filtrate distilled *in vacuo* to a solid residue which, after two crystallizations from hexane–carbon tetrachloride, yielded 3.6 g. (68%) of 4-carbomethoxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone (XVII), m.p. 89–90°.

Method B. Esterification was accomplished by conversion of the acid to the acid chloride and subsequent reaction with anhydrous methanol. Thus, 1 g. of 4-carboxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone (XII) was refluxed with 5 ml. of thionyl chloride for 5 min. The solution then was added dropwise to 10 ml. of anhydrous methanol. The mixture, after standing overnight, was evaporated to dryness on a hot plate yielding 4-carbomethoxy-4,5-dimethyl-5-isobutyl-2-oxazolidinone (XVII), m.p. 88–91° after recrystallization from hexane–carbon tetrachloride (not depressed by mixture with the product obtained by method A).

Alkaline hydrolysis of 4-carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone. To a solution of 15.8 g. (0.05 mole) of barium hydroxide in 160 ml. of water (*ca.* 5% by weight) contained in a 500-ml. round bottom flask was added 5.85 g. (0.025 mole) of 4-carbamyl-4,5-dimethyl-5-phenyl-2-oxazolidinone (VII). After 30 min. of reflux, oily droplets began to appear in the refluxing distillate and the evolution of ammonia was evident. After 22 hr. of reflux, the oily layer was steam distilled out of the reaction mixture, the oil extracted twice from the distillate with 50 ml. portions of ether, and the combined ethereal extracts dried over anhydrous sodium sulfate. The ether solution then was filtered and the solvent removed by distillation *in vacuo* leaving 3.0 g. of acetophenone (quantitative). A 2,4-dinitrophenylhydrazone derivative was prepared, m.p. (corr.) 248.5–249° (lit.[8] m.p. 250°) after crystallization from ethyl alcohol–ethyl acetate. Mixture with the 2,4-dinitrophenylhydrazone derivative of an authentic sample of acetophenone did not depress the melting point.

The original reaction mixture was filtered to remove the precipitated barium carbonate, neutralized with dilute sulfuric acid, and again filtered to remove the precipitated barium sulfate. The filtrate was concentrated by distillation to *ca.* 25 ml., diluted with 200 ml. of absolute ethanol and refrigerated yielding 1.46 g. (66%) of alanine. A phenylureido derivative was prepared, m.p. (corr.) 167–168° (lit.[9] m.p. 168°) after two crystallizations from water. Mixture with the phenylureido derivative of an authentic sample of *dl*-alanine produced no depression in the melting point.

5-Methyl-5-(α-methoxy-α-phenethyl)hydantoin. A mixture of 55 g. (0.31 mole) of 3-phenyl-3-methoxy-2-butanone, 33 g. (0.5 mole) of potassium cyanide, 96 g. (1 mole) of ammonium carbonate, and 500 ml. of 50% ethyl alcohol was placed in a 2-liter 3-neck flask fitted with a thermometer and an air condenser. The reaction mixture was maintained at 55–60° for 5.5 hr. and then allowed to cool overnight. The resultant white precipitate was filtered off, yielding 20 g. (26%) of 5-methyl-5-(α-methoxy-α-phenethyl)hydantoin melting at 224–226° after two recrystallizations from aqueous ethanol. Concentration of the mother liquor provided further crops of product, consisting of mixtures of the two diastereoisomeric products, from which neither isomer could be obtained pure by the ordinary crystallization techniques.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.28. Found: C, 62.88; H, 6.51; N, 11.52.

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(9) S. P. Mulliken, *Identification of Pure Organic Compounds*, II, John Wiley & Sons, New York, 1916, p. 222.