THE α-KETO ACIDS

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A review of the known α-keto acids of the type formula $C_nH_{2n-2}O_3$ and those keto acids which may be considered the precursors of the naturally occurring α-amino acids is presented. Their general physical and chemical properties are discussed. Four methods which have been most successful in the preparation of the α-acids are illustrated. A table which lists references to the chemical methods for the preparation of the thirty-eight known α-keto acids which have been reported in the literature is given. Since pyruvic, hydroxypyruvic, oxaloacetic, and α-ketoglutaric acids are somewhat atypical and since they have received such extensive attention from investigators, it is thought that complete coverage of these four acids would be beyond the scope of this paper.

Berzelius (14) described the properties of pyruvic acid in 1835, and since then considerable interest has been shown in the α-keto acids. Biochemists have stressed the prevalence and the importance of these compounds. Westerkamp (135) isolated a number of the acids from the blood serum of horses and hogs. Neuberger and Sanger (110) indicated that the metabolism of lysine passes through its keto analog to glutaric acid, suggesting that a knowledge of keto acids is desirable for an understanding of amino acid metabolism. The interaction of amino acids with pyruvic acid has been proposed as a part of the biological mechanism of the inversion and acetylation of amino acids (45). Long and Peters (101) have observed that the rate of the decarboxylation of α-keto-*n*-valeric acid by yeast in the presence of essential carboxylase is increased by thiamine hydrochloride. The usefulness of the α-keto acids for synthetic purposes has been demonstrated by Bergmann and Grafe (13) and extended by Shemin and Herbst (127) to the synthesis of peptides. Kraft and Herbst (94) condensed carbamates with aliphatic aldehydes and with pyruvic acid to form compounds which were generally non-toxic and exerted some sedative and analgesic action in mice. Syntheses of α-amino acids from α-keto acids (90, 104) have also been proposed.

The increasing significance of this group of acids warrants a review, especially since they receive such meager treatment in organic treatises. Elementary textbooks usually dismiss the subject after a brief discussion of pyruvic acid, and some of the advanced texts do but little better. Richter (123) gives a description of five α-keto acids and outlines two general methods for their preparation. Some evidence of the voluminous literature on the α-keto acids is indicated by the fourteen and a half pages which the third edition of Beilstein devotes to pyruvic acid alone. The completed survey of phenylpyruvic acid yielded about one hundred and twenty references, including fourteen different procedures for its

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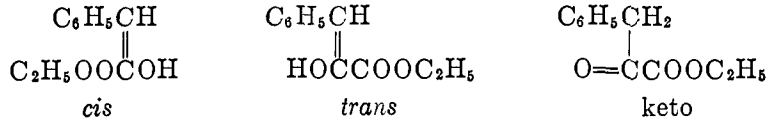
its preparation. Four of the α-keto acids,—namely, pyruvic, hydroxypyruvic, oxaloacetic, and α-ketoglutaric,—have received extensive attention from investigators. To summarize the methods of preparation and the reactions of these four acids would be beyond the scope of this paper. Since many of the chemical reactions and methods of preparation of the typical α-keto acids are not readily available from reference works on organic chemistry, it seemed desirable to review some of their reactions and to compile a list of the methods of preparation of the known α-keto acids. This information is summarized as follows: (I) A discussion of the general properties of the α-keto acids; (II) a discussion of the methods which have been found to be most general for their preparation; and (III) the presentation of a table which gives references to the preparation of the known α-keto acids of the type formula $C_nH_{2n-2}O_3$.

I. PROPERTIES OF THE α-KETO ACIDS

The branched-chain and the phenyl-substituted α-keto acids vary in physical characteristics from liquids to high-melting solids. The straight-chain α-keto acids are either liquids or low-melting solids. Adickes and Andresen (3) have pointed out that if the straight-chain α-keto acids, together with their melting points, are tabulated in two series according to whether the acids contain an odd or an even number of carbon atoms, it will be noted (*a*) that the melting points of the acids in each series increase as the molecular weights increase, and (*b*) that the difference between the melting points of any two successive members in either series becomes smaller with increasing length of the carbon chain. For example, an increase in the number of carbon atoms from five to seven increases the melting point 23°C., and an increase from six to eight carbon atoms increases the melting point 26°C.; an increase from seven to nine causes an increase of 14°C., and from eight to ten causes an increase of 14°C. It may also be observed that a keto acid has a higher melting point than the corresponding fatty acid. Table 1 serves to illustrate these observations.

Gault and Weicke (68) have shown that the ethyl ester of phenylpyruvic acid exists in three forms: the *cis–trans* enol forms, and the keto form.



Other α-keto acids capable of enolization also show this tendency (66, 67, 78).

Some α-keto acids are unstable on standing in the air; benzaldehyde, benzoic acid, and oxalic acid have been detected as decomposition products of phenylpyruvic acid (78). Their decomposition by microörganisms and by enzymes has been studied extensively; generally carbon dioxide and the lower alcohol or aldehyde are formed. Lead tetraacetate effects a quantitative evolution of carbon dioxide (7). Pyrolysis yields carbon dioxide, carbon monoxide, a lower aldehyde or acid, and dehydration products (86). Although the α-keto acids appear to be somewhat unstable, some show remarkable stability when heated with acids

and bases. This is evidenced by the fact that many keto acids have been prepared by heating the immediate precursor in the synthesis with acid or alkali. A typical example of this is the preparation, described in *Organic Syntheses* (81), of phenylpyruvic acid by boiling α-acetaminocinnamic acid with 1 *N* hydrochloric acid for 3 hr.:

$$C_6H_5CH{=}C(NHCOCH_3)COOH + 2H_2O + HCl \rightarrow C_6H_5CH_2COCOOH + CH_3COOH + NH_4Cl$$

Erlenmeyer's hydrolysis of phenylcyanopyruvic acid ester by heating for 12 hr. with dilute sulfuric acid (1 part acid to 2 parts water) to yield phenylpyruvic acid may also be mentioned (51):

$$C_6H_5CH(CN)COCOOC_2H_5 \xrightarrow{\text{dilute acid}} C_6H_5CH_2COCOOH$$

However, Karrer (88) states that all known α-keto acids yield carbon monoxide when warmed with concentrated sulfuric acid.

TABLE 1

Melting points of straight-chain α-keto acids and of fatty acids

ODD			EVEN		
Number of carbon atoms	Melting point of α-keto acid	Melting point of fatty acid	Number of carbon atoms	Melting point of α-keto acid	Melting point of fatty acid
	°C.	°C.		°C.	°C.
3	14	−24	4	31	−5
5	6	−34	6	7	−1
7	29	−10	8	33	16
9	43	12	10	47	31
11	55	29	12	57	43
13	62	44	14	64	54
15	68	53	16	69	63

The α-keto acids generally form well-defined ketone derivatives. The oximes are usually stable compounds and are not easily reconverted to the original acids; these oximes are stable to alkali and with dilute acids lose carbon dioxide to form a nitrile with one less carbon atom (27, 134):

$$RC(=NOH)COOH \xrightarrow{\text{dilute acid}} RCN + CO_2 + H_2O$$

With ferric chloride many α-keto acids develop characteristic colors. The acids may be titrated with bases; they form well-defined calcium, barium and silver salts. The sodium bisulfite addition compound of phenylpyruvic acid has been described (78). As a rule the acids reduce ammoniacal silver nitrate solution and are reduced by hydrogen to the corresponding hydroxy acid:

$$RCOCOOH \xrightarrow{H_2} RCHOHCOOH$$

McKenzie (103) showed that α-keto acids which were esterified with an optically active alcohol could be reduced, in part at least, to an optically active α-hydroxy acid.

Knoop and Oesterlin (90) employed catalytic hydrogenation in the presence of mono- and of di-methylamine, respectively, to obtain several methylamino acids.

$$RCOCOOH + CH_3NH_2 \xrightarrow[\text{catalyst}]{H_2} RCH(NHCH_3)COOH$$

Catalytic hydrogenation of keto acids in the presence of ammonia yields amino acids. Amino acids are also formed from the keto acids when the reaction with ammonia is catalyzed by ferrous sulfate or by cysteine (1, 91). When an α-keto acid is mixed with dog's blood containing ammonium salts, amino acids are obtained (47, 93). Transamination occurs when an amino acid is allowed to react with a keto acid, the amino acid forming a lower aldehyde (79, 80):

$$RCH(NH_2)COOH + R'COCOOH \rightarrow RCH(COOH)N{=}C(COOH)R'$$
$$\rightarrow RC(COOH){=}NCH(COOH)R' \rightarrow RCHO + R'CH(NH_2)COOH$$

The condensation of the α-keto acids with acetamide has been investigated by Shemin and Herbst (126). They state that the first reaction is the formation of an α-hydroxy-α-acetoamino acid; this then reacts with another molecule of acetamide, either directly or by dehydration followed by the addition of acetamide to the unsaturated intermediate.

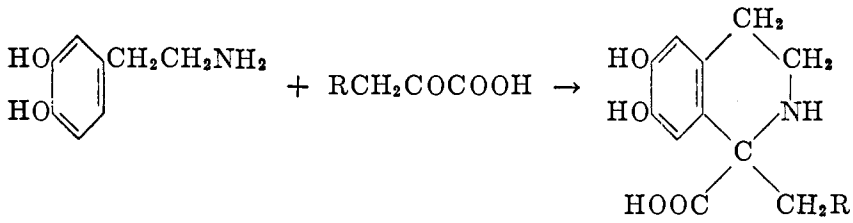
$$RCOCOOH + CH_3CONH_2 \rightarrow \underset{\displaystyle NHCOCH_3}{\overset{\displaystyle |}{RC(OH)COOH}} \rightarrow \underset{\displaystyle NHCOCH_3}{\overset{\displaystyle NHCOCH_3\ |}{RCCOOH}}$$

With benzoylformic acid the disubstituted derivative was isolated; with phenylpyruvic acid a molecule of water is apparently lost, with the formation of α-acetaminocinnamic acid; with α-ketoglutaric acid decarboxylation takes place with the formation of γ,γ-diacetaminobutyric acid. Shive and Shive (128) have condensed pyruvic acid with formamide to obtain α-hydroxy-α-formaminopropionic acid. Martell and Herbst (104) have condensed benzyl carbamate with α-keto acids to form a wide variety of products, depending upon the conditions employed. Catalytic hydrogenation of the dicarbamate condensation product constitutes a new method for the conversion of α-keto acids into α-amino acids:

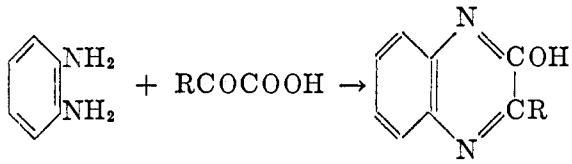
$$RCOCOOH + C_6H_5CH_2OCONH_2 \rightarrow RC(NHCOOCH_2C_6H_5)_2COOH$$
$$\xrightarrow[\text{catalyst}]{H_2} RCH(NH_2)COOH$$

Shemin and Herbst (127) have used the α-keto acids to prepare dipeptides.

A number of investigators have condensed amines with the α-keto acids. Hahn and coworkers (72, 73, 74) have reported the reaction with tryptamine and have shown that those acids capable of enolizing react with the 3,4-dihydroxyphenethylamine derivatives to form the corresponding tetrahydroisoquinoline-1-carboxylic acids:



With *o*-phenylenediamine an α-keto acid effects ring closure to give a quinoxaline derivative (89):



In the presence of strong acids or alkalies the α-keto acids show a tendency to condense with themselves (34, 53, 56, 78). The condensation also takes place with aldehydes (50) and with ketones (38), following the aldol condensation pattern. Pyruvic acid (125) and phenylpyruvic acid (37) have been condensed with benzyl cyanide to form the corresponding cyanohydro derivative:

$$RCOCOOH + C_6H_5CH_2CN \rightarrow \begin{matrix} RC(OH)COOH \\ | \\ C_6H_5CHCN \end{matrix}$$

It has been shown (119) that dimethylpyruvic acid reacts with benzene in the presence of concentrated sulfuric acid to form an addition product which is then dehydrated to β,β-dimethyl-α-phenylacrylic acid:

$$(CH_3)_2CHCOCOOH + C_6H_6 \rightarrow (CH_3)_2CHC(OH)(C_6H_5)COOH \rightarrow (CH_3)_2C{=}C(C_6H_5)COOH$$

Toluene reacts with phenylpyruvic acid in the presence of cold concentrated sulfuric acid to form α,α-ditoluyl-β-phenylpropionic acid (15); ethylbenzene and xylene react similarly.

II. PREPARATION OF THE α-KETO ACIDS

Probably more α-keto acids have been prepared as oxidative degradation products in the course of proving the structure of a more complex compound than by any other method. Frequently special methods for preparing the individual acids are better than many of the so-called "general" methods. Notable among these are: the preparation of phenylpyruvic acid (81) and of benzoylformic acid (39) as described in *Organic Syntheses*; the preparation of pyruvic acid by the distillation of tartaric acid (84); and the preparation of hydroxypyruvic acid (102) by the breakdown of nitrocellulose. Krebs (95) developed a biological technique for the deamination of the α-amino acids by means of kidney slices, which has

been used by a number of biological chemists for the preparation of the α-keto acids. Mild oxidation of the corresponding α-hydroxy acid, which is frequently mentioned as a method for preparing α-keto acids, does not seem to have been used extensively. Moureu *et al.* (107, 108) have recently succeeded in preparing keto acids from α,β-dibromo acids by forming an addition compound with piperidine and then hydrolyzing with dilute sulfuric acid. Four chemical methods are rather general for the preparation of α-keto acids. These are summarized briefly as follows:

A. Hydrolysis of the acyl cyanide

$$RCOX + MCN \rightarrow RCOCN \rightarrow RCOCOOH$$

This method was first proposed by Claisen and Moritz (35) in 1880; they employed Hubner's (85) procedure, using silver cyanide to prepare the acyl cyanide. In 1929 Tschelinzeff and Schmidt (131) improved the procedure by substituting cuprous cyanide for silver cyanide. The acyl bromide and cuprous cyanide were warmed together on a water bath under reflux for about 2 hr. Yields of the acyl cyanide usually varied from 60 to 87 per cent. In the case of pyruvic acid and α-keto-*n*-butyric acid the hydrolysis of the cyanide was accomplished with cold concentrated hydrochloric acid and gave yields of about 75 per cent. In order to hydrolyze the isobutyl cyanide successfully, it was necessary to use dilute acid at room temperature. Neither Tschelinzeff and Schmidt (131) nor Claisen and Moritz (35) were able to hydrolyze isovaleryl cyanide. Many elementary and advanced textbooks in organic chemistry state that the hydrolysis of the acyl cyanides is a general procedure for preparing the α-keto acids. However, a survey of the literature indicates that the procedure has been employed only for the short-chain acids and it has been suggested (131) that the method is inapplicable for obtaining keto acids having more than five carbon atoms.

B. The hydrolysis of the oxime ester

$$RC(=NOH)COOR' \xrightarrow[HOSO_2ONO]{\text{formic acid}} RCOCOOR' \rightarrow RCOCOOH$$

This method as orginally used by Bouveault and Locquin (26) in 1902 calls for 85 per cent formic acid and lead chamber crystals. Many variations of the method have been tried; however, no recent comprehensive study has been made. The best yields are probably obtained when the oxime is dissolved in 85 per cent formic acid, cooled to 0°C., and nitrosyl sulfuric acid added in small portions, with careful control of the temperature. Although yields of the order of 90 per cent have been reported for some of the acids, Adickes and Andresen (3) state that the conversion from the oxime to the keto acid is generally poor. Nevertheless this method has been more frequently used than any other for the general preparation of α-keto acids. Since compounds of the type RC(=NOH)COOH can be obtained in excellent yields from the substituted acetoacetic (77) and the substituted malonic esters (9), this method lends itself to the preparation of the α-keto acids. It has been reported that phenylpyruvic acid cannot be obtained

from the oxime (76, 134); consequently it must not be assumed that the method is applicable to the preparation of all α-keto acids.

C. Hydrolysis of ethyl esters of oxalo acids

$$\begin{array}{l} COOC_2H_5 \\ | \\ COOC_2H_5 \end{array} + \begin{array}{l} H_2CCOOH \\ | \\ R \end{array} \xrightarrow{NaOC_2H_5} \begin{array}{l} COCHRCOOC_2H_5 \\ | \\ COOC_2H_5 \end{array} \xrightarrow[H_2SO_4]{\text{10 per cent}} RCH_2COCOOH$$

Adickes and Andresen (3) advanced this as a new method in 1943; however, Wislicenus (138) had suggested an analogous reaction using oxaloacetic ester in place of diethyl oxalate. Nine of the α-keto acids have been prepared by refluxing the fatty acid ester, diethyl oxalate, and sodium ethoxide in ether for about 16 hr. The keto acid was obtained by treating the isolated α-oxaloester with boiling dilute sulfuric acid for 6 hr. In order to prepare three of the longer chain acids (α-ketocapric, α-ketotridecanoic, and α-ketolauric) it was necessary to use potassium ethoxide in pyridine and heat for 100 hr. at 70°C. Yields of the purified α-keto acids varied from 8 to 94 per cent; however, yields of the crude product were considerably higher. This method is one of the most recent and probably the most general yet developed.

D. Hydrolysis of the addition product of Grignard reagents and diethyloxamates

$$\begin{array}{l} COOC_2H_5 \\ | \\ COOC_2H_5 \end{array} + HN(C_2H_5)_2 \rightarrow \begin{array}{l} COOC_2H_5 \\ | \\ CON(C_2H_5)_2 \end{array} + RMgX \rightarrow \begin{array}{l} COR \\ | \\ CON(C_2H_5)_2 \end{array} \rightarrow RCOCOOH$$

Barre (8) proposed this method in 1927 and showed its applicability in the preparation of four compounds. It would seem that the method should be very general; however, the condensation at −15°C. and the tediously long refluxing time requisite for the preparation of ethyl *N,N*-diethyloxamate have probably discouraged other investigators from extending the method. The author claimed 60 per cent yields and said that, when one considers the difficulties of the other methods for the preparation of α-keto acids, this method could be used to advantage.

III. ADDITIONAL INFORMATION ON α-KETO ACIDS

In table 2 is summarized part of the information which has been accumulated in the course of a literature survey. It is the purpose of the table to serve as a ready reference for anyone interested in preparing an α-keto acid. The melting points are given in a separate column, since they are not easily found in reference works. Where conflicting melting points have been reported, these are recorded. The data cover only the α-keto acids having the general formula $C_nH_{2n-2}O_3$, those

TABLE 2

Information on α-keto acids

R	R′	R″	MELTING POINT	FIRST PREPARED BY	GENERAL METHOD (AS DESCRIBED ABOVE)	REFERENCES TO OTHER METHODS OF PREPARATION
			°C.			
H	H	H	13.6	Berzelius, 1835 (14)		Beilstein, Vol. III, p. 608
H	H	CH_3	31	Claisen and Moritz, 1880 (35)	A (35, 131) B (26, 99) C (139) D (8)	(5, 33, 40, 49, 52, 57, 63, 108, 120, 132, 140)
H	H	C_2H_5	6	Moritz, 1881 (106)	A (106) B (99) C (3)	(16, 58, 60)
H	CH_3	CH_3	31	Moritz, 1881 (106) Brunner, 1894 (29)	A (106, 131) C (121)	(2, 21, 25, 29, 42, 64, 70, 82, 92, 97, 114, 130)
H	H	*n*-C_3H_7	7	Kondo, 1912 (93)	B (93) C (3) D (8)	
H	H	*i*-C_3H_7	−1.5	Locquin, 1904 (99)	B (99) C (3)	(2, 36, 70, 115)
CH_3	CH_3	CH_3	125	Glucksmann, 1889 (69)		(4, 18, 19, 32, 122)
H	CH_3	C_2H_5	35	Mebus, 1905 (105) Bouveault and Locquin, 1905 (28)	B (28, 100) C (69)	
H	H	*n*-C_4H_9	52	Prezwalsky, 1913 (118)		
			29	Adickes and Andresen, 1943 (3)	C (3)	
H	H	*i*-C_4H_9	22	Fittig and Kaehlbrandt, 1899 (61)	B (99)	
CH_3	CH_3	C_2H_5	Liquid	Anschutz and Rauff, 1903 (4)		

TABLE 2—*Continued*

R	R′	R″	MELTING POINT	FIRST PREPARED BY	GENERAL METHOD (AS DESCRIBED ABOVE)	REFERENCES TO OTHER METHODS OF PREPARATION
			°C.			
H	H	n-C_5H_{11}	118	Smedley-MacLean and Pearce, 1934 (129)	B (129)	
			33	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-C_6H_{13}	106	Smedley-MacLean and Pearce, 1934 (129)	B (129)	
			43	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-C_7H_{15}	60	Smedley-MacLean and Pearce, 1934 (129)	B (129)	
			47	Adickes and Andresen, 1943 (3)	C (3)	
H	CH_3	n-C_6H_{13}	Liquid	Locquin, 1904 (99)	B (99)	
H	H	n-C_8H_{17}	55	Adickes and Andresen, 1943 (3)	C (3)	
H	i-C_4H_9	i-C_4H_9	Liquid	Freylon, 1910 (65)		
H	H	n-C_9H_{19}	57	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-$C_{10}H_{21}$	62	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-$C_{12}H_{25}$	68	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-$C_{13}H_{27}$	65	Kuwata, 1938 (98)	(6)	
			87	Darnstaedter and Lifschutz, 1896 (41)		
H	H	n-$C_{15}H_{29}$	83	Windaus and Van Schoor, 1926 (137)		
H	H	OH	Liquid	Wichelhaus, 1867 (136)		Beilstein, Vol. III, p. 869

TABLE 2—*Concluded*

R R′—C—COCOOH R″			MELTING POINT	FIRST PREPARED BY	GENERAL METHOD (AS DESCRIBED ABOVE)	REFERENCES TO OTHER METHODS OF PREPARATION
R	R′	R″				
			°C.			
H	H	SH		Parrod, 1942 (112)		
H	OH	CH_3		Hoff-Jorgensen, 1940 (83)		
H	H	CH_3SCH_2		Waelsch and Borek, 1939 (113)		(30, 113)
H	H	COOH	176	Fenton and Jones, 1900 (55)		Beilstein, Vol. III, p. 777
H	H	CH_2COOH	113	Blaise and Gault, 1908 (17)		Beilstein, Vol. III, p. 789
H	H	C_6H_5	153	Plochl, 1883, (116)	C (138) D (8)	(12, 22, 23, 24, 43, 44, 48, 49, 51, 81, 107, 124)
H	H	2-HOC_6H_4	153	Plochl and Wolfrum, 1885 (117)		(58, 62)
H	H	3-HOC_6H_4	165	Flatow, 1910 (62)		(75)
H	H	4-HOC_6H_4	220	Neubauer, 1909 (109)		(12)
H	H	$NH_2(CH_2)_3$	103	Wolffenstein, 1893 (141)		(Author in doubt as to exact formula)
H	H	$NH_2(CH_2)_2$		Krebs, 1939 (96)		
H	H	Imidazolyl		Novello, Harrow, and Sherwin, 1926 (111)		
H	H	β-Indolyl	212	Ellinger and Matsuoka, 1920 (46)		(10, 11, 20, 70, 87)
Thyroxine analog			173	Canzanelli, Guild, and Harington, 1935 (31)		

acids which can be considered as precursors of the naturally occurring α-amino acids, and a few acids which were noted in the course of the survey.

The acids are classified as derivatives of pyruvic acid. In the fourth column, under "general method," the letters A, B, C, and D refer to the four general methods, respectively, discussed above. In the last column are given literature references to other methods of synthesis. Beilstein references are given for the four acids on which the survey is incomplete. References to the numerous chemical and biological reactions of the α-keto acids are not included in the table.

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