CCLV.—*The Reaction of Bromine with Aliphatic Acids. Part III. α- and γ-Ketonic Acids.*

By Edward David Hughes and Herbert Ben Watson.

The well-known tautomerism of the β-diketones and β-ketonic esters (*e.g.*, acetylacetone, ethyl acetoacetate), which has been studied extensively by K. H. Meyer and others, has a parallel among the α-diketones and α-ketonic acids. Thus, the existence of keto-enol tautomerism has been established in the case of phenyl benzyl diketone by Widman (*Ber.*, 1916, **49**, 484), Jörlander (*ibid.*, 1917, **50**, 406), Malkin and Robinson (J., 1925, **127**, 371), and Dufraisse and Moureu (*Compt. rend.*, 1925, **180**, 1946; *Bull. Soc. chim.*, 1927, **41**, 1607); the last-named investigators obtained pure specimens of three isomerides, *viz.*, the diketonic and two stereoisomeric mono-enolic forms. Phenyl anisyl diketone and benzyl methyl diketone behave similarly (Dufraisse and Moureu, *loc. cit.*; Moureu, *Compt. rend.*, 1928, **186**, 380, 503; 1929, **188**, 504; Lowry, Moureu, and MacConkey, J., 1928, 3167). The enolic forms always react instantaneously with bromine. Certain reactions of α-ketonic acids and their esters led Schiff (*Ber.*, 1898, **31**, 1304) and Bougault and Hemmerlé (*Compt. rend.*, 1915, **160**, 100) to postulate the presence of an enolide here also, and Gault and Weick (*Compt. rend.*, 1920, **170**, 1392) isolated three forms of ethyl phenylpyruvate.

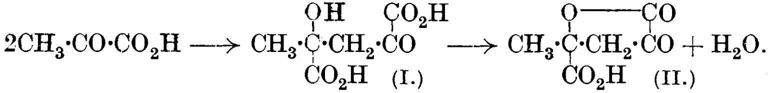
Although keto-enol tautomerism is clearly possible also in γ-diketones and γ-ketonic acids, its existence has not hitherto been demonstrated, but the authors have now obtained such evidence in the case of the acids, and also further evidence of the enolisation of α-ketonic acids, by investigating the kinetics of bromination of pyruvic and lævulic acids.

1. *Pyruvic Acid.*—Pure monobromopyruvic acid was obtained by Ward (J., 1923, **123**, 2207) by treating pyruvic acid with bromine (1 mol.) at temperatures up to 50°, and it is evident from his results that under these conditions the bromination does not proceed further. This had already been indicated by Wislicenus (*Annalen*, 1868, **148**, 208) and Wichelhaus (*Ber.*, 1868, **1**, 263; *Annalen*, 1869, **152**, 264), and Gans had isolated the monobrominated acid (*Annalen*, 1891, **264**, 233) by bromination in concentrated hydrochloric acid at 12—15°.

Ward suggested that pyruvic acid reacts with halogens in its enolic form, $CH_2{:}C(OH){\cdot}CO_2H$. If a comparatively slow change to enolide is followed by very rapid reaction with bromine, the velocity of bromination will be independent of the concentration of the halogen (compare the bromination of acetone, Lapworth, J., 1904, **85**, 30), and if the acid originally contains enolide, this measurable reaction will be preceded by instantaneous disappearance of a portion of the bromine. Evidence bearing upon an "enolic" mechanism should therefore be provided by measurements of the velocity of bromination, and this method has been adopted by the authors.

In no case has a measurable quantity of bromine been observed to disappear instantaneously in reaction with *pure* pyruvic acid, and the existence in the acid of any appreciable quantity of an enolide which reacts with halogens at great speed is therefore excluded. This is in harmony with the results of physical measurements by Perkin (J., 1892, **61**, 801) and by Brühl (*Ber.*, 1894, **27**, 2378). Measurements of ultra-violet absorption, however, led Henri and Fromageot (*Bull. Soc. chim.*, 1925, **37**, 845) to believe that, although concentrated aqueous solutions of the acid are almost entirely ketonic, dilution produces some enolide; and Pascal (*Bull. Soc. chim.*, 1926, **39**, 396), from determinations of its magnetic rotation, suggested that the pure acid contained 20% of the enolic form, which increased to 38% in a 90% aqueous solution. This supposed existence of enolide is now shown to be due to the presence of impurities, for fractional distillation of pyruvic acid—the method used by the above investigators—even under reduced pressure yields a yellowish product, which gives very discordant results, pointing to the presence of small quantities of a substance which reacts readily with bromine at 25°. The impurity can be removed, however, and the acid obtained colourless, by repeated freezing out.

It has long been known that, on heating, or even on standing at the ordinary temperature, pyruvic acid undergoes decomposition, giving " syrupy pyruvic acid " (Berzelius, *Ann. Physik*, 1830, **36**, 1; Völckel, *Annalen*, 1854, **89**, 71; Bottinger, *ibid.*, 1874, **172**, 258; 1877, **188**, 300), which consists principally (Wolff, *ibid.*, 1899, **305**, 154; 1901, **317**, 1; De Jong, *Rec. trav. chim.*, 1901, **20**, 81) of parapyruvic acid (I) and α-ketovalerolactone-γ-carboxylic acid (II).



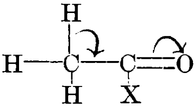
$$2\mathrm{CH_3{\cdot}CO{\cdot}CO_2H} \longrightarrow \mathrm{CH_3{\cdot}}\overset{\mathrm{OH}}{\underset{\mathrm{CO_2H}}{\mathrm{C}}}\mathrm{{\cdot}CH_2{\cdot}}\overset{\mathrm{CO_2H}}{\mathrm{CO}}\ \text{(I.)} \longrightarrow \mathrm{CH_3{\cdot}}\overset{\mathrm{O}}{\underset{\mathrm{CO_2H}}{\mathrm{C}}}\mathrm{{\cdot}CH_2{\cdot}}\overset{\mathrm{CO}}{\mathrm{CO}}\ \text{(II.)} + \mathrm{H_2O}.$$

The authors find that neither of these substances reacts rapidly with bromine at 25°, and the discordant results with impure acid are therefore attributed to the presence of one or more of the other substances which have been detected in the decomposition products of pyruvic acid, *e.g.*, uvic, hydroxydihydrobenzoic, or citraconic acid, all of which react readily with bromine (Bottinger, *loc. cit.*; *Ber.*, 1876, **9**, 1821; Simon, *Compt. rend.*, 1900, **131**, 586, 618).

When a 5·6*M*-aqueous solution of the purified acid reacts with bromine (*ca.* 0·07*M*) at 25°, the speed is constant throughout, and independent of the initial concentration of the halogen. It is clear, therefore, that the reaction occurs in at least two stages, the measured velocity being that of a stage in which bromine takes no part, probably enolisation. It appears strange that the formation of hydrogen bromide during the reaction does not result in autocatalysis (compare lævulic acid, below); measurements of the velocity of bromination in presence of mineral acids added initially, however, have shown that their catalytic influence is relatively small, and the effect of hydrogen bromide at the concentration developed during the reaction would not be perceptible. More dilute solutions of pyruvic acid (*e.g.*, of $\frac{1}{2}$ or $\frac{1}{5}$ the above concentration) give a short initial period of greater speed, which is removed by the addition of an excess of mineral acid; this could be accounted for by the formation of a small amount of unsaturated impurity which is removed by the acid.

In chloroform solution, the bromination of pyruvic acid proceeds with increasing speed *after* a latent period, this period being of variable duration in reactions carried out under apparently identical conditions. The bromination of acetone in chloroform or carbon tetrachloride shows the same peculiarity. (Glass flasks were used in both series of observations.) A similar phenomenon was observed by Ward (*loc. cit.*), who found that different portions of the same sample of pyruvic acid reacted with bromine after intervals varying from 4 to 10 hours. The arrests are not comparable in duration with those produced by a trace of quinoline (Watson, J., 1927, 3065). A trace of mineral acid removes the latent period and induces a rapid reaction; in chloroform saturated with water, also, there is no such period, but the reaction, although gradually increasing in speed, is comparatively slow throughout.

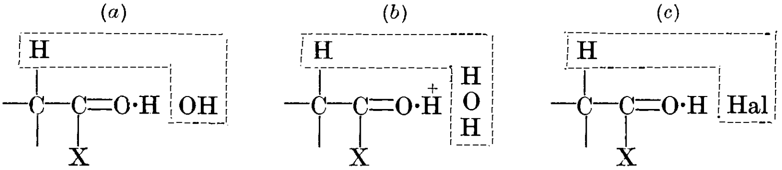
The mechanism of enolisation and other prototropic changes has recently been discussed in terms of the electronic theory of valency by Lowry (J., 1925, **127**, 1382; 1927, 2557), by Ingold, Shoppee, and Thorpe (J., 1926, 1480), by Baker (J., 1928, 1583), and by Orton, Watson, and Hughes (J., 1927, 2460). In the compound $CH_3{\cdot}CO{\cdot}X$ ($X = CH_3$ or CO_2H), a partial appropriation of electrons by the carbonyl oxygen atom (Rây and Robinson, J., 1925, **127**, 1618; Baker and Ingold, J., 1927, 832) will result in one of the hydrogen atoms in the adjoining methyl group being in a state of " incipient ionisation " (Holmes and Ingold, J., 1926, 1307; Ingold, Shoppee, and Thorpe, *loc. cit.*).



$$\mathrm{H{-}\overset{H}{\underset{H}{C}}{-}\underset{X}{C}{=}O}$$

In view of the irregular period of induction referred to above, which recalls the arrests of mutarotation observed by Lowry and Richards (J., 1925, **127**, 1385), and may be defined in their words as " a period of time during which a pure material is taking up the impurities that are needed to promote the change," it would appear that enolisation consists, not (as assumed by Orton, Watson, and

Hughes *) in the mere transference of the ionised proton from one point in the molecule to another, but in the release of this proton to, and the acceptance of another proton from, an outside agent. This view has already been put forward by Lowry (*loc. cit.*). In the authors' experiments, the necessary agent is (*a*) water, (*b*) the ion H_3O^+, provided either by an added acid or by the pyruvic acid itself, (*c*) covalent halogen or other acid; (*a*) and (*b*) refer to the experiments in water or moist chloroform, and (*c*) refers to the experiments in dry chloroform medium. These agents may be considered to co-ordinate with the carbonyl oxygen, to give respectively



The co-ordinated group thus provides a proton, and the remainder of the group (OH, H_2O, or Hal) will withdraw the incipiently ionised hydrogen atom. These processes, together with the consequent movement of electrons through the molecule (somewhat as indicated by Lowry), will result in the production of the enolide.

In cases (*b*) and (*c*), the influence (" inductive effect "; Ingold, *Ann. Reports*, 1926, **23**, 140) of the positive pole or of the halogen atom (compare Baker and Ingold, J., 1926, 2466; Ingold, *loc. cit.*) will augment the electron shifts which lead to the ionising of the proton, and will thus facilitate enolisation. The superiority of covalent to ionised acids as catalysts (which has frequently been observed, *e.g.*, Meyer, *Annalen*, 1911, **380**, 238; see also above) is easily understood, since the proton will unite with a bromine ion more readily than with a neutral water molecule.

According to the scheme suggested above, only one catalyst appears to be necessary to bring about enolisation. The single molecule then functions both as proton donator and proton acceptor (compare Lowry, *loc. cit.*), and in cases (*b*) and (*c*) it also " facilitates indirectly the liberation of the ionising proton," and thus combines the characters of the two types of catalyst postulated by Baker (*loc. cit.*).

2. *Lævulic Acid.*—The reaction of molecular proportions of bromine and lævulic acid in concentrated hydrochloric acid solution gives rise (Wolff, *Annalen*, 1891, **264**, 233; *Ber.*, 1887, **20**, 425) to the β-monobrominated derivative; with more bromine the reaction

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* These authors discussed only relative rates of enolisation, and in that connexion the history of the ionised proton was immaterial.

proceeds further, giving βδ-dibromolævulic acid (Hell and Kehrer, *Ber.*, 1884, **17**, 1981), which is invariably the principal product when bromination is carried out in ethereal or chloroform solution (Wolff, *Annalen*, 1885, **229**, 266; *Ber.*, 1893, **26**, 2216; Hell and Kehrer, *loc. cit.*). The authors have confirmed these results.

The rate at which lævulic acid reacts with bromine in aqueous solution, in presence of a mineral acid as catalyst, is independent of the concentration of the halogen, but proportional to that of the acid. The effect of mineral acid is here more marked than in the case of pyruvic acid, and in absence of added catalyst the reaction proceeds with steadily increasing velocity (autocatalysis). The halogen apparently reacts with the enolic form of the lævulic acid :

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H \longrightarrow CH_3{\cdot}C(OH){:}CH{\cdot}CH_2{\cdot}CO_2H \xrightarrow{Br_2} CH_3{\cdot}CO{\cdot}CHBr{\cdot}CH_2{\cdot}CO_2H + HBr$$

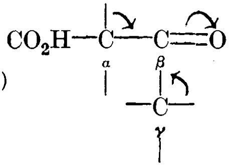
although physical measurements (Perkin, *loc. cit.*; Brühl, *loc. cit.*; Auwers and Heinze, *Ber.*, 1919, **52**, 584) indicate the absence of enolide in the acid itself.

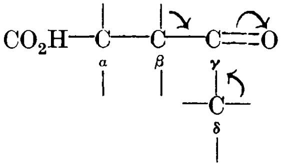
A study of the velocity of bromination of β-monobromolævulic acid in aqueous solution in presence of mineral acid has shown that this reaction, as would be expected, is comparatively slow; the velocity is independent of the concentration of halogen, a fact which suggests that the monobrominated acid reacts in the enolic form, $CH_2{:}C(OH){\cdot}CHBr{\cdot}CH_2{\cdot}CO_2H$.

In chloroform solution, bromine reacts with lævulic acid, as with pyruvic, *after* a latent period of variable duration; traces of water and of mineral acid have the effects described above.

As already pointed out, application of the electronic theory of valency leads to the idea that a hydrogen atom of the methyl group in pyruvic acid is incipiently ionised, owing to the partial appropriation of electrons by the carbonyl oxygen. In acetoacetic and lævulic acids, this effect will be shared by an α- and a γ-hydrogen atom (III), and by a β- and a δ-hydrogen atom (IV), respectively.

(III.)





(IV.)

Superimposed on this, however, is the "inductive effect" of the carboxyl group, and the two effects co-operate in promoting the ionisation of the α-hydrogen atom in acetoacetic acid and of the β-hydrogen atom in lævulic acid. This is in harmony with the facts that in ethyl acetoacetate only the one enolide, $CH_3\cdot C(OH)\colon CH\cdot CO_2H$, is known, and that the β-hydrogen atom of lævulic acid enolises more readily than the δ-hydrogen atom. The tendency towards enolisation is undoubtedly stronger in acetoacetic than in lævulic acid, and this may be attributed to a screening of the effect of the carboxyl group in the latter by the α-carbon atom (compare Ingold, *Ann. Reports*, 1926, **23**, 130; 1928, **25**, 137).

The results described above have furnished definite evidence that the reaction of bromine with α- and γ-ketonic acids, as with β-ketonic acids, is preceded by a change of the acid to its enolic form, which reacts with the halogen at great speed. The phenomena observed are such as would be anticipated from the application of the electronic theory of valency.

EXPERIMENTAL.

The pyruvic acid was obtained by distillation of tartaric acid with potassium hydrogen sulphate, and on fractionation it boiled at 62°/12 mm. or 48°/2·5 mm. From this acid a pure product was obtained after two or three freezings, the portion of lower melting point being rejected in each case. In cold weather it was found convenient, after removal of the liquid from the first freezing, to melt the solid *almost* completely, and then set it outside over-night; slow crystallisation took place, and a colourless product was obtained, m. p. 11·8°. [Ward (*loc. cit.*), who used the same method, does not record a m. p., but Simon (*Bull. Soc. chim.*, 1893, **9**, 111; 1895, **13**, 336), who used fractional distillation under reduced pressure, gives both 9° and 13·63°.] The lævulic acid was purified by a similar process; the product obtained by fractionation was yellowish, but after two freezings, colourless crystals resulted, m. p. 31·5—32° (compare Grote, Kehrer, and Tollens, *Annalen*, 1881, **206**, 207; Conrad, *ibid.*, 1877, **188**, 223).

The water was distilled from permanganate and potash, and the chloroform and carbon tetrachloride were washed with acid, alkali, and water, dried, and distilled. The acetone was purified by the sodium iodide method, dried, and distilled. The bromine was treated as described in Part I. In the velocity measurements (which were carried out in glass flasks), 2 c.c. of the reaction mixture were withdrawn at suitable intervals, added to potassium iodide, and the iodine was titrated with thiosulphate. Titres are expressed throughout in c.c. of $N/50$-thiosulphate, and concentrations (mols./l.) of pyruvic and lævulic acids are denoted by P and L respectively.

Bromination of Pyruvic Acid in Aqueous Solution.

(*a*) At 25°.

			Fall in titre after (mins.)							
P.	Substance added.	Initial titre.	15.	30.	45.	60.	90.	120.	240.	360.
5·60	—	13·40	2·60	4·70	6·70	8·80	13·05			
2·80	—	10·10	1·80	2·75	3·55	4·35	5·85	7·40	gone	
1·12	—	7·20	1·50	2·20	2·55	2·90	3·50	4·05	5·80	gone
0·97	—	7·10	1·20	1·80	2·10	2·50	2·80	3·25	4·90	6·60
1·12	0·07M-HBr	8·55	0·70	0·95	1·15	1·40	1·80	2·20	4·00	5·70
0·91	1·70M-HBr	6·40	0·25	0·50	0·70	0·95	1·50	2·00	3·95	5·95
0·91	1·15M-HCl	6·00	0·35	0·60	0·75	1·00	1·45	2·00	3·85	5·70
0·91	1·15M-HCl	12·20	0·40	0·60	0:75	1·00	1·50	2·00	3·90	5·75
0·95	4·40M-H_2SO_4	6·10	0·60	1·35	2·05	2·80	4·30	5·70	gone	

(*b*) At 0°.

			Fall in titre after (hrs.)					
P.	Substance added.	Initial titre.	5.	10.	20.	40.	60.	90.
0·95	—	6·55	1·50	2·05	2·75	3·75	4·60	5·95
0·95	1·70M-HBr	6·70	0·35	0·65	1·40	2·80	4·25	6·40
0·95	1·15M-HCl	6·70	0·50	0·80	1·45	2·70	4·00	5·85
0·95	4·40M-H_2SO_4	6·30	1·20	2·35	4·75	gone		

Bromination of Pyruvic Acid in Chloroform Solution.—(i) *Dry chloroform.* The variable duration of the latent period is illustrated by the following reactions : $P = 1·01$; temp. = 25°.

	Fall in titre after (mins.)				
Initial titre.	90.	120.	135.	150.	170.
8·50	0	0	0·70	2·60	6·90
8·10	0	0·90	2·70	6·20	gone
8·30	0	0·50	1·70	4·30	gone
8·30	0·20	1·75	3·95	7·80	gone
16·70	0	0	0·25	1·55	5·25

Similar experiments carried out at 0° gave arrests of several hours.

(ii) *Moist chloroform.* $P = 1·01$; initial titre = 8·30 ; temp. = 25°.

Time (mins.)	30	60	90	120	240	360
Fall in titre	0·10	0·20	0·30	0·40	1·10	3·95

(iii) *Chloroform containing a trace of mineral acid.* $P = 1·01$; temp. = 25°.

HBr = 0·38M ; initial titre = 8·00.

Time (mins.)	0·5	1·0	1·5	2·0	2·5
Fall in titre	1·10	2·90	4·10	5·65	7·15

HCl = 0·14M ; initial titre = 11·30.

Time (mins.)	10	20	30	40
Titre	0·80	2·00	4·40	7·70

H_2SO_4 = trace ; initial titre = 7·60.

Time (mins.)	10	20	30	40	50
Fall in titre	0·20	0·70	1·70	3·25	5·60

Bromination of α-Ketovalerolactone-γ-carboxylic Acid.—This substance separated from the residues after distillation of pyruvic acid. After recrystallisation from chloroform it melted at 115—116° (De Jong gives 115—116°, and Wolff 116—117°). Bromination in water at 25° gave the following result :

Conc. of lactonic acid = 0·14*M*; initial titre = 7·50.

Time (hrs.)	3	23	94	166
Fall in titre	0·40	1·50	4·30	5·80

Bromination of Parapyruvic Acid.—Barium parapyruvate was prepared as described by Wolff (*Annalen*, 1899, **305**, 157), from pyruvic acid and barium carbonate, potassium hydroxide being used as condensing agent; yield, 90% (Found : Ba, 43·2. Calc. for $C_6H_6O_6Ba$: Ba, 44%). The calculated amount of dilute sulphuric acid was added to a quantity of this salt, and the solution, after removal of barium sulphate, was treated with bromine, at 25°.

$[C_6H_8O_6]$ = 0·13*M*; initial titre = 6·60.

Time (hrs.)	1	2	3	4
Fall in titre	1·85	2·90	3·80	4·75

Bromination of Acetone.—In chloroform medium (acetone = 0·11*M*, Br_2 = 0·05*M*) the reaction at 25° became measurable after intervals varying from 10 to 60 minutes, and was then complete in a few minutes. Reagents dried over calcium chloride and over phosphoric oxide gave similar results. Variable arrests were obtained by using acetone in concentrations up to 5·5*M*. In carbon tetrachloride medium the arrests were, as a rule, somewhat less variable, but occasionally very long arrests were observed, *e.g.*, with acetone = 0·045*M*, Br_2 = 0·07*M*, the mean of four similar experiments gave

Time (mins.)	30	45	60	90	110
Fall in titre	0	0·10	10·05	11·60	12·15

but in two experiments carried out under the same conditions there was no fall in titre after several hours.

Bromination of Lævulic Acid.—Bromine (1 mol.) was added in small amounts to lævulic acid dissolved in water containing hydrochloric acid at 25°. After extraction with ether, a solid was obtained, m. p. 48—52°; after recrystallisation from carbon disulphide, this melted at 56° (Wolff gives 59°) (Found : Br, 41·22. Calc. for $C_5H_7O_3Br$: Br, 41·02%). When 2 mols. of bromine were employed, the product (recrystallised from hot water) had m. p. 113° (Hell and Kehrer give 112—113°, and Wolff 114—115°) (Found : Br, 58·02. Calc. for $C_5H_6O_3Br_2$: Br, 58·39%). The dibrominated acid was also isolated when molecular proportions of lævulic acid and bromine reacted in chloroform medium at 25°.

Velocity of bromination in aqueous solution at 25°.

			Fall in titre after (hrs.)						
L.	Substance added.	Initial titre.	10.	20.	30.	40.	50.	60.	80.
0·690	nil	7·20	0·80	1·70	2·55	3·60	4·90	6·50	gone
0·690	nil	13·95	0·80	1·70	2·60	3·70	5·00	6·65	11·10

			Fall in titre after (mins.)						
L.	Substance added.	Initial titre.	30.	60.	90.	120.	150.	180.	240.
0·690	0·69M-HBr	14·50	2·00	4·05	6·00	7·90	9·90	11·90	gone
0·690	0·69M-HBr	7·15	1·95	3·90	5·85	gone			
0·690	0·46M-HCl	6·90	1·60	3·10	4·70	6·30	gone		
0·690	0·46M-HCl	13·70	1·60	3·20	4·65	6·30	7·85	9·45	12·60
0·690	0·46M-HCl	22·30	1·60	3·25	4·75	6·30	7·95	9·60	12·65
0·690	0·23M-HCl	6·70	0·75	1·55	2·35	3·10	3·90	4·70	6·20
0·345	0·46M-HCl	6·85	0·80	1·55	2·30	3·10	3·85	4·60	6·15
0·690	1·48M-H_2SO_4	12·10	3·50	7·10	10·60	gone			

In chloroform solution ($L = 0{\cdot}28M$, $\mathrm{Br}_2 = 0{\cdot}05M$) there was an arrest varying from 4 to 12 minutes, after which the reaction was complete in about 2 minutes.

Bromination of β-Monobromolævulic Acid in Aqueous Solution at 25°.

Conc. of acid = 0·5M; HCl = 0·46M; initial titre = 8·30.

Time (hrs.)	2	4	6	8	10
Fall in titre	1·05	2·10	3·10	4·20	5·30

In conclusion, the authors wish to express their appreciation of Professor Orton's interest and helpful criticism, and of grants from the Chemical Society's Research Fund and from Messrs. Imperial Chemical Industries, Ltd.

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