620. *The Reaction of 2-Keto-carboxylic Acids and Esters with Aromatic Compounds in Sulphuric Acid.**

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Reactions of pyruvic acid, ethyl pyruvate, benzoylformic acid, ethyl benzoylformate, benzilic acid, and atrolactic acid with benzene, toluene, *o*-, *m*-, and *p*-xylene, *tert.*-butylbenzene and phenyl*cyclo*hexane in concentrated sulphuric acid at low temperatures have been studied.

The ketone-oxygen atom of the 2-keto-acids and -esters was exchanged in this reaction for two aryl groups and the hydroxyl group of the 2-hydroxy-acids for one aryl group. It is suggested that the reaction is an aromatic electrophilic substitution.

CONDENSATION of pyruvic acid with aromatic compounds in concentrated sulphuric acid was discovered by Bottinger [1,2] and further investigated by Bistrzycki *et al.*[3,4] They found that, depending on the reaction temperature, the product is either an αα-diaryl-propionic acid or a 1 : 1-diarylethylene, which may be formed from the former by loss of water and carbon monoxide:

$$Me{\cdot}CO{\cdot}CO_2H + 2ArH \longrightarrow Me{\cdot}CAr_2{\cdot}CO_2H \longrightarrow Ar_2C{:}CH_2 + CO + H_2O$$

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[1] Bottinger, *Ber.*, 1881, **14**, 1595.
[2] *Idem*, *Ber.*, 1883, **16**, 2071.
[3] Bistrzycki and Reintke, *Ber.*, 1905, **38**, 839.
[4] Bistrzycki and Mauron, *Ber.*, 1910, **43**, 2883.

The reaction is useful for preparative purposes, and in some cases is the most convenient route to 1 : 1-diarylethylenes, *e.g.*, 1 : 1-di-*p*-tolylethylene.[3] Bistrzycki [4] found that phenylpyruvic acid reacts in a similar manner to pyruvic acid, although satisfactorily only with more active aromatic compounds. He also found [3] that of the three xylenes, *o*- and *m*-xylene react normally but *p*-xylene gives α-(2 : 5-dimethylphenyl)acrylic acid as the final product, *i.e.*, condensation takes place with only one molecule of *p*-xylene and is followed by dehydration. On the basis of further work we propose a mechanism for this reaction which we believe to be an electrophilic aromatic substitution.

Experimental

Reagents were purified commercial products or were prepared according to well-known procedures. M. p.s are corrected. Atrolactic acid (α-hydroxy-α-phenylpropionic acid) was prepared from pyruvic acid and an excess of phenylmagnesium bromide.[5] Pure concentrated sulphuric acid (*d* 1·83) was used.

Reaction of α-keto- and α-hydroxy-acids with aromatic hydrocarbons in concentrated sulphuric acid.

CO cpd. and wt. (g.)	H_2SO_4 (ml.)	ArH and amount	Temp.	Time (hr.)	Products	No.
$Ac{\cdot}CO_2H$ 10	80	*o*-Xylene 26 g.	−10°	0·5	$(3:4\text{-}C_6H_3Me_2)_2CMe{\cdot}CO_2H$	1
,,	,, [a]	*m*-Xylene ,,	,,	3	$(2:4\text{-}C_6H_3Me_2)_2CMe{\cdot}CO_2H$	2
,,	,,	*p*-Xylene ,,	,,	0·5	$CH_2{:}C(2:5\text{-}C_6H_3Me_2){\cdot}CO_2H$	3
,,	,,	$C_6H_5{\cdot}C_6H_{11}$ [k] 22 g.	−10° to −6°	1	$(p\text{-}C_6H_{11}{\cdot}C_6H_4)_2CMe{\cdot}CO_2H$	4
,,	120	$PhBu^t$ 25 ml.	−10° to −5°	0·5	$CH_2{:}C(C_6H_4Bu^t\text{-}p)_2$	5
$Ac{\cdot}CO_2Et$,,	80	Toluene 20 g.	−10° to −8°	1	$(p\text{-}C_6H_4Me)_2CMe{\cdot}CO_2Et$	6
					$CH_2{:}C(C_6H_4Me\text{-}p)_2$ [d]	7
					$CH_3{\cdot}C(C_6H_4Me\text{-}p)_3$ [d]	8
$Bz{\cdot}CO_2Et$,,	80	,, 15 g.	,,	1	$(p\text{-}C_6H_4Me)_2CPh{\cdot}CO_2Et$	9
					$p\text{-}C_6H_4Me)_2CPh{\cdot}CO_2H$ [e]	10
$Bz{\cdot}CO_2H$ 5	,, [f]	,, ,,	10° to −5°	1	$(p\text{-}C_6H_4Me)_2CPh{\cdot}OH$	11
Benzilic acid 5	150 [f]	Benzene 30 ml.	−5° to −3° [i]	1·5	$CPh_3{\cdot}CO_2H$	12
		Toluene ,,	,,	1·5	$p\text{-}C_6H_4Me{\cdot}CPh_2{\cdot}OH$ [g]	13
Atrolactic acid 3·5	100	Benzene ,,	−12° to −8°	1	$p\text{-}C_6H_4Me{\cdot}CHPh{\cdot}CO_2H$	14

No.	M. p.	Yield (%)	Form (solvent)	Formula	Required (%) C	Required (%) H	Found (%) C	Found (%) H
1	146—147° [l]	30	—	—	—	—	—	—
2	169 [l]	28	—	—	—	—	—	—
3	128 [l]	20	—	—	—	—	—	—
4	246 [b]	25	Needles (dil. EtOH or AcOH)	$C_{27}H_{34}O_2$	83·1	8·7	83·2	9·2
5	103	26	Plates (acetone)	$C_{22}H_{28}$	90·4	9·6	90·3	9·4
6	Oil [c]	61	—	$C_{19}H_{22}O_2$	81·0	7·8	81·2	7·3
7	62 [l]	2	—	—	—	—	—	—
8	112	4	Needles (dil. EtOH)	$C_{23}H_{24}$	92·0	8·0	91·5	7·9
9	87·5	51	Needles (EtOH)	$C_{24}H_{24}O_2$	83·7	7·0	83·0	7·2
10	220	—	,,	$C_{22}H_{20}O_2$	83·5	6·4	83·5	6·7
11	80 [m]	68	,,	$C_{21}H_{20}O$ [h]	87·5	6·9	87·5	6·8
12	257 [n]	48	,,	—	—	—	—	—
13	74 [p]	58	Needles (ligroin)	$C_{20}H_{18}O$ [h]	87·6	6·6	87·2	6·9
14	138	44	Needles (dil. EtOH)	$C_{16}H_{16}O_2$	80·0	6·66	80·4	6·9

[a] 90% H_2SO_4. [b] Starts to sublime at 200—210°. [c] B. p. 152—153°/2·5 mm. [d] By-products from residue after distillation. [e] Obtained by hydrolysis (10% KOH in EtOH; 5 hr. reflux). [f] Suspension of carbonyl compound in the ArH added to H_2SO_4. [g] From the same reactants with stannic chloride Bistrzycki and Wehrbein (*Ber.*, 1901, **34**, 3080) obtained diphenyl-*p*-tolylacetic acid. [h] Known compound. [i] Same product obtained in slightly lower yield at room temperature. [k] Phenyl*cyclo*hexane. [l] Ref. 3. [m] Kovache, *Ann. Chim. Phys.*, 1919, **10**, 198. [n] Bistrzycki and Mauron, *Ber.*, 1907, **40**, 4062. [p] Bistrzycki and Gyr, *Ber.*, 1904, **37**, 656, 663.

Method.—The carbonyl compound was first slowly added, with cooling and stirring, to the concentrated sulphuric acid. The aromatic hydrocarbon was added to the mixture at the temperature stated in the Table. Stirring was continued for 0·5—3 hr. more. The mixture

[5] Peters, Griffith, Briggs, and French, *J. Amer. Chem. Soc.*, 1925, **47**, 453.

was poured on ice. The product was separated from the acid mixture by filtration or by extraction and purified by crystallisation or distillation *in vacuo*.

The optimal temperature for the condensation varied with compounds of different reactivity. Toluene and pyruvic acid at $-11°$ to $-7°$ gave up to 38% yields of αα-di-*p*-tolylpropionic acid; at 0—5°, yields of up to 80% of 1 : 1-di-*p*-tolylethylene were obtained. With benzene and pyruvic acid at low temperatures the benzene freezes and there is no reaction, whereas at 5° the yield of αα-diphenylpropionic acid [m. p. 172° (from dilute ethanol); lit.,[1] 171—172°] is only 10—12%, some 1 : 1-diphenylethylene being also formed.

Attempted Decarbonylation of αα-Diarylpropionic Acids.—Decarbonylation of the αα-diarylpropionic acids could be carried out only in concentrated sulphuric acid, in heterogeneous mixtures. In a desire to determine the kinetics, we studied homogeneous solutions, namely, in ethanol containing up to 25% (vol.) of sulphuric acid, in acetic acid containing up to 50% of sulphuric acid, and 1 : 1 (vol.) perchloric acid (70%)–ethanol, but there was no gas evolution up to 70°.

Attempted Reaction of Other Dicarbonyl Compounds with Toluene.—No analogous reaction was observed with toluene and acetylacetone, ethyl acetoacetate, diacetyl, benzil, or pyruvoylbenzene: the starting materials were partly recovered, and partly non-crystallisable gums were obtained which gave neither oximes nor 2 : 4-dinitrophenylhydrazones. Pyruvoylbenzene gave a small amount of benzoic acid.

Discussion

In the conditions used it is most probable that the reaction takes place by an ionic mechanism. Similar Friedel–Crafts type electrophilic substitutions of aromatic compounds by 2-keto-acids have been described. *E.g.*, benzoylformic acid reacts with benzene or toluene, in the presence of aluminium chloride, to give benzilic or 4-methylbenzilic acid, which then reacts further.[6]

Aluminium chloride seems to be a much stronger and much less discriminating catalyst than sulphuric acid. Practically any carbonyl group in a ketone, acid, acid chloride, ester, etc., can be used [7] as the source of an electrophilic reagent to attack aromatic compounds in the presence of aluminium chloride. On the other hand, in the presence of sulphuric acid, the same groups react much more slowly, if at all, giving generally very poor yields. *E.g.*, acetoacetic ester reacts with phenol, with aluminium chloride as the catalyst, to give a 30—40% yield of 4-methylcoumarin, but only 3% in the presence of sulphuric acid; [8] and less reactive aromatic compounds, such as toluene or benzene, seem not to react at all in the presence of sulphuric acid.

In our experiments, we obtained no products from toluene with ethyl acetoacetate, acetylacetone, or benzil. Similarly, simple esters, which in the presence of aluminium chloride give a mixture of acylated and alkylated products [9] with benzene, seem not to react in the presence of sulphuric acid.

It can safely be assumed that the first step in the reaction of 2-keto-acids and esters is protonation. As the ketone-carbonyl group is a stronger base in sulphuric acid than the carboxyl group,[10] the subsequent reaction takes place on the ketone-carbon atom only. We believe that the following mechanism is in accordance with the experimental facts, although other interpretations may also be possible:

(1) $R{\cdot}CO{\cdot}CO_2R' + H^+ \rightleftharpoons {}^+HO{=}CR{\cdot}CO_2R' \longleftrightarrow HO{\cdot}{}^+CR{\cdot}CO_2R'$

(2) $HO{\cdot}{}^+CR{\cdot}CO_2R' + ArH \longrightarrow HO{\cdot}CRAr{\cdot}CO_2R' + H^+$

(3) $HO{\cdot}CRAr{\cdot}CO_2R' + H^+ \rightleftharpoons {}^+H_2O{\cdot}CRAr{\cdot}CO_2R'$

(4) $^+H_2O{\cdot}CRAr{\cdot}CO_2R' \longrightarrow {}^+CRAr{\cdot}CO_2R' + H_2O$

(5) $^+CRAr{\cdot}CO_2R' + ArH \longrightarrow CRAr_2{\cdot}CO_2R' + H^+$

[6] Vorlander and Pritsche, *Ber.*, 1913, **46**, 1793.
[7] See Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold Publ. Co., New York, 1941, pp. 493—497, 632—639, 673–680.
[8] Sethna, Shah, and Shah, *Current Sci.*, 1937, **6**, 93.
[9] Ref. 6, pp. 673—674.
[10] Wiles, *J.*, 1953, 996.

In the case of pyruvic acid derivatives, a second mechanism involving the enol-form of the 2-keto-acid could be postulated:

$$Me{\cdot}CO{\cdot}CO_2R \rightleftharpoons CH_2{=}C(OH){\cdot}CO_2R \xrightarrow{H^+} CH_2{=}C(OH_2^+){\cdot}CO_2R \xrightarrow{-H_2O} CH_2{=}{}^+C{\cdot}CO_2R \xrightarrow{ArH}$$

$$CH_2{=}CAr{\cdot}CO_2R \xrightarrow{H^+} {}^+CMeAr{\cdot}CO_2R \xrightarrow{ArH} CMeAr_2{\cdot}CO_2R$$

The probability of the existence of enolic forms in concentrated sulphuric acid should be rather low. Moreover, it is excluded for benzoylformic acid and ester, which have no hydrogen atom available for the enolisation. Accordingly, as there seems to be no reason to believe that benzoylformic acid should react by a different mechanism than pyruvic acid, we believe that the mechanism described by steps 1—5 is correct.

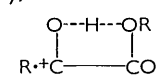
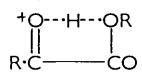
Further support is found in the similar reactions of benzilic and atrolactic acid, which exchange their hydroxyl group for a further aryl group.

It is interesting that Bistrzycki [3] found that pyruvic acid reacts normally with 2 mols. of *o*- and *m*-xylene, but only with 1 mol. of *p*-xylene. We verified this and obtained, as he did, α-(2 : 5-dimethylphenyl)acrylic acid as the only product from *p*-xylene. It seems that in this case dehydration of the product of step (3) interrupts and finishes the reaction sequence, double-bond formation by elimination of a proton being much faster in this case than attack of the carbonium ion on a second *p*-xylene molecule. Models of compounds (I, II, and III) show that only the *o*-methyl group causes steric hindrance and the same will be true for replacement of the hydroxyl group by a second aromatic ring. The difference in behaviour between the 2 : 4- (II) and the 2 : 5-compound (III), therefore,

$Ar{\cdot}CMe(OH){\cdot}CO_2R$	(I)	(II)	(III)
	$Ar = 3 : 4\text{-}C_6H_3Me_2$	$2 : 4\text{-}C_6H_3Me_2$	$2 : 5\text{-}C_6H_3Me_2$

cannot be due to steric factors. On the other hand, considerable differences are known to exist between the reactivity of *o*-, *m*-, and *p*-xylene in electrophilic substitutions. Condon [11] showed that the relative rates of the chlorination are $4{\cdot}6 \times 10^3$ for *o*-xylene, $4{\cdot}3 \times 10^5$ for *m*-xylene and $2{\cdot}2 \times 10^3$ for *p*-xylene (benzene = 1). Probably, therefore, the reaction of compound (I) with an additional *o*-xylene molecule takes place easily, there being no steric hindrance, whereas the reaction of the isomer (II) with a second *m*-xylene molecule is still possible, owing to the large relative reactivity of the *m*-xylene molecule, which is enough to counteract the steric hindrance caused by the *o*-methyl group. On the other hand, the same steric hindrance in the reaction of isomer (III) with a second *p*-xylene molecule, the reactivity of which is only 1/200th that of *m*-xylene, seems to be sufficient to slow the reaction so as to allow the elimination of a proton from the carbonium ion corresponding to (III) to be the dominating reaction.

There remains the question why only the $R{\cdot}CO{\cdot}CO_2R'$ system reacts and the formally similar $R{\cdot}CO{\cdot}CO{\cdot}R'$ does not (although, *e.g.*, diacetyl reacts easily with aromatic compounds in the presence of aluminium chloride [12]). We are able to put forward only a tentative explanation: in α-keto-acids and esters there exists the possibility of hydrogen-bond formation between the protonated keto-group and the OH or OR group of the acid or ester. This may stabilise the carbonium ion, with the positive charge on the ketone-carbon atom as in (IV), which is one of the contributing resonance forms of the protonated

(IV)   (V)

keto-ester (V). This type of stabilisation should be absent in 1 : 2-diketones, where the carbonyl groups are in their most stable conformation when the distance between the two oxygen atoms is at a maximum and where there should be no possibility of intramolecular hydrogen bonding.

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[11] Condon, *J. Amer. Chem. Soc.*, 1948, **70**, 1963; see also Brown and McGary, *ibid.*, 1955, **77**, 2310.
[12] Wegmann and Dahn, *Helv. Chim. Acta*, 1946, **29**, 101.