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The Reaction of Acetals with Malonic Acid and its Derivatives. A Contribution to the Knowledge of the Knoevenagel–Doebner Reaction

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The acetals of aromatic aldehydes, cinnamic aldehydes and—with lower yields—also of aliphatic aldehydes react with malonic acid in the presence of pyridine and piperidine in the manner of a Knoevenagel reaction. The reaction does not proceed *via* the free aldehydes. Ethyl hydrogen malonate reacts with these acetals analogously in the absence of any catalyst, giving the corresponding ethyl hydrogen arylidene- and cinnamylidene-malonates. A reaction mechanism is proposed, invoking the formation of a hydrogen-bonded complex between the two components of the reaction mixture.

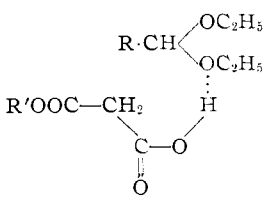
In a study to be published elsewhere, it was found that the acetals of 2-phenyl-1,2,3,6-tetrahydro- and 2-phenyl-hexahydrobenzaldehyde react with malonic acid in the presence of pyridine and piperidine in the manner of a Knoevenagel reaction, giving the corresponding hydrogenated 2-phenylcinnamic acids, with liberation of carbon dioxide. A systematic study of the reaction between dialkyl acetals of aldehydes and malonic acid led to the following conclusions: the diethylacetals of aromatic and of cinnamic aldehydes condense with malonic acid in quantitative yields. The aromatic aldehyde acetals thus give cinnamic acids. This is particularly noteworthy in the case of *p*-dimethylaminobenzaldehyde diethylacetal; this aldehyde is refractory in the Perkin reaction[1] but gives[2] by Doebner's method a yield of 85%. Bulky *o*-substituents (not, *e.g.*, *o*-methoxy) decrease the yield under the same operating conditions (to 50–60%); prolongation of the reaction time gives satisfactory yields also in these cases. It appears that these substituents decrease the rate at which condensation takes place. The acetals of aliphatic and hydroaromatic aldehydes react more slowly than those of aromatic ones, giving α,β-unsaturated monocarboxylic acids. The yields were low, but at least in a number of these cases the acetals have been recovered, so that not the yield but rather the conversion rates appear to be affected adversely.

The reaction between the acetals of cinnamic aldehydes and malonic acid leads to mixtures of the corresponding malonic and monocarboxylic acids; it has been shown that the former are decarboxylated only slowly, even in boiling pyridine.[3] Thus it must be assumed that the proximity of the aryl groups accelerates the decarboxylation. This assumption is supported by the observation that ethyl hydrogen (*p*-methylbenzylidene)-malonate (see below) is decarboxylated within a few minutes, when heated in boiling piperidine.

The mechanism of these reactions is not without interest. Under the experimental conditions employed, the acetals appear to condense directly and not *via* the aldehydes.[4,5] This point is emphasized by analogous experiments carried out with ethyl hydrogen malonate, which has been used before[6,7] in the Knoevenagel reaction with aromatic aldehydes, giving substituted ethyl cinnamates in the presence of pyridine and piperidine. Heated with the acetals of *p*-tolualdehyde and cinnamaldehyde in benzene without any addition of a catalyst, good yields (60 and 89% respectively) of ethyl hydrogen (*p*-methylbenzylidene)- and cinnamylidene-malonates were obtained. Under the same conditions, *free p*-tolualdehyde did not give appreciable amounts (6%) of ethyl hydrogen (*p*-methylbenzylidene)-malonate; also when an azeotropic trap was used to remove the water formed during the reaction, about the same yield (4%) of ethyl hydrogen (*p*-methylbenzylidene)-malonate was obtained.

Whilst in the reaction with the acetal of *p*-tolualdehyde only one of the possible stereoisomers was isolated, there is strong indication that with the acetal of cinnamaldehyde a mixture of two stereomeric compounds is formed, one of which has been isolated in pure form. The unresolved remaining mixture had the theoretically expected molecular weight and practically the same absorption spectrum as the pure isomer.

For an understanding of the reaction mechanism, it is of importance to note that diethyl malonate under the same conditions, *i.e.*, without catalyst, does not condense at all with *p*-tolualdehyde: at least one free carboxyl group is necessary for the reaction. Addition of piperidine caused the condensation to proceed with a yield of 2%, and alternative addition of *p*-toluenesulfonic acid led to about 5% of diethyl (*p*-methylbenzylidene)-malonate. In the latter case, incidentally, ethyl alcohol is liberated more quickly, but this is not followed by condensation. We believe, therefore, that the primary reaction is the formation of a complex between the acetal and the acid, based on a hydrogen bond



(1) H. Meyer and R. Beer, *Monatsh.*, **34**, 649 (1913).

(2) Ch. W. Shoppee, *J. Chem. Soc.*, 968 (1930).

(3) The relatively high stability of substances such as cinnamylidenemalonic acid has been commented upon before. See J. R. Johnson, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 210, especially p. 227.

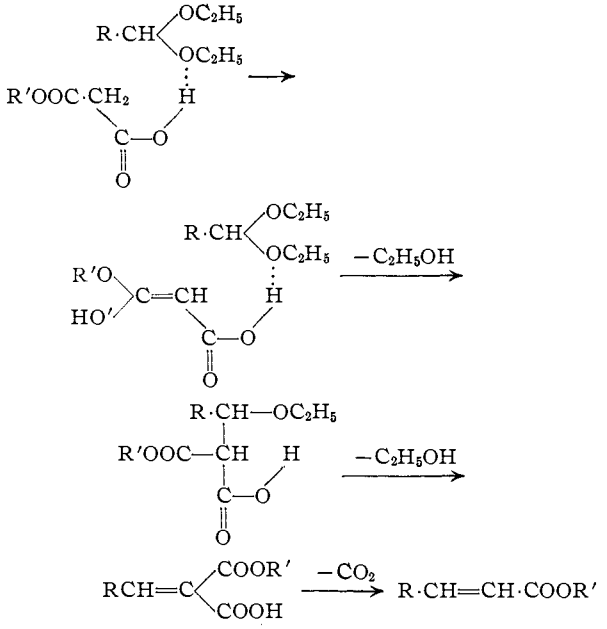
(4) G. Charles (*Compt. rend.*, **242**, 2468 (1956)) has reported that benzophenoneimine reacts more quickly and with better yields with substances like malononitrile than benzophenone, even in the presence of catalysts.

(5) It is interesting to recall that originally W. A. Perkin (*J. Chem. Soc.*, **31**, 424 (1877); **49**, 317 (1886)) had suggested as the intermediate steps in the reaction of benzaldehyde and acetic anhydride the two compounds: $C_6H_5CH(OCOCH_3)_2$ and $C_6H_5(OCOCH_3)CH_2COOH$. However, this hypothesis has been refuted by the studies of F. Boeck, G. Lock and K. Schmidt, *Monatsh.*, **64**, 401 (1934).

(6) A. Galat, THIS JOURNAL, **68**, 376 (1946).

(7) K. Freudenberg and H. Schraube, *Ber.*, **88**, 16 (1955).

Thus the methylene group of the acid component is brought into the immediate vicinity of the central atom of the acetal molecule which then reacts



As in the case of the Knoevenagel reaction in the classical sense, the decarboxylation step requires the presence of pyridine,[8] whilst the elimination of ethanol from the ethoxydicarboxylic acid or its monoester appears to be spontaneous.

It is interesting to note that the cyclic acetal formed from benzaldehyde and ethylene glycol (2-phenyl-1,3-dioxolane) is capable of the same reaction with malonic acid as the diethylacetal, giving cinnamic acid. However, under comparable conditions, the yield is very much lower for the cyclic acetal. It seems likely that the oxygen atoms in the cyclic structure are less prone to form hydrogen bonds than those in an open acetal.

Whether this hypothesis really represents the facts can only be decided by kinetic measurements which will be reported in a later publication. The possibility that this condensation proceeds *via* the free cation $ArCH^{+}\cdot OC_2H_5$ which may be formed under the influence of the acid present in the reaction mixture is made improbable by the observation that when *p*-tolualdehyde diethylacetal was heated with diethyl malonate in the presence of equimolar amounts of *p*-nitrobenzoic or chloroacetic acids (these acids having approximately the same *pK* as hydrogen ethyl malonate), only 1–4% of the condensation product was obtained.

(8) *Cf.* P. N. Kuriyan, K. C. Pande and V. R. Surange, *J. Indian Chem. Soc.*, **11**, 823 (1934) (*C. A.*, **29**, 3325 (1935)).

Experimental

Preparation of Diethylacetals. Method I.—The aldehyde (1 mole), ethyl orthoformate (1.1 mole) and anhydrous ethanol (three times the weight of the orthoformate) were kept for 12 hr. at room temperature, after a few drops of a saturated solution of hydrogen chloride in alcohol had been added. The mixture was stirred with an excess of solid sodium carbonate for 15 minutes, diluted with an equal volume of ether, filtered and distilled.

Method II.—Instead of hydrogen chloride, ammonium nitrate[9] (1 g.) was used as catalyst and the mixture refluxed for 30 minutes, cooled, treated with solid sodium carbonate and worked up as above. The properties of the diethylacetals are recorded in Table I.

Acetaldehyde dibutylacetal was prepared according to Weizmann, Bergmann and Sulzbacher,[10] b.p. 184°, and 2-phenyl-1,3-dioxolane according to Hibbert and Timm,[11] b.p. 134° (40 mm.).

Reaction of the Acetals with Malonic Acid.—The mixture of the acetal (0.1 mole), malonic acid (0.2 mole), pyridine (42 ml.) and piperidine (2 ml.) was heated at 100° for 3 hr. and at 140° for 30 minutes; it was then cooled and poured into a mixture of ice and concentrated hydrochloric acid. Crystalline products were filtered, oily ones isolated by extraction with ether. These ether extracts were treated with 5% sodium carbonate solution and the acidic products liberated with dilute acid and extracted again with ether. The results are summarized in Table II.

Reaction of *p*-Tolualdehyde Diethylacetal with Ethyl Hydrogen Malonate.—Ethyl hydrogen malonate was prepared according to Breslow, Baumgarten and Hauser.[12,13] (a) From a solution of 9.7 g. of the acetal in 65 ml. of benzene, 15 ml. of the solvent was distilled off, in order to remove

TABLE I

Aldehyde	Method of prepn.	Yield, %	B.p. °C.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzaldehyde[a]	I	83	215–218					
p-Methylbenzaldehyde[b]	I	85	128–130	30				
p-Methoxybenzaldehyde[c]	I	95	140	16				
o-Methoxybenzaldehyde	I	83	155	30	68.6	68.8	8.6	8.2
p-Dimethylaminobenzaldehyde	I	90	155	3.5	70.0	70.6[d]	9.4	9.2
2,4-Dichlorobenzaldehyde	II	60	154–155	21	53.2	53.3	5.6	5.7
3,4-Dichlorobenzaldehyde	I	90	175	30	53.2	52.6	5.6	5.4
Cinnamaldehyde[e]	II	95	155	23				
o-Nitrocinnamaldehyde[e]	II	93	166–170	1.5	62.2	62.7	6.8	7.0
2-Phenyl-1,2,3,6-tetrahydrobenzaldehyde[f]	I	94	124	0.9				
2-Phenylhexahydrobenzaldehyde[g,f]		98	117	0.6				
Crotonaldehyde[e,h]	I	30	143–145					

[a] E. Fischer and G. Giebe, *Ber.*, **30**, 3053 (1897); **31**, 548 (1898). [b] H. W. Post, *J. Org. Chem.*, **5**, 244 (1940). [c] L. Claisen, *Ber.*, **31**, 1010 (1898). [d] The acetal is very prone to hydrolysis, which is the reason for the unsatisfactory analysis. [e] The quantity of ethanol used was only 40% of the weight of the ethyl orthoformate. [f] E. D. Bergmann and J. Klein, unpublished results. [g] Prepared by hydrogenation of the acetal of 2-phenyl-1,2,3,6-tetrahydrobenzaldehyde. [h] A. Wohl and F. Frank, *Ber.*, **35**, 1904 (1902).

(9) See, *e.g.*, H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 514 (1935).

(10) Ch. Weizmann, E. Bergmann and M. Sulzbacher, *J. Org. Chem.*, **15**, 918 (1950).

(11) H. Hibbert and J. A. Timm, THIS JOURNAL, **46**, 1283 (1924); *cf.* M. Sulzbacher, E. Bergmann and R. Parlser, *ibid.*, **70**, 2827 (1948).

(12) D. S. Breslow, E. Baumgarten and Ch. R. Hauser, *ibid.*, **66**, 1286 (1944).

(13) *Cf.* K. Freudenberg and H. F. Huebner, *Ber.*, **85**, 1181 (1952).

TABLE II

Acetal of	Product, acid	M.p., °C.	Yield, %	Remarks
Benzaldehyde	Cinnamic	133	89	
p-Methylbenzaldehyde	*p*-Methylcinnamic	198	100	[a]
p-Methoxybenzaldehyde	*p*-Methoxycinnamic	173	100	[b]
o-Methoxybenzaldehyde	*o*-Methoxycinnamic	180	100	[c]
p-Dimethylaminobenzaldehyde	*p*-Dimethylaminocinnamic	216	100	[d]
2,4-Dichlorobenzaldehyde	2,4-Dichlorocinnamic	230	15	[e,f]
3,4-Dichlorobenzaldehyde	3,4-Dichlorocinnamic	218	31	[f]
Cinnamaldehyde	Cinnamylidene-malonic	208	27	[g]
	β-Styrylacrylic[h]	165	17	[i]
o-Nitrocinnamaldehyde	*o*-Nitrocinnamylidene-malonic	212	35	[k]
	β-(*o*-Nitrostyryl)-acrylic	217	25	[m]
2-Phenyltetrahydrobenzaldehyde	2-Phenyl-1,2,3,6-tetrahydrocinnamic	126	30[n]	[o]
2-Phenylhexahydrobenzaldehyde	2-Phenylhexahydrocinnamic	115	33[p]	[o]
Crotonaldehyde	Sorbic	134	20	
Acetaldehyde	Crotonic	72	20	

[a] V. Hanzlik and Al. Bianchi, *Ber.*, **32**, 1285 (1899). [b] R. Robinson and J. Shinoda, *J. Chem. Soc.*, **127**, 1973 (1925). [c] A. Reychler, *Bull. soc. chim. France*, [4] **3**, 552 (1927). [d] L. Weil, *Monatsh.*, **29**, 895 (1908). [e] From glacial acetic acid. [f] Ch. Walling and K. B. Wolfstirn, THIS JOURNAL, **69**, 852 (1947). [g] C. Liebermann, *Ber.*, **28**, 1438 (1895). [h] The separation was carried out by fractional crystallization from boiling benzene, in which β-styrylacrylic acid is easily soluble. A certain quantity of an acidic oil also was obtained, which was not further investigated. [i] H. Lohaus, *Ann.*, **513**, 219 (1934). [k] A. Einhorn and C. Gehrenbeck, *Ann.*, **253**, 348 (1889). [l] Separation by fractional crystallization from glacial acetic acid. [m] S. Diehl and A. Einhorn, *Ber.*, **18**, 2331 (1885). [n] 56% of the acetal was recovered. [o] E. Bergmann and J. Klein, unpublished results. [p] 55% of the acetal was recovered.

traces of water, and 7.3 g. of ethyl hydrogen malonate was added. The mixture was refluxed for 10 hr. and the volatile products were removed, ultimately at 150° in a vacuum of 20 mm. The residue solidified and was recrystallized from ligroin, whereupon it melted at 95–115° (yield 6 g.). Recrystallization from benzene raised the m.p. to 124–126° and finally 127°. Analysis indicated that the product was ethyl hydrogen (*p*-methylbenzylidene)-malonate.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.7; H, 6.0. Found: C, 67.1; H, 6.1.

When the same reaction was carried out using 8 g. of *diethyl malonate*, the starting materials were recovered unchanged, after 6 hr. at reflux temperature.

(b) When the same reaction was carried out in the presence of 3 drops of piperidine and the benzene solution was extracted with 5% sodium carbonate solution, acidification gave 7 g. of a product of m.p. 118–120°, which after two recrystallizations from benzene rose to 127°. The benzene solution contained 2.8 g. of an oil which, according to the boiling point and the ability to form a dinitrophenylhydrazone under acidic conditions, was unchanged acetal.

When the reaction was repeated with 8 g. of *diethyl malonate*, 0.4 g. of diethyl *p*-methylbenzylidene-malonate was obtained.

(c) The reaction was repeated, but 50 mg. of *p*-toluenesulfonic acid was added as catalyst. Alcohol was liberated very quickly. After 24 hr., the reaction mixture was washed with water, dried and distilled. A fraction amounting to 7.8 g. boiled between 90 and 110° (20 mm.) and 4.3 g. between 155 and 185° (1.5 mm.). The latter fraction solidified quickly. It was recrystallized from ligroin (1.5 g., m.p. 100–118°) and benzene, m.p. 124–125°.

When this reaction was repeated, using 8 g. of *diethyl malonate*, there was obtained after 6 hr. of refluxing 1 g. of diethyl (*p*-methylbenzylidene)-malonate which gave, after hydrolysis, *p*-methylbenzylidenemalonic acid, m.p. 214°, after recrystallization from butyl acetate.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 63.9; H, 4.7.

(d) When 4 g. of *p*-tolualdehyde, 4.5 g. of ethyl hydrogen malonate and 30 ml. of benzene were refluxed for 10 hr., the work-up gave 2.8 g. of *p*-tolualdehyde, identified as dinitrophenylhydrazone and semicarbazone, and 0.5 g. of crude ethyl hydrogen (*p*-methylbenzylidene)-malonate, m.p. 112–120°.

(e) When 2.2 g. of ethyl hydrogen (*p*-methylbenzylidene)-malonate was refluxed for 30 minutes in 10 ml. of piperidine, 1.3 g. of ethyl *p*-methylcinnamate, b.p. 142° (1 mm.), was obtained. It was identified by analysis and ultraviolet spectrum.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 76.1; H, 7.4; ultraviolet spectrum (in ethanol), 223 mμ (4.23), 285 mμ (4.27).

Reaction of Cinnamaldehyde Diethylacetal and Ethyl Hydrogen Malonate.—From 10.3 g. of the acetal, 7.3 g. of ethyl hydrogen malonate, 50 ml. of benzene and 3 drops of piperidine, which were refluxed together for 10 hr., there was obtained by the usual work-up 10.5 g. of an acidic, yellow product of m.p. 75–110°. Successive recrystallization from benzene and carbon tetrachloride gave pure ethyl hydrogen cinnamylidene-malonate of sharp m.p. 119–120°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.7; H, 5.6; ultraviolet spectrum, 315 mμ (log ε 4.51).

The mother liquors of the recrystallization left a solid product of m.p. 69–72°, which has a molecular weight corresponding to the above compound (calcd., 246; found, 243) and practically the same absorption spectrum; however, the extinction coefficient was somewhat lower: 315 mμ (log ε 4.34).

When the reaction was repeated in the presence of 50 mg. of *p*-toluenesulfonic acid as catalyst, the yield of the crude acid (m.p. 75–110°) was only 5 g.

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