

197. *Chalcones and Related Compounds. Part II.* Addition of Thiols and Esters to the Chalcone System.*

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Addition of thiols and esters usually requires catalysis by alkali. Hydrolysis and decarboxylation of ester adducts from substituted chalcones were not generally successful.

PREVIOUS work on the addition of thiols to chalcones has dealt solely with chalcone itself. Addition of toluene- ω -thiol,¹ *p*-thiocresol,¹ or octane-1-thiol² has been effected by simple admixture of the compounds, but generally a catalyst is necessary. Dry hydrogen chloride has been used³ for the addition of ethanethiol or thiophenol, but there is then a tendency for addition at the keto-group as well as at the ethylenic bond. Ruhemann⁴ used piperidine to effect the addition of thiophenol or 3-methylbutane-1-thiol to chalcone; this catalyst acts as a strong base in the non-aqueous medium employed and is generally to be preferred to sodium ethoxide, introduced by the same worker; thus Nicolet⁵ showed that the adduct from chalcone and thio-*p*-cresol or mercaptoacetic acid is readily hydrolysed by free caustic alkali; consequently, piperidine was generally used in the present work, though diethylamine also proved of value. Addition of mercaptoacetic acid was very difficult to effect, except in the case of 4'-iodochalcone, where good yields were obtained from alcoholic solution in the presence of a little hydrochloric acid.

Acetoacetic ester adducts have previously been obtained from chalcone^{6,7,8} itself and from hydroxy- or methoxy-chalcones.^{9,10} A catalyst is generally necessary, sodium ethoxide^{6,8} or diethylamine⁷ having been used. In the present work, gums were readily formed; in particular, any attempts at acid or alkaline hydrolysis led to intractable oils. Earlier workers have shown that the adducts readily undergo ring closure to cyclic ketones, and it seems probable that the oils now obtained represent mixtures of products of this type.

The addition of malonic ester requires the presence of a catalyst. Piperidine has been used,¹¹⁻¹³ and also sodium methoxide or ethoxide.¹²⁻¹⁴ The ethoxides are said to be the more effective, but excess of them may lead to the corresponding enolate, and thence, on hydrolysis, the lactone. The molecular compound between potassium hydroxide and acetaldehyde diisopropyl acetal has also been claimed¹⁵ as an effective catalyst. In the present work, diethylamine, piperidine, and sodium ethoxide were used, and yields tended to decrease in that order, generally being rather poor, and much gum was formed. To reduce the possibility of side reactions,^{16,17} a large excess of malonic ester was used.

The adduct of chalcone and malonic ester may be hydrolysed to the dicarboxylic acid, and this on fusion gives carboxymethylchalcone.¹⁸ For the substituted chalcones now studied, it proved essential to purify the adduct as otherwise hydrolysis gave intractable

* Part I, preceding paper.

¹ Nicolet, *J. Amer. Chem. Soc.*, 1935, **57**, 1098.

² Frank and Smith, *ibid.*, 1946, **68**, 2103.

³ Posner, *Ber.*, 1901, **34**, 1395; 1902, **35**, 808.

⁴ Ruhemann, *J.*, 1905, **87**, 461.

⁵ Nicolet, *J. Amer. Chem. Soc.*, 1931, **53**, 3066.

⁶ Knoevenagel, *Annalen*, 1894, **281**, 58.

⁷ Knoevenagel and Speyer, *Ber.*, 1902, **35**, 397.

⁸ Dieckmann and von Fischer, *Ber.*, 1911, **44**, 969.

⁹ Forster and Heilbron, *J.*, 1924, **125**, 340.

¹⁰ Petrow, *Ber.*, 1930, **63**, 898.

¹¹ Kohler, *Amer. Chem. J.*, 1911, **46**, 481.

¹² Michael and Ross, *J. Amer. Chem. Soc.*, 1932, **54**, 407.

¹³ Connor and Andrews, *ibid.*, 1934, **56**, 2715.

¹⁴ Kohler and Conant, *ibid.*, 1917, **39**, 1104.

¹⁵ Weizmann, B.P. 594,182/1947.

¹⁶ Dieckmann and Kron, *Ber.*, 1908, **41**, 1277.

¹⁷ Michael and Ross, *J. Amer. Chem. Soc.*, 1933, **55**, 1632.

¹⁸ Vorländer and Knötzsch, *Annalen*, 1897, **294**, 332.

gums. Even so, only 4-nitrochalcone gave the corresponding diacid, and this was not satisfactorily decarboxylated. It seems, therefore, that, under the conditions used, side reactions tend to occur rather more readily.

EXPERIMENTAL

Results are summarised in the accompanying Tables.

Addition of Thiols.—(a) *Ethanethiol.* The chalcone (5 g.) was dissolved in the minimum amount of methyl alcohol (3-nitrochalcone required toluene as well), and ethanethiol (1 ml.) and piperidine (2 drops) were added. After 7 days at room temperature the mixture was steam-distilled, and the resultant gum fractionated from alcohol.

TABLE I. *Addition of thiols to certain chalcones.*

Chalcone	Thiol *	Catalyst †	Adduct		Found (%)		Formula	Required (%)	
			Yield (%)	M. p.	Hal	S		Hal	S
Unsub.	CMe ₂ Et-SH	Pip	87	40°	—	10.0	C ₂₀ H ₂₄ OS	—	10.3
3-NO ₂	PhSH	"	91	106	a	8.7	C ₂₁ H ₁₇ O ₃ NS	a	8.9
"	EtSH	"	—	Gum	—	—	—	—	—
"	MAA	"	44	65	—	9.4	C ₁₇ H ₁₅ O ₅ NS	—	9.3
"	"	NHEt ₂	Trace	—	—	—	—	—	—
"	"	HCl	0	—	—	—	—	—	—
4-NMe ₂	PhSH	Pip	83	157	b	8.8	C ₂₃ H ₂₃ ONS	b	8.9
"	MAA	"	Trace	—	—	—	—	—	—
"	"	NEt ₂	—	Oil	—	—	—	—	—
4-MeO-4'-Br	CMe ₂ Et-SH	Pip	79	149	19.1	7.5	C ₂₁ H ₂₅ O ₃ SBr	19.2	7.6
3'-NO ₂	PhSH	"	31	62	c	8.8	C ₂₁ H ₁₇ O ₃ NS	c	8.9
"	EtSH	"	—	Oil	—	—	—	—	—
"	MAA	"	29	100°	—	9.0	C ₁₇ H ₁₅ O ₅ NS	—	9.3
"	"	NEt ₂	Trace	—	—	—	—	—	—
"	"	HCl	0	—	—	—	—	—	—
4'-Br	PhSN	NHEt ₂	83	114	20.3	7.8	C ₂₁ H ₁₇ OSBr	20.4	8.0
4'-I	"	Pip	60	104	28.6	7.2	C ₂₁ H ₁₇ OSI	28.6	7.2
"	EtSH	"	59	92	31.9	7.8	C ₁₇ H ₁₇ OSI	32.1	8.1
"	MAA	"	0	—	—	—	—	—	—
"	"	HCl	74	60	29.5	7.4	C ₁₇ H ₁₅ O ₃ SI	29.8	7.5

* MAA = Mercaptoacetic acid.

† Pip = Piperidine.

a, Found: N, 3.7. Reqd.: N, 3.9%. b, Found: N, 3.7. Reqd.: N, 3.9%. b, Found: N, 3.8. Reqd.: N, 3.9%.

TABLE 2. *Addition of esters to chalcones.*

Chalcone Subst.	M. p.	Yield (%) by catalyst			Adduct, m. p.	Found (%)		Formula	Required (%)	
		Pip *	NHEt ₂	NaOEt		Hal	N		Hal	N
<i>With ethyl acetoacetate.</i>										
2-Cl	52°	—	Oil	37	110°	10.2	—	C ₂₁ H ₂₁ O ₄ Cl	9.5	—
3-NO ₂	148	—	"	—	—	—	—	—	—	—
3'-NO ₂	129	—	"	85	129	—	3.5	C ₂₁ H ₂₁ O ₄ N	—	3.4
4-NMe ₂ -4'-Cl	50	—	50	144	114	8.8	3.5	C ₂₃ H ₂₆ O ₄ NCl	8.5	3.4
4'-Br	104	36	45	Gum	63	17.7	—	C ₂₁ H ₂₁ O ₄ Br	18.0	—
4'-I	115	—	67	—	130	27.6	—	C ₂₁ H ₂₁ O ₄ I	27.3	—
<i>With ethyl malonate.</i>										
3-NO ₂	—	32	52	25	98	—	3.3	C ₂₁ H ₂₃ O ₇ N	—	3.4
4-NO ₂	164	—	49	Gum	113—114	—	3.6	"	—	3.4
2'-NO ₂	124	—	0	—	—	—	—	—	—	—
3'-NO ₂	—	0	78	29	76	—	3.2	C ₂₂ H ₂₃ O ₇ N	—	3.2
4-NMe ₂	112.5	38	—	Gum	85	—	3.5	C ₂₄ H ₂₉ O ₅ N	—	3.4
4-NMe ₂ -4'-Cl	—	36	—	"	114	8.2	3.3	C ₂₄ H ₂₈ O ₅ NCl	8.0	3.1
4'-Br	—	36	45	"	63	17.7	—	C ₂₂ H ₂₃ O ₅ Br	19.1	—
4'-I	—	45	—	—	75	25.6	—	C ₂₂ H ₂₃ O ₅ I	25.7	—

* Pip = Piperidine.

(b) *Other thiols.* Reactions were generally effected as above, but the mixtures were heated on the water-bath for 1—4 hr. Where the adduct did not readily separate on cooling, the solution was steam-distilled.

Addition of Acetoacetic Ester.—(i) *Catalysis by sodium ethoxide.* Acetoacetic ester (10 ml.)

was mixed with sodium ethoxide (from 2.5 g. of sodium) in absolute ethanol (50 ml.), and the chalcone (5 g.) added. The mixture was heated on the water-bath for 2 hr., neutralised with 5*N*-hydrochloric acid, and steam-distilled. The crude residue was extracted with alcohol (benzene for the 4'-bromo-chalcone adduct) in the presence of charcoal. The reaction with 3'-nitrochalcone also yielded a small amount of material melting at 220° (insufficient for analysis).

(ii) *Catalysis by diethylamine or piperidine.* The chalcone (5 g.) was dissolved in the ester (20 ml.), absolute ethanol being added if necessary. The mixture was heated on the water-bath for 2 hr. with the catalyst (5 drops). In the case of diethylamine, further catalyst was added from time to time. The final solution was treated as before.

Addition of Malonic Ester.—This was conducted essentially as for acetoacetic ester, but with a large excess of ester. Steam-distillation readily removed the excess of ester when reaction was complete.

Hydrolysis of Malonic Ester Adducts.—Hydrolysis of adduct mixtures *in situ* with alcoholic potassium hydroxide yielded only intractable oils, and acid hydrolysis gave the original chalcone and ester. Adducts were therefore first separated and purified. A portion (1.0 g.) was then refluxed for 2 hr. with 0.5*N*-alcoholic potassium hydroxide (20 ml.), the resultant solution acidified with *N*-hydrochloric acid (20 ml.), and most of the alcohol distilled off. Material separating on cooling was filtered off and recrystallised from alcohol. The adducts from 3- and 3'-nitrochalcone yielded products of m. p. 310° and 195°, respectively, while only gum was obtained from 4'-iodochalcone; in no case was titratable acidity detectable. The adduct from 4-nitrochalcone apparently yielded *dicarboxymethyl-4-nitrochalcone* (0.6 g., 69%) (Found : N, 3.7%; equiv., 182. $C_{18}H_{15}O_7N$ requires N, 3.9%; equiv., 178.5), m. p. (from alcohol) 140°. Cautious fusion yielded only a gum, not completely melted at 320°, and with negligible titratable acidity.

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