THE THERMAL REVERSIBILITY OF THE MICHAEL REACTION

IV. THIOL ADDUCTS

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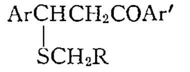
ABSTRACT

The hydrochlorides of 27 Michael adducts, formed from alkylthiols and chalcones monosubstituted successively in each ring by nitro, chloro, and methoxy groups, were thermally cleaved by hot water. The amount of cleavage was readily determined iodimetrically.

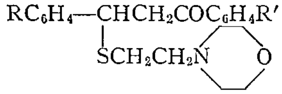
A systematic study of the thermal reversibility of Michael adducts, formed by the addition of mercaptans to the conjugated system of double bonds present in ketones, esters, and the like, is believed to be new. The only instances on record are those described in one of our previous papers (1). The current account is limited to adducts which are formed from chalcones and which have β-alkylmercapto substituents. They comprise a new class that can be used for a study of thermal cleavage. A following paper will contain an account of similar adducts derived from unsaturated esters, nitriles, ketones with fewer substituents, and the like. It has been found that they are not sufficiently active to reverse thermally.

The extent of thermal cleavage is susceptible to quantitative estimation, since the mercapto addends regenerated can be titrated against standard iodine solutions. This operation is much more convenient than the use of gas chromatography, as previously employed (1). Since these adducts can give only normal cleavage, it makes possible an examination of the effect, if any, of substituents in different positions of both benzene rings on the extent of the reversal. The extent of cleavage of all the adducts is summarized in Table I.



$$\underset{\displaystyle SCH_2R}{ArCH}CH_2COAr'$$

I



II

The adducts investigated were mainly those (II) formed from β-morpholinoethanethiol, because of its availability (2), because the hydrochloride salts are easily crystallized solids, because of their increased solubility, and because they give good cleavage rates. A few preliminary experiments showed that other thiols could be so used (Table I, Nos. 1, 2, 3, 7, 8), that the reversal was general, and that it was not confined to β-mercaptoethylamines. Three kinds of ring substituents were employed—nitro (strong electron-withdrawing), chloro (weak electron-withdrawing), and methoxy (electron-donating). These groups, one at a time, were located in ortho-, meta-, and para-positions in both rings.

The process may depend upon (*a*) the activity of the α-hydrogen atom of the adduct, (*b*) the resonance stabilization of the structure $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$ formed by cleavage, and

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TABLE I

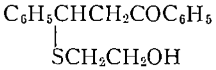
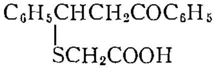
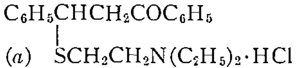
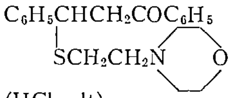
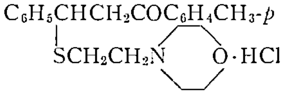
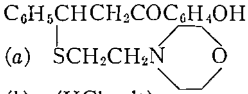
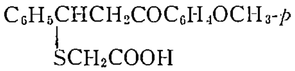
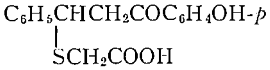
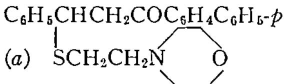
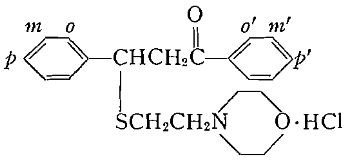
No.	Adduct	% yield	m.p., °C	Empirical formula	Analyses Calcd. C	Analyses Calcd. H	Analyses Calcd. N	Analyses Found C	Analyses Found H	Analyses Found N	% cleavage at 100° in H_2O 2 min	% cleavage at 100° in H_2O 30 min
1.	 $C_6H_5CH(SCH_2CH_2OH)CH_2COC_6H_5$	85[a]	68	$C_{17}H_{18}O_2S$	71.3	6.3	—	71.6	6.3	—	16.6	—
2.	 $C_6H_5CH(SCH_2COOH)CH_2COC_6H_5$	83	126[h]		—	—	—	—	—	—	6.8	57.5
3. (a)	 $C_6H_5CH(SCH_2CH_2N(C_2H_5)_2\cdot HCl)CH_2COC_6H_5$	96[b] (crude)	110	$C_{21}H_{28}ClNOS$	66.7 (S, 8.7)	7.5		66.6 (S, 8.5)	7.7		69.2	—
(b)	($HClO_4$ salt)	57[e]	92	$C_{21}H_{28}ClNO_5S$	57.1	6.4	3.2	57.3	6.5	3.2	—	—
4. (a)		92[c]	67	$C_{21}H_{25}NO_2S$	71.0	7.1	3.9	71.3	7.2	4.1	18.5, 18.0	43.5
(b)	(HCl salt)	87[d]	149	$C_{21}H_{26}ClNO_2S$	64.3	6.7	3.6	64.1	6.8	3.5	55.0, 59.0	—
5.		80[d]	137	$C_{22}H_{28}ClNO_2S$	65.1	7.0	3.4	65.1	7.2	3.5	36.2, 36.2	—
6. (a)		59[f]	127	$C_{21}H_{25}NO_3S$	68.0	6.8	3.8	68.0	6.8	3.9	—	—
(b)	(HCl salt)	—	201	$C_{21}H_{26}ClNO_3S$	61.8	6.4	3.4	61.4	6.6	3.4	38.9	—
7.	 $C_6H_5CH(SCH_2COOH)CH_2COC_6H_4OCH_3\text{-}p$	82[a]	90	$C_{18}H_{18}O_4S$	65.4	5.5	—	65.5	5.8	—	—	39.8
8.	 $C_6H_5CH(SCH_2COOH)CH_2COC_6H_4OH\text{-}p$	80[a]	130	$C_{17}H_{16}O_4S$	64.5	5.1	—	64.1	4.8	—	—	28.6

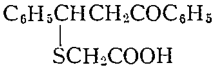
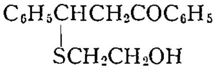
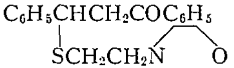
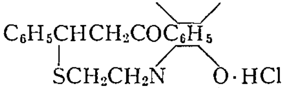
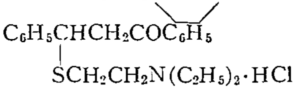
TABLE I *(Concluded)*

					Analyses						% cleavage at 100° in H_2O	
					Calcd.			Found				
No.	Adduct	% yield	m.p., °C	Empirical formula	C	H	N	C	H	N	2 min	30 min
9.	$C_6H_5CHCH_2COC_6H_4C_6H_5$-*p* (*a*) 	89^e	116–7	$C_{27}H_{29}NO_2S$	75.2	6.8	3.2	75.2	7.0	3.2	0	40.8
	(*b*) (HCl salt)	—	114–6	$C_{27}H_{30}ClNO_2S$	69.1	6.5	3.0	68.8	6.8	2.9	—	—
												
10.	*p*′-NO_2	78^d	154	$C_{21}H_{25}ClN_2O_4$	57.7	5.8	6.4	57.5	5.9	6.6	88.1, 88.4	—
11.	*o*′-NO_2	79^d	135	$C_{21}H_{25}ClN_2O_4$	57.7	5.8	6.4	57.9	5.8	6.6	91.0, 91.4	—
12.	*m*′-NO_2	80^d	141	$C_{21}H_{25}ClN_2O_4$	57.7	5.8	6.4	57.3	5.8	6.7	87.8, 87.7	—
13.	*p*-NO_2	81^d	175	$C_{21}H_{25}ClN_2O_4$	57.7	5.8	6.4	57.9	5.6	6.1	77.4, 77.8	—
14.	*o*-NO_2	69^c	191–2	$C_{21}H_{25}ClN_2O_4$	57.7	5.8	6.4	57.6	5.9	6.4	68.2, 68.2	—
15.	*m*-NO_2	85^e	188	$C_{21}H_{25}ClN_2O_4$	57.7	5.8	6.4	57.5	5.9	6.3	63.8, 64.1	—
16.	*p*′-OCH_3	72^d	147	$C_{22}H_{28}ClNO_3S$	62.6	6.7	3.3	62.5	6.6	3.3	34.0	—
17.	(*a*) *o*′-OCH_3	—	150	$C_{22}H_{28}ClNO_3S$	62.6	6.7	3.3	62.2	6.8	3.2	47.8, 49.6	—
	(*b*) *o*′-$OCH_3 \cdot$MeOH	74^d	108	$C_{23}H_{32}ClNO_4S$	60.9	7.0	3.1	60.9	6.7	3.3	—	—
18.	*m*′-OCH_3	80^d	161	$C_{22}H_{28}ClNO_3S$	62.6	6.7	3.3	62.4	6.8	3.3	60.8, 62.2	—
19.	*p*-OCH_3	72^d	138	$C_{22}H_{28}ClNO_3S$	62.6	6.7	3.3	62.3	6.3	3.2	66.8^g	—
20.	*o*-OCH_3	57^d	67	$C_{22}H_{28}ClNO_3S$	62.6	6.7	3.3	62.2	6.9	3.3	53.3^g	—
21.	*m*-OCH_3	83^d	151	$C_{22}H_{28}ClNO_3S$	62.6	6.7	3.3	62.5	6.8	3.3	54.6^g	—
22.	*p*′-Cl	81^d	159	$C_{21}H_{25}Cl_2NO_2S$	59.1	5.9	3.3	58.9	6.2	3.2	51.4, 50.2	—
23.	*o*′-Cl	46^d	114	$C_{21}H_{25}Cl_2NO_2S$	59.1	5.9	3.3	58.8	5.9	3.6	88.2, 88.2	—
24.	(*a*) *m*′-Cl	82^c	124–6	$C_{21}H_{25}Cl_2NO_2S$	59.1	5.9	3.3	58.7	6.1	3.4	—	—
	(*b*) *m*′-Cl·MeOH	83^d	69–70	$C_{22}H_{20}Cl_2NO_3S$	57.6	6.4	3.1	57.5	6.4	3.1	64.2, 64.3	—
25.	*p*-Cl	78^d	179	$C_{21}H_{25}Cl_2NO_2S$	59.1	5.9	3.3	59.3	6.0	3.2	43.2, 46.2	—
26.	(*a*) *o*-Cl·MeOH	83^d	75–77	$C_{22}H_{29}Cl_2NO_3S$	57.6	6.4	3.1	57.5	6.2	3.4	54.8, 54.0	—
	(*b*) *o*-Cl	—	133	$C_{21}H_{26}Cl_2NO_2S$	59.1	5.9	3.3	59.5	6.2	3.3	55.0	—
27.	*m*-Cl	79^d	194–5	$C_{21}H_{25}Cl_2NO_2S$	59.1	5.9	3.3	59.1	6.2	3.7	47.2, 40.4	—

[a] From ether–ligroin (b.p. 35–60°).
[b] From ethyl acetate.
[c] From isopropanol.
[d] From methanol – ethyl acetate.
[e] From ethanol.
[f] From ether.
[g] Mean of four determinations.
[h] Reference 5.

(*c*) the anionic stability of RS^- (3). Different degrees of reactivity of adducts towards thermal reversal are observed to be dependent upon the kind of mercaptan added (Table II).

TABLE II

Adduct	Cleavage, % (2 min in H_2O at 100 °C)
 $C_6H_5\underset{\substack{\vert \\ SCH_2COOH}}{C}HCH_2COC_6H_5$	6.8
 $C_6H_5\underset{\substack{\vert \\ SCH_2CH_2OH}}{C}HCH_2COC_6H_5$	16.6
	18.5, 18.0
	55, 59
 $C_6H_5\underset{\substack{\vert \\ SCH_2CH_2N(C_2H_5)_2\cdot HCl}}{C}HCH_2COC_6H_5$	69.2

The adducts (as their salts) were cleaved at 100 °C by a simple rapid procedure. The titration results suggest that the activity of the α-hydrogen atom of the adducts influences the extent of release of mercaptan.

Cleavage of adducts of chalcones to form a conjugated system, that is, a product having greater resonance, may be a predominant factor in heat-induced reversal. The adduct of methyl vinyl ketone with β-morpholinoethanethiol is incompletely reversed by alkali and only slightly affected by heat. However, the adduct of benzalacetone with this mercaptan is almost completely cleaved by alkali, as will be described in a forthcoming paper. All of the corresponding adducts of substituted chalcones are rapidly cleaved nearly quantitatively by alkali and, in addition, are reversed by heat.

The Conjugate Addition

Addition of β-morpholinoethanethiol to chalcones occurs rapidly in refluxing alcohol. The salts were formed by replacement of the solvent by ether and the addition of hydrogen chloride.

Addition of mercaptoethanol or mercaptoacetic acid by refluxing in acetic acid for 15 min forms adducts in 80–99% yield.

Sodium methoxide catalyzed addition of mercaptoacetic acid in alcohol produced the adduct in only a 17% yield (4). The data are included in Table I.

EXPERIMENTAL

Preparation of Starting Materials

3′-Methoxyacetophenone (5), b.p. 131° at 19 mm, n_D^{25} 1.5391; 2′-chloroacetophenone (6), b.p. 100° at 10 mm, n_D^{25} 1.5409; 3′-chloroacetophenone (7), b.p. 52–54° at 0.25 mm, n_D^{25} 1.5472; and β-morpholinoethanethiol, b.p. 97–98° at 15 mm, n_D^{25} 1.5020 (2) were prepared as described in the literature. All the chalcones were known: NO_2 and Cl (8), *o*-OCH_3 (9), *m*-OCH_3 (10), *p*-OCH_3 (11), *o*′-OCH_3 (12), *m*′-OCH_3 (13), *p*′-OCH_3 (14), *p*′-OH (15), *p*-CH_3 (16), and *p*′-C_6H_5 (17). The melting points agreed with the reported values except for the *o*′-chloro (9), which did not crystallize.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.2; H, 4.6; Cl, 14.6. Found: C, 74.5; H, 4.5; Cl, 14.4.

Preparation of Adducts

(a) From Chalcones and β-Morpholinoethanethiol or N,N-Diethylaminoethanethiol (2)

Equimolar amounts of the chalcone and the thiol were refluxed in absolute ethanol for 1 h and evaporated to dryness *in vacuo*. In some instances, the oils crystallized and the adduct was purified as the free base. The free base, oil or solid, was dissolved in ether and converted to the hydrochloride with hydrogen chloride. Perchlorates were prepared by treating the hydrochlorides with aqueous sodium perchlorate.

(b) From Chalcones and β-Mercaptoethanol or Mercaptoacetic Acid

A solution containing 1 mole of the chalcone and 1.5 moles of the mercaptan in glacial acetic acid was boiled for 15 min and allowed to cool. On addition of water an oil separated. The water was decanted and the oil rinsed with water two or three times, after which the oil crystallized. The products were recrystallized from ether – petroleum ether, b.p. 35–60°. The analyses are included in Table I.

Cleavage of Adduct and Titration of the Thiol

Approximately 1 meq of the adduct in a small aluminium foil "boat" was weighed exactly. The boat and the sample were then immersed for exactly 2 min in 100 ml of vigorously boiling water (in a 500-ml Erlenmeyer flask), at which time solution generally occurred, followed by formation of solids. Then 100 g of ice and water was added, the flask was set in an ice bath, and 50 ml of glacial acetic acid was added. These additions took 5–6 s. Ten milliliters of 0.25% starch indicator was then added and the mixture was titrated with a standard 0.1 *N* iodine solution to a blue end point.

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