was added. The filtered solution was run directly onto the substance under examination. Two equivalents of the base were used with 2 to 3 g. of the addition product. The mixture was heated for a few minutes only; then it was kept at room temperature for 12 to 15 hours. The precipitate that formed was filtered, thoroughly washed with water and then with cold alcohol. The pyrazolones were not further purified.

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Summary

The addition products formed by the action of aromatic mustard oils on ethyl aceto-acetate condense with hydroxylamine and hydrazine to form substituted 3-amino-isoxazolones and pyrazolones.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TUFTS COLLEGE]

THE ADDITION OF SODIUM ETHYLACETO-ACETATE TO SUBSTITUTED AROMATIC MUSTARD OILS

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Introduction

It was shown in a previous paper[1] that *para*-substituted mustard oils react readily with ethyl aceto-acetate, through the sodium derivative, to form monothio-amides of ethyl acetylmalonate. These addition products readily undergo acid hydrolysis with dilute solutions of sodium hydroxide, but the resulting acids lose carbon dioxide when warmed so that ultimately thio-amides of acetic acid are obtained. Thus with *p*-bromo mustard oil the following series of changes takes place.

$$CH_3CONa.CHCOOC_2H_5 + BrC_6H_4NCS \longrightarrow CH_3COCH(CSNa.NC_6H_4Br)COOC_2H_5 \xrightarrow{HCl} CH_3COCH(CSH.NC_6H_4Br)COOC_2H_5 \longrightarrow CH_3COCH(CSNHC_6H_4Br)COOC_2H_5 \quad (1)$$

$$CH_3COCH(CSNHC_6H_4Br)COOC_2H_5 + 2H_2O \longrightarrow CH_3COOH + CH_2(CSNHC_6H_4Br)COOH + C_2H_5OH \quad (2)$$

$$CH_2(CSNHC_6H_4Br)COOH \longrightarrow CO_2 + CH_3CSNHC_6H_4Br \quad (3)$$

The compounds formed with *o*- and *m*-methylphenyl mustard oils react in a different manner. They are most sensitive to acid, changing into substances that were regarded as ketones.

$$CH_3COCH(CSNHC_6H_4CH_3)COOC_2H_5 + H_2O \longrightarrow CH_3COOH_2CSNHC_6H_4CH_3 + CO_2 + C_2H_5OH \quad (4)$$

Moreover, no evidence was found of acid splitting (Equation 2), a reaction so characteristic of the other esters of this type studied. The matter has been re-investigated to make sure that such differences in behavior exist.

[1] Worrall, THIS JOURNAL, **40**, 415 (1918).

It has now been found that all the substituted mustard oils examined form addition compounds with ethyl aceto-acetate and that the addition compounds readily undergo acid hydrolysis (Equation 2). The acid, to be sure, cannot be isolated in certain cases because of instability. No new evidence was found of ketone splitting (Equation 4).

Addition to sodium ethylaceto-acetate takes place within a few minutes in most cases with the *para*-substituted mustard oils. The anisyl and phenetyl derivatives acted more sluggishly. The speed of reaction was slowed up with the *meta* series and still more so with the *ortho* series, although no difference was found in the ultimate amount of substance formed. The sodium derivatives on treatment with acid change to viscid oils that usually become crystalline on standing overnight in a cool place. These esters are somewhat difficult to manipulate, as first obtained. As they cool from warm solutions they easily separate as oils that do not readily crystallize even in the presence of the solid phase. Hydrolysis and oxidation both take place readily. The solid phase was not obtained at all in several cases (*o*-toluide, *o*-aniside and *m*-aniside). That addition products were formed in all cases, however, was proved by the formation of isoxazolones and pyrazolones, sparingly soluble compounds easily isolated and purified.

It is now clear why acid hydrolysis was not previously observed with *m*- and *o*-toluides. Hydrolysis with alkali does take place as in the *para* series, but the acids formed are low-melting solids that spontaneously lose carbon dioxide at ordinary temperatures. Hence, the products actually isolated are the thio-amides of acetic and not of malonic acid. This explains the presence of thio-acetyl-*o*-toluide previously noticed[2] in the ether layer after addition of water to sodium ethylacetomalonate-monothio-*o*-toluide. The monothio-*m*-toluide of malonic acid may even be isolated temporarily by working with cold solutions. It rapidly loses carbon dioxide when warmed to room temperature,[3] changing to thio-acetyl-*m*-toluide. Malonic acid monothio-*m*-aniside under similar conditions separates as an oil that foams when warmed and changes into the corresponding acetic acid derivative.

Ethylacetylmalonate-monothio-*o*-toluide on standing (as the impure wet oil) changes overnight even in the cold into a pasty mass containing, among other substances, acetic acid. A substance is obtained by extraction with alcohol that was reported[1] as thio-aceto-acetyl-*o*-toluide, nearly colorless needles melting at 73–75°, since on standing acetic acid and thio-acetyl-*o*-toluide melting at 91–92° were formed. An analysis for nitrogen supported the inference. This work has now been repeated several times and no such compound could be isolated. Instead, the

[2] Ref. 1, p. 419.

[3] This work was done during the summer months.

compound melting at 91–92° has been obtained, after several crystallizations from alcohol. It seems extremely doubtful whether thio-aceto-acetyl-*o*-toluide was isolated; it is more probable that the substance examined was an impure form of thio-acetyl-*o*-toluide.

Ethylacetomalonate-monothio-*o*-aniside is less easily hydrolyzed and the crude oil does not perceptibly change after several days, although boiling it with concd. hydrochloric acid or simply dissolving it in dil. sodium hydroxide solution quickly changes it into thio-acetyl-*o*-aniside.

Ethylacetomalonate-monothio-*m*-toluide may be prepared in the crystalline form. It decomposes on standing, taking up moisture and setting free acetic acid, even in a stoppered bottle. The substance previously reported as thio-aceto-acetyl-*m*-toluide obviously was an impure form of this ester. The only evidence for the other view was an analysis for nitrogen, after the substance had stood for several days on a porous plate. The existence of the ester is proved by the reactions with hydroxylamine and hydrazine; also by the formation of malonic acid monothio-*m*-toluide on hydrolysis with alkali.

Experimental Part

A uniform method of procedure was used unless otherwise stated. Ethyl aceto-acetate equivalent to 10 g. of the mustard oil was mixed with 20–30 volumes of dry ether containing finely divided sodium, the container connected to a return condenser and allowed to stand for 12 hours. The mustard oil was added and the mixture kept for at least 24 hours. Then an equal volume of ice water was added directly to the container. The unchanged sodium present floated on top of the moist ether layer where it reacted until consumed. The water layer was stirred slowly into crushed ice containing dil. sulfuric or hydrochloric acid. The resulting oil usually solidified overnight when kept in an ice chest. Crystal formation took place in a few minutes when the crude mixture was seeded with a little pure substance from a previous preparation. Purification was effected by thorough washing with water containing some alcohol, followed by solution in approximately two volumes of alcohol. After the liquid had been filtered and the filtrate cooled to room temperature, water was added to faint turbidity and the mixture placed in an ice chest for a few hours. The yield of the ester thus prepared was approximately 50% in most cases. No attempt was made to work up the residue.

Hydrolysis with alkali took place very readily; simply dissolving the ester in an excess of 10% sodium hydroxide solution at room temperature sufficed. It was then cooled with ice and filtered into stirred ice and water containing dil. sulfuric acid. The resulting malonic acid derivatives were purified by crystallization from warm water in which they are soluble, separating usually in brilliant, pale yellow plates. They

melted with foaming when heated, due to the evolution of carbon dioxide. The resulting thio-amides of acetic acid were purified by crystallization from alcohol.

Considerable trouble was experienced in completely oxidizing these compounds even with fuming nitric acid; consequently, the results obtained in the determination of sulfur were not always satisfactory.

TABLE I

THIO-AMIDES

Name	Formula	M. p. °C.	Decomp. °C.	Cryst. form	Analysis Calcd. %	Analysis Found %	Remarks
OF ETHYL ACETOMALONATE							
Ethylacetomalonate-monothio-							
o-Toluide	$C_{14}H_{17}O_3NS$	oil	.....	.....	...	...	Not obtained in pure condition
o-Aniside	$C_{14}H_{17}O_4NS$	oil	.....	.....	...	...	Not isolated
m-Toluide	$C_{14}H_{17}O_3NS$	78–80	.....	prismatic crystals	S,11.5	S,10.8	
m-Aniside	.....	oil	.....	.....	...	...	Not isolated
m-Bromo-anilide	$C_{13}H_{14}O_3NSBr$	81–82	.....	prismatic	Br,23.2	Br,22.7	
p-Aniside	$C_{14}H_{17}O_4NS$	97–98	.....	prismatic	S,10.8	S,10.6	
p-Phenetide	$C_{15}H_{17}O_4NS$	87–88	.....	prismatic	S,10.4	S,9.8	
p-Chloro-anilide	$C_{13}H_{14}O_3NSCl$	77–79	.....	prismatic	Cl,11.7	Cl,11.7	
p-Iodo-anilide	$C_{13}H_{14}O_3NSI$	63–65	.....	needles	I,32.5	I,32.1	
α-Naphthylamide	$C_{17}H_{17}O_3NS$	82–84	.....	prismatic	N,4.4	N,5.0	
OF MALONIC ACID							
Malonic acid monothio-							
m-Aniside	.....	oil	.....	.....	...	...	Obtained as an oil which lost CO_2 on standing
m-Toluide	$C_{10}H_{11}O_2NS$	room temp.	.....	plates	..	...	
m-Bromo-anilide	$C_9H_8O_2NSBr$	101	101	plates	Br,29.2	Br,28.8	
p-Aniside	$C_{10}H_{11}O_3NS$	90–91	90–91	plates	N,6.2	N,6.5	
p-Phenetide	$C_{11}H_{13}O_2NS$	105	105	plates	...	...	No analysis made
p-Chloro-anilide	$C_9H_8O_2NSCl$	113–114	113–114	flat needles	Cl,15.6	Cl,15.3	Substance heated quickly to obtain m. p.
p-Iodo-anilide	$C_9H_8O_2NSI$	132–133	132–133	plates	I,39.6	I,39.3	Quick heating of solid to obtain m. p.
α-Naphthylamide	$C_{13}H_{11}ONS$	56–57	.....	narrow plates	...	...	Compound obtained by evaporation of water solution
OF ACETIC ACID							
Thioacetyl							
o-Toluide	.....	.....	.....	.....	...	...	
o-Aniside	$C_9H_{11}ONS$	52–53	.....	yellow irreg. plates	N,7.7	N,8.2	
m-Toluide	$C_9H_{11}NS$	42–43	.....	needles	S,19.0	S,17.5	
m-Bromo-anilide	C_8H_8NSBr	75–76	.....	needles	Br,34.8	Br,34.1	
p-Aniside	$C_9H_{11}ONS$	114	.....	needles	N,7.7	N,8.1	

TABLE I (*Concluded*)

Name Ethylacetomalonate-monothio-	Formula	M. p. °C.	Decomp. °C.	Cryst. form	Analysis Calcd. %	Analysis Found %	Remarks
p-Phenetide[a]	.....	113–114	.....	yellow needles	..	...	
p-Chloro-anilide	.....	141–142	.....	slender needles	...	...	First prepared by S. and L.
p-Iodo-anilide	C_8H_8NSCl	149	.....	needles	Cl,19.1	Cl,18.8	
α-Naphthylamide	.....	111	.....	pale yellow needles	...	...	Prepared also by Jacobsen[4]

[a] This substance has been prepared by Sachs and Loeng [*Ber.*, **37**, 876 (1904)] who describe it as yellow plates from acetic acid melting at 99–100°.

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Summary

A number of substituted aromatic mustard oils have been found to react with sodium ethylaceto-acetate, forming thio-amides of ethyl acetyl-malonate.

The resulting amides easily hydrolyze with alkali to form monothio-amides of malonic acid. Carbon dioxide is evolved on heating the latter so that thio-amides of acetic acid are formed.

The non-existence of thio-aceto-acetyl-*o*-(and *m*)-toluides has been indicated.

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THE SYNTHESIS OF SOME POSSIBLE PRECURSORS OF LYSINE

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It is generally known that the animal body can synthesize certain amino acids such as glycine. However, the so-called "essential" amino acids must be present in the diet and are not synthesized in the body from the ordinary products of metabolism. Perfusion experiments with surviving livers have indicated that α-hydroxy acids can be converted to α-amino acids and *vice versa*. If this is a normal reaction in the body, then a diet containing the hydroxy acids corresponding to the essential amino acids should be equivalent to a diet containing the amino acids themselves.

Lysine, *l*-α,ε-diaminocaproic acid, is one of the essential amino acids. It was thought that considerable evidence concerning possible synthetic reactions in the animal body could be obtained by supplementing a diet deficient in lysine with various caproic acid derivatives

[4] Jacobsen, *Ber.*, **20**, 1897 (1887).