[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KENTUCKY]

THE PREPARATION AND PROPERTIES OF SOME METHYL SUBSTITUTED TETRAHYDRO-1,4-THIAPYRONES

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Very few substituted tetrahydro-1,4-thiapyrones have been made. Arndt and his co-workers (1) have prepared 2,6-diphenyl-, 2-phenyl-6,6-dimethyl-, and 2,2,6,6-tetramethyl-tetrahydro-1,4-thiapyrone by the reaction of hydrogen sulfide with an $\alpha,\beta,\alpha',\beta'$-unsaturated ketone as illustrated in Equation 1.

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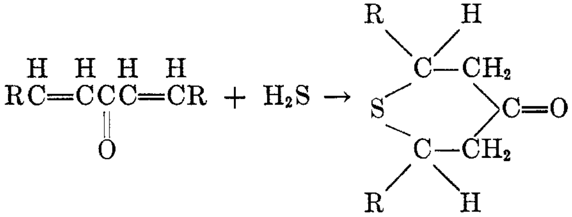

Though this method gave good yields it is limited by the number of unsaturated ketones of this type that are readily available.

Another approach to the synthesis of tetrahydro-1,4-thiapyrones has been the use of the Dieckmann condensation starting with esters of β,β'-thiodipropionic acid (Equation 2). Bennett and Scorah (2), using this method for the first time, prepared tetrahydro-1,4-thiapyrone.

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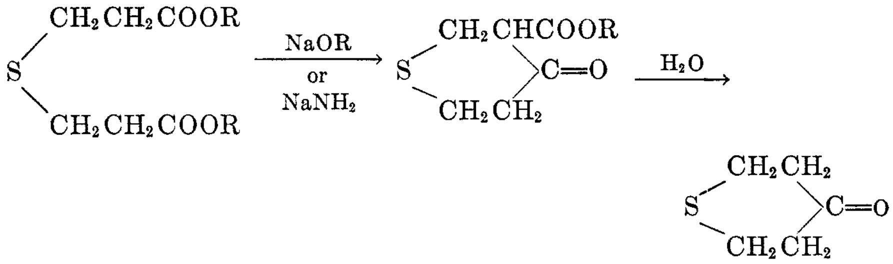

Arndt (1) mentions the preparation of 2,6-dimethyltetrahydro-1,4-thiapyrone though he gave no details and this is the only substituted tetrahydro-1,4-thiapyrone that has been prepared by this type of condensation.

The yields have been uniformly poor, though recently Fehnel and Carmack (3) report an over-all yield of 54.6% for tetrahydro-1,4-thiapyrone. The purpose of the present work was to prepare some methyl substituted tetrahydro-1,4-thiapyrones from substituted methyl β,β'-thiodipropionates by means of the Dieckman condensation.

The recent work of Hurd and Gershbein (4, 5) on the addition of hydrogen sulfide or mercaptoesters to conjugated unsaturated esters such as methyl acrylate offers a convenient way of making alkyl substituted methyl β,β'-thiodipropionates where the substitition may be on one or both of the α- or β- carbons. Equations 3 and 4 illustrate the possibilities of synthesizing a variety of esters of this type.

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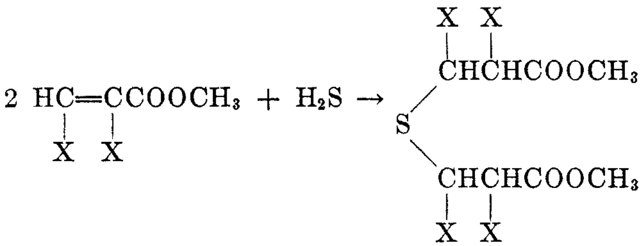

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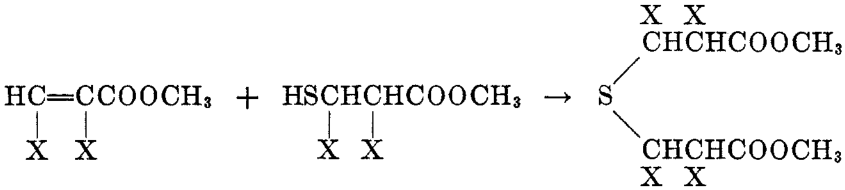

The commercial availability of crotonic acid, β-mercaptopropionic acid, methyl acrylate, and methyl methacrylate also makes the synthesis of certain esters of β,β′-thiodipropionic acid more convenient.

It has been found that methyl β-mercaptopropionate adds readily to methyl acrylate, methyl methacrylate, methyl crotonate, and methyl cinnamates, when piperidine plus B.T.A.[1] are used as catalysts, to give in excellent yields methyl β-(2-carbomethoxyethylmercapto)propionate, methyl α-methyl-β-(2-carbomethoxyethylmercapto)propionate, methyl β-methyl-β-(2-carbomethoxyethylmercapto)propionate, and methyl β-phenyl-β-(2-carbomethoxyethylmercapto)propionate.

The addition of hydrogen sulfide to the esters mentioned above to give symmetrically substituted methyl β,β′-thiodipropionates takes place smoothly, though the yields in most cases are not as good. Hurd and Gershbein (4) state that hydrogen sulfide does not add to methyl methacrylate; however, in this work it was found that hydrogen sulfide not only reacts with methyl methacrylate but also with methyl crotonate, if a mixture of piperidine and B.T.A. is used as a catalyst, to give methyl α-methyl-β-(2-methyl-2-carbomethoxyethylmercapto)propionate and methyl β-methyl-β-(1-methyl-2-carbomethoxyethylmercapto)propionate. Under the conditions used, hydrogen sulfide would not react with methyl cinnamate. Data on the new esters prepared are collected in Table I.

Since the literature indicated that the Dieckmann condensation of esters of β,β′-thiodipropionic acid gave poor yields, the pyrolysis of salts of β,β′-thiodipropionic acid was thoroughly investigated. This method, though satisfactory for the preparation of many cyclic ketones, gave no tetrahydro-1,4-thiapyrone.

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[1] B.T.A. is a 30% solution of benzyltrimethylammonium hydroxide in methyl alcohol.

Pronounced decomposition indicated that the sulfide linkage is unstable at the high temperatures necessary for this reaction.

The availability of acrylonitrile and the ease of making β,β′-thiodipropionitrile from it led to the investigation of Ziegler's (6) method of condensing dinitriles by means of lithiumethylaniline. Again no condensation could be observed.

The Dieckmann condensation seems to be the best approach to the synthesis of this kind of cyclic ketone, even though the yields leave much to be desired. Fehnel and Carmack (3) in obtaining their over-all yield of 54.6% of tetrahydro-1,4-thiopyrone state that they used alcohol-free sodium methoxide though they did not indicate how this was prepared. In repeating this synthesis it was found that if the sodium methoxide used was prepared under ether the yields stated could be obtained. If the sodium methoxide was prepared by dissolving sodium in methyl alcohol and distilling off the excess alcohol under nitrogen, the yields decreased to 25%, which is the approximate yield of previous workers. This marked difference in yields could not be due to traces of alcohol since as much alcohol as five percent could be added to the alcohol-free sodium methoxide prepared under ether without lowering the yields. In fact this excess alcohol appeared to give approximately five percent better yields, which may or may not be significant.

TABLE I

METHYL β,β′-THIODIPROPIONATES

ESTER	EMPIRICAL FORMULA	YIELD, %	B.P., °C./MM.	n^{25}_{D}	S	
					Calc'd	Found
Methyl α-methyl-β-(2-carbomethoxyethylmercapto)-propionate	$C_9H_{16}O_4S$	54.3	120–121/2	1.4695	14.56	14.48
Methyl α-methyl-β-(2-carbomethoxypropylmercapto)-propionate	$C_{10}H_{18}O_4S$	84.7	121–124/2	1.4656	13.69	13.75
Methyl β-methyl-β-(2-carbomethoxyethylmercapto)-propionate	$C_9H_{16}O_4S$	92.8	127–130/2.5	1.4690	14.56	14.42
Methyl β-methyl-β-(2-carbomethoxy-1-methylethylmercapto)propionate	$C_{10}H_{18}O_4S$	51.3	114–117/1.5	1.4654	13.69	13.65
Methyl β-phenyl-β-(2-carbomethoxyethylmercapto)-propionate	$C_{14}H_{18}O_4S$	86	171–174/2.5	1.5260	11.36	11.40

It is well known that sodium methoxide reacts readily with oxygen to form sodium formate and sodium hydroxide (7). In preparing the sodium methoxide from excess alcohol all reasonable precautions were taken to eliminate oxygen but it is possible that the product prepared in this manner had a slightly higher percentage of sodium hydroxide. In some cases the quality of the sodium methoxide is critical (8) and it is possible that the methyl β,β′-thiodipropionate used in this condensation is very susceptible to small amounts of sodium hydroxide.

Sodamide appears to be the only other condensation agent that has been used in this synthesis. Arndt, *et al.* obtained slightly better yields using this reagent but they did not approach the yields of Fehnel and Carmack using their sodium methoxide. In this work it was found that metallic sodium plus a trace of alcohol gave yields nearly as good as the sodium methoxide, while diisopropylaminomagnesium bromide recently used by Hauser (9) gave very poor yields. It was also observed that commercially available sodium methoxide when used immediately or stored under absolute ether gave yields as good as the freshly prepared material.

The condensation is accompanied by some cleavage of the sulfide linkage of the ester, resulting in the formation of methyl β-methoxypropionate, methyl β-mercaptopropionate, and hydrogen sulfide—all of which can be isolated from the reaction mixture. This cleavage is more pronounced the higher the temperature, and the condensation is best run between 20 and 40°. These products are the results of "*beta*-cleavage" of the sulfide linkage, a reaction first observed for sulfides by Nicolet (10).

The method finally used is described in the experimental part and combines both the condensation and hydrolysis reactions. Consistent 50—55% yields of tetrahydro-1,4-thiapyrone were obtained by this method. Lower yields were obtained when this method was used on the substituted esters. No ketone was obtained when methyl α-methyl-β-(2-carbomethoxy-1-propylmercapto)propionate was used. Since substitution on an *alpha*-carbon usually lowers the yields obtained from this type of condensation, it is not surprising that no condensation took place with this ester where both *alpha*-carbons are substituted.

When methyl β-methyl-β-(2-carbomethoxy-2-propylmercapto)propionate was used 2,6-dimethyl-3-carbomethoxytetrahydro-1,4-thiapyrone was obtained instead of 2,6-dimethyltetrahydro-1,4-thiapyrone. This β-keto ester is very stable toward acid hydrolysis, but was hydrolyzed with water in an atmosphere of hydrogen at 200° and 2000 p.s.i.

Methyl β-phenyl-β-(2-carbomethoxyethylmercapto)propionate did not give any 2-phenyltetrahydro-1,4-thiapyrone. The only product that could be isolated was methyl cinnamate which was identified by its melting point and saponification equivalent. It is apparent that the presence of the phenyl group on the *beta*-carbon accelerates the *beta*-cleavage of the sulfide linkage to such an extent that no condensation can take place. Since the methyl cinnamate produced does not add methyl alcohol readily, no methyl β-methoxyhydrocinnamate was formed.

In Table II are collected the data pertaining to the tetrahydro-1,4-thiapyrones made.

The sulfones of the tetrahydro-1,4-thiapyrones were made by the method of Fehnel and Carmack (3) using acetic acid and 30% hydrogen peroxide. If an excess of hydrogen peroxide is used, the stable coördinated compound with hydrogen peroxide is formed. It was found that the sulfones of 2-methyl- and 2,6-

dimethyl-tetrahydro-1,4-thiapyrone could not be made by this method or by any modification tried. A water-soluble oxidation product was always obtained which gave no reactions for ketones. Substitution on the 2- or 2,6-position by a methyl group either causes the sulfone to be more readily hydrolyzed or oxidized. In view of this observation it is surprising that the β-ketoester, 2,6-dimethyl-3-carbomethoxytetrahydro-1,4-thiapyrone, oxidized smoothly to the corresponding sulfone. Table III lists the properties of the sulfones made.

TABLE II

TETRAHYDRO-1,4-THIAPYRONES[a]

COMPOUND	EMPIRICAL FORMULA	YIELD, %	B.P., °C./MM.	n^{25}_{D}	S		2,4-DINITROPHENYLHYDRAZONE		
					Calc'd	Found	M.P., °C.	S	
								Calc'd	Found
Unsubstituted		50–55	65–66[d,c]				181–182	$C_{11}H_{12}N_4O_4S$ 10.82	10.60
3-Methyl-	$C_6H_{10}OS$	26.0	43–48/1.5	1.5175	24.63	24.98	163–165	$C_{12}H_{14}N_4O_4S$ 10.33	10.71
2-Methyl-	$C_6H_{10}OS$	24.6	41–45/2	1.5125	24.63	24.86	143–145	$C_{12}H_{14}N_4O_4S$ 10.33	10.55
2,6-Dimethyl-[b]	$C_7H_{12}OS$	23.9	46–49/2.5	1.4906	22.23	21.80	160–162	$C_{13}H_{16}N_4O_4S$ 9.89	9.77
2,6-Dimethyl-3-carbomethoxy-[b]	$C_9H_{14}O_3S$	33.0	83.5[c]		15.85	15.94	183–185	$C_{15}H_{18}N_4O_6S$ 8.39	8.60

[a] All melting points are uncorrected.

[b] Compounds mentioned in literature but not fully described.

[c] M.p.,°C.

[d] Reported by previous investigators.

EXPERIMENTAL[2]

Preparation of methyl β-methyl-β-(2-carbomethoxyethylmercapto)propionate. To 100 g. (1 mole) of methyl crotonate, which was prepared from crotonic acid in 70% yield by the method of Church and Lynn (11), was added 10 ml. of dry piperidine and 15 ml. of B.T.A. To this solution 121.2 g. (1.01 mole) of methyl β-mercaptopropionate was added slowly with cooling. The mixture was then heated to 60° for 10 hours. After cooling, the mixture was extracted with ether and the ether extract washed with dilute sulfuric acid, saturated sodium acid carbonate solution, and water. The ether solution was dried with magnesium sulfate, the ether evaporated, and the remaining ester fractionated *in vacuo*. By substituting methyl methacrylate and methyl cinnamate for methyl crotonate the corresponding esters were made. Yields and boiling points are recorded in Table I. Methyl cinnamate was made in 93% yield from cinnamic acid using the method of Clinton and Laskowski (12).

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[2] The Tennessee Eastman Company furnished the crotonic acid, the B. F. Goodrich Chemical Company the β-mercaptopropionic acid, and the Rohm and Haas Company the B.T.A. used in this study. We wish to express our appreciation to these companies for their generous cooperation.

Preparation of methyl α-methyl-β-(2-methyl-2-carbomethoxyethylmercapto)propionate. In a dry flask fitted with a stirrer was placed 100 g. (1 mole) of methyl methacrylate, 5 ml. of dry piperidine, and 5 ml. of B.T.A. After the flask had been swept out with hydrogen sulfide it was closed and kept connected to the hydrogen sulfide source. The temperature gradually rose to 55° and was kept between 50–55° by careful cooling. Occasional sweeping out of the flask with hydrogen sulfide was necessary to remove the oxygen that had accumulated from the Kipp generator. When the temperature dropped below 45°, 5 ml. each of piperidine and B.T.A. were added. The temperature rose to 55° again and, after about one hour, the temperature dropped and could not be brought up by further additions of the catalysts. Water and ether were added and the ether extract washed well with dilute sulfuric acid, saturated sodium acid carbonate solution, and water. After drying over magnesium sulfate, the ether was evaporated and the crude ester distilled *in vacuo*. Methyl crotonate reacted in a similar manner but under these conditions methyl cinnamate did not. Yields and boiling points are recorded in Table I.

TABLE III

TETRAHYDRO-1,4-THIAPYRONE-1,1-DIOXIDES[a]

	EMPIRICAL FORMULA	M.P., °C.	S		2,4-DINITROPHENYL HYDRAZONE			
			Calc'd	Found	M.P., °C.	Empirical formula	S	
							Calc'd	Found
Tetrahydro-1,4-thiapyrone-1,1-dioxide	—	170[c]			244.5–246.5[b]	$C_{11}H_{11}N_4O_6S$	9.77	9.94
3-Methyltetrahydro-1,4-thiapyrone-1,1-dioxide	$C_6H_{10}O_3S$	119–120	19.77	20.20	245–247[b]	$C_{12}H_{13}N_4O_6S$	9.37	9.80
2,6-Dimethyl-3-carbomethoxytetrahydro-1,4-thiapyrone-1,1-dioxide	$C_9H_{14}O_5S$	174–175	13.69	14.10	224–226[b]	$C_{15}H_{17}N_4O_8S$	7.74	7.99

[a] All melting points are uncorrected.

[b] With decomposition.

[c] Reported by previous workers.

Preparation of pure sodium methoxide. In a bottle swept out with dry nitrogen was placed 200 ml. of ether, previously dried over sodium wire, and approximately 0.5 mole of 0.5-mm. diam. sodium wire. The sodium was weighed accurately. The bottle was attached to a reflux condenser, a slow stream of dry nitrogen was passed through, and slightly less than the equivalent amount of methyl alcohol, freshly distilled from sodium, was slowly added. After the first vigorous reaction was over, the bottle was shaken vigorously and allowed to stand overnight. The bottle was then stoppered tightly and shaken for six hours. At the end of this time several large pieces of sodium were added and the bottle shaken again for three hours. This procedure collected the needle-like pieces of excess sodium on the large pieces which could then easily be removed. The highly dispersed sodium methoxide which is free of sodium can be used directly or the ether can be evaporated off under a partial vacuum in an atmosphere of nitrogen. In the latter case the product was dried to constant weight over sulfuric acid in an atmosphere of nitrogen. The white fluffy powder analyzed 99.8% sodium methoxide and gave no test for formates.

In preparing sodium methoxide free of sodium formate but containing 5% by weight of methyl alcohol the sodium does not need to be accurately weighed. The calculated amount of methyl alcohol plus 5% excess is added and the preparation is ready for use when all of the sodium has reacted.

Preparation of tetrahydro-1,4-thiapyrone. To the ether suspension of approximately 0.5 mole of sodium methoxide containing 5% excess methyl alcohol as made above was added slowly with shaking 51.5 g. (0.25 mole) of methyl β,β′-thiodipropionate. The mixture after shaking for six hours was cooled with an ice-salt mixture and 500 ml. of 15% sulfuric acid was added slowly with stirring. The ether was distilled off and the mixture heated in an oil-bath at 110° with vigorous stirring for five hours. The mixture was then cooled and extracted well with ether. The ether extract was washed several times with saturated sodium acid carbonate solution, with water, and dried over magnesium sulfate. After evaporation of the ether the solid tetrahydro-1,4-thiapyrone was crystallized from petroleum ether; yield, 50–55%. If the stirring during hydrolysis is not efficient some unhydrolyzed ester may remain and the product is oily. In this case the product is again hydrolyzed. In making the substituted tetrahydro-1,4-thiapyrones the resulting liquids were carefully fractionated under diminished pressure and only those fractions having an index of refraction differing by not more than eight parts in the fourth place were collected as the product. In making 2,6-dimethyltetrahydro-1,4-thiapyrone the intermediate β-ketoester, 2,6-dimethyl-3-carbomethoxytetrahydro-1,4-thiapyrone was obtained as a white crystalline solid which could not be hydrolyzed by this method. The ester was hydrolyzed to the ketone by heating for 12 hours with water in an atmosphere of hydrogen at 200° and 2000 p.s.i.

SUMMARY

The conditions necessary for preparing tetrahydro-1,4-thiapyrones by the Dieckmann condensation have been investigated and 2-methyl- and 3-methyltetrahydro-1,4-thiapyrone have been made for the first time. 2,6-Dimethyl- and 2,6-dimethyl-3-carbomethoxy-tetrahydrothiapyrone have been fully described. It was not possible to prepare 3,5-dimethyl- or 2-phenyl-tetrahydro-1,4-thiapyrone by this condensation. Sulfones of 2-methyl- and 2,6-dimethyl-tetrahydrothiapyrone could not be made.

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