DEHALOGENATION OF ETHYL 2,5-DICHLORO-3-THIENYLGLYOXYLATE IN THE PRESENCE OF SUPPORTED PALLADIUM COMPLEXES

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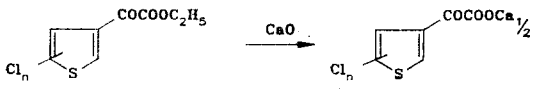
The dependence of the rate and selectivity of the catalytic hydrodehalogenation of ethyl 2,5-dichloro-3-thienylglyoxylate over immobilized palladium complexes on the nature of the solvent and HCl acceptor has been investigated. Hydrogenation of the C=O group also occurs. Reductive dechlorination of methyl and ethyl 2,5-dichloro-3-thienylacetates occurs selectively, at a slower rate than in the case of the 3-thienylglyoxylate.

We have shown [1] that in the presence of a Pd complex supported on silica gel modified with γ-aminopropyl groups, there is a stepwise dehalogenation of 2,5-dichloro-3-acetothiophene to form 3-acetothienone without hydrogenation of the carbonyl group.

We proposed that ethyl 3-thienylglyoxylate could be obtained in this way; this compound could be used as an intermediate in the synthesis of 3-thienylmalonic acid, which is useful in the synthesis of the antibiotic thicarcillin [2]. In connection therewith we have studied the dehalogenation of ethyl 2,5-dichloro-3-thienylglyoxylate and methyl and ethyl 2,5-dichloro-3-thienyl acetates in the presence of supported palladium metallocomplex catalysts.

Preliminary tests showed that at 70° and 1 atm H_2, in the presence of palladium immobilized on silica gel containing γ-aminopropyl groups (CaO as HCl acceptor), chlorine is cleaved rapidly from ethyl 2,5-dichloro-3-thienylglyoxylate.



n=0,1,2

But within 5-10 min after the reaction starts, the reaction rate begins to decrease, and the reaction stops because of competing ester hydrolysis and the formation of difficultly soluble calcium salts of thienylglyoxylic acid derivatives. Similar results were obtained with other HCl acceptors that promote ester hydrolysis, such as Na_2CO_3, $KHCO_3$, amines, and Zn.

Evidently the reaction must be carried out in the presence of bases that do not promote the side reaction of hydrolysis.

Indeed, by using phosphate salts, namely NaH_2PO_4 and particularly Na_2HPO_4, we succeeded in the dehalogenation of compound I without complication by hydrolysis (Table 1).

As Fig. 1 shows, the catalytic dehalogenation of dichloride I in the presence of the palladium complex with γ-aminopropyl-silica gel proceeds stepwise. Cleavage of the first halogen atom (predominantly at position 2) is finished in 20 min, and the concentration of monochloride II reaches 80%. According to the GLC data, 93-95% of the monochloride is the isomer with halogen at position 5. It must be noted that at this stage there is no reduction of the carbonyl or the thiophene nucleus of I.

Cleavage of the second halogen atom starts after accumulation of 50-60% of ester II. The rate of formation of III is 1/4 that of ester II (Table 1).

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TABLE 1. Dehalogenation of Ester I in the Presence of Palladium Complex Catalyst (70°)

HCl acceptor	Solvent	Initial rate, M/liter · min · mole Pd		Yield of hydrogenation by products, %	
		II	III	V	IV
Na_2HPO_4	C_2H_5OH	55	15	7	27
NaH_2PO_4	C_2H_5OH	150	41	13	40
NaH_2PO_4	$C_2H_5OH : CH_3COC_2H_5$ (1 : 1)	83	8	7	30
NaH_2PO_4	$C_2H_5OH : CH_3COOC_2H_5$ (1 : 1)	43	4	7	30

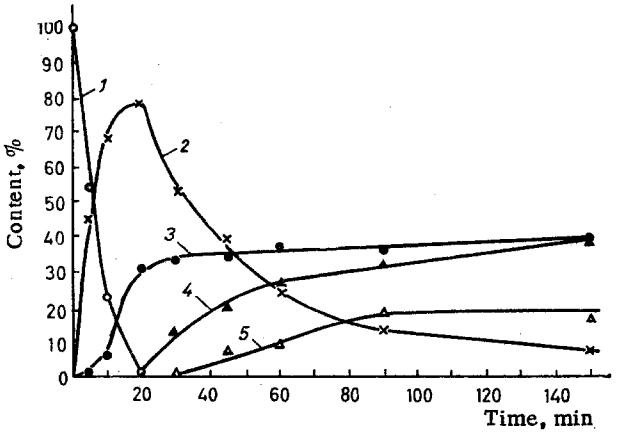
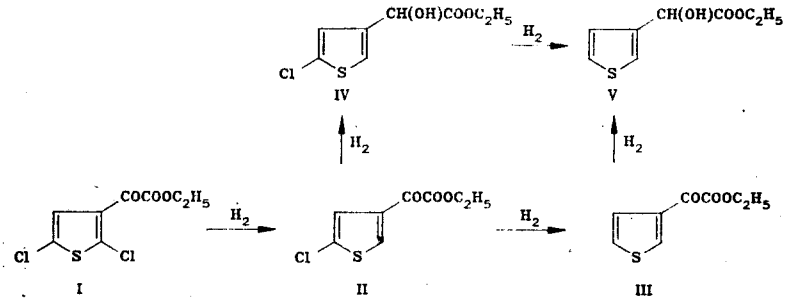


Fig. 1. Hydrodechlorination of ethyl 2,5-dichloro-3-thienylglyoxylate in presence of Pd complex on γ-aminopropyl-silica gel (70°, 1 atm H_2, 10 ml C_2H_5OH, 0.25 g NaH_2PO_4). 1) Starting material I; 2) ester II; 3) ester III; 4) byproduct IV; 5) byproduct V.



After I has disappeared from the reaction mixture, along with dehalogenation of II there begins the side reaction of C=O hydrogenation in II and III to form the respective alcohols IV and V (Fig. 1).

The probable reason for the reduced dehalogenation rate of II is that the halogen at position 5 is substantially less activated than at position 2 in ester I [1]. Along with the reduced concentration of Cl-containing substrate, this leads to coordination of the chloride of II predominantly at the keto group, and then to its reduction of the latter to alcohol. The result is that the course of the reaction changes; dehalogenation practically stops, and only reduction of the keto group takes place.

According to our data [1, 3], in the presence of a supported palladium catalyst an unactivated carbonyl group (e.g., in aryl or dialkyl ketones) is not reduced. We have established that under the same conditions the benzene analog of III, methyl phenylglyoxylate, also is not reduced. Reduction of II and III at the C=O group is probably due to a specific effect of the thiophene ring, on the one hand, and of the ester group, on the other.

In order to reduce the rate of C=O hydrogenation and increase of III, we studied the effect of ketone or ether solvents on the reaction rate and selectivity. It was kept in mind that such solvents might prevent formation of alcohols IV and V by competitive coor-

TABLE 2. Dehalogenation of Ester I in the Presence of Added Acetonitrile (AN), Benzonitrile (BN), and DMFA on Palladium Complex Catalyst (70°)

Solvent (ml)		Initial rate, M/liter · min · moles Pd		Maximum amount of monohalogen derivative, %	Yield of hydrogenation products, %	
		II	III		III	II
C_2H_5OH	(9,8)					
AN	(0,2)	100	34	82	11	21
C_2H_5OH	(9)					
AN	(1)	62	33	76	8	19
C_2H_5OH	(5)					
AN	(5)	63	3,3	90	0	0
C_2H_5OH	(0)					
AN	(10)	170	1	95,5	0	0
C_2H_5OH	(9,8)	75	33	83	18	30
BN	(0,2)					
C_2H_5OH	(9,8)					
DMFA	(0,2)	83	33	79	16	33
C_2H_5OH	(8)					
DMFA	(2)	83	20	85	12	24
C_2H_5OH	(5)					
DMFA	(5)	83	21	90	2	15

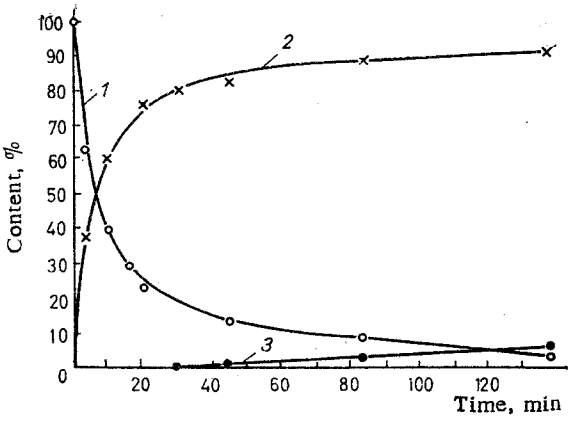


Fig. 2. Catalytic dechlorination of ethyl 2,5-dichloro-3-thienylglyoxylate in acetonitrile solution (70°, 1 atm H_2). 1) Starting material I, 2) ester II, 3) ester III.

dination. But the addition of ketone (methyl ethyl ketone) or ester (ethyl acetate) to the reaction mixture did not reduce the amount of byproducts. Moreover they reduce the rate of cleavage of the first halogen atom by 1/2 and 1/4, respectively (Table 1).

We assumed that the addition of nitrogen compounds capable of coordinating palladium would inhibit the side reaction. Indeed, the addition of acetonitrile to the solvent suppresses C=O reduction and simultaneously reduces the rate of hydrodehalogenation of chloride II (Table 2). Addition of DMFA or benzonitrile has practically no effect on selectivity, but the rate decreases by one-half (Table 2). Noteworthy is the increased selectivity of dehalogenation with respect to monochloride in the presence of CH_3CN; cleavage of the second chlorine begins after accumulation of 40-90% of monohalo derivative (after 5-30 min, depending on CH_3CN concentration). When dichloride I is dehalogenated in CH_3CN, the high rate of cleavage of the first halogen atom (170 M/liter·min·mole Pd), and the low rate for the second halogen (1 M/liter·min·mole Pd) are the reason for the accumulation of 95% of chloride II. Dehalogenation of II and III begins only after 30 min after the start of the reaction (Fig. 2). Apparently in this case there is a coordinate displacement of monochloro compound II by the solvent. Byproducts do not form, but the accumulation rate of III is low.

We showed that the rate and selectivity of dehalogenation of I in the presence of equivalent amounts of CH_3CN, PhCN, and DMFA do not change in the absence of an HCl acceptor.

I was also dehalogenated in the presence of palladium supported on silica gel containing $-(CH_2)_3\overset{+}{N}C_5H_5Cl^-$ and $-(CH_2)_3\overset{+}{N}(CH_2COOH)_2$ groups. These catalysts showed high activity for the cleavage of the first chlorine atom (100 and 180 M/liter·min·mole Pd, respectively). But

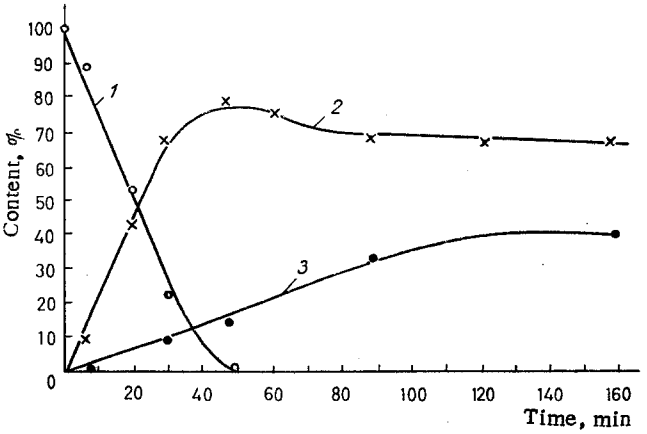
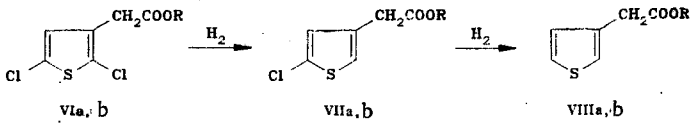


Fig. 3. Catalytic dechlorination of ethyl 2,5-dichloro-3-thienylacetate (70°, 1 atm H_2, 9.8 ml C_2H_5OH + 0.2 ml CH_3CN). 1) Starting compound VIb, 2) ester VIIb, 3) ester VIIIb.

the rate of formation of final product III is 1/8 (5 M/liter·min·mole Pd) that of the propylamine complex. Hydrogenation byproducts do not form. The low cleavage rate of the second chlorine increases the reaction time. Due to partial deactivation of the catalyst, the yield of III does not exceed 20-30% after 5 h.

Since dehalogenated ester III is a starting compound for the synthesis of 3-thienylacetic acids, we attempted to dehalogenate methyl and ethyl 2,5-dichloro-3-thienylacetates in the presence of a palladium complex supported on γ-aminopropyl-silica gel. The reaction goes stepwise through the monohalo compound.



VI—VIII a R=CH_3; b R=C_2H_5

The rates of accumulation of monohalide VII and final product VIII are similar for the methyl and ethyl esters (Table 3). Variation of HCl acceptor did not increase the yield of final product VIII. The decrease of rate in comparison with dehalogenation of I is explained by the absence of the activating electron-acceptor C=O group conjugated with the thiophene ring. The ester group that is separated from the thiophene nucleus by the methylene unit has little effect on halogen lability. It should be noted that reduction of methyl ester VIa in an autoclave (70 atm. H_2, 100°) did not increase the reaction rate.

EXPERIMENTAL

Starting compounds and products were analyzed by GLC at 160° on a LKhM-8MD chromatography with flame ionization detector, stainless steel column 1 m × 3 mm, liquid phase SE-30, 10% on Chromosorb W, nitrogen carrier gas.

Palladium complexes supported on silica gel containing $-(CH_2)_3NH_2$, $-(CH_2)_3\overset{+}{N}C_6H_4Cl^-$, and $-(CH_2)_3N(CH_2COOH)_2$ and pretreated with $NaBH_4$ were prepared by the procedure of [4]. The palladium concentrations on the supports were 3, 2, and 1.2%, respectively. The principal data were obtained on the Pd complex on silica gel modified with aminopropyl groups (3% Pd).

Tests were carried out at 50-70° and 1 atm H_2 [4]. Into a "duck" type reactor attached to a rocker were introduced catalyst, HCl acceptor, and $NaBH_4$; the system was flushed with hydrogen for 10 min, and then 8 ml of solvent was added by syringe through a self-sealing tube and the rocker was turned on. After 20 min (catalyst activation) the system was thermostated and a weighed amount of reagent in 2 ml of solvent was added by syringe. When acetonitrile, benzonitrile, or DMFA were used as HCl acceptors they were introduced in a solution of reagent. The reaction conditions were 300-400 oscillations per min, which insured that the reaction took place in the kinetic region.

TABLE 3. Dehalogenation of 2,5-Dichloro-3-thienyl Esters in the Presence of Palladium Complex

Compound	Reaction temp., °C	HCl acceptor	Initial rate of accumulation, M/liter·min·moles Pd		Maximum VII content, %	Reaction time, min	Yield of VIII, %
			VII	VIII			
VIa	50	Na_2HPO_4	40	1	83	200	10
	50	DMFA	10	2	75	200	18
VIb	50	CH_3CN	17	2	83	180	23
	70	CH_3CN	40	8	80	160	40
	70	DMFA	36	7	78	180	42
	70	PhCN	32	6	73	180	38

In an experiment there were used 0.2 g catalyst ($2.4\text{-}6\cdot10^{-5}$ mole Pd), $1\cdot10^{-2}$ g $NaBH_4$, $1\cdot10^{-3}$ mole substrate, $2\cdot10^{-3}$ mole HCl acceptor, and 10 ml of solvent.

Ethyl 2,5-dichloro-3-thienylglyoxylate (I) was synthesized by acylation of 2,5-dichlorothiophene with the acid chloride of ethyl oxalate in the presence of $AlCl_3$ by the procedure of [5]. Bp 110° (0.8 mm).

Ethyl phenylglyoxylate was synthesized by acylation of benzene with the acid chloride of monoethyl oxalate in the presence of $AlCl_3$ by the method of [6]. Bp 114-115° (6 mm), n_D^{20} 1.5160.

2,5-Dichlorothienylacetic acid was synthesized by Kishner reduction with simultaneous hydrolysis of ester I in water under the conditions used for the synthesis of 2-thienylacetic acid [7]. Freshly distilled ester I, 40.8 g (0.16 mole) was added to a warm solution of 40.8 g of potassium hydroxide in 100 ml of water, and 20 ml (0.4 mole) of hydrazine hydrate was added to the mixture. The warm solution was boiled for 2 h and cooled, and an equal volume of water was added, and the solution was washed with 100 ml of ether. The aqueous layer was acidified to Congo with 1:1 HCl, and the dark oil that separated was extracted with ether (2 × 100 ml). The extract was washed with water and dried over $MgSO_4$. The ether was distilled off on a water bath. The partly crystalline dark residue was distilled to yield a fraction with bp 160-170° (10 mm). A yellow oil, 13.5 g, was obtained which crystallized on standing, mp 88-95°. This product was dissolved in 100 ml of 10% sodium hydroxide and washed with ether. The yellow aqueous layer was treated with carbon, and the nearly colorless filtrate was acidified with dilute HCl and left in the refrigerator. The precipitate was filtered off, washed with cold water and dried in vacuum over P_2O_5. There was obtained 11.6 g (34% yield) of 2,5-dichlorothienylacetic acid, mp 99-101°. According to [8], mp 103°.

Methyl 2,5-dichlorothienylacetate was synthesized by the reaction of an excess of ethereal solution of diazomethane on a solution of 2,5-dichlorothienylacetic acid in ether. Yield 90%, bp 122-125 (16 mm), n_D^{23} 1.5430.

Ethyl 2,5-dichloro-3-thienylacetate. A mixture of 11.5 g of 2,5-dichloro-3-thienylacetic acid, 100 ml of absolute alcohol, and 2.5 g p-toluenesulfonic acid was boiled for 3 h and 50 ml of alcohol was distilled off. To the residue was added 150 ml of water, and the oil that separated was extracted with ether. The extract was washed with water, sodium hydroxide solution, and again water. When the alkaline solution was acidified, 1.3 g of acid precipitated, mp 89-93°. The extract was dried with $MgSO_4$. By distillation there was separated 8.3 g (71.6%) of ester with bp 123-127° (7 mm) (according to [9], bp 118-123° (1 mm)); n_D^{20} 1.5240. Found: C 40.2; H 3.4; Cl 29.3; S 13.2%. $C_8H_8Cl_2O_2S$. Calculated: C 40.2; H 3.3; Cl 29.7; S 13.4%.

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SYNTHESIS AND SOME PROPERTIES OF AMIDES OF 4-CARBOXYMETHYL-2-THIOLENE 1,1-DIOXIDE

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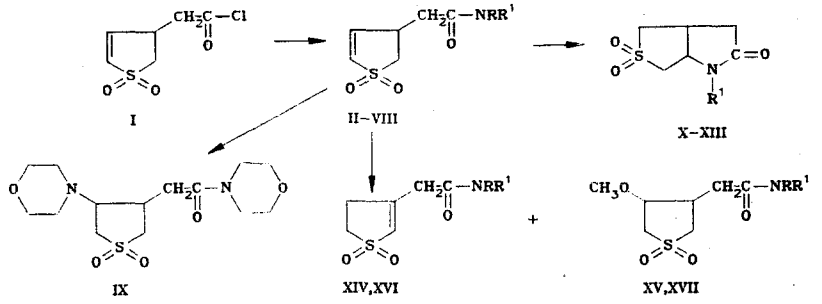
Amides of 4-carboxymethyl-2-thiolene 1,1-dioxide were obtained with aliphatic, heterocyclic, and aromatic amines. A study was carried out on the reactions of these amides with various nucleophilic reagents.

Actinonine analogs with a 1,1-dioxothiolane ring [1] and amides of thiolane 1,1-dioxide have been reported to have pesticide activity [2]. Amides of 4-carboxymethyl-2-thiolene 1,1-dioxide have not been described. We synthesized these compounds by the reaction of the acid chloride of the corresponding acid I, described in our previous work [3], with amines in 1:2 ratio at room temperature in acetone or dioxane solution.

Argyle et al. [4] have reported that the double bond in 2-thiolene 1,1-dioxides is active in nucleophilic addition, although acrylamines [5] and acid amides [6] add only with difficulty. However, as shown in our work, the intramolecular cyclization of N-alkyl- and aryl-amides of 4-carboxymethyl-2-thiolene 1,1-dioxide proceeds rather readily. Thus, a mixture of amides II-V and lactams X-XIII is formed upon reaction with ammonia, primary amines, aniline and p-substituted aniline derivatives (see Table 1). These lactams are the major reaction products if amides II-V are heated for 1 h in an equimolar amount of aqueous alkali.



II—V, XI—XV R=H; II, X, XIV, XV R^1=H; III, XI R^1=*t*-Bu; IV, XII R^1=Ph; V, XIII R^1=*p*-$CH_3C_6H_4$; VI R=R^1=Et; VII R—R^1=C_5H_{10}; VIII, IX, XVI, XVII R—R^1=C_4H_8O

Other addition reactions occur as readily: The reaction of I with excess morpholine leads to addition of the amine at the double bond of amide VIII to form sulfone IX, while heating amides II and VIII with sodium methylate gives both isomerization products XIV and XVI and addition products XV and XVII, as indicated by thin-layer chromatography.

Products XVI and XVII were identified by their thin-layer chromatographic R_f values. The position of the double bond in II-VIII was supported by the finding of a PMR signal for the two vicinal protons which form an AB quartet centered at 6.5-6.8 ppm, J_{AB} = 6.5-7.0 Hz. The complex multiplets with intensity 1H centered at 4.45, 4.65, 5.09, and 5.0 ppm in the PMR spectra of X-XIII were assigned to the proton at the carbon atom bound to the lactam ring nitrogen. The spectrum of X also has a broad NH proton singlet at 7.8 ppm. Of the two possible structures for amide XIV (3-thiolene or 2-thiolene 1,1-dioxide), the latter was as-

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