REACTIONS OF AROMATIC AND HETEROAROMATIC COMPOUNDS HAVING ELECTRON-ACCEPTOR SUBSTITUENTS

VII.* CHLOROMETHYLATION OF 2-ACETOTHIENONE AND 2-FORMYLTHIOPHENE IN SULFURIC ACID

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The chloromethylation of 2-acetothienone and 2-formylthiophene with α,α'-bischloromethyl ether in 60-100% sulfuric acid was studied. An increase in the acidity of the medium promotes the formation of 4-substituted products, which, as in nitration and bromination, is explained by protonation of the carbonyl group, leading to intensification of its electron-acceptor capacity.

In [1,2], we demonstrated that the protonation of the carbonyl group, by increasing its electron-acceptor capacity, makes it possible to change the specificity of such electrophilic substitution reactions of 2-acetothienone and 2-formylthiophene as bromination and nitration to favor the primary formation of 4-substituted products. Continuing our research in this direction, we have studied the chloromethylation of the same carbonyl compounds with α,α'-bischloromethyl ether (BCME) in sulfuric acid,† i.e., under the conditions that are often used for the chloromethylation of deactivated aromatic compounds [3,4].

As far as we know, the mechanism of this reaction has not been specially studied, but it can be assumed that it should have much in common with the mechanism of alkylation of aromatic compounds with simple ethers [5] and should include a step involving protonation of the ether at the oxygen atom (see [6,7] also):

$$(ClCH_2)_2O + H_2SO_4 \rightleftharpoons (ClCH_2)_2\overset{+}{O}H\ HSO_4$$

This step precedes cleavage of the C–O bond of the ether, during which a $\overset{+}{C}H_2Cl$ cation [7] can be formed; the cation apparently is not in a kinetically free state but in a transition complex and, in our opinion, is the true chloromethylating agent under the conditions under consideration. We note in this connection that the chloromethylation proceeds more readily when sulfuric acid is replaced by oleum [3,8] or by chlorosulfonic acid [8,9], i.e., by reagents that cleave BCME more readily than sulfuric acid [10]. The cleavage of BCME may lead to the formation of di(chloromethyl) sulfate, which, however, as we have shown, is not a chloromethylating agent under the conditions used.

An alternative mechanism for the chloromethylation, which we consider to be more probable when the reaction is carried out in the presence of $AlCl_3$ [11], provides for participation of the $\overset{+}{C}H_2OR$ cation with subsequent cleavage of the resulting ether of the benzyl type ($ArCH_2OR$, where R = CH_2Cl or CH_2Ar) by the action of HCl. This mechanism is scarcely realized in the catalysis of the reaction by sulfuric acid: the

*See [1] for communication VI.

† As we have shown, monochloromethyl ether can also be used in addition to BCME for the chloromethylation; when this is done, the character of the reaction product changes only slightly, but the yields in this case are substantially lower.

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TABLE 1. Results of the Chloromethylation of 2-Acetothienone and 2-Formylthiophene by α,α'-Bischloromethyl Ether in Sulfuric Acid

H_2SO_4 conc., wt.%	Molar ratio of BCME/ carbonyl compound	Comp. of chloromethylation prod., mole %			Overall yield, %	Degree of conversion of the carbonyl compound, %	4 Isomer : 5 isomer ratio
		4-	5-	4,5-bis-			
Chloromethylation of 2-acetothienone							
61,5	0,5	51	49	—	24	70	51 : 49
	1,0	39	41	20	53	92	49 : 51
70,1	0,5	58	38	4	31	77	60 : 40
	1,0	30	28	42	60	100	52 : 48
80,0	0,5	69	28	43	21	75	70 : 30
	1,0	34	20	46	62	100	63 : 37
92,6	0,5	71	21	8	28	69	77 : 23
	1,0	56	20	24	50	100	74 : 26
100,3	0,5	80	20	—	21	64	80 : 20
	1,0	67	18	15	45	88	79 : 21
Chloromethylation of 2-formylthiophene							
61,5	0,5	35	65	—	9	48	35 : 65
	1,0	33	50	17	50	92	40 : 60
70,1	0,5	44	50	6	13	74	47 : 53
	1,0	50	43	7	46	91	54 : 46
80,0	0,5	57	33	10	25	87	63 : 37
	1,0	27	18	55	57	100	60 : 40
92,6	0,5	74	19	7	15	72	80 : 20
	1,0	36	22	42	43	100	62 : 38
100,3	0,5	65	31	4	28	67	68 : 32
	1,0	34	31	35	59	92	52 : 48

TABLE 2. Reaction of Mixtures of 4- and 5-Chloromethyl-Substituted 2-Acetothienone and 2-Formylthiophene with α,α'-Bischloromethyl Ether in Sulfuric Acid (92 wt.% H_2SO_4)

Starting mixture		Molar ratio	Reaction products			$\frac{k_4}{k_5}$
4 isomer, %	5 isomer, %	BCME/ mixture	4 isomer recovered, %	5 isomer recovered, %	4,5-disubst. product, yield, %	
Mixture of 4- and 5-chloromethyl-2-formylthiophenes						
55	45	0,25	30	21	5	0,8
55	45	0,5	22	9	9	0,6
Mixture of 4- and 5-chloromethyl-2-acetothienones						
63	37	0,5	20	14	28	1,2

formation of the CH_2OR^+ cation, which requires cleavage of the C−Cl bond in BCME, is unlikely, since it is quite resistant to the action of sulfuric acid. Thus the C−Hal bond is not involved in the haloalkylation of aromatic compounds by halo olefins [12-14] and halo alcohols [15], for which sulfuric acid is a specific catalyst.

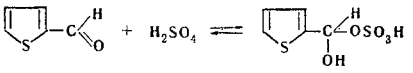
A peculiarity of the transformations that we studied, the results of which are presented in Table 1, is the fact that they do not cease with the formation of monosubstituted compounds: 4,5-bis(chloromethyl)-substituted products, as well as undistillable products, are formed in considerable amounts. The formation of the latter (their structures were not investigated) occurs even when 0.5 mole of BCME is used per mole of carbonyl compound, when a considerable portion of the starting aldehyde or ketone (from one-fourth to one-third) is recovered unchanged. Special experiments demonstrated that the starting carbonyl compounds and their monochloromethyl-substituted products are quite stable in concentrated sulfuric acid, and an undistillable residue is formed only in the presence of chloromethylating agent; i.e., it is a reaction product of the latter with the chloromethyl-substituted compounds. The reaction of a mixture of monochloromethyl-substituted compounds with unchanged 2-acetothienone proceeds to a considerable degree, and the ratio of the 4 and 5 isomers in the recovery is substantial and does not change as compared with the starting mixture.

Considering these facts, we carried out the comparative chloromethylation of mixtures of 4- and 5-chloromethyl-substituted products that were isolated by distillation of the reaction products. The results (see Table 2) demonstrated that the subsequent conversions of the 4 and 5 isomers proceed at approximately the same rate.* The k_4/k_5 values presented in Table 2 were calculated from the equation [17]

$$k_4/k_5 = \frac{\lg(c_4/c_4^0)}{\lg(c_5/c_5^0)},$$

where k_4 and k_5 are rate constants for the conversion, respectively, of the 4- and 5-chloromethyl-substituted compounds; c_4 and c_5 are the final concentrations, and c_4^0 and c_5^0 are the starting concentrations of the same isomers determined from their relative percentages in mixtures before and after the reaction.

Knowing the k_4/k_5 values, which, to a first approximation, can be considered to be equal to one on the basis of the data in Table 2, it is easy to judge the ratio of the monosubstituted products directly formed during chloromethylation from the relative amount of these isomers (see Table 1). The permissibility of this sort of assumption ($k_4/k_5 \approx 1$) is seen also from Table 1: reaction products with close ratios of 4- and 5-monochloromethyl-substituted compounds are obtained when 0.5 or 1 mole of BCME is used, i.e., for different degrees of conversion of the starting carbonyl compounds. The results of our experiments, which are presented in Table 1 (the mixtures were analyzed by PMR spectroscopy [11, 18], and the accuracy of the determination was 5%) demonstrate that the ratio of 4- and 5-chloromethyl-substituted products changes as the concentration increases to favor an increase in the percentage of the 4 isomers, similar to what is observed in the nitration [2] and bromination [1] of 2-acetothienone and 2-formylthiophene. An exception to this is the chloromethylation of 2-formylthiophene in 100% sulfuric acid, during which relatively more 5-substituted product is formed than in 90% acid. It seems to us that the reason for this may be the participation in the reaction not only of the protonated form of the aldehyde but also of molecules of some other type in which the electron-acceptor ability of the functional group is reduced, for example, through the addition of sulfuric acid to the C =O bond (see [19]):

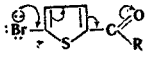


This sort of modification of the aldehyde group is perhaps one of the factors responsible for the relatively lesser formation of 4-substituted product in the chloromethylation of 2-formylthiophene as compared with that which occurs in the case of 2-acetothienone. No increase in the relative amount of the 5 isomer was observed during nitration on passing from 90 to 100% sulfuric acid [2]. This is possibly explained by the substantially lower rate of chloromethylation as compared with nitration; as a result, even a low concentration of the proposed less deactivated (in the protonated form) product of the addition of sulfuric acid to the aldehyde group could prove to be sufficient to increase the percentage of the 5-substituted isomer.

EXPERIMENTAL

Chloromethylation of 2-Formylthiophene and 2-Acetothienone. Bis(chloromethyl) ether (the molar ratios are indicated in Table 1) was added dropwise with stirring to a solution of 3 g of carbonyl compound in 25 ml of sulfuric acid at 0-2°. The reaction mass was allowed to stand for 24 h at room temperature and poured over ice, and the mixture was extracted with chloroform. The extract was washed with water,

*At first glance, this result contradicts our conclusion that 4-bromo-substituted 2-acetothienone and 2-formylthiophene are brominated considerably more rapidly that the 5 isomer [1]. However, one must bear in mind that, although both the $ClCH_2$ and bromine groups are substituents of the first order, their orienting effects are different in nature and are caused by a comparatively weak +I effect for the chloromethyl group and by a +M effect for the bromine group. In the case of 5-bromo-substituted compounds, the ortho-orienting effect of the bromine atom may be weakened due to conjugation with the carbonyl group; this does not occur in the 4 isomer:



We note that the orienting effect of bromine surpasses that of the acyl group: 2,5-dibromoacetophenone rather than 3,5-dibromoacetophenone is obtained by bromination of m-bromoacetophenone [16].

$NaHCO_3$ solution, water, and dried with $MgSO_4$. The solvent was removed by distillation, and the residue was vacuum-distilled at 45-180° (1-4 mm) with separation of the unchanged carbonyl compound.* The isolated mixture of mono- and bis(chloromethyl)-substituted products was analyzed by PMR spectroscopy (see Table 1).

Chloromethylation of 2-Acetothienone with Monochloromethyl Ether in 92.6% H_2SO_4. This reaction was carried out by the above method using 1 mole of ether per mole of ketone. The usual workup yielded a mixture of 4- and 5-chloromethyl-substituted and 4,5-bis(chloromethyl)-substituted products (70 : 26 : 4). The overall yield was 15%, and 77% of the 2-acetothienone was recovered.

Competitive Chloromethylation of 4- and 5-Chloromethyl-Substituted Compounds. This reaction was carried out in 92.6% H_2SO_4 as in the preceding experiments. The compositions of the starting mixtures and reaction products are presented in Table 2.

Transformations of 2-Acetothienone and Its Chloromethyl-Substituted Derivatives in Sulfuric Acid. A solution of 2.0 g (0.016 mole) of 2-acetothienone and 4.0 g (0.023 mole) of a mixture of 4- and 5-chloromethyl-2-acetothienones (the ratio of the 4 and 5 isomers was 1 : 1.5)† in 25 ml of 92.6% H_2SO_4 was held at 20° for 24 h. The usual workup yielded 1.38 g (69%) of unchanged 2-acetothienone and 3.85 g (84%) of a mixture of 4- and 5-chloromethyl-2-acetothienone in a ratio of 1 : 1.4. The weight of the undistillable residue was 0.45 g; repeated refluxing of it with heptane yielded 0.32 g of a mixture of isomeric diacetyldithienylmethanes (according to gas-liquid chromatography).

When the individual 2-acetothienone, 2-formylthiophene, and mixtures of their 4- and 5-chloromethyl-substituted derivatives were held for 24 h at 20° in 92.6% sulfuric acid, the recovery of the starting compound after the usual workup was 70-80%.

Reaction of 2-Acetothienone with Bis(chloromethyl) Sulfate. A solution of 3.0 g (0.024 mole) of 2-acetothienone and 4.65 g (0.024 mole) of bis(chloromethyl) sulfate [10] in 25 ml of 92.6% H_2SO_4 was held at 20° for 24 h. The usual workup yielded 5.8 g of a substance with bp 113-117° (25 mm) and n_D^{20} 1.5050, which was a mixture of 2-acetothienone and bis(chloromethyl) sulfate in a ratio of 10 : 9 (according to the refractive indexes); the recovery was 81 and 73%, respectively. The weight of undistillable residue was 0.75 g, and its composition was not investigated. No other reaction products were isolated.

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* There was virtually no recovery when one mole of BCME per mole of aldehyde or ketone was used.

† The mixture was obtained by chloromethylation of 2-acetothienone by the method in [20] (see [18]).

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