HYDROXY KETONES—PART XIII—FRIES REARRANGEMENT OF THE PHENYL ESTERS OF THIOPHENE-2-CARBOXYLIC ACID

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(*Received* 10 *January* 1970 ; *revised* 30 *July* 1971)

Fries migration of the esters of phenol, isomeric cresols and naphthols with thiophene-2-carboxylic acid has been investigated at 120° C and 160°C in absence of a solvent, with a view to study the behaviour of the sulphur atom in the thiophene ring towards an acid catalyst and its interference in the complex formation necessary for the migration. The isomeric ortho- and para-hydroxy ketones have been isolated employing chemical methods and each is characterised by the preparation of its 2 : 4-dinitrophenylhydrazone. The yields of the hydroxy ketones were poor and ranged from 4–8% in the case of para and from 9–18% in the case of ortho. Further, in all cases studied, above 50% of the ester was recovered unchanged. These suggest that the charge density at the sulphur atom is greater than at the phenoxyl oxygen atom as compared with similar migrations with the esters of furane-2-carboxylic acid where the yields of the hydroxy ketones were quite high and no unreacted ester was encountered.

Probably one of the earliest and certainly one of the most remarkable cases of chemical and physical isosterism came to light as compounds of thiophene were examined and it was shown that they had an intense similarity to those of benzene extending even to the odours of the aldehydes and mono-nitro compounds. Since these properties showed a certain degree of parallelism, it is not surprising that the comparative physiological properties of these compounds were examined.

Whilst thiophene itself had similar but rather more acute activity for mice, nitrothiophene has long been known[1] to give rise to toxic symptoms almost indistinguishable from those of nitrobenzene.

It would be easy to cite many instances where in so far as physiological action is concerned, the replacement of a benzene by a thiophene residue made very little difference[2]. Many examples of bio-isosterism between benzene and thiophene derivatives can be found among anaesthetics, antihistaminics, hypnotics, analgesics, anticonvulsants and many others.

In general it may be said that in the majority of cases the thiophene ring can replace the benzene ring without much alteration of the physiological activity. Apparently, exceptional cases are occasionally encountered such as the inability of thienylalanine[3,4] to take the place of phenyl alanine in nutrition.

It is well known that ketones in general possess narcotic properties and the hypnotic action is shown by mixed ketones and further that the entrance of a phenolic hydroxyl group or a chlorine atom into the ketonic compound produces a marked change in their physiological properties. Though only a few simple thiophene ketones[5-9] have been mentioned in literature, no work has so far been reported on the preparation and study of the physiological properties of the hydroxyphenylthienyl ketones.

In continuation of work[10] on the synthesis of hydroxy ketones, it was thought of interest to prepare some of these by the Fries migration of the phenyl esters of thiophene-2-carboxylic acid and reduce these by the Clemmensen method and evaluate the antibacterial properties of these hydroxy ketones as well as their reduced products[11].

The main object of this investigation was (*i*) to study the behaviour of the sulphur atom in the thiophene ring towards an acid catalyst (Aluminium Chloride) and its interference in the proposed formation of the complex necessary for the migration of the thienyl esters and to compare it with the observations already reported on the migrations of the phenyl esters of 2-furoic acid[12] and (*ii*) to prepare substituted aryl thienyl methanes obtainable by the reduction of the hydroxy aryl thienyl ketones.

Aluminium chloride is an acid catalyst and when a base (Bronsted concept) is brought in contact with it, it forms complexes. Thus in the case of simple esters the oxygen atoms of the ester act as base and form complexes which after fragmentation give rise to hydroxy ketones. In thienyl esters, there is another electron-donor position in the sulphur atom of the thiophene ring where a complex formation is also possible. When equimolecular quantities of the ester and aluminium chloride are used, complex formation may take place either with the oxygen atom of the ester or the sulphur atom of the thiophene ring depending upon the charge density of the two positions. If the charge density of the phenoxyl oxygen atom is great, normal Fries migration would take place, otherwise the thiophene ring would decompose and give different products. Experimental results indicate that the elctron density is greater at the sulphur atom than at the phenoxyl oxygen as the migration products were obtained in very low yields and in every reaction studied above 50 per cent of the unchanged ester was recovered unreacted. The observations reveal that the behaviour of the thiophene ring is quite different from that of the furan ring in this migration.

These migrations have been studied by heating the ester (1 mol) with anhydrous aluminium chloride (1·3 mol) in the absence of a solvent at 120°C and 160°C the ortho- and para-hydroxy ketones were separated by their solubility difference in aqueous sodium bicarbonate. It was observed that the yields of the hydroxy ketones were poor and ranged between 4–8% in the case of para and 9–18% in the case of ortho ; above 50% of the unreacted ester was also recovered in each reaction studied. All the hydroxy ketones have been characterised through their 2 : 4-dinitrophenylhydrazones.

Since the yields of the hydroxy aryl thienyl ketones were very poor, further work on their reduction could not be carried out.

EXPERIMENTAL PROCEDURE

Thiophene-2-carboxylic acid chloride

Thiophene-2-carboxylic acid (10 g) was refluxed with thionyl chloride (10 ml) on a water bath for 4 hours and after removing the unchanged thionyl chloride, pure acid chloride had b.p. 80°C/12 mm (lit. b.p. 208°C). (yield : 11 g ; 96·1%).

Preparation of esters

A mixture of thiophene-2-carboxylic acid chloride (1 mol) and phenol (1·1 mol) was shaken with excess of aqueous sodium hydroxide (10 per cent) and cooled. The separated ester was extracted with ether, the ethereal solution washed free of the phenol and finally

with water. After drying the ethereal solution, ether was stripped off and the liquid esters purified by distillation while the solid ones were crystallised; the phenol esters are listed out in Table 1.

TABLE 1

PHENOL ESTERS

Phenol esters	b.p./m.p. (°C)	Yield (%)	Formula	Percentage found		Percentage required	
				C	H	C	H
Phenyl thiophene-2′-carboxylate	54	65	$C_{11}H_8O_2S$	64·6	3·8	64·7	3·9
2-Methyl phenyl thiophene-2′-carboxylate	180–1/11mm	53·5	$C_{12}H_{10}O_2S$	65·9	4·4	66·0	4·5
3-Methyl phenyl thiophene-2′-carboxylate	61	72	$C_{12}H_{10}O_2S$	66·0	4·5	66·0	4·5
4-Methyl phenyl thiophene-2′-carboxylate	91–2	76	$C_{12}H_{10}O_2S$	65·8	4·5	66·0	4·5
1-Naphthyl thiophene-2′-carboxylate	275/7 mm*	52	$C_{15}H_{10}O_2S$	70·6	3·8	70·9	3·9
2-Naphthyl thiophene-2′-carboxylate	112	63	$C_{15}H_{10}O_2S$	70·8	3·9	70·9	3·9

*Lit. m.p. 80°C.

Fries migration of the esters and the isolation of the hydroxy ketones

Phenyl thiophene-2-carboxylate :—(2·0 g) at 120°C gave :

(*a*) 2-Hydroxyphenyl-2′-thienyl ketone, b.p. 175–6°C/10 mm.

(yield : 0·2 g ; 10%).

(found : C=64·6% ; H=3·8%. $C_{11}H_8O_2S$ requires C=64·7% ; H=3·9%).

It gave a violet colour with ferric chloride ; its 2 ; 4-dinitrophenylhydrazone had m.p. 200°C.

(found : N=14·4%. $C_{17}H_{12}O_5N_4S$ (requires N=14·6%).

(*b*) 4-Hydroxyphenyl-2′-thienyl ketone, m.p. 111°C.

(yield : 0·1 g ; 5%).

(found : C=64·7%, H=3·8%. $C_{11}H_8O_2S$ requires C=64·7% ; H=3·9%).

It gave no colouration with ferric chloride ; its 2 : 4-dinitrophenylhydrazone had m.p. 194°C.

(found : N=14·3%. $C_{17}H_{12}O_5N_4S$ requires N=14·6%), and

(*c*) Unchanged ester (1·0 g).

Migration of the ester (2·0 g) at 160°C gave 0·31 g of the hydroxy ketone (*a*), 0·1 g of the hydroxy ketone (*b*) and 1·4 g of the unchanged ester.

2-*Methylphenyl thiophene-2′-carboxylate* :—(2·2 g) at 120°C gave :

(*a*) 2-Hydroxy 3-methylphenyl-2′-thienyl ketone, m.p. 162°C.

(yield : 0·2 g ; 9·1%).

(found : C=65·9% ; H=4·5%. $C_{12}H_{10}O_2S$ requires C=66·0% ; H=4·5%).

It gave a violet colour with ferric chloride ; its 2 : 4-dinitrophenylhydrazone had m.p. 208°C.

(found : N=13·9%. $C_{18}H_{14}O_5N_4S$ requires N=14·0%).

(*b*) 4-Hydroxy-3-methylphenyl-2′-thienyl ketone, m.p. 151°C.

(yield : 0·1 g ; 4·51%).

(found : C=66·0% ; H=4·4%. $C_{12}H_{10}O_2S$ requires C=66·0% ; H=4·5%).

It gave no colouration with ferric chloride, its 2 : 4-dinitrophenylhydrazone had m.p. 211°C.

(found : N=14·1%. $C_{18}H_{14}O_5N_4S$ requires N=14·0%, and

(*c*) Unchanged ester : (1·0 g).

Migration of the ester (2·2 g) at 160°C yielded the hydroxy ketone (*a*) 0·2 g and the hydroxy ketone (*b*) 0·1 g and 0·8 g of the unchanged ester.

3-*Methylphenyl thiophene-2′-carboxylate* :—(2·2 g) at 120°C furnished :

(*a*) 2-Hydroxy-6-methyl or 2-hydroxy 4-methylphenyl-2′-thienyl ketone, b.p. 140°C/4 mm.

(yield : 0·2 g ; 0·09%).

(found : C=65·9% ; H=4·5%. $C_{12}H_{10}O_2S$ requires C=66·0% ; H=4·5).

It gave a violet colouration with ferric chloride and a 2 : 4-dinitrophenylhydrazone, m.p. 176°C.

(found : N=14·0%. $C_{18}H_{14}O_5N_4S$ requires N=14.0%).

(*b*) 4-Hydroxy-2-methylphenyl-2′-thienyl ketone, b.p. 220°C/6 mm.

(yield : 0·13 g ; 5·4%).

(found : C=66·0% ; H=4·4%. $C_{12}H_{10}O_2S$ requires C=66·0% ; H=4·5%).

It gave no colouration with ferric chloride ; its 2 : 4 dinitrophenylhydrazone had m.p. 172°C.

(found : N=14·1%. $C_{18}H_{14}O_5N_4S$ requires N=14·0%), and

(*c*) Unchanged ester (1·0 g).

Migration of the ester (2·2 g) at 160°C gave the hydroxy ketone (*a*) 0·24 g, the hydroxy ketone (*b*) 0·1 g and 1·2 g of the unchanged ester.

4-*Methylphenyl thiophene-2′-carboxylate* :— (2·2 g) at 120°C gave :

(*a*) 2-Hydroxy-5-methylphenyl-2′-thienyl ketone, b.p. 182–3°C/8 mm.

(yield : 0·4 g ; 18·18%).

(found : C=65·9% ; H=4·5%. $C_{12}H_{10}O_2S$ requires C=66·0% ; H=4·5%).

It gave a violet colouration with ferric chloride and a 2 : 4-dinitrophenylhydrazone m.p. 197°C.

(found : N=13·9%. $C_{18}H_{14}O_5N_4S$ requires N=14·0%), and

(*b*) Unchanged ester (1·4 g).

Migration of the ester (2·2 g) at 160°C gave the hydroxy ketone (*a*) 0·2 g and 1·0 g of the unchanged ester.

1-*Naphthyl thiophene-2'-carboxylate* :—(2·5 g) at 120°C yielded :

(*a*) 1-Hydroxy-2-naphthyl-2'-thienyl ketone, m.p. 107°C.

(yield : 0·2 g ; 8·0%).

(found : C=70·2% ; H=3·7%. $C_{15}H_{10}O_2S$ requires C=70·9% ; H=3·9%).

It gave a violet colouration with ferric chloride and a 2 : 4-dinitrophenylhydrazone, m.p. 198°C.

(found : N=12·8%. $C_{21}H_{14}O_5N_4S$ requires N=12·9%).

(*b*) 1-Hydroxy-4-naphthyl-2'-thienyl ketone, m.p. 101°C.

(yield : 0·1 g ; 4·0%).

(found : C=70·4% ; H=3·8%. $C_{15}H_{10}O_2S$ requires, C=70·9% ; H=3·9%).

It gave no colouration with ferric chloride and its 2 : 4-dinitrophenylhydrazone had m.p. 205°C.

(found : N=13·0% ; $C_{21}H_{14}O_5N_4S$ requires N=12·9%), and

(*c*) Unchanged ester (1·4 g).

Migration of the ester (2·5 g) at 160°C gave the hydroxy ketone (*a*) 0·3 g, the hydroxy ketone (*b*) 0·1 g and 1·2 g of the unchanged ester.

2-*Naphthyl thiophene-2'-carboxylate* :—(2·5 g) on migration at 120°C gave :

(*a*) 2-Hydroxy-1-naphthyl-2'-thienyl ketone, b.p. 218°C/7 mm.

(yield : 0·25 g ; 10·0%).

(found : C=70·6% ; H=3·8%. $C_{15}H_{10}O_2S$ requires C=70·9% ; H=3·9%).

It gave a violet colouration with ferric chloride and a 2 : 4-dinitrophenylhydrazone, m.p. 206°C.

(found : N=12·7%. $C_{21}H_{14}O_5N_4S$ requires N=12·9%).

(*b*) 2-Hydroxy-6-naphthyl-2'-thienyl ketone, b.p. 194°C/7 mm.

(yield : 0·1 g ; 4·0%).

(found : C=70·7% ; H=3·7%. $C_{15}H_{10}O_2S$ requires C=70·9% ; H=3·9%).

It gave no colouration with ferric chloride and its 2 : 4-dinitrophenylhydrazone had m.p. 215°C.

(found : N=12·8%. $C_{21}H_{14}O_5N_4S$ requires N=12·9%), and

(*c*) Unchanged ester (1·0 g).

Migration of the ester (2·5 g) at 160°C furnished the hydroxy ketone (*a*) 0·2 g, the hydroxy ketone (*b*) 0·1 g and 1·0 g of the unchanged ester.

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