Bromination of Alkyl Thienyl Ketones

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Abstract

Full Text

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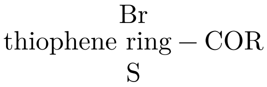
In 1959 we showed (^{1}) that, when bromine acts on 2-acetothienone in the presence of 2.5 moles of anhydrous aluminum chloride without solvent, bromine enters not the side chain, as usually occurs in the bromination of this and other similar aromatic ketones (^{2,3}), but position 4 of the thiophene nucleus. The role of the excess aluminum chloride is probably reduced to blocking the acyl group through formation of a complex with the ketone. In this connection it was of interest to investigate, under similar conditions, the bromination of higher ketones of the thiophene series, both normal and iso-structured, since in such cases, owing to steric or other factors, the complexes might either not form or prove to be insufficiently stable.

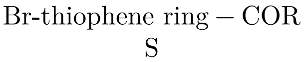
Before the appearance of the work of Pearson and Pope (^{4}), who succeeded in introducing halogen into the aromatic ring of acetophenone and of certain other aromatic ketones and aldehydes by their direct halogenation, the literature contained no indications of the possibility of replacing hydrogen of the ring by halogen in simple aromatic ketones containing groups of lower activating power than NH_2 or OH. Thus Buu-Hoï and co-workers (^{5,6}), using aqueous acetic acid as the medium, carried out bromination of *o*- and *p*-oxyacetophenone and certain of their homologs in the ring. If aqueous acetic acid is replaced by anhydrous acid, substitution by bromine in the indicated ketones takes place in the side chain.

In the present investigation it is shown that the homologs of 2-acetothienone—2-propiothienone, 2-*n*-butyrothienone, 2-isobutyrothienone, and 2-isovalerothienone—in the presence of 2.5 moles of aluminum chloride, without solvent, like 2-acetothienone, are brominated only in the ring, forming 4-bromo-2-acylthiophenes (I). The corresponding 5-bromoketones were not isolated from the reaction products.



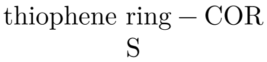
$\underset{\text{S}}{\overset{\text{Br}}{\text{thiophene ring}}} - \text{COR}$

(I)



$\underset{\text{S}}{\text{Br-thiophene ring}} - \text{COR}$

(II)



$\underset{\text{S}}{\text{thiophene ring}} - \text{COR}$

(III)

a) $R = \mathrm{C_2H_5}$		a) $R = \mathrm{CHBrCH_3}$
b) $R = n\text{-}\mathrm{C_3H_7}$	b) $R = n\text{-}\mathrm{C_3H_7}$	b) $R = \mathrm{CHBrCH_2CH_3}$
c) $R = iso\text{-}\mathrm{C_3H_7}$	c) $R = iso\text{-}\mathrm{C_3H_7}$	c) $R = \mathrm{CBr(CH_3)_2}$
d) $R = iso\text{-}\mathrm{C_4H_9}$	d) $R = iso\text{-}\mathrm{C_4H_9}$	d) $R = \mathrm{CHBrCH_2CH(CH_3)_2}$

The basis for the conclusion that bromine is absent from the side chain of I is the fact that they give neither a precipitate nor turbidity with an alcoholic solution of silver nitrate. The presence of bromine in the 4-position of the ring was confirmed for Ia by oxidizing it to 4-bromo-2-thiophenecarboxylic acid, and for the remaining bromoketones (it was not possible to oxidize them in satisfactory yield) by the noncoincidence of their constants and of the constants of the 2,4-dinitrophenylhydrazones formed by them with the constants of 5-bromo-2-acylthiophenes (II) synthesized by acylation of 2-bromothiophene, and of their 2,4-dinitrophenylhydrazones.

As is known, 2-acetothienone in the presence of catalysts (^{2}) is brominated in the side chain. By analogy, one might have expected that other ketones of the thiophene series, differing from it by a longer straight or branched chain, would interact with bromine in exactly the same way in the presence of catalytic amounts of aluminum chloride. However, examination of the literature data concerning higher aromatic ketones shows that the oxy derivatives of the latter (4-oxystearophenone, respropiophenone, 2- and 4-acetyl-1-naphthols) (^{6}) are brominated only in the nucleus, even in the absence of catalysts of the $AlCl_3$ type, which, as is known, is a catalyst for nuclear bromination (^{7}). In connection with these considerations it became obvious that the question of the direction of the bromination process for higher ketones of the thiophene series could not be decided in advance, since thiophene, in its activity in electrophilic substitution reactions—for example, acylation (^{8})—is close to certain activated benzene derivatives, for example anisole. To verify this, four of the above-mentioned ketones of the thiophene series were brominated by the known method for obtaining phenacyl bromide (^{9}), in the presence of catalytic amounts of aluminum chloride in dry ether. The results of bromination showed that these ketones, like 2-acetothienone, are brominated in the side chain, forming 2-α-bromoacylthiophenes (III), which, through thienylacylpyridinium bromides, were oxidized to 2-thiophenecarboxylic acid.

Experimental Part

Bromination of ketones in the nucleus in the presence of an excess of aluminum chloride. To 16.6 g (0.125 mole) of $AlCl_3$, with stirring for 5 min, 0.05 mole of ketone was added dropwise. Into the resulting liquid complex, at 30–40° over 10 min, 2.8 ml (0.055 mole) of bromine was added dropwise; after 2 h of stirring the mass was worked up as described previously (^{1}). The residue after distilling off the ether was twice distilled in vacuo. The results of the bromination and the properties of the 4-bromoketones obtained are presented in Table 1.

Table 1

Bromination of ketones in the nucleus

Bromination product	Yield, %	B.p., °C/mm	n_D^{20}	Calculated, % C	Calculated, % H	Found, % C	Found, % H	2,4-Dinitrophenylhydrazones m.p., °C	Calculated N, %	Found N, %
1a	46.1	130-132°/9*	–	38.37	3.22	38.47 38.21	3.18 3.10	222-223**	14.04	14.26 14.27
1b	47.1	144-144.5°/11	1.5765	41.21	3.89	41.61 41.74	4.10 4.22	201-201.5	13.55	13.34 13.54
1c***	61.2	127-129°/8	1.5751	41.21	3.89	41.11 40.93	3.95 3.72	202.5-203	13.55	13.46 13.21
1d	43.2	114-114.5°/4	1.5649	43.72	4.46	43.84 44.17	4.18 4.42	217-218	13.11	13.28 13.09

* M.p. 41-41.5° (from hexane).
** Semicarbazone, m.p. 188.5-189.5° (from alcohol). Found, %: N 14.95, 14.81; $C_8H_{10}BrN_3OS$; calculated, %: N 15.16.
*** A little dibromide was also isolated, m.p. 60-61° (from hexane). Found, %: C 30.90; 31.09; H 2.62; 2.69; $C_8H_8Br_2OS$; calculated, %: C 30.79; H 2.58.

Oxidation of 4-bromo-2-propiothienone (^{10}). To a solution of sodium hypochlorite (from 4.4 g of $NaOH$ in 6 ml of water, 25 g of ice, and 3.2 g of chlorine) at 68°, 2.2 g of bromoketone was added, the mixture was cooled to 25°, and 2 ml of sodium bisulfite solution was added to it. Neutral ···

tral substances, the aqueous layer was acidified, and the separated oil was extracted with ether. The extracts were dried over $CaCl_2$. After removal of the ether, the residue gave 1.83 g (yield 87.8%) of 4-bromo-2-thiophenecarboxylic acid, which after three recrystallizations from water melted at 120.5-121° (literature data (⌒11), mp 122-123.5°) and gave no depression on mixed melting with the acid obtained by oxidation of 4-bromo-2-acetothienone (⌒1).

Bromination of ketones in the side chain (⌒9). To a solution of 0.05 mole of ketone and 0.06 g of $AlCl_3$ in 10-15 ml of absolute ether, 2.55 ml (0.05 mole) of bromine was added dropwise.

Table 2

Bromination of ketones in the side chain and their oxidation

Bromination product	Yield, %	Bp, °C/mm	n_D^{20}	Calculated, % C	Calculated, % H	Calculated, % Br	Found, % C	Found, % H	Found, % Br total	Found, % Br in side chain	Acid yield, %
IIIa*	94.5	140–142°/14	1.6022	38.37	3.22	36.48	37.79 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]
IIIb	76.8	124–124.5°/4	1.5878	41.21	3.89	34.28	41.28 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]
IIIv	42.6	130–131°/10	1.5830	41.21	3.89	34.28	41.20 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]
IIIg	42.6	129–131°/4	1.5797	43.72	4.46	32.32	43.42 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* Lacrimator!

In the case of propiothienone the color of bromine disappeared immediately as it was added; for decolorization of solutions of ketones of higher molecular weight, more prolonged stirring was required, and in the case of isovalerothienone, gentle heating. After decolorization, the solution was stirred for 40–90 min, and, with slight dilution, ether and HBr were distilled off; the residue was distilled twice in vacuum.

Table 3

Acylation of 2-bromothiophene

Acylation product	Yield, %	Bp, °C/mm	n_D^{20}	Calculated, % C	Calculated, % H	Found, % C	Found, % H	2,4-Dinitrophenylhydrazone mp, °C	2,4-Dinitrophenylhydrazone calculated N, %	2,4-Dinitrophenylhydrazone found N, %
IIb	62.8	147–150°/12*	–	41.21	3.89	–	–	185.5–186.5	13.55	13.37 13.40
IIv	64.6	128.5–129.5°/8	1.5762	41.21	3.89	41.43 [illegible]	[illegible]	165–168**	13.55	13.52 13.52
IIg	69.5	149–150°/13	1.5672	43.72	4.46	43.87 43.85	4.50 4.45	176–177	13.11	12.98 13.11

* Mp 36–37° (from alcohol); literature data (^14), bp 155°/13 mm, mp 38–39°.
** Sintering begins at ~128°.

The halogen in the side chain was determined by boiling the bromoketone with alcoholic alkali, followed by titration according to Volhard. The results of bromination and the properties of the α-bromoketones obtained are presented in Table 2.

2-Thiophenecarboxylic acid from bromoketones III (ˆ12). A mixture of 0.5 g of bromoketone and 3–5 ml of dry pyridine was heated on a boiling water bath for 30 min. The pyridine was completely distilled off in vacuum. To the residue of the pyridinium salt, which was a brown glass-

···resinous mass (in the case of thienylpropionylpyridinium bromide—very hygroscopic crystals), a solution of 1 g of NaOH in 40 ml of water and 15 ml of alcohol was added. The resulting solution was heated on a boiling water bath for 15 min, acidified, and extracted with ether. From the extract the acid was removed with a soda solution and then with water; the alkaline extract was acidified and again extracted with ether. The 2-thiophenecarboxylic acid obtained after removal of the solvent was weighed, recrystallized from water, and had a melting point of 128-129° (literature data [10]: m.p. 129-130°). The yields of the acid are presented in Table 2.

5-Bromo-2-thienyl ketones were obtained by acylating 0.05 mole of 2-bromothiophene with 0.055 mole of the acid chloride of the corresponding acid in dry benzene in the presence of 0.05 mole of $SnCl_4$ [13]. The results of the acylation and the properties of the 5-bromoketones obtained are presented in Table 3.

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Note: Figure translations are in progress. See original paper for figures.