RADICAL BROMINATION OF METHYL 2,5-DIMETHYL-3-THIOPHENECARBOXYLATE*

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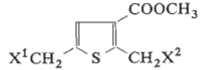
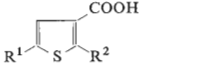
In connection with considerations on different electron interactions between methyl groups and the carboxylic function, the radical bromination of methyl 2,5-dimethyl-3-thiophenecarboxylate (*I*) was observed to afford the two monobromomethyl derivatives in the ratio of 1·21 : 1 in favour of the bromo derivative with the substituted 5-methyl group; this ratio is almost identical with that obtained with the furan analogue of *I*.

In an earlier paper[1] some observations have been reported concerning the selectivity in the radical bromination of methyl groups in methyl 2,5-dimethyl-3-furoate by the action of N-bromosuccinimide. In accordance with findings on the radical bromination of methyl groups at the double bond (unfavourable effect of substituents of a -I, -M character), the methyl group of a lower interaction with the carboxylic group was preferentially brominated. Notwithstanding, the ratio of the 5-bromomethyl derivative to the 2-bromomethyl derivative (1·20 : 1) does not allow to use this bromonation on a preparative scale.



I; $X^1 = X^2 = H$
II; $X^1 = Br$, $X^2 = H$
III; $X^1 = H$, $X^2 = Br$



IV; $R^1 = R^2 = CH_3$
V; $R^1 = H$, $R^2 = CH_3$
VI; $R^1 = CH_3$, $R^2 = H$
VII; $R^1 = R^2 = H$

It was of interest to compare the results obtained in the furan series with the radical bromination of the analogous thiophene derivative, namely, methyl 2,5-dimethyl-3-thiophenecarboxylate (*I*). In this reaction, compounds *II* and *III* may be considered as possible products. To estimate the degree of interaction, dissociation constants of some model compounds have been measured (Table I). As expected, the presence

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of methyl groups leads to increased pK values. Since the methyl group at position 2 shows a higher interaction with the carboxylic group, a decreased reactivity towards the radical bromination of this methyl group may be assumed. The shift of ν(C=O) values in infrared spectra of methyl esters of acids *IV*–*VII* corresponds to the acidity measurements. The doublet occurring with the 2-methyl substituted acids may be ascribed to steric effects. The reactivity of methyl groups in radical brominations of similar compounds is however hardly lowered by steric effects. Thus, the radical bromination of esters of β,β'-dimethylacrylic acid, substituted at the α-position by various substituents, may be effected on both methyl groups even in the case of the sterically hindered α-bromo derivative[2].

TABLE I
Dissociation Constants of Model Compounds

Acid	pK_a^a	Methyl ester, ν(C=O) cm^{-1}
IV	5·05	1 721, 1 711
V	4·75	1 717[b]
VI	4·45	1 723
VII	4·35	1 724

[a] Determined potenciometrically in 1 : 1 (v/v) aqueous ethanol as apparent constants; [b] quasi-doublet.

The methyl ester *I* was brominated with one equivalent of N-bromosuccinimide in tetrachloromethane and in the presence of dibenzoyl peroxide. The reaction product could be examined by means of NMR spectroscopy without any previous separation of the particular bromo derivatives. The spectrum shows the presence of compounds *II* and *III*. The lower field methyl group signal is attributable to compound *II* because of the deshielding effect of the vicinal carboxylic group. The higher field methyl group signal forms a doublet of the coupling constant[4] $J \approx 1$ Hz and is ascribed to compound *III*. This assignment is analogous to that with senecic acid[3] and β-crotonates[4] (*cis*-methyl with respect to the carboxyl). By the action of methanolic sodium methoxide, the crude reaction product was converted into the stable methoxy derivatives. The ratio of compound *II* to compound *III* is on the basis of intensity integration of the corresponding signals equal to 1·21 : 1, *i.e.*, almost identical to that of the furan series. Consequently, the reaction examined is not influenced by the nature of the heteroatom.

EXPERIMENTAL

Melting points and boiling points were not corrected. Analytical solid samples were dried at 20°C/0·5 Torr for 8 h.

Methyl 2,5-Dimethyl-3-thiophenecarboxylate (*I*)

2,5-Dimethyl-3-acetylthiophene[5] was converted by the Lieben reaction to 2,5-dimethyl-3-thiophenecarboxylic acid (*IV*), m.p. 117—118°C (reported[6], m.p. 119—120°C). Esterification of *IV* with ethereal diazomethane afforded in 80% yield the methyl ester *I*, b.p. 108°C/8 Torr. For $C_8H_{10}O_2S$ (170·2) calculated: 56·44% C, 5·92% H, 18·84% S; found: 56·53% C, 6·03% H, 18·61% S.

3-Bromo-2-methylthiophene

To a suspension of zinc dust (28·7 g; 0·44 mol) in water (66 ml) there was added dropwise with stirring 25·7 ml of acetic acid and the mixture was heated to the reflux temperature. 3,5-Dibromo--2-methylthiophene[7] (75 g; 0·42 mol) was then added, the whole refluxed for 90 min, kept at room temperature for one day, refluxed again additional 1 h, and steam-distilled. The distillate was neutralised with potassium carbonate, extracted with ether, the extract dried over anhydrous sodium sulfate, evaporated, and the residue distilled to afford 27·65 g of the title compound, b.p. 117—130°C/120 Torr. For C_5H_5BrS (177·1) calculated: 33·91% C, 2·85% H, 45·13% Br, 18·11% S; found: 33·70% C, 2·83% H, 46·68% Br, 17·90% S.

3-Cyano-2-methylthiophene

To a refluxing mixture of quinoline (54 ml) and cuprous cyanide (10·8 g; 0·12 mol) there was added dropwise over 15 minutes 3-bromo-2-methylthiophene, the whole refluxed for 3 h, and distilled. The distillate was diluted with ether, poured onto ice and water, and adjusted with hydrochloric acid to pH 3. The organic layer was separated and the aqueous layer was extracted with ether. The organic phases were combined, dried over anhydrous sodium sulfate, and evaporated. Distillation of the residue under diminished pressure afforded 10·9 g (88·7%) of 3-cyano--2-methylthiophene, b.p. 98—102°C/13 Torr. For C_6H_5NS (123·1) calculated: 58·80% C, 4·00% H, 11·37% N, 26·03% S; found: 58·30% C, 4·25% H, 11·33% N, 26·97% S.

2-Methyl-3-thiophenecarboxylic Acid (*V*)

To a refluxing solution of potassium hydroxide (9·4 g; 0·17 mol) in water (38 ml), there was added portionwise 3-cyano-2-methyl-thiophene (7 g; 57 mmol). The heterogeneous mixture was then refluxed for 6 h, allowed to cool, and washed with ether to remove the unhydrolysable portion. The alkaline aqueous layer was acidified with hydrochloric acid to Congo Paper, the acid *V* dissolved in ether, and the aqueous layer extracted with ether. The ethereal phases were combined, dried over anhydrous sodium sulfate, and evaporated to afford 7·8 g (96%) of compound *V*, m.p. 116—117°C (water). For $C_6H_6O_2S$ (124·2) calculated: 50·67% C, 4·25% H, 22·55% S; found: 50·91% C, 4·31% H, 22·14% S.

Methyl ester, b.p. 87°C/12 Torr, was prepared in 87% yield by esterification of the acid *V* with ethereal diazomethane. For $C_7H_8O_2S$ (156·2) calculated: 53·83% C, 5·16% H, 20·52% S; found: 53·66% C, 5·50% H, 20·81% S.

Bromination of Methyl 2,5-Dimethyl-3-thiophenecarboxylic Acid (*I*)

Dibenzoyl peroxide (0·16 g) was added to a mixture of the ester *I* (4·68 g; 30 mmol), N-bromosuccinimide (5·88 g; 33 mmol), and tetrachloromethane (60 ml), the whole heated on a steam bath for 90 min, and allowed to cool. The succinimide was filtered off, the filtrate washed with cold aqueous sodium hydroxide and water, dried over anhydrous calcium chloride, filtered, and the filtrate evaporated under diminished pressure. The crude residue was examined in $CDCl_3$ by means of NMR. Compound *II* (p.p.m.): 7·36 (s), 1 H, CH=C; 4·60 (s), 2 H, $BrCH_2$; 3·80 (s), 3 H, $COOCH_3$; 2·66 (s), 3 H, C=C.CH_3. Compound *III* (p.p.m.): 7·03 (s), 1 H, CH=C; 5·03 (s), 2 H, $BrCH_2$; 3·84 (s), 3 H, $COOCH_3$; 2·39 (d) ($J \approx 1$ Hz), 3 H, C=C.CH_3.

To a solution of the product (2·6 g; 10·4 mmol) in several ml of methanol there was added dropwise methanolic sodium methoxide (prepared from 0·265 g of sodium and 5 ml of methanol), the whole refluxed for 1 h, evaporated, the residue diluted with water to dissolve the inorganic salts, and extracted with ether. The ethereal extracts were combined, dried over anhydrous sodium sulfate, evaporated, and the residue distilled to afford 1·13 g (53·8%) of the methoxy derivatives, b.p. 70–80°C/0·3 Torr. For $C_9H_{12}O_3S$ (200·3) calculated: 53·98% C, 6·04% H, 16·01% S, 30·99% OCH_3; found: 54·42% C, 6·22% H, 16·10% S, 29·83% OCH_3.

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