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RADICAL BROMINATION OF METHYL 2,5-DIMETHYL-3-FUROATE

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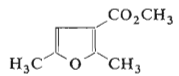
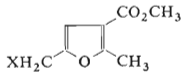
The ratio of monobromomethyl derivatives after the bromination of the methyl groups in methyl 2,5-dimethyl-3-furoate is 1·20 : 1 in favour of the bromoderivative substituted in the 5-methyl group. The result is discussed in connection with the electronic interaction of the methyl groups with the carboxyl group.

For radical bromination, in furan series, of the methyl group on the double bond with N-bromosuccinimide (Wohl–Ziegler reaction) a number of examples was described. From the results of the bromination of 2,5-dimethylfuran[1] affording with one equivalent of N-bromosuccinimide exclusively 5-bromo-methyl-2-methylfuran, when no formation of at least bis-bromomethyl derivative has been observed, it can be judged that the presence of methyl and the bromomethyl groups has different effects on the course of the bromination of the second methyl group. The favourable effect of the methyl group in this reaction may be documented in the case of the crotonic acid ester the methyl group of which is brominated more slowly than in the case of its α-methyl or β-methyl derivative[2,3]. As for the conformation of the effect of the methyl and bromomethyl groups on the bromination course, a study of the bromination possibility of both methyl groups of α-substituted esters of β-methylcrotonic acids[4] is very illustrative. In the presence of substituents of −M type the bromination ability of the second methyl group is distinctly decreased in comparison with the original senecioic acid ester; this may be interpreted by the loss of the positive effect of the methyl group after its substitution with bromine group.

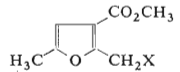
The object of this study is radical bromination of methyl 2,5-dimethyl-3-furoate (*I*) to bromo derivative *II* and *III*. We consider this substance as a suitable model in which present day knowledge on the unfavourable effect of −M substituents affecting the brominated propenyl group[5] may be checked on the basis of the different positions of the methyl groups with respect to the carboxyl group.



I



II, X = Br
IV, X = OCH_3



III, X = Br
V, X = OCH_3

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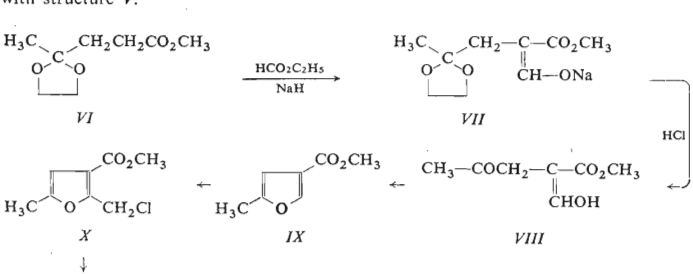
The study of UV spectra[6] disclosed in the methyl ester of 3-furoic acid a larger interaction of the π-electrons of the methoxycarbonyl group with position 2 than with position 5. In connection with this we also measured the IR spectra of 2- and/or 5-methyl derivatives of the methyl ester of 3-furoic acid, from which it follows that the interaction of the ester function with methyls in position 2 is clearly greater than with those in position 5 (ν(C=O); methyl 3-furoate 1740; 5-methyl derivative 1732; 2-methyl 1728, 2,5-dimethyl 1724 cm^{-1}). With a similar model, such as the ester of senecioic acid, it was observed that sterical effects were not as important[4] and that it can be supposed that the formation of derivative *III* will not be substantially affected either. However, from the data mentioned it may be expected that in *I* the methyl group in position 5 will be brominated preferentially.

In view of the instability of bromomethyl derivatives of this type the reaction of substances formed with sodium methoxide was studied in order to determine the structure of products in the form of their stable derivatives. In this context we synthetised as standards substances *IV* and *V*. Methyl 2-methyl-5-methoxymethyl-3-furoate (*IV*) was obtained on reaction of methyl 2-methyl-5-chloromethylfuroate with sodium methoxide. The chloromethyl derivative used was prepared by a modification of the procedure used by Winberg and coworkers[7] who used the corresponding ethyl ester. Methyl 5-methyl-2-methoxymethyl-3-furoate (*V*) was synthetised by a sequence of reactions starting from methyl 5-methyl-3-furoate (*IX*) (Scheme 1). The latter was prepared according to a known method[8] which was modified by protecting the keto group in the starting ethyl levulinate with ethylene glycol instead of ethyl orthoformate. Chloromethylation of compound *IX* gave methyl 5-methyl-2-chloromethyl-3-furoate (*X*) in 54% yield. This result is considered as characteristic of the furane series where the presence of a group of −I, −M character does not prevent the electrophilic substitution in the vicinal position relative to this function. From substance *X* it was impossible to obtain the pure compound *V*; however, mass spectrographic data of the main peak in gas chromatography agree with structure *V*.



VI *VII* *VIII* *IX* *X* *V*

SCHEME 1

Substance *I* necessary for the study of radical bromination was prepared from ethyl acetonylacetoacetate the dehydration of which gave ethyl 2,5-dimethyl-4-furoate[9]. We found that the use of *p*-toluenesulfonic acid instead of sulphuric acid affords higher yields. The ethyl ester obtained was hydrolysed with alkali and the liberated acid was esterified with methanolic hydrogen chloride to methyl ester *I*.

Bromination of compound *I* was carried out using one equivalent of N-bromosuccinimide in tetrachloromethane in the presence of dibenzoyl peroxide. After working up the reaction mixture and distilling off the solvent the product was investigated by means of NMR spectroscopy without previous separation of single bromomethyl derivatives. The spectrum shows the presence of two monobromo derivatives; compound *II* : 2·57 p.p.m. (s), 3 H, C=C.CH_3; 3·80 (s), 3 H, $COOCH_3$; 4·42 (s), 2 H, $BrCH_2$; 6·62 (s), 1 H, CH=C; compound *III*: 2·29 (d), $^4J \doteq 1$ Hz, 3 H, C=C.CH_3; 3·83 (s), 3 H, $COOCH_3$; 4·77 (s), 2 H, $BrCH_2$; 6·27 (s), 1 H, CH=C. In our interpretation we started by assigning the methyl group signal at a lower field to substance *II* in view of the deshielding effect of the neighbouring carboxyl group; in addition to this the signal of the methyl group at a higher field is split to a doublet of $J \approx 1$ Hz, which corresponds to structure III. This assumption has precedents in senecioic acid[10] and β-chlorocrotonates[11] where this effect is manifest in the case of the *cis*-position of the methyl group with respect to carboxyl. Integration of the intensities of single peaks demonstrated that the ratio of compounds *II* : *III* is 1·2 : 1.

For an unambiguous proof of the structure of the formed bromo derivatives their mixture was converted on reaction with sodium methoxide to a mixture of corresponding methoxy derivatives, and using gas chromatography coupled with mass spectrometry the identity of the substances formed, with the models *IV* and *V*, was confirmed. According to the integrals of the peaks of single substances on chromatograms the ratio of compounds *IV* and *V* is 1·33 : 1. Hence, on nucleophilic substitutions of bromo derivatives with alcoholate the ratio of bromination in corresponding methyl groups is not substantially changed, *i.e.* neither an electronic nor steric effect of the carboxyl group could be observed in this reaction.

The result of the study of bromination of *I* shows that the methyl in position 5 is preferred as was supposed. Nonetheless – as can be deduced from the determined ratio of the formed bromo derivatives – the differences in reactivity of both methyl groups are not as pronounced as to make synthetic utilisation practical for selective bromination.

EXPERIMENTAL

Solid substances were dried before analysis at 0·5 Torr vacuum for 8 hours. Gas chromatography was carried out on a Chrom II apparatus provided with a flame ionisation detector. Chromatographic analyses were carried out using a column filled with poly(propylene sebacate) at 0·35 atm. pressure of nitrogen. Infrared spectra were measured on a Zeiss UR 10 spectrophotometer in tetrachloromethane. The NMR spectra were taken on a BS 477 Tesla Brno apparatus of 60 MHz in deuteriochloroform using tetramethylsilane as the internal standard. Mass spectra were obtained with a Gas Chromatograph-Mass Spectrometer LKB 9000, Stockholm.

Methyl 2-Methyl-5-methoxymethyl-3-furoate (*IV*)

A mixture of 14 g (0·1 mol) of methyl 2-methyl-3-furoate, b.p. 64—65°C/12 Torr, 3·12 g paraformaldehyde, and 52 ml of methylene chloride was saturated with gaseous hydrogen chloride for 45 minutes and then poured into 100 ml of cold water. After the addition of 30 ml of chloroform the organic layer was separated, washed twice with 20 ml of water and dried over potassium carbonate. Distillation of the product gave 10·3 g (55%) of methyl 2-methyl-5-chloromethyl-3-furoate, b.p. 90—102°C/1·3 Torr. To a cooled solution of 1 g (43 mmol) of sodium in 40 ml of methanol 5 g of chloromethyl derivative from the preceding operation, dissolved in 20 ml of methanol, were added. The mixture was refluxed for two hours and methanol was then distilled off. The residue was dissolved in a mixture of 100 ml of ether and 20 ml of water. The ethereal layer was separated and dried over anhydrous magnesium sulfate. After distillation off of ether and vacuum distillation of the residue 3 g of compound *IV* were obtained (65% yield), b.p. 112—121°C/11 Torr. For $C_9H_{12}O_4$ (184·2) calculated: 58·69% C, 6·57% H; found: 58·73% C, 6·67% H. The following peaks in the mass spectrum of the substance were abundant: *m/e* 153 (100%), 121 (53%), 43 (37%), 184 (28%), 79 (11%), 154 (11%).

Methyl 5-Methyl-2-methoxymethyl-3-furoate (*V*)

A solution of 26 g (0·2 mol) of methyl levulinate, b.p. 81—85°C/9 Torr, 13·6 g (0·22 mol) of ethylene glycol, and several crystals of *p*-toluenesulfonic acid in 125 ml of benzene were refluxed in an apparatus fitted with a device for azeotropic dehydration. After the calculated amount of water had separated the mixture was distilled. Yield 30·9 g (89%) of 1,2-ethylene acetal of methyl levulinate (*VI*), b.p. 103°C/15 Torr. For $C_7H_{12}O_4$ (174·2) calculated: 55·16% C, 8·10% H; found: 55·28% C, 8·10% H.

To a suspension of 9·6 g (0·4 mol) of sodium hydride in 100 ml of ether substance *VI* (34·8 g; 0·2 mol) and ethyl formate (22·2 g; 0·22 mol) in ether (20 ml) was added dropwise under stirring. The mixture was stirred for 4 hours, until the content of the flask solidified completely. The separated sodium salt was dissolved on addition of 100 ml of water and the aqueous layer was extracted with ether. The solution of salt *VII* was acidified with conc. hydrochloric acid (Congo red) and extracted with ether. The ethereal extract was dried over sodium sulfate, filtered and evaporated, to give 8 g (25%) of crude product *VIII* which was poured into 35 ml of conc. sulfuric acid. The mixture was cooled to approximately 50°C and after 8 minutes standing it was poured onto ice. Organic substances were extracted with ether, the extract was washed with saturated sodium hydrogen carbonate solution, and dried over magnesium sulfate. Distillation gave 1 g (13%) of a compound boiling at 75—80°C/10 Torr. The product was submitted to alkaline hydrolysis to give the free acid which was esterified again with diazomethane. The formed ester had b.p. 75—80°C/10 Torr. IR spectrum: 1 556 (m), 1 616 (w), 1 732 (s) cm^{-1}.

To a solution of 4 g (31 mmol) of methyl 5-methyl-3-furoate in 30 ml of dichloromethane 1·4 g (46 mmol) of paraformaldehyde and 1·3 g of anhydrous zinc chloride were added and the mixture was saturated with dry hydrogen chloride for one hour. The volume of the mixture was then made up to 40 ml and 5 ml of chloroform were added to the mixture. It was then washed with water and dried over anhydrous sodium sulfate. Distillation of the product gave 2·6 g (54%) of a liquid, b.p. 50—70°C/0·3 Torr.

A solution of 2·4 g of chloromethyl derivative from the preceding operation in 10 ml of methanol was mixed with a solution of 0·5 g (22 mmol) of sodium in 20 ml of methanol. The yellow colored reaction mixture was heated on a water bath for 30 minutes, methanol was distilled off, and the solidified residue was triturated with 30 ml of ether and 10 ml of water. The aqueous layer was extracted with ether and the combined ethereal extracts were dried over anhydrous sodium sulfate. Distillation of the product gave 0·17 g (7·2) of a liquid, b.p. 85°C/9 Torr. The

substance was not analytically pure, but more than 85% of all substances present in the mixture satisfied the formula of methyl 5-methyl-2-methoxymethyl-3-furoate *V* (according to mass spectral data). The most abundant ionic species in the spectrum of this substance is *m/e* 43, followed by *m/e* 153 (84%), 137 (81%), 169 (62%), 184 (30%), 123 (18%).

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

A mixture of ethyl acetonylacetoacetate[9] (29·2 g; 0·174 mol), *p*-toluenesulfonic acid (2·94 g), and toluene (235 ml) was refluxed for 3 hours in an apparatus fitted with a device for azeotropic dehydration. The mixture was shortly boiled with charcoal and filtered. After cooling *p*-toluenesulfonic acid crystallised out which was filtered off. The remaining solution was neutralized with a solution of potassium hydrogen carbonate, washed with water, and dried over anhydrous sodium sulfate. After the solvents had been distilled off the residue was submitted to vacuum rectification, affording 17·2 g (65%) of a compound b.p. 86–89°C/10 Torr. Alkaline hydrolysis gave 11·2 g (96%) of a yellow compound, m.p. 135–136°C; literature[12] gives for 2,5-dimethyl-3-furoic acid (uvinic acid), m.p. 134–135°C. Esterification with diazomethane in methanol (80% yield) and esterification with methanolic hydrogen chloride (65%) gave the methyl ester of 2,5-dimethylfuroic acid (*I*), b.p. 80°C/10 Torr. The substance is chromatographically pure on poly(propylene sebacate); IR spectrum: 1 592 (m), 1 627 (m), 1 724 (s) cm^{-1}.

Radical Bromination of Methyl 2,5-Dimethyl-3-furoate

To a solution of 3·08 g (20 mmol) of ester *I* in 30 ml of tetrachloromethane 3·9 g (22 mmol) of N-bromosuccinimide and 0·1 g of dibenzoyl peroxide were added and the mixture was refluxed for one hour on a water bath. The mixture was cooled and the crystalline precipitated succinate was filtered off and washed with tetrachloromethane. The solution of the bromination products in tetrachloromethane was washed with ice-cold 1M-NaOH and water, and dried over calcium chloride. After the evaporation of the solvent 4·2 g (90%) of crude bromomethyl derivatives were obtained which were investigated by NMR spectroscopy. The brominated products (4·2 g; 18 mmol) were dissolved in 10 ml of methanol and mixed with a solution of 0·5 g (22 mmol) of sodium in 20 ml of methanol. The mixture was refluxed on a water bath for 45 minutes. The residue was additioned with 10 ml of water and the organic material was extracted with ether. The ethereal extract was dried over magnesium sulfate and then distilled to give 2 g (60·5%) of a liquid, b.p. 108–115°C/11 Torr which was analysed by gas chromatography and mass spectroscopy, using standards *IV* and *V*.

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