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# ACTION OF ALKALI METALS IN LIQUID AMMONIA ON SUBSTITUTED THIOPHENES. COMMUNICATION 10.* OPENING OF THE THIOPHENE RING IN THIOPHENE-3-CARBOXYLIC ACIDS

E. P. Zakharov, F. M. Stoyanovich, and Ya. L. Gol'dfarb

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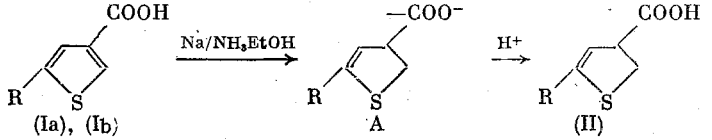
The high regio- and stereoselectivity of the opening of the thiophene ring in thiophene-2-carboxylic and 2,5-dihydrothiophene-2-carboxylic acids [2] is apparently due to the high stabilization of the intermediate carbanion with adjacent carboxyl group, sulphur atom and double bond. If this is so and reduction takes place through formation of an allyl type α-carboxycarbanion then, in the case of thophene-3-carboxylic acid (I), one would expect initial reduction of the 2,3- bond of the thiophene ring with formation of carbanion A.




R = H (Ia), (II); Me (Ib).

In support of this proposition, the electrochemical reduction of Ia gives 2,3-dihydrothiophene-3-carboxylic acid (II) [3]. With more active chemical reduction using solvated electrons it is further possible to hydrogenolyze the C—S bond with formation of the thermodynamically stable vinylthiolate anion.

Experiments basically supported this proposal. The main product of reduction of Ia using 5 equivalents of Na and alcohol in liquid ammonia is the thiolate IIIa. Benzylation using $PhCH_2Cl$ with subsequent $CH_2N_2$ esterifcation gave the methyl ester of 2-methyl-4-benzylthio-cis-butenoic acid (IVa), the structure of which was confirmed by spectral data. In particular, the spin—spin coupling constant for the vinyl protons ($H^3$ and $H^4$) in the PMR spectrum of IVa has a value of 9.1 Hz. Together with IVa there are formed 11% of the methyl ester of 2-methyl-4-benzylthiobutyric acid (V) and other products which were not identified (Scheme).

Greater selectivity occurs with reduction of 5-methylthiophene-3-carboxylic acid (Ib) to thiolate (IIIb). Benzylation and esterification gave 84% of the methyl ester of 2-methyl-4-benzylthio-3-Z-pentenoic acid (IVb). Thiolate IIIb gives 2-methyl-4-benzylsulfonyl-3-Z-pentenoic acid (VI) on acidic oxidation with $H_2O_2$. The geometry of the methyl ester of

*For Communication 9 see [1].

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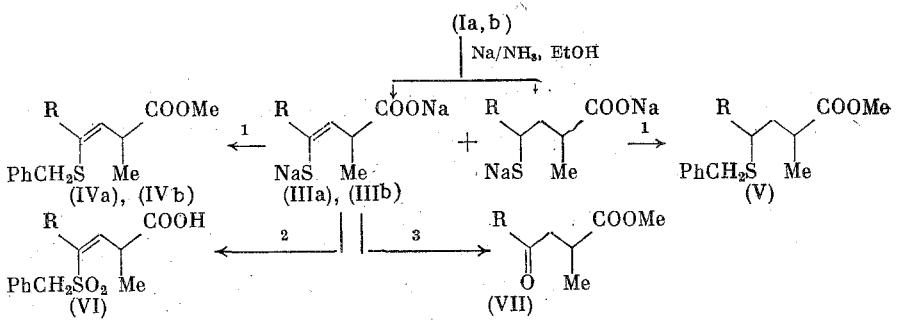
Scheme




R = H (IIIa), (IVa), (V); Me (IIIb), (IVb), (VI), (VII).

1. a) $PhCH_2Cl$; b) $H_3^+O$; c) $CH_2N_2$. 2. a) $PhCH_2Cl$; b) $H_3^+O$; c) $H_2O_2$, AcOH.
3. a) $TsOH \cdot H_2O$; b) MeI, DMAA

this acid was determined by NMR using the differential changes in the chemical shift (CS) of $H^2$ and $H^3$ in $CCl_4$ and $C_6D_6$. From data in [4] the differences in the analogous Z- and E- isomers of 2-phenylsulfonylbut-2-ene are 0.37 and 0.64 ppm, respectively. In VI this has a value of 0.34 ppm. In addition, the CS of the vinyl proton in VI corresponds with the CS of 2-phenylsulfonyl-2-Z-butene (6.07 ppm in $CCl_4$).

Hydrolysis of the thiolate (IIIb) gives the sodium salt of 2-methyllevulinic acid, the methyl ester of which (VII) was obtained in 55% yield.

## EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer as films or in KBr. Mass spectra were obtained on a Varian CH-6 instrument. PMR spectra were recorded on BS-467 (60 MHz) and BS-497 (100 MHz) machines using $CDCl_3$ solvent and referred to TMS as standard. GLC was carried out on an LKM-8MD chromatograph (helium carrier, 20 ml/min, 100 × 0.3 cm column, 7% SE-30 on Chromaton N-AW-HMDS). Thiophene-3- and 5-methylthiophene-3-carboxylic acid (1a, b) were obtained from the corresponding 2-bromothiophene [5] by exchange of Br for Li with subsequent carbonation [6].

Methyl Ester of 2-Methyl-4-benzylthio-cis-3-butenoic Acid (IVa). To a solution of Ia (1.28 g, 0.01 mole) and absolute ethanol (4.7 ml) in liquid ammonia (100 ml) stirred in an atmosphere of inert gas at −40°C there was slowly added Na (1.15 g, 0.05 g-atom). Stirring was continued for 30 min then $NH_4Cl$ (2.7 g, 0.05 mole) was added. After cooling to −80°C benzyl chloride (1.9 g, 0.015 mole) was run in. After 30 min, cooling was removed, ammonia evaporated off, water (50 ml) added to the residue, the solution washed many time with ether, acidified with dilute HCl and extracted with ether. After evaporation the residue was treated with $CH_2N_2$. Distillation (bath temperature 135-145°C, 0.05 mm) gave 1.71 g of liquid product consisting (by PMR and chromatography/mass spectrometry) of 70% of the methyl ester of 2-methyl-4-benzylthio-cis-3-butenoic acid (IVa) (yield 55% based on Ia). PMR spectrum (δ, ppm): 1.18 d (3H, $CH_3C$, J = 7.2 Hz), 3.42 m (1H, CHCHO), 3.62 s (3 H, $CH_3O$), 3.82 s (2H, $CH_2Ph$), 5.60 dd (1H, $=CH^3$, $J_{3,4} = J_{2,3} = 9.1$ Hz), 6.07 d (1H, =CH, $J_{3,4} = 9.1$ Hz), 7.26 (5H, $C_6H_5$). Mass spectrum, m/z (relative intensity, %), fragment: 236 (10), $M^+$; 177 (10), $[M - CH_3OCO]^+$; 91 (100), $PhCH_2^+$. By GLC and PMR, 11% of the methyl ester of 2-methyl-4-benzylthiobutyric acid (V) was also detected in the mixture. PMR spectrum (δ, ppm): 0.89 d (3H, $CH_3C$), 1.6-2.4 m (4H, $CH_2CH_2$), 2.55 m (1H, CH), 3.62 s (3H, $CH_3O$), 3.82 s (2H, $CH_2Ph$), 7.26 s (5H, $C_6H_5$). Mass spectrum, m/z (relative intensity, %), fragment: 238 (7), $M^+$; 179 (10), $[M - CH_3OCO]^+$; 91 (100), $PhCH_2$.

Methyl Ester of 2-Methyl-4-benzylthio-3-Z-pentenoic Acid (IVb). Obtained analogously to the above method from Ib (1.42 g, 0.01 mole), Na (1.15 g, 0.05 g-atom), ethanol (4.7 ml), and benzyl chloride (1.9 g). Yield 84%, bp 155-165°C (0.3 mm), $n_D^{20}$ 1.5434. Found: C 66.85; H 7.43; S 12.91%. $C_{14}H_{18}O_2S$. Calculated: C 67.16; H 7.25; S 12.81%. PMR spectrum (δ, ppm): 1.02 d (3H, $CH_3CH$, J = 6.8 Hz), 2.00 (3H, $CH_3C=$, $J_{CH_3H^3} = 1.6$ Hz), 3.59 s (3H, $CH_3O$), 3.70 m (1H, CH), 3.85 s (2H, $CH_2$), 5.43 dd (1H, CH=, $J_{2,3} = 09.1$, $J_{H^3,CH_3} = 1.6$ Hz), 7.25 s (5H, $C_6H_5$).

2-Methyl-4-benzylsulfonyl-3-Z-pentenoic Acid (VI). To a solution of 2-methyl-4-benzylthio-cis-3-butenoic acid (1.4 g, 0.006 mole) in AcOH (15 ml) there was added portionwise 28% $H_2O_2$ (5 ml) and the product was allowed to stand for 48 h at 20°C. Evaporation in vacuo

(bath temperature not greater than 40°C) gave a residue which was dissolved in ether (50 ml), washed with water, dried and the ether evaporated to give the acid IV (1.57 g, 99%) with mp 140-141°C (from benzene). Found: C 58.36; H 6.17; S 11.46%. $C_{13}H_{16}O_4S$. Calculated: C 58.19; H 6.01; S 11.94%. IR spectrum (ν, $cm^{-1}$): 2500-3200 (OH), 1700 (C=O), 1500, 1600 ($C=C_{arom}$), 1300, 1150 ($SO_2$). Methyl ester: mp 75-75.5°C (from benzene/hexane 1:10). Found: C 59.77; H 6.71; S 11.00%. Mol. wt. 282 (mass spectrometric). $C_{14}H_{18}O_4S$. Calculated: C 59.55; H 6.42; S 11.35%. Mol. wt. 282.3. PMR spectrum (δ, ppm in $CCl_4$): 1.08 d (3H, $\underline{CH_3}CH$, J = 7.2 Hz), 1.82 d (3H, $CH_3C=$, $J_{Me,H^3}$ = 1.7 Hz), 3.60 s (3H, $CH_3OCO$), 3.95 m (1H, CHCOO), 4.12 s (2H, $CH_2$), 6.07 dq (1H, CH=, $J_{2,3}$ = 10.2, $J_{Me,H^3}$ = 1.7 Hz), 7.28 s (5H, $C_6H_5$). In benzene solvent 0.98 d (3H, $\underline{CH_3}OCO$), 3.85 s (2H, $CH_2$), 4.10 m (1H, CHCOO), 5.88 dq (1H, CH=, $J_{2,3}$ = 10.2, $J_{Me,H^3}$ = 1.6 Hz), 7.05 s (5H, $C_6H_5$).

Methyl Ester of 2-Methyllevulinic Acid (VII). Using the conditions described above with Ib (1.42 g, 0.01 mole), Na (1.15 g, 0.05 mole), absolute ethanol (5.8 ml) and liquid ammonia (100 ml). To the residue after evaporation of ammonia there was added ethanol (50 ml), the solid filtered off and the filtrate evaporated in vacuo. To the residue there was added a solution of p-toluenesulphonic acid monohydrate (1.9 g, 0.01 mole) in methanol (25 ml) and benzene (50 ml) and the product refluxed until evolution of $H_2S$ ceased. After separation of the solid, the liquid was poured into water (60 ml), the aqueous layer separated, washed with ether, made alkaline to pH 8 and evaporated in vacuo. The residue was treated with absolute ethanol (20 ml), the solid separated and the filtrate evaporated. After drying over $P_2O_5$, the residue was dissolved in anhydrous dimethylacetamide (DMAA), methyl iodide (5 ml) added and the mixture stirred for 48 h at 20°C (compare [7]). The product was poured into water (100 ml), extracted with $CHCl_3$, the extract washed several times with water and dried with $MgSO_4$. After removal of solvent it was distilled to give VII (0.8 g, 55%), bp 85-90°C (8 mm), $n_D^{20}$ 1.4238. Found: C 58.230; H 8.57%. $C_7H_{12}O_3$. Calculated: C 58.31; H 8.39%. PMR spectrum (δ, ppm): 1.13 d (3H, $\underline{CH_3}CH$, J = 7.0 Hz), 2.08 s (3H, $CH_3CO$), 2.39 m (1H, CH), 2.81 br d (2H, $CH_2$, J = 7.8 Hz), 3.61s (3H, $CH_3$]$^+$; Mass spectrum, m/z (relative intensity, %), fragment: 144 (19), $M^+$; 129 (31), $[M - CH_3]^+$; 113 (66), $[M - OCH_3]^+$. IR spectrum (ν, $cm^{-1}$): 1718 (C=O), 1740 (COOMe), 1265, 1070 (C–O–C).

## CONCLUSIONS

A regio- and stereoselective method of synthesis of γ-alkylthio-β-Z-alkenoic or γ-oxoalkanoic acids has been developed by reductive opening of the thiophene-3-carboxylic acids using Na and alcohol in liquid ammonia.

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