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A Facile Ring-opening in the Thiophene Series

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Attempts to brominate 2,4-di-*t*-butyl-5-bromothiophene according to the method of Derbyshire and Waters [5] led to 2-*t*-butyl-4,4-dihydroxy-5,5-dimethyl-2-hexenoic acid γ-lactone *i.e.* the pseudo-acid form of 2-*t*-butyl-5,5-dimethyl-4-oxo-2-hexenoic acid (IV).

In connection with other work we were interested in preparing 3,5-dibromo-2,4-di-*t*-butylthiophene. The starting material, 5-bromo-2,4-di-*t*-butylthiophene, was prepared in the following way: The mixture of 2,5- and 2,4-di-*t*-butylthiophene, obtained as a by-product in the *t*-butylation of thiophene with isobutylene using sulphuric acid as a catalyst,[1] (which by GLC analysis was shown to consist of 75 % of the 2,5-isomer and 25 % of the 2,4-isomer) was treated with butyllithium and carbon dioxide, converting the 2,4-di-*t*-butylthiophene (I) to 2,4-di-*t*-butyl-5-thiophenecarboxylic acid (II). This product can be readily separated from the 2,5-isomer, which having no free α-position is not metalated by butyllithium. Repeating the butyllithium-carbon dioxide treatment with the neutral fraction twice led to isomer-free 2,5-di-*t*-butylthiophene. This is a very convenient method of separating the di-*t*-butylthiophenes on a larger scale.

II is easily decarboxylated. We first used the copper and quinoline method [2] which yielded GLC-pure 2,4-di-*t*-butylthiophene in 92 % yield. Subsequent bromination of (I) with one mole of bromine in acetic acid gave 5-bromo-2,4-di-*t*-butylthiophene (III). We discovered, however, that the reaction of II with bromine also led to III in good yield. In order to determine, whether this reaction was a one-step direct bromodecarboxylation, we studied this reaction a little closer. We found that II did not decarboxylate when refluxed in acetic acid. However, addition of small amounts of hydrobromic acid lead to smooth decarboxylation yielding isomer-free (I) in 88 % yield. Although these results do not eliminate the possibility of direct bromodecarboxylation in the presence of bromine, it seems likely that traces of hydrogen bromide first cause decarboxylation followed by normal bromination. However, it should be mentioned that evidence exists that the decarboxylative nitration of substituted 2-thiophenecarboxylic acids is a direct electrophilic substitution by the

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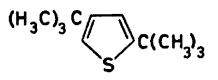
nitronium cation.[3] It has long been known that vigorous bromination of 2-thiophenecarboxylic acid leads to tetrabromothiophene.[4]

Bromination of III with molecular bromine in chloroform or acetic acid did not succeed. Even upon refluxing in acetic acid mainly starting material was recovered and GLC indicated the formation of three or four other components in smaller amounts. Among them was the compound to be described below, which crystallized from the distillate, and a compound, m.p. 20°, separated by preparative GLC which analyzed correctly as a mono bromo-di-*t*-butylthiophene ($C_{12}H_{19}BrS$) and also showed an NMR-spectrum consistent



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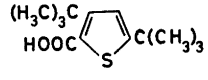

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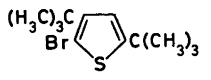

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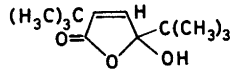

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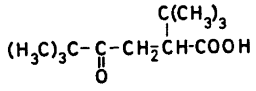

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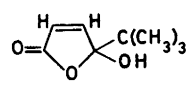

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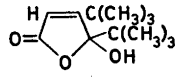

VII

with this structure ($\tau_{C(CH_3)_3}$ 8.54, 8.61; τ_{CH} 3.29). It was not identical (IR, GLC) with 2,5-di-*t*-butyl-3-bromothiophene prepared through bromination of 2,5-di-*t*-butylthiophene and could therefore be 2,4-di-*t*-butyl-3-bromothiophene.

We then tried the powerful bromination method of Derbyshire and Waters [5] using bromine in acetic acid-nitric acid mixture in the presence of silver nitrate. It is assumed that Br^+ is the brominating agent in this case. From this reaction we isolated in 70 % yield a compound, which did not contain any bromine or sulphur and which analyzed correctly for $C_{12}H_{20}O_3$. It was soluble in sodium hydroxide and was recovered unchanged upon acidification. Its NMR-spectrum in CS_2 showed two bands at 8.85 τ and 9.09 τ, each containing nine hydrogens and two bands at 3.34 τ and 5.67 τ, each containing one hydrogen. In its IR-spectrum, it showed a sharp peak at 2.95 μ which was assigned to OH-stretching, a band at 5.82 μ characteristic of C=O stretching and a band at 6.12 μ indicating a C=C bond. This is also clear from the fact that it was possible to hydrogenate this compound over palladium at normal pressure to a compound (V) analysing as $C_{12}H_{22}O_3$. The above-mentioned

results indicate that the compound obtained is the cyclic lactol form (pseudo acid form) of *cis* α-*t*-butyl-β-pivaloyl acrylic acid (IV), or according to the nomenclature of Chemical Abstracts, 2-*t*-butyl-4,4-dihydroxy-5,5-dimethyl-2-hexenoic acid γ-lactone. The hydrogenated product (V), thus being 2-*t*-butyl-5,5′-dimethyl-4-oxohexanoic acid.

It could be argued that the C=O frequency is rather low for a pseudo acid form.[6,7] However, on the other hand a chemical shift of 5.67 τ for a carboxylic hydrogen is quite unheard. Both the *cis* and *trans* form of the close analogue, β-pivaloyl acrylic acid, are known.[8] The *cis* form has been shown to be cyclic (VI), based on a detailed analysis of its IR-spectrum and NMR-spectrum. It shows a very strong absorption in the carbonyl stretching region with peaks at 5.60 μ and 5.77 μ. However, in the OH and CH stretching region IV and VI show a very similar pattern. The NMR-spectrum of VI in carbon disulphide shows the *t*-butyl group at 8.97 τ, the OH resonance at 4.56 τ and the two ethylenic hydrogens at 2.80 τ and 4.56 τ, with a coupling of 5.7 c/s.[8]

3-*t*-Butyl-5,5′-dimethyl-4-oxo-2-hexenoic acid (VII), isomeric with IV, was prepared some years ago by Neuman and Kahle [9] through Reformatsky reaction between dipivaloyl and ethyl bromo acetate followed by dehydration. From UV-spectral investigation this acid is claimed to exist to 57 % in the cyclic form in dilute alcohol.

IV was also isolated as mentioned above in small amounts from the direct bromination attempt of III and also from the reaction of II with bromine, when an excess of bromine was used.

In contrast to β-acetylacrylic acid,[10] IV apparently does not add bromine. However, from the treatment of IV with bromine, we isolated a compound isomeric with IV, m.p. 41—45°, which could be the *trans* isomer. We are continuing our study of the chemical properties of IV.

Formally one can imagine the formation of IV from 5-bromo-2,4-di-*t*-butylthiophene through hydrolytic opening of the thiophene ring followed by dehydrogenation through the bromine. Although, as far as the present authors know, such ring-opening has not been observed before in the thiophene series it has been long known in furan chemistry. Thus Fecht [11] obtained formylacrylic acid by treating furancarboxylic acid with bromine in alkaline solution. However, the yield is low, and in addition decarboxylation occurs. A somewhat different reaction but leading to the same type of product is the photo-sensitized autoxidation of 2-methylfuran in ethanol giving the pseudo ethyl ester of *cis* β-acetylacrylic acid.[12]

It remains to investigate if the facile ring-opening is a consequence of the steric demands of the *t*-butyl groups or if it is more general in nature.

EXPERIMENTAL

2,4-Di-t-butyl-5-thiophenecarboxylic acid and 2,5-di-t-butylthiophene. 627 g (3.20 moles) of a mixture of di-*t*-butylthiophene which according to gas-chromatographical analysis consisted of 75 % 2,5-di-*t*-butylthiophene and 25 % of 2,4-di-*t*-butylthiophene, dissolved in 300 ml of anhydrous ether were added with stirring and under nitrogen to 1800 ml of 0.9 N butyllithium. The mixture was refluxed for 4 h, cooled and poured onto solid carbon dioxide, and after the temperature had risen to −10°, the mixture was

hydrolysed with 2 N hydrochloric acid in excess. The aqueous layer was extracted once with ether and the combined ether phases were extracted several times with 2 N sodium hydroxide until all the acid was removed from the ether phase. Acidification yielded 111 g (58 % calculated on 2,4-di-*t*-butylthiophene present) of 2 4-di-*t*-butyl-5-thiophenecarboxylic acid, m.p. 197—198° after recrystallization from ethanol. (Found: C 64.83; H 8.33; S 13.30. Calc. for $C_{13}H_{20}O_2S$: (240.3). C 64.97; H 8.37; S 13.34). The ether phase was dried and fractionated *in vacuo* yielding 455 g of 2,5-di-*t*-butylthiophene, b.p. 88—90°/10 mm Hg, which GLC showed to contain only traces of 2,4-di-*t*-butylthiophene although in its IR-spectrum the strong peaks at 11.98 μ and 15.18 μ of 2,4-di-*t*-butylthiophene were absent. Most of the traces of 2,4-di-*t*-butylthiophene could be removed by repeating the above mentioned procedure using, however, smaller amounts of butyllithium. The pure 2,5-di-*t*-butylthiophene is crystalline having a m.p. of 20°C.

GLC was carried out on an Aerograph, Autoprep A-700. A 12′ × ¼″ column packed with 60/80 mesh acid-washed Chromosorb W coated with Apiezon L (30 %) was used. The mixture of di-*t*-butylthiophenes was analysed at a column temperature of 167°C with a helium flow rate of 40 ml/min giving a retention time of 17.5 min for 2,4-di-*t*-butylthiophene and 19.8 min for 2,5-di-*t*-butylthiophene. The chromatogram was not fully resolved but a rough estimation was carried out using a Disc-Integrator Model 201 R.

2,4-Di-t-butylthiophene. Method I. 20 g (0.083 mole) of 2,4-di-*t*-butyl-5-thiophenecarboxylic acid, 50 ml of quinoline and 4 g of copper powder were carefully heated under nitrogen until reaction started and then refluxed for 2 h. Most of the liquid was distilled off from the copper and the distillate treated with excess of 4 N hydrochloric acid. The organic layer was taken up in ether, washed with 2 N hydrochloric acid and water, dried and fractionated, yielding 15 g (92 %) of 2,4-di-*t*-butylthiophene, b.p. 88—89°/10 mm Hg. In the GLC the peak of 2,5-di-*t*-butylthiophene was absent as was its characteristic peak at 12.58 μ in the IR-spectrum.

Method II. 15 g (0.063 mole) of 2,4-di-*t*-butyl-5-thiophenecarboxylic acid was dissolved in 150 ml of acetic acid, 10 ml of 66 % hydrobromic acid added and the solution refluxed for 6 h, cooled and poured into 600 ml of water. The oil which separated was taken up in ether, and the ether solution extracted with 2 N sodium hydroxide in order to remove acetic acid. The ether solution was dried and fractionated yielding 10.8 g (88 %) of 2,4-di-*t*-butylthiophene, b.p. 84—85°/9 mm Hg, having the same IR-spectrum as the sample described above.

2,4-Di-t-butyl-5-bromothiophene. To a hot solution of 12.0 g (0.05 mole) of 2,4-di-*t*-butyl-5-thiophenecarboxylic acid in 100 ml of acetic acid was added drop-wise 8.0 g (0.05 mole) of bromine in 20 ml of acetic acid and the mixture refluxed for 3 h. After cooling, the mixture was poured into four times its volume of water and the separated oil taken up in ether. The ether phase was washed with an excess of 2 N sodium hydroxide solution, dried and distilled, yielding 8.5 g (61 %) of 5-bromo-2,4-di-*t*-butylthiophene, b.p. 130—131°/14 mm Hg. NMR (CCl_4): $\tau_{C(CH_3)_3}$ 8.63, 8.70; τ_H 3.49.

2,4-Di-t-butyl-5-bromothiophene. 3.0 g (0.015 moles) of 2,4-di-*t*-butylthiophene in 40 ml of acetic acid was treated with 2.45 g (0.015 mole) of bromine in 15 ml of acetic acid in the same way as described above, yielding 1.75 g (42 %) of 2,4-di-*t*-butyl-5-bromothiophene, b.p. 127—130°/13 mm Hg, having the same IR-spectrum as the sample described above. (Found: C 52.72; H 6.89; Br 28.84; S 11.37. Calc. for $C_{12}H_{19}BrS$ (275.3): C 52.36; H 6.95; Br 29.03; S 11.64).

2-t-Butyl-4,4-dihydroxy-5,5-dimethyl-2-hexenoic acid γ-lactone, (Pseudo acid form of 2-t-butyl-5,5-dimethyl-4-oxo-2-hexenoic acid). To a solution of 8.3 g (0.03 mole) of 2,4-di-*t*-butyl-5-bromothiophene and 4.8 g (0.03 mole) of bromine in a mixture of 180 ml of acetic acid, 33 ml of conc. nitric acid, and 25 ml of water was added at room temperature and with vigorous stirring 10.2 g (0.060 mole) of silver nitrate in 60 ml of water. The mixture was stirred for 3 h and allowed to stand over night. The precipitated silver bromide was filtered off and the filtrate poured into three times its volume of water. The aqueous solution and the oily precipitate formed were extracted four times with ether. The combined ether phases were extracted with 2 N sodium hydroxide solution until the aqueous extracts gave an alkaline reaction. The aqueous extracts were combined with the original aqueous phase and the pH adjusted to about 4. The crystals formed were filtered off the next day, yielding 4.3 g (68 %) of 2-*t*-butyl-4,4-dihydroxy-5,5-dimethyl-2-hexenoic acid γ-lactone. Recrystallization from petrolether did not change

the IR-spectrum, m.p. 96–97°. NMR (CS_2): $\tau_{C(CH_3)_2}$ 8.85, 9.09, τ_{OH} 5.67, τ_{CH} 3.34. (Found: C 68.06; H 9.66. Calc. for $C_{12}H_{20}O_3$: (212.3) C 67.89; H 9.49).

2-t-Butyl-5,5-dimethyl-4-oxohexanoic acid. 1.06 g of 2-*t*-butyl-4,4-dihydroxy-5,5-dimethyl-2-hexenoic acid γ-lactone was dissolved in 25 ml of 80 % methanol, 0.15 g of palladium black added and the mixture hydrogenated over night at normal pressure and room temperature. The palladium was filtered off, the solvent evaporated and the residue recrystallized from petrol-ether yielding 0.93 g (87 %) of 2-*t*-butyl-5,5-dimethyl-4-oxohexanoic acid, m.p. 78–82°. (Found: C 67.26; H 10.45. Calc. for $C_{12}H_{22}O_3$: (214,3) C 67.25; H 10.34).

The NMR-spectra were obtained on a Varian Associates DP-60 model V-4302 NMR-spectrometer operating at 60 Mc/s and a 12″ Varian magnet V-4012A, equipped with integrator and back-ground stabilizer. The magnet sweep was calibrated using the modulation side-band technique. The variable frequency was obtained from a Hewlett Packard Wide range oscillator model 200 CD and measured with a Beckman Model 6146 Universal EPUT-timer.

The IR-spectra were recorded on a Beckman IR-5A infra-red spectrophotometer.

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REFERENCES

1. Caesar, P. D. *J. Am. Chem. Soc.* **70** (1948) 3623.
2. Nishimura, S., Motoyama, R. and Imoto, E. *Bull. Univ. Osaka Prefect. Ser. A* **6** (1958) 127.
3. Campaigne, E. and Grove, H. G. *J. Am. Chem. Soc.* **73** (1951) 3812.
4. Bonz, R. *Ber.* **18** (1885) 2308.
5. Derbyshire, D. H. and Waters, W. A. *J. Chem. Soc.* **1950** 573.
6. Grove, J. F. and Willis, H. A. *J. Chem. Soc.* **1951** 877.
7. Bellamy, L. J. *The Infrared Spectra of Complex Molecules*, Chapter 9–11, London 1958.
8. Hellström, N. and Gronowitz, S. *Kgl. Lantbruks-Högskol. Ann.* **25** (1959) 363.
9. Newman, M. S. and Kahle, G. R. *J. Org. Chem.* **23** (1958) 666.
10. Wolff, L. *Ann.* **264** (1891) 229.
11. Fecht, H. *Ber.* **38** (1905) 1272.
12. Schenk, G. O. *Ann.* **584** (1953) 156.

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