

## Preparation of the 'Fixed Conformation Esters' 4,5-Dihydrofuro- and 4,5-Dihydrothieno-[2,3-c]pyran-7-one

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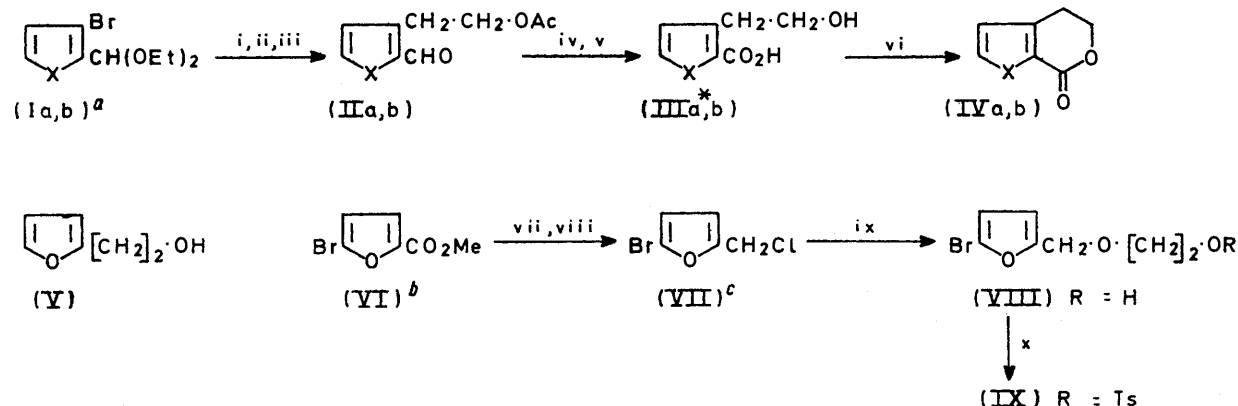
The title compounds, required as models in spectrometric work, have been synthesised by a six-stage route from 3-bromofuran-2-carbaldehyde diethyl acetal and the corresponding thiophen acetal.

THE i.r. spectra of many alkyl furan- and thiophen-2-carboxylates contain carbonyl doublets which have been attributed to the occurrence of rotational isomerism.<sup>1</sup> In order to correlate the components of the doublets with the individual rotamers it was necessary to prepare reference compounds with the ester group constrained in a particular conformation. Two such compounds, the lactones (IVa and b) reported here, serve as spectrometric models for the *syn*-forms of the esters.

heterocyclic materials, particularly the very reactive intermediates in the furan series. [2-(2-Furyl)ethanol (V) was prepared from furyl-lithium and ethylene oxide in rehearsal for the corresponding reactions with the bromoacetals.] An alternative approach, in which it was intended to convert methyl 5-bromofuran-2-carboxylate<sup>1b</sup> (VI) into a bromo-lactone was frustrated by the failure of the tosylate (IX) to undergo the desired intramolecular displacement involving cyclisation at the  $\beta$ -position of the

### SCHEME

References are given to known compounds; the rest are new. For furans (series a), X = O; for thiophens (series b), X = S



Reagents: i, Bu<sup>n</sup>Li, then ethylene oxide; ii, Ac<sub>2</sub>O-C<sub>6</sub>H<sub>5</sub>N; iii, 2N-HCl, 20 °C; iv, Ag<sub>2</sub>O-NH<sub>3</sub>; v, 10% aq. NaOH, heat, then 2N-HCl, 20 °C; vi, H<sub>2</sub>SO<sub>4</sub>-dioxan, heat; vii, LiAlH<sub>4</sub>; viii, SOCl<sub>2</sub>-Et<sub>2</sub>O; ix, HO-[CH<sub>2</sub>]<sub>2</sub>-OH-Et<sub>2</sub>O; x, TsCl-C<sub>6</sub>H<sub>5</sub>N.

<sup>\*</sup> Not fully characterised. <sup>\*</sup> Refs. 2 and 3. <sup>b</sup> Ref. 1b. <sup>c</sup> Ref. 4.

The work is portrayed in the Scheme, and needs little comment. Efficient syntheses of the starting materials, the bromo-acetals (Ia and b), from furan and thiophen have been described recently;<sup>2,3</sup> the route from these to the lactones (IVa and b) has the merit of leaving no ambiguity about the structures of the intermediates and products. In several stages careful control of conditions is necessary to avoid extensive decomposition of the

furan ring. The spectra of the lactones (IVa and b) will be discussed in a later paper dealing with rotational isomerism in heterocyclic esters.

### EXPERIMENTAL

For general directions see ref. 1b. Detailed descriptions of the compounds reported here are given by R. L. Snowden (D.Phil. Thesis, Oxford, 1973).

<sup>2</sup> R. Sornay, J.-M. Meunier, and P. Fournari, *Bull. Soc. chim. France*, 1971, 990.

<sup>3</sup> D. J. Chadwick, J. Chambers, P. K. G. Hodgson, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin I*, 1974, 1141.

<sup>1</sup> D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. (a) Perkin II*, 1972, 1959; (b) *Perkin I*, 1973, 1766.

*Preparation of the Lactones (IVa and b).*—3-Bromofuran-2-carbaldehyde diethyl acetal<sup>2</sup> (Ia) (30 g) in Et<sub>2</sub>O (30 ml) was added during 30 min to a solution of Bu<sup>n</sup>Li [prepared under Ar from Li wire (2 g), Bu<sup>n</sup>Br (21 g), and Et<sub>2</sub>O (60 ml)] which was stirred vigorously at -70 °C. After a further 40 min ethylene oxide (12 ml) was added, and the temperature of the mixture was allowed to reach 0 °C during 3 h. H<sub>2</sub>O (40 ml) was added, and the stirring was continued for 30 min. Extraction with Et<sub>2</sub>O gave material (18 g),  $\nu_{\max}$  3640 cm<sup>-1</sup>, which was dissolved in C<sub>5</sub>H<sub>5</sub>N (100 ml)-Ac<sub>2</sub>O (140 ml) at 20 °C. After 2 days, 2N-HCl (1100 ml) was added; the mixture was shaken for 15 min, and then extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O solution was extracted with portions of aq. Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>. The combined aq. extracts were basified with aq. Na<sub>2</sub>CO<sub>3</sub> and extracted with Et<sub>2</sub>O to give 3-(2-acetoxyethyl)furan-2-carbaldehyde (IIa) (3.7 g), b.p. 103–106° (bath temp.) at 0.2 mmHg (Found: C, 59.5; H, 5.6. C<sub>9</sub>H<sub>10</sub>O<sub>4</sub> requires C, 59.3; H, 5.5%),  $\nu_{\max}$  1745 and 1687 cm<sup>-1</sup>, *m/e* 182 (*M*<sup>+</sup>, 0.4%) and 122 (100).

The foregoing aldehyde was oxidised with Tollens reagent under the conditions described previously.<sup>1b</sup> A mixture of the product and 10% aq. NaOH (35 ml) was boiled under reflux for 30 min, cooled to 5 °C, and carefully acidified (to pH 2) with 2N-HCl. Extraction with EtOAc gave 3-(2-hydroxyethyl)furan-2-carboxylic acid (IIIa) (1.7 g), *m/e* 156 (*M*<sup>+</sup>, 2%) and 122 (100). A solution of this acid in dioxan (30 ml) containing H<sub>2</sub>SO<sub>4</sub> (0.2 ml) was boiled under reflux for 1 day. Neutralisation with anhydrous Na<sub>2</sub>CO<sub>3</sub>, addition of H<sub>2</sub>O (20 ml), extraction with Et<sub>2</sub>O, and purification by p.l.c. [4 large plates, 2 × petrol-Me<sub>2</sub>CO (10:3)] gave 4,5-dihydrofuro[2,3-c]pyran-7-one (IVa) (650 mg), m.p. 72–73° (from CCl<sub>4</sub>) (Found: C, 60.7; H, 4.6. C<sub>7</sub>H<sub>6</sub>O<sub>3</sub> requires C, 60.9; H, 4.4%), *m/e* 138 (*M*<sup>+</sup>, 61%) and 108 (100), *M* (Mechrolab vapour pressure osmometer) 138 ± 5.

In a similar sequence, the 3-bromothiophen acetal<sup>3</sup> (Ib) (8.1 g) was converted into (i) 3-(2-acetoxyethyl)thiophen-2-carbaldehyde (IIb) (2.9 g), b.p. 103–106° (bath temp.) at 0.3 mmHg (Found: C, 54.8; H, 5.0; S, 15.9. C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>S requires C, 54.5; H, 5.1; S, 16.15%),  $\nu_{\max}$  1745 and 1671 cm<sup>-1</sup>, *m/e* 198 (*M*<sup>+</sup>, 0.6%) and 138 (100); (ii) 3-(2-hydroxyethyl)thiophen-2-carboxylic acid (IIIb) (1.5 g) (Found: C, 48.6; H, 4.8; S, 18.4. C<sub>7</sub>H<sub>6</sub>O<sub>3</sub>S requires C, 48.8; H, 4.7; S, 18.6%), *m/e* 172 (*M*<sup>+</sup>, 2%) and 138 (100); and (iii) 4,5-dihydrothieno[2,3-c]pyran-7-one (IVb) (1.1 g), m.p. 53–54° (from CCl<sub>4</sub>) (Found: C, 54.2; H, 4.1; S, 20.6. C<sub>7</sub>H<sub>6</sub>O<sub>2</sub>S requires C, 54.55; H, 3.9; S, 20.8%), *m/e* 154 (*M*<sup>+</sup>, 98%) and 124 (100).

*Compounds (V)–(IX).*—Furan (6.8 g) in Et<sub>2</sub>O (15 ml) was added during 15 min to a stirred solution of Bu<sup>n</sup>Li [from Li (1.4 g), Bu<sup>n</sup>Br (14.5 g), and Et<sub>2</sub>O (20 ml)] at -30 °C.

The temperature of the solution was allowed to reach 20 °C during 3 h. The solution was boiled under reflux for 4 h, and then cooled to -30 °C. Reaction with ethylene oxide (10 ml) and work-up gave 2-(2-furyl)ethanol (V) (6.3 g), b.p. 80–82° (bath temp.) at 12 mmHg (Found: C, 64.4; H, 7.1. C<sub>6</sub>H<sub>8</sub>O<sub>2</sub> requires C, 64.3; H, 7.1%),  $\nu_{\max}$  3630 cm<sup>-1</sup>, *m/e* 112 (*M*<sup>+</sup>, 63%) and 81 (100).

Methyl 5-bromofuran-2-carboxylate<sup>1b</sup> (VI) (20 g) in Et<sub>2</sub>O (160 ml) was added during 40 min to a stirred slurry of LiAlH<sub>4</sub> (2.75 g) in Et<sub>2</sub>O (160 ml) at 0 °C, and the temperature of the stirred mixture was allowed to reach 20 °C during 2.5 h. After the cautious addition of wet Et<sub>2</sub>O, the mixture was cooled to 10 °C, carefully acidified (to pH 2) with 2N-HCl, and extracted with Et<sub>2</sub>O to give 5-bromofurfuryl alcohol<sup>4</sup> (14.5 g),  $\nu_{\max}$  3628 cm<sup>-1</sup>, judged pure by t.l.c. (This material, a portion of which decomposed on attempted distillation *in vacuo*, was stored in Et<sub>2</sub>O at 0 °C.) SOCl<sub>2</sub> (14 g) in Et<sub>2</sub>O (20 ml) was added during 30 min to a stirred solution of 5-bromofurfuryl alcohol (13.5 g) in Et<sub>2</sub>O (50 ml)-C<sub>5</sub>H<sub>5</sub>N (12 ml) at -5 °C, and the solution was kept at 0 °C for 12 h. Work-up gave 5-bromofurfuryl chloride<sup>4</sup> (*ca.* 8 g),  $\nu_{\max}$  1270 and 1150 cm<sup>-1</sup>, which was stored in Et<sub>2</sub>O at 0 °C.

The foregoing chloride (*ca.* 2 g) in Et<sub>2</sub>O (20 ml) was added to HO·[CH<sub>2</sub>]<sub>2</sub>·OH (12 ml) at 20 °C. The Et<sub>2</sub>O was removed by distillation at 20 °C and 5 cmHg and the mixture was stirred at 20 °C for 1 h (during which time it became homogeneous). Work-up and p.l.c. [6 large plates; 2 × petrol-Me<sub>2</sub>CO (10:1)] gave 2-(5-bromofurfuryloxy)ethanol (VIII) (960 mg), *R<sub>F</sub>* 0.17, b.p. 94–97° (bath temp.) at 0.1 mmHg (Found: C, 38.1; H, 4.1. C<sub>7</sub>H<sub>8</sub>BrO<sub>3</sub> requires C, 38.0; H, 4.1%), *m/e* 220 (*M*<sup>+</sup>, 11%) and 115 (100), and 1,2-bis-(5-bromofurfuryloxy)ethane (440 mg), *R<sub>F</sub>* 0.34 (Found: C, 38.0; H, 3.1. C<sub>12</sub>H<sub>12</sub>Br<sub>2</sub>O<sub>4</sub> requires C, 37.9; H, 3.2%),  $\nu_{\max}$  1128 and 1905 cm<sup>-1</sup>, *m/e* 380 (*M*<sup>+</sup>, 6%) and 115 (100). Treatment of the alcohol (VIII) (1.1 g) in C<sub>5</sub>H<sub>5</sub>N (12 ml) with TsCl (1.05 g) at 5 °C and work-up after 15 h gave 5-bromofurfuryloxyethyl toluene-4-sulphonate (IX) (1.4 g) as an oil, *R<sub>F</sub>* 0.25 [petrol-Me<sub>2</sub>CO (10:1)] (Found: C, 44.7; H, 4.0. C<sub>14</sub>H<sub>15</sub>-BrO<sub>5</sub>S requires C, 44.8; H, 4.0%), *m/e* 376 (*M*<sup>+</sup>, 3%) and 155 (100). This compound gave complex mixtures on treatment, in separate experiments, with HCO<sub>2</sub>H, CF<sub>3</sub>·CO<sub>2</sub>H, and AgClO<sub>4</sub>-dioxan at various temperatures.

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<sup>4</sup> K. Hayes, G. Gever, and J. Orcutt, *J. Amer. Chem. Soc.*, 1950, **72**, 1205.