Preparation of Thiophen Esters by the Hinsberg Reaction

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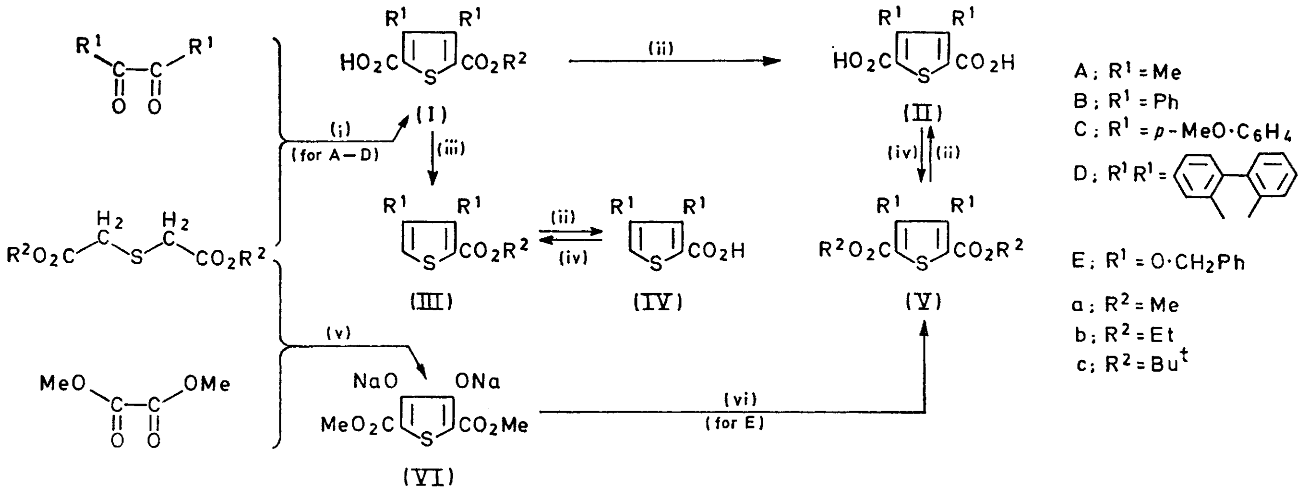
The Hinsberg reaction (interaction between an α-diketone and a dialkyl thiodiacetate) has been used to prepare a series of 3,4-disubstituted thiophen-2-carboxylates and -2,5-dicarboxylates.

For spectrometric investigations[1] of heterocyclic compounds with carbonyl groups at the α-position(s), we required a series of thiophen mono- and di-esters of types (III) and (V). The Hinsberg[2] reaction has been used fairly extensively for obtaining the 2,5-diacids (II) and their derivatives. Mechanistic studies by Wynberg *et al.*[3] established that the initial products from α-diketones and dialkyl thiodiacetates are the half-esters (I): these had not been detected in the earlier work, which involved saponification as part of the general procedure. Since the half-esters can be decarboxylated,[3] the Hinsberg reaction appeared well suited to our purpose (see Scheme).



SCHEME

Reagents: (i), KOBu^t; (ii), NaOH; (iii), Cu–heat; (iv), H_2SO_4–MeOH, or EtOH, or $Me_2CH{:}CH_2$; (v), NaOMe; (vi) $PhCH_2Cl$

Although most of the condensations shown in the Scheme have been reported previously (references in the Experimental section), there is considerable variation

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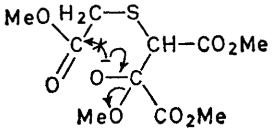
[1] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, in the press.

[2] O. Hinsberg, *Ber.*, 1910, **43**, 901.

[3] (*a*) H. Wynberg and H. J. Kooreman, *J. Amer. Chem. Soc.*, 1965, **87**, 1739; (*b*) H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, 1964, **29**, 1919.

in the extent to which they have been studied. For example, only one derivative, the diacid (IID),[2] of phenanthraquinone is recorded. All the t-butyl esters, which are especially important for the spectrometric work, are new. With one exception, the half-esters (I) were smoothly decarboxylated by heating with copper bronze: the t-butyl ester (IBc), obtained from benzil and di-t-butyl thiodiacetate, gave mainly 3,4-diphenylthiophen.[4]

When oxalic esters rather than α-diketones are used in the Hinsberg reaction, the products are the salts of 3,4-dihydroxy-2,5-diesters, *e.g.*, the salt (VI)[5] from dimethyl oxalate and dimethyl thiodiacetate. Presumably the first negatively-charged adduct loses methoxide anion rather than forming a δ-lactone as in the case of the adduct from an α-diketone.[3]



EXPERIMENTAL

Preparative details are given for the series of compounds derived from one α-diketone; with the other series, procedures are described only if they were not used in, or if they differ from those of the first series. The n.m.r. and mass spectra of the products were as expected, and only a few are reported. U.v. spectra were obtained for EtOH solutions. Petrol refers to light petroleum, b.p. 60—80°.

Products from 4,4′-*Dimethoxybenzil*.—A mixture of 4,4′-dimethoxybenzil (dried at 80° *in vacuo*; 9·5 g) and dimethyl thiodiacetate (freshly distilled; 12 g) was added to a solution, which was stirred at 60°, made from K (4·2 g) and Bu^tOH (freshly distilled from CaH_2; 100 ml). After 30 min the mixture was cooled, acidified with 5N-HCl (20 ml), and the solvents were removed at 40° and 10 mmHg. The residue was extracted with portions (50 ml) of 2N-NH_4OH until acidification of a sample of the alkaline solution did not give a precipitate. Acidification of the combined extracts, and isolation with Et_2O gave 5-*methoxycarbonyl*-3,4-*di*-(p-*methoxyphenyl*)*thiophen*-2-*carboxylic acid* (ICa) (6·8 g), m.p. 220—225° (decomp.) (from MeOH) (Found: C, 62·9; H, 4·6; S, 8·2. $C_{21}H_{18}O_6S$ requires C, 63·3; H, 4·55; S, 8·0%), τ [$(CD_3)_2SO$] 2·99, 3·13, 3·22, 3·26 (8H, A_2B_2 resonances, ArH), 6·30 (6H, s, ArOMe), and 6·33 (3H, s, CO_2Me), *m/e* 398 (M^+, 100%) and 354 (18). Diethyl thiodiacetate (14 g) similarly gave 5-*ethoxycarbonyl*-3,4-*di*-(p-*methoxyphenyl*)*thiophen*-2-*carboxylic acid* (ICb) (7·6 g), m.p. 192—194° (decomp.) (Found: C, 64·2; H, 4·9; S, 8·2. $C_{22}H_{20}O_6S$ requires C, 64·1; H, 4·9; S, 7·8%).

An intimate mixture of the 5-methoxycarbonyl acid (ICa) (2 g) and Cu bronze (1 g) was heated at 300° for 1 h. The material extracted with Et_2O was chromatographed on SiO_2 (75 g). Petrol–Me_2CO mixtures eluted 3,4-di-(*p*-methoxyphenyl)thiophen (250 mg), m.p. 107—108° (from MeOH) (lit.,[6] 117—118°), and then *methyl* 3,4-*di*-(p-*methoxyphenyl*)*thiophen*-2-*carboxylate* (IIICa) (850 mg), m.p. 126° (from MeOH) (Found: C, 67·7; H, 5·1; S, 9·2. $C_{20}H_{18}O_4S$ requires C, 67·8; H, 5·1; S, 9·0%), τ (CCl_4) 2·61 (1H, s, 5-H), *ca.* 3·22 (8H, m, ArH), 6·20 (3H, s, 3-ArOMe), 6·27 (3H, s, 4-ArOMe), and 6·29 (3H, s, CO_2Me), *m/e* 354 (M^+, 100%). The 5-ethoxycarbonyl acid (ICb) (3 g), on heating with Cu bronze (1 g) at 250 °C for 20 min, gave the *ethyl ester* (IIICb) (1·2 g), m.p. 83—84° (from MeOH) (Found: C, 68·7; H, 5·3; S, 8·5. $C_{21}H_{20}O_4S$ requires C, 68·5; H, 5·5; S, 8·7%).

Saponification of the half-ester (ICb) by heating under reflux with 20% aqueous NaOH for 2 h followed by the standard work-up gave 3,4-di-(*p*-methoxyphenyl)thiophen-2,5-dicarboxylic acid (IIC) (75%), m.p. 273—274° (lit.,[6] 269—270°), $\lambda_{max.}$ (EtOH) 235 (ε 18,200) and 259 nm (12,400). Similarly the ethyl ester (IIICb) gave 3,4-*di*-(p-*methoxyphenyl*)*thiophen*-2-*carboxylic acid* (IVC) (72%), m.p. 205—215° (decomp.) (from MeOH) (Found: C, 67·3; H, 5·0. $C_{19}H_{16}O_4S$ requires C, 67·05; H, 4·75%), τ (Me_2SO) 2·28 (1H, s, 5-H).

Isobutene (20 ml) was added to the 2-acid (IVC) (500 mg) in dry Et_2O (40 ml)–H_2SO_4 (2 ml) which was cooled to −30° in a thick-walled flask fitted with a magnetic stirrer. A well-fitting rubber bung was securely wired into position and the mixture was left to reach 20° with stirring. After 3 d the flask was cooled to −30°, opened cautiously, and the solution was poured slowly, with stirring, into cold 5% aqueous KOH (250 ml). Isolation with Et_2O and p.l.c. [1 large plate, 4 × petrol–Me_2CO (4 : 1)] afforded *t-butyl* 3,4-*di*-(p-*methoxyphenyl*)*thiophen*-2-*carboxylate* (IIICc) (325 mg), m.p. 123—125° (from MeOH) (Found: C, 69·8; H, 6·1. $C_{23}H_{24}O_4S$ requires C, 69·7; H, 6·1%), τ (CCl_4) 2·72 (1H, s, 5-H) and 8·65 (9H, s, CO_2Bu^t), *m/e* 396 (M^+, 35%) and 340 (100).

Products from Biacetyl.—5-Ethoxycarbonyl-3,4-dimethylthiophen-2-carboxylic acid[3b] (IAb) (2 g) was heated with Cu bronze (1 g) at 300° for 1 h to give *ethyl* 3,4-*dimethylthiophen*-2-*carboxylate* (IIIAb) (1·2 g), b.p. 98—102° (bath) at 0·02 mmHg (Found: C, 58·95; H, 6·7. $C_9H_{12}O_2S$ requires C, 58·7; H, 6·6), n_D^{20} 1·5294. Saponification of this ester afforded the 2-acid (IVA), m.p. 184—186° (lit.,[7] 187—188°), which was converted into *t-butyl* 3,4-*dimethylthiophen*-2-*carboxylate* (IIIAc) (81%), b.p. 100—105° (bath) at 0·04 mmHg, m.p. 50—52° (Found: C, 62·5; H, 7·35; S, 15·25. $C_{11}H_{16}O_2S$ requires C, 62·25; H, 7·6; S, 15·1%).

A mixture of the 2,5-diacid (IIA)[8] (500 mg), EtOH (20 ml), and H_2SO_4 (1·5 ml) was boiled under reflux for 2 h. Work-up gave *diethyl* 3,4-*dimethylthiophen*-2,5-*dicarboxylate* (VAb) (505 mg), m.p. 79—80° (from MeOH) (Found: C, 56·2; H, 6·3. $C_{12}H_{16}O_4S$ requires C, 56·2; H, 6·3%). The diacid (IIA) was also converted into *di-t-butyl* 3,4-*dimethylthiophen*-2,5-*dicarboxylate* (VAc) (78%), m.p. 167—168° (from MeOH) (Found: C, 61·4; H, 7·8; S, 10·1. $C_{16}H_{24}O_4S$ requires C, 61·5; H, 7·75; S, 10·2%).

Products from Benzil.—Isobutene (50 ml), thiodiacetic acid (15 g), and Et_2O (100 ml)–H_2SO_4 (3 ml) were used as described earlier to give *di-t-butyl thiodiacetate* (19·5 g), b.p. 121—122° at 1·5 mmHg (Found: C, 55·2; H, 8·5; S, 12·1. $C_{12}H_{22}O_4S$ requires C, 54·95; H, 8·45; S, 12·2%), τ (CCl_4) 6·79 (s, S·CH_2) and 8·35 (s, CO_2Bu^t). Reaction of this ester (2 g) with benzil (1 g) at 30° for 15 min in a solution prepared from K (1·4 g) and Bu^tOH (30 ml) gave 2-*t*-*butoxycarbonyl*-3,4-*diphenylthiophen*-5-*carboxylic acid* (IBc)

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[5] E. W. Fager, *J. Amer. Chem. Soc.*, 1945, **67**, 2217.

[6] O. Dann and H. Hauck, *Arch. Pharm.*, 1960, **293**, 187.

[7] H. Fiesselmann and H. Habicht, G. P. 1,092,929 (Cl. 2q) 1960 (*Chem. Abs.*, 1962, **57**, 5894).

[8] R. Seka, *Ber.*, 1925, **58**, 1783.

(1·3 g), m.p. 210—220° (decomp.) (from MeOH) (Found: C, 69·6; H, 5·2; S, 8·6. $C_{22}H_{20}O_4S$ requires C, 69·5; H, 5·3; S, 8·4%). The ester (IBc) (500 mg) and Cu bronze (500 mg) at 240° for 10 min gave 3,4-diphenylthiophen (310 mg), m.p. 112—114° (lit.,[4] 114°).

With isobutene, the 2-acid (IVB)[4] gave *t-butyl* 3,4-*diphenylthiophen*-2-*carboxylate* (IIIBc) (68%), m.p. 90—91° (from MeOH) (Found: C, 74·8; H, 6·2. $C_{21}H_{20}O_2S$ requires C, 75·0; H, 6·0%), and the 2,5-diacid (IIB)[4] gave *di-t-butyl* 3,4-*diphenylthiophen*-2,5-*dicarboxylate* (VBc) (67%), m.p. 172—174° (from MeOH) (Found: C, 71·7; H, 6·65; S, 7·55. $C_{26}H_{28}O_4S$ requires C, 71·5; H, 6·5; S, 7·3%).

Products from Phenanthraquinone.—Reaction of phenanthraquinone (8 g) with dimethyl thiodiacetate (12 g) at 30° for 15 min in a solution prepared from K (4·2 g) and Bu^{t}OH (100 ml) gave 3-*methoxycarbonylphenanthro*[9,10-c]-*thiophen*-1-*carboxylic acid* (IDa) (3·5 g), m.p. 215—220° (decomp.) (from MeOH) (Found: C, 67·4; H, 3·7. $C_{19}H_{12}O_4S$ requires C, 67·85; H, 3·6%), $\lambda_{max.}$ (EtOH) 250 (ε 21,900) and 267 nm (21,200). Decarboxylation of this half-ester (1 g) gave *methyl phenanthro*[9,10-c]*thiophen*-1-*carboxylate* (IIIDa) (620 mg), m.p. 151—152° (from MeOH) (Found: C, 73·9; H, 4·1. $C_{18}H_{12}O_2S$ requires C, 74·0; H, 4·1%).

3,4-*Dibenzyloxythiophen*-2,5-*dicarboxylic Acid* (IIE) *and Dimethyl* 3,4-*Dibenzyloxythiophen*-2,5-*dicarboxylate* (VEa).—A suspension of the disodium salt of dimethyl 3,4-dihydroxythiophen-2,5-dicarboxylate (VI)[5] (13·5 g) in $PhCH_2Cl$ (100 ml)–$Me_2N{\cdot}CHO$ (250 ml) was stirred at 100° for 2·5 h. The cooled mixture was filtered, the filtrate was evaporated *in vacuo*, and the residue was crystallised from MeOH to give the *dimethyl ester* (VEa) (15·1 g), m.p. 104—106° (Found: C, 63·9; H, 5·2; S, 7·7. $C_{22}H_{20}O_6S$ requires C, 64·1; H, 4·9; S, 7·8%), $\lambda_{max.}$ 282 nm (ε 8900), *m/e* 412 (M^+, 1%) and 91 (100). Hydrolysis of this ester by heating under reflux for 1 h with 3% aqueous NaOH gave the *dicarboxylic acid* (IIE) (80%), m.p. 205—206° (from MeOH) (Found: C, 62·2; H, 4·3; S, 8·4. $C_{20}H_{16}O_6S$ requires C, 62·5; H, 4·2; S, 8·3%), $\lambda_{max.}$ 281 nm (ε 9900).

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