140. *Compounds of Potential Pharmacological Interest. Part II.* Some Heterocyclic and Carbocyclic Systems Related to 1-Phenylindane.*

By R. M. Acheson, K. E. MacPhee, P. G. Philpott, and J. A. Barltrop.

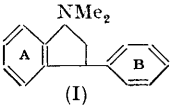
Attempts to prepare the thiophen analogues of 1-dimethylamino-3-phenylindane are described. 3′-Dimethylamino-5′-phenyl*cyclo*penteno(1′ : 2′-2 : 3)thiophen (IV) has been synthesised from phenyl 2-thienyl ketone. 9-Dialkylaminoalkyl-9-ethoxycarbonyl-xanthen and -dihydroanthracene have been obtained by alkylating the potassio-derivatives of 9-ethoxycarbonylxanthen and -dihydroanthracene with primary dialkylaminoalkyl halides. A similar alkylation in the xanthen series, involving the secondary halide, 2-chloro-1-dimethylaminopropane, led to the amino-ester (XXIII) formed by reaction at the ester group. 9-Dimethylaminoxanthen has also been prepared.

In Parts I * and IV [1] are reported the analgesic activity associated with 1-dimethylamino-3-phenylindane (I) and attempts to augment the activity of the system by structural modifications. This communication is concerned with a similar investigation into the behaviour of related heterocyclic compounds. Replacement of a benzene ring in a pharmacologically active substance by a thiophen nucleus sometimes increases the activity but rather more frequently decreases it (see the thienyl analogues of amidone and pethidine [2]). However, some 3-dialkylamino-1 : 1-di-2′-thienyl-but-1-enes (II) and -butanes (III), prepared by Adamson,[3] exhibited such high analgesic acitivity as to encourage us to pursue similar investigations and in particular to synthesise the compounds (IV) and (V), which are related cyclically to Adamson's substances.

* Part I, preceding paper.

[1] Acheson, Philpott, MacPhee, Hunt, and Barltrop, to be published.
[2] Blicke, U.S.P. 2,425,721: Brown, Cook, and Heilbron, *J.*, 1949, S 113; Leonard and Ehrenthal, *J. Amer. Chem. Soc.*, 1951, **73**, 2216.
[3] Adamson, *J.*, 1950, 885; *Nature*, 1950, **165**, 122; 1951, **167**, 153.

Attempts to prepare β-phenyl-β-2-thienylpropionic acid (VI; R = H) as an intermediate by alkylating thiophen with cinnamic acid (cf. Pfeiffer and de Waal,[4] for the preparation of 3 : 3-diphenylpropionic acid) in presence of aluminium chloride or boron trifluoride, led to recovery of most of the cinnamic acid and destruction of the bulk of the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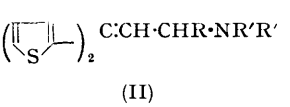
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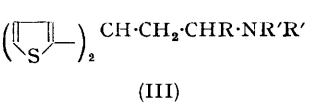
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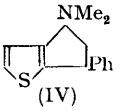
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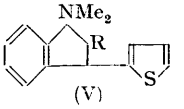
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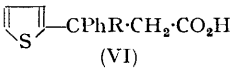
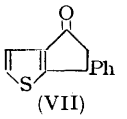

(VI)

thiophen, though in one case a very low yield of the ketone (VII) was obtained. In an alternative approach a Reformatsky reaction between phenyl 2-thienyl ketone [5] and ethyl bromoacetate gave an 86% yield of ethyl β-hydroxy-β-phenyl-β-2-thienylpropionate (as VI; R = OH) which was dehydrated by aqueous oxalic acid [6] to the acrylic ester. This, on reduction with sodium amalgam and hydrolysis, gave the desired propionic acid (VI; R = H) in 78% yield. Efforts to cyclise the derived acid chloride with aluminium chloride, or with stannic chloride in carbon disulphide or benzene, resulted in resins from which traces of ketonic material but no acid could be isolated. Ultimately, under precisely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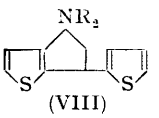
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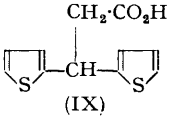
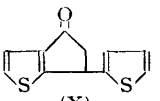

(IX)

defined conditions, polyphosphoric acid was found to cyclise the acid to a ketone albeit in only moderate yields. That the cyclisation involved the thiophen rather than the benzene ring, and gave (VII), was proved by first desulphurising the ketone with Raney nickel [7] and then oxidising the product with alkaline potassium permanganate : benzoic acid was obtained in 33% yield and no phthalic acid.

The ketone (VII) was reduced to the alcohol by lithium aluminium hydride, and this was converted into the bromide and then allowed to react with dimethylamine. 3′-Dimethylamino-5′-phenyl*cyclo*penteno(1′ : 2′-2 : 3)thiophen (IV), so obtained, appeared to exist as a mixture of *cis–trans*-isomers, which were separated.

An attempt was now made to prepare the bases (VIII) in which both rings A and B in the phenylindane (I) were replaced by thiophen nuclei. 2-Thienoic acid was prepared by a modification of Gilman and Shirley's method [8] and converted into 2 : 2′-dithienyl ketone by condensing it with thiophen in the presence of phosphoric oxide. This ketone was converted, as in the previous case, into ββ-di-2-thienylpropionic acid (IX). It was found to be impossible to cyclise this acid, even polyphosphoric acid yielding only tars. Pre-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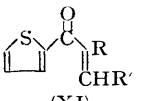
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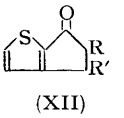
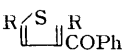

(XII)

sumably, these difficulties arise from the facility of intermolecular condensation involving the reactive position 5 of the thiophen ring, compared with the difficulty of intramolecular condensation on to the relatively inert position 3; the substance (IX) with two such reactive positions would be expected to be more intractable than (VI; R = H) which possesses only one.

[4] Pfeiffer and de Waal, *Annalen*, 1935, **520**, 185.
[5] Minnis, *Org. Synth.*, Coll. Vol. II, p. 520.
[6] Cf. Miller and Nord, *J. Org. Chem.*, 1950, **15**, 89.
[7] Cf. Blicke and Sheets, *J. Amer. Chem. Soc.*, 1949, **71**, 4010.
[8] Gilman and Shirley, *ibid.*, p. 1870.

Equally unsuccessful was an attempt to prepare the intermediate (XII; R = H, R′ = Ph). Burckhalter and Sam [9] reported the cyclisation of the olefin (XI; R = Me, R′ = H) to the ketone (XII; R = Me, R′ = H) by means of concentrated sulphuric acid, but styryl 2-thienyl ketone (XI; R = H, R′ = Ph), under the catalytic influence of



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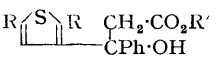

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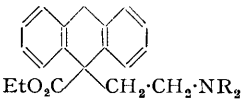


(XIX)

sulphuric acid, aluminium chloride, boron trifluoride or polyphosphoric acid, gave only starting material or red gums. This result, and the considerations advanced in the previous paragraph, suggested that it might be more profitable to turn to syntheses which depended on cyclisation on to the position 2 of the thiophen ring.

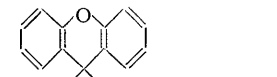
(XV) (XVI) (XVII) (XVIII)

(Th = 2-thienyl.)

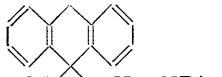
3-Benzoyl-2 : 5-dichlorothiophen (XIII; R = Cl) was obtained by benzoylation of 2 : 5-dichlorothiophen, and converted into the ester (XIV; R = Cl, R′ = Et) by a Reformatsky reaction with ethyl bromoacetate. Difficulty was experienced with the dehydration of this substance, so it was immediately reduced with sodium amalgam, giving the dehalogenated acid (XIV; R, R′ = H). Further experiments along this route are proceeding.

A more promising reaction sequence suggested by the work of Burton and Shoppee [10] appeared to be (XV) ⟶ (XVIII). 2-Methylindenone (XV) [10] and 2-thienylmagnesium iodide gave 1-hydroxy-2-methyl-1-2′-thienylindene (XVI), which on acetylation gave the acetoxy-compound (XVII). This, on hydrolysis with alcoholic potassium hydroxide, underwent a prototropic rearrangement to the thienylindanone (XVIII). The transformation of this substance into the amine (V; R = Me) is under investigation.

Another aspect of this work, studied simultaneously, was the synthesis of molecules of the types (XIX), (XX), and (XXI), which are carbocyclic and heterocyclic analogues of the amidone group of analgesics. Ethyl 9 : 10-dihydroanthracene-9-carboxylate, prepared in excellent yield by carboxylating the lithio-derivative of dihydroanthracene and esterifying the acid, was converted into its potassio-derivative and alkylated in toluene with 2-diethylaminoethyl chloride, giving the amine (XIX; R = Et). An attempt



(XX)



(XXI)

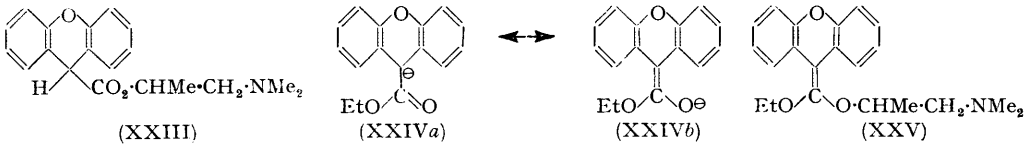
(XXII)

to prepare the corresponding 2-dimethylaminoethyl derivative (XIX; R = Me) under similar conditions gave a product containing two basic residues, evidently (XXII), in which further alkylation of the primary product (XIX; R = Me) had occurred.

Attempts to prepare the amino-ketone (XXI; R = R′ = Et) by alkylating 9 : 10-dihydro-9-propionylanthracene [11] with diethylaminoethyl chloride in the presence of sodamide gave only degradation products, from which ultimately anthracene and anthraquinone were isolated. Further investigation was curtailed by the publication of the successful synthesis of this and related compounds by Cusic.[12]

[9] Burkhalter and Sam, *ibid.*, 1951, **73**, 4460.
[10] Burton and Shoppee, *J.*, 1935, 1156.
[11] May and Mosettig, *J. Amer. Chem. Soc.*, 1948, **70**, 688.
[12] Cusic, U.S.P. 2,551,316.

Analogous compounds (XX; R′ = H, R″ = Me and Et) were prepared similarly from ethyl xanthen-9-carboxylate. However, reaction with 2-chloropropyldimethylamine was very slow and the product had the formula $C_{19}H_{21}O_3N$ instead of the expected $C_{21}H_{25}O_3N$: clearly, an ethyl group had been lost. There are two likely structures for the substance: first, an amino-acid formulation (XX; R′ = R″ = Me, CO_2H replacing CO_2Et), which was excluded because of the insolubility of the substance in alkali; and, secondly, the amino-ester formulation (XXIII), which was proved by alkaline hydrolysis to xanthen-9-carboxylic acid.



(XXIII) (XXIV*a*) (XXIV*b*) (XXV)

This anomalous alkylation presumably occurs because the potassio-derivative of ethyl xanthen-9-carboxylate is mesomeric (XXIV*a* ⟷ *b*). With primary alkyl halides, alkylation proceeds predominantly on $C_{(9)}$ *via* the canonical form (*a*). However, $C_{(9)}$ is less accessible than the negatively charged oxygen atom in (XXIV*b*), and with the more hindered secondary halides substitution at this point is so retarded that the main reaction takes place at the oxygen atom, leading to the keten acetal (XXV). This would be hydrolysed under the acidic working-up procedures to the ester (XXIII) or to ethyl xanthen-9-carboxylate. This abnormal alkylation finds a parallel in the work of Laakso [13] who showed that certain dithio-esters, when alkylated, gave keten mercaptals.

Finally, the synthesis of 9-dimethylaminomethylxanthen was accomplished by reducing *NN*-dimethylxanthen-9-carboxyamide with lithium aluminium hydride.

Through the courtesy of Dr. G. E. Ullyot, these compounds were examined pharmacologically by Smith, Kline and French Laboratories, Philadelphia. Significant analgesic activity was not observed in these substances. 9-Dimethylaminomethylxanthen showed activity as an antihistaminic (demonstrated by protection afforded to guinea pigs in bronchospasm induced by histamine) and as a sedative for the central nervous system. The amino-esters of the xanthen series possessed antispasmodic activity.

Experimental

Ethyl β-Hydroxy-β-phenyl-β-2-thienylpropionate.—A mixture of phenyl 2-thienyl ketone [5] (38·8 g.), ethyl bromoacetate (14 g.), zinc turnings (17 g.), and benzene (200 c.c.) was boiled under reflux for 4 hr. The mixture was cooled and decomposed with ice and sulphuric acid, and the benzene layer separated, washed with water, sodium hydrogen carbonate solution, and water, dried and evaporated. The solid residue, when crystallised from ligroin (b. p. 40—60°) gave the desired *ester* (49 g., 86%) as needles, m. p. 65—66° (Found : C, 65·4; H, 6·0; S, 11·9. $C_{15}H_{16}O_3S$ requires C, 65·3; H, 5·8; S, 11·6%).

Ethyl β-Phenyl-β-2-thienylacrylate.—The preceding hydroxy-ester (48 g.) was boiled under reflux for 3 hr. with 6% aqueous oxalic acid (500 c.c.). The oily layer was separated, dried, and distilled. *Ethyl β-phenyl-β-2-thienylacrylate* (40 g., 83%) was collected at 135—140°/0·2 mm. (Found : C, 70·1; H, 5·5; S, 12·7. $C_{15}H_{14}O_2S$ requires C, 69·8; H, 5·4; S, 12·4%).

Hydrolysis gave the *acrylic acid*, which crystallised from ligroin in colourless elongated needles, m. p. 136—137° (Found : C, 68·1; H, 4·6; S, 13·7. $C_{13}H_{10}O_2S$ requires C, 67·8; H, 4·4; S, 13·9%).

β-Phenyl-β-2-thienylpropionic Acid.—A mixture of ethyl β-phenyl-β-2-thienylacrylate (40 g.), sodium amalgam (3%; 960 g.), and ethanol (500 c.c.) was boiled under reflux for 7 hr. The solution was decanted from mercury, diluted with water (200 c.c.), and boiled for a further 2 hr. The bulk of the ethanol was distilled off, and the residual solution was washed with ether and acidified. The precipitated acid was crystallised from ligroin. The *propionic acid* (28·2 g., 78%) formed colourless needles, m. p. 147—148° (Found : C, 67·0; H, 5·14; S, 13·9. $C_{13}H_{12}O_2S$ requires C, 67·3; H, 5·2; S, 13·8%). The *amide* separated from water in needles, m. p. 115—116° (Found : C, 67·8; H, 5·7; N, 6·2; S, 13·6. $C_{13}H_{13}ONS$ requires C, 67·6; H, 5·6; N, 6·1; S, 13·9%).

[13] Laakso, *Suomen Kem.*, 1944, **17**, *B*, 1, 3.

*3'-Oxo-5'-phenyl*cyclo*penteno*(1' : 2'-2 : 3)*thiophen.*—(*A*) β-Phenyl-β-2-thienylpropionic acid (1·5 g.) was added to a stirred mixture of phosphoric anhydride (10 g.) in phosphoric acid (85%; 9 c.c.) at 145—150° and kept at that temperature for 5 min. The mixture was diluted with ice and extracted with ether (3 × 30 c.c.). The extract was washed with water, sodium carbonate solution, and water, and dried. Unchanged acid was recovered from the sodium carbonate washings. In total, 33 g. of acid were treated in this manner. The ether solution was evaporated and the residue distilled. The *ketone* (11·5 g., 35%) was collected at 130—135°/0·1 mm. It crystallised from ligroin in pale yellow rhombs, m. p. 93—94° (Found: C, 73·2; H, 5·0; S, 14·7. $C_{13}H_{10}OS$ requires C, 72·9; H, 4·7; S, 15·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in brick-red needles, m. p. 250° (Found: C, 58·3; H, 3·9; S, 8·0. $C_{19}H_{14}O_4N_4S$ requires C, 57·8; H, 3·6; S, 8·1%), and the *oxime* from aqueous ethanol in pale yellow needles, m. p. 214° (decomp.) (Found: N, 6·0. $C_{13}H_{11}ONS$ requires N, 6·1%).

(*B*) Thiophen, cinnamic acid, and aluminium chloride were allowed to react in nitrobenzene for 60 hr. at 10—15° under conditions described by Pfeiffer and de Waal[4] for the alkylation of cinnamic acid with benzene. Cinnamic acid (75%) and thiophen (10%) were recovered. Vacuum-distillation gave a very low yield of a ketonic oil. The 2 : 4-dinitrophenylhydrazone had m. p. 250° alone and when mixed with the dinitrophenylhydrazone described above.

*Degradation of 3'-Oxo-5'-phenyl*cyclo*penteno*(1' : 2'-2 : 3)*thiophen.*—A mixture of the ketone (1 g.), Raney nickel[14] (40 g.), and ethanol (200 c.c.) was boiled under reflux for 30 min., cooled, and filtered. The ethanol washings from the catalyst were combined with the filtrate and evaporated. The residual, sweet-smelling oil was boiled with stirring for 4 hr. with a solution of potassium hydroxide (3·4 g.) and potassium permanganate (9·5 g.) in water (300 c.c.). The cool mixture was decolorised with sulphur dioxide, strongly acidified, and extracted with ether (3 × 60 c.c.). The ethereal solution was extracted with sodium hydrogen carbonate solution, and the aqueous phase acidified, and extracted several times with ether. Evaporation of the dried ethereal solution gave a solid residue, which on sublimation *in vacuo* gave benzoic acid (0·2 g., 33%), m. p. and mixed m. p. 122°

*3'-Hydroxy-5'-phenyl*cyclo*penteno*(1' : 2'-2 : 3)*thiophen.*—3'-Oxo-5'-phenyl*cyclo*penteno-(1' : 2'-2 : 3)thiophen (7·8 g.) in dry ether (200 c.c.) was boiled with lithium aluminium hydride (0·45 g.) in ether (200 c.c.) for 1 hr. On cooling, excess of reagent was destroyed with a few drops of water and the complex decomposed with 10% sulphuric acid. The ether layer was separated, and the aqueous layer extracted with ether (3 × 30 c.c.). The combined ether fractions were washed with water, sodium hydrogen carbonate solution, and water and dried ($MgSO_4$). On removal of the ether the residue solidified. *3'-Hydroxy-5'-phenyl*cyclo*penteno*-(1' : 2'-2 : 3)*thiophen* (6·6 g., 85%) crystallised from ligroin in colourless needles, m. p. 133—134° (Found: C, 72·1; H, 5·6; S, 14·6. $C_{13}H_{12}OS$ requires C, 72·2; H, 5·6; S, 14·8%).

*3'-Dimethylamino-5'-phenyl*cyclo*penteno*(1' : 2'-2 : 3)*thiophen.*—A solution of 3'-hydroxy-5'-phenyl*cyclo*penteno(1' : 2'-2 : 3)thiophen (7·2 g.) in benzene (300 c.c.) was saturated with hydrogen bromide at 0°. Water separated and in an hour the solution became dark greenish-blue. The benzene solution was washed with water, 5% sodium hydrogen carbonate solution, and water, and the benzene removed under reduced pressure. The residue was dissolved in dry dioxan (30 c.c.) and together with anhydrous dimethylamine (7 g.) was transferred to a pressure bottle at 0°. Reaction was allowed to proceed for 12 hr. at room temperature. The dimethylamine hydrobromide was collected and the filtrate concentrated under reduced pressure. The residual oil was dissolved in dry ether and saturated with dry hydrogen chloride at 0°. After 1 hr. the ether was decanted and the gummy solid dried *in vacuo* over sodium hydroxide. *3'-Dimethylamino-5'-phenyl*cyclo*penteno*(1' : 2'-2 : 3)*thiophen hydrochloride* (*isomer A*; 2·5 g.) crystallised from ethyl acetate–ethanol in colourless needles, m. p. 196—197° (Found: C, 64·3; H, 6·7; S, 11·8. $C_{15}H_{17}NS,HCl$ requires C, 64·4; H, 6·4; S, 11·5%). The *picrate* (of isomer A) separated from ethanol in bright yellow needles, m. p. 150—151° (Found: C, 53·8; H, 4·3. $C_{15}H_{17}NS,C_6H_3N_3O_7$ requires C, 53·4; H, 4·2%).

The mother-liquors from crystallisation of isomer A yielded an isomeric (*B*) *amine hydrochloride*, which crystallised from ethyl acetate–ethanol in colourless rhombs (2 g.), m. p. 150—151° (Found: C, 64·2; H, 6·5; S, 11·2%). The derived *picrate* separated from ethanol in yellow needles, m. p. 129—130° (Found: C, 53·6; H, 4·2; N, 11·6%).

A saturated solution of isomer B in ethyl acetate–ethanol, seeded with isomer A, does not give isomer A; isomer B is recovered unchanged.

2-Thienoic Acid.—A solution of *n*-butyl bromide (54·8 g.) in dry ether (100 c.c.) was added

[11] Mozingo, Wolf, Harris, and Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1013.

in an atmosphere of dry nitrogen to a stirred mixture of small strips of lithium (8 g.) in dry ether (300 c.c.). When reaction was complete, the solution was blown, under pressure of nitrogen, through small-bore tubing into a two-necked flask containing a stirred solution of thiophen (16·8 g.) in ether (100 c.c.). The mixture was stirred for a further 15 min. and then blown (by nitrogen) through tubing on to a stirred slurry of crushed solid carbon dioxide and ether. Water (100 c.c.) was added cautiously to the mixture. The aqueous layer was separated and acidified with concentrated hydrochloric acid, and the 2-thienoic acid collected. This (18·2 g., 71%) crystallised from ligroin in colourless needles, m. p. 128°.

Di-2-thienyl Ketone.—2-Thienoic acid (36·5 g.) in benzene (300 c.c.) was boiled for 2 hr. under reflux with thiophen (25·2 g.), phosphoric anhydride (48 g.), and benzene (300 c.c.). Another portion of phosphoric anhydride (48 g.) was added and the mixture boiled under reflux for a further 2 hr. The benzene solution was decanted, washed with water, sodium hydroxide solution, and water, and then dried and distilled. The ketone (36·4 g., 66%), b. p. 185—190°/10 mm., crystallised from ligroin in colourless needles, m. p. 88—89°. Hartough and Kosak[15] record a yield of 50%.

Ethyl β-Hydroxy-ββ-di-2-thienylpropionate.—A mixture of di-2-thienyl ketone (36·4 g.), ethyl bromoacetate (40 g.), and zinc turnings (15 g.) in dry benzene (400 c.c.) was boiled under reflux for 4 hr. The mixture was cooled and decomposed with 10% sulphuric acid. The benzene layer was separated, washed with water, 5% sodium hydrogen carbonate solution, and water, and the benzene removed under reduced pressure; the residue solidified. The *hydroxy-ester* crystallised from ligroin in colourless rods, m. p. 55—56° (Found: C, 55·7; H, 5·2; S, 22·5. $C_{13}H_{14}O_3S_2$ requires C, 55·3; H, 5·0; S, 22·7%).

Ethyl ββ-Di-2-thienylacrylate.—The crude hydroxy-ester, suspended in aqueous oxalic acid (500 c.c.; 6%), was boiled under reflux for 3 hr. The mixture was cooled, and the oil separated, dried, and distilled. The *acrylate* (35 g.) was collected at 140—145°/0·2 mm. (Found: C, 58·9; H, 4·3. $C_{13}H_{12}O_2S_2$ requires C, 59·1; H, 4·5%).

Hydrolysis afforded the *acrylic acid*, needles, m. p. 137° (from ligroin))Found: C, 56·1; H, 3·6; S, 27·1. $C_{11}H_8O_2S_2$ requires C, 55·9; H, 3·4; S, 27·1%).

ββ-Di-2-thienylpropionic Acid.—Ethyl ββ-di-2-thienylacrylate (34 g.), sodium amalgam (3%; 800 g.), and ethanol (500 c.c.) were boiled under reflux for 11 hr., decanted from mercury, diluted with water (100 c.c.), and boiled under reflux for a further 2 hr. The bulk of the ethanol was removed under reduced pressure, the cooled aqueous solution acidified, and the precipitated acid collected and dried at 100°. *ββ-Di-2′-thienylpropionic acid* (22·2 g.) crystallised from ligroin in colourless needles, m. p. 118° (Found: C, 55·6; H, 4·5; S, 27·0. $C_{11}H_{10}O_2S_2$ requires C, 55·4; H, 4·2; S, 26·9%). The *amide* separated from water in needles, m. p. 126° (Found: C, 55·3; H, 4·3; N, 5·8; S, 27·4. $C_{11}H_{11}ONS_2$ requires C, 55·7; H, 4·6; N, 5·9; S, 27·0%).

Styryl 2-Thienyl Ketone.[16]—Sodium (0·5 g.) was dissolved in ethanol (10 c.c.) and added to a solution of 2-acetylthiophen[15] (5 g.) and benzaldehyde (4·2 g.) in ethanol (50 c.c.), and the solution kept at 0° for 24 hr. Styryl 2-thienyl ketone was collected, washed with cold ethanol, and dried. It crystallised from ligroin in colourless rods, (7·1 g.) m. p. 85—86° (Brunswig gives m. p. 80°) (Found: C, 72·7; H, 4·8; S, 14·7. Calc. for $C_{13}H_{10}OS$: C, 72·9; H, 4·7; S, 15·0%).

3-Benzoyl-2 : 5-dichlorothiophen.—Powdered, aluminium chloride (37·5 g.) was added, during 30 min., to a stirred solution of 2 : 5-dichlorothiophen (38·3 g.) and benzoyl chloride (38 g.) in carbon disulphide (200 c.c.) at 15°. The mixture became deep black almost immediately. Stirring was continued for a further 2 hr. and the mixture then set aside at room temperature for 12 hr. The complex was decomposed with ice and concentrated hydrochloric acid. The carbon disulphide layer was washed with water, 10% sodium hydrogen carbonate solution (3 × 50 c.c.), and water, and dried, and distilled. *3-Benzoyl-2 : 5-dichlorothiophen* (16·8 g.) was collected at 125—130°/0·2 mm. It was a pale yellow mobile oil which darkened rapidly in light and air. The *2 : 4-dinitrophenylhydrazone* crystallised from acetic acid in orange needles, m. p. 208° (Found: C, 47·0; H, 2·6; N, 12·7; S, 6·9. $C_{17}H_{10}O_4N_4Cl_2S$ requires C, 46·7; H, 2·3; N, 12·8; S, 7·3%).

Ethyl β-(2 : 5-Dichloro-3-thienyl)-β-hydroxy-β-phenylpropionate.—A mixture of 3-benzoyl-2 : 5-dichlorothiophen (5 g.), zinc turnings (1·7 g.), and ethyl bromoacetate (3·5 g.) in dry benzene (100 c.c.) was heated under reflux for 4 hr. The mixture was cooled and decomposed with sulphuric acid. The benzene layer was separated, washed with water, sodium hydrogen

[15] Hartough and Kosak, *ibid.*, 1947, **69**, 3093.
[16] Cf. Brunswig, *Ber.*, 1886, **19**, 2895.

carbonate solution, and water, and dried, and distilled. The *hydroxy-ester* (5·5 g.), a yellow, mobile oil, was collected at 150—155°/0·2 mm. (Found: C, 52·5; H, 4·1; Cl, 20·3; S, 9·7. $C_{15}H_{14}O_3Cl_2S$ requires C, 52·2; H, 4·1; Cl, 20·6; S, 9·3%).

Hydrolysis afforded the *hydroxy-acid*, which crystallised from ligroin in pale brown needles, m. p. 115° (Found: C, 49·5; H, 3·5; Cl, 22·2; S, 9·9. $C_{13}H_{10}O_3Cl_2S$ requires C, 49·2; H, 3·2; Cl, 22·4; S, 10·1%).

An attempt to dehydrate the hydroxy-ester by 6% aqueous oxalic acid gave an unstable oil; hydrolysis of this afforded the hydroxy-acid, identified by analysis and mixed m. p. 115°. The impure hydroxy-ester (from the attempted dehydration) with 3% sodium amalgam (10 equivs.) in aqueous ethanol was heated under reflux for 10 hr.: this gave an acid which crystallised from ligroin in pale yellow rhombs, m. p. 114°, and still contained a small amount of halogen (Beilstein test). It may be impure β-hydroxy-β-phenyl-β-3-thienylpropionic acid (Found: C, 61·9; 60·8; H, 4·6, 4·4; S, 11·4, 11·8. Calc. for $C_{13}H_{12}O_3S$: C, 62·9; H, 4·8; S, 12·9%).

1-*Hydroxy*-2-*methyl*-1-2′-*thienylindene*.—A solution of 2-iodothiophen[17] (10·5 g.) and methyl iodide (7 g.) in dry ether (50 c.c.) was added to magnesium (1·3 g.), and the mixture heated under reflux for 4 hr. The solution was cooled and 2-methylindenone (6 g.) in dry ether (30 c.c.) was added. A transient red colour was formed, which during 3 hr. at room temperature became orange-yellow. The mixture was decomposed with saturated aqueous ammonium chloride, and the ether layer separated. The aqueous layer was extracted with ether (3 × 30 c.c.), and the combined ether extracts were washed as above, dried, and distilled, yielding 1-hydroxy-1:2-dimethylindene (0·9 g.), b. p. 110°/1 mm., in colourless rhombs (from ligroin), m. p. 84—85° (Found: C, 82·2; H, 7·3. Calc. for $C_{11}H_{12}O$: C, 82·5; H, 7·5%) (Stoermer and Laage[18] give m. p. 82°), and 1-*hydroxy*-2-*methyl*-1-2′-*thienylindene* (4·5 g.), an orange-yellow viscous oil, b. p. 153—155°/1 mm. (Found: C, 74·0; H, 5·2; S, 13·6. $C_{14}H_{12}OS$ requires C, 73·6; H, 5·3; S, 14·0%).

1-*Acetoxy*-2-*methyl*-3-2′-*thienylindene*.—1-Hydroxy-2-methyl-1-2′-thienylindene (1 g.) and acetic anhydride (10 c.c.) were heated under reflux for 7 hr., during which the colour had changed from pale yellow to a deep purple. The mixture was poured into cold water (100 c.c.) to decompose the excess of acetic anhydride and extracted with ether (3 × 30 c.c.). The combined ether extracts were washed with water, sodium carbonate solution, and water, and dried, and distilled. 1-*Acetoxy*-2-*methyl*-3-2′-*thienylindene* (0·4 g.) was obtained as a pale yellow oil, b. p. 125°/0·6 mm., forming rhombs, m. p. 100° (from ligroin) (Found: C, 71·5; H, 5·5; S, 12·2. $C_{16}H_{14}O_2S$ requires C, 71·1; H, 5·2; S, 11·9%).

2-*Methyl*-3-2′-*thienylindan*-1-*one*.—A solution of 1-acetoxy-2-methyl-3-2′-thienylindene (0·5 g.) in ethanolic potassium hydroxide (20 c.c.; 5%) was boiled under reflux for 2 hr. There was a colour change from yellow to red. The solution was poured into water (100 c.c.), and the aqueous mixture extracted with ether (3 × 30 c.c.). The ether extracts were washed with water, dried, and evaporated. The ketone (*ca.* 0·3 g.) was obtained as a dark red mobile oil. The 2:4-*dinitrophenylhydrazone* crystallised from acetic acid in dark red plates, m. p. 198° (Found: C, 59·0; H, 4·1; N, 13·5. $C_{20}H_{16}O_4N_4S$ requires C, 58·8; H, 3·9; N, 13·7%).

Ethyl 9-2′-*Diethylaminoethyl*-9:10-*dihydroanthracene*-9-*carboxylate*.—Potassium (1·75 g., 1 atom-equiv.) was added in small pieces to a dry toluene solution of ethyl 9:10-dihydroanthracene-9-carboxylate (11·5 g., 1 mol.). The solution was stirred at room temperature for 2 hr. and then warmed gently to reflux for ½ hr., by which time all the potassium had dissolved. The brown suspension was cooled, freshly prepared 2-diethylaminoethyl chloride (6·1 g., 1 mol.) was added, and the solution was heated under reflux for 3 hr., then cooled and extracted with dilute hydrochloric acid. The acid solution was strongly basified and extracted with ether. The residue from the dried extracts was heated *in vacuo* at 100° for ½ hr. and then dried *in vacuo* over concentrated sulphuric acid to remove any residual 2-diethylaminoethyl chloride. The hydrochloride was prepared in the usual way but failed to crystallise. The *picrate*, crystallised from ethanol, had m. p. 104° (Found: C, 60·0; H, 5·6; N, 9·4. $C_{23}H_{29}O_2N,C_6H_3O_7N_3$ requires C, 60·0; H, 5·6; N, 9·7%).

An attempt to prepare the corresponding 2-dimethylaminoethyl compound under similar conditions gave N-2-*dimethylaminoethyl*-N-2-(9-*ethoxycarbonyl*-9:10-*dihydro*-9-*anthryl*)*ethyl*-NN′-*dimethylammonium chloride hydrochloride* (from ethyl acetate–ethanol), m. p. 226° (Found: C, 60·0; H, 7·8; N, 5·7. $C_{25}H_{35}O_2N_2Cl,HCl,2H_2O$ requires C, 59·6; H, 8·0; N, 5·6%). The *dipicrate*, crystallised from ethanol, had m. p. 212° (Found: C, 52·5; H, 4·9; N, 14·4. $C_{25}H_{35}O_2N_2,C_6H_2O_7N_3,C_6H_3O_7N_3$ requires C, 52·1; H, 4·7; N, 13·1%).

[17] Minnis, *Org. Synth.*, 1932, **12**, 44.
[18] Stoermer and Laage, *Ber.*, 1917, **50**, 981.

Ethyl Xanthen-9-carboxylate.—Xanthen-9-carboxylic acid (7·8 g.), prepared by carboxylating the lithio-derivative of xanthen, was esterified by saturated ethanolic hydrogen chloride under reflux for 2 hr. Next morning the solution was evaporated under reduced pressure, the residual oil was dissolved in ether, and the solution washed with sodium carbonate solution, dried, and evaporated, to give *ethyl xanthen-9-carboxylate* (7·45 g., 85·5%). Recrystallisation from aqueous ethanol gave plates, m. p. 58° (Found : C, 75·5; H, 5·5. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%).

Ethyl 9-2′-Dimethylaminoethylxanthen-9-carboxylate.—Ethyl xanthen-9-carboxylate (7·45 g.) was alkylated with 2-dimethylaminoethyl chloride (4·5 g., 1·4 mol.) under the conditions described for alkylation of the corresponding anthracene ester, to give *ethyl 9-2′-dimethylaminoethylxanthen-9-carboxylate hydrochloride hemihydrate* (3·7 g., 34%) which, crystallised from ethyl acetate–ethanol, had m. p. 194° (Found: C, 65·1; H, 7·0; N, 3·4. $C_{20}H_{23}O_3N,HCl,\frac{1}{2}H_2O$ requires C, 64·8; H, 6·71; N, 3·8%). The *picrate*, crystallised from ethanol, had m. p. 154° (Found : C, 55·9; H, 4·75; N, 10·6. $C_{20}H_{23}O_3N,C_6H_3O_7N_3$ requires C, 56·3; H, 4·7; N, 10·1%).

Ethyl 9-2′-Diethylaminoethylxanthen-9-carboxylate.—Ethyl xanthen-9-carboxylate (10·0 g.) was alkylated with 2-diethylaminoethyl chloride (5·35 g., 1 mol.) as for the 2′-dimethylamino-compound, to give the corresponding *hydrochloride hemihydrate* (6·4 g., 41%), m. p. 106° (from ethyl acetate) (Found : C, 65·9; H, 7·5; N, 3·3; loss at 110°/vac., 2·4. $C_{22}H_{27}O_3N,HCl,\frac{1}{2}H_2O$ requires C, 66·2; H, 7·3; N, 3·5; $\frac{1}{2}H_2O$, 2·3%). The derived *picrate*, crystallised from ethanol, had m. p. 151° (Found : C, 57·9; H, 5·2; N, 9·5. $C_{22}H_{27}O_3N,C_6H_3O_7N_3$ requires C, 57·7; H, 5·2; N, 9·6%).

Attempted Preparation of Ethyl 9-2′-Dimethylamino-1′-methylethylxanthen-9-carboxylate.—Ethyl xanthen-9-carboxylate (7·0 g.) was alkylated with 2-chloropropyldimethylamine (3·5 g., 1·05 mol.) under the same conditions as for the previous alkylations of this ester. Reaction was incomplete after 24 hours' heating under reflux. The cooled toluene solution was washed with water, and the basic product isolated by acid-extraction. The acid solution was strongly basified and extracted with ether, and a hydrochloride prepared in the usual way. Recrystallisation from ethyl acetate–ethanol gave colourless *2-dimethylamino-1-methylethylxanthen-9-carboxylate hydrochloride*, m. p. 190° (Found : C, 60·0; H, 7·2; N, 3·7; loss at 120°/vac., 7·8. $C_{19}H_{21}O_3N,HCl,1\frac{1}{2}H_2O$ requires C, 59·8; H, 6·9; N, 3·8; loss, 7·2%). At 140° partial sublimation occurred. The *picrate*, crystallised from ethanol, had m. p. 161° (Found : C, 55·4; H, 4·6; N, 10·4. $C_{19}H_{21}O_3N,C_6H_3O_7N_3$ requires C, 55·55; H, 4·5; N, 10·4%). The hydrochloride with alcoholic potassium hydroxide gave an acid, m. p. 198—202°, mixed m. p. with xanthen-9-carboxylic acid (m. p. 218°) 209—210°.

NN-*Dimethylxanthen-9-carboxyamide.*—Xanthen-9-carboxylic acid was converted into the acid chloride with thionyl chloride. An ether solution of this was added with stirring to aqueous (33% w/v) dimethylamine. The *dimethylamide* was collected and recrystallised from aqueous ethanol as needles (8 g., 71·5%), m. p. 140° (Found : C, 75·5; H, 6·15; N, 5·7. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0; N, 5·5%).

9-*Dimethylaminomethylxanthen.*—Finely powdered lithium aluminium hydride (1·52 g., 0·04 mol.) was heated under reflux with dry ether (250 c.c.) for 2 hr. A dry ether solution of the dimethylamide (7·6 g., 0·03 mol.) was added and the whole heated under reflux for 20 hr. The excess of lithium aluminium hydride was decomposed with a few drops of ethyl acetate and then water. Concentrated sodium hydroxide solution was added, and the aqueous layer extracted with ether. The ether solution was extracted with dilute hydrochloric acid, and the acid solution basified and extracted with ether. Evaporation of the dried extracts gave 9-*dimethylaminomethylxanthen* (6·3 g., 88%), m. p. 94° (from aqueous methanol) (Found : C, 80·4; H, 6·9; N, 5·45. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·85%). The *hydrochloride*, crystallised from ethyl acetate–ethanol, had m. p. 229—230° (Found : C, 69·5; H, 6·6; N, 5·4. $C_{16}H_{17}ON,HCl$ requires C, 69·7; H, 6·6; N, 5·1%). The *picrate*, crystallised from ethanol, had m. p. 187° (decomp.) (Found : C, 56·7; H, 4·3; N, 12·2. $C_{16}H_{17}ON,C_6H_3O_7N_3$ requires C, 56·4; H, 4·3; N, 11·9%).

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