Esters of Furan-, Thiophen-, and *N*-Methylpyrrole-2-carboxylic Acids. Bromination of Methyl Furan-2-carboxylate, Furan-2-carbaldehyde, and Thiophen-2-carbaldehyde in the Presence of Aluminium Chloride

By **Derek J. Chadwick, John Chambers, G. Denis Meakins,* and Roger L. Snowden,** Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY

Convenient routes from readily available starting materials to furan- and thiophen-2-carboxylic acids with substituents (mainly halogen atoms) at various positions are described. A series of esters (methyl, ethyl, t-butyl, and 17-oxo-5α-androstan-3β-yl) have been prepared from these acids and from the unsubstituted heterocyclic 2-carboxylic acids.

Methyl furan-2-carboxylate reacts with bromine in the presence of aluminium chloride to give the 4,5-dibromo-ester. The presence of 1,2-dichloroethane changes the course of the reaction, the product then being the 4-bromo-5-chloro-ester. Furan-2-carbaldehyde shows the opposite behaviour, giving as the main products the 4-bromo-5-chloro-aldehyde in the absence of a solvent and the 4,5-dibromoaldehyde when 1,2-dichloroethane is present. Careful control of conditions is necessary in the preparation of 4-bromothiophen-2-carbaldehyde from thiophen-2-carbaldehyde, bromine, and aluminium chloride.

DURING an investigation of rotational isomerism by spectrometric methods we prepared several series of heterocyclic compounds containing a C=O group at position 2. Most of them are aldehydes, esters, and acid halides derived from furan and thiophen, and their derivatives having substituents (chiefly halogen, deuterium, alkyl, or aryl) at other nuclear positions. The synthetic [1] and spectrometric [2] aspects of the work are being reported separately; this paper deals with the preparation of methyl, ethyl, t-butyl, and 17-oxo-5α-andostan-3β-yl esters of heterocyclic 2-carboxylic acids. (The second C=O group in the steroidal compounds, well separated from the ester function, serves as an internal standard for i.r. spectrometry.) Much of the work (portrayed in Schemes 1—3) is unexceptional, and requires little comment. The more interesting results, on the brominations in the presence of aluminium chloride, are shown in Scheme 4.

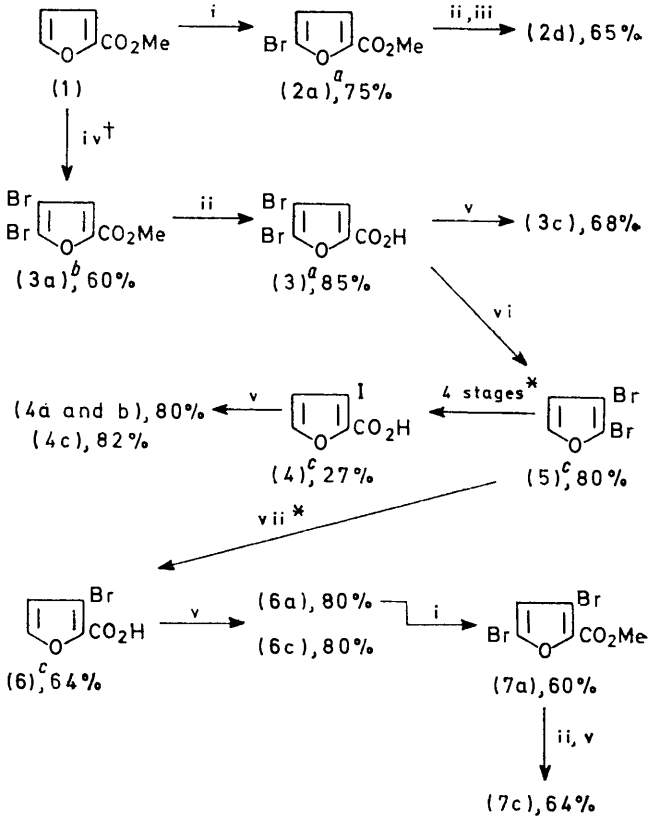
Recent investigations by French authors [3,4] have led to a range of halogenated furan-2-carboxylic acids, and a number of their useful sequences involving furyl-lithium intermediates are incorporated in Schemes 1 and 2. Several of the methyl and ethyl esters of the acids involved were known, and these are not shown in the Schemes unless they were involved as intermediates. Although all but one of the acids had been described previously it was difficult to discern good routes to some of them. Stages scattered through the literature, some in sources not easily accessible, had to be pieced together; for a number of the basic steps [*e.g.* the bromination of

References are given to known products: the rest are new. Stages conducted by the published methods (see references to products) are marked with an asterisk, and where several steps are involved the reagents are not shown. In the other stages (those described in the Experimental section) the product is new, or the conversion has not previously been carried out by use of the reagent(s) specified, or the present procedure differs significantly from that in the literature. Stages marked with a dagger are shown, together with related reactions, in Scheme 4.

Esters are indicated by letters following the formulae numbers of the corresponding acids: a, R = Me in $-CO_2R$; b, R = Et; c, R = Bu^t; and d, R = 17-oxo-5α-androstan-3β-yl.

SCHEME 1

Starting material is methyl furan-2-carboxylate (1)



Reagents: i, Br_2–$Cl[CH_2]_2Cl$; ii, 20% aq. NaOH, then 5N-HCl; iii, $SOCl_2$, then 17-oxo-5α-androstan-3β-ol–C_5H_5N; iv, Br_2–$AlCl_3$; v, H_2SO_4–MeOH, or EtOH, or $Me_2C{:}CH_2$; vi, $HgCl_2$–H_2O; vii, Bu^{n}Li, then CO_2

[a] Ref. 8. [b] See Scheme 4. [c] Ref. 3.

[1] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin I*, 1972, 2079; 1973, 201.

[2] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Chem. Comm.*, 1972, 742; *J.C.S. Perkin II*, 1972, 1959.

[3] R. Sornay, J.-M. Meunier, and P. Fournari, *Bull. Soc. chim. France*, 1971, 990.

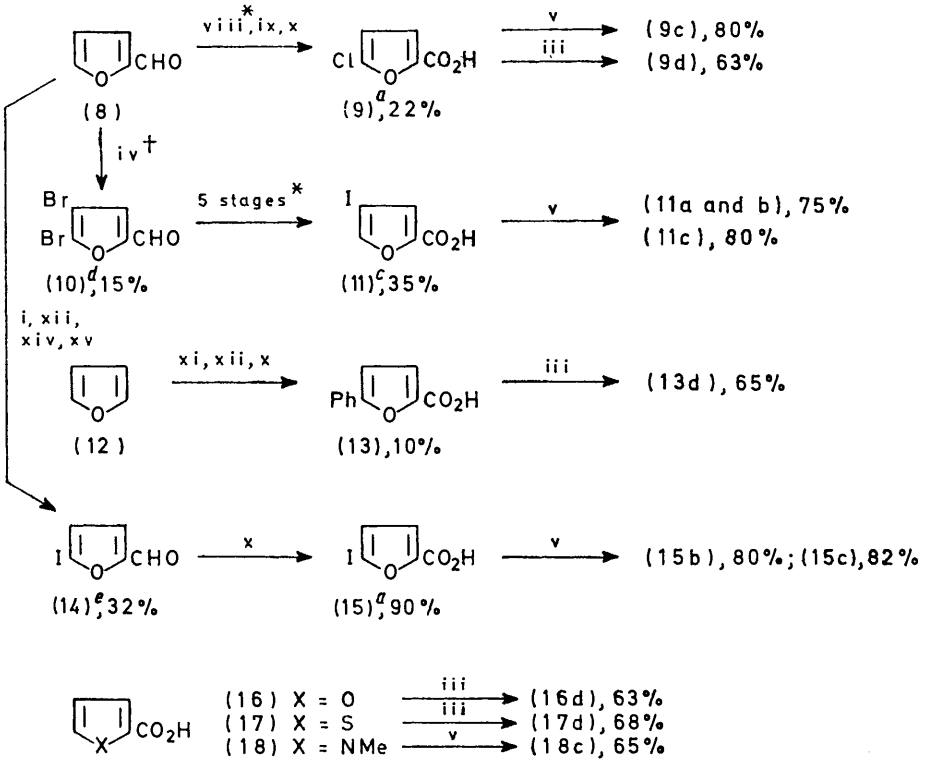
[4] M.-C. Zaluski, M. Robba, and M. Bonhomme, *Bull. Soc. chim. France*, 1970, 1838.

methyl furan-2-carboxylate (1)] the published procedures are either lacking in detail or unsatisfactory with regard to yield. For introducing a 5-bromo-substituent it was found advantageous to use the methyl esters (1) and (6a) rather than the corresponding acids. Tollens reagent was employed generally for obtaining the heterocyclic acids, in high yield, from the corresponding aldehydes.

suitable conditions. It transpired that brominations in the presence of aluminium chloride are markedly influenced by the nature of the heterocyclic compound and by the presence or absence of halogen-containing solvents. The broader investigation of the furan compounds thus occasioned led to the results shown in Scheme 4. [Experiments *a*—*o* were carried out on *ca.* 1 g of the esters; for the preparation of large quantities of the disubstituted

SCHEME 2

Starting materials are furan-2-carbaldehyde (8), furan (12), and the 2-carboxylic acids (16)—(18)



Reagents as in Scheme 1, and viii, Ac_2O–H_2SO_4; ix, SO_2Cl_2–CS_2; x, Ag_2O–NH_3; xi, $(PhN_2^+)_2ZnCl_4$–NaOH; xii, POCl – Me_2N·CHO; xiii, EtOH–CH(OEt)$_3$–HCl; xiv, Bu^nLi, then I_2; xv, 5N-HCl

Refs. as in Scheme 1, and [d] Ref. 5(*a*); [e] Ref. 14.

These preparations involve the 4,5-dibromo-compounds (3a) and (10) derived from methyl furan-2-carboxylate (1) and furan-2-carbaldehyde (8), and the two bromo-derivatives (24) and (25) of thiophen-2-carbaldehyde (21). With bromine (1 mol. equiv.) in the presence of aluminium chloride at temperatures below 60 °C furan-2-carbaldehyde [5] and thiophen-2-carbaldehyde [5b] are reported to give 4-monobromo-derivatives; an excess of bromine at higher temperatures leads to the 4,5-dibromo-compounds.[5] Similar treatment of methyl furan-2-carboxylate followed by saponification yields the 4,5-dibromo-2-carboxylic acid.[3] Since the procedures used in these brominations were not described in detail, trial experiments were carried out with furan-2-carbaldehyde and methyl furan-2-carboxylate in order to establish

esters (3a) and (31) a longer reaction time and a lowe temperature are advantageous (see Experimental section).]

When two molecular proportions of bromine are used methyl furan-2-carboxylate (1) gives, in the absence of a solvent, the 4,5-dibromo-compound (3a) (experiment *b*); however when either 1,2-dichloroethane or carbon tetrachloride is present a bromo-chloro-ester, shown to have structure (31), is formed in similarly high yield (experiments *d* and *h*). Conversely, furan-2-aldehyde (8) is converted into a bromo-chloro-aldehyde, of structure

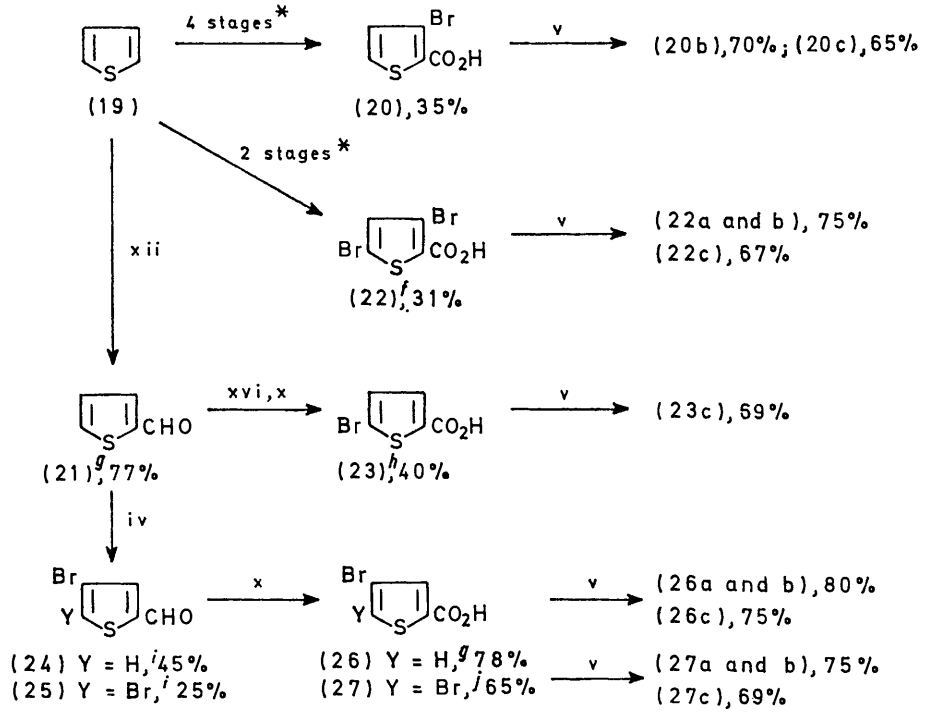
[5] (*a*) Y. L. Goldfarb and L. D. Tarasova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1965, **6**, 1079; (*b*) Y. L. Goldfarb, Y. B. Volkenshtein, and B. V. Lopatin, *Zhur. obshchei Khim.*, 1964, **34**, 949; *J. Gen. Chem.* (*U.S.S.R.*), 1964, **34**, 961.

(32), in the *absence* of a solvent (reaction *p*), and, less efficiently, into the 4,5-dibromo-aldehyde (10) when 1,2-dichloroethane is used as solvent (experiment *q*).

N.m.r. and mass spectral examination established that the ester (31) and the aldehyde (32) have either a chlorine or a bromine atom at position 4 and the other halogeno-substituent at position 5. Hydrolysis of the ester and oxidation of the aldehyde gave the same bromo-chloro-acid. Reduction of esters of 5-bromo- and 4,5-dibromo-furan-2-carboxylic acids with zinc and acetic acid re-removes the 5-bromo-substituent:[3,6] the ester (31) was similar sequence of bromination followed by halogen exchange at position 5, as depicted in the lower part of Scheme 4, presumably occurs when the solvent is carbon tetrachloride (experiment *h*). Experiments *j*—*o* show that the 4-bromine atom is not labile, and that exchange at position 5 can be bromine ⟶ chlorine or *vice versa* under appropriate conditions. Surprisingly, within the range of variables examined here, halogen exchange appears to require the presence of *four* components, *viz.* a 5-halogeno-ester, aluminium chloride, bromine, and a halogen-containing solvent (*cf.* the sets of experiments

SCHEME 3

Starting material is thiophen (19)



Reagents as in Schemes 1 and 2, and xvi, Br_2–$CHCl_3$

Refs. as in Scheme 2, and [f] S. O. Lawesson, *Acta Chem. Scand.*, 1956, **10**, 1020; [g] Ref. 15; [h] Ref. 13; [i] Ref. 5(*b*); [j] Ref. 16.

unchanged, and is therefore more probably a 5-chloro-ester. Structures (31) and (32) are also supported by the nature of the sequences leading to them, as explained later; for example, the mono-halogenated products accompanying the bromo-chloro-aldehyde (32) are the 4-bromo- and the 5-chloro-aldehydes (28) and (30).

In the absence of a solvent the reaction of methyl furan-2-carboxylate with bromine and aluminium chloride is straightforward, giving first the 5-bromo-ester (2a) and then the 4,5-dibromo-ester (3a) (experiments *a* and *b*). When 1,2-dichloroethane is present this path is still followed (experiment *e*) but the 5-bromo-substituents subsequently replaced by chlorine (experiment *d*). A *j*—*l*, *m*—*o*, and experiments *r* and *s*). In different experiments both aluminium chloride and the halogen-containing solvent can act as the source of halogen for replacing the original 5-halogeno-substituent, but the present investigation is not sufficiently detailed to reveal the mechanism of the exchange reaction.

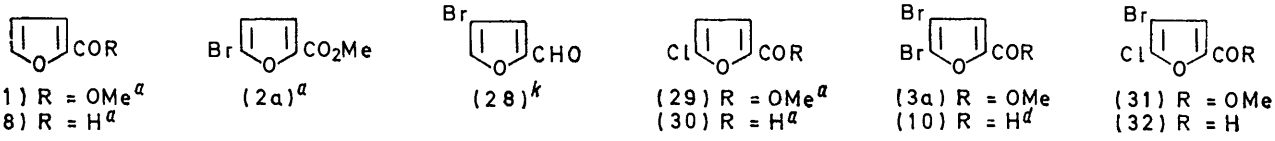
The reported[5] influence of aluminium chloride in changing the orientation of the monobromination of furan-2-carbaldehyde from position 5 to position 4 accords with the results of experiment *q*. However, in the absence of a solvent the initial products appear to be the 4-bromo-aldehyde (28) and the 5-chloro-aldehyde (30) (*sic*), and under these conditions (experiment *p*) alumin-

[6] D. J. Chadwick, D.Phil. Thesis, Oxford, 1972.

ium chloride must be the source of the chlorine in the main product, the bromo-chloro-aldehyde (32). The paths of these halogenations may well be different from those of the furan ester discussed previously. Methyl furan-2-carboxylate (1) forms a relatively weak complex here a stable complex (33) (see Scheme 4) is probably the entity undergoing substitution. Bromination of the complex at position 4 would afford an intermediate (34) which is less unstable than that resulting from attack at position 5. Chlorination, which appears to occur at

SCHEME 4

Reaction of esters (1), (3a), and (31) for 2·5 h (unless otherwise specified) at 60 °C, and of furan-2-carbaldehyde (8) for 3 h at 50 °C with aluminium chloride (or, in experiment *i*, aluminium bromide) and bromine, and (in some experiments) a halogen-containing solvent. A plus or a minus sign in a column indicates the presence or the absence of a particular reactant

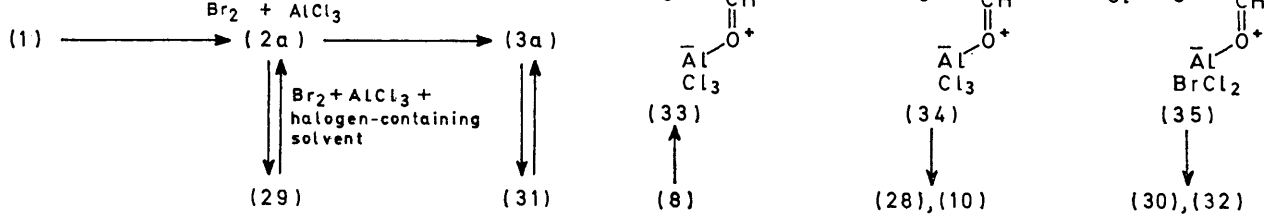


Refs. as in Scheme 1, and [k] Ref. 6.

The bromo-chloro-compounds (31) and (32) are new, and the properties of the dibromo-ester (3a) are not recorded in the literature. The entries under Products show the compounds and their percentages, by g.l.c. analysis, in the total volatile material obtained after work-up.

	Reactants				Products (%)					
Experiment	Substrate (1 mol. equiv.)	$AlCl_3$ (2·5 mol. equiv.)	Br_2 (1 or 2 mol. equiv.)	Solvent (12 mol. equiv.)						
a	(1)	+	1	—	(1), 30	(2a), 30		(3a), 40		
b	(1)	+	2	—		(2a), 4		(3a), 96		
c	(1)	+	1	$Cl[CH_2]_2Cl$		(2a), 9	(29), 45	(3a), 37	(31), 9	
d	(1)	+	2	$Cl[CH_2]_2Cl$		(2a), 1	(29), 5	(3a), 4	(31), 90	
e	As in *d*, but reaction stopped after 5 min					(2a), 3	(29), 7	(3a), 60	(31), 30	
f	(1)	+	2	$Br[CH_2]_2Br$		(2a), 5		(3a), 90	(31), 5	
g	As in *f*, but reaction stopped after 5 min					(2a), 15	(29), 5	(3a), 80		
h	(1)	+	2	CCl_4		(2a), 2	(29), 5	(3a), 5	(31), 88	
[*i*	(1)	$AlBr_3$ (2·5 mol. equiv.)	2	$Cl[CH_2]_2Cl$		(2a), 30		(3a), 10		]
j	(3a)	+	2	$Cl[CH_2]Cl$				(3a), 5	(31), 95	
k	(3a)	+	2	$Br[CH_2]_2Br$				(3a), 80	(31), 20	
l	(3a)	+	—	$Cl[CH_2]_2Cl$				(3a), 100		
m	(31)	+	2	$Br[CH_2]_2Br$				(3a), 75	(31), 25	
n	(31)	+	2	$Cl[CH_2]_2Cl$					(31), 96 *	
o	(31)	+	—	$Br[CH_2]_2Br$					(31), 100	
p	(8)	+	2	—		(28), 3	(30), 3	(10), 19	(32), 75	
q	(8)	+	2	$Cl[CH_2]_2Cl$	(8), 34	(28), 20	(30), 2	(10), 40	(32), 4	
[*r*	—	+	—	$Br[CH_2]_2Br$	} No chlorine-containing solvent detected					]
s	+	+	2	$Br[CH_2]_2Br$						

* Plus 4% of a product which may be methyl 4,5-dichlorofuran-2-carboxylate.



with aluminium chloride; in the bromination, the aluminium chloride initially plays the normal role of a Lewis acid in promoting halogenation. This contrasts with the behaviour of furan-2-carbaldehyde (8), which reacts so exothermically with aluminium chloride that the mixture must be cooled before the bromine is added; position 5, may be the result of an intramolecular halogenation proceeding through an intermediate such as (35) which is favoured by the absence of a solvent.

The reaction of thiophen-2-carbaldehyde with bromine and aluminium chloride in the absence of a solvent was less thoroughly investigated, no attempt being made to

detect any possible chlorination products. Even with a limited amount of bromine (1 mol. equiv.) the 4-monobromo- and 4,5-dibromo-aldehydes (24) and (25) may be formed. The critical factor is the thoroughness with which the very viscous mixture of the aldehyde and aluminium chloride is stirred during the addition of bromine. (Preparations of both aldehydes are described in the Experimental section.)

Methyl 5-chlorofuran-2-carboxylate (29), required for g.l.c. comparison, was obtained by treating the unsubstituted ester (1) with iodine monochloride at 70 °C. Attempts to use this reagent, at a lower temperature, for preparing the 5-iodo-ester were unsuccessful. Thus, the furan ester (1) is not sufficiently reactive to be attacked at a temperature below that at which dismutation of the reagent gives chlorine and iodine.[7]

EXPERIMENTAL

Spectra were measured using Perkin-Elmer R10 (60 MHz) or R14 (100 MHz) spectrometers with CCl_4 solutions (n.m.r.), a Perkin-Elmer 257 with CCl_4 (i.r.), and a Cary 14 with C_6H_{14} (u.v.). Analytical g.l.c. was carried out on a Pye Argon Chromatograph with a 1 m column of 10% polypropylene adipate on Embacel at a pressure of 10 lb in^{-2}. For details of preparative layer chromatography (p.l.c.) see *J. Chem. Soc.* (*C*), 1971, 1136.

Procedures are given fully only where they are first mentioned. The yields of experiments not described in detail are given in the Schemes. The properties of the new esters and the analytical data are tabulated at end of this section; the purity of all the esters was checked by g.l.c. Petrol refers to light petroleum (b.p. 60—80°).

Methyl 5-Bromofuran-2-carboxylate (2a).—Br_2 (130 g) in $Cl[CH_2]_2Cl$ (125 ml) was added during 1 h to a vigorously stirred solution of methyl furan-2-carboxylate (1) (100 g) in $Cl[CH_2]_2Cl$ (125 ml) at 20 °C. The solution was boiled under reflux for 1 h, and left for a further 3 h to reach 25 °C. Work-up, which included washing with saturated aq. $NaHCO_3$, and fractional distillation gave methyl 5-bromofuran-2-carboxylate (2a) (120 g), b.p. 80° at 0·7 mmHg, m.p. 64—65° (lit.,[8] 59°).

2,3-*Dibromofuran* (5).—Methyl 4,5-dibromofuran-2-carboxylate (3a) (200 g) was boiled under reflux with 20% aq. NaOH (3·5 l) for 5 h. Acidification with 5N-HCl and isolation with EtOAc gave a white solid (160 g), m.p. 161—167°. A portion was sublimed *in vacuo* to give 4,5-dibromofuran-2-carboxylic acid (3), m.p. 168—169° (lit.,[8] 167—168°). A mixture of this acid (150 g), $HgCl_2$ (150 g), and H_2O (3 l) was distilled in steam for 6 h. Extraction of the distillate with Et_2O gave 2,3-dibromofuran (5) (100 g), b.p. 55—56° at 12 mm Hg (lit.,[3] 58° at 12 mmHg).

Methyl 3,5-Dibromofuran-2-carboxylate (7a).—Br_2 (1·9 g) in $Cl[CH_2]_2Cl$ (25 ml) was added during 15 min to a solution of methyl 3-bromofuran-2-carboxylate (6a) (2·1 g) in $Cl[CH_2]_2Cl$ (25 ml) boiling under reflux. More Br_2 (1·9 g) in $Cl[CH_2]_2Cl$ (25 ml) was added after 1 day and the boiling was continued for a further 1·5 day. After work-up the main fraction obtained by p.l.c. [4 large plates; 4 × petrol–Me_2CO (50 : 1)] was distilled at 140° (bath) and 1·5 mmHg to give the 3,5-*dibromo-ester* (7a) (1·9 g), m.p. 64—66°. Saponification of this ester (1 g) gave 3,5-dibromofuran-2-carboxylic acid (7) (740 mg), m.p. 196—198° (lit.,[3] 201°).

5-*Chlorofuran-2-carboxylic Acid* (9).—SO_2Cl_2 (freshly distilled; 180 g) was added to a stirred solution of 2-(diacetoxymethyl)furan [8] (137 g) in dry CS_2 (800 ml). The mixture was boiled under reflux for 12 h and left at 25 °C for a further 16 h. Removal of CS_2 by distillation and basification with 50% aq. NaOH gave a black liquid (1 l). Distillation in steam (4 h), followed by extraction of the distillate with Et_2O, gave an oil (30 g) from which 5-chlorofuran-2-carbaldehyde (21 g), b.p. 72—74° at 12 mmHg, m.p. 34—35° (lit.,[9] 36°), was obtained by fractional distillation.

Solutions of $AgNO_3$ (51 g) in H_2O (510 ml) and of NaOH (51 g) in H_2O (510 ml) were mixed with rapid stirring, and aq. NH_3 (*d* 0·88 g ml^{-1}) was added until a clear solution was obtained. The foregoing aldehyde (19·2 g) was added, and the mixture was stirred at 25 °C for 3 h. Filtration, acidification of the filtrate with 30% aq. H_2SO_4, and isolation with EtOAc gave 5-chlorofuran-2-carboxylic acid (9) (19·0 g), m.p. 180—181° (lit.,[8] 179—180°).

5-*Phenylfuran-2-carboxylic Acid* (13).—$NaNO_2$ (13·8 g) in H_2O (20 ml) was added during 20 min to a stirred solution of $PhNH_2$ (freshly distilled; 18·6 g) in 5N-HCl (100 ml) at 5 °C. The solution was filtered and the filtrate was stirred vigorously with furan (300 ml) at 5—10 °C; 5N-NaOH (120 ml) was added during 1 h. Stirring was continued for 5 h at 5 °C, and for 39 h at 25 °C. Work-up and distillation gave 2-phenylfuran (7·6 g), b.p. 97—102° at 12 mmHg (lit.,[10] 94° at 10 mmHg).

A mixture of $POCl_3$ (9·7 g) and $Me_2N{\cdot}CHO$ (4·6 g) was kept at 25 °C for 30 min, and then cooled to 0 °C. 2-Phenylfuran (7·6 g) was added, and the mixture was heated at 100 °C for 1 h. Work-up gave 5-phenylfuran-2-carbaldehyde (3·9 g), b.p. 125—130° (bath) at 0·05 mmHg (lit.,[11] 122—123° at 0·25 mmHg). Oxidation of this aldehyde as described in the previous experiment gave 5-*phenylfuran-2-carboxylic acid* (13) (3·2 g), m.p. 146—148° (from MeOH) (Found: C, 69·9; H, 4·5. $C_{11}H_8O_3$ requires C, 70·2; H, 4·3%), τ ($CDCl_3$) −1·02 (CO_2H), 2·68 (m, Ph and 3-H), and 3·27 (d, *J* 3·7 Hz, 4-H), *m/e* 188 (M^+, 100%).

5-*Iodofuran-2-carboxylic Acid* (15).—Br_2 (57·6 g) in $Cl[CH_2]_2Cl$ (60 ml) was added during 1 h to a stirred solution of furan-2-carbaldehyde (28·8 g) in $Cl[CH_2]_2Cl$ (60 ml) boiling under reflux, and the boiling was continued for a further 3 h. The mixture was distilled in steam for 2 h, and the distillate was extracted with Et_2O to give a pale yellow solid (24 g). Recrystallisation of a portion from EtOH–H_2O and sublimation *in vacuo* gave 5-bromofuran-2-carbaldehyde, m.p. 81—82° (lit.,[8] 82°). A mixture of this aldehyde (21 g), $CH(OEt)_3$ (24 g), dry EtOH (120 ml), and 10N-HCl (0·4 ml) was boiled under reflux for 2 h. Evaporation at 100 °C followed by fractional distillation gave 5-*bromofuran-2-carbaldehyde diethyl acetal* (26·6 g), b.p. 72—76° at 0·03 mmHg (Found: C, 43·7; H, 5·2; Br, 31·8. $C_9H_{13}BrO_3$ requires C, 43·4; H, 5·2; Br, 32·1%), τ 3·74 (four-line m, *J* 0·8 and 3·3 Hz, 3-H), 3·83 (d, *J* 3·3 Hz, 4-H), and 4·63 [d, *J* 0·8 Hz, $CH(OEt)_2$], *m/e* 205 [M^+ ($C_9H_{13}{}^{81}BrO_3$), 44%].

[7] L. J. Lambourne and P. W. Robertson, *J. Chem. Soc.*, 1947, 1167.

[8] A. Dunlop and F. Peters, 'The Furans,' Reinhold, New York, 1953.

[9] H. Gilman and G. Wright, *Rec. Trav. chim.*, 1931, **50**, 838.

[10] D. C. Ayres and J. R. Smith, *J. Chem. Soc.* (*C*), 1968, 2737.

[11] Norwich Pharmacal Co., Neth. P. Appl., 6,612,588 (*Chem. Abs.*, 1967, **67**, 108,657).

The foregoing acetal (25 g) in Et_2O (dried over Na; 50 ml) was added during 30 min to a solution of Bu^nLi [prepared at −10 °C from Li wire (1·7 g), Bu^nBr (dried over molecular sieve; 17 g), and Et_2O (100 ml)] which was stirred at −70 °C. The temperature of the mixture was allowed to reach −10 °C during 2 h, and I_2 (30·5 g) in Et_2O (150 ml) was then added during 30 min. 5N-HCl (100 ml) was added during 20 min and the stirring was continued for 1 h at 0 °C. Extraction with Et_2O (including removal of the excess of I_2 with 10% aq. $Na_2S_2O_3$) gave a red solution which was shaken for 10 min with portions of 10% aq. $Na_2S_2O_5$. The combined aqueous solutions were basified with aq. Na_2CO_3 and extracted with Et_2O to give 5-iodofuran-2-carbaldehyde (16 g), m.p. 127—129° after sublimation *in vacuo* (lit.,[12] 127—128°). Oxidation of this aldehyde (13 g) with Tollens reagent gave 5-iodofuran-2-carboxylic acid (15) (11·5 g), m.p. 191—193° after sublimation *in vacuo* (lit.,[8] 193°).

5-Bromothiophen-2-carboxylic Acid (23).—$POCl_3$ (48 g) was added dropwise with stirring to thiophen (20·5 g)–Me_2N·CHO (24 g) at −5 °C, and the solution was stirred at 60 °C for 1 h. Work-up gave thiophen-2-carbaldehyde (21) (21·5 g), b.p. 83—85° at 18 mmHg (lit.,[13] 44—45° at 1·1 mmHg). Br_2 (5 ml) in $CHCl_3$ (15 ml) was added during 30 min to a stirred solution of the aldehyde (11 g) in $CHCl_3$ (15 ml) at 20 °C, and the solution was boiled under reflux for 3 h. Work-up gave 5-bromothiophen-2-carbaldehyde (10·7 g), b.p. 110—114° at 5 mmHg (lit.,[14] 105—107° at 11 mmHg), which was oxidised with Tollens reagent to 5-bromofuran-2-carboxylic acid (23) (8·3 g), m.p. 140—142° (lit.,[14] 141—142°).

Bromination of Thiophen-2-carbaldehyde (21).—(*a*) The aldehyde (33·6 g) was added during 15 min to anhydrous $AlCl_3$ (finely powdered; 100 g) which was stirred manually (glass rod) in a beaker cooled in ice–H_2O. Br_2 (18 ml) was added to the stirred mixture during about 20 min, the rate being such that the temperature did not exceed 50 °C and the foaming did not become excessive. After 12 h, work-up and repeated fractional distillation gave 4-bromothiophen-2-carbaldehyde (24) (31·5 g), b.p. 110—117° at 16 mmHg (lit.,[5b] 125—132° at 20 mmHg), m.p. 44—45° (from EtOH–H_2O) (lit.,[5b] 46·6—47·4°), g.l.c. retention time (at 125 °C) 12·5 min, τ (CCl_4) 2·38 (m, 3-H and 5-H), τ (Me_2CO) 2·02 (three-line m, *J* 1·4 and 1·3, 5-H), and 2·09 (d, *J* 1·4, 3-H).

(*b*) An attempt was made to carry out the foregoing experiment with a mechanical stirrer. After the addition of about half the Br_2 the mixture became so viscous that mechanical stirring was no longer possible. The main products obtained by fractional distillation were thiophen-2-carbaldehyde (94% pure; 9 g), b.p. 119—122° at 18 mmHg, and 4,5-dibromothiophen-2-carbaldehyde (25) (15 g), b.p. 132—135° at 2 mmHg, m.p. 78—79° (from EtOH–H_2O) (lit.,[5b] 82—82·5°), g.l.c. retention time (at 150 °C) 35·5 min, τ 2·51 (s, 3-H).

(*c*) Experiment (*a*) was repeated, but the temperature was allowed to reach 60 °C while Br_2 (36 ml) was added during 30 min. Work-up and fractional distillation gave 4,5-dibromothiophen-2-carbaldehyde (25) (34 g), identified by g.l.c. and n.m.r. examination.

4-Bromo- and 4,5-Dibromo-thiophen-2-carboxylic Acids.—Oxidation of the foregoing aldehydes (24) and (25) with Tollens reagent gave the 4-bromo-acid (26), m.p. 121—123° (lit.,[15] 122—124°), and the 4,5-dibromo-acid (27), m.p. 197—198° (lit.,[16] 198°).

Methyl 4,5-Dibromofuran-2-carboxylate (3a).—Br_2 (290 ml) was added during 1 h to a vigorously stirred slurry of anhydrous $AlCl_3$ (finely powdered; 760 g) and methyl furan-2-carboxylate (344 g) at 25 °C, and the mixture was kept at 25 °C for 20 h. H_2O (2 l) was added during 4 h while the stirred mixture was cooled in a large bath of ice–H_2O. Extraction with Et_2O (4 l), washing (H_2O, aq. $NaHCO_3$, and aq. NaCl), drying ($MgSO_4$), and evaporation gave a red oil (600 g). Fractional distillation afforded the *dibromo-ester* (430 g), b.p. 105—110° at 0·8 mmHg, m.p. 55—56° (Found: C, 25·6; H, 1·2; Br, 56·7. $C_6H_4Br_2O_3$ requires C, 25·4; H, 1·4; Br, 56·3%), *m/e* 284 [M^+ ($C_6H_4^{79}Br^{81}BrO_3$), 86%], τ 2·88 (s, 3-H).

Methyl 4-Bromo-5-chlorofuran-2-carboxylate (31).—Br_2 (290 ml) was added during 1 h to a vigorously stirred slurry of anhydrous $AlCl_3$ (finely powdered; 760 g), methyl furan-2-carboxylate (344 g), and $Cl[CH_2]_2Cl$ (1200 ml) at 25 °C. After 20 h at 25 °C the mixture was poured onto crushed ice (5 kg). Isolation with Et_2O gave material (540 g) shown by g.l.c. to contain 80% of the ester (31). Three fractional distillations afforded *methyl 4-bromo-5-chlorofuran-2-carboxylate* (230 g), b.p. 102—104° at 2 mmHg, m.p. 35—36° (Found: C, 30·1; H, 1·6; Br, 33·8; Cl, 14·5. $C_6H_4BrClO_3$ requires C, 30·1; H, 1·7; Br, 33·4; Cl, 14·8%), *m/e* 238 [M^+ ($C_6H_4^{79}Br^{35}ClO_3$), 46%], τ 2·91 (s, 3-H). Appropriate combination of other fractions gave material (104 g) containing 85% of the ester (31).

The ester (6 g) was boiled under reflux with 20% NaOH aq. (100 ml) for 3 h. Acidification with 5N-HCl and isolation with Et_2O gave *4-bromo-5-chlorofuran-2-carboxylic acid* (4·2 g), m.p. 150—152° (after sublimation at 100 °C and 12 mmHg) (Found: C, 26·9; H, 0·9; Br, 35·1; Cl, 15·3. $C_5H_2BrClO_3$ requires C, 26·6; H, 0·9; Br, 35·5; Cl, 15·7%), *m/e* 224 [M^+ ($C_5H_2^{79}Br^{35}ClO_3$), 90%], τ ($CDCl_3$) 2·71 (s, 3-H).

The ester (1 g) in AcOH (3 ml) was stirred at 100 °C for 3 h with Zn dust (0·5 g). Work-up gave starting material (0·92 g), identified by n.m.r. examination.

Experiments c—o, r, *and* s, *on the Halogenation of the Esters* (1), (3a), *and* (31).—Br_2 (1 or 2 mol. equiv.) was added during 20 min to a stirred slurry of the ester (1 mol. equiv. 1·26 g) and the other compounds listed in Scheme 4. (In experiments *l*, *o*, and *s*, either the Br_2 or the ester was omitted; both were omitted in experiment *r*.) The mixtures were stirred at 60 °C for 2·5 h and worked up, and the volatile materials were analysed by g.l.c. The retention times (min) of the esters, and of the aldehydes involved in experiments *p* and *q* (described later), were: (1), 1·8; (8), 1·3; (2a), 8·4; (28), 5·5; (29), 3·9; (30), 2·6; (3a), 24·7; (10), 15·7; (31), 11·0; (32), 7·3. [The preparations of the halogen-containing compounds, apart from the bromo-aldehyde (28) [6] and the chloro-aldehyde (30),[8] are recorded at various places in this Experimental section.] The compositions of the mixtures are shown in Scheme 4.

Experiment p. Furan-2-carbaldehyde (8) (288 g) was added during 1 h to anhydrous $AlCl_3$ (finely powdered; 880 g), which was stirred and cooled in a large bath of ice–H_2O. The mixture was warmed to 50 °C, and Br_2 (320 ml) was added, with stirring, during 3 h. After 20 h, H_2O

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New esters

2-Carboxylate	M.p. [B.p. (bath temp.)] (°C)	Analytical figures (%)	C	H	Hal	N.m.r.† (τ values)	Abundance (%) of M^+
17-Oxo-5α-androstan-3β-yl 5-bromofuran (2d)	230—232	Found	62·2	6·7	17·6	2·93 (d, *J* 4·2, 3-H)	6
		$C_{24}H_{31}BrO_4$ req.	62·3	6·7	17·3		
t-Butyl 4,5-dibromofuran (3c)	[109—111 (0·2 mmHg)]	Found	33·3	3·2	49·5	2·99 (s, 3-H)	0
		$C_9H_{10}Br_2O_2$ req.	33·1	3·1	49·1		[$(M - 56)^+ \equiv 100\%$]
Methyl 3-iodofuran (4a)	[63—65 (0·4 mmHg)]	Found	28·5	1·95	50·0	2·53 (d, *J* 1·8, 5-H)	77
		$C_6H_5IO_3$ req.	28·6	2·0	50·4	3·36 (d, *J* 1·8, 4-H)	
Ethyl 3-iodofuran (4b)	[83—86 (0·4 mmHg)]	Found	31·4	2·5		2·54 (d, *J* 1·8, 5-H)	68
		$C_7H_7IO_3$ req.	31·6	2·6		3·36 (d, *J* 1·8, 4-H)	
t-Butyl 3-iodofuran (4c)	[89—91 (0·1 mmHg)]	Found	37·0	4·05	42·9	2·58 (d, *J* 1·8, 5-H)	16
		$C_9H_{11}IO_3$ req.	36·7	3·8	43·2	3·42 (d, *J* 1·8, 4-H)	
Methyl 3-bromofuran (6a)	52·5—53·5	Found	34·9	2·3	38·5	2·55 (d, *J* 1·9, 5-H)	52
		$C_6H_5BrO_3$ req.	35·1	2·5	39·0	3·48 (d, *J* 1·9, 4-H)	
t-Butyl 3-bromofuran (6c)	[83—85 (0·1 mmHg)]	Found	43·7	4·6	32·1	2·56 (d, *J* 1·9, 5-H)	16
		$C_9H_{11}BrO_3$ req.	43·7	4·5	32·4	3·51 (d, *J* 1·9, 4-H)	
Methyl 3,5-dibromofuran (7a)	64—66	Found	25·3	1·4	56·1	3·52 (s, 4-H)	59
		$C_6H_4Br_2O_3$ req.	25·4	1·4	56·3		
t-Butyl 3,5-dibromofuran (7c)	[99—101 (0·5 mmHg)]	Found	33·4	3·1	48·8	3·50 (s, 4-H)	12
		$C_9H_{10}Br_2O_3$ req.	33·1	3·1	49·0		
t-Butyl 5-chlorofuran (9c)	[69—71 (0·1 mmHg)]	Found	53·7	5·5	17·1	3·15 (d, *J* 3·5, 3-H)	15
		$C_9H_{11}ClO_3$ req.	53·3	5·4	17·5	3·82 (d, *J* 3·5, 4-H)	
17-Oxo-5α-androstan-3β-yl 5-chlorofuran (9d)	219—221	Found	69·0	7·5	8·3	2·97 (d, *J* 3·6, 3-H)	2
		$C_{24}H_{31}ClO_4$ req.	68·8	7·4	8·5	3·79 (d, *J* 3·6, 4-H)	
Methyl 4-iodofuran (11a)	43—45	Found	28·9	2·3	50·2	2·48 (d, *J* 0·8, 5-H)	100
		$C_6H_5IO_4$ req.	28·6	2·0	50·4	2·82 (d, *J* 0·8, 3-H)	
Ethyl 4-iodofuran (11b)	54—56	Found	31·6	2·8	47·9	2·50 (d, *J* 0·8, 5-H)	98
		$C_7H_7IO_3$ req.	31·6	2·6	47·7	2·85 (d, *J* 0·8, 3-H)	
t-Butyl 4-iodofuran (11c)	[84—87 (0·2 mmHg)]	Found	36·8	3·9	43·5	2·54 (d, *J* 0·8, 5-H)	16
		$C_9H_{11}IO_3$ req.	36·7	3·8	43·2	2·94 (d, *J* 0·8, 3-H)	
17-Oxo-5α-androstan-3β-yl 5-phenylfuran (13d)	235—236	Found	82·3	8·2		2·63 (3-H) ‡	16
		$C_{30}H_{36}O_4$ req.	82·6	8·3		3·28 (d, *J* 4·0, 4-H)	
Ethyl 5-iodofuran (15b)	[88—90 (0·3 mmHg)]	Found	31·3	2·9	48·05	3·03 (d, *J* 3·6, 3-H)	86
		$C_7H_7IO_3$ req.	31·6	2·6	47·7	3·38 (d, *J* 3·6, 4-H)	
t-Butyl 5-iodofuran (15c)	[98—100 (0·03 mmHg)]	Found	36·7	3·7	43·05	3·12 (d, *J* 3·5, 3-H)	7
		$C_9H_{11}IO_3$ req.	36·7	3·8	43·2	3·43 (d, *J* 3·5, 4-H)	
17-Oxo-5α-androstan-3β-yl furan (16d)	254—256	Found	74·8	8·3		2·46 (*4*, *J* 1·8 and 0·9, 5-H)	8
		$C_{24}H_{32}O_4$ req.	75·0	8·3		2·88 (*4*, *J* 3·6,and 0·9, 3-H)	
						3·55 (*4*, *J* 3·6 and 1·8, 4-H)	
17-Oxo-5α-androstan-3β-yl thiophen (17d)	256—257	Found	72·0	8·0	S, 8·2	2·23 (*4*, *J* 3·6 and 1·2, 3-H)	6
		$C_{24}H_{32}O_3S$ req.	72·0	8·0	S, 8·0	2·47 (*4*, *J* 5·4 and 1·2, 5-H)	
						2·94 (*4*, *J* 5·4 and 3·6, 4-H)	
t-Butyl *N*-methylpyrrole (18c)	[103—105 (15 mmHg)]	Found	65·9	8·1	N, 7·5	3·32 (*4*, *J* 4·0 and 1·8, 3-H)	19
		$C_{10}H_{15}NO_2$ req.	66·3	8·3	N, 7·7	3·42 (*4*, *J* 2·6 and 1·8, 5-H)	
						4·08 (*4*, *J* 4·0 and 2·6, 4-H)	
Ethyl 3-bromothiophen (20b)	[63—66 (0·8 mmHg)]	Found	36·1	3·35	34·2	2·52 (d, *J* 5·2, 5-H)	31
		$C_7H_7BrO_2S$ req.	35·8	3·0	34·0	2·99 (d, *J* 5·2, 4-H)	
t-Butyl 3-bromothiophen (20c)	[69—71 (0·8 mmHg)]	Found	41·4	4·4	30·3	2·65 (d, *J* 5·2, 5-H)	5
		$C_9H_{11}BrO_2S$ req.	41·05	4·2	30·3	3·02 (d, *J* 5·2, 4-H)	
Methyl 3,5-dibromothiophen (22a)	100—102	Found	24·4	1·5	52·9	2·93 (s, 4-H)	29
		$C_6H_4Br_2O_2S$ req.	24·0	1·3	53·3		
Ethyl 3,5-dibromothiophen (22b)	[104—106 (0·2 mmHg)]	Found	26·8	2·2	50·7	2·95 (s, 4-H)	24
		$C_7H_6Br_2O_2S$ req.	26·8	1·95	50·9		
t-Butyl 3,5-dibromothiophen (22c)	[113—115 (0·2 mmHg)]	Found	32·0	3·25	46·9	2·80 (s, 4-H)	9
		$C_9H_{10}Br_2O_2S$ req.	31·6	2·95	46·7		
t-Butyl 5-bromothiophen (23c)	[89—91 (1 mmHg)]	Found	41·0	4·2	30·4	2·62 (d, *J* 3·7, 3-H)	13
		$C_9H_{11}BrO_2S$ req.	41·1	4·2	30·4	3·05 (d, *J* 3·7, 4-H)	
Methyl 4-bromothiophen (26a)	[63—65 (1 mmHg)]	Found	32·3	2·3	36·1	2·39 (d, *J* 1·5, 3-H)	45
		$C_6H_5BrO_2S$ req.	32·6	2·3	36·1	2·64 (d, *J* 1·5, 5-H)	
Ethyl 4-bromothiophen (26b)	[77—79 (1 mmHg)]	Found	35·8	3·0	33·9	2·44 (d, *J* 1·5, 3-H)	27
		$C_7H_7BrO_2S$ req.	35·8	3·0	34·0	2·69 (d, *J* 1·5, 5-H)	
t-Butyl 4-bromothiophen (26c)	[89—91 (1 mmHg)]	Found	41·0	4·3	30·3	2·49 (d, *J* 1·4, 3-H)	15
		$C_9H_{11}BrO_2S$ req.	41·1	4·2	30·4	2·71 (d, *J* 1·4, 5-H)	
Methyl 4,5-dibromothiophen (27a)	75—77	Found	24·2	1·6	53·6	2·52 (s, 3-H)	27
		$C_6H_4Br_2O_2S$ req.	24·0	1·3	53·3		
Ethyl 4,5-dibromothiophen (27b)	43—43·5	Found	27·0	2·1	51·3	2·52 (s, 3-H)	42
		$C_7H_6Br_2O_2S$	26·8	1·9	50·9		
t-Butyl 4,5-dibromothiophen (27c)	29—30	Found	31·7	2·9	46·4	2·50 (s, 3-H)	1
		$C_9H_{10}Br_2O_2S$ req.	31·6	2·9	46·7		

† Of heterocyclic ring protons (*J* in Hz). ‡ Overlapped by signals of phenyl protons.

(2 l) was added slowly (during 4 h), with efficient cooling. The mixture was distilled in steam, and the distillate (6 l) was extracted with Et_2O (2 l). The Et_2O solution, after washing and drying, gave an oil (540 g) whose composition (see Scheme 4) was determined by g.l.c Repeated fractional distillation gave two products. The higher-boiling was 4,5-dibromofuran-2-carbaldehyde (10) (94 g), b.p. 86—90° at 0·8 mmHg, m.p. 35—36° (lit.,[5a] 36—37°) (Found: C, 23·7; H, 0·9; Br, 63·4. Calc. for $C_5H_2Br_2O_2$: C, 23·6; H, 0·8; Br, 63·4%), τ 2·84 (s, 3-H), *m/e* 254 [M^+ ($C_5H_2^{79}Br^{81}BrO_2$), 100%]. The lower-boiling product (212 g), b.p. 77—80° at 1 mmHg, was 95% pure. Preparative g.l.c. (at 100 °C) of a portion gave *4-bromo-5-chlorofuran-2-carbaldehyde* (32), m.p. 21—22° (Found: C, 28·4; H, 1·2; Br, 38·55; Cl, 16·8. $C_5H_2BrClO_2$ requires C, 28·6; H, 0·95; Br, 38·2; Cl, 17·0%), τ 2·80 (s, 3-H), *m/e* 210 [M^+ ($C_5H_2^{81}Br^{35}ClO_2$), 100%].

Oxidation of the aldehyde (32) (1 g) with Ag_2O–NH_3 [1] gave 4-bromo-5-chlorofuran-2-carboxylic acid (0·85 g), m.p. and mixed m.p. 149—151°.

Experiment q. Anhydrous $AlCl_3$ (finely powdered; 6·44 g) was sifted during 30 min into a stirred solution of furan-2-carbaldehyde (1·92 g) in $Cl[CH_2]_2Cl$ (10 ml) cooled in ice–H_2O. The mixture was warmed to 50 °C, and Br_2 (6·4 g) in $Cl[CH_2]Cl$ (10 ml) was added during 40 min. After 3 h at 50 °C the mixture was worked up to give volatile material (2·3 g) whose composition is shown in Scheme 4.

Methyl 5-Chlorofuran-2-carboxylate (29).—A solution of ICl (6 g) and methyl furan-2-carboxylate (1) (3·6 g) in CCl_4 (60 ml) was boiled under reflux for 6 h. Work-up, followed by chromatography on SiO_2 (400 g), gave methyl 5-chlorofuran-2-carboxylate [eluted with petrol–Me_2CO (25 : 1); 3·7 g], m.p. 38—40° (lit.,[8] 40—42°).

Esters.—The new esters other than those [(3a), (7a), and (31)] described earlier in this section were prepared from the acids as follows.

The 2-carboxylic acid (500 mg) was boiled under reflux with H_2SO_4 (1·5 ml)–MeOH (20 ml) or –EtOH (20 ml) for 3 h. Work-up gave the methyl or ethyl ester. $Me_2C{:}CH_2$ (10 ml) was added to a solution or a suspension of the 2-acid (500 mg) in dry Et_2O (20 ml)–H_2SO_4 (1 ml) which was cooled to −40 °C in a thick-walled flask fitted with a magnetic stirrer. A well-fitting rubber bung was securely wired into position, the cooling mixture was removed, and the mixture was stirred at 20 °C for 3 days. The flask was cooled to −30 °C, then opened cautiously, and the solution was poured slowly, with stirring, into 5% KOH aq. (120 ml). Isolation of the t-butyl ester with Et_2O was usually followed by p.l.c. [petrol–Me_2CO (50 : 1)].

The 2-acid (500 mg) was boiled under reflux with $SOCl_2$ (purified immediately before use; 5 ml) for 1 h. The 2-carbonyl chloride, isolated by distillation *in vacuo*, was added to 3β-hydroxy-5α-androstan-17-one (500 mg)–C_5H_5N (4 ml) at 20 °C. After 20 h work-up gave the 17-oxo-5α-androstan-3β-yl ester, which was purified by chromatography on Al_2O_3 (neutral, deactivated with 5% H_2O; 20 g).

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