Novel Base-induced Reactions of Substituted (1,2-Benzisoxazol-3-yl)acetates

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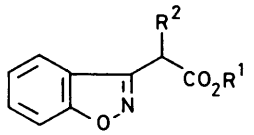
The reactions of substituted (1,2-benzisoxazol-3-yl)acetates with strong bases are described. The esters (**1**) and (**2**) having electron-donating and dialkylamino substituents undergo novel ring transformations on treatment with NaH, Bu^{t}OK, or MeONa in DMF to afford the 2*H*-azirines (**8**) and the 3-iminobenzofurans (**18**), respectively, while under similar conditions the halogeno esters (**3**) dimerize to give the ethylenedicarboxylate (**24**). Treatment of the esters (**4**)—(**7**) having electron-withdrawing substituents with NaH in DMF results in the recovery of the starting esters. However, on treatment of the sulphinyl esters (**6**) with MeONa in methanol, C-S bond cleavage occurs to afford methyl arylsulphinates (**27**).

Many studies on 1,2-benzisoxazole derivatives have been carried out as a result of their biological and chemical interest.[1] We have also been studying the chemical and pharmacological properties of 1,2-benzisoxazole derivatives having various substituents at the 3-position.[2]

A previous paper[2i] reported that the reaction of methyl 1,2-benzisoxazol-3-ylacetate (**4**) and cyclohexyl iodide in the presence of NaH afforded methyl 2-cyclohexyl-3-(2-hydroxyphenyl)-2*H*-azirine-2-carboxylate (**8c**) as a by-product together with the desired cyclohexylated ester (**1c**). We were interested in the formation of this azirine ester (**8c**) and found that it was obtained from the ester (**1c**) *via* rearrangement induced by NaH. In order to examine the extent of the reaction, the 1,2-benzisoxazol-3-ylacetates (**1**)—(**7**) having a variety of substituents on the α-position were prepared and subjected to reaction with strong bases such as NaH, Bu^{t}OK, and MeONa. As a result, the esters (**1**)—(**7**) were found to undergo the following five modes of reactions depending on the nature of the substituent and the reaction conditions: (*a*) ring contraction to the 2*H*-azirines (electron-donating substituents);[3] (*b*) ring transformation to the 3-imino-2,3-dihydrobenzofurans (dialkylamino substituents);[3] (*c*) dimerization to the ethylenedicarboxylate (halogeno substituents); (*d*) the recovery of the starting esters (electron-withdrawing substituents); and (*e*) C-S bond cleavage to methyl arylsulphinates (arylsulphinyl substituents, MeONa in methanol).

Results and Discussion

The preparations of (**1c**),[2i] (**3a**),[2a] and (**4**)[2a] have already been reported in earlier papers. The alkylated esters (**1a**) and (**1b**) were prepared by treating the ester (**4**) with NaH, followed by alkyl halides. The phenoxy ester (**1d**) was synthesized from the reaction of (1,2-benzisoxazol-3-yl)bromoacetic acid[2a] with phenoxide, followed by esterification. The dialkylamino esters (**2**) were prepared by treating (**3a**) with an excess of the corresponding amines, and the chlorinated ester (**3b**) was prepared from chlorination[2b] of 1,2-benzisoxazol-3-ylacetic acid with *N*-chlorosuccinimide, followed by esterification. The cyano ethyl ester (**5**) was obtained by treating 1,2-benzisoxazol-3-ylacetonitrile[2a] with NaH, followed by ethyl chloroformate. Attempts to prepare the cyano methyl ester derivative were unsuccessful because it was fairly unstable and decomposed during purification. The phenylthio, arylsulphinyl, and arylsulphonyl esters (**1e**), (**6**), and (**7**) respectively were prepared by esterification of arylthio(1,2-benzisoxazol-3-yl)acetic acids,[2g]

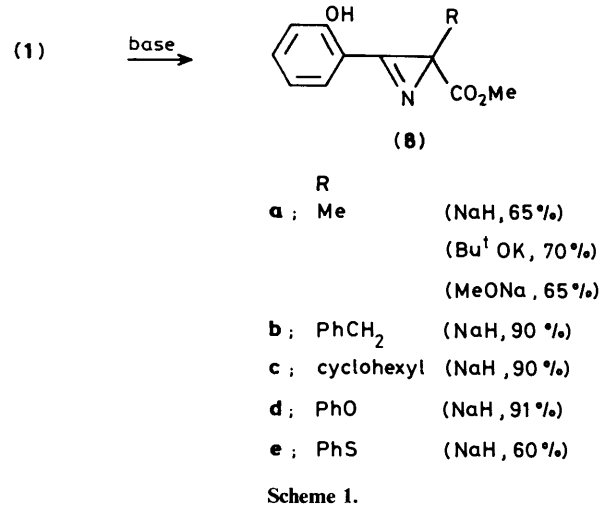


	R^1	R^2
(**1**) **a**;	Me	Me
b;	Me	CH_2Ph
c;	Me	cyclohexyl
d;	Me	OPh
e;	Me	SPh
(**2**) **a**;	Me	NMe_2
b;	Me	morpholino
c;	Me	hexahydro-1*H*-azepinyl
d;	Me	4-phenylpiperazinyl
(**3**) **a**;	Me	Br
b;	Me	Cl
(**4**)	Me	H
(**5**)	Et	CN
(**6**) **a**;	Me	S(O)Ph
b;	Me	$S(O)C_6H_4Me$-*p*
(**7**) **a**;	Me	SO_2Ph
b;	Me	$SO_2C_6H_4Me$-*p*

followed by oxidation with sodium metaperiodate and/or *m*-chloroperbenzoic acid.

(a) *Ring Contraction to* 2H-*Azirines.*—The esters (**1**) having electron-donating substituents such as methyl, benzyl, cyclohexyl, phenoxy, and phenylthio groups underwent, on treatment with an equimolar amount of NaH, Bu^{t}OK, or MeONa in dimethylformamide (DMF), ring contraction to give the 2*H*-azirine-2-carboxylates (**8**) (Scheme 1).

The characteristic structure of compounds (**8**) having an *ortho*-phenol entity at the 3-position of an azirine ring was deduced from the spectral data and also by the chemical transformations shown in Scheme 2. Compounds (**8**) were further converted into the more stable *O*-alkyl and *O*-acetyl



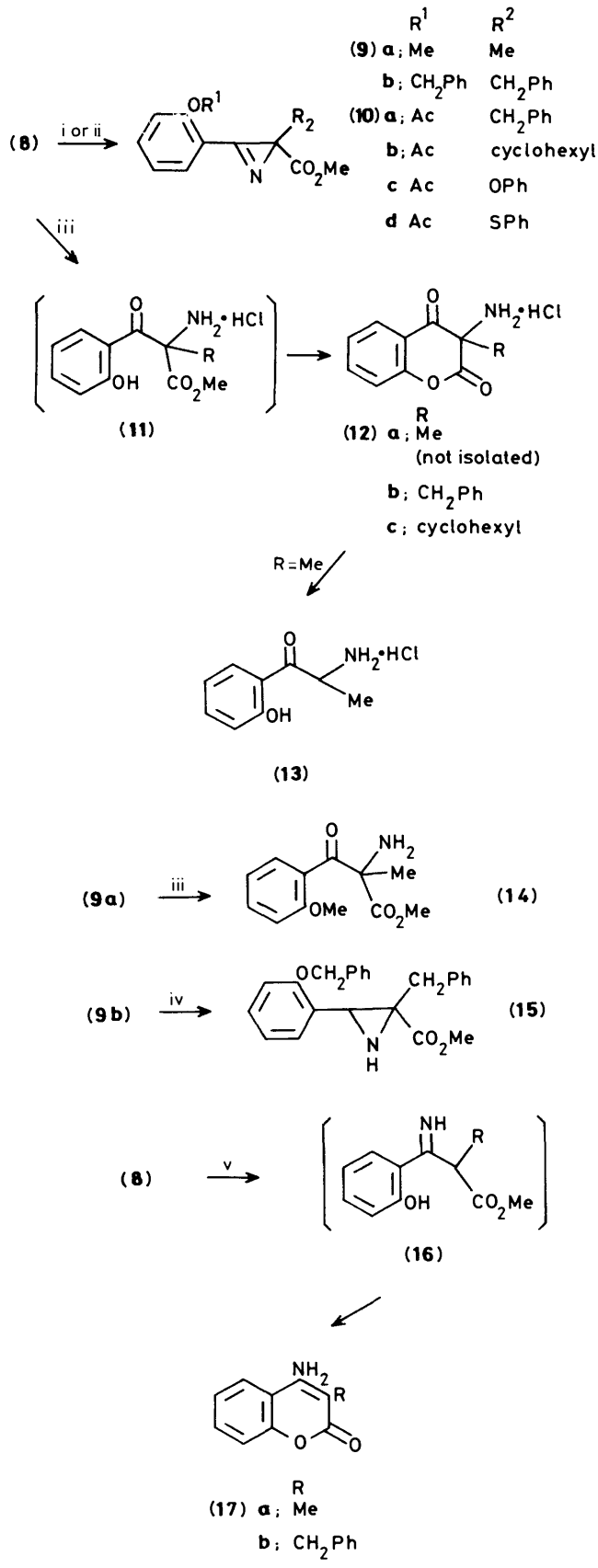
Scheme 1.

derivatives (**9**) and (**10**), respectively, by the usual methods. The i.r. spectra of compounds (**8**)—(**10**) showed the characteristic C=N band[4] at *ca.* 1 750 cm^{-1}, and the ^{13}C n.m.r. spectra showed signals due to the C-2 and C-3 carbons of the 2*H*-azirine ring at around δ 40 and δ 160,[5] respectively.

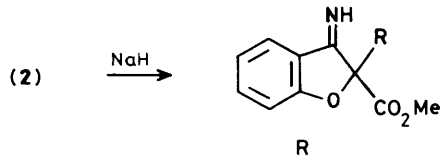
On acidic hydrolysis of compounds (**8b**) and (**8c**), ring expansion took place to give the 3-aminochroman-2,4-dione derivatives (**12b**) and (**12c**) which were presumed to be formed by recyclization of the initially formed α-amino-β-oxo esters (**11**) having a phenolic OH function. Under similar conditions, however, compound (**8a**) underwent further hydrolysis and decarboxylation to afford the amino ketone (**13**). As expected, similar hydrolysis of compound (**9a**), in which the OH function was protected by methylation, gave the α-amino-β-oxo ester (**14**). Reduction of compound (**9b**) with sodium borohydride gave the expected aziridine derivative (**15**). Meanwhile, catalytic hydrogenation of compounds (**8**) with palladium–carbon caused ring enlargement to the 4-aminocoumarin derivatives (**17**) *via* recyclization and isomerization of the initially formed imino esters (**16**).

(b) *Ring Transformation to* 3-*Imino*-2,3-*dihydrobenzofurans* (**18**).—When the dialkylamino esters (**2**) were treated with NaH under the same conditions as above, ring transformation took place to afford the title compounds (**18**) (Scheme 3).

The presence of the imino function of compounds (**18**) was confirmed by spectral data and the reactions shown in Scheme 4. The i.r. spectra of compounds (**18**) showed the characteristic NH and C=N absorption bands at around 3 230 and 1 650 cm^{-1}, respectively. The *N*-acetyl derivatives (**19**) were obtained by treating compound (**18**) with acetic anhydride in pyridine and showed iminoacetyl absorption bands at 1 690—1 700 cm^{-1} in the i.r. Compounds (**18**) gave the methyl 2-dialkylamino-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (**20**) when treated with oxalic acid in aqueous methanol at room temperature. The ^{13}C n.m.r. spectrum of compound (**20a**) is similar to that of compound (**18a**) (except for the chemical shift of C-3), and also to the reported data[6] for 2-methoxy-2-(4-methoxybenzoyl)-benzofuran-3(2*H*)-one. Meanwhile, hydrolysis of compound (**18a**) with hydrochloric acid in methanol afforded the 2-hydroxybenzofuranone (**22**) which would arise *via* recyclization of the dioxo ester intermediate (**21**). Its i.r. carbonyl absorptions at 1 750 and 1 720 cm^{-1} are similar to those of compound (**20**), but not in agreement with the reported data[7] for ethyl 3-aryl-2,3-dioxopropionates, indicating that the structure of compound (**22**) is of the benzofuranone type but not the 2,3-dioxopropionate type (**21**).

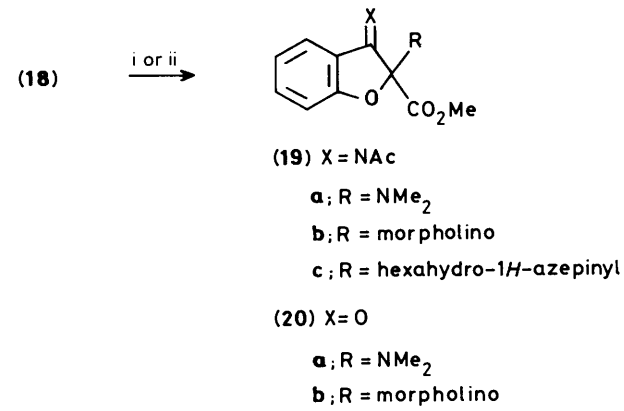


Scheme 2. i, NaH, R^1X; ii, Ac_2O–pyridine; iii, aq. HCl; iv, $NaBH_4$; v, H_2, Pd–C



(18) a; NMe_2 (76%)
b; morpholino (66%)
c; hexahydro-1*H*-azepinyl (45%)
d; 4-phenylpiperazinyl (60%)

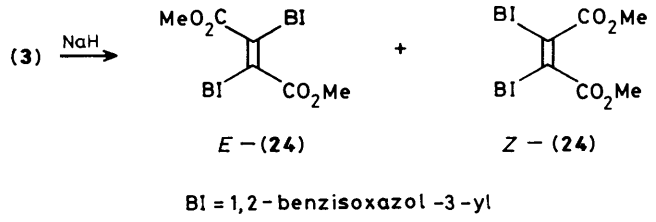
Scheme 3.



Scheme 4. i, Ac_2O–pyridine; ii, $(CO_2H)_2$–H_2O; iii, HCl–H_2O

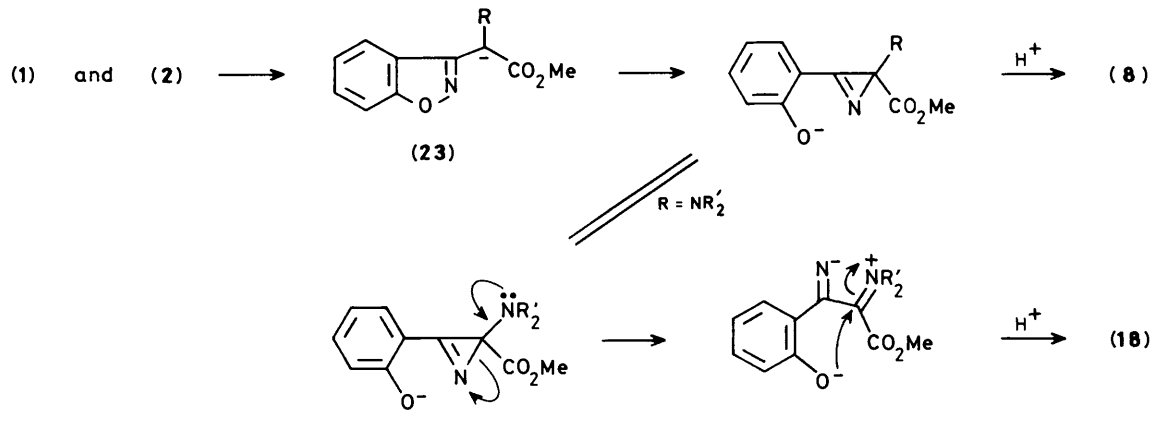
azirines. In the case of the dialkylamino esters (**2**), it is assumed that the initially formed azirines, which could not be isolated, may undergo further cleavage of the azirine C–N bond by participation of the amino group, followed by recyclization to give the benzofurans (**18**). The present azirine formation is the first example of the Neber-type rearrangement which proposes the involvement of a phenoxide as a leaving group.

(c) *Dimerization to Ethylenedicarboxylate.*—On treatment with NaH in DMF at 0 °C, the bromo ester (**3a**) afforded a mixture (87% yield) of dimethyl (*E*)- and (*Z*)-1,2-di(1,2-benzisoxazol-3-yl) ethylene-1,2-dicarboxylates (**24**) which were separable in 14% and 63% yields, respectively. Under similar conditions, the chloro ester (**3b**) gave a 1:5 mixture (51% yield) of *E*- and *Z*-(**24**) (Scheme 6). The stereochemistries of *E*- and *Z*-(**24**) were deduced from comparison of their n.m.r. spectra in consideration of the anisotropic effect of the benzisoxazole ring: thus, a singlet methyl signal of the *E*-isomer appeared at a higher field (δ 3.64) than that of the *Z*-isomer (δ 3.92), while aromatic protons of the *E*-isomer absorbed at a lower field (δ 7.36—7.72) than those of the *Z*-isomer (δ 7.16—7.50).



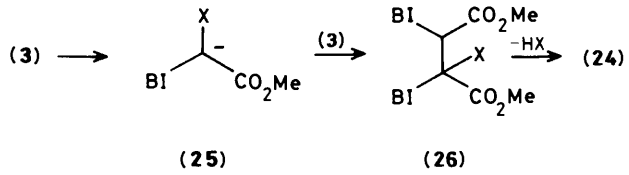
Scheme 6.

Addition of cyclohexene had little effect on the yield of the dimerization product (**24**), ruling out the formation of a carbene intermediate *via* α-elimination. A possible mechanism for this dimerization is illustrated in Scheme 7. Intermolecular attack of the carbanion (**25**) onto another molecule of (**3**) (having a halide as a good leaving group), occurred more easily than intra-



Scheme 5.

A possible mechanism for the novel ring transformations of the esters (**1**) and (**2**) to the 2*H*-azirines (**8**) and the 3-iminobenzofurans (**18**) is illustrated in Scheme 5. The azirine formation may proceed *via* a mechanism similar to the Neber arrangement. Because the nucleophilicity of the carbanion (**23**) is strengthened by an electron-donating substituent, the carbanion can attack the ring nitrogen (which carries a phenoxide considered to be a poor leaving group), affording the molecular Neber-type reaction, and was followed by dehydrohalogenation of the resulting dimer (**26**) to afford (**24**). However, attempts to isolate the intermediate (**26**) were unsuccessful under the conditions using less than half an equimolar amount of NaH, only the starting ester (**3**) and the ethylene compound (**24**) being isolated. Because the methine proton of (**26**) is more acidic than that of (**3**), elimination of (**26**) is considered to proceed faster than the reaction of (**25**) with (**3**).

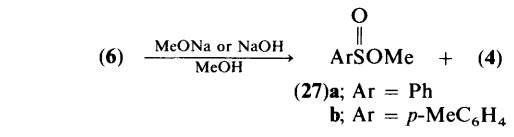


Scheme 7.

(d) *Recovery of Starting Esters.*—The non-substituted ester (**4**) and the esters (**5**)—(**7**) having electron-withdrawing substituents such as cyano, arylsulphinyl, and arylsulphonyl groups were similarly treated with NaH in DMF—this resulted only in the recovery of the starting materials (80—90%), although the generation of the carbanion species was evidenced by the evolution of hydrogen and also the above mentioned fact that the alkylated compounds (**1a**—**c**) were obtained by successive treatment with alkyl halides. Furthermore, the reaction of the sulphinyl ester (**6a**) with NaH in tetrahydrofuran (THF) at 0 °C gave its sodium salt (**6a**)·Na as a white precipitate, which was reconvertible to the starting ester (**6a**) by acid treatment.

The carbanion species of compounds (**4**)—(**7**) appears to be unable to undergo the Neber-type reaction because of the lack of an electron-donating substituent or stabilization by the electron-withdrawing substituent.

(e) C-S *Bond Cleavage to Methyl Arylsulphinates.*—Sulphoxides having at least one hydrogen are known to yield readily the sulphinyl carbanions on treatment with strong bases such as NaH, alkoxide, and hydroxide.[8] As described in (*d*), indeed, the phenylsulphinyl ester (**6a**) gave the carbanion as an isolable sodium salt when treated with NaH in THF. We found nevertheless that an unexpected C-S bond fission occurred, on treatment of the sulphinyl esters (**6**) with MeONa in methanol at room temperature, to afford methyl arylsulphinates (**27**) and methyl 1,2-benzisoxazol-3-ylacetate (**4**). The same results were obtained on reaction of (**6**) with NaOH in methanol and by treating (**6a**)·Na with methanol alone (Scheme 8). The results



Scheme 8.

are summarized in the Table. The reaction proceeded likewise even in the presence of less than half an equimolar amount of base though the reaction rate was markedly retarded. Meanwhile, under the same conditions, the sulphonyl derivatives (**7**) underwent no reaction.

Although the mechanism for this interesting reaction is as yet uncertain, the nucleophilic attack of methoxide ion seems to take place directly on the sulphinyl sulphur atom of (**6**) to afford the products; this is the first example of the preparation of a sulphinate ester from a sulphoxide.

A number of general methods including the modified Neber reaction, thermolysis and photolysis of vinyl azides and isoxazoles, and thermolysis of oxazaphospholines are available for the synthesis of 2*H*-azirines,[9] however there are some limitations in the preparation of precursors, the yields, the reaction conditions, and so on. The substituted (1,2-benzisoxazol-3-yl)acetates are found to undergo interesting base-induced reactions of new types and proved to be key compounds for the preparation of a wide variety of heterocycles including 2*H*-azirines *via* the Neber-type rearrangement as a key reaction.

Table. C-S Bond cleavage of the sulphinyl esters (**6**)

Compound	Reaction conditions	Products and yields (%)[a]	
		(**27a**)	(**4**)
(**6a**)	MeONa (1 equiv.), 3 h	61	81
(**6a**)	MeONa (0.5 equiv.), 4 h	65 (70)[b]	84 (95)[b]
(**6a**)	NaOH (1 equiv.), 3 h	63	83
(**6a**)	NaOH (0.5 equiv.), 5 h	66 (71)[b]	84 (96)[b]
(**6a**)·Na	MeOH, 2.5 h	57	71
		(**27b**)	(**4**)
(**6b**)	MeONa (1 equiv.), 2 h	75	86
(**6b**)	NaOH (0.5 equiv.), 2 h	73	85

[a] Isolated yields. [b] Determined by h.p.l.c. before isolation.

Experimental

M.p.s were determined on a Yanagimoto micro melting point apparatus and are uncorrected. I.r. spectra were recorded on a Hitachi 260-10 spectrometer and n.m.r. spectra were recorded in [$^2H_1$]chloroform on Varian EM-360 (^{1}H, 60 MHz) (unless otherwise stated), Varian FT-80A (^{1}H, 80 MHz), Varian HA-100D (^{1}H, 100 MHz), and Varian XL-300 (^{1}H, 300 MHz and ^{13}C) instruments using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi RMU-6L spectrometer.

Preparation of the Alkylated Esters (**1a**) *and* (**1b**).—(*a*) *Methyl* (1,2-*benzisoxazol*-3-*yl*)*methylacetate* (**1a**). Sodium hydride (60% dispersion in mineral oil) (1.1 g, 26.3 mmol) was added to a solution of the ester (**4**) (5.0 g, 26.2 mmol) in toluene (140 ml) under ice-cooling. After being stirred for 1 h at room temperature, methyl iodide (4.0 g, 28.2 mmol) was added and the resulting mixture was stirred for 1 h at room temperature. After addition of water, the toluene layer was separated, washed with water, dried, and evaporated to dryness. Chromatography of the residue on silica gel with chloroform as eluant gave the methylated ester (**1a**) (4.0 g, 74%) as a colourless oil; ν(NaCl) 1 735 cm^{-1} (C=O); δ_H 1.74 (3 H, d, *J* 7 Hz), 3.72 (3 H, s), 4.32 (1 H, q, *J* 7 Hz), and 7.1—7.9 (4 H, m); *m*/*z* 205 (M^+) (Found: C, 64.7; H, 5.4; N, 6.8. $C_{11}H_{11}NO_3$ requires C, 64.38; H, 5.40; N, 6.83%).

(*b*) *Methyl* (1,2-*benzisoxazol*-3-*yl*)*benzylacetate* (**1b**). In the same manner as that described above, the benzylated ester (**1b**) (10.8 g, 73%) was obtained from (**4**) (10.0 g) and benzyl bromide (9.9 g) as a colourless oil; ν(NaCl) 1 735 cm^{-1} (C=O) cm^{-1}; δ_H(80 MHz) 3.35 (1 H, dd, *J* 8 and 14 Hz), 3.61 (1 H, dd, *J* 8 and 14 Hz), 3.64 (3 H, s), 4.47 (1 H, t, *J* 8 Hz), and 7.0—7.9 (9 H, m); *m*/*z* 281 (M^+) (Found: C, 72.9; H, 5.4; N, 5.1. $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.37; N, 4.98%).

Preparation of Methyl (1,2-*Benzisoxazol*-3-*yl*)*phenoxyacetate* (**1d**).—A solution of phenol (4.0 g, 43 mmol), sodium hydroxide (1.8 g, 45 mmol), water (10 ml), and ethanol (10 ml) was added to a mixture of (1,2-benzisoxazol-3-yl)bromoacetic acid (10.2 g, 40 mmol), sodium hydroxide (1.6 g, 40 mmol), water (20 ml), and ethanol (50 ml) and the mixture stirred for 2 h at room temperature and then for a further 1.5 h at 45 °C. After evaporation of the solvent, the residue was dissolved in water, washed with chloroform, and the aqueous layer acidified with hydrochloric acid and extracted with chloroform. The chloroform layer was dried and evaporated to dryness. A solution of the residue in methanol (150 ml) containing conc. sulphuric acid

(0.7 ml) was refluxed for 19 h then the solvent was evaporated off. Toluene was added to the residue, and the resulting solution was washed with aqueous sodium carbonate, dried, and evaporated to dryness. Chromatography of the crude product on silica gel with toluene as eluant gave the phenoxy ester (**1d**) (5.5 g, 49%), m.p. 78—79 °C (from acetone–hexane); ν(KBr) 1 740 cm^{-1} (C=O); δ_H 3.80 (3 H, s), 6.25 (1 H, s), and 6.9—8.2 (9 H, m) (Found: C, 67.8; H, 4.6; N, 4.8. $C_{16}H_{13}NO_4$ requires C, 67.84; H, 4.63; N, 4.94%).

Preparation of Methyl (1,2-*Benzisoxazol*-3-*yl*)(*phenylthio*)-*acetate* (**1e**).—A solution of (1,2-benzisoxazol-3-yl)(phenylthio)-acetic acid [2g] (28.5 g, 0.1 mol) in methanol (300 ml) containing conc. sulphuric acid (1 ml) was refluxed for 20 h. After evaporation of the solvent, the residue was dissolved in chloroform and the resulting solution was washed with aqueous potassium carbonate, dried, and evaporated to dryness. The residual oil was subjected to chromatography on silica gel to give the *phenylthio ester* (**1e**) (22.8 g, 76%) as a colourless oil; ν(NaCl) 1 735 cm^{-1} (C=O); δ_H 3.74 (3 H, s), 5.42 (1 H, s), and 7.1—8.2 (9 H, m); *m/z* 299 (M^+) (Found: C, 64.4; H, 4.1; N, 4.5; S, 10.9. $C_{16}H_{13}NO_3S$ requires C, 64.20; H, 4.38; N, 4.68; S, 10.71%).

General Procedure for Preparation of the Dialkylamino Esters (**2**).—A solution of compound (**3a**) and an excess of dialkylamine in acetone was stirred for 3—5 h at room temperature. After evaporation of the solvent, the residue was dissolved in 5% aqueous hydrochloric acid and washed with toluene. The aqueous layer was basified with sodium carbonate, extracted with toluene, and the organic layer dried and evaporated to dryness. The residue was subjected to chromatography on silica gel with methanol–chloroform (1:20) as eluant to give the dialkylamino ester (**2**). The oily esters were further characterized by preparation of the appropriate crystalline salts.

(*a*) *Methyl* (1,2-*benzisoxazol*-3-*yl*)*dimethylaminoacetate* (**2a**) (16.5 g, 95%) was obtained from (**3a**) (20.0 g, 74 mmol) and 50% aqueous dimethylamine solution (15 ml) as a colourless oil; ν(NaCl) 1 740 cm^{-1} (C=O); δ_H 2.40 (6 H, s), 3.77 (3 H, s), 4.73 (1 H, s), and 7.2—8.1 (4 H, m); *m/z* 234 (M^+). The hydrochloride, m.p. 156—158 °C (from methanol–diethyl ether); ν(KBr) 1 750 cm^{-1} (C=O) (Found: C, 53.05; H, 5.6; N, 10.3; Cl, 13.1. $C_{12}H_{14}N_2O_3$·HCl requires C, 53.24; H, 5.59; N, 10.35; Cl, 13.10%).

(*b*) *Methyl* (1,2-*benzisoxazol*-3-*yl*)*morpholinoacetate* (**2b**) (8.0 g, 97%) was obtained from (**3a**) (8.0 g, 2.96 mmol) and morpholine (8 ml) as a colourless oil; ν(NaCl) 1 735 cm^{-1} (C=O); δ_H 2.5—2.8 (4 H, m), 3.5—4.0 (4 H, m), 3.73 (3 H, s), 4.76 (1 H, s), and 7.1—8.2 (4 H, m); *m/z* 276 (M^+). The hydrochloride, m.p. 140—142 °C (from methanol–diethyl ether); ν(KBr) 1 745 cm^{-1} (C=O) (Found: C, 53.65; H, 5.4; N, 8.8; Cl, 11.2. $C_{14}H_{16}N_2O_4$·HCl requires C, 53.77; H, 5.48; N, 8.96; Cl, 11.34%).

(*c*) *Methyl* (2,3,4,5,6,7-*hexahydro*-1H-*azepinyl*)(1,2-*benzisoxazol*-3-*yl*)*acetate* (**2c**) (4.6 g, 98%) was obtained from (**3a**) (4.5 g, 16.6 mmol) and hexahydro-1*H*-azepine (4 ml), m.p. 37—39 °C (from hexane); ν(KBr) 1 740 cm^{-1} (C=O); δ_H(80 MHz) 1.58 (8 H, br s), 2.85 (4 H, br s), 3.78 (3 H, s), 4.99 (1 H, s), and 7.1—8.0 (4 H, m); δ_C 27.0, 29.3, 52.0, 52.7, 65.5, 109.8, 121.0, 123.0, 123.5, 130.0, 155.7, 163.4, and 170.2 (Found: C, 66.3; H, 6.9; N, 9.4. $C_{16}H_{20}N_2O_3$ requires C, 66.65; H, 6.99; N, 9.72%).

(*d*) *Methyl* (1,2-*benzisoxazol*-3-*yl*)(4-*phenylpiperazinyl*)-*acetate* (**2d**) (9.7 g, 93%) was obtained from (**3a**) (8.0 g) and 1-phenylpiperazine (10.0 g) as a colourless oil; ν(NaCl) 1 740 cm^{-1} (C=O); δ_H 2.6—3.0 (4 H, m), 3.0—3.4 (4 H, m), 3.76 (3 H, s), 4.84 (1 H, s), and 6.8—8.2 (9 H, m); *m/z* 351 (M^+). The oxalate, m.p. 170—172 °C (from ethanol–diethyl ether); ν(KBr) 1 735 cm^{-1} (C=O) (Found C, 59.5; H, 5.1; N, 9.45. $C_{20}H_{21}N_3O_3$·$C_2H_2O_4$ requires C, 59.86; H, 5.25; N, 9.52%).

Preparation of Methyl (1,2-*Benzisoxazol*-3-*yl*)*chloroacetate* (**3b**).—A solution of 1,2-benzisoxazol-3-ylacetic acid (17.7 g, 0.1 mol) and *N*-chlorosuccinimide (14.7 g, 0.11 mol) in carbon tetrachloride (400 ml) was refluxed for 3 h, and the reaction mixture extracted with 1M aqueous sodium hydroxide. The aqueous layer was separated, acidified with conc. hydrochloric acid, and extracted with chloroform, the extracts were dried and evaporated to dryness. The residue was subjected to chromatography on silica gel with chloroform–methanol (20:1) as eluant to give a mixture (13.0 g) of the starting acid and (1,2-benzisoxazol-3-yl)chloroacetic acid.[2b] A solution of this mixture (13.0 g) in methanol (300 ml) containing a catalytic amount of conc. sulphuric acid was refluxed for 8 h. After evaporation of the solvent, the residue was dissolved in chloroform and the resulting solution was washed with aqueous potassium carbonate, dried, and evaporated to dryness. The residue was subjected to chromatography on silica gel with chloroform–hexane (1:1) as eluant to give (**4**) (5.7 g, 30%) and the *chloro ester* (**3b**) (5.6 g, 25%), m.p. 39—40 °C (from hexane); ν(KBr) 1 730 cm^{-1} (C=O); δ_H 3.82 (3 H, s), 5.86 (1 H, s), and 7.2—8.1 (4 H, m) (Found: C, 53.4; H, 3.35; Cl, 15.7; N, 6.1. $C_{10}H_8ClNO_3$ requires C, 53.23; H, 3.57; Cl, 15.71; N, 6.21%).

Preparation of Ethyl (1,2-*Benzisoxazol*-3-*yl*)*cyanoacetate* (**5**).—Sodium hydride (0.76 g, 19 mmol) was added to a solution of 1,2-benzisoxazol-3-ylacetonitrile [2a] (3.0 g, 19 mmol) in DMF (20 ml) was added under ice-cooling, and the mixture was stirred for 20 min. Ethyl chloroformate (2.1 g, 19.4 mmol) was added, the resulting solution was stirred for 10 min at room temperature, and the reaction mixture diluted with water, acidified with hydrochloric acid, and extracted with toluene. The extracts were washed with water, dried, and evaporated to dryness. The residue was recrystallized from ethanol to give the *cyano ester* (**5**) (1.3 g, 30%), m.p. 83—88 °C, the spectral data of which showed it to exist as the enol form in crystals and as the keto form in solution; ν(KBr) 3 160 (OH), 2 200 (CN), and 1 640 cm^{-1} (C=C); ν($CHCl_3$) 1 750 (C=O) cm^{-1}; δ_H 1.30 (3 H, t, *J* 8 Hz), 4.33 (2 H, q, *J* 8 Hz), 5.33 (1 H, s), and 7.2—8.2 (4 H, m) (Found: C, 62.5; H, 4.5; N, 12.2. $C_{12}H_{10}N_2O_3$ requires C, 62.61; H, 4.38; N, 12.17%).

Preparation of Methyl (1,2-*Benzisoxazol*-3-*yl*)-*phenylsulphinyl- and -phenylsulphonyl-acetates* (**6a**) *and* (**7a**).—A solution of sodium metaperiodate (17.0 g, 80 mmol) in water (150 ml) was added to a solution of (**1e**) (16.1 g, 54 mmol) in methanol (400 ml), and the mixture was stirred for 18 h at 50 °C. After evaporation of the solvent, the residue was extracted with chloroform and the organic layer was dried and evaporated to dryness. The residue was chromatographed on silica gel to give the *phenylsulphinyl ester* (**6a**) (12.0 g, 70%) as a *ca.* 1:2.2 mixture of stereoisomers, m.p. 109—112 °C (from methanol); ν(KBr) 1 740 (C=O), 1 270, and/or 1 240 cm^{-1} (SO); δ_H([$^2H_6$]DMSO) 3.73 (*ca.* 0.9 H, s), 3.80 (*ca.* 2.1 H, s), 6.01 (1 H, s), and 7.1—7.9 (9 H, m) (Found: C, 61.1; H, 4.1; N, 4.5; S, 10.2. $C_{16}H_{13}NO_4S$ requires C, 60.94; H, 4.15; N, 4.44; S, 10.17%).

m-Chloroperbenzoic acid (2.1 g, 10 mmol) was added to a solution of (**6a**) (3.0 g, 9.5 mmol) in chloroform (40 ml) and the mixture was stirred for 30 min at room temperature. The reaction mixture was washed with aqueous potassium carbonate, dried, and evaporated to dryness. The residue was chromatographed on silica gel with chloroform as eluant to give the *phenylsulphonyl ester* (**7a**) (2.9 g, 92%), m.p. 82—85 °C (from ethanol); ν(KBr) 1 740 (C=O), 1 320, and 1 155 cm^{-1} (SO_2); δ_H 3.80 (3 H, s), 5.72 (1 H, s), and 7.2—8.3 (9 H, m) (Found: C, 58.1;

H, 4.2; N, 4.1; S, 9.6. $C_{16}H_{13}NO_5S$ requires C, 58.00; H, 3.95; N, 4.23; S, 9.68%).

Preparation of Methyl (1,2-*Benzisoxazol*-3-*yl*)-p-*tolylsulphinyl- and* -p-*tolylsulphonyl-acetates* (**6b**) *and* (**7b**).—A solution of (1,2-benzisoxazol-3-yl)(*p*-tolylthio)acetic acid[2g] (10.5 g, 35 mmol) in methanol (300 ml) containing a catalytic amount of conc. sulphuric acid was refluxed for 15 h after which the solvent was evaporated off. The residue was dissolved in chloroform, washed with aqueous potassium carbonate, dried, and evaporated to dryness. The residue was subjected to chromatography on silica gel to give *methyl* (1,2-*benzisoxazol*-3-*yl*)(p-*tolylthio*)*acetate* (8.0 g, 73%) as a colourless oil; ν(NaCl) 1 735 (C=O) cm^{-1}; δ_H 2.28 (3 H, s), 3.75 (3 H, s), 5.35 (1 H, s), and 6.9—8.2 (8 H, m).

m-Chloroperbenzoic acid (5.5 g, 25.5 mmol) was added to a solution of the above ester (7.0 g, 22.4 mmol) in chloroform (150 ml) and the mixture was stirred for 1 h at room temperature. The reaction mixture was washed with aqueous potassium carbonate, dried, and evaporated to dryness. The residue was subjected to chromatography on silica gel with chloroform as eluant. From the first fraction, the *tolylsulphonyl ester* (**7b**) (1.5 g, 19%) was obtained, m.p. 123—125 °C (from ethanol); ν(KBr) 1 745 (C=O), 1 330, and 1 145 cm^{-1} (SO_2); δ_H 2.39 (3 H, s), 3.81 (3 H, s), 5.68 (1 H, s), and 7.1—8.3 (8 H, m) (Found: C, 59.2; H, 4.1; N, 3.9; S, 9.3. $C_{17}H_{15}NO_5S$ requires C, 59.12; H, 4.38; N, 4.06; S, 9.28%). The next fraction was evaporated to give the *tolylsulphinyl ester* (**6b**) (4.8 g, 65%) as a *ca.* 1:1 mixture of stereoisomers, a colourless oil, which was incomplete to crystallize; ν(NaCl) 1 740 (C=O), 1 085, and/or 1 060 cm^{-1} (SO); δ_H 2.29 (1.5 H, s), 2.34 (1.5 H, s), 3.77 (1.5 H, s), 3.82 (1.5 H, s), 5.09 (0.5 H, s), 5.19 (0.5 H, s), and 6.9—8.2 (8 H, m); *m/z* 329 (M^+) (Found: C, 61.8; H, 4.7; N, 4.2; S, 9.4. $C_{17}H_{15}NO_4S$ requires C, 61.99; H, 4.59; N, 4.25; S, 9.73%).

General Procedure for Ring Contraction of the Esters (**1**) *to the* 2H-*Azirines* (**8**).—To a solution of the ester (**1**) (*ca.* 5—6 mmol) in DMF (10 ml) was added an equimolar amount of NaH, Bu^{t}OK, or MeONa under ice-cooling, and the mixture was stirred for 30 min at room temperature except that (**1d**) was treated at 80 °C. After the reaction mixture had been quenched with aqueous ammonium chloride or acidified (pH *ca.* 6) with cold dil. hydrochloric acid, the resulting solution was extracted with diethyl ether, and the extracts were washed with water, dried, and evaporated to dryness. The residue was purified by chromatography on silica gel with chloroform as eluant and/or by recrystallization to give the product (**8**). The yields are summarized in Scheme 1.

(*a*) *Methyl* 3-(2-*hydroxyphenyl*)-2-*methyl*-2H-*azirine*-2-*carboxylate* (**8a**), m.p. 74—77 °C (from diethyl ether–hexane); ν(KBr) 3 250 (OH), 1 750 (C=N), and 1 720 cm^{-1} (C=O); δ_H 1.62 (3 H, s, CMe), 3.70 (3 H, s, OMe), 6.4 (1 H, br s, OH), and 6.8—7.8 (4 H, m, ArH) (Found: C, 64.15; H, 5.4; N, 6.8. $C_{11}H_{11}NO_3$ requires C, 64.38; H, 5.40; N, 6.83%).

(*b*) *Methyl* 2-*benzyl*-3-(2-*hydroxyphenyl*)-2H-*azirine*-2-*carboxylate* (**8b**), m.p. 107—109 °C (from diethyl ether–hexane); ν(KBr) 3 250 (OH), 1 760 (C=N), and 1 725 cm^{-1} (C=O); δ_H 3.19 (1 H, d, *J* 14 Hz, CH_aHPh), 3.62 (1 H, d, *J* 14 Hz, CHH_bPh), 3.70 (3 H, s, Me), and 6.8—7.7 (10 H, m, OH and ArH, 1 H exchanged by D_2O); δ_C 37.5, 37.9 (C-2), 52.7, 108.8, 116.9, 120.5, 126.6, 128.4, 129.7, 131.1, 135.4, 137.1, 158.6, 160.8 (C-3), and 173.1; *m/z* 281 (M^+) (Found: C, 72.5; H, 5.3; N, 4.95. $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.37; N, 4.98%).

(*c*) *Methyl* 2-*cyclohexyl*-3-(2-*hydroxyphenyl*)-2H-*azirine*-2-*carboxylate* (**8c**), m.p. 125—127 °C (from diethyl ether–hexane); ν(KBr) 3 250 (OH), 1 760 (C=N), and 1 725 cm^{-1} (C=O); δ_H(100 MHz) 0.6—1.9 (10 H, m, $CH_2 \times 5$), 2.4—2.8 (1 H, m, CH), 3.68 (3 H, s, Me), and 6.9—7.6 (5 H, m, OH and ArH, 1 H exchanged by D_2O); δ_C 26.0, 26.1, 29.0, 30.7, 36.8, 41.4 (C-2), 52.5, 109.6, 117.1, 120.7, 131.1, 135.3, 158.7, 161.2 (C-3), and 172.8; *m/z* 273 (M^+) (Found: C, 70.3; H, 7.2; N, 5.2. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N, 5.13%).

(*d*) *Methyl* 3-(2-*hydroxyphenyl*)-2-*phenoxy*-2H-*azirine*-2-*carboxylate* (**8d**), colourless oil; ν(NaCl) 3 300 (OH) and 1 730 (br, C=N and C=O) cm^{-1}; δ_H 3.77 (3 H, s, Me), 5.8—6.7 (1 H, br, OH), and 6.8—7.8 (9 H, m, ArH); *m/z* 283 (M^+) (Found: C, 67.6; H, 4.7; N, 5.0. $C_{16}H_{13}NO_4$ requires C, 67.84; H, 4.63; N, 4.94%).

(*e*) *Methyl* 3-(2-*hydroxyphenyl*)-2-*phenylthio*-2H-*azirine*-2-*carboxylate* (**8e**), m.p. 112—114 °C (from diethyl ether–hexane); ν(KBr) 3 300 (OH), 1 760 (C=N), and 1 725 cm^{-1} (C=O); δ_H 3.72 (3 H, s, Me), 6.70 (1 H, br s, OH), and 6.8—7.8 (9 H, m, ArH); δ_C 44.2 (C-2), 53.6, 107.8, 117.1, 120.7, 128.1, 129.0, 131.2, 133.2, 136.2, 158.6 (C-3), and 170.6 (Found: C, 64.3; H, 4.2; N, 4.7; S, 10.5. $C_{16}H_{13}NO_3S$ requires C, 64.20; H, 4.38; N, 4.68; S, 10.71%).

O-*Alkylation of the* o-*Hydroxyphenyl*-2H-*azirines* (**8**) *to* (**9**).—(*a*) *Methyl* 3-(2-*methoxyphenyl*)-2-*methyl*-2H-*azirine*-2-*carboxylate* (**9a**). Sodium hydride (0.2 g, 5 mmol) was added to a solution of compound (**8a**) (1.0 g, 4.9 mmol) in DMF (10 ml) under ice-cooling and the mixture was stirred for 30 min at 0 °C. Methyl iodide (0.7 g, 4.9 mmol) was added to the mixture and the resulting mixture was stirred for a further 30 min at room temperature. The reaction mixture was quenched with ice-water and extracted with toluene. The extracts were washed with water, dried, evaporated to dryness and the residue was recrystallized from hexane to give the *o*-methoxyphenyl-2*H*-azirine (**9a**) (0.98 g, 92%), m.p. 54—56 °C; ν(KBr) 1 750 (C=N) and 1 710 cm^{-1} (C=O); δ_H 1.58 (3 H, s), 3.67 (3 H, s), 3.97 (3 H, s), and 6.9—7.9 (4 H, m); δ_C 18.0, 33.7 (C-2), 52.3, 56.0, 111.5, 111.6, 120.9, 132.1, 135.3, 159.9, 160.5 (C-3), and 173.9; *m/z* 219 (M^+) (Found: C, 65.5; H, 6.1; N, 6.4. $C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98; N, 6.39%).

(*b*) *Methyl* 2-*benzyl*-3-(2-*benzyloxyphenyl*)-2H-*azirine*-2-*carboxylate* (**9b**). The same treatment as described above using compound (**8b**) (0.16 g, 0.6 mmol) and benzyl bromide (0.11 g, 0.63 mmol) gave the *o*-benzyloxyphenyl-2*H*-azirine (**9b**) (0.17 g, 81%), m.p. 117—118 °C (from dichloromethane–hexane); ν(KBr) 1 760 (C=N) and 1 710 cm^{-1} (C=O); δ_H(100 MHz) 3.21 (1 H, d, *J* 15 Hz), 3.42 (1 H, d, *J* 15 Hz), 3.58 (3 H, s), 5.16 (2 H, s), and 6.9—7.6 (14 H, m); δ_C 37.6, 38.9 (C-2), 52.2, 70.4, 112.2, 112.8, 121.0, 126.2, 127.2, 128.1, 128.6, 129.9, 131.9, 135.0, 136.0, 137.6, 158.5, 159.4 (C-3), and 173.2; *m/z* 371 (M^+) (Found: C, 77.6; H, 5.4; N, 3.7. $C_{24}H_{21}NO_3$ requires C, 77.60; H, 5.70; N, 3.77%).

O-*Acetylation of the* o-*Hydroxyphenyl*-2H-*azirines* (**8**) *to* (**10**).—A solution of (**8**) (*ca.* 1—2 mmol), acetic anhydride (1 ml), and pyridine (2 ml) was kept at room temperature for 10 h and was then evaporated to dryness. The residue was purified by silica gel column chromatography with chloroform as eluant to give the o-*acetoxyphenyl*-2H-*azirine* (**10**) in nearly quantitative yield.

(*a*) Methyl 3-(2-acetoxyphenyl)-2-benzyl-2*H*-azirine-2-carboxylate (**10a**), colourless oil; ν(NaCl) 1 760 (C=N) and 1 720 cm^{-1} (C=O); δ_H 2.30 (3 H, s), 3.17 (1 H, d, *J* 14 Hz), 3.50 (1 H, d, *J* 14 Hz), 3.61 (3 H, s), and 7.0—7.8 (9 H, m); *m/z* 323 (M^+).

(*b*) Methyl 3-(2-acetoxyphenyl)-2-cyclohexyl-2*H*-azirine-2-carboxylate (**10b**), m.p. 97—98 °C (from diethyl ether–hexane); ν(KBr) 1 760 (C=N) and 1 720 cm^{-1} (C=O); δ_H(100 MHz) 0.5—2.0 (10 H, m), 2.38 (3 H, s), 2.4—2.7 (1 H, m), 3.63 (3 H, s), and 7.2—7.9 (4 H, m); δ_C 20.9, 25.9, 26.1, 28.9, 30.3, 36.9, 42.5 (C-2), 52.1, 117.1, 123.7, 126.6, 131.6, 134.6, 150.6, 159.8 (C-3), 168.7, and 172.6 (Found: C, 68.65; H, 6.8; N, 4.65. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44%).

(*c*) Methyl 3-(2-acetoxyphenyl)-2-phenoxy-2*H*-azirine-2-carboxylate (**10c**), m.p. 68—69 °C (from diethyl ether–hexane);

ν(KBr) 1 770 (C=N) and 1 735 cm^{-1} (C=O); δ_H(100 MHz) 2.45 (3 H, s), 3.74 (3 H, s), and 7.04—8.04 (9 H, m); δ_C 20.9, 53.1, 64.3 (C-2), 114.7, 116.7, 122.7, 123.8, 126.8, 129.5, 131.6, 135.7, 151.1, 155.1, 160.6 (C-3), 168.7, and 168.8; *m/z* 325 (M^+) (Found: C, 66.5; H, 4.8; N, 4.3. $C_{18}H_{15}NO_5$ requires C, 66.46; H, 4.65; N, 4.31%).

(*d*) Methyl 3-(2-acetoxyphenyl)-2-phenylthio-2*H*-azirine-2-carboxylate (**10d**), m.p. 66—69 °C (from diethyl ether–hexane); ν(KBr) 1 765 (C=N) and 1 730 cm^{-1} (C=O); δ_H 2.42 (3 H, s), 3.68 (3 H, s), and 7.1—7.9 (9 H, m); *m/z* 341 (M^+) (Found: C, 63.3; H, 4.3; N, 4.1; S, 9.3. $C_{18}H_{15}NO_4S$ requires C, 63.33; H, 4.43; N, 4.10; S, 9.39%).

Acidic Hydrolysis of the 2H-*Azirine Esters* (**8**).—(*a*) 3-*Amino*-3-*benzylchroman*-2,4-*dione hydrochloride* (**12b**). A solution of compound (**8b**) (0.25 g, 0.89 mmol), ethanol (40 ml), water (0.3 ml), and 35% HCl–EtOH (0.3 ml) was stirred for 40 min at 70 °C. After evaporation of the solvent, the residue was recrystallized from ethanol–diethyl ether to give the benzylaminochromandione (**12b**) (0.1 g, 37%), m.p. 143—145 °C; ν(KBr) 3 300, 2 820, 1 775, and 1 705 cm^{-1}; *m/z*, 267 (M^+ – HCl). Because this compound did not give satisfactory analyses, further identification was carried out by preparation of the N-*acetyl derivative*, m.p. 206—208 °C (from diethyl ether–hexane); ν(KBr) 3 260, 3 200, 3 050, 1 770, 1 700, and 1 610 cm^{-1}; δ_H 2.05 (3 H, s, Ac), 3.26 (2 H, s, CH_2), and 6.8—8.1 (10 H, m, NH and ArH); *m/z* 309 (M^+) (Found: C, 70.05; H, 4.9; N, 4.6. $C_{18}H_{15}NO_4$ requires C, 69.89; H, 4.89; N, 4.53%).

(*b*) 3-*Amino*-3-*cyclohexylchroman*-2,4-*dione hydrochloride* (**12c**). In the same manner as above, the cyclohexylchromandione (**12c**) (0.12 g, 85%) was obtained from compound (**8c**) (0.13 g), m.p. 152—154 °C (ethanol–hexane); ν(KBr) 2 940, 1 780, 1 700, and 1 610 cm^{-1}; δ_H(100 MHz, [$^2H_6$]DMSO) 0.8—1.9 (10 H, m), 1.9—2.3 (1 H, m), 7.3—7.6 (2 H, m), 7.8—8.1 (2 H, m), and 8.4—9.6 (2 H, br); *m/z* 259 (M^+ – HCl) (Found: C, 60.6; H, 6.0; N, 4.7; Cl, 11.8. $C_{15}H_{17}NO_3$·HCl requires C, 60.91; H, 6.13; N, 4.73; Cl, 11.99%). Treatment of (**12c**) with acetic anhydride–pyridine gave the N-*acetyl derivative*, m.p. 221—223 °C (from diethyl ether–hexane); ν(KBr) 3 350, 1 775, 1 700, 1 640, and 1 610 cm^{-1}; δ_H(100 MHz) 0.8—2.0 (11 H, m), 2.03 (3 H, s), 6.59 (1 H, br s), and 7.18—8.04 (4 H, m); δ_C 21.7, 25.6, 26.1, 26.2, 27.3, 27.4, 44.9, 70.7, 117.7, 120.1, 124.9, 127.2, 136.8, 154.5, 167.6, 170.8, and 190.3; *m/z* 301 (M^+) (Found: C, 67.5; H, 6.5; N, 4.7. $C_{17}H_{19}NO_4$ requires C, 67.75; H, 6.35; N, 4.65%).

(*c*) 2-*Amino*-2′-*hydroxypropiophenone hydrochloride* (**13**). A solution of (**8a**) (1.8 g, 8.78 mmol), methanol (40 ml), and 10% hydrochloric acid (6 ml) was refluxed for 30 min. After evaporation of the solvent, the residue was recrystallized from methanol–diethyl ether to give the aminopropiophenone (**13**) (1.2 g, 68%), m.p. 228—229 °C; ν(KBr) 3 000, 2 920, and 1 630 cm^{-1} (Found: C, 53.5; H, 6.0; N, 6.9; Cl, 17.7. $C_9H_{11}NO_2$·HCl requires C, 53.61; H, 6.00; N, 6.95; Cl, 17.58%). Treatment of (**13**) with acetic anhydride –pyridine gave the N,O-*diacetyl derivative*, m.p. 87—88 °C (from ethanol–hexane); ν(KBr) 3 290, 1 740, 1 680, and 1 630 cm^{-1}; δ_H 1.33 (3 H, d, *J* 7 Hz, CMe), 2.00 (3 H, s, *N*Ac), 2.34 (3 H, s, *O*-Ac), 5.46 (1 H, quintet, *J* 7 Hz, CH, quartet after deuteriation), 6.60 (1 H, br d, NH, exchanged by D_2O), and 7.0—8.0 (4 H, m, ArH) (Found: C, 62.35; H, 5.9; N, 5.6. $C_{13}H_{15}NO_4$ requires C, 62.64; H, 6.07; N, 5.62%).

Hydrolysis of the o-*Methoxyphenyl*-2H-*azirine* (**9a**) *to the Alanine Ester* (**14**).—A mixture of (**9a**) (1.0 g, 4.56 mmol), methanol (30 ml), and 10% hydrochloric acid (3 ml) was refluxed for 3 h. After evaporation of the solvent, the residue was dissolved in water, basified with sodium carbonate, and extracted with chloroform. The extracts were dried and evaporated to dryness. The residue was subjected to chromatography on silica gel to give methyl 2-(2-methoxybenzoyl)alaninate (**14**) (1.0 g, 97%) as a colourless oil; ν(NaCl) 3 400, 3 330 (NH), 1 740, and 1 680 (C=O) cm^{-1}; δ_H 1.56 (3 H, s, C-Me), 2.20 (2 H, br s, NH_2), 3.70 (3 H, s, COOMe), 3.81 (3 H, s, OMe), and 6.8—8.0 (4 H, m, ArH); *m/z* 237 (M^+) (Found: C, 59.5; H, 6.55; N, 5.7. $C_{12}H_{15}NO_4$·0.25H_2O requires C, 59.62; H, 6.46; N, 5.79%). Further identification was carried out by preparation of the N-*acetyl derivative*, m.p. 182—183 °C (from methanol); ν(KBr) 3 360, 1 720, 1 680, and 1 660 cm^{-1}; δ_H 1.72 (3 H, s), 1.85 (3 H, s), 3.76 (3 H, s), 3.79 (3 H, s), and 6.7—7.7 (5 H, m, 1 H exchanged by D_2O) (Found: C, 60.2; H, 5.9; N, 4.8. $C_{14}H_{17}NO_5$ requires C, 60.21; H, 6.14; N, 5.02%).

Reduction of the o-*Benzyloxyphenyl*-2H-*azirine* (**9b**) *with Sodium Borohydride to the Aziridine* (**15**).—Sodium borohydride (1.0 g, 26.3 mmol) was added to a solution of compound (**9b**) (2.0 g, 5.4 mmol) in dioxane (50 ml)–methanol (10 ml) and the mixture was stirred for 10 min at 70 °C. After evaporation of the solvent, the residue was extracted with diethyl ether, and the extracts were washed with water, dried, and evaporated to dryness. The residue was recrystallized from methanol to give *methyl* 2-*benzyl*-3-(2-*benzyloxyphenyl*)*aziridine*-2-*carboxylate* (**15**) (1.2 g, 60%), m.p. 110—112 °C; ν(KBr) 3 300 (NH) and 1 710 cm^{-1} (C=O); δ_H(100 MHz) 2.13 (1 H, d, *J* 15 Hz, CCH_aHPh), 2.20 (1 H, d, *J* 10 Hz, NH, exchanged by D_2O), 3.13 (1 H, d, *J* 15 Hz, $CCHH_bPh$), 3.60 (1 H, d, *J* 10 Hz, CH, singlet after deuteriation), 3.63 (3 H, s, Me), 5.09 (2 H, s, OCH_2), and 6.85—7.60 (14 H, m, ArH); δ_C 32.9, 42.7, 45.2, 52.6, 69.9, 111.3, 120.8, 125.1, 126.1, 127.1, 127.8, 128.0, 128.5, 128.7, 129.2, 137.2, 138.8, 157.6, and 174.2; *m/z* 373 (M^+) (Found: C, 77.3; H, 6.3; N, 4.1. $C_{24}H_{23}NO_3$ requires C, 77.19; H, 6.21; N, 3.75%).

Catalytic Reduction of the 2H-*Azirines* (**8**) *with Palladium–carbon to the* 4-*Aminocoumarins* (**17**).—(*a*) Compound (**8a**) (1.00 g) was hydrogenated over 5% palladium–carbon (350 mg) in methanol (40 ml). After the absorption of hydrogen had been completed, the catalyst was removed and the solution was evaporated to dryness. The residue was recrystallized from ethanol–water to give 4-*amino*-3-*methylcoumarin* (**17a**) (0.61 g, 72%), m.p. 187—188 °C; ν(KBr) 3 420, 3 370, 1 630, 1 600, and 1 540 cm^{-1}; δ_H(80 MHz, [$^2H_6$]DMSO) 1.93 (3 H, s, Me), 6.90 (2 H, br s, NH_2), and 7.1—8.1 (4 H, m, ArH) (Found: C, 68.7; H, 5.1; N, 7.9. $C_{10}H_9NO_2$ requires C, 68.56; H, 5.18; N, 8.00%).

(*b*) In the same manner as above, 4-*amino*-3-*benzylcoumarin* (**17b**) (0.67 g, 75%) was obtained from compound (**8b**) (1.0 g), m.p. 200—201 °C (from ethanol); ν(KBr) 3 450, 3 340, 1 660, 1 630, 1 600, and 1 550 cm^{-1}; δ_H(80 MHz, [$^2H_6$]DMSO) 3.82 (2 H, s, CH_2), 7.07 (2 H, br s, NH_2), and 7.1—8.2 (9 H, m, ArH) (Found: C, 76.4; H, 5.3; N, 5.5. $C_{16}H_{13}NO_2$ requires C, 76.48; H, 5.21; N, 5.57%).

General Procedure for Ring Transformations of the Dialkylamino Esters (**2**) *to the* 3-*Iminobenzofurans* (**18**).—To a solution of the ester (**2**) (*ca.* 5—6 mmol) in DMF (10 ml) was added an equimolar amount of NaH under ice-cooling, and the mixture was stirred for 30 min at room temperature. After the reaction mixture had been quenched with aqueous ammonium chloride, the resulting solution was extracted with diethyl ether, and the extracts were washed with water, dried, and evaporated to dryness. The residue was purified by chromatography on silica gel, followed by recrystallization to give the product (**18**). The yields are summarized in Scheme 3. (*a*) *Methyl* 2-*dimethylamino*-3-*imino*-2,3-*dihydrobenzofuran*-2-*carboxylate* (**18a**), m.p. 119—121 °C (from diethyl ether–hexane); ν(KBr) 3 210 (NH), 1 740 (C=O), and 1 650 cm^{-1} (C=N); δ_H (300 MHz) 2.41 (6 H, s, NMe_2), 3.82 (3 H, s, OMe), 7.04—7.14 (2 H, m, ArH), 7.48—7.56 (2 H, m, ArH), and 10.0 (1 H, br s, NH); δ_C 38.7 (NMe), 53.7 (OMe), 103.6 (C-2), 111.7 (C-7), 121.1 (C-3a), 121.9 (C-4), 123.7 (C-5), 135.5 (C-6), 166.1 (C-3), 166.7 (C-7a), and 172.5 (CO_2);

m/z 234 (M^+) (Found: C, 61.3; H, 6.3; N, 11.9. $C_{12}H_{14}N_2O_3$ requires C, 61.53; H, 6.02; N, 11.96%).

(*b*) *Methyl* 3-*imino*-2-*morpholino*-2,3-*dihydrobenzofuran*-2-*carboxylate* (**18b**), m.p. 136—137 °C (from di-isopropyl ether); ν(KBr) 3 210 (NH), 1 745 (C=O), and 1 645 cm^{-1} (C=N); δ_H 2.5—2.9 (4 H, m), 3.5—4.0 (4 H, m), 3.80 (3 H, s), 6.9—7.9 (4 H, m), and 10.1 (1 H, br s) (Found: C, 60.8; H, 5.9; N, 9.9. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14%).

(*c*) *Methyl* 2-(2,3,4,5,6,7-*hexahydro*-1H-*azepinyl*)-3-*imino*-2,3-*dihydrobenzofuran*-2-*carboxylate* (**18c**), m.p. 93—95 °C (from diethyl ether–hexane); ν(KBr) 3 245 (NH), 1 740 (C=O), and 1 650 cm^{-1} (C=N); δ_H(80 MHz) 1.64 (8 H, s), 2.78 (4 H, br s), 3.75 (3 H, s), 6.9—7.8 (4 H, m), and 9.5—10.6 (1 H, br); δ_C 26.8, 29.3, 49.8, 53.5, 106.0, 111.8, 121.3, 121.6, 123.7, 135.4, 166.3, 167.0, and 172.9; *m/z* 288 (M^+) (Found: C, 66.4; H, 7.1; N, 9.6. $C_{16}H_{20}N_2O_3$ requires C, 66.65; H, 6.99; N, 9.72%).

(*d*) *Methyl* 3-*imino*-2-(4-*phenylpiperazinyl*)-2,3-*dihydrobenzofuran*-2-*carboxylate* (**18d**), m.p. 178—180 °C (from methanol); ν(KBr) 3 225 (NH), 1 745 (C=O), and 1 650 cm^{-1} (C=N); δ_H 2.6—3.5 (8 H, m), 3.81 (3 H, s), 6.6—8.5 (9 H, m), and 10.1 (1 H, br s) (Found: C, 68.4; H, 5.7; N, 11.9. $C_{20}H_{21}N_3O_3$ requires C, 68.36; H, 6.02; N, 11.96%).

N-*Acetylation of the* 3-*Iminobenzofurans* (**18**) *to the* N-*Acetyliminobenzofurans* (**19**).—A mixture of (**18**) (*ca.* 0.5—1 mmol), Ac_2O (1 ml), and pyridine (2 ml) was kept for 10 h at room temperature then evaporated to dryness. The residue was purified by chromatography on silica gel to give the N-*acetyl derivative* (**19**) in nearly quantitative yield.

(*a*) Methyl 3-acetylimino-2-dimethylamino-2,3-dihydrobenzofuran-2-carboxylate (**19a**), m.p. 90—91 °C (from diethyl ether–hexane); ν(KBr) 1 755, 1 700 (C=O), and 1 660 cm^{-1} (C=N); δ_H 2.36 (3 H, s, NAc), 2.52 (6 H, s, NMe_2), 3.86 (3 H, s, OMe), and 6.8—7.8 (4 H, m, ArH); *m/z* 276 (M^+) (Found: C, 60.9; H, 5.9; N, 9.9. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14%).

(*b*) Methyl 3-acetylimino-2-morpholino-2,3-dihydrobenzofuran-2-carboxylate (**19b**), m.p. 107—109 °C (from methanol–water); ν(KBr) 1 750, 1 690 (C=O), and 1 660 cm^{-1} (C=N); δ_H 2.35 (3 H, s), 2.6—3.2 (4 H, m), 3.6—4.2 (4 H, m), 3.85 (3 H, s), and 6.9—7.8 (4 H, m); *m/z* 318 (M^+) (Found: C, 60.3; H, 5.5; N, 8.7. $C_{16}H_{18}N_2O_5$ requires C, 60.37; H, 5.70; N, 8.80%).

(*c*) Methyl 3-acetylimino-2-(2,3,4,5,6,7-hexahydro-1*H*-azepinyl)-2,3-dihydrobenzofuran-2-carboxylate (**19c**), colourless oil; ν(NaCl) 1 745, 1 700 (C=O), and 1 660 cm^{-1} (C=N); δ_H(100 MHz) 1.66 (8 H, br s), 2.33 (3 H, s), 2.7—3.2 (4 H, m), 3.80 (3 H, s), 6.85—7.18 (2 H, m), and 7.35—7.64 (2 H, m); δ_C 24.5, 26.9, 29.0, 50.0, 53.6, 105.6, 112.6, 117.4, 121.8, 125.5, 136.8, 160.1, 166.4, 167.3, and 183.9; *m/z* 330 (M^+) (Found: C, 65.3; H, 6.6; N, 8.3. $C_{18}H_{22}N_2O_4$ requires C, 65.44; H, 6.71; N, 8.48%).

Hydrolysis of the 3-*Iminobenzofurans* (**18**) *with Oxalic Acid to the Benzofuranones* (**20**).—(*a*) A mixture of (**18a**) (0.23 g, 1 mmol), oxalic acid dihydrate (0.19 g, 15 mmol), methanol (10 ml), and water (0.8 ml) was stirred for 16 h at room temperature. After evaporation of the solvent, the residue was dissolved in dichloromethane and washed with aqeuous sodium carbonate. The organic layer was washed with water, dried, and evaporated to dryness. The residue was recrystallized from diethyl ether–hexane to give *methyl* 2-*dimethylamino*-3-*oxo*-2,3-*dihydrobenzofuran*-2-*carboxylate* (**20a**) (0.22 g, 93%), m.p. 120—121 °C; ν(KBr) 1 755 and 1 715 cm^{-1} (C=O); δ_H 2.45 (6 H, s, NMe_2), 3.84 (3 H, s, OMe), and 6.9—7.9 (4 H, m, ArH); δ_C 39.0 (NMe), 53.9 (OMe), 103.8 (C-2), 113.4 (C-7), 119.0 (C-3a), 122.4 (C-4), 125.2 (C-5), 139.4 (C-6), 164.8 (C-7a), 172.3 (CO_2), and 192.9 (C-3) (Found: C, 61.1; H, 5.5; N, 6.0. $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.96%).

(*b*) *Methyl* 2-*morpholino*-3-*oxo*-2,3-*dihydrobenzofuran*-2-*carboxylate* (**20b**) (52 mg, 82%) was obtained from (**18b**) (63 mg) in the same manner as above, m.p. 141—142 °C (from diethyl ether); ν(KBr) 1 760 and 1 710 cm^{-1} (C=O); δ_H 2.6—2.9 (4 H, m), 3.6—4.0 (4 H, m), 3.80 (3 H, s), and 6.9—7.9 (4 H, m) (Found: C, 60.5; H, 5.6; N, 5.0. $C_{14}H_{15}NO_5$ requires C, 60.64; H, 5.45; N, 5.05%).

Hydrolysis of the 3-*Iminobenzofuran* (**18a**) *with Hydrochloric Acid to the* 2-*Hydroxybenzofuranone* (**22**).—A mixture of compound (**18a**) (0.25 g, 1.1 mmol), methanol (20 ml), and 10% hydrochloric acid (5 ml) was stirred for 4 h at room temperature. After evaporation of the solvent, the residue was extracted with dichloromethane, and the extracts were washed with water, dried, and evaporated to dryness. The residue was purified by silica gel column chromatography, followed by recrystallization from diethyl ether–hexane to afford *methyl* 2-*hydroxy*-3-*oxo*-2,3-*dihydrobenzofuran*-2-*carboxylate* (**22**) (0.10 g, 43%), m.p. 109—112 °C; ν(KBr) 3 325 (OH), 1 750, and 1 720 cm^{-1} (C=O); δ_H 3.84 (3 H, s, OMe), 5.31 (1 H, s, OH), and 7.0—8.0 (4 H, m, ArH) (Found: C, 57.8; H, 3.8. $C_{10}H_8O_5$ requires C, 57.70; H, 3.87%).

Dimerization of the Halogeno Esters (**3**) *to the* (E)- *and* (Z)-*Ethylenedicarboxylate* (**24**).—(*a*) *Reaction of the bromo ester* (**3a**). Sodium hydride (0.4 g, 10 mmol) was added to a solution of compound (**3a**) (2.7 g, 10 mmol) in DMF (50 ml) under ice-cooling and the mixture was stirred for 10 min at 0 °C. The reaction mixture was diluted with cold water, acidified with dil. hydrochloric acid, and extracted with chloroform. The extracts were washed with water, dried, and evaporated to dryness; the residue was then purified by chromatography on silica gel with chloroform as eluant to give a mixture of *dimethyl* (E)- *and* (Z)-1,2-*di*(1,2-*benzisoxazol*-3-*yl*)*ethylene*-1,2-*dicarboxylates* (**24**) (1.64 g, 87%). This mixture was further subjected to chromatography on silica gel with hexane–ethyl acetate (3:1) as eluant to afford *E*-(**24**) (0.27 g, 14%) and *Z*-(**24**) (1.20 g, 63%). *E*-(**24**), m.p. 163—165 °C (from methanol); ν(KBr) 1 740 and 1 720 cm^{-1}; δ_H(300 MHz) 3.64 (3 H, s, Me) and 7.36—7.72 (4 H, m, ArH) (Found: C, 63.5; H, 3.7; N, 7.2. $C_{20}H_{14}N_2O_6$ requires C, 63.49; H, 3.73; N, 7.40%). *Z*-(**24**), m.p. 128—130 °C (from ethanol); ν(KBr) 1 725 cm^{-1}; δ_H(300 MHz) 3.92 (3 H, s, Me) and 7.16—7.50 (4 H, m, ArH) (Found: C, 63.7; H, 3.6; N, 7.2. $C_{20}H_{14}N_2O_6$ requires C, 63.49; H, 3.73; N, 7.40%).

(*b*) *Reaction of compound* (**3a**) *in the presence of cyclohexene.* In the same manner, a mixture of compound (**3a**) (0.50 g, 1.85 mmol) and cyclohexene (1.5 g, 18 mmol) in DMF (20 ml) was treated with NaH (80 mg, 2.0 mmol) and worked up to give a *ca.* 1:5 mixture of *E*- and *Z*-(**24**) (0.30 g, 86%).

(*c*) *Reaction of the chloro ester* (**3b**). Sodium hydride (0.4 g, 10 mmol) was added to a solution of compound (**3b**) (2.0 g, 8.9 mmol) in DMF (30 ml) and the mixture stirred for 30 min at room temperature. The reaction mixture was worked up in the same manner as above to give a *ca.* 1:5 mixture of *E*- and *Z*-(**24**) (0.86 g, 51%).

Preparation of the Sodium Salt (**6a**)·Na *of the Phenylsulphinyl Ester* (**6a**).—Sodium hydride (70 mg, 1.6 mmol) was added to a solution of compound (**6a**) (0.5 g, 1.59 mmol) in THF (15 ml) under ice-cooling and the mixture stirred for 1 h at 0 °C. The precipitate was collected by filtration and washed with cold THF to give the *sodium salt* (**6a**)·Na (0.52 g). This salt did not give satisfactory elementary analyses and its i.r. and n.m.r. spectra showed the presence of water and THF even after drying at 80 °C for 10 h under reduced pressure; ν(KBr) 3 400, 1 580br, and 1 295 cm^{-1}; δ_H([$^2H_6$]DMSO) 1.6—2.0 (*ca.* 3.2 H, m), 3.3—3.8 and 3.50 (*ca.* 6.8 H, m and s), and 6.9—8.2 (9 H, m). After the salt (**6a**)·Na (0.20 g) had been shaken with dil. hydrochloric acid and chloroform for a few min, the organic layer was dried and evaporated to give the phenylsulphinyl ester (**6a**) (0.15 g).

C-S *Bond Cleavage of the Sulphinyl Esters* (**6**).—The arylsulphinyl ester (**6**) (*ca.* 2.5 mmol) was treated with MeONa or NaOH in methanol (30 ml) under the conditions stated in the Table, the mixture was concentrated under reduced pressure, and the residue was dissolved in chloroform, washed with water, dried, and evaporated to dryness. The residue was subjected to chromatography on silica gel with hexane–ethyl acetate (4:1) as eluant to give compound (**4**) and methyl arylsulphinate (**27**). Similarly, (**6a**)·Na prepared from (**6a**) (1.0 g) in the manner described above was treated with methanol (30 ml) and worked up to give (**4**) and (**27a**). Methyl arylsulphinates (**27**) were identified by comparison of their spectral data with those of samples prepared from sodium arylsulphinates and dimethyl sulphate.[10] The yields are summarized in the Table.

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