The Synthesis and Oxidation of *N*-Hydroxy-derivatives of the β-Adrenoceptor Antagonists Bufuralol and Toliprolol

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The *m*-tolyloxy-epoxide (5) reacts with *N*-isopropylhydroxylamine to give the hydroxylamine (7). Similarly, the benzofuran epoxide (21) reacts with *N*-t-butylhydroxylamine to give the hydroxylamine (13). These *N*-hydroxy-derivatives of the β-adrenoceptor antagonists toliprolol (6) and bufuralol (12) are possible metabolites involved in the *in vivo* degradation of the β-hydroxylamine side-chains of these compounds. The hydroxylamines (7) and (13), although stable in the form of their hydrochloride salts, undergo oxidation in solution. The hydroxylamine (7) is readily oxidised to the nitrone (8), whereas the hydroxylamine (13) gives a mixture of t-butylammonium salts of the acids (16) and (22). The synthesis of the oximes (29), (32), and (33) is also described.

THE metabolism of many β-adrenoceptor antagonists has been extensively studied in animals and man.[1] One of the common features in the metabolism of almost all β-adrenoceptor antagonists is oxidative degradation of the β-hydroxy-amine side-chain. Compounds with general structure (1) often undergo oxidative degradation leading to the formation of metabolites (2)—(4).[1] Bufuralol (12) [2] undergoes metabolic degradation of the β-hydroxy-amine side-chain to give the α-hydroxy-acid (15) [3] as one of its metabolites.

In view of the hypothesis that the diverse activities of the β-adrenoceptor antagonists may be related to the formation of active metabolites,[4] and the extensive evidence of metabolic *N*-hydroxylation of various aliphatic amines such as amphetamine,[5] *N*-methyl-amphetamine,[6] and chlorpromazine,[7] we decided to attempt to synthesise *N*-hydroxy-derivatives of the β-adrenoceptor antagonists bufuralol (12),[2,3] and toliprolol (6),[8] a compound which is known to undergo extensive metabolism by microsomal liver enzymes *in vivo* and *in vitro*.[9] These derivatives may be intermediates in the metabolic degradation of the β-hydroxy-amine side-chains.

The *m*-tolyloxy-epoxide (5),[10] prepared from *m*-cresol and epichlorohydrin,[11] reacted smoothly with *N*-isopropylhydroxylamine [12] at room temperature to give the hydroxylamine (7) (61%) as a fairly unstable oil. Immediate treatment of the product with ethanolic hydrogen chloride gave the stable crystalline hydrochloride salt. The structure of the product was confirmed by the n.m.r. spectrum which showed the protons in close proximity to the N·OH group to be deshielded by 0.06—0.27 p.p.m. compared with the equivalent protons in toliprolol (6), and by the mass spectrum which showed the base peak at *m/e* 88, corresponding to fission at (a) (see Scheme 1). The base peak in the mass spectrum of toliprolol was shown to be at *m/e* 72.

The 5-bromo-7-ethyl-benzofuran (26) [13] was hydrogenated to give the 7-ethyl-benzofuran (18). This reacted smoothly with sulphuryl chloride [14] to give the chloroacetyl-derivative (19), which after reduction with sodium borohydride followed by treatment with potassium hydroxide gave the unstable epoxide (21). This epoxide reacted smoothly with *N*-t-butylhydroxylamine [15] to give the hydroxylamine (13) which was isolated as its stable crystalline hydrochloride salt after treatment with ethanolic hydrogen chloride. The 5-bromo-analogue (14) was similarly prepared from the 5-bromo-7-ethyl-benzofuran epoxide (27) [13] and t-butylhydroxylamine. The structures of the hydroxylamines (13) and (14) were confirmed by their mass spectra which showed strong ions at *m/e* 102 corresponding to fission at (a) (see Scheme 2).

In view of the interest in the pathways involved in the

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[2] G. A. Fothergill, R. J. Francis, T. C. Hamilton, J. M. Osbond, and M. W. Parkes, *Experientia*, 1975, **31**, 1322.
[3] R. J. Francis, J. G. Allen, P. B. East, and R. J. Ruane, *European J. Drug Metab. and Pharmacokinetics*, 1976, 113.
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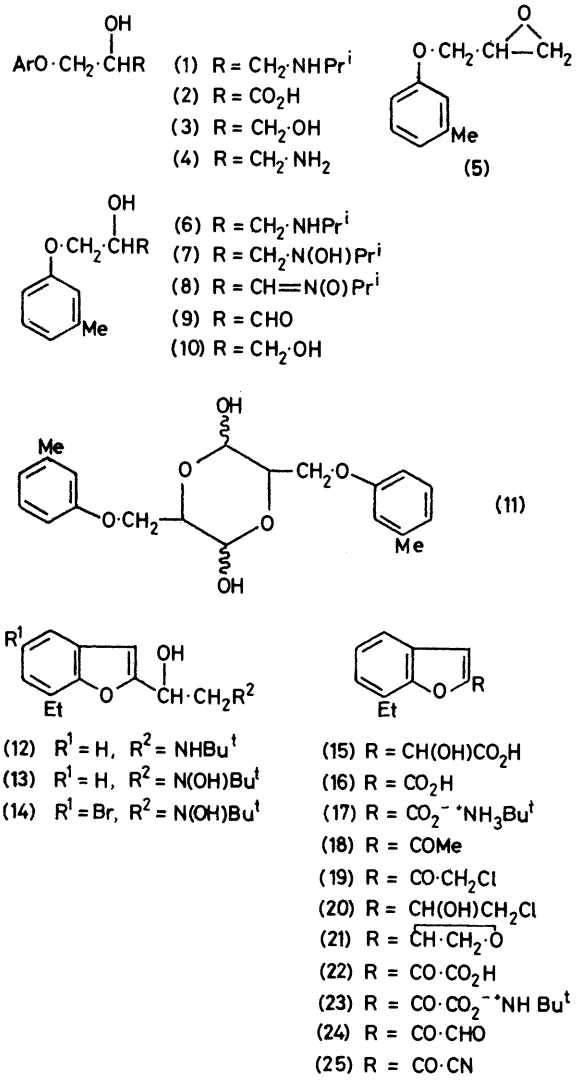
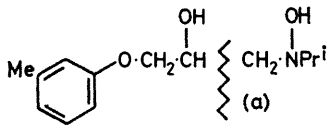
chemical oxidation of hydroxylamines,[6] the nature of the products obtained when the hydroxylamines (7) and (13) were set aside in solution at room temperature was determined. The hydroxylamine (7) was found to be

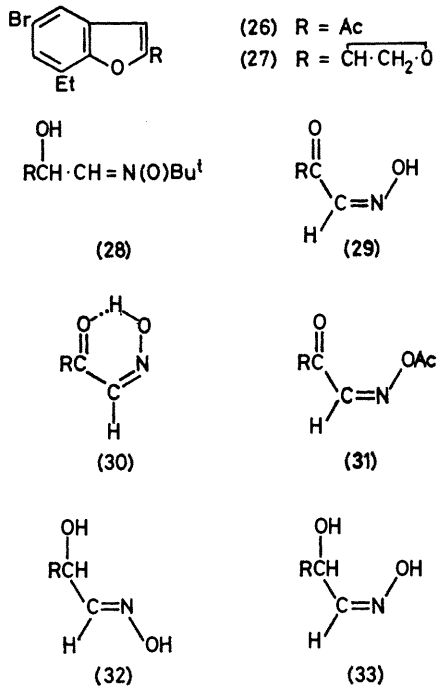


fairly stable in acid solution, but at neutral and alkaline pH, oxidation occurred to give the nitrone (8) as the major product. This same nitrone was produced, and



Scheme 1

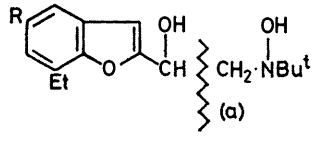
in improved yield, by oxidation with mercuric oxide.[16] Acid hydrolysis of the nitrone (8) gave an insoluble product, which was initially assigned the hydroxyaldehyde structure (9) on the basis of its (E.I.) mass spectrum (M^+ 180). The product, however, showed no carbonyl absorption in its i.r. spectrum. Field desorption mass spectrometry, which often records the molecular ion when other mass spectrometric techniques do not,[17] showed M^+ 360. We therefore tentatively assign the dimeric hemiacetal structure (11) to the nitrone hydrolysis product. In support of this structure,



R = 7-ethylbenzofuran-2-yl

reduction with sodium borohydride gave the diol (10),[18] which was also prepared by hydrolysis of the epoxide (5).

The hydroxylamine (13) slowly decomposed on storage at room temperature, and more rapidly in ether solution, to afford a mixture of the t-butylammonium salts of the 2-oxalobenzofuran (22) and the benzofuran-2-carboxylic acid (16). On one occasion a small quantity of the t-butylammonium salt of the benzofuran-2-ylglyoxylic



Scheme 2

acid (22) was obtained pure. When the mixture of t-butylammonium salts (17) and (23) was neutralised, and the resulting mixture of free acids recrystallised, a pure sample of the benzofuran-2-carboxylic acid (16) was isolated. Treatment of the carboxylic acid (16) with t-butylamine gave a pure sample of the t-butylammonium salt (17).

NN-Disubstituted hydroxylamines are known to undergo ready oxidation to give nitrones and oximes as

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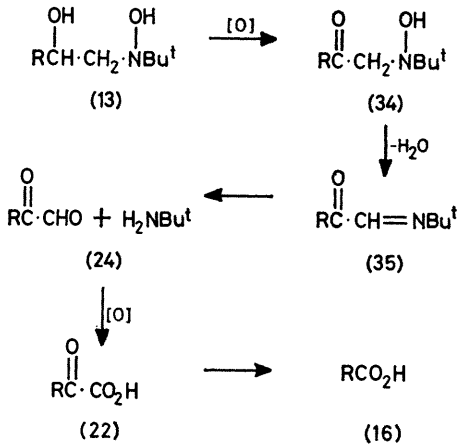
primary products.[6,19,20] The mixture of t-butylammonium salts of the acids (16) and (22) is, however, unlikely to be formed *via* the intermediacy of a nitrone [*e.g.* (28)] or an oxime [*e.g.* (29), (32), or (33)] since none of these intermediates would liberate t-butylamine on hydrolysis.[16] We suggest that the mixture of acids (16) and (22) may be formed as shown in Scheme 3.

Oxidation of the ' benzylic-like ' hydroxy-group would give the β-oxo-hydroxylamine (34) which could undergo dehydration to give the imine (35), a reaction for which there is precedent.[21] Hydrolysis to the glyoxaldehyde (24), followed by oxidation would give the benzofuran-2-ylglyoxylic acid (22) which may undergo decarbonylation to give the benzofuran-2-carboxylic acid (16).



SCHEME 3

In support of this mechanism a small quantity of the glyoxaldehyde (24) was isolated from the reaction mixture and identified by comparison with an authentic sample prepared by selenium dioxide oxidation [22] of the 2-acetylbenzofuran (18). When the glyoxaldehyde (24) was set aside in ether in the presence of t-butylamine, slow oxidation occurred and the mixture of t-butylammonium salts of the acids (16) and (22) was isolated. Oxidation of the aldehyde (24) with Jones reagent gave the benzofuran-2-carboxylic acid (16) as the only isolated product, indicating that benzofuran-2-glyoxylic acid readily undergoes decarbonylation under oxidising conditions.

It was of interest to establish whether oximes such as (29), (32), or (33) were products of oxidation of the hydroxylamine (13). The glyoxaldehyde (24), on treatment with hydroxylamine yielded the (*Z*)-oxime (29) as the only product. The oxime product, which was shown to be a single isomer from the n.m.r. spectrum,[23] was assigned the (*Z*)-stereochemistry on the basis of its i.r. spectrum which showed hydrogen bonding [24] between the oxo-group and the hydroxy-group of the oxime ($\nu_{max.}$ 3 200 and 1 630 cm^{-1}) [see structure (30)]. The stereochemistry of the oxime was confirmed by the following reactions. Although it was stable when heated in glacial acetic acid, treatment with acetic anhydride at 100 °C gave the unstable α-oxo-nitrile (25) ($\nu_{max.}$ 2 230 and 1 665 cm^{-1}) presumably *via* the (*Z*)-acetoxy-oxime (31). Treatment of the α-oxo-nitrile (25) with sodium carbonate gave the benzofuran-2-carboxylic acid (16). The corresponding (*E*)-isomer would not be expected to undergo elimination to give the nitrile (25).

Reduction of the (*Z*)-oxime (29) with sodium borohydride gave a mixture of (*E*)- and (*Z*)-oximes (32) and (33) as shown by the n.m.r. spectrum which showed two sets of signals for the $-CH{=}N{\cdot}OH$ and $-CH{\cdot}OH$ protons. The formyl proton of a (*Z*)-aldoxime usually appears at lower field in the n.m.r. spectrum than the equivalent proton of an (*E*)-aldoxime [23] and so the proportions of (*Z*)- and (*E*)-oximes in the mixture could be tentatively assigned (see Experimental section). Oxime isomers are often interconvertible and this isomerisation is catalysed by both acids and bases.[24] It is probable, therefore, that isomerisation occurs during the basic conditions of the sodium borohydride reduction.

When the hydroxylamine (13) was allowed to decompose in ether solution, analysis by t.l.c. showed negligible quantities of the oximes (29), (32), and (33) in the solution.

Preliminary biological results [25] suggest that the hydroxylamines (7) and (13), the nitrone (8), and the oximes (29), (32), and (33) possess none of the biological activities normally associated with β-adrenoceptor antagonists.

EXPERIMENTAL

Details of chromatographic materials and conditions for determination of physical data, *etc.*, are reported in ref. 26. Field desorption (F.D.) mass spectra were run on a Varian-MAT CH5 mass spectrometer. Light petroleum had b.p. 40—60 °C.

Reaction of 1,2-*Epoxy*-3-(m-*tolyloxy*)*propane* (5) *with* N-*Isopropylhydroxylamine*.—The epoxide (5) (900 mg) in isopropyl alcohol (10 ml) was treated with *N*-isopropylhydroxylamine (450 mg) at room temperature for 72 h. The solvent was evaporated off *in vacuo* and the residue, in chloroform (40 ml), was extracted with 2N-hydrochloric acid (4 × 50 ml). The acidic fraction was neutralised with 2N-sodium carbonate and extracted with chloroform (4 × 50 ml). The chloroform fraction was washed with water, dried, and evaporated to dryness *in vacuo* to give 1-(hydroxyisopropylamino)-3-(*m*-tolyloxy)propan-2-ol (7) (805 mg) as an unstable oil; it was homogeneous by t.l.c. [methanol–benzene (1 : 9)] (Found: M^+ 239. $C_{13}H_{21}NO_3$ requires *M*, 239), $\nu_{max.}$ (film) 3 400 cm^{-1}; δ 1.13 (6 H, d, *J* 6 Hz, $CH{\cdot}Me_2$), 2.32 (3 H, s, $Ar{\cdot}Me$), 2.93 (2 H, m, $CH_2{\cdot}N$), 3.0 (1 H, m, $CH{\cdot}Me_2$), 4.0 (2 H, m, $O{\cdot}CH_2$), 4.30 (1 H, m, $CH{\cdot}OH$), 5.35

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[26] S. Jordan and R. E. Markwell, *J.C.S. Perkin I*, 1978, 419.

(2 H, bs, OH), and 6.75—7.1 (4 H, m, aromatic H); *m/e* 239 (8%), 224 (3), 195 (10), 131 (10), 116 (15), 108 (10), 91 (15), 88 (100), and 46 (60).

A portion of the oily product in ethanol was treated with ethanolic hydrogen chloride and evaporated to dryness *in vacuo*. Crystallisation from ethanol–ether gave 1-(*hydroxyisopropylamino*)-3-(m-*tolyloxy*)*propan*-2-*ol hydrochloride* (7), m.p. 93—95.5 °C (Found: C, 56.5; H, 8.15; Cl, 12.85; N, 5.05. $C_{13}H_{21}NO_3$·HCl requires C, 56.65; H, 8.05; Cl, 12.85; N, 5.05%).

1-(*Isopropylamino*)-3-(m-*tolyloxy*)*propan*-2-*ol* (6).—The free base, m.p. 80—81 °C, (lit.,[27] 79 °C) had δ 1.07 (6 H, d, *J* 6 Hz, CH·*Me*$_2$), 2.30 (3 H, s, Ar·*Me*), 2.80 (3 H, m, C*H*$_2$·NH·C*H*), 3.94 (2 H, m, O·CH$_2$), 4.02 (1 H, m, C*H*·OH), and 6.7—7.3 (4 H, m, aromatic H); *m/e* 223 (3%), 208 (3), 179 (8), and 72 (100).

Effect of pH *on the Oxidation of* 1-(*Hydroxyisopropylamino*)-3-(m-*tolyloxy*)*propan*-2-*ol* (7).—Solutions of the hydroxylamine (7) (40 mg) in methanol (2 ml) and water (1 ml), adjusted to the following pH (i) 1, (ii) 4, (iii) 7, and (iv) 9 with 2M-hydrochloric acid or 2M-sodium carbonate, were set aside at room temperature for 7 days. Analysis by t.l.c. [methanol–benzene (1 : 9)] showed the following amount (±10%) of hydroxylamine (7) remaining, (i) 90%, (ii) 90%, (iii) 70%, (iv) 10%.

Oxidation of 1-(*Hydroxyisopropylamino*)-3-(m-*tolyloxy*)-*propan*-2-*ol* (7) *in Solution at* pH 9.—A solution of the hydroxylamine (7) (150 mg) in methanol (10 ml) and water (5 ml) was treated with 2M-sodium carbonate until the pH of the solution was *ca.* 9, and was then set aside at room temperature for 7 days. The methanol was evaporated off *in vacuo* and the residue was extracted with chloroform. The recovered product (130 mg) crystallised from chloroform–hexane to give 1-(*isopropylamino*)-3-(m-*tolyloxy*)-*propan*-2-*ol* N-*oxide* (8) (85 mg), m.p. 105—106 °C (Found: C, 65.8; H, 8.3; N, 5.95. $C_{13}H_{19}NO_3$ requires C, 65.8; H, 8.05; N, 5.9%), $\nu_{max.}$ 3 140, 1 615, and 1 590 cm^{-1}; δ 1.42 (6 H, d, *J* 6 Hz, CH·*Me*$_2$), 2.34 (3 H, s, Ar·*Me*), 4.08 (1 H, m, C*H*·Me$_2$), 4.20 (2 H, d, *J* 5 Hz, O·CH$_2$), 4.96 (1 H, m, C*H*·OH), 5.68 (1 H, bs, OH), and 6.7—7.3 (5 H, m, Ar H and CH=N); *m/e* 237 (2%), 219 (6), 208 (14), 193 (46), 163 (80), 133 (36), 130 (44), 121 (64), 116 (36), 108 (50), 100 (48), 91 (85), 88 (80), 74 (100), and 43 (85).

Oxidation of 1-(*Hydroxyisopropylamino*)-3-(m-*tolyloxy*)-*propan*-2-*ol* (7) *with Mercuric Oxide*.—The hydroxylamine (7) (400 mg) in methanol (10 ml) and water (10 ml) was treated with yellow mercuric oxide (728 mg) at room temperature for 30 min. The reaction mixture was filtered and the filtrate was diluted with water and extracted with chloroform. The recovered product crystallised from chloroform–hexane to give the *N*-oxide (8) (198 mg), identical (m.p. and i.r., n.m.r., and mass spectra) with the sample prepared above.

Hydrolysis of 1-(*Isopropylamino*)-3-(m-*tolyloxy*)*propan*-2-*ol* N-*oxide* (8).—The *N*-oxide (8) (300 mg) was shaken with 2M-hydrochloric acid (10 ml) until the solid had dissolved (5 min), and was then set aside at room temperature for 3 h. The resulting precipitate was collected, washed with water, and dried to give 3,6-*bis*-(m-*tolyloxymethyl*)-1,4-*dioxan*-2,5-*diol* (11) (218 mg), m.p. 163—166 °C (Found: C, 66.4; H, 6.75. $C_{20}H_{24}O_6$ requires C, 66.65; H, 6.7%), $\nu_{max.}$ 3 440 cm^{-1}; δ [(CD$_3$)$_2$SO] 2.30 (6 H, s, Ar·*Me*), 3.4 (2 H, s, OH), 4.2 (6 H, m, O·CH$_2$·CH<), 4.85 [2 H, m, O·C*H*(OH)], and 6.65—7.5 (8 H, m, Ar H); *m/e* (E.I.), 180 (50%), 121 (85), 108 (85), and 91 (100); (F.D.), 361 (25%), 360 (100), 180 (28), and 58 (33).

Hydrolysis of 1,2-*Epoxy*-3-(m-*tolyloxy*)*propane* (5).—The epoxide (5) (12 g) in methanol (50 ml), water (100 ml), and toluene-4-sulphonic acid (250 mg) were heated under reflux for 5 h. The methanol was evaporated off *in vacuo* and the residue was extracted with chloroform. The recovered product was chromatographed on silica gel (150 g). Elution with chloroform–hexane (1 : 1) gave 3-(*m*-tolyloxy)propane-1,2-diol (10) (7.2 g), m.p. 71.5—73 °C (lit.,[18] 65—67 °C), $\nu_{max.}$ 3 300 cm^{-1}; δ 2.30 (3 H, s, Ar·*Me*), 2.8 (2 H, bs, OH), 3.8—4.2 [5 H, m, O·C*H*$_2$·C*H*(OH)·C*H*$_2$(OH)], and 6.6—7.4 (4 H, m, Ar H); *m/e* 182 (20%), 108 (100), and 91 (24).

Reduction of 3,6-*Bis*-(m-*tolyloxymethyl*)-1,4-*dioxan*-2,5-*diol* (11) *with Sodium Borohydride*.—A suspension of the diol (11) (36 mg) in methanol (2 ml) was treated with sodium borohydride (12 mg) at room temperature for 1 h, water was added and the solution was extracted with chloroform. The recovered product crystallised from chloroform–hexane to give 3-(*m*-tolyloxy)propane-1,2-diol (10) (21 mg), m.p. 67—69 °C, identical (i.r. and mass spectra) with the sample prepared above.

Hydrogenation of 5-*Bromo*-7-*ethylbenzofuran*-2-*yl Methyl Ketone* (26).—The 5-bromobenzofuran (26) (10 g) in ethanol (300 ml) and triethylamine (4.6 g) was hydrogenated over 5% palladium–carbon (2 g) until uptake of hydrogen ceased. The solution was filtered, evaporated to dryness, and recrystallised from light petroleum to give 7-*ethylbenzofuran*-2-*yl methyl ketone* (18) (6.4 g), m.p. 58—60 °C (Found: C, 76.5; H, 6.65. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.4%), $\nu_{max.}$ 1 682 cm^{-1}; δ 1.34 (3 H, t, *J* 8 Hz, CH$_2$·*Me*), 2.60 (3 H, s, CO·Me), 3.0 (2 H, q, *J* 8 Hz, C*H*$_2$·Me), and 7.2—7.6 (4 H, m, Ar H); *m/e* 188 (52%), 173 (100), 131 (8), 117 (8), and 115 (10).

Reaction of 7-*Ethylbenzofuran*-2-*yl Methyl Ketone* (18) *with Sulphuryl Chloride*.—The benzofuran (18) (7.5 g) in chloroform (250 ml) was treated with sulphuryl chloride (7 g) at room temperature for 30 min. The solution was washed with 2M-sodium carbonate solution and water, and dried. The recovered product crystallised from ethanol to give *chloromethyl* 7-*ethylbenzofuran*-2-*yl ketone* (19) (7.8 g), m.p. 91—92 °C (Found: C, 64.85; H, 5.3; Cl, 15.75. $C_{12}H_{11}ClO_2$ requires C, 64.75; H, 5.0; Cl, 15.95%), δ 1.34 (3 H, t, *J* 8 Hz, CH$_2$·*Me*), 2.98 (2 H, q, *J* 8 Hz, C*H*$_2$·Me), 4.70 (2 H, s, CO·CH$_2$·Cl), and 7.2—7.65 (4 H, m, Ar H); *m/e* 224 (9%), 222 (20), 188 (6), 173 (100), 117 (12), and 115 (14).

Preparation of 2-*Epoxyethyl*-7-*ethylbenzofuran* (21).—The chloromethyl ketone (19) (8.6 g) in methanol (70 ml) was treated with sodium borohydride (600 mg) at 10 °C for 1.5 h. The solution was diluted with water (60 ml) and the pH was adjusted to *ca.* 6 with 2N-sodium carbonate solution. Water (40 ml) was added and the solution was extracted with chloroform. The chloroform fraction was washed with water, dried, and evaporated to dryness *in vacuo* to give 2-(2-chloro-1-hydroxyethyl)-7-ethylbenzofuran (20) (7.9 g) as an oil (9 g) [Found: M^+ 224, 226. $C_{12}H_{13}ClO_2$ requires *M* 224, (*M* + 2) 226], δ 1.35 (3 H, t, *J* 8 Hz, CH$_2$·*Me*), 2.95 (2 H, q, *J* 8 Hz, C*H*$_2$·Me), 3.90 (2 H, m, CH$_2$·Cl), 5.05 (1 H, q, *J* 6 Hz, C*H*·OH), 6.70 (1 H, s, 3-H), and 7.1—7.5 (3 H, m, Ar H); *m/e* 226 (6%), 224 (15), 175 (100), and 91 (14).

The chlorohydrin (20) (9 g) in dioxan (25 ml) was treated with a solution of potassium hydroxide (2.25 g) in water

[27] A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, and T. M. Wood, *J. Medicin. Chem.*, 1969, **12**, 638.

(75 ml) and the resulting solution was heated at 50 °C for 1.5 h. The reaction mixture was cooled and extracted with hexane. The hexane solution was washed with water, dried, and evaporated to dryness *in vacuo* to give the unstable 2-epoxyethyl-7-ethylbenzofuran (21) (7.5 g) as an oil, which was used immediately for further reaction. T.l.c. [methanol–benzene (1 : 9)] showed the epoxide (21) (R_F 0.9) as a faster running spot than the chlorohydrin (20) (R_F 0.7).

Reaction of 2-Epoxyethyl-7-ethylbenzofuran (21) *with N-t-Butylhydroxylamine.*—The epoxide (21) (2 g) in isopropyl alcohol (40 ml) was treated with *N*-t-butylhydroxylamine (2 g) at room temperature for 72 h. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in ethyl acetate (100 ml), washed with water (3 × 40 ml), and dried. The recovered product was treated with an excess of ethanolic hydrogen chloride, evaporated to dryness *in vacuo*, and recrystallised from ethanol–ether to give *7-ethylbenzofuran-2-yl(hydroxy-t-butylamino)methanol* (13) *hydrochloride* (1.04 g), m.p. 161—163° (Found: C, 60.95; H, 7.55; Cl, 11.55; N, 4.35. $C_{16}H_{23}NO_3$·HCl requires C, 61.25; H, 7.7; Cl, 11.3; N, 4.45%), δ 1.32 (3 H, t, *J* 8 Hz, CH_2·*Me*), 1.50 (9 H, s, C·Me_3), 2.90 (2 H, q, *J* 8 Hz, *CH*$_2$·Me), 3.58 (2 H, m, CH_2·N^+), 5.65 (1 H, dd, *J* 4, 9 Hz, *CH*·OH), 6.80 (1 H, s, 3-H), and 7.1—7.4 (3 H, m, aromatic H); *m/e* 175 (14%), 174 (16), 173 (8), 172 (16), 159 (26), 102 (28), and 57 (100).

Reaction of 5-Bromo-2-epoxyethyl-7-ethylbenzofuran (27) *with N-t-Butylhydroxylamine.*—The epoxide (27) (3.4 g) in isopropyl alcohol (40 ml) was treated with *N*-t-butylhydroxylamine (1.5 g) at room temperature for 4 days. The product was recovered and treated with ethanolic hydrogen chloride as described above for the reaction of the epoxide (21) with *N*-t-butylhydroxylamine. Crystallisation from ethanol–ether gave *5-bromo-7-ethylbenzofuran-2-yl(hydroxy-t-butylaminomethyl)methanol* (14) *hydrochloride* (2.4 g), m.p. 171—172 °C (Found: C, 48.7; H, 5.8; Br, 20.55; Cl, 9.1; N, 3.6. $C_{16}H_{22}BrNO_3$·HCl requires C, 48.95; H, 5.9; Br, 20.35; Cl, 9.05; N, 3.55%), δ 1.34 (3 H, t, *J* 8 Hz, CH_2·*Me*), 1.60 (9 H, s, C·Me_3), 2.90 (2 H, q, *J* 8 Hz, *CH*$_2$·Me), 3.60 (2 H, m, CH_2·N^+), 5.75 (1 H, dd, *J* 9, 4 Hz, *CH*·OH), 6.80 (1 H, s, 3-H), and 7.1—7.6 (3 H, m, Ar H); *m/e* 297 (8%), 295 (8), 265 (8), 266 (8), 267 (8), 255 (50), 253 (55), 235 (20), 237 (22), 115 (16), 102 (36), and 57 (100).

Oxidation of 7-Ethylbenzofuran-2-yl(hydroxy-t-butylaminomethyl)methanol (13) *in Ether Solution.*—A solution of the hydroxylamine (13) (1.5 g) in ether (200 ml) was set aside at room temperature for 14 days. The resulting precipitate was collected to give a mixture of t-butylammonium 7-ethylbenzofuran-2-ylglyoxylate (23) and t-butylammonium 7-ethylbenzofuran-2-ylcarboxylate (17) (1.02 g), m.p. 170—172 °C (decomp.) (Found: *m/e* 218 and 190. $C_{12}H_{10}O_4$ requires M^+ 218. $C_{11}H_{10}O_3$ requires M^+ 190), $\nu_{max.}$ 3 100br, 2 740, 2 640, 2 540, 1 655br, and 1 640 cm^{-1}; δ([CD_3)$_2$SO] 1.38 (12 H, m, CH_2·*Me* and C·Me_3), 2.95 (2 H, q, *J* 8 Hz, *CH*$_2$·Me), and 7.1—8.0 (4 H, m, ArH); *m/e* (E.I.) 218 (30%), 190 (60), 175 (100), 173 (95), and 58 (50); (F.D.) 218 (100%) and 190 (85). Analysis of the ether solution containing the hydroxylamine (13) by t.l.c. [methanol–benzene (1 : 6)] showed negligible quantities of the oximes (29), (32), and (33) present.

In one experiment when the precipitate was collected after 5 h, a small quantity of t-butylammonium 7-ethylbenzofuran-2-ylglyoxylate (23), m.p. 178—180 °C (decomp.), was isolated (Found: C, 66.0; H, 7.6; N, 4.65. $C_{12}H_{10}O_4$·$C_4H_{11}N$ requires C, 65.95; H, 7.25; N, 4.8%), $\nu_{max.}$ 3 040, 2 740, 2 640, 2 540, 1 660br, and 1 640 cm^{-1}; *m/e* 218 (90%), 173 (100), 117 (40), 115 (45), and 58 (100).

The mixture of t-butylammonium salts (17) and (23) (900 mg) was dissolved in water (100 ml) and made acidic with 2M-hydrochloric acid. The resulting precipitate was collected, washed with water, and recrystallised from ethanol–water to give 7-ethylbenzofuran-2-carboxylic acid (16) (360 mg), m.p. 195—196 °C, identical (m.p., i.r., and mass spectrum) with an authentic sample.[28]

The carboxylic acid (16) (40 mg) in ethanol (3 ml) was treated with t-butylamine (1 ml), and the solution was evaporated to dryness *in vacuo*. The residue was recrystallised from ethanol–water to give t-butylammonium 7-ethylbenzofuran-2-ylcarboxylate (17) (28 mg), m.p. 215—217 °C (Found: C, 68.15; H, 8.0; N, 5.15. $C_{11}H_{10}O_3$·$C_4H_{11}N$ requires C, 68.4; H, 8.05; N, 5.3%), $\nu_{max.}$ 3 060, 2 760, 2 640, 2 540, and 1 640 cm^{-1}; *m/e* 190 (70%), 175 (100), 145 (8), 115 (10), 91 (6), 77 (10), and 58 (70).

Isolation of the Glyoxaldehyde (24) *from the Oxidation of 7-Ethylbenzofuran-2-yl(hydroxy-t-butylaminomethyl)methanol* (13).—A solution of the hydroxylamine (13) (0.1 g) in ether (30 ml) was set aside at room temperature for 4 days, when it was evaporated to dryness *in vacuo* and the product was chromatographed by p.l.c. [methanol–benzene (1 : 9)]. Recovery of the band with R_F 0.5 gave 7-ethylbenzofuran-2-ylglyoxaldehyde (24) (0.5 mg) identical [t.l.c. (methanol–benzene 1 : 9) and mass spectrum] with an authentic sample (see below).

Oxidation of 2-Acetyl-7-ethylbenzofuran (18) *with Selenium Dioxide.*—The 2-acetylbenzofuran (18) (1 g) in dioxan (10 ml) was treated with selenium dioxide (13.2 g) and the solution was heated under reflux for 18 h. The reaction mixture was filtered and the filtrate was diluted with water (30 ml) and extracted with ethyl acetate. The recovered product was recrystallised from benzene to give *7-ethylbenzofuran-2-ylglyoxaldehyde hemihydrate* (24) (650 mg), m.p. 129—130 °C (Found: C, 68.1; H, 5.45. $C_{12}H_{10}O_3$·0.5H_2O requires C, 68.25, H, 5.25%), $\nu_{max.}$ 3 480w, 3 380w, and 1 692 cm^{-1}; δ[(CD_3)$_2$SO] 1.20 (3 H, t, *J* 8 Hz, CH_2·*Me*), 3.02 (2 H, q, *J* 8 Hz, *CH*$_2$·Me), 6.20 (1 H, s, 3-H), 7.4 (3 H, m, ArH), and 8.0 (1 H, s, CHO); *m/e* 202 (20%), 173 (100), 117 (25), and 115 (22).

Oxidation of 7-Ethylbenzofuran-2-ylglyoxaldehyde (24).—(a) *In ether solution.* To a suspension of the glyoxaldehyde (24) (50 mg) in ether (25 ml) was added t-butylamine (20 mg) and the solution was set aside at room temperature for 4 days. The resulting precipitate was collected to give a mixture of t-butylammonium 7-ethylbenzofuran-2-ylglyoxylate (23) and t-butylammonium 7-ethylbenzofuran-2-carboxylate (17) (6 mg), m.p. 179—181 °C, identical mass spectrum with the product obtained from the oxidation of the hydroxylamine (13).

(b) *With Jones reagent.*[29] The glyoxaldehyde (24) (1.0 g) in acetone (150 ml) was treated with an excess of Jones reagent (3.0 ml) at room temperature for 1 h. The solution was evaporated to one quarter volume *in vacuo*, water (100 ml) was added, and the solution was extracted with ethyl acetate. The recovered product crystallised from ethanol–water to give 7-ethylbenzofuran-2-carboxylic acid (16) (0.6 g) identical (m.p. and i.r. spectrum) with an authentic sample.

[28] G. A. Fothergill, unpublished data.

[29] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

Reaction of 7-Ethylbenzofuran-2-ylglyoxaldehyde (24) *with Hydroxylamine.*—The glyoxaldehyde (24) (3.5 g) in ethanol (100 ml) was treated with a solution of hydroxyammonium chloride (0.98 g) and sodium acetate (2.94 g) in water (30 ml) and the solution was set aside at room temperature for 30 min. It was evaporated to one third volume *in vacuo*, diluted with water, and the resulting product recrystallised from ethanol–water to give *7-ethylbenzofuran-2-ylglyoxaldehyde* (Z)-2-*oxime* (29) (2.1 g), m.p. 127—131 °C (Found: C, 66.55; H, 5.2. $C_{12}H_{11}NO_3$ requires C, 65.5; H, 5.1%), $\nu_{max.}$ 3 200, 1 630, 1 610, and 1 595 cm^{-1}; $\lambda_{max.}$ 323, 274, and 237 nm (ε 18 420, 3 640, and 12 770); δ[$(CD_3)_2SO$] 1.36 (3 H, t, *J* 8 Hz, CH_2·*Me*), 2.95 (2 H, q, *J* 8 Hz, CH_2·Me), 7.4 (3 H, m, ArH), 7.90 (1 H, s) and 8.0 (1 H, s) (3-H and CN=N), and 12.3 (1 H, s, =N–OH); *m/e* 217 (100%), 202 (40), 184 (20), 173 (85), 117 (20), and 115 (30).

Treatment of 7-Ethylbenzofuran-2-ylglyoxaldehyde (Z)-2-*Oxime* (29) *with Acetic Acid.*—The (*Z*)-oxime (29) (35 mg) in glacial acetic acid (10 ml) was heated under reflux for 10 h, and then evaporated to dryness *in vacuo*. The crystalline product had an identical n.m.r. spectrum [$(CD_3)_2SO$] with the original (*Z*)-oxime (29).

Reaction of 7-Ethylbenzofuran-2-ylglyoxaldehyde (Z)-2-*Oxime* (29) *with Acetic Anhydride.*—The (*Z*)-oxime (29) (0.5 g) was heated in acetic anhydride (10 ml) at 100 °C for 12 h, poured into water, and extracted with ether (3 × 40 ml). The ether layer was washed with 2M-sodium carbonate, water, and dried. Evaporation of the solvent *in vacuo*, followed by crystallisation from ether–hexane gave the unstable *7-ethylbenzofuran-2-ylglyoxylonitrile* (25) (0.22 g), m.p. 70—71 °C (Found: M^+ 199.063 3. $C_{12}H_9NO_2$ requires *M* 199.063 3), $\nu_{max.}$ 2 230 and 1 665 cm^{-1}; δ 1.38 (3 H, t, *J* 8 Hz, CH_2·*Me*), 2.98 (2 H, q, *J* 8 Hz, CH_2·Me), 7.1—7.7 (3 H, m, ArH), and 7.9 (1 H, s, 3-H); *m/e* 199 (45%), 184 (100), 145 (12), 128 (10), 115 (12), 102 (10), and 101 (8).

Treatment of 7-Ethylbenzofuran-2-ylglyoxylonitrile (25) *with Sodium Carbonate.*—The nitrile (25) (0.15 g) in methanol (10 ml) and water (2 ml) was treated with 2M-sodium carbonate (0.5 ml) for 3 h at room temperature. The methanol was evaporated off *in vacuo* and the residue was extracted with ether (2 × 20 ml). The aqueous fraction was acidified with 2M-hydrochloric acid and the precipitate was washed with water, and recrystallised from ethanol–water to give 7-ethylbenzofuran-2-carboxylic acid (16) (0.13 g), identical (m.p., i.r., and mass spectra) with an authentic sample.

Reduction of 7-Ethylbenzofuran-2-ylglyoxaldehyde (Z)-2-*Oxime* (29).—The oxime (29) (1.75 g) in methanol (25 ml) at 0 °C was treated with sodium borohydride (86 mg) for 30 min. Most of the methanol was evaporated off *in vacuo* and the residue was diluted with water and extracted with chloroform. The recovered product was chromatographed on silica gel (150 g). Elution with chloroform gave a 4 : 1 mixture of *7-ethylbenzofuran-2-ylglycolaldehyde* (Z)-*oxime* (33), and *7-ethylbenzofuran-2-ylglycolaldehyde* (E)-*oxime* (32) (1.48 g) [homogeneous by t.l.c. (methanol–benzene 1 : 6)] as an unstable oil which decomposed on attempted distillation (Found: C, 65.9; H, 6.05; N, 6.15. $C_{12}H_{13}NO_3$ requires C, 65.75; H, 6.0; N, 6.4%), $\nu_{max.}$ (film) 3 340 cm^{-1}; δ 1.30 (3 H, t, *J* 8 Hz, CH_2·*Me*), 2.88 (2 H, q, *J* 8 Hz, CH_2·Me), 5.48 [0.8H, d, *J* 8 Hz, C*H*·OH in (33)], 6.03 [0.2 H, d, *J* 6 Hz, C*H*·OH in (32)], 6.65 (1 H, s, 3-H), 7.2 (0.2 H, d, *J* 6 Hz, –*H*C=N·OH in (32)], 7.05—7.4 (3 H, m, ArH), and 7.74 [0.8 H, d, *J* 6 Hz, –HC=N·OH in (33)]; irradiation at the frequency of the signal at δ 6.03 reduced the doublet at δ 7.2 to a singlet; *m/e* 219 (56%), 202 (12), 190 (20), 175 (100), and 159 (40).

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