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STUDIES ON 5-BENZOYL-3-ISOTHIAZOLINONES

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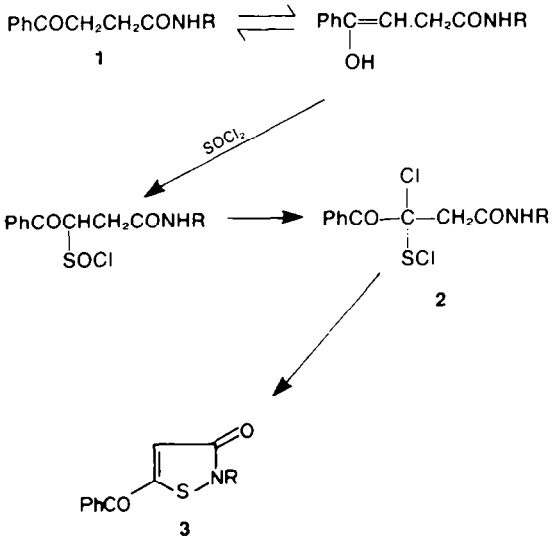
Abstract—5-Benzoyl-3-isothiazolinones are obtained when β-benzoylpropionamides are heated with thionyl chloride. Some reactions of 5-benzoyl-2-phenyl-3-isothiazolinone are described, the most interesting being that with dimethyl and diethyl malonate carbanions, in which ring opening, loss of sulphur, and subsequent ring closure occur, leading to maleimide derivatives.

The isothiazole ring system has attracted considerable attention[1] since the synthesis of a mononuclear isothiazole was first reported in 1956.[2] One area of active interest has been the chemistry of 3-hydroxyisothiazoles and 3-isothiazolinones, methods of synthesis of which have been reviewed.[3]

We wish to report a new synthesis of 3-isothiazolinones (see Scheme 1) which was discovered in the course of studies on cyclisation reactions of β-benzoylpropionamides.[4] When the amide **1** (R = H) was heated with thionyl chloride, a sulphur containing product was obtained;[5] subsequent studies suggested that the product was 5-benzoyl-3-isothiazolinone **3** (R = H) or its tautomer, 5-benzoyl-3-hydroxyisothiazole **4**.

In an extension of this earlier work, we have shown that the synthesis is a general one, and is most effective when applied to the preparation of *N*-substituted 5-benzoyl-3-isothiazolinones **3** (R ≠ H).

The mechanism of the cyclisation is probably that outlined in Scheme 1. The literature contains numerous examples of attack by thionyl chloride at "active" methylene groups with subsequent Pummerer-type rearrangement to α-chlorosulphenylchloride structures analogous to our suggested intermediate **2**.[7]



Scheme 1.

The product obtained from β-benzoylpropionamide (4-oxo-4-phenylbutanamide) exists in the hydroxyisothiazole form **4** since the IR spectrum shows only one carbonyl band. Like other 3-hydroxyisothiazoles,[1] this compound gives rise to *O*- methyl and *N*-methyl derivatives. Of these, the former resembles the parent compound in its ultraviolet and visible spectrum, whilst the latter shows a long wave absorption at 350 nm, responsible for its yellow colour, which is characteristic of the *N*-substituted-5-benzoyl-3-isothiazolinones.

Four members of the *N*-substituted series **3** (R = Ph, *p*-Cl.C$_6$H$_4$, *p*-O$_2$N.C$_6$H$_4$, PhCH$_2$) were made from the appropriate amides. Marginally better yields were obtained when the thionyl chloride reaction was carried out in the presence of traces of pyridine but, with the two amides **1** (R = Ph, *p*-Cl.C$_6$H$_4$), when larger amounts of pyridine were added, the major products were found to be the 4-chloroisothiazolinones **5** (R = Ph, *p*-Cl.C$_6$H$_4$), as indicated by the disappearance in the NMR spectra of the singlet for the 4-proton. In other respects, these chlorinated compounds resembled the normal products of type **3**.

Clearly, in the presence of pyridine, the reaction sequence shown in Scheme 1 is modified, probably so as to produce an αβ-dichlorosulphenyl chloride related to compound **2**. Higa and Kruksack[8] have provided examples of this "β-chlorination" process and have suggested a mechanism.

Some of the reactions reported in the literature for *N*-substituted-3-isothiazolinones have been applied to 5-benzoyl-2-phenyl-3-isothiazolinone (R = Ph). Thus treatment with phosphoryl chloride, and reaction of the resulting quaternary salt with ammonia, gave the product **6** expected on the basis of earlier work by Rokach *et al.*,[9] which indicates a ring-breaking nucleophilic attack on sulphur in the second step. In a similar sequence, using aniline instead of ammonia, the intensely coloured phenylimine **7** was obtained. Other examples are given in the experimental section.

Crow and Gosney[10] have shown that carbanions also attack 3-isothiazolinones at the sulphur atom bringing about ring fission to sulphur-containing acrylamides. When the 5-benzoyl-3-isothiazolinone **3** (R = Ph) was allowed to react with diethyl malonate in methanolic sodium methoxide, and the resulting sodium salt was treated with acid, the red product which was isolated was found to be sulphur-free.

The structure of this product was not immediately apparent but the discovery that it readily loses methanol,

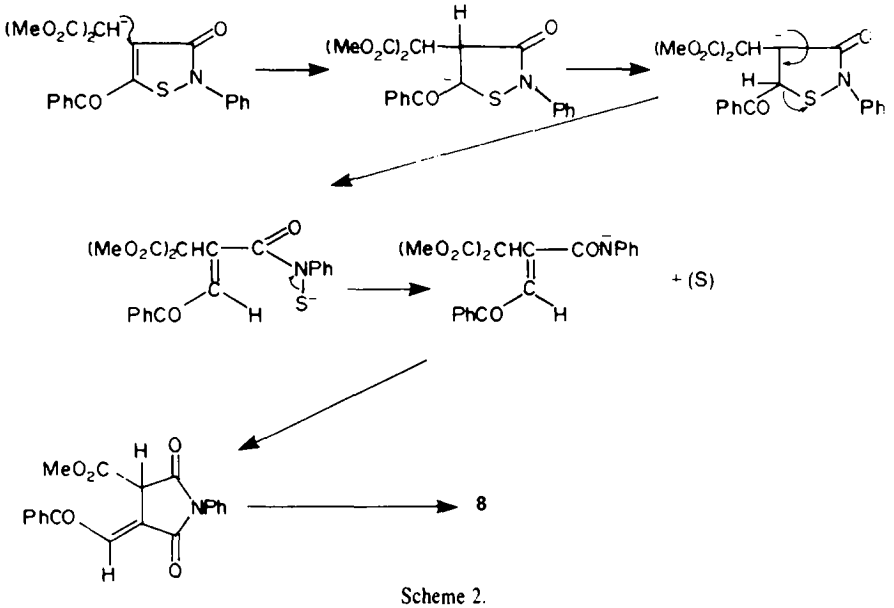
on being heated, giving a well-defined yellow compound, and a consideration of the spectroscopic and analytical data for both compounds, suggested that the red compound had structure **8**. The thermal reaction is thus explained as a lactonisation giving the pyronomaleimide **9**. The ethyl ester corresponding to **8**, made using sodium ethoxide in ethanol in the original reaction, is converted thermally to the same product **9**.

Further support for structure **9** comes from the addition reaction with dimethyl acetylenedicarboxylate, which occurs with loss of carbon dioxide, and yields a product satisfactorily formulated as the bismethoxycarbonylphthalimide derivative **10**.

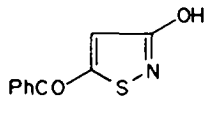
The formation of the sulphur-free product **8** from the isothiazolinone **3** (R = Ph) presumably involves the sequence of reactions shown in Scheme 2, initiated by the addition of the carbanion to the isothiazolinone 4, 5 double bond. This double bond would be expected to be more electron deficient in the 5-benzoylisothiazolinones than in the examples studied by Crow and Gosney, in which the S–N bond is broken by attack at the sulphur atom.

We have been unable to arrive at an equally satisfactory solution to the structural problem posed by compound **8** assuming either attack at sulphur or attachment of the carbanion residue to the 5-position of the isothiazolinone system.

Oxidation of 5-benzoyl-2-phenyl-3-isothiazolinone with *m*-chloroperbenzoic acid leads, as anticipated,[11] to the sulphoxide **11** in which the 4, 5-double-bond is even more electron deficient than in the parent compound **3** (R = Ph). The sulphoxide reacts with cyclopentadiene at room temperature, giving an adduct with the expected composition.



Scheme 2.



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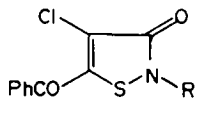

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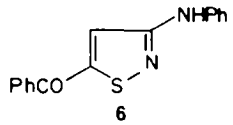

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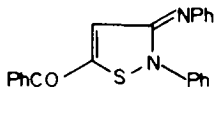

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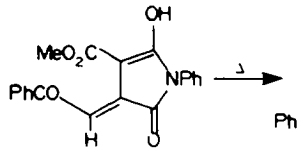

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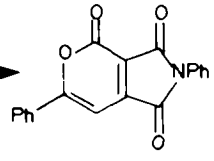

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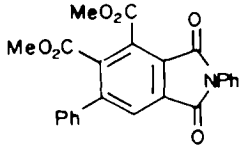

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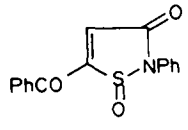

11

EXPERIMENTAL

5-Benzoyl-3-hydroxyisothiazole **4**

4-Oxo-4-phenylbutanamide[12] (40g) was heated under reflux with thionyl chloride (100 ml) for 2 hr and the excess of thionyl chloride was then removed *in vacuo*. The black oily residue was repeatedly extracted with large volumes of boiling water. The hydroxyisothiazole separated from the cooled extracts as a buff solid (6–10g); recrystallisation from water gave hair-like crystals, m.p. 148–50°; ν_{max} (KBr) 1635, 3100–2500 cm^{-1}; λ_{max} (EtOH) 260, 320 nm (ϵ13,200, 1900); $\delta(CDCl_3)$ 7.03 (1H, s), 7.54–7.68 (3H, m), 7.95 (2H, dd), *ca.* 10 (1H, broad OH signal) (Found: C, 58.65; H, 3.6; N, 6.55. $C_{10}H_7NO_2S$ requires C, 58.5; H, 3.5; N, 6.8%). With phenyl isocyanate in methylene chloride (12 hr at room temperature) the isothiazole was converted to the *N*-phenylcarbamoyl derivative which formed yellow needles, m.p. 124–5°, from acetonitrile; ν_{max} (KBr) 1640, 1720 (broad) cm^{-1}; $\delta(CDCl_3)$ 6.80 (1H, s), 7.2–7.8 (9H, m), 7.96 (2H, dd). (Found: C, 62.9; H, 3.5; N, 8.5 $C_{17}H_{12}N_2O_3S$ requires C, 63.0; H, 3.7; N, 8.6%).

N-Methyl and O-Methyl derivatives. Treatment of the hydroxyisothiazole with diazomethane in ether gave a mixture of the two derivatives from which the *N*-methyl compound was separated in 40% yield by chromatography on silica (elution first with 20% ether–benzene, to remove the *O*- methyl ether, and then with 80% ether–benzene); 5-benzoyl-2-methyl-3-isothiazolinone formed yellow microcrystals, m.p. 141–3°; ν_{max} (KBr) 1630, 1660 cm^{-1}; λ_{max} (EtOH) 267, 347 nm (ϵ9800, 2500); $\delta(CDCl_3)$ 3.49 (3H, s), 6.80 (1H, s), 7.59–7.72 (3H, m), 7.94 (2H, dd) (Found: C, 60.15; H, 4.3; N, 6.2. $C_{11}H_9NO_2S$ requires C, 60.3; H, 4.1; N, 6.4%).

The *O*-methyl compound was obtained in 65% yield by heating together for 2 hr a solution of 5-benzoyl-3-hydroxyisothiazole (0.2 g) in ethanol (60 ml) containing sodium hydroxide (0.05 g) with methyl iodide (0.2g). The mixed product was fractionated by chromatography on silica as above and yielded the methyl ether as a colourless oil, b.p. 92–3°/0.1 mm; ν_{max} (KBr) 1640 cm^{-1}; λ_{max} (EtOH) 258 nm (ϵ 8000) and shoulder at 320 nm; $\delta(CDCl_3)$ 3.99 (3H, s), 6.96 (1H, s), 7.4–7.6 (3H, m), 7.90 (2H, dd). (Found: 59.9; H, 4.2; N, 6.2. $C_{11}H_9NO_2S$ requires C, 60.3; H, 4.1; N, 6.4%).

5-Benzoyl-2-phenyl-3-isothiazolinone (**3**, R = Ph). 4-Oxo-4, *N*-diphenylbutanamide[12] (50g) was heated under reflux with redistilled thionyl chloride (120 ml) for 2 hr. After vacuum distillation to remove the excess of thionyl chloride, and two further distillations of added toluene, the residue was chromatographed on silica in 80% ether/benzene. Crystallisation from methanol gave yellow needles (21.5 g), m.p. 144–5°; ν_{max} (KBr) 1640, 1665 cm^{-1} (PhCO, C = 0); λ_{max} (EtOH) 275, 360 nm (ϵ 10,900, 4400); $\delta(CDCl_3)$ 6.84 (1H, s), 7.3–7.7 (8H, m), 7.95 (2H, dd). (Found: C, 68.5; H, 3.9; N, 4.9. $C_{16}H_{11}NO_2S$ requires C, 68.3; H, 3.9; N, 5.0%).

Under the same conditions, but with added pyridine (3 ml), the anilide (15g) and thionyl chloride (100 ml) gave 5-benzoyl-4-chloro-2-phenyl-3-isothiazolinone (7.7g), isolated after chromatography on silica with 50% ether/light petroleum as yellow prisms, m.p. 88–9°; ν_{max} (KBr) 1630, 1660 cm^{-1}; λ_{max} 264, 343 sh. (ϵ15,000, 3000); $\delta(CDCl_3)$ 7.3–7.7 (8H, m), 7.95 (2H, dd). (Found: C, 60.8; H, 3.3; N, 4.5. $C_{16}H_{10}ClNO_2S$ requires C, 60.9; H, 3.2; N, 4.4%).

5-Benzoyl-2-benzyl-3-isothiazolinone (**3**, R = $PhCH_2$). *N*-Benzyl-4-oxo-4-phenylbutanamide (20g) with thionyl chloride (60ml) gave, after being heated under reflux for 2 hr, the 2-benzylisothiazolinone (9.5g), m.p. 130–1°; ν_{max} (KBr) 1640 cm^{-1} (broad); λ_{max} (EtOH) 268, 348 nm (ϵ13,600 2700); $\delta(CDCl_3)$ 5.0 (2H, s), 6.77 (1H, s), 7.36 (5H, s), 7.5–7.7 (3H, m), 7.9 (2H, dd). (Found: C, 69.4; H, 4.5; N, 4.7. $C_{17}H_{13}NO_2S$ requires C, 69.2; H, 4.4; N, 4.75%).

5-Benzoyl-2-p-chlorophenyl-3-isothiazolinone (**3**, R = *p*-$Cl.C_6H_4$). *N-p*-Chlorophenyl-4-oxo-4-phenylbutanamide (20g) was similarly converted to the isothiazolinone (10g) isolated as yellow needles (from methanol), m.p. 189–90°; ν_{max} (KBr) 1635, 1670 cm^{-1}; $\delta(CDCl_3)$ 6.78 (1H, s), 7.4–7.7 (7H, m), 7.92 (2H, dd). (Found: C, 61.0; H, 3.3; N, 4.25; S, 10.4. $C_{16}H_{10}ClNO_2S$ requires C, 60.9; H, 3.2; N, 4.4; S, 10.1%).

With added pyridine (3 ml), this procedure gave 5-benzoyl-4-chloro-2-*p*-chlorophenyl-3-isothiazolinone in 37% yield; yellow plates from ethanol-water, m.p. 137–8°; ν_{max} (KBr) 1630, 1660 cm^{-1}; $\delta(CDCl_3)$ 7.4–7.8 (7H, m), 7.95 (2H, dd). (Found: C, 54.9; H, 2.7; N, 4.0. $C_{16}H_9Cl_2NO_2S$ requires C, 54.9; H, 2.6; N, 4.0%).

5-Benzoyl-2-p-nitrophenyl-3-isothiazolinone (**3**, R = *p*-$NO_2 \cdot C_6H_4$). Prepared by the standard procedure in 32% yield, this product was obtained as a yellow powder, m.p. 240–2°, which was extremely insoluble in the usual solvents and difficult to purify. (Found: C, 58.4; H, 3.0; N, 8.35. $C_{16}H_{10}N_2O_4S$ requires C, 58.9; H, 3.1; N, 8.6%).

3-Anilino-5-benzoylisothiazole **6**. 5-Benzoyl-2-phenyl-3-isothiazolinone (2.8g) was stirred with phosphorus oxychloride (10 ml) at 50° for 4 hr. The residue left after vacuum evaporation of the excess phosphorus oxychloride was dissolved in acetonitrile (60 ml) and the solution cooled to 0°. Ammonia was passed through the cooled solution until the colour changed to yellow and a precipitate appeared. The following morning, the mixture was added to water (500 ml) and the product extracted with methylene chloride (3 × 50 ml). The combined extracts were washed with water, dried ($MgSO_4$), and the solvent evaporated to give an orange solid which was purified by chromatography on alumina in ether–light petroleum. The anilinoisothiazole crystallised from methanol in golden plates (2.25g), m.p. 138–9°; ν_{max} (KBr) 1630, 3370 cm^{-1}; λ_{max} (EtOH) 267, 390 nm (ϵ33,400, 4700); $\delta(CDCl_3)$ 7.0–7.7 (10 H, m), 7.94 (2H, dd). (Found: C, 68.5; H, 4.4; N, 10.0. $C_{16}H_{12}N_2OS$ requires C, 68.6; H, 4.3; N, 10.0%).

5-Benzoyl-2-phenyl-3-phenyliminoisothiazoline **7**. The preceding experiment was repeated with aniline (4 ml) replacing ammonia. The reaction mixture was stirred at 50° for 3 hr, left overnight, and then added to water (500 ml). Extraction with methylene chloride (3 × 150 ml) (wash with dilute aqueous sodium hydroxide) yielded the phenyliminoisothiazoline which crystallised from hexane in deep red prisms (2.1g), m.p. 115–6°; ν_{max} (KBr) 1625, 1600, 1590 cm^{-1}; λ_{max} (EtOH) 267, 458 (ϵ24,700, 4600); $\delta(CDCl_3)$ 6.81 (1H, s), 6.9–7.6 (11H, m), 7.75–7.85 (4H, m). (Found: C, 74.2; H, 4.4; N, 7.6. $C_{22}H_{16}N_2OS$ requires C, 74.2; H, 4.5; N, 7.9%).

Two analogues of this product were prepared using *p*-chloroaniline and 2, 6-dimethylaniline in place of aniline. 5-Benzoyl-3-*p*-chlorophenylimino-2-phenylisothiazoline (or 5-benzoyl-2-*p*-chlorophenyl-3-phenyliminoisothiazoline) crystallised from hexane in dark red prisms, m.p. 156–7°. (Found: C, 67.6; H, 3.6; N, 6.9. $C_{22}H_{15}ClN_2O$ S requires C, 67.6; H, 3.5; N, 7.2%). 5-Benzoyl-3-(2, 6-dimethylphenylimino)-2-phenylisothiazoline [or 5-benzoyl-2-(2, 6-dimethylphenyl) -3 - phenyliminoisothiazoline] crystallised from chloroform-hexane in dark red prisms, m.p. 225–6°. (Found: C, 74.6; H, 5.4; N, 7.1. $C_{24}H_{20}N_2O$ S requires C, 75.0; H, 5.2; N, 7.3%).

2-Hydroxy-3-methoxycarbonyl-4-phenacylidene-1-phenyl-Δ^2-pyrrolin-5-one **8**. A solution of 5-benzoyl-2-phenyl-3-isothiazolinone (1.4g) in dry methylene chloride (10 ml) was added over 10 min to a stirred solution of diethyl malonate (0.8g) in methanol (70 ml) containing sodium methoxide (from 0.12g of sodium). The mixture, which gradually deposited a red precipitate, was stirred at room temperature overnight. The suspension was then poured into dilute hydrochloric acid (300 ml). The product was extracted with methylene chloride (3 × 70 ml) and crystallised from methanol, when it formed red hair-like needles (0.8g), m.p. 142–3° (decomp.); ν_{max} (KBr) 1742, 1690, 1655, 3300–3600 cm^{-1}; λ_{max} (EtOH) 275, 482 nm (ϵ27,300, 12,000); $\delta(CDCl_3)$ 3.89 (3H, s), 7.3–7.5 (9H, m), 7.64 (1H, s), 7.96 (2H, dd) (Found: C, 68.4; H, 4.3; N, 3.9. $C_{20}H_{15}NO_5$ requires C, 68.8; H, 4.3; N, 4.0%).

The corresponding ethyl ester, obtained by the same procedure using sodium ethoxide in ethanol in place of sodium methoxide in methanol, formed orange hair-like crystals, m.p. 114–5° from methanol; λ_{max} (EtOH) 274, 484 nm (ϵ27,800, 12,300) (Found: C, 69.5; H, 4.6; N, 4.1. $C_{21}H_{17}NO_5$ requires C, 69.4; H, 4.7; N, 3.9%).

Both esters, heated under reflux in xylene for 1 hr, yield the same pyronomaleimide (**9**), 1, 3, 4-trioxo-2, 6-diphenyl-(2H-pyrano [3, 4-c]-Δ^3-pyrroline), which formed yellow microneedles, m.p. 278–80°, from benzene; ω_{max} (KBr) 1790, 1755, 1715 cm^{-1}; λ_{max} (EtOH) 247, 372 nm (ϵ14,400, 16,600); $\delta(d_6$DMSO) 7.3–7.7 (8H, m), 7.8 (1H, S), 8.1 (2H, dd) (Found: C, 71.7; H, 3.4; N, 4.5. $C_{19}H_{11}NO_4$ requires C, 71.9; H, 3.5; N, 4.4%).

When heated under reflux for 1 hr in dimethyl acetylenedicarboxylate (3 ml), the pyronomaleimide (0.5g) was converted to 3, 4-bismethoxycarbonyl-5, *N*-diphenylphthalimide (0.7g), which was purified by chromatography on silica (elution with 50% ether/light petroleum) and formed pale yellow crystals from methylene chloride/benzene, m.p. 196–8°; ν_{max} 1780, 1745, 1720 cm^{-1}; $\delta(CDCl_3)$ 3.60 (3H, s), 4.00 (3H, s), 7.3–7.55 (10H, m), 8.02 (1H, s). (Found: C, 69.0; H, 4.2; N, 3.6. $C_{24}H_{17}NO_6$ requires C, 69.4; H, 4.1; N, 3.4%).

5-Benzoyl-2-phenyl-3-isothiazolinone-1-oxide **11**. *m*-Chloroperbenzoic acid (0.65g) was added slowly to a stirred solution of 5-benzoyl-2-phenyl-3-isothiazolinone (0.57g) in dry methylene chloride at 0°. The mixture was kept overnight at room temperature and then poured into aqueous sodium hydrogencarbonate (100 ml) with stirring. Isolated with methylene chloride (3 × 20 ml), the product was purified by chromatography on silica with 70% ether-light petroleum. Crystallisation from ethanol gave colourless hair-like crystals of the ethanol solvate (0.4g), m.p. 145–7°; ν_{max} (KBr) 1080, 1675, 1740, 3600–3700 cm^{-1} (Found: C, 63.0; H, 5.15; N, 4.3. $C_{16}H_{11}NO_2S \cdot C_2H_5OH$ requires C, 63.0; H, 5.0; N, 4.1%).

The cyclopentadiene adduct was prepared from the sulphoxide (0.5g) in methylene chloride (20 ml) and cyclopentadiene at −20°. The mixture was allowed to come slowly to room temperature and was then set aside for 24 hr. The major product, isolated by preparative t.l.c. on silica, formed colourless needles from methylene chloride–hexane, m.p. 177–8°; ν_{max} (KBr) 1712, 1678 cm^{-1}; $\delta(CDCl_3)$ 1.45 (1H, d), 1.65 (1H, d), broad singlets (1H) at 3.6, 4.1, 4.6, 6.5 (2H, s), 7.2–7.7 (8H, m), 8.05 (2H, d). (Found: C, 69.65; H, 4.75; N, 3.6. $C_{21}H_{17}NO_3S$ requires C, 69.4; H, 4.7; N, 3.9%).

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