Studies on Quinones. VII (1). Synthesis of Some Benzo[*b*]thiophene-4,7-diones

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The synthesis of methyl 4,7-dihydro-4,7-dioxobenzo[*b*]thiophene-2-carboxylate (**20**) based on the reaction of methyl mercaptoacetate with activated 1,4-benzoquinones is described. Methyl 4,7-dihydro-4,7-dioxo-5-hydroxybenzo[*b*]thiophene-2-carboxylate (**24**) and its corresponding methyl ether **26** were obtained through a Thiele-Winter acetoxylation on **20**. On the basis of the properties of methyl 4,7-dihydro-4,7-dioxo-6-methoxybenzo[*b*]thiophene-2-carboxylate (**21**) obtained from 2,4,5-trimethoxybenzaldehyde (**32**), the structures of the products **24** and **26** are proposed.

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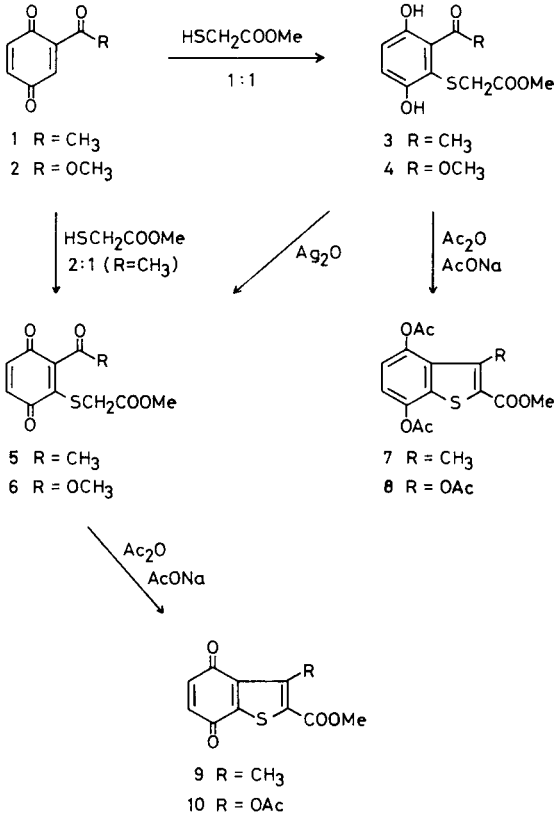
Introduction.

In previous papers (2,3,4,5) we have described that 1,4-benzoquinones bearing electron-withdrawing groups, *e.g.*, 2-acetyl- and 2-methoxycarbonyl-1,4-benzoquinone (**1**,**2**) are very reactive at C-3 position towards various nucleophiles. All of these reactions involve a conjugate addition of the nucleophile to the C=C-C=O system of the quinone and, depending on the nature of the nucleophile, an addition or addition-cyclization product can be isolated.



Scheme I

During the investigation on the reaction of **1** and **2** with thiols (4) it was found that the treatment of products **3**, **4** and **5**, **6** with acetic anhydride-sodium acetate, affords the benzo[*b*]thiophene derivatives **7** and **8** and benzo[*b*]thiophene-4,7-diones **9** and **10** respectively (Scheme I).

In relation with our interest in the synthesis of a benzo[*b*]thiophene-4,7-dione bearing a hydroxyl group on the quinone ring, we wish to report the preparation of the benzo[*b*]thiophene-4,7-dione **20** using 2-formyl-1,4-benzoquinone (**13**) and methyl mercaptoacetate, as well as the synthesis of the hydroxybenzo[*b*]thiophene-4,7-dione **24** through a Thiele-Winter acetoxylation (T-W) (6) on **20**.

Results and Discussion.

Bruce and Creed (7) describe the preparation of 2-formyl-1,4-benzoquinone (**13**), in fair yield, by oxidation of 2,5-dihydroxybenzaldehyde (**11**) in benzene solution with silver(I) oxide. Our experience has shown that isolation of **13** is not convenient and better results were obtained working with this quinone in the same solution in which it was generated.

When **13** was allowed to react with methyl mercaptoacetate at room temperature, methyl (3,6-dihydroxy-2-formylphenyl)thioacetate (**15**) was obtained in 86% yield based on **11**. The cyclization of **15** in hot acetic anhydride containing sodium acetate gave methyl 4,7-*bis*(acetyloxy)benzo[*b*]thiophene-2-carboxylate (17) in high yield. Alcoholysis of the diacetate **17** with acidic methanol under reflux, gave methyl 4,7-dihydroxybenzo[*b*]thiophene-2-carboxylate (**19**). Subsequent oxidation of the latter with ferric chloride produced the expected methyl 4,7-dihydro-4,7-dioxobenzo[*b*]thiophene-2-carboxylate (**20**) in 86% yield. These reactions are summarized in Scheme II.

T-W reaction on **20** gave only one of the two possible acetates **22** and **23** in high yield. The triacetate was then deacetylated in methanol-sulphuric acid followed by oxi-

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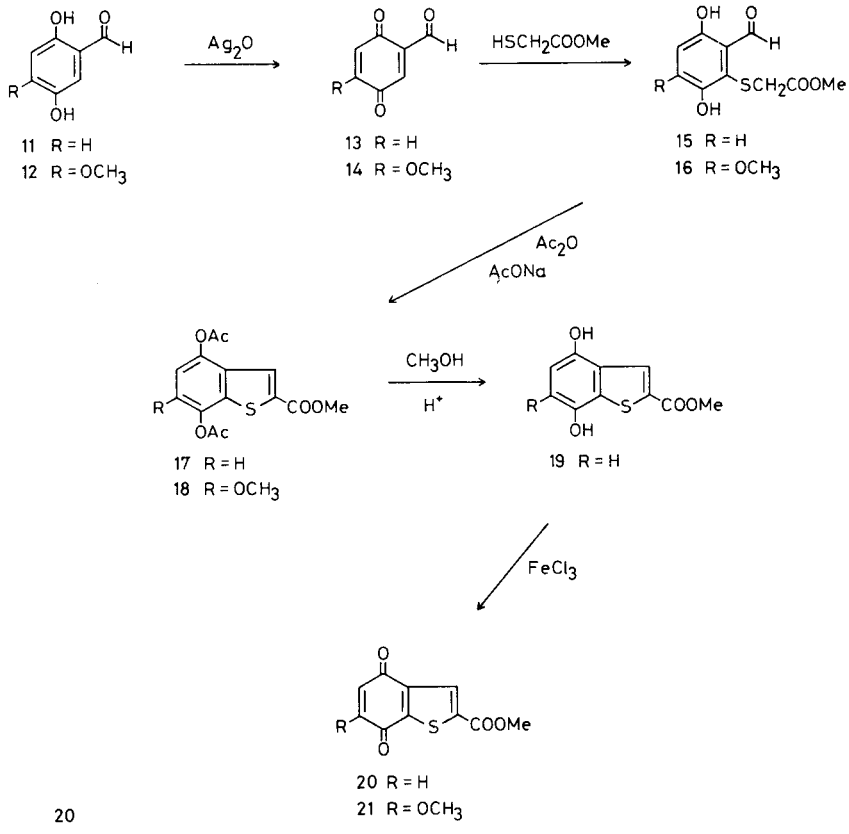
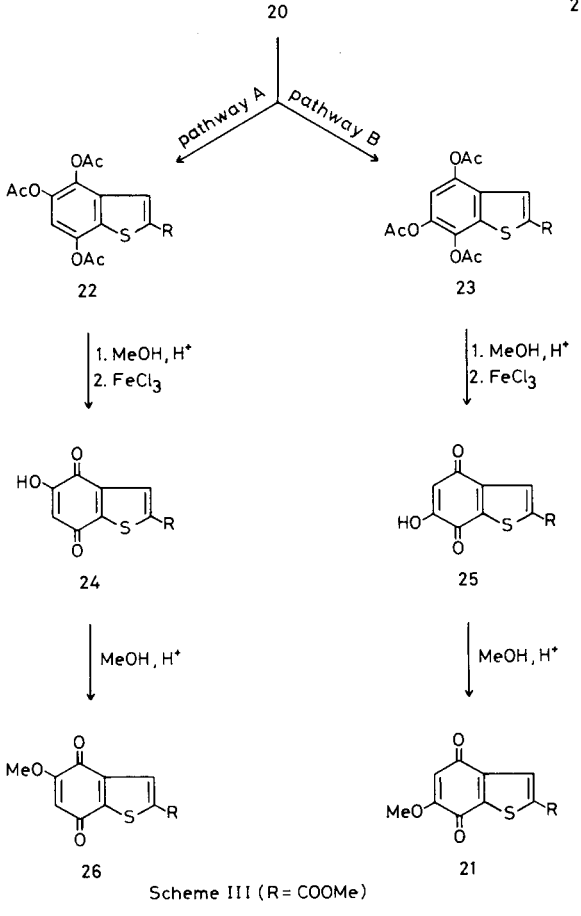


Scheme II

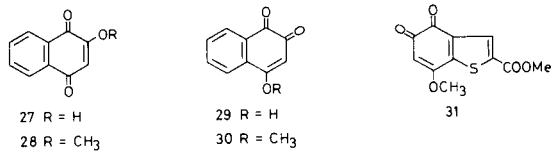


Scheme III (R = COOMe)

dation with ferric chloride to give methyl 4,7-dihydro-4,7-dioxo-5(or 6)-hydroxybenzo[*b*]thiophene-2-carboxylate **24** (or **25**) in good yield. The hydroxyquinone **24** (or **25**) was converted into its methyl ether **26** (or **21**) by treatment with methanol in the presence of sulphuric acid. These transformations and the two possible pathways of the T-W reaction on **20** are summarized in Scheme III.

It is interesting to note that based on the known tautomerism of 2-hydroxy-1,4-naphthoquinone (**27**) $\rightleftharpoons$ 4-hydroxy-1,2-naphthoquinone (**29**) (8), the formation of an *o*-quinone ether such as **31** may also be possible in the esterification of **24** with methanol in acid media. However, it has been shown that the methyl ether **30** is converted rapidly and completely into the *p*-quinone ether **28** when warming it with methanol containing hydrogen chloride (9). These results suggest that the structure of the esterification product of **24** (or **25**) is the *p*-quinone **26** (or **21**).

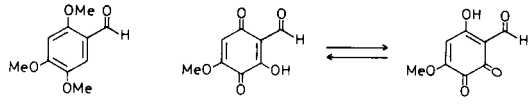
Although Fieser demonstrated that the T-W reaction on



benzo[*b*]thiophene-4,7-dione occurs at 5-position (10), it seemed necessary to establish unambiguously the structure of the products obtained through the T-W reaction on **20**. For this purpose the synthesis of the benzo[*b*]thiophenequinone **21** from 2-formyl-6-methoxy-1,4-benzoquinone (**14**) based on Scheme II was studied in order to compare its properties with those obtained for the methyl ether **26** (or **21**).

In order to obtain the required quinone **14**, the oxidative demethylation of 2,4,5-trimethoxybenzaldehyde (**32**) employing Rapoport's procedure (11) was attempted. Treatment of **32** with silver(II) oxide at low temperature (−10°) afforded 2-formyl-3-hydroxy-5-methoxyquinone (**33**) (12). This hydroxyquinone, generated under oxidative conditions, probably arises from the addition of water at the 3-position of the nascent quinone **14** followed by oxidation.

It is interesting to note that the nmr spectrum of **33** in deuteriochloroform solution, shows the presence of two slowly interconverting tautomers **33** and **34** in approximately equal amounts. This was confirmed by addition of acetic acid which produced averaged signals.



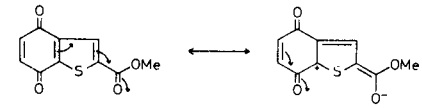
32 33 34

When the oxidative demethylation of **32** was attempted at −10° employing a short reaction time, a mixture of **33** and a second product was obtained. It was not possible to separate these products. Nevertheless, compound **12** was isolated when the reaction mixture was treated with sodium bisulphite. These results are in agreement with the presence of **14** in the reaction mixture obtained by oxidative demethylation of **32**.

Compound **12** was employed in order to obtain the methoxyquinone **21**. Oxidation of **12** with silver(I) oxide followed by treatment of the reaction mixture with methyl mercaptoacetate yielded the addition product **16**. Ring closure of **16** with acetic anhydride and sodium acetate afforded the benzo[*b*]furan **18** which by alcoholysis and oxidation gave the quinone **21** (Scheme II).

The melting point and spectral properties (uv, ir and nmr) of **21** were different from those of the methoxyquinone obtained through the T-W reaction with **20**. These results imply that the course of such a reaction and the subsequent transformation are in accordance with the pathway A of Scheme III.

The major reactivity at the 5-position of **20** could be explained by the high contribution of the polar structure **35**, in which the 7-carbonyl group is more electron-deficient than the 4-carbonyl group. The lower electron density may induce a polarization of the 5,6-double bond as shown and this leads to electron deficiency and observed nucleophilic attack at the 5-position.



20 35

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. Unless otherwise stated, ir spectra were recorded in nujol mulls on a Perkin-Elmer 567 spectrometer. Uv-visible spectra were taken in ethanol solution and recorded on a Pye Unicam SP-1800 spectrometer. Nmr spectra were measured in deuteriochloroform solution on a Varian XL-100 spectrometer using TMS as internal standard. Elemental analyses were obtained courtesy of Instituto de Química General (CSIC), Madrid, Spain.

Methyl (3,6-Dihydroxy-2-formylphenyl)thioacetate (**15**).

Into 100 ml of dry benzene was added 1.0 g (7.25 mmoles) of 2,5-dihydroxybenzaldehyde (**11**), 3.0 g (12.9 mmoles) of silver(I) oxide and 2 g of anhydrous sodium sulphate. The mixture was stirred at room temperature for two hours and then filtered. The solution was allowed to react with methyl mercaptoacetate (0.85 g, 8.02 mmoles) in benzene solution (10 ml) at room temperature. After one day the solvent was evaporated to give a yellow oil which solidified in the presence of carbon tetrachloride to give 1.5 g (85%) of **15**. A crude sample of **15** was purified by sublimation under vacuum, yielding an analytical sample as a yellow powder, mp 84-85°; ir (potassium bromide): ν 3370 (broad, OH), 1735 (C=O) and 1635 (C=O) cm^{-1}; nmr: δ 11.73 (s, 1H), 10.67 (s, 1H), 7.32 (s, 1H), 7.28 (d, 1H, J = 9 Hz), 7.00 (d, 1H, J = 9 Hz), 3.76 (s, 3H) and 3.52 (s, 2H) ppm.

Anal. Calcd. for $C_{10}H_{10}O_5S$: C, 49.58; H, 4.16; S, 13.24. Found: C, 49.73; H, 4.25; S, 12.85.

Methyl 4,7-*bis*(Acetyloxy)benzo[*b*]thiophene-2-carboxylate (**17**).

A solution of 1 g (4.13 mmoles) of **15**, in 15 ml of acetic anhydride and 1 g of anhydrous sodium acetate was refluxed for one hour. The mixture was cooled and diluted with cold water to give 1.2 g (97%) of the diacetate **17** which melted at 124-125° (from methanol-water), ir: ν 1756 (C=O) and 1723 (C=O) cm^{-1}; nmr: δ 7.94 (s, 1H), 7.27 (d, 1H, J = 8 Hz), 7.15 (d, 1H, J = 8 Hz), 3.93 (s, 3H) and 2.40 (s, 6H) ppm.

Anal. Calcd. for $C_{14}H_{12}O_6S$: C, 54.54; H, 3.92; S, 10.40. Found: C, 54.76; H, 3.90; S, 10.56.

Methyl 4,7-Dihydroxybenzo[*b*]thiophene-2-carboxylate (**19**).

Into 50 ml of methanol was added 1.70 g (5.52 mmoles) of **17** and two drops of concentrated sulphuric acid. The reaction mixture was refluxed for 2 hours. Then the solution still hot was diluted with water affording **19** (1.2 g, 97%) as colorless needles, mp 210° dec; ir: ν 3400 and 3320 (O-H) and 1700 (C=O) cm^{-1}; nmr (hexadeuteriodimethyl sulphoxide): δ 9.72 (s, 1H), 9.56 (s, 1H), 8.10 (s, 1H), 6.74 (d, 1H, J = 8 Hz), 6.61 (d, 1H, J = 8 Hz) and 3.88 (s, 3H) ppm.

Anal. Calcd. for $C_{10}H_8O_4S$: C, 53.56; H, 3.60; S, 14.29. Found: C, 53.53; H, 3.42; S, 14.49.

Methyl 4.7-Dihydro-4,7-dioxobenzo[*b*]thiophene-2-carboxylate (**20**).

Ferric chloride hexahydrate (5.0 g, 18.5 mmoles) in water (40 ml) was slowly dropped to a stirred slurry of 1.0 g (4.46 mmoles) of **19** in methanol (15 ml). After the addition was completed, the mixture was stirred for 30 minutes. Filtration of the solid afforded 0.92 g (93%) of **20**. The product was purified by column chromatography on a silica gel using benzene as eluent to give **20** (0.85 g, 85%) mp 140-141°; ir: ν 1720 (C=O), 1667 and 1656 (C=O, quinone) cm^{-1}; uv: λ (log ϵ): 250 (4.10) and 338 (3.49) nm; nmr: δ 8.14 (s, 1H), 6.92 (d, 1H, J = 10 Hz), 6.85 (d, 1H, J = 10 Hz) and 4.00 (s, 3H) ppm.

Anal. Calcd. for $C_{10}H_6O_4S$: C, 54.06; H, 2.72; S, 14.40. Found: C, 54.11; H, 3.01; S, 14.67.

Methyl 4,5,7-*tris*(Acetyloxy)benzo[*b*]thiophene-2-carboxylate (**22**).

Into 20 ml of acetic anhydride was added 1.0 g (4.5 mmoles) of **20**, five drops of concentrated sulphuric acid and 1 ml of boron trifluoride etherate. The mixture was allowed to stand at room temperature overnight. Evaporation of the acetic anhydride followed by water addition gave 1.6 g (97%) of the triacetate **22** which after recrystallization from methanol gave **22** as colorless needles melting at 155-156°; ir: ν 1768, 1757 and 1712 (C=O) cm^{-1}; rmn: δ 7.94 (s, 1H), 7.32 (s, 1H), 3.96 (s, 3H), 2.42 (s, 6H) and 2.32 (s, 3H) ppm; ms: m/e 366 (M^+) (obtained from a Varian MAT-111 spectrometer).

Anal. (13), for $C_{16}H_{14}O_8S$: C, 54.46; H, 3.85; S, 8.75. Found: C, 52.39; H, 4.19; S, 9.18.

Methyl 4,7-Dihydro-4,7-dioxo-5-hydroxybenzo[*b*]thiophene-2-carboxylate (**24**).

A solution of 0.5 g (1.37 mmoles) of **22** in 25 ml of aqueous methanol (80%) containing two drops of concentrated sulphuric acid was heated under reflux for 2 hours. The cooled mixture was further treated with 1.5 g (5.56 mmoles) of ferric chloride hexahydrate in 12 ml of water affording 0.28 g (86%) of **24**. The hydroxyquinone **24** was purified by sublimation and melted at 192-193°, ir: ν 3470 (O-H), 1723 (C=O), 1678 and 1633 (C=O), 1678 and 1633 (C=O, quinone) cm^{-1}; uv: λ (log ϵ): 267 (4.29), 290 (4.21), 332 sh (3.40) and 412 (3.07) nm; nmr: δ 8.14 (s, 1H), 6.28 (s, 1H) and 3.97 (s, 3H) ppm.

Anal. Calcd. for $C_{10}H_6O_5S$: C, 50.43; H, 2.54; S, 13.44. Found: C, 50.18; H, 2.61; S, 13.37.

Methyl 4,7-Dihydro-4,7-dioxo-5-methoxybenzo[*b*]thiophene-2-carboxylate (**26**).

A solution of 50 mg (0.21 mmoles) of **24** in 25 ml of methanol and a drop of concentrated sulphuric acid was refluxed for 3 hours. Evaporation of the solvent followed by recrystallization from cyclohexane gave 40 mg (75%) of **26** as yellow crystals melting at 246-247°; ir: ν 1730 (C=O), 1685 and 1630 (C=O, quinone) cm^{-1}; uv: λ (log ϵ): 264 (4.13), 278 (4.08) and 382 sh (2.95) nm; nmr: δ 8.15 (s, 1H), 6.08 (s, 1H), 3.96 (s, 3H) and 3.91 (s, 3H) ppm.

Anal. Calcd. for $C_{11}H_8O_5S$: C, 52.39; H, 3.20; S, 12.67. Found: C, 52.51; H, 3.38; S, 12.67.

Oxidative Demethylation of 2,4,5-Trimethoxybenzaldehyde (**32**).

a) To a stirred mixture of 2,4,5-trimethoxybenzaldehyde (**32**) (392 mg, 2.0 mmoles), silver (II) oxide (740 mg, 6.0 mmoles) in thf (20 ml) was added dropwise 6*N* nitric acid (2.0 ml) at $-10°$.

After 3 minutes the mixture was diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulphate and evaporated to dryness *in vacuo*. The residue was crystallized from chloroform to give the 4-methoxy-2-hydroxy-3,6-dioxo-1,4-cyclohexadienecarbaldehyde (**33**), as an orange solid (150 mg, 41%), mp 151-152°; ir: ν 3400 broad (O-H), 1680 (C=O) and 1600 (C=O) cm^{-1}; nmr: δ 9.86 and 9.04 (2s, 1H), 6.08 and 5.96 (2s, 1H), 3.94 and 3.88 (2s, 3H) ppm. The acidic proton was detected by addition of deuterium oxide.

Anal. Calcd. for $C_8H_6O_5$: C, 52.76; H, 3.32. Found: C, 52.72; H, 3.31.

b) To a stirred solution of 1.57 g (8.0 mmoles) of **32** in 60 ml of thf, and 3.0 g (24.2 mmoles) of silver(II) oxide was added in one portion 7.2 ml of 6*N* nitric acid. The mixture was quenched by the addition of 30 ml of distilled water and extracted wtih chloroform. The extract was shaked with aqueous sodium bisulphite (5%) in a separatory funnel, dried over magnesium sulphate and evaporated to dryness. Recrystallization from ethanol afforded 205 mg (15%) of **11** as yellow needles, mp 207-208° (lit (14), 209°).

Methyl (3,6-Dihydroxy-2-formyl-5-methoxyphenyl)thioacetate (**16**).

A mixture of 160 mg (0.95 mmoles) of **11**, 350 mg (1.56 mmoles) of silver(I) oxide in benzene (25 ml) was refluxed for 30 minutes in the presence of anhydrous sodium sulphate. The solution was filtered and poured on a solution of 100 mg of methyl mercaptoacetate in benzene (10 ml) and the resulting mixture was allowed to stand overnight at room temperature. Evaporation of the solvent followed by recrystallization from methanol-water afforded 200 mg (77%) of **16**, mp 156-157°; ir: ν 3260 (O-H), 1734 (C=O) and 1618 (C=O) cm^{-1}; nmr: δ 12.4 (s, 1H), 10.47 (s, 1H), 6.55 (s, 1H), 6.49 (s, 1H), 3.99 (s, 3H), 3.72 (s, 3H) and 3.60 (s, 2H) ppm.

Anal. Calcd. for $C_{11}H_{12}O_6S$: C, 48.52; H, 4.44; S, 11.78. Found: C, 48.50; H, 4.20; S, 11.97.

Methyl 4,7-*bis*(Acetyloxy)-6-methoxybenzo[*b*]thiophene-2-carboxylate (**18**).

A suspension of **16** (200 mg, 0.74 mmoles) 5 ml of acetic anhydride and 200 mg of anhydrous sodium acetate was heated under reflux for one hours. The mixture was evaporated under reduced pressure and the residue was crystallized from methanol-water to give 200 mg (80%) of **18**, mp 142-143°; ir: ν 1768 and 1712 (C=O) cm^{-1}; nmr: δ 7.86 (s, 1H), 6.98 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H) and 2.41 (s, 6H) ppm.

Anal. Calcd. for $C_{15}H_{14}O_7S$: C, 53.25; H, 4.17; S, 9.48. Found: C, 52.9 H 4.14; S, 9.76.

Methyl 4,7-Dihydro-4,7-dioxo-6-methoxybenzo[*b*]thiophene-2-carboxylate (**21**).

A solution of 150 mg (0.44 mmoles of **18**, in 10 ml of methanol and a drop of concentrated sulphuric acid was refluxed for 3 hours. The cooled solution was treated with 0.5 g (1.85 mmoles) of ferric chloride in 4 ml of water at room temperature. Work-up with water and extraction with chloroform followed by evaporation yielded 80 mg (71%) of the methoxyquinone **21** mp 176-177° (from cyclohexane); ir: ν 1700 (C=O), 1667 and 1644 (C=O, quinone) cm^{-1}; uv, λ (log ϵ): 257 (4.18), 293 (4.10) and 322 sh (360) nm; nmr: δ 8.10 (s, 1H), 6.00 (s, 1H), 3.98 (s, 3H) and 3.91 (s, 3H) ppm.

Anal. Calcd. for $C_{11}H_8O_5S$: C, 52.39; H, 3.20; S, 12.67. Found: C, 52.49; H, 3.55; S, 12.67.

Acknowledgement.

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REFERENCES AND NOTES

(1) For part VI of this series see: L. Barrios, V. M. Ruiz, R. Tapia, J. Valderrama and J. C. Vega, *Chem. Letters*, 187 (1980).

(2) F. Fariña and J. Valderrama, *Synthesis*, 315 (1971).

(3) F. Fariña and J. Valderrama, *An. Quím.*, **70**, 258 (1974).

(4) F. Fariña and J. Valderrama, *ibid.*, **72**, 902 (1976).

(5) J. Valderrama and J. C. Vega, *ibid.*, **73**, 1212 (1977).

(6) J. F. W. McOmie and J. M. Blatchly, *Org. React.*, **19**, 199 (1972).

(7) J. M. Bruce and D. Creed, *J. Chem. Soc. (C)*, 649 (1970).

(8) L. F. Fieser, *J. Am. Chem. Soc.*, **50**, 439 (1928).

(9) L. F. Fieser, *ibid.*, **48**, 2922 (1926).

(10) L. F. Fieser and R. G. Kennelly, *ibid.*, **57**, 1611 (1935).

(11) C. D. Snyder and H. Rapoport, *ibid.*, **94**, 227 (1972).

(12) The hydroxyquinone nature of this compound was confirmed by its solubility in aqueous sodium bicarbonate.

(13) The compound **22** loses acetic acid on standing and increasing amounts of the quinone **23** are detected. This fact accounts for a not entirely satisfactory result in its CHS analytical determination.

(14) F. S. H. Head and A. Robertson, *J. Chem. Soc.*, 2434 (1930).