

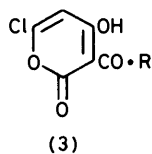
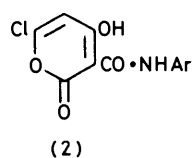
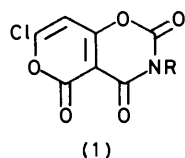
Heterocyclic Syntheses with Malonyl Dichloride. Part 13.¹ 6-Chloro-4-hydroxy-2-oxopyran-3-carboxanilides from *N*-Sulphinylanilines and Further Reactions of Malonyl Dichloride with Thiocyanates

By Mohammed S. Al-Ajely and Jasim M. A. Al-Rawi, Chemistry Department, College of Science, University of Mosul, Mosul, Iraq

John A. Elvidge,* Chemistry Department, University of Surrey, Guildford GU2 5XH

N-Sulphinylanilines react with malonyl dichloride to give 6-chloro-4-hydroxy-2-oxopyran-3-carboxanilides with loss of the sulphoxide moiety as thionyl chloride. Milder conditions and electron-withdrawing substituents do not alter the course of the reaction of thiocyanates with malonyl dichloride to give 2-substituted-thio-7-chloro-4*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-4,5-diones.

STUDIES of the interactions of malonyl dichloride with compounds having unsaturated functional groups,²⁻⁸ which lead to heterocycles, have now been extended to *N*-sulphinylanilines. These contain the $-N=S=O$ function but, in contrast to isocyanates $R-N=C=O$, which with malonyl dichloride yielded bicyclic dihydro-trioxopyrano-1,3-oxazines (1),⁶ the sulphinylanilines afforded simple carboxanilide derivatives of the 2-pyrone (2). There was loss of the sulphoxide group and the reaction did not lead to pyrano-oxathiazine *S*-oxides (Scheme).



a; R = OH
b; R = Cl

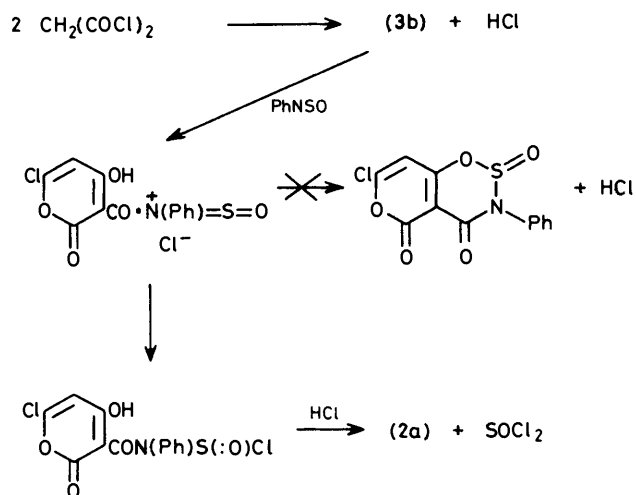
a; Ar = Ph
b; Ar = C₆H₄Me-*p*
c; Ar = C₆H₄Cl-*p*
d; Ar = C₆H₄NO₂-*p*
e; Ar = C₆H₄NO₂-*o*
f; Ar = C₆H₄OMe-*o*
g; Ar = C₆H₄OMe-*p*

We also report a brief investigation of the effects of reaction conditions on the course of the reaction of some organic thiocyanates with malonyl dichloride.⁸ This was undertaken because in other cases, such as with nitriles, milder conditions and electron-withdrawing substituents had a profound effect on the course of the interaction.^{5,7}

RESULTS AND DISCUSSION

Formation of the 2-Pyrones (2) from *N*-Sulphinylanilines.—A mixture of malonyl dichloride with *N*-sulphinylaniline (which had been purified and characterised) (0.5 mol equiv.) evolved pungent fumes and solidified during 3 d. From its properties the product with the molecular formula C₁₂H₈ClNO₄, was identified as 6-chloro-4-hydroxy-2-oxopyran-3-carboxanilide (2a), a compound

previously obtained⁶ from the 3-carboxypyrene (3a) and phenyl isocyanate. The same product (2a) also arose when the most rigid precautions were taken to exclude moisture, when the reaction was carried out in dry, hot benzene solution, and when the 3-chlorocarbonylpyrone (3b) was treated with the pure sulphinylaniline.

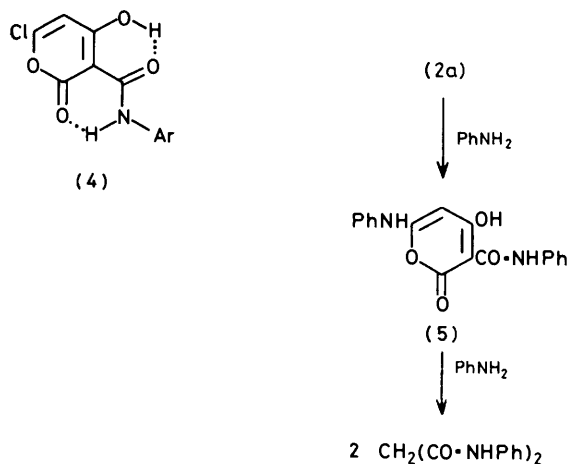


Initial concern that traces of moisture were present and were leading to hydrolysis of the hoped for bicyclic product was thus finally dispelled.

These findings suggested that, as in the reactions with ketones,^{2,3} nitriles,⁴ and isocyanates,⁶ there was self-condensation of malonyl dichloride (as induced even by dioxan³) to give the chlorocarbonylpyrone (3b) and hydrogen chloride, followed (or possibly preceded) by *N*-acylation of the sulphinylaniline. However, rather than cyclisation ensuing to give a bicyclic heterocycle, there was clearly loss of the sulphoxide moiety, very probably as thionyl chloride. By passing the gases evolved from the reaction into an iodine-starch solution, the blue colour was discharged, a result consistent with the presence of thionyl chloride (or sulphur dioxide). Although heating aniline with thionyl chloride is the method for preparing *N*-sulphinylaniline, hydrogen chloride being driven off, it appears that these last two

compounds will interact readily to yield anilinium chloride and thionyl chloride.⁹ Hence we envisage steps as in the Scheme.

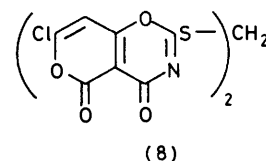
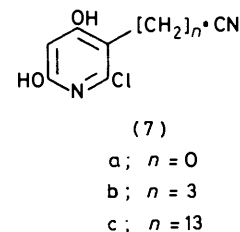
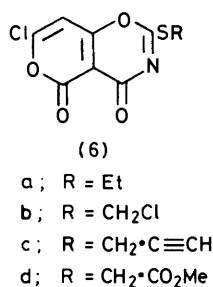
Analogous pyrone products (2b—g) were prepared from the purified and characterised *N*-sulphinyl derivatives of *p*-toluidine, *p*-chloroaniline, *o*- and *p*-nitroaniline, and *o*- and *p*-anisidine. The 6-chloro-4-hydroxy-2-oxopyran-3-carboxanilides [e.g. (2a)] gave a reddish colour with iron(III) chloride,⁶ and showed maximum u.v. absorption in the 300 nm region. In the i.r. spectrum, the carbonyl absorptions at 1700 and 1620 cm⁻¹ were indicative of the doubly hydrogen-bonded conformation (4), similar to that proposed⁴ for a close analogue. Further support for the conformation (4) came from the ¹H n.m.r. spectra of compounds (2a and b) which gave δ 16.5 and 10.5 for the chemical shifts of the hydroxy and amide protons, respectively, in line with their being strongly bonded.



Unlike the corresponding 3-carboxy-2-pyrone and esters,² the anilide (2a) was stable towards water and alcohols, being recovered *ca.* quantitatively after being refluxed in dioxan with water or ethanol (1 mol equiv.) for 15 min. Aniline, however, readily replaced the 6-chloro-substituent in compound (2a) to yield 6-anilino-4-hydroxy-2-oxopyran-3-carboxanilide (5), and when in excess reacted further to give malondianilide as the sole product. These reactions were fully in agreement with the pyrone structures (2a) and (5).

Reactions of Thiocyanates with Malonyl Dichloride.—Simple organic thiocyanates had been found to yield substituted pyrano-oxazines⁸ (6) in a 1 : 2 reaction when heated with malonyl dichloride, in a manner analogous to the reaction between aryl cyanides and acetonitrile at 100 °C.⁴ At ambient temperature and depending on their constitution, nitriles underwent 2 : 1 and 1 : 1 reactions with malonyl dichloride to yield, respectively, pyrimidines⁷ and pyridines.^{5,7} It therefore seemed worthwhile investigating the effects of both reaction conditions and the nature of the substituent group on the course of the reaction of thiocyanates with malonyl

dichloride. Bernatek *et al.*¹⁰ obtained pyrimidines from thiocyanates and *substituted* malonyl dichlorides but isolated no product from ethyl thiocyanate and malonyl dichloride kept together at room temperature (unspecified). However, at 22 °C (ambient) we obtained 7-chloro-2-ethylthio-4*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (6a) which we had previously prepared at 100 °C.⁸



Analogous bicyclic products (6b—d) were slowly formed from malonyl dichloride with chloromethyl, prop-2-ynyl, and methoxycarbonylmethyl thiocyanate under similar mild conditions: much better yields were obtained at 100 °C. The products showed one or more i.r. absorptions in the 1760—1790 cm⁻¹ region and u.v. absorptions at 280 and 329—342 nm, as expected.^{3,8} The ¹H n.m.r. spectra of the products were also in accord with the bicyclic structures (6b—d). No evidence accrued for the possible formation of pyrimidine products, indicating that their formation from thiocyanates was restricted to the reaction with mono-substituted malonyl dichlorides.¹⁰

Finally, the interaction of di-thiocyanates with malonyl dichloride was briefly examined. In the case of di-nitriles, the course of the reaction appeared to depend on the separation between nitrile functions. Thus with succino- and glutaro-nitrile the 3-carboxypyrene (3a), derived from self-condensation of malonyl dichloride, was the only product isolated,⁵ whereas with malononitrile, adiponitrile, and hexadecanedinitrile, 3-substituted pyridines (7a—c) were formed.⁷ In no case was there evidence of reaction at both nitrile functions. With di-thiocyanates and chloromalonyl dichloride, Bernatek *et al.*¹⁰ obtained a dipyrimidine only from 1,3-dithiocyanatopropane. We found that with methylene dithiocyanate, malonyl dichloride reacted, as might have been expected, to yield the bis-bicyclic pyrano-oxazine product (8).

EXPERIMENTAL

U.v. and i.r. spectra were obtained with Unicam SP 800B and SP 200 spectrophotometers, respectively. ¹H N.m.r.

spectra (SiMe₄ as internal reference) were recorded with a Varian A-60D instrument. Light petroleum refers to that fraction boiling in the range 40–60 °C.

N-Sulphinylanilines.—Anilinium chlorides were prepared by slow addition of concentrated hydrochloric acid to the corresponding anilines in acetone at 0 °C; the salts were washed with benzene and then crystallised from ethanol–acetone. Thionyl chloride (2 mol equiv.) was added to a suspension of the anilinium chloride (50 g) in dry benzene (200 ml); the mixture was then refluxed until all the solid had dissolved. Evaporation under reduced pressure and distillation or crystallisation of the residue gave *N*-sulphinylaniline¹¹ (40 g, 74%), as a yellow oil, b.p. 200 °C (Found: N, 15.2. Calc. for C₆H₇NOS: N, 15.2%; *m/z* 139 (*M*⁺). Similarly prepared were *N*-sulphiny-*p*-toluidine¹¹ (56%), b.p. 224 °C; *m/z* 153 (*M*⁺); δ 2.8 (3 H, s, Me) and 7.02 and 7.75 (total 4 H, *ca.* ABq, *J* 8 Hz, C₆H₄); *p*-chloro-*N*-sulphinylaniline¹² (61%), b.p. 237 °C; *m.p.* 36 °C (from CCl₄); *m/z* 175 [(*P* + 2)⁺] and 173 (*M*⁺); δ 7.27 and 7.77 (total 4 H, *ca.* ABq, *J* 9 Hz, C₆H₄); *p*-nitro-*N*-sulphinylaniline¹² (87%), *m.p.* 72 °C (from CCl₄); *m/z* 184 (*M*⁺); δ 7.92 and 8.20 (total 4 H, *ca.* ABq, *J* 9 Hz, C₆H₄); *o*-nitro-*N*-sulphinylaniline¹³ (75%), b.p. 120 °C at 540 mmHg; *m/z* 184 (*M*⁺); *N*-sulphiny-*o*-anisidine¹³ (83%), b.p. 244 °C; *m.p.* 30 °C (from hexane); δ 4.2 (3 H, s, OMe) and 7.2–8.5 (m, C₆H₄); *N*-sulphiny-*p*-anisidine¹⁴ (75%), *m.p.* 34 °C (from CCl₄); δ 4.20 (3 H, s, OMe), and 7.20 and 8.20 (total 4 H, *ca.* ABq, *J* 8 Hz, C₆H₄).

Reactions of Malonyl Dichloride with N-Sulphinylanilines.—(a) Malonyl dichloride (8.6 g, 0.06 mol) was mixed with *N*-sulphinylaniline (4.2 g, 0.03 mol) with exclusion of moisture. Pungent fumes were slowly evolved, and discharged the blue colour of an iodine–starch solution. After 3 d at 20 °C, the solid product (2 g) was washed with dry light petroleum and was recrystallised (dry benzene) to give 6-chloro-4-hydroxy-2-oxopyran-3-carboxanilide (2a), *m.p.* and mixed *m.p.* 153–156 °C (lit.,⁶ 160 °C) (Found: N, 5.1. Calc. for C₁₂H₉ClNO₄: N, 5.3%; *m/z* 267 [(*P* + 2)⁺] (31%) and 265 (*M*⁺); λ_{max.} (EtOH) 300 nm (ε 15 000); ν_{max.} (CHCl₃) 1 700s, 1 620s, (hydrogen-bonded C(2)=O and 3-CO, respectively), 1 600s, 1540s, and 1 500s cm⁻¹; δ(CDCl₃) 6.3 (1 H, s, 5-H), 7.15–7.75 (5 H, m, Ph), 10.5br (1 H, NH), and 16.5 (1 H, s, OH).

(b) A solution of malonyl dichloride (0.06 mol) in dry benzene (50 ml) was added dropwise to a stirred solution of *N*-sulphinylaniline (0.03 mol) in dry benzene (10 ml) at 60 °C and the solution was refluxed for 4 h with exclusion of moisture. With continued exclusion of moisture, the solution was evaporated under reduced pressure, and the solid residue (6 g) was washed (hexane) and recrystallised (from benzene) to give the anilide (2a), identical (analytical and spectral data) with the previous sample.

(c) Direct interaction of malonyl dichloride with the appropriate sulphinyaniline, as in (a), yielded 6-chloro-4-hydroxy-4'-methyl-2-oxopyran-3-carboxanilide (2b) (72%), *m.p.* 160 °C (from CCl₄) (Found: N, 4.9. C₁₃H₁₀ClNO₄ requires N, 5.0%; *m/z* 281 [(*P* + 2)⁺] and 279 (*M*⁺); λ_{max.} (EtOH) 300 nm (ε 14 300); ν_{max.} (CHCl₃) 1 700s, 1 620s, 1 600sh, 1 540s, and 1 500w cm⁻¹; δ(CDCl₃) 2.4 (3H, s, 4'-Me) 6.45 (1 H, s, 5-H), 7.20 and 7.55 (total 4 H, *ca.* ABq, *J* 8 Hz, C₆H₄), 10.5br (1 H, NH), and 16.5 (1 H, s, OH); 4',6-dichloro-4-hydroxy-2-oxopyran-3-carboxanilide (2c) (62%), *m.p.* 188 °C (from acetone–charcoal) (Found: N, 4.6. C₁₂H₇Cl₂NO₄ requires N, 4.7%; *m/z* 304 [(*P* + 4)⁺], 302 [(*P* + 2)⁺], and 300 (*M*⁺); λ_{max.} (EtOH) 305 nm; ν_{max.} (Nujol) 1 700s,

1 621s, 1 600s, 1 540, and 1 500w cm⁻¹; 6-chloro-4-hydroxy-4'-nitro-2-oxopyran-3-carboxanilide (2d) (62%), *m.p.* 211 °C (from acetone) (Found: C, 46.7; H, 2.4; N, 9.2. C₁₂H₇ClN₂O₆ requires C, 46.4; H, 2.3; N, 9.0%); *m/z* 312 [(*P* + 2)⁺] and 310 (*M*⁺); λ_{max.} (EtOH) 308 nm; ν_{max.} (KBr) 1 700s, 1 620s, 1 600s, 1 530w, and 1 500s cm⁻¹.

Reaction of the 3-Chlorocarbonylpyrone (3b) with N-Sulphinyanilines.—(a) The acid chloride (3b)³ (0.3 g) and *o*-nitro-*N*-sulphinyaniline (0.5 g) were heated together at 100 °C for 10 min and the solid product was then crystallised from acetone to give leaflets of 6-chloro-4-hydroxy-2'-nitro-2-oxopyran-3-carboxanilide (2e) (24%), *m.p.* 210 °C (Found: C, 46.35; H, 2.5; N, 8.7. C₁₂H₇ClN₂O₆ requires C, 46.4; H, 2.3; N, 9.0%); λ_{max.} (EtOH) 300 nm. (b) Similarly, the acid chloride (3b) (0.5 g) and *σ*-methoxy-*N*-sulphinyaniline yielded 6-chloro-4-hydroxy-2'-methoxy-2-oxopyran-3-carboxanilide (2f) (0.3 g), *m.p.* 187 °C (from acetone) (Found: C, 52.8; H, 3.4. C₁₃H₁₀ClNO₅ requires C, 52.8; H, 3.4%); λ_{max.} (EtOH) 280 nm. (c) *p*-Methoxy-*N*-sulphinyaniline similarly afforded 6-chloro-4-hydroxy-4'-methoxy-2-oxopyran-3-carboxanilide (2g) (46%), *m.p.* 194 °C (from acetone) (Found: C, 53.1; H, 3.6. C₁₃H₁₀ClNO₅ requires C, 52.8; H, 3.4%); λ_{max.} (EtOH) 280 nm. Each of the compounds (2b–g) in aqueous ethanol gave a reddish orange colour with iron(III) chloride.

Action of Aniline on the 2-Oxopyran-3-carboxanilide (2a).—A solution of compound (2a) (1 g) in dry chloroform (30 ml) was mixed with a solution of aniline (0.7 g) in the same solvent (10 ml) and the mixture was kept overnight. Evaporation yielded a solid that was washed (water) and recrystallised (from acetone) to give plates, *m.p.* 216 °C, of 6-anilino-4-hydroxy-2-oxopyran-3-carboxanilide (5) (1.1 g) (Found: C, 67.2; H, 4.4; N, 8.6. C₁₈H₁₄N₂O₄ requires C, 67.1; H, 4.4; N, 8.7%); λ_{max.} (Me₂SO) 328.2 nm (ε 38 000). With an excess of aniline in chloroform overnight, only malonanilide (77%) was obtained on evaporation under reduced pressure, *m.p.* 226 °C (from acetic acid) (Found: C, 70.7; H, 5.5; N, 10.9. Calc. for C₁₅H₁₄N₂O₂: C, 70.85; H, 5.55; N, 11.0%); *m/z* 254 (*M*⁺); δ [(CD₃)₂SO] 5.6 (H, s, CH₂), 7.1–7.8 (10 H, m, 2 × Ph), and 10.5br (2 H, 2 × NH).

Reactions of Malonyl Dichloride with Thiocyanates.—(a) Malonyl dichloride (6.4 g, 0.045 mol) and chloromethyl thiocyanate (2.4 g, 0.023 mol) were left together with exclusion of moisture for 8 d. Recrystallisation of the solid product from chloroform (charcoal) gave needles of 7-chloro-2-chloromethylthio-4,5-dioxo-4H,5H-pyrano[3,4-e][1,3]oxazine (6b) (1.55 g, 24%), *m.p.* 157 °C (Found: C, 34.3; H, 1.05; N, 5.1. C₈H₃Cl₂NO₄S requires C, 34.3; H, 1.1; N, 5.0%); *m/z* 284 [(*P* + 4)⁺], 282 [(*P* + 2)⁺], and 280 (*M*⁺); λ_{max.} (CHCl₃) 329 (ε 20 800) and 280 nm 19 800); ν_{max.} (CHCl₃) 1 780sh, 1 700s, 1 600s, 1 590sh, and 1 520s cm⁻¹; δ [(CD₃)₂CO] 5.48 (2 H, s, CH₂) and 6.58 (1 H, s, 8-H).

(b) Similarly, prop-2-ynyl thiocyanate¹⁵ afforded, after 15 d, pale yellow needles (from CCl₄–charcoal) of 7-chloro-2-(prop-2-ynylthio)-4,5-dioxo-4H,5H-pyrano[3,4-e][1,3]oxazine (6c) (31%), *m.p.* 130 °C (Found: C, 44.8; H, 1.4; N, 5.0; S, 11.5. C₁₀H₄ClNO₄S requires C, 44.5; H, 1.5; N, 5.2; S, 11.9%); λ_{max.} (CHCl₃) 337 (ε 15 000) and 280 nm (15 000); ν_{max.} (CHCl₃) 3 300, 2 400w, 1 790sh, 1 760s, 1 600s, 1 590sh, and 1 520s cm⁻¹; δ[(CD₃)₂CO] 2.4 (1 H, t, C≡CH), 4.08 (2 H, d, CH₂), and 6.49 (1 H, s, 8-H).

(c) Similarly, methyl thiocyanatoacetate¹⁶ afforded, after 12 d, fine yellow needles of 7-chloro-2-methoxycarbonylmethylthio-4,5-dioxo-4H,5H-pyrano[3,4-e][1,3]oxazine (6d) (19%), *m.p.* 158 °C (from CHCl₃–charcoal) (Found: C,

39.9; H, 1.7; N, 4.7; S, 10.5. $C_{10}H_9ClNO_6S$ requires C, 39.6; H, 2.0; N, 4.6; S, 10.5%; λ_{max} ($CHCl_3$) 342 (ϵ 12 800) and 279 nm (9 900); ν_{max} ($CHCl_3$) 1 780sh, 1 760, 1 600sh, and 1 520s cm^{-1} ; $\delta(CDCl_3)$ 3.75 (3 H, s, OMe), 4.18 (2 H, s, CH_2), and 6.5 (1 H, s, 8-H).

In each case the yield was increased (by up to 3 \times) by heating the reaction mixtures on a steam-bath until solidification of the product was complete.

Reaction with Methylene Dithiocyanate.—A solution of the dithiocyanate (2.6 g, 0.02 mol) in dry, hot dioxan (10 ml) was added dropwise to malonyl dichloride (5.6 g, 0.04 mol) in refluxing dioxan (50 ml). After 6 h the solution was evaporated under reduced pressure and the product was washed with hot acetonitrile and dried to yield yellow bis-(7-chloro-4,5-dioxo-4H,5H-pyrano[3,4-e][1,3]oxazin-2-ylthio)methane (8) (4 g, 85%), m.p. 240 °C (Found: C, 37.9; H, 0.9; N, 6.1; S, 13.9. $C_{15}H_4Cl_2N_2O_8S_2$ requires C, 37.9; H, 0.8; N, 5.9; S, 13.5%); ν_{max} (Nujol) 1 780s [C(5)=O], 1 740sh [C(4)=O], 1 600s and 1 550s (C=C), and 1 590sh cm^{-1} (C=N).

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