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# A convenient preparation of 2-thioxo-4(3*H*)-quinazolinones

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**Abstract.** A simple method is described for the preparation of 3-aryl-2-thioxo-4(3*H*)-quinazolinones (4) by the reaction of anthranilic acids and ammonium or triethylammonium N-aryl-dithiocarbamates in ethanol. The method is also applicable to the preparation of 3-ethyl-2-thioxo-4(3*H*)-quinazolinone.

**Keywords.** 2-Thioxo-4(3*H*)-quinazolinone; anthranilic acid; ammonium aryldithiocarbamate; triethylammonium aryldithiocarbamate.

## 1. Introduction

Diverse biological and pharmacological profiles are associated with the 2-thioxo-4(3*H*)-quinazolinone ring system such as plant growth regulators and fungicides (Suesse *et al* 1990 and antihypertensive agents (compounds 1–3 (Cree *et al* 1981; Janssen 1985; Liu and Hsu 1985).

The three general approaches made for the synthesis of 2-thioxo-4(3*H*)-quinazolinone derivatives (4) are – the interaction of anthranilic acid (Lakhan and Singh 1985, 1988; Lakhan and Rai 1987), its methyl ester (McCarty *et al* 1960) or anthranilarylamide (Toyoshima *et al* 1965) with isothiocyanate (McCarty *et al* 1960; Lakhan and Singh 1985, 1988; Lakhan and Rai 1987), arylthiourea/thiourea (Dave *et al* 1962; Toyoshima *et al* 1965) or methyl N-aryldithiocarbamate (Mayoral *et al* 1981).

All these methods usually suffer from the disadvantage of having to obtain the nitrogen–sulphur containing reagent from readily available alkyl(aryl) amines. To avoid this problem, we have developed a new synthetic methodology. The compounds (4a–u) are prepared by the interaction of anthranilic acids with ammonium or triethylammonium N-aryl dithiocarbamates (scheme 1) using absolute ethanol or dimethylformamide as solvent. To widen the scope of this method, 3-ethyl-2-thioxo-4(3*H*)-quinazolinone (4v) has been prepared similarly from sodium ethyldithiocarbamate (see § 3).

## 2. Results and discussion

The reagents, ammonium/sodium aryl(alkyl) dithiocarbamates, are readily obtained from the corresponding primary amines by known methods (Moore and Crossley

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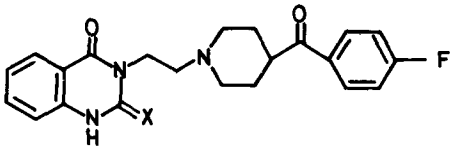
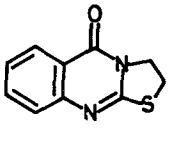
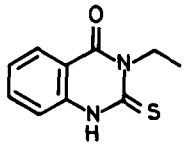


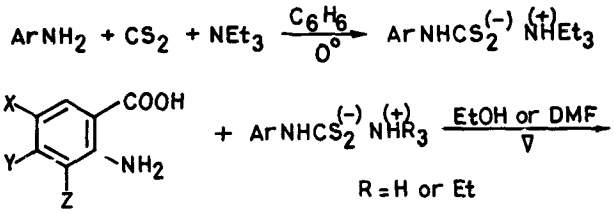
(1) X = O
(2) X = S



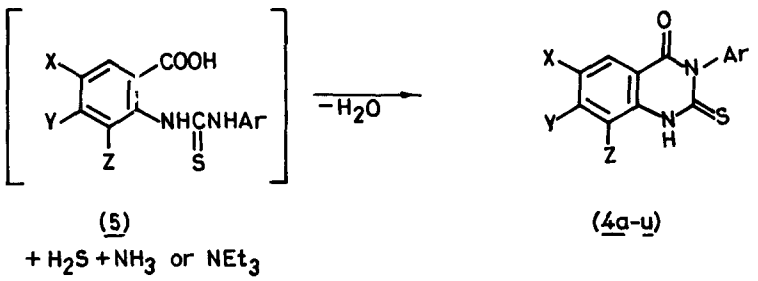
(3)



(4v)



R = H or Et



(5)
+ $H_2S$ + $NH_3$ or $NEt_3$

(4a-u)

**Scheme 1.**

1955; Vogel 1978). For 2,3- and 2,4-dichloroanilines, the triethylammonium N-aryldithiocarbamates were the reagents of choice (Hodgkins and Reeves 1964). Equimolar quantities of the appropriate anthranilic acid and the dithiocarbamate salts are heated under reflux in absolute ethanol or DMF for 5 h and worked up to give 4.

The reaction mechanism involves an initial nucleophilic attack by the amino group of anthranilic acid on the aryldithiocarbamate to form an unstable intermediate (5) which immediately cyclises to form 3-substituted 2-thioxo-4-(3*H*)-quinazolinone (4) by the loss of a molecule of water. The reaction takes place successfully in both ethanol and DMF as solvent as exemplified in the three selected cases (table 1). The yields of the isolated products were generally lower in DMF (50–62%) than in ethanol (65–75%). This may be attributed to some differences in the work-up procedures employed.

The structures of the new compounds were determined on the bases of their analytical and spectral (infrared, ultraviolet-visible, and $^1$H NMR) data. For example,

**Table 1.** Characterisation data of the prepared 3-aryl-2-thioxo-4(3*H*)-quinazolinones (4).

| Compound | Ar group | X | Y | Z | Method | Yield (%) | M.P. (°C) | Molecular formula or lit. m.p. (°C) | IR (nujol) $\nu_{max}(cm^{-1})$ |
|---|---|---|---|---|---|---|---|---|---|
| 4a | $C_6H_5$ | H | H | H | A, B | 75, 60 | 302 | 304–305[a] | 3280, 1710, 1250 |
| 4b | $4\text{-}CH_3C_6H_4$ | H | H | H | A, B | 75, 62 | 298 | 302[a] | 3250, 1700, 1260 |
| 4c | $4\text{-}CH_3OC_6H_4$ | H | H | H | A, B | 65, 50 | 274 | 275[a] | 3240, 1700, 1260 |
| 4d | $4\text{-}BrC_6H_4$ | H | H | H | A | 70 | 320 | 320[a] | 3250, 1720, 1250 |
| 4e | $3\text{-}Cl\text{-}2\text{-}CH_3C_6H_3^{\dagger}$ | H | H | H | A | 75 | 286 | 288[b] | 3220, 1670, 1260 |
| 4f | $3\text{-}Cl\text{-}4\text{-}CH_3C_6H_3$ | H | H | H | A | 70 | 295 | 298[c] | 3260, 1680, 1265 |
| 4g | $5\text{-}Cl\text{-}2\text{-}CH_3C_6H_3$ | H | H | H | A | 70 | 230 | 230[c] | 3280, 1685, 1260 |
| 4h | $2,3\text{-}Cl_2C_6H_3$ | H | H | H | C | 50 | 260 | $C_{14}H_8Cl_2N_2OS$ | 3220, 1720, 1220 |
| 4i | $2,4\text{-}Cl_2C_6H_3$ | H | H | H | C | 60 | 254 | $C_{14}H_8Cl_2N_2OS$ | 3260, 1720, 1250 |
| 4j | $4\text{-}CH_3OC_6H_4$ | H | Cl | H | A | 50 | > 300 | > 300[b] | 3200, 1700, 1260 |
| 4k | $3\text{-}Cl\text{-}4\text{-}CH_3C_6H_3$ | H | Cl | H | A | 70 | 180 | $C_{15}H_{10}Cl_2N_2OS$ | 3200, 1710, 1250 |
| 4l | $C_6H_5$ | Cl | H | Cl | A | 65 | 214 | 215[d] | 3460, 3380*, 1710, 1220 |
| 4m | $4\text{-}CH_3C_6H_4$ | Cl | H | Cl | A | 70 | 229 | 231[d] | 3460, 3390*, 1710, 1220 |
| 4n | $C_6H_5$ | Br | H | H | A | 75 | > 300 | 325[e] | 3220, 1720, 1260 |
| 4o | $4\text{-}CH_3OC_6H_4$ | Br | H | Br | A | 70 | 230 | 228[f] | 3480, 3380*, 1680, 1240 |
| 4p | $3\text{-}Cl\text{-}2\text{-}CH_3C_6H_3$ | Br | H | Br | A | 70 | 210 | 210[g] | 3460, 3380*, 1680, 1230 |
| 4q | $5\text{-}Cl\text{-}2\text{-}CH_3C_6H_3$ | Br | H | Br | A | 72 | 195 | 195[g] | 3450, 3360*, 1700, 1230 |
| 4r | $C_6H_5$ | I | H | H | A | 70 | 295 | 295[h] | 3240, 1710, 1240 |
| 4s | $3\text{-}Cl\text{-}4\text{-}CH_3C_6H_3$ | I | H | H | A | 60 | 295 | 295[i] | 3220, 1720, 1220 |
| 4t | $5\text{-}Cl\text{-}2\text{-}CH_3C_6H_3$ | I | H | H | A | 60 | 290 | 290[i] | 3250, 1710, 1240 |
| 4u | $2,4\text{-}Cl_2C_6H_3$ | I | H | H | C | 50 | 195 | $C_{14}H_7Cl_2IN_2OS$ | 3240, 1720, 1250 |

*An overtone band; †PMR:2·44(*s*, 3H,$CH_3$), 6·83–7·90(*m*, 7H, Ar-H), 12·74(*s*, 1H, NH); UV(log ε): 221(4·22), 296(4·15); [a]Armarego (1967), [b]Mayoral *et al* (1981); [c]Lakhan and Singh (1990); [d]Prasad (1980); [e]Bhargava and Lakhan (1967); [f]Bhargava and Chaurasia (1968); [g]Lakhan and Rai (1987); [h]Bhargava and Singh (1968); [i]Lakhan and Singh (1985).

**Table 2.** UV-visible and elemental analytical data of new 3-aryl-2-thioxo-4-(3*H*)-quinazolinones prepared (4).

| Compound | UV-visible (EtOH) $\lambda_{max}$(log ε) | Found (%) (Calc.) | | |
|---|---|---|---|---|
| | | C | H | N |
| 4h | 222(4·21), 258(3·86), | 51·9 | 2·3 | 8·5 |
| | 294(4·35), 340(3·26)* | (52·0) | (2·5) | (8·7) |
| 4i | 220(4·34), 248(3·92), | 51·8 | 2·4 | 8·8 |
| | 300(3·56), 340(3·48) | (52·0) | (2·5) | (8·7) |
| 4k | 220(4·08), 235(3·88), | 53·6 | 3·2 | 8·5 |
| | 320(3·78) | (53·4) | (3·0) | (8·3) |
| 4u | 222(4·26), 250(3·86), | 37·6 | 1·6 | 6·0 |
| | 301(3·68), 345(3·41) | (37·4) | (1·6) | (6·2) |

*Shoulder

the $^1$H NMR spectrum of 2-thioxo-3-(3-chloro-2-methylphenyl)-4(3*H*)-quinazolinone (4e) in DMSO-$d_6$ shows a singlet of 3H intensity at $\delta$ 2·44 for the methyl substituent and a complex multiplet of seven aromatic protons between $\delta$ 6·83–7·90 ppm. A singlet of 1H intensity at 12·74 ppm is observed for the proton attached to the nitrogen at position 1. Its IR spectrum in the nujol phase shows absorption bands at 3220 and 1530 cm$^{-1}$ indicating the presence of >N–H and a thioureide group (>N–C=S), respectively. It also displays a strong absorption peak at 1670 due to C=O stretching and a medium band at 1260 cm$^{-1}$ due to C=S stretching. The absence of any band in the region 2600–2550 cm$^{-1}$ (characteristic of an SH group) indicates that the compound exists in the solid state in the thione form. Its UV-visible spectrum in ethanol shows absorption maxima (log ε) at 221 (4·22) and 296 (4·15) nm. Details of UV spectral data for other compounds are given in table 2.

In some instances, the compounds (4f, i) have been further characterised by preparing alkylated thio derivatives. Thus 4f was transformed into its ethyl derivative by reaction with ethyl iodide under alkaline conditions. The product 2-ethylthio-3-(3-chloro-4-methylphenyl)-4(3*H*)-quinazolinone had its $^1$H NMR spectrum as expected. Its IR spectrum lacks any absorption due to N–H stretching which is a characteristic feature of the starting material. It shows, however, a strong absorption band at 1690 cm$^{-1}$ for the endocyclic carbonyl group.

## 3. Experimental

Melting points were determined in open capillaries on a Gallenkamp apparatus and are uncorrected. Elemental microanalyses (C, H and N) were carried out on a Perkin–Elmer CHN analyzer model 240 C. IR spectra were recorded in nujol on Perkin–Elmer 720 and 783 spectrophotometers ($\nu_{max}$ in cm$^{-1}$) and $^1$H NMR spectra in DMSO-$d_6$ on a Jeol FX 90Q spectrometer (90 MHz) at 25°C using TMS as an internal standard (chemical shifts in $\delta$, ppm). The electronic absorption spectra were obtained on Cary-2390 and Shimadzu UV-160 A model spectrophotometers in

ethanol ($\lambda_{max}$ in nm). Homogeneity of compounds was routinely checked by TLC (silica gel G).

Ammonium N-aryldithiocarbamates and sodium N-ethyldithiocarbamate were prepared by known methods (Moore and Crossley 1955; Vogel 1978).

### 3.1 *Triethylammonium N-(2,4-dichlorophenyl)dithiocarbamate*

2,4-Dichloroaniline (16·2 g, 0·1 mol) was dissolved in a minimum amount of benzene and treated with a mixture of carbon disulphide (7·6 g, 0·1 mol) and triethylamine (10·12 g, 0·1 mol). The reaction mixture was cooled to 0°C and shaken. After complete precipitation of the yellow-coloured triethylammonium dithiocarbamate salt, the product was filtered, washed with anhydrous ether and dried, and recrystallised from chloroform, m.p. 155°C (60% yield). Analysis found: C, 46·0; H, 5·7; N, 8·05%; $C_{13}H_{20}Cl_2N_2S_2$ requires C, 46·0; H, 5·9; N, 8·25%; IR: 3350 (NH), 1040 (C=S).

### 3.2 *Triethylammonium N-(2,3-dichlorophenyl)dithiocarbamate*

This salt was prepared as described above, m.p. 95°C (yield 56%). Analysis found: C, 46·2; H, 5·9; N, 8·1; S, 18·6%; $C_{13}H_{20}Cl_2N_2S_2$ requires C, 46·0; H, 5·9; N, 8·25; S, 18·9%.

### 3.3 *3-Phenyl-2-thioxo-4(3H)-quinazolinone (4a)*

*Method A*: A mixture of ammonium phenyldithiocarbamate (3·72 g, 0·02 mol) and anthranilic acid (2·88 g, 0·021 mol) in absolute ethanol (20 ml) was refluxed on a water bath for 5 h. On cooling, the solid product was filtered and washed with water. It was dissolved in 10% ethanolic NaOH solution, filtered and reprecipitated by the addition of dil. HCl. The product was filtered, washed with water and crystallised from ethanol to give 4a in 75% yield, m.p. 302°C [literature (Armarego 1967) m.p. 304–305°]; IR; 3280*m* (NH), 1710*s* (C=O), 1640*m*, 1250*m* (C=S), 960*m*, 800*s*; $^1$H NMR: 7·19–8·09 (*m*, 9H, Ar-H), 13·0 (*s*, 1H, NH).

*Method B*: A mixture of ammonium phenyldithiocarbamate (3·72 g) and anthranilic acid (2·88 g) in DMF (20 ml) was refluxed in an oil bath at 150–160°C for 5 h. The solvent was removed by distillation and residue worked up as described above to afford 4a as white crystals in 60% yield, m.p. 302°C [literature (Armarego 1967) m.p. 304–305°].

### 3.4 *2-Thioxo-3-(2,4-dichlorophenyl)-4(3H)-quinazolinone (4i)*

*Method C*: Interaction of an equimolar ratio of triethylammonium 2,4-dichlorophenyldithiocarbamate and anthranilic acid in absolute ethanol, as described earlier, formed 4i as white crystals from ethanol in 60% yield, m.p. 254°C. Analysis found: C, 51·8; H, 2·4; N, 8·8%; $C_{14}H_8Cl_2N_2OS$ requires, C, 52·0; H, 2·5; N, 8·7%; IR: 3260*m* (NH), 1720*s* (C=O), 1660*m*, 1250*m*, 900*w*, 780*m*, 700*m*; UV (log $\varepsilon$): 220 (4·34), 248 (3·92), 300 (3·56), 340 (3·48); $^1$H NMR: 7·02–7·95 (*m*, 7H, Ar–H), 12·93 (*s*, 1H, NH).

Following the above methods *A*, *B* and *C*, several 3-aryl-2-thioxo-4(3*H*)-

quinazolinones (4) were prepared. Their yields, melting points and characteristic spectral data are recorded in tables 1 and 2.

### 3.5 *3-Ethyl-2-thioxo-4(3H)-quinazolinone (4v)*

A reaction utilising sodium ethyldithiocarbamate (2·86 g, 0·02 mol), in method *A* afforded 4v in 70% yield, m.p. 250°C [literature (Vasilev *et al* 1969) m.p. 250–251°C]; IR: 3250*m*, 1710*s*, 1650*m*, 1260*m*, 1210*m*, 760*m*.

### 3.6 *2-Ethylthio-3-(3-chloro-4-methylphenyl)-4(3H)-quinazolinone*

A solution of 4f (3·0 g, 10 mmol) in 2·5 N ethanolic NaOH (10 ml) was stirred with ethyl iodide (1·72 g, 11 m mol) for 2 h. The solid product was filtered, washed with water and dried. It was recrystallised from ethanol to form white crystals in 50% yield, m.p. 125°C. Analysis found: C, 61·5; H, 4·3; N, 8·4%; $C_{17}H_{15}ClN_2OS$ requires C, 61·7; H, 4·5; N, 8·5%; IR; 1690*s* (C=O), 1610*m*, 880*m*, 790*m*, 775; $^1$H NMR: 1·30 (*t*, $J = 8$ Hz, 3H; $-SCH_2\underline{CH}_3$), 2·44 (*s*, 3H, $C\underline{H}_3$), 3·07 (*q*, $J = 8$ Hz, 2H, $SC\underline{H}_2CH_3$), 7·02–8·00 (*m*, 7H, Ar–H).

### 3.7 *2-Methylthio-3-(2,4-dichlorophenyl)-4(3H)-quinazolinone*

The above compound was obtained from 4i (3·12 g, 10 m mol) and methyl iodide (1·45 g, 11 m mol) as detailed in §3·6 and recrystallised from ethanol to form white crystals in 48% yield, m.p. 170°C. Analysis found: C, 53·1; H, 2·9; N, 8·3%; $C_{15}H_{10}Cl_2N_2OS$ requires C, 53·4; H, 3·0; N, 8·3%; IR: 1700*s* (C=O), 1610*m*, 860*w*, 760*w*; $^1$H NMR: 2·46 (*s*, 3H, $C\underline{H}_3$), 6·60–8·00 (*m*, 7H, Ar–H).

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