

## Production of 3-Benzoyl-2,1-benzisoxazoles, 2-Phenyl-4*H*-3,1-benzoxazin-4-ones, and Novel Quinolinone Derivatives from 2-Phenylquinolin-4(1*H*)-ones and Sodium Dichloroisocyanurate

Benjamin Staskun<sup>\*,a</sup> and Theodor van Es<sup>b,†</sup>

<sup>a</sup> Department of Chemistry, University of the Witwatersrand, Johannesburg, Republic of South Africa

<sup>b</sup> Department of Molecular Biology and Biochemistry, Rutgers—The State University, New Jersey, 08854, USA

A simple synthesis of certain 3-benzoyl-2,1-benzisoxazoles **6** is accomplished *via* treatment of the corresponding 2-phenylquinolin-4(1*H*)-one **1** with sodium dichloroisocyanurate **2** in methanolic aq. alkali; the isomeric 2-phenyl-4*H*-3,1-benzoxazin-4-one **7** is also a product. Under different conditions the same reactants furnish two new types of quinolinone derivative, *viz.* 3,3-dichloro-2-phenylquinolin-4(3*H*)-one **4** and 2-alkoxy-3,3-dichloro-2,3-dihydro-2-phenylquinolin-4(1*H*)-one **5**, as chief products; the former is an intermediate in the synthesis of products **6** and **7**. Some of the chemical properties of the dichloro compounds **4** and **5** are described. Mechanistic pathways and proposals to explain the results and observations are presented.

Unusual transformations of 2-phenylquinolin-4(1*H*)-ones **1** and related compounds by means of singlet oxygen,<sup>1</sup> sodium hypochlorite,<sup>2</sup> and sodium dichloroisocyanurate **2**,<sup>1</sup> have been the subject of previous papers in this series. Recently<sup>3</sup> we showed that when compounds **1a** and **1b** were separately treated with the isocyanurate **2** (2.25 molar proportions) in methanol-aq. 2 mol dm<sup>-3</sup> sodium hydroxide-water (2:4:1, v/v) solvent mixture for 1 h, each afforded (~30%) the corresponding 3-benzoyl-2,1-benzisoxazole **6** (Scheme 1). Here we report that with use of a reduced reaction time of 10 min which does not significantly alter the yield of product **6**, but which minimizes loss of alkali-sensitive material, the synthesis also furnishes the isomeric 2-phenyl-4*H*-3,1-benzoxazin-4-one **7**, and that in a modified solvent system the reaction between substrates **1** and **2** provides hitherto unreported quinolinone derivatives of type **4** and **5**, respectively. Exemplifying the former outcome, substrate **1b** afforded compound **6b** (30–35%) together with the benzoxazinone **7b** (6%) and by-products derived therefrom, *viz.* acid **8b** (6%), and methyl ester **9b** (5%); this is the first verified production of heterocyclic system **7** from the quinolinones **1**.

The generality of the new benzisoxazole **6** synthesis<sup>3</sup> using the aforementioned reaction conditions (for 10 min) was examined with a number of other quinolinones **1** with the following results: substrates **1c**, **1d**, **1f** and **1g** each gave none of the benzisoxazole **6** but afforded instead the corresponding benzoxazinone **7** (1.5–20%) and derived products **8** and **9**; only substrate **1g** provided, in addition, the desired new 3-benzoyl-5-chloro-2,1-benzisoxazole **6c** (4%). In the case of substrate **1e** the sole product (82%) was the novel quinolinone adduct **5g** which with additional reagent **2** was transformed into the 3,3,6,8-tetrachloro derivative **5h**. The above diversity of outcomes makes it evident that the current methodology succeeds, to a moderate extent, only with substrates **1a** and **1b**, and it would seem that the production of products **6** (and of **7**) from reagents **1** and **2** is affected not only by the reactant stoichiometry and solvent composition (*vide infra*), but also by the nature and disposition of the R substituent in quinolinone **1**. It has already been demonstrated<sup>1</sup> that treatment of compound **1b** with a decreased molar proportion of reagent **2** provides principally the 3-chloroquinolinone **3b**, while here we report that in a methanol-enriched solvent mixture [MeOH–2 mol

dm<sup>-3</sup> NaOH–water (5:1:1, v/v)] the chief product from reagents **1** and **2** is adduct **5** (65–75%) in a seemingly general reaction.

Members of this new class of quinolinone derivatives **5** (Table 1) exhibited a strong IR (KBr) absorption near 3350 (NH) and one near 1680 (C=O) cm<sup>-1</sup>, and displayed the NH proton near  $\delta$  5.2 in the <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectrum. The precursor for compound **5c**, *viz.* 3,3-dichloro-6-methyl-2-phenylquinolin-4(3*H*)-one **4b**‡ was obtained by eliminating MeOH from compound **5c** with conc. sulfuric acid, and more directly from reagents **1b** and **2** in aq. alkali–tetrahydrofuran (THF) medium.

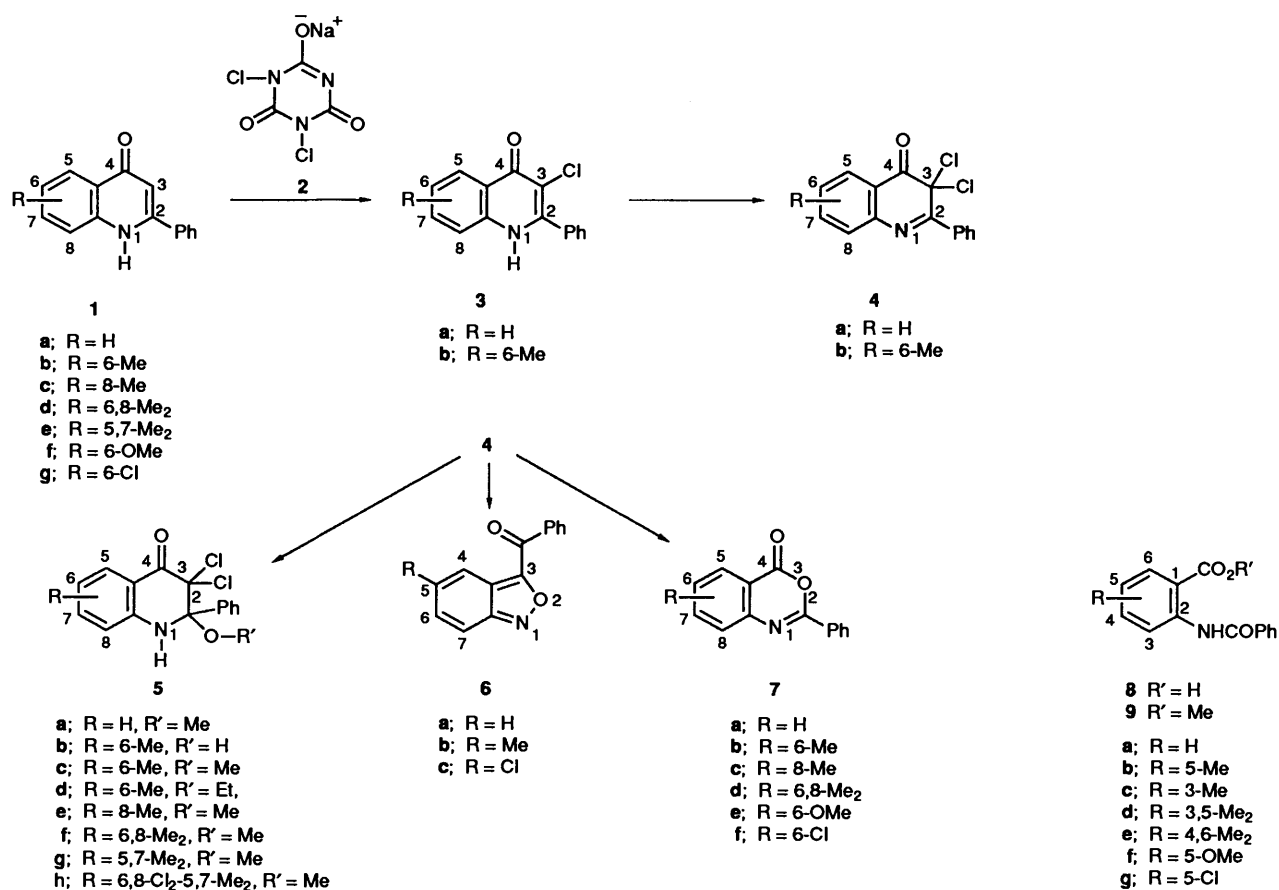
Exploratory investigations with substrates **4b** and **5c** have revealed some of their chemical potentialities. Heating of compounds **4b** and **5c** separately in ethanol gave, in each case, the EtOH adduct, *viz.* the 2-ethoxyquinolinone **5d**, which was also derived directly from substrates **1b** and **2** in EtOH-containing solvent. Both products **4b** and **5c** suffered loss of positive chlorine ion (or equivalent species), and in the case of compound **5c**, also of MeOH, when dissolved in acidified aq. acetone to yield the 3-chloroquinolinone **3b**. Application of this observation led to a satisfactory quantitative analysis of the 'available' chlorine in compound **4b** and in several of the compounds **5** (Table 1), by iodometric analysis. The aforementioned behaviour of compounds **4b** and **5c** in dil. acid is rationalized in Scheme 2 (with **4a** and **5a**).

In acid-free aq. acetone solution, water effectively added across the imine function in compound **4b**; evaporation of solvent provided an unstable product, tentatively formulated as 2-hydroxyquinolinone adduct **5b**.

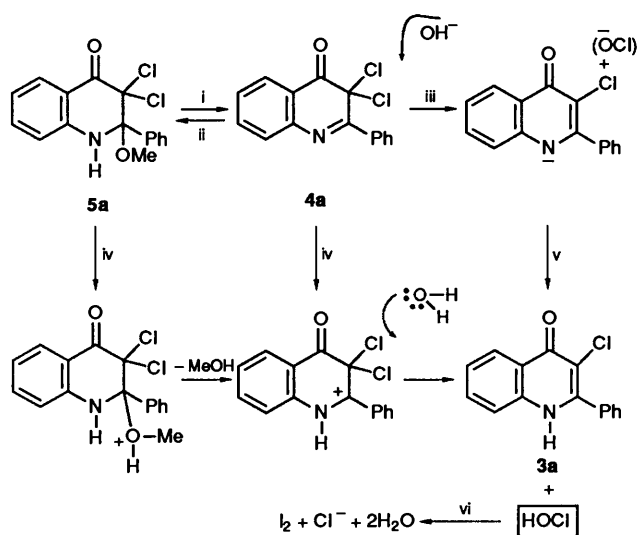
Treatment of compound **4b** with reagent **2** in aq. alkali–methanol–THF solvent furnished both products **6b** and **7b** and supported the intermediacy of dichloro compound **4b** in the synthesis of benzisoxazole **6b** from **1b**; in the absence of the 'salt' **2** the product was the 3-chloroquinolinone **3b**, and this established compound **2** as requisite in the pathway leading from **4b** on to **6b** and **7b**. Also of mechanistic significance were the following observations: (i) Chloroform extraction of the alkaline mixture after completion of the reaction between

‡ A product described as 3,3,6-trichloro-3,4-dihydro-4-oxoquinoline has been reported (ref. 4). However, this assignment is now made doubtful in view of the high m.p. (> 320 °C), and properties (crystals; not affected by hot ethanol) which contrast markedly with those of compound **4b**.

† Visiting Professor at the University of the Witwatersrand, 1990–1991.



Scheme 1



**Scheme 2** Reagents: i, c. H<sub>2</sub>SO<sub>4</sub>; ii, MeOH; iii, OH<sup>-</sup>; iv, H<sub>3</sub>O<sup>+</sup>; v, water; vi, 2I<sup>-</sup> + H<sub>3</sub>O<sup>+</sup>

reagents **1b** and **2** in methanolic aq. alkali provided negligible quantities of compounds **6b** and **7b**; the products were, however, extracted following acidification. (ii) Proposed intermediate **4b** (*vide infra*) in the aforementioned synthesis was isolated within 30 s of reaction. (iii) Treatment of compound **3b** with an appropriate molar proportion of reagent **2** gave adduct **5c** (66%); **5c** reacted further with compound **2** to yield compound **6b** (34%). (iv) Compounds **6a** and **7a** did not interconvert under the standard conditions (10 min) and were recovered

unchanged. By comparison, benzisoxazole **6b** was isomerized to the corresponding benzoxazine **7b** in refluxing acetic anhydride-pyridine mixture, and on heating in the absence of solvent, as had previously<sup>5,6</sup> been demonstrated in the case of substrate **6a**. The isomerization of compounds **6a** and **7a** occurs also in the gas phase,<sup>5</sup> and in this respect it is noteworthy that the mass spectra (70 eV) of benzisoxazoles **6b** and **6c** exhibited loss of a prominent *m/z* 44 (CO<sub>2</sub>)<sup>7</sup> fragment, which is suggestive of the production of species **7** during the electron-impact process. (v) Access to compound **6a** and to compound **6b** from substrates **1a** and **1b**, respectively, was achieved also, albeit in lower yields (~13%) with sodium hypochlorite as reagent, and with reagent **2** in a solely aq. alkaline (heterogeneous) medium, thus substantiating the role of chlorinium ion and obviating that of MeOH in the reaction pathway.

**Reaction Mechanism.**—Taking cognisance of the above, we explain the formation of compounds **4**, **5**, **6** and **7** from reagents **1** and **2** by the mechanism shown (with **1a**) in Scheme 3. Isolable<sup>1</sup> intermediate **3a** may derive from substrates **1a** and **2** either (i) *via* an *N*-chloro<sup>8-10</sup> derivative **A** which subsequently undergoes a 1,3-Cl migration,<sup>8</sup> or (ii) from direct electrophilic substitution by compound **2** (or equivalent species) at C-3 of the enamine-like substrate **1** (or its anion). In any event repetition of the chlorination process with compound **3a** as substrate *via* route (i) and/or (ii) rapidly furnishes the dichloro compound **4a**. The latter compound is then competitively attacked by MeOH in the solvent to give compound **5a**, and by OH<sup>-</sup> and substrate **2** to provide, initially, moiety **B** (analogous to adduct **5b**) and eventually, *via* a sequence of reactions including a semibenzilic rearrangement,<sup>11</sup> intermediate **C**, assigned the role of common precursor for both products **6** and

**Table 1** Physical data for compounds **5** and **6**

Compound M.p. (°C)	% Found/(% Required)				$\nu_{\max}/\text{cm}^{-1}$	$\delta_{\text{H}}(\text{CDCl}_3)$	$m/z$
	C	H	N	Cl <sup>a</sup>			
<b>5a</b> 135				10.3 (11.00)	3325, 1680, 1615	3.08 (3 H, s, OMe), 5.39 (1 H, br s, NH), 6.84 (1 H, d, <i>J</i> 8, 8-H), 7.0 (1 H, t, <i>J</i> 8, 6-H), 7.4–7.55 (4 H, m, ArH), 7.8–7.85 (2 H, m, ArH), 8.0 (1 H, dd, <i>J</i> 1.4 and 8, 5-H)	
<b>5b</b> 111–113				10.4 (11.00)	3400–3300, 1690, 1680, 1620	2.32 (3 H, s, ArMe), 3.24 (1 H, br s, OH, removed by D <sub>2</sub> O), 5.15 (1 H, br s, NH, removed by D <sub>2</sub> O), 6.68 (1 H, d, <i>J</i> 8, 8-H), 7.3 (1 H, dd, <i>J</i> 2 and 8, 7-H), 7.5 (3 H, m, ArH), 7.8–7.9 (3 H, m, ArH) <sup>a</sup>	
<b>5c</b> 137–138	60.5 (60.73)	4.4 (4.50)	4.2 (4.17)	10.4 (10.55)	3350, 1680, 1620	2.33 (3 H, s, ArMe), 3.07 (3 H, s, OMe), 5.29 (1 H, br s, NH), 6.76 (1 H, d, <i>J</i> 8, 8-H), 7.31 (1 H, dd, <i>J</i> 2 and 8, 7-H), 7.5 (3 H, m, ArH), 7.8 (3 H, m, ArH)	
<b>5d</b> 152–154	61.6 (61.73)	4.8 (4.89)	4.0 (4.00)		3325, 1680, 1620, 1585, 1500	1.06 (3 H, t, <i>J</i> 7, OCH <sub>2</sub> Me), 2.32 (3 H, s, ArMe), 3.09–3.39 (2 H, symmetrical 9-line m, OCH <sub>2</sub> Me), 5.25 (1 H, br s, NH), 6.72 (1 H, d, <i>J</i> 8, 8-H), 7.3 (1 H, dd, <i>J</i> 2 and 8, 7-H), 7.5 (3 H, m, ArH), 7.8 (3 H, m, ArH) <sup>b</sup>	349 (M <sup>+</sup> ), 314 (M – 35), 303, 269
<b>5e</b> 135–136					3440, 1695	2.28 (3 H, s, ArMe), 3.02 (3 H, s, OMe), 5.14 (1 H, s, NH), 6.91 (1 H, t, <i>J</i> 8, 6-H), 7.37 (1 H, d, <i>J</i> 7, 7-H), 7.5–7.6 (3 H, m, ArH), 7.8–8.0 (3 H, m, ArH)	
<b>5f</b> 132–133	61.4 (61.73)	4.75 (4.89)	4.0 (4.00)		3430, 1700, 1610	2.25 (3 H, s, ArMe), 2.30 (3 H, s, ArMe), 3.01 (3 H, s, OMe), 5.04 (1 H, br s, NH), 7.21 (1 H, d, <i>J</i> 0.6, 7-H), 7.5–7.6 (3 H, m, ArH), 7.73 (1 H, d, <i>J</i> 0.6, 5-H), 7.8–7.9 (2 H, m, ArH)	
<b>5g</b> 130–131	61.6 (61.73)	4.65 (4.89)	4.0 (4.00)	9.9 (10.12)	3350, 1678, 1615	2.31 (3 H, s, ArMe), 2.64 (3 H, s, ArMe), 3.10 (3 H, s, OMe), 5.27 (1 H, s, NH), 6.49 (1 H, d, <i>J</i> 0.6, ArH), 6.60 (1 H, d, <i>J</i> 0.6, ArH), 7.5 (3 H, m, ArH), 7.8 (2 H, m, ArH)	
<b>5h</b> 148–149	51.65 (51.58)	3.5 (3.61)	3.3 (3.34)		3390, 1705	2.60 (3 H, s, ArMe), 2.77 (3 H, s, ArMe), 3.08 (3 H, s, OMe), 6.0 (1 H, s, NH), 7.53 (3 H, m, ArH), 7.82 (2 H, m, ArH)	417 (M <sup>+</sup> )
<b>6a</b> 95					1645, 1622, 1595, 1575, 1555, 1520	7.27–7.8 (6 H, m, ArH), 8.1–8.2 (1 H, m, ArH), 8.3 (3 H, m, ArH)	
<b>6b</b> 114–115	75.9 (75.93)	4.6 (4.67)	5.9 5.91		1645s, 1625m, 1596m, 1575w, 1555m, 1451s, 1355s, 1275s, 1236s, 1189w, 1180m, 895s	2.45 (3 H, s, ArMe), 7.28 (1 H, dd, <i>J</i> 1.5 and 9, 6-H), 7.5–7.7 (4 H, m, ArH), 7.9 (1 H, s, ArH), 8.3 (2 H, m, ArH)	237 (M <sup>+</sup> ), 193 (M – 44), 160 (M – 77), 105, 77, 51
<b>6c</b> 115–116	64.9 (65.26)	3.0 (3.13)	5.35 (5.44)		1650, 1620, 1595	7.38 (1 H, dd, <i>J</i> 2 and 9, ArH), 7.55–7.78 (4 H, m, ArH), 8.2 (1 H, d, <i>J</i> 2, 4-H), 8.28–8.34 (2 H, m, ArH)	257 (M <sup>+</sup> ), 213 (M – 44), 180 (M – 77), 124, 105, 77, 51

<sup>a</sup> Percentage of 'available' chlorine. <sup>b</sup> The spectrum, following addition of D<sub>2</sub>O to the CDCl<sub>3</sub> solution and prolonged storage, was drastically altered.

7. It is further proposed that intermediate **C** is acted on by OH<sup>−</sup> to generate two alkali-soluble intermediates **D** and **E** which separately give rise to product **6** and product **7**, respectively, as outlined in the Scheme 3. This mechanism stresses the importance of both substrate **2** and OH<sup>−</sup> in the synthesis, emphasizes the key role of intermediate **4**, makes provision for steric impediment to approach of reagent **2** and/or OH<sup>−</sup> in the R-substituted moiety **B** and species arising thereafter, thereby influencing to different extents the yields of products **6** and **7**, and rationalizes the observation that both compounds **6** and **7** become isolable subsequent to acidification of the reaction mixture.

In summary, we have extended the scope of 2-phenylquinolin-4(1*H*)-one **1** chemistry by demonstrating that certain quinolinones **1** on treatment with sodium dichloroisocyanurate **2** in methanolic aq. alkali medium are transformed into a mixture of the corresponding 3-benzoyl-2,1-benzisoxazole **6** and 2-phenyl-4*H*-3,1-benzoxazin-4-one **7**. The current methodology, is as yet not of general application and remains to be optimized, but nevertheless offers a simple and relatively rapid entry to the interesting benzisoxazole **6** heterocyclic system. We also show that the same reactants under different conditions

provide hitherto unreported types of quinolinone derivatives, *viz.* species **4** and **5**, and have also attempted to explain how products **6** and **7** derive from substrates **1** and **2** *via* intermediate **4**, and from a postulated common precursor **C**.

### Experimental

**General.**—M.p.s were taken on a Kofler hot-stage apparatus and are uncorrected. IR spectra (KBr disc) were obtained on a Pye-Unicam SP3-300 spectrophotometer. <sup>1</sup>H NMR spectra were recorded on a Bruker AC 200 MHz instrument for solutions in CDCl<sub>3</sub> with SiMe<sub>4</sub> as internal standard. *J*-Values are given in Hz. Mass spectra were measured on a Varian MAT CH7 spectrometer at 70 eV. Column chromatography was on Merck Kieselgel 60 (70–230 mesh) with benzene as eluent. TLC was performed on plastic plates (Merck, silica gel 60F<sub>254</sub>) with the same solvent, and compounds were visualized under UV light and/or in an iodine chamber.

**Materials.**—Sodium dichloroisocyanurate **2** (Hunter Chemicals, purity 93%) was used as purchased. Quinolinones **1a–g** were prepared by condensation of the appropriate arylamine



for an X-ray structure determination.<sup>3</sup> Other observations with compound **1b** (500 mg) are as follows: (i) In the course of the synthesis of compound **6b** (*vide supra*) an aliquot (1 cm<sup>3</sup>) of the reaction mixture was removed 30 s after addition of the reagent **2**, and extracted with EtOH-free CHCl<sub>3</sub>; evaporation of the washed (water) and dried (MgSO<sub>4</sub>) extract gave a residue rich in compound **4b** (*vide infra*) (TLC, benzene).

(ii) Reagent **2** (1.1 g, 5.0 mmol) was added in one portion to a stirred, heterogeneous mixture of compound **1b** (500 mg, 2.13 mmol) in 2 mol dm<sup>-3</sup> NaOH (10 cm<sup>3</sup>)-water (20 cm<sup>3</sup>); the mixture developed a brown colour and the odour of benzaldehyde within minutes. At the end of 20 min, water (10 cm<sup>3</sup>) was added and the alkaline reaction was extracted with CHCl<sub>3</sub> to afford a gum (20–30 mg) containing little, if any, of compound **6b** or **7b** (TLC, benzene). Acidification (conc. HCl) of the stirred alkaline aq. phase led to separation of a product (~200 mg) from which was isolated (method A) compound **6b** (67 mg, ~13%).

(iii) To a solution of compound **1b** (500 mg) in 2 mol dm<sup>-3</sup> NaOH (25 cm<sup>3</sup>)-water (35 cm<sup>3</sup>) was added ~2 mol dm<sup>-3</sup> NaOCl (14 cm<sup>3</sup>, ~28 mmol) in one portion and the mixture was stirred for 30 min. The chilled (~10 °C) reaction was acidified (conc. HCl) and the brown gum which gradually separated (30 min) was extracted into CHCl<sub>3</sub> to afford (method A) the benzisoxazole **6b** (68 mg, 13%) and the benzoxazinone **7b** (20 mg).

Compound **1c** gave 3,3-dichloro-2,3-dihydro-2-methoxy-8-methyl-2-phenylquinolin-4(1H)-one **5e**, which separated from the reaction mixture and was collected by filtration (65 mg). Acidification of the filtrate provided (method A) 8-methyl-2-phenyl-4H-1,3-benzoxazin-4-one **7c** (39 mg), and the acid **8c**, which was converted with Ac<sub>2</sub>O into compound **7c** (157 mg).

Compound **1d** (after reaction for 75 min) gave 6,8-dimethyl-2-phenyl-4H-3,1-benzoxazin-4-one **7d** (26 mg) and acid **8d** (59 mg).

Compound **1e** gave 3,3-dichloro-2,3-dihydro-2-methoxy-5,7-dimethyl-2-phenylquinolin-4(1H)-one **5g**, which separated from the reaction mixture (0.58 g, 82%). To a stirred solution of compound **5g** (1.50 g) in MeOH (150 cm<sup>3</sup>) was added 2 mol dm<sup>-3</sup> NaOH (15 cm<sup>3</sup>) followed by a solution of compound **2** (1.8 g) in water (12 cm<sup>3</sup>). After reaction for 10 min, insoluble material was collected by filtration, washed with hot water, dried (over P<sub>2</sub>O<sub>5</sub>), and chromatographed to provide 3,3,6,8-tetrachloro-2,3-dihydro-2-methoxy-5,7-dimethyl-2-phenylquinolin-4(1H)-one **5h** (237 mg, 13%).

Compound **1f** gave 6-methoxy-2-phenyl-4H-3,1-benzoxazin-4-one **7e** (7 mg, 1.5%) and the acid **8f** (converted with Ac<sub>2</sub>O into compound **7e**).

Compound **1g** gave 3-benzoyl-5-chloro-2,1-benzisoxazole **6c** (4%), 6-chloro-2-phenyl-4H-3,1-benzoxazin-4-one **7f** (20%), methyl 2-benzamido-5-chlorobenzoate **9g** (5%), and 2-benzamido-5-chlorobenzoic acid **8g**.

*Isomerization of Benzisoxazoles 6a, 6b into Benzoxazinones 7a, 7b.*—(i) *In solution.* A solution of compound **6b** (300 mg) in a mixture of pyridine (8 cm<sup>3</sup>) and acetic anhydride (2.5 cm<sup>3</sup>) was refluxed (~115 °C) for 4 days; there was minor change before 24 h (TLC, benzene), and ~50% conversion at the end. Evaporation of solvent gave a residue, which was chromatographed (benzene) to obtain the benzoxazinone **7b** (65 mg) and unchanged substrate **6b** (95 mg).

(ii) *In the absence of solvent.* The benzisoxazole **6a** (60 mg) was gradually heated up to 200 °C during which period samples were taken at intervals for analysis (TLC, benzene): 120–125 °C (1 h), no change; 145–150 °C (30 min), no change; 170–175 °C (30 min), **7a** detected; 195–200 °C (~5 h), a mixture of **6a** and **7a**. Separation on a column provided uncontaminated samples of compound **7a** (15 mg) and unchanged substrate **6a** (20 mg).

*Preparation of 2-Alkoxy-3,3-dichloro-2,3-dihydro-2-phenylquinolin-4(1H)-ones 5.*—The general procedure is illustrated for compound **5c**; reagent **2** (1.10 g, 5.0 mmol) was added in one portion to a stirred solution of the quinolinone **1b** (500 mg, 2.13 mmol) in a mixture of MeOH (25 cm<sup>3</sup>), 2 mol dm<sup>-3</sup> NaOH (5 cm<sup>3</sup>), and water (5 cm<sup>3</sup>). After 10 min water (20 cm<sup>3</sup>) was added and the sparingly soluble solid **5c** was collected and washed on the filter with hot (~90 °C) water (530 mg, 74%). The physical properties of compound **5c** and of the other compounds **5** similarly obtained are listed in Table 1. Use of a lesser (0.90 g, 4.1 mmol) or greater (1.30 g, 5.9 mmol) amount of reagent **2** in the reaction with compound **1b** gave compound **5c** in reduced yield (390 and 420 mg, respectively). With EtOH (25 cm<sup>3</sup>) in place of MeOH in the general procedure, reagent **1b** provided 3,3-dichloro-2-ethoxy-2,3-dihydro-6-methyl-2-phenylquinolin-4(1H)-one **5d** (60–70%; Table 1). Treatment of the 3-chloroquinolinone **3b** (2.00 g, 7.42 mmol) with reagent **2** (2.25 g, 10.2 mmol) in the aforementioned MeOH–2 mol dm<sup>-3</sup> NaOH–water mixture (140 cm<sup>3</sup>) for 90 min gave compound **5c** in comparable yield (1.65 g, 66%); the combined filtrate and washings was acidified (conc. HCl) and allowed to evaporate slowly, when the benzisoxazole **6b** (40 mg, m.p. 104–114 °C) gradually separated.

#### 3,3-Dichloro-6-methyl-2-phenylquinolin-4(3H)-one **4b**.—

*Method a.* A solution of adduct **5c** (200 mg) in conc. H<sub>2</sub>SO<sub>4</sub> (3 cm<sup>3</sup>) was kept at room temperature for 1 h (negligible Cl<sub>2</sub> and/or HCl was evolved), and then poured onto ice. The yellow solid which precipitated was collected by filtration, washed with water, and dried (over P<sub>2</sub>O<sub>5</sub>) [183 mg; TLC (benzene) showed a mixture rich in compound **4b** (R<sub>f</sub> ~0.7); no substrate **5c** remained]. Chromatography (benzene) provided title compound **4b** (75 mg, virtually free from contaminants): yellow crystals from CHCl<sub>3</sub>-hexane, m.p. 125–126 °C; ν<sub>max</sub>/cm<sup>-1</sup> 1700s (C=O), 1605w, 1585m and 1565w; δ<sub>H</sub> 2.48 (3 H, s, ArMe), 7.4–7.65 (5 H, m, ArH), 7.95 (1 H, d, J<sub>1,5</sub>-H) and 8.2–8.3 (2 H, m, ArH); m/z 303 (M<sup>+</sup>, 2 Cl),\* 268 (M – 35, Cl)\* and 240 (268 – CO, Cl)\* [Found: C, 62.0; H, 3.7; N, 4.5; Cl (available), 11.0. C<sub>16</sub>H<sub>11</sub>Cl<sub>2</sub>NO requires C, 63.18; H, 3.64; N, 4.61; Cl, 11.66%].

*Method b.* Reagent **2** (1.20 g, 5.45 mmol) was added in one portion to a stirred mixture of the quinolinone **1b** (500 mg, 2.13 mmol), THF† (25 cm<sup>3</sup>) and 1 mol dm<sup>-3</sup> NaOH (10 cm<sup>3</sup>); reaction was accompanied by a mild exothermic effect. After 30 min water (30 cm<sup>3</sup>) was added and the mixture was extracted with alcohol-free CHCl<sub>3</sub>. The organic phase was washed successively with saturated aq. NaHCO<sub>3</sub> and water, dried (MgSO<sub>4</sub>), and evaporated to give an orange syrup [680 mg, rich in compound **4b** and containing negligible amounts of compounds **6b** and **7b** (TLC, benzene)] from which the last vestiges of solvent proved difficult to remove even *in vacuo*. Addition of MeOH to the syrup gave adduct **5c**; on prolonged storage the product **4b** in the syrup was converted into the 3-chloroquinolinone **3b**.

The following exploratory reactions [(i)–(v)] with compounds **4b** (Method a) and **5c** are described: (i) Refluxing of compound **4b** or **5c** in EtOH solution for 1 h, followed by evaporation of solvent, gave adduct **5d** in almost quantitative yield.

(ii) A solution of compound **4b** (100 mg) in acid-free (reagent

\* Number of chlorine atoms in molecular or fragment ion estimated from relative intensities of isotopic peaks.

† 'Old' (*i.e.*, peroxide-containing) THF was utilized. The yield of product **4b** appears to depend on the peroxide content of the solvent, and this aspect remains to be clarified. Hence, reaction in peroxide-free THF led to diminished yields of compound **4b** and a concomitantly enhanced production of compound **6b** and **7b**.

grade) acetone–water (5 cm<sup>3</sup>; 20:1 v/v) was allowed to evaporate slowly (overnight); the residue consisted principally (TLC, benzene) of highly reactive 3,3-dichloro-2,3-dihydro-2-hydroxy-6-methyl-2-phenylquinolin-4-(1*H*)-one **5b** (Table 1).

(iii) To a solution of compound **4b** (25 mg) or **5c** (25 mg) in reagent-grade acetone (2 cm<sup>3</sup>) was added one drop (~0.05 cm<sup>3</sup>) of 2 mol dm<sup>-3</sup> HCl; crystals of the 3-chloroquinolinone **3b** began to separate within minutes and were collected by filtration (~15 mg) after 30 min.

(iv) To a stirred mixture of compound **5c** (500 mg, 1.5 mmol), MeOH (75 cm<sup>3</sup>), and 2 mol dm<sup>-3</sup> NaOH (10 cm<sup>3</sup>) was added reagent **2** (0.50 g, 2.3 mmol), and after 30 min insoluble, reagent-derived material was separated. The filtrate was similarly treated with additional reagent **2** (0.50 g), after which the filtered mixture was cooled (~10 °C), acidified (conc. HCl), and extracted with CHCl<sub>3</sub>. Evaporation of the washed (saturated aq. NaHCO<sub>3</sub>, water) and dried (MgSO<sub>4</sub>) extract afforded an orange gum [~300 mg, rich in compound **6b** (TLC)], which was triturated with cold MeOH to provide sparingly soluble compound **6b** (120 mg; IR spectrum). In the absence of reagent **2**, the reaction yielded the 3-chloroquinolinone **3b** (30–45%).

(v) A solution of compound **4b** (500 mg) in peroxide-free THF\* (15 cm<sup>3</sup>) was added (5 min) to a stirred mixture of MeOH (13 cm<sup>3</sup>), 2 mol dm<sup>-3</sup> NaOH (27 cm<sup>3</sup>), water (6 cm<sup>3</sup>), and reagent **2** (1.1 g). Reaction for (a total of) 15 min afforded [method A (*vide supra*)] compounds **6b** (92 mg), **7b** (17 mg), acid **8b** (70 mg), and methyl ester **9b** (70 mg). In the absence of reagent **2**, the reaction gave the 3-chloroquinolinone **3b** (47%) and no compound **6b** or **7b**.

#### Acknowledgements

B. S. is grateful to the Senate Research Council of the University of the Witwatersrand and to the CSIR, Pretoria, for financial

support, and thanks Dr. L. Carlton and Mrs. S. Heiss for the <sup>1</sup>H NMR spectra.

#### References

- 1 B. Staskun, *J. Org. Chem.*, 1988, **53**, 5287.
- 2 J. C. A. Boeyens, L. Denner, J. L. C. Marais and B. Staskun, *S. Afr. J. Chem.*, 1986, **39**, 221.
- 3 A Preliminary account of some of the findings has appeared: B. Staskun, T. van Es, D. G. Billing and J. C. A. Boeyens, *J. Chem. Soc., Chem. Commun.*, 1991, 927.
- 4 K. Schofield and T. Swain, *J. Chem. Soc.*, 1950, 384.
- 5 J. L. Pinkus, H. A. Jessup and T. Cohen, *J. Chem. Soc. C*, 1970, 242.
- 6 R. K. Smalley, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1981, vol. 29, p. 34.
- 7 D. R. Eckroth, *Chem. Commun.*, 1970, 465.
- 8 M. De Rosa, L. Carbognani and A. Febres, *J. Org. Chem.*, 1981, **46**, 2054.
- 9 A. R. Katritzky, G. R. Khan, D. E. Leahy and M. De Rosa, *J. Org. Chem.*, 1984, **49**, 4784.
- 10 P. G. Gassman, G. A. Campbell and G. Mehta, *Tetrahedron*, 1972, **28**, 2749.
- 11 J. March, *Advanced Organic Chemistry*, 3rd edn., Wiley, New York, 1985, p. 974.
- 12 B. Staskun and S. S. Israelstam, *J. Org. Chem.*, 1961, **26**, 3191.
- 13 G. Fenton, C. G. Newton, B. M. Wyman, P. Bagge, D. I. Dron, D. Riddell and G. D. Jones, *J. Med. Chem.*, 1989, **32**, 265.
- 14 G. Heller and G. Fiesselmann, *Justus Liebig's Ann. Chem.*, 1902, **324**, 134.
- 15 B. Staskun and C. S. Foote, *S. Afr. J. Chem.*, 1984, **37**, 182.
- 16 C. Mentzer, D. Molho and Y. Berguer, *Bull. Soc. Chim. Fr.*, 1950, 555.
- 17 T. L. Gilchrist, P. F. Gordon, D. F. Pipe and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2303.
- 18 D. R. Desai, V. S. Patel and S. R. Patel, *J. Indian Chem. Soc.*, 1966, **43**, 351.
- 19 A. I. Vogel, *A Text Book of Quantitative Inorganic Analysis*, 3rd edn., Longman and Green, London, 1961, p. 392.

\* 'Old' (*i.e.*, peroxide-containing) THF was utilized. The yield of product **4b** appears to depend on the peroxide content of the solvent, and this aspect remains to be clarified. Hence, reaction in peroxide-free THF led to diminished yields of compound **4b** and a concomitantly enhanced production of compound **6b** and **7b**.

Paper 2/04185E

Received 4th August 1992

Accepted 2nd November 1992