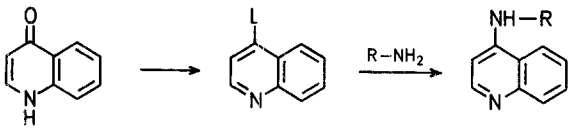
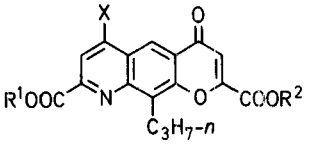


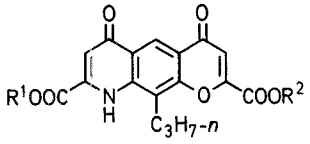
R = H, alkyl
L = leaving group

Scheme **A**

This transformation is inappropriate however when the 4-oxo-1,4-dihydro-quinoline bears other functional groups which react with amines. In particular, attempts at synthesising dialkyl esters (**1**) of 6-methylamino-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylic acid (minocromil), a promising anti-allergic agent, from the corresponding dihydro-oxoquinoline derivative **2** via the chloroquinoline **3** were unsuccessful.



1 X = NH—CH_3 ; R^1,R^2 = alkyl
3 X = Cl ; R^1, R^2 = alkyl



2 R^1,R^2 = alkyl

We now report a successful new approach to the synthesis of derivatives of 4-aminoquinoline-2-carboxylates from the corresponding 4-oxo-1,4-dihydroquinolines. The reaction of the 4-oxo-1,4-dihydroquinolines, **4a–c**[3], with chlorosulphonyl isocyanate, followed by *in situ* treatment with acid, yields aminoquinoline derivatives, **5a–c** (Method A; Table 1). Surprisingly, we found that in the formation of **5b**, ethyl 4,8-dichloro-3-phenylquinoline-2-carboxylate (*m/e* = 345, 347, 349) was also formed in 23% yield. To minimise such side reactions, we repeated the reaction of **4a–c**, replacing chlorosulphonyl isocyanate by 4-chlorophenoxysulphonyl isocyanate[2], to give on acid work up, **5a–c** in 66–90% yield (Method B; Table 1). In addition we were able to effect a very easy conversion of **4g** to **6**, using chlorosulphonyl isocyanate (Table 1).

We found that simple derivatives of 4-aminoquinoline-2-carboxylates **7a–g**, **8**, **9** could be formed in 65–92% yield (Table 2) by the reaction of **4a–g**[3] with 4-toluenesulphonyl isocyanate, 4-chlorophenoxysulphonyl isocyanate, or trichloroacetyl isocyanate as appropriate (Method C).

A Simple One-Pot Conversion of Alkyl 4-Oxo-1,4-dihydroquinoline-2-carboxylates to 4-Aminoquinoline-2-carboxylates using Reactive Isocyanates

R. Gordon McR. Wright

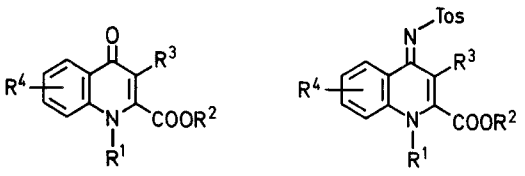
Fisons plc, Pharmaceutical Division, Chemical Process Research and Development Department, Science and Technology Laboratories, Bakewell Road, Loughborough, Leicestershire, U K.

The classic transformation of 4-oxo-1,4-dihydroquinolines to the corresponding 4-aminoquinoline relies on the conversion of the oxygen function to a leaving group, followed by nucleophilic displacement of the leaving group by an amine (Scheme **A**)[1].

Table 1. Compounds **5a–c**, **6** prepared

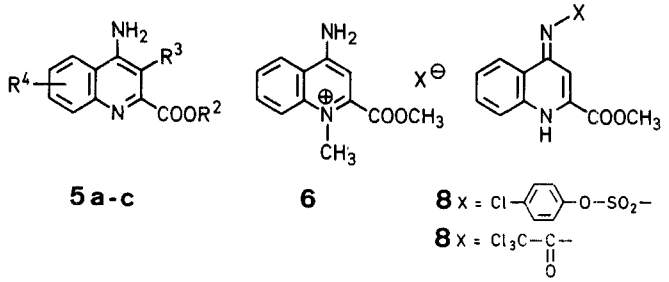
Product	Reaction Conditions Method/Time/Solvent	Yield [%]	m.p. [°C]	Molecular Formular[a]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]	M.S. *m/e* (M^+; base)
5a	A/5 min/CH_3CN B/30 min/CH_3CN	89 84	225–227°	$C_{11}H_{10}N_2O_2$ (202.2)	3.90 (s, 3H); 7.10 (br. s, 2H); 7.27 (s, 1H); 7.4–8.0 (m, 3H); 8.22 (d, 1H, J = 7.6 Hz)	202; 144
5b	A/30 min/$ClCH_2CH_2Cl$ B/60 min/$ClCH_2CH_2Cl$	30[b] 66	165–166°	$C_{18}H_{15}ClN_2O_2$ (326.8)	0.92 (t, 3H, J = 7.1 Hz); 4.04 (q, 2H, J = 7.1 Hz); 5.05 (br. s, 2H); 7.2–7.7 (m, 8H)[c]	328, 326; –
5c	A/60 min/$ClCH_2CH_2Cl$ B/60 min/$ClCH_2CH_2Cl$	50[d] 90[d]	193–195°	$C_{16}H_{20}N_2O_2$ (272.3)	1.00 (t, 3H, J = 7.2 Hz); 1.17 (t, 3H, J = 7.2 Hz); 1.42 (t, 3H, J = 7.2 Hz); 2.59 (m, 2H); 2.69 (s, 3H); 2.61 (t, 2H, J = 7.2 Hz); 3.80 (q, 2H, J = 7.2 Hz); 4.51 (q, 2H, J = 7.2 Hz); 7.4–7.9 (m, 2H); 8.64 (d, 1H, J = 8.2 Hz); 9.0 (br. s, 2H)	
6	A/5 min/$ClCH_2CH_2Cl$	73[e]	188–191°	$C_{12}H_{13}N_2O_2$ (217.3)	3.42 (s, 3H); 4.09 (s, 3H); 4.11 (s, 3H); 7.18 (s, 1H); 7.78 (t, 1H, J = 8.4 Hz); 8.0–8.3 (m, 2H); 8.56 (d, 1H, J = 8.4 Hz); 9.5 (br. s, 2H)	217; –

[a] Satisfactory microanalyses obtained: C ±0.18, H ±0.26, N ±0.38 (R^1–R^3 in **5** as in **4** and **7a–c**).
[b] Ethyl 4,8-dichloro-3-phenylquinoline-2-carboxylate also isolated; yield: 23%.
[c] In $CDCl_3$.
[d] $C_2H_5OSO_3H$ salt.
[e] H_3COSO_3H salt.



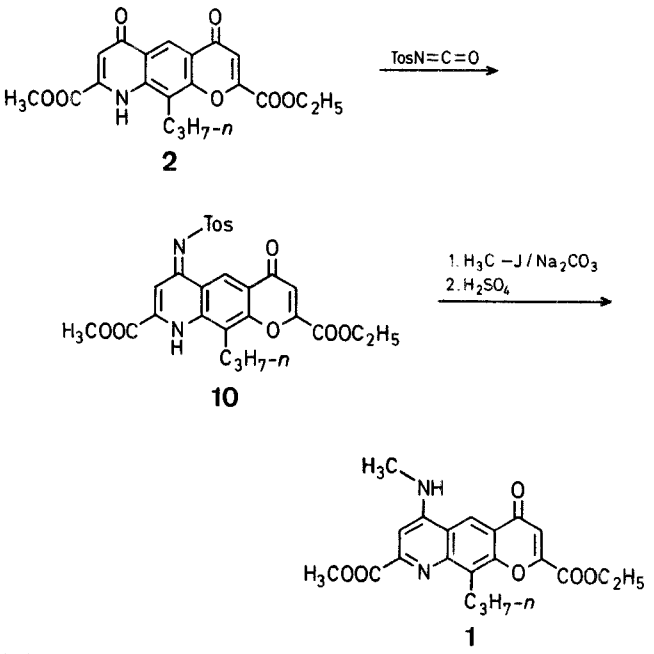
4a-g **7a-g**

4,7	R^1	R^2	R^3	R^4
a	H	CH_3	H	H
b	H	C_2H_5		8-Cl
c	H	C_2H_5	n-C_3H_7	8-CH_3
d	H	C_2H_5	H	5,8-di-H_3CO
e	H	C_2H_5	H	7-H_3CO
f	H	C_2H_5	H	6-H_3CO
g	CH_3	CH_3	H	H



5a-c **6** **8** X = Cl–⟨⟩–O–SO_2– **8** X = Cl_3C–C(=O)–

This new synthetic transformation was applied to an efficient synthesis of the methylaminopyranoquinoline derivative **1**, in which the dihydrooxoquinoline **2** was reacted with 4-toluenesulphonyl isocyanate to give the tosylimino derivative **10** in 82% yield. Alkylation (methyl iodide/sodium carbonate) yielded the corresponding *N*-methyl-*N*-tosyl derivative (98% yield) which was readily detosylated with sulphuric acid to give the diester of minocromil (**1**; 95% yield; Scheme **B**)[4].



2 **10** **1**

Scheme **B**

In preliminary experiments, we have successfully converted 9(10*H*)-acridanone derivatives to the corresponding 9-aminoacridine in high yield, using Method A. These transformations represent a further development of the synthetic uses of reactive isocyanates. Previously the reactions of isocyanates with tertiary amides to yield amidines have been reported[5].

Table 2. Compounds **7a–g**, **8**, and **9** prepared

Product	Reaction Conditions Time/Solvent	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. *m/e* (M^+; base)
7a	6 h/CH_3CN	76	241–242°	$C_{18}H_{16}N_2O_4S$ (356.3)	3280, 1610, 1585	2.38 (s, 3H); 4.08 (s, 3H); 7.31 (d, 2H, J = 8.5 Hz); 7.89 (d, 2H, J = 8.5 Hz); 7.4–8.2 (m, 3H); 8.02 (s, 1H); 8.48 (d, 1H, J = 8.0 Hz)	356; 298
7b	16 h/$ClCH_2CH_2Cl$	82	175–177°	$C_{25}H_{21}ClN_2O_4S$ (481.0)	3260, 1600, 1580	0.91 (t, 3H, J = 7.5 Hz); 2.42 (s, 3H); 4.01 (q, 2H, J = 7.5 Hz); 6.7–7.5 (m, 10H); 7.58 (d, 1H, J = 8.0 Hz); 7.02 (d, 1H, J = 8.0 Hz); 8.46 (d, 1H, J = 8.0 Hz)	482; 253
7c	20 h/$ClCH_2CH_2Cl$	75	129–130°	$C_{23}H_{26}N_2O_4S$ (426.5)	3280, 1600, 1585	0.83 (t, 3H, J = 7.5 Hz); 1.42 (t, 3H, J = 7.5 Hz); 2.40 (s, 3H); 2.3–2.6 (m, 2H); 2.71 (t, 2H, J = 7.5 Hz); 2.79 (s, 3H); 4.45 (q, 2H, J = 7.5 Hz); 6.80 (br. s, 1H, exchanges with D_2O); 7.1–7.8 (m, 7H)	426; 197
7d	1 h/$ClCH_2CH_2Cl$[b]	92	168–169°	$C_{21}H_{22}N_2O_6S$ (430.5)	3260, 1615, 1600	1.47 (t, 3H, J = 7.2 Hz); 2.36 (s, 3H); 3.99 (s, 3H); 4.06 (t, 3H, J = 7.2 Hz); 6.92 (s, 2H); 7.27 (d, 2H, J = 8.2 Hz); 7.91 (d, 2H, J = 8.2 Hz); 8.18 (s, 1H); 10.53 (br. s, 1H)	430; 401
7e	1 h/$ClCH_2CH_2Cl$	76	172–174°	$C_{20}H_{20}N_2O_5S$ (400.5)	3240, 1620, 1600	1.42 (t, 3H, J = 7.4 Hz); 2.40 (s, 3H); 3.87 (s, 3H); 4.41 (q, 2H, J = 7.4 Hz); 6.91 (dd, 1H, J = 8.2 Hz, 1.7 Hz); 7.08 (d, 1H, J = 1.7 Hz); 7.24 (d, 2H, J = 8.0 Hz); 7.86 (s, 1H); 7.96 (d, 2H, J = 8.0 Hz); 8.18 (d, 1H, J = 8.2 Hz)	400; 328
7f	18 h/$ClCH_2CH_2Cl$	65	212–215°	$C_{20}H_{20}N_2O_4S$ (384.5)	3240, 1605, 1595	1.42 (t, 3H, J = 7.3 Hz); 2.37 (s, 3H); 2.48 (s, 3H); 4.47 (q, 2H, J = 7.3 Hz); 7.21 (d, 2H, J = 8.0 Hz); 7.48 (d, 2H, J = 8.2 Hz); 7.88 (d, 1H, J = 8.2 Hz); 7.92 (d, 2H, J = 8.0 Hz); 7.97 (s, 1H); 8.31 (s, 1H)	384; 312
7g	24 h/$ClCH_2CH_2Cl$[b]	70	191–193°	$C_{19}H_{18}N_2O_4S$ (370.4)	1600, 1545	2.31 (s, 3H); 3.80 (s, 3H); 3.95 (s, 3H); 7.26 (d, 2H, J = 8.0 Hz); 7.3–7.7 (m, 3H); 7.99 (s, 1H), 7.91 (d, 2H, J = 8.0 Hz); 8.51 (d, 1H, J = 8.2 Hz)	370; 306
8	1 h/CH_3CN	84	185°[c]	$C_{17}H_{13}ClN_2O_5S$ (392.8)	3275, 1610, 1595	2.40 (s, 3H); 7.25 (d, 2H, J = 7.5 Hz); 7.47 (d, 2H, J = 7.5 Hz); 7.4–8.5 (m, 5H); 7.90 (s, 1H)	383; 128
9	1 h/CH_3CN	76	91–93°	$C_{13}H_9Cl_3N_2O_3$[c] (347.6)	3300 (br.), 1560, 1530	4.10 (s, 3H); 7.7–8.0 (m, 3H); 8.38 (d, 1H, J = 8.3 Hz); 8.82 (s, 1H); 9.38 (br. s, 1H)	–

[a] Satisfactory microanalyses obtained: C ±0.35, H ±0.26, N ±0.33.
[b] Reaction at room temperature.
[c] Recrystallised product contains 1 mol of ethanol of crystallisation.

Ethyl (or Methyl) 4-Aminoquinoline-2-carboxylates 5a–c, 6; General Procedure for Method A:

Chlorosulphonyl isocyanate (0.001 mol) is added to a solution of **4a–c**, (0.001 mol) in acetonitrile or dichloroethane (5 ml) at room temperature. The resulting mixture is heated at reflux until the evolution of carbon dioxide ceases. A solution of hydrogen chloride in ethanol (or methanol) (5 ml), is then added, and the whole cooled to room temperature. Evaporation and crystallisation from ethanol/ethyl acetate (**5c**) or methanol (**6**) gives the salt of the aminoquinoline. This salt is dissolved in water (50 ml), neutralised with sodium carbonate solution (8%, 10 ml), and extracted with ethyl acetate (2 × 25 ml). The organic extracts are combined, dried, and evaporated, to give the quinoline, which is then purified by crystallisation from methanol (**5a**) or ethyl acetate/petroleum ether (b.p. 40–60°C) 1:1 (**5b**).

General Procedure for Method B:
The reaction is carried out as described in Method A, except that *p*-chlorophenoxysulphonyl isocyanate (0.001 mol) is added in place of the chlorosulphonyl isocyanate, in the conversion of **4a–c** to **5a–c**.

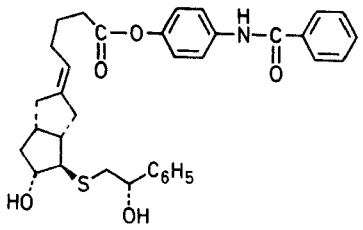
Ethyl (or Methyl) 4-(4-Tosylimino)-(or Trichloroacetylimino- or 4-Chlorophenoxysulphonylimino)-1,4-dihydroquinoline-2-carboxylates; 7a–g, 8, 9; General Procedure for Method C:
4-Toluenesulphonyl isocyanate **(7a–g)** or 4-chlorophenoxysulphonyl isocyanate **(8a)** or trichloroacetyl isocyanate **(9a)**, (0.001 mol) is added to **4a–g**, (0.001 mol) in acetonitrile or dichloromethane (5 ml) at room temperature. The resulting mixture is heated at reflux until the evolution of carbon dioxide ceases. Cooling, and evaporation of the solvent gives the pure quinoline. A single recrystallisation from ether **(7a, 8)**, ethanol **(7b, 7d–g, 9)** or ether/petroleum ether (b.p. 40–60 °C) **(7c)** gives analytically pure samples.

Received: April 16, 1984

[1] G. Jones, Ed., *The Chemistry of Heterocyclic Compounds*, Vol. 32, part 1, *Quinolines*, John Wiley & Sons, London, 1977.
[2] G. Lohaus, *Chem. Ber.* **105**, 2791 (1970).
[3] S.C.W. Coltman, S.C. Eyley, R.A. Raphael, *Synthesis* **1984**, 150.
[4] R.G. McR. Wright, *European Patent Application* 0077090, Fisions plc (1983); *C.A.* **99**, 70698 (1983).
[5] C. King, *J. Org. Chem.* **25** 352 (1960).

R.F. Newton, S.M. Roberts, R.J.K. Taylor, *Synthesis* **1984** (6), 449–478:

The structure of compound **305** (p. 475) should be:



305 (EMD 46335)

H. Sard, R.P. Duffley, L.R. Robertson, R.K. Razdan, *Synthesis* **1984** (6), 506–509:

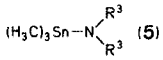
The fourth sentence in the paragraph above Scheme **A** (p. 507) should read:
This racemic compound could be preferentially enriched by a single recrystallization from ethanol as the (−)-dibenzoyl-L-tartrate salt **5a** (96% yield).

C.K. Ghosh, N. Tewari, A. Bhattacharya, *Synthesis* **1984** (7), 614–615:

Compounds **2a–d** should be named as 3-ethoxy-10-oxo-4,4a-dihydro-3*H*,10*H*-pyrano[4,3-*b*][1]benzopyrans.

Abstract 6925, *Synthesis* **1984** (7), 624:

The structure of reagent **5** should be:



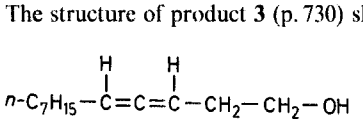
5

M. Sato, N. Katsumata, S. Ebine, *Synthesis* **1984** (8), 685:

The title compound should be named 4,5-Dihydrobenzocyclobutene-4,5-dione.

R.E. Doolittle, *Synthesis* **1984** (9), 730–732:

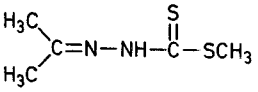
The structure of product **3** (p. 730) should be:



3

Y. Nakayama, Y. Sanemitsu, *Synthesis* **1984** (9), 771–772:

The structure of compound **6** (p. 772) should be:



6

I. Reichelt, H.-U. Reissig, *Synthesis* **1984** (9), 786–787:

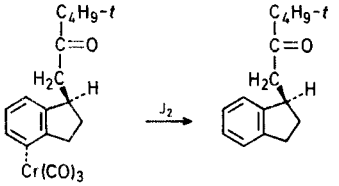
The title compounds **2** should be named as 3-oxo-2,3,4,5-tetrahydropyridazines

M. Tirant, T.D. Smith, *Synthesis* **1984** (10), 833–834

The names for products **2a** and **3a** should be bis[2-hydroxybenzylidenehydrazino] sulfide and 2-hydroxyethyl 2-hydroxybenzylidenehydrazino sulfide, respectively.

Abstract 6971, *Synthesis* **1984** (10), 892:

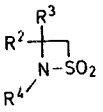
The structures of products **4** and **5** should be:



4 **5**

Abstract 6976, *Synthesis* **1984** (10), 894:

The structure of product **8** should be:



8

E.A. Mistryukov, I.K. Korshevetz, *Synthesis* **1984** (11), 947–949:

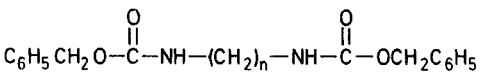
Compound **10** should be named as 1-(1-cyclohexenyl)-3-diethylaminopropyne.

Z. Arnold, V. Kral, G.V. Kryshtal, L.A. Yanovskaya, *Synthesis* **1984** (11), 974–976:

The title compounds **5** should be named as 3-substituted 2,2-diethoxycarbonyl-4-formyl-2,3-dihydrofurans.

G.J. Atwell, W.A. Denny, *Synthesis* **1984** (12), 1032–1033:

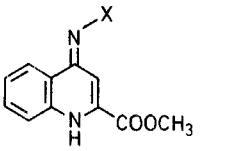
The structure of products **4a–f** (p. 1032) should be:



4a-f

R.G. McR. Wright, *Synthesis* **1984** (12), 1058–1061:

Formula **8** should be replaced by:



8 X = Cl–C6H4–O–SO2–

9 X = Cl3C–C(=O)–