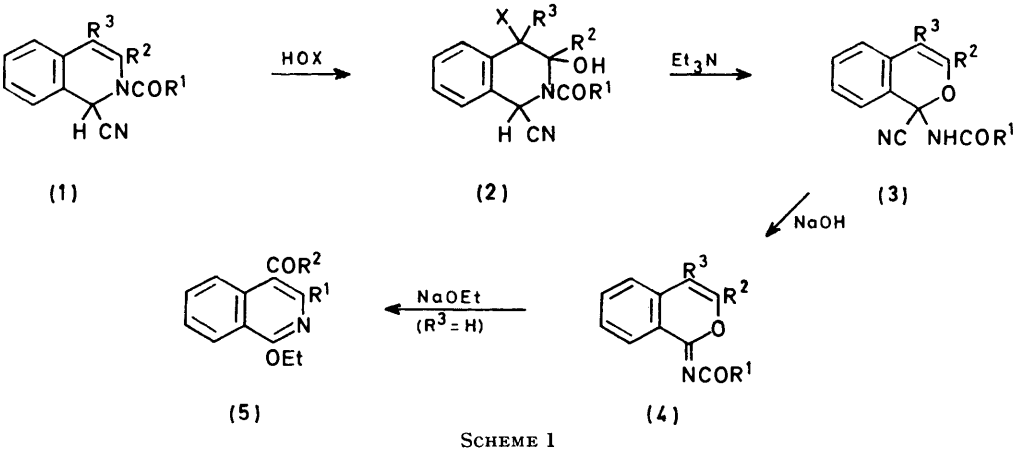
Halohydrins of Isoquinoline Reissert Compounds: Base-induced Rearrangement Reactions providing Isochromenes and New Isoquinolines

By **Gordon W. Kirby** * and **John W. M. Mackinnon**, Department of Chemistry, University of Glasgow, Glasgow G12 8QQ
Stewart Elliott and **Barrie C. Uff**,* Department of Chemistry University of Technology, Loughborough, Leicestershire LE11 3TU

Various 3- or 4-methyl and unsubstituted 2-acyl-1-cyano-1,2-dihydroisoquinolines (Reissert compounds) have been converted into the corresponding chloro- or bromo-hydrins by treatment with aqueous hypochlorous acid or aqueous 1,3-dibromo-5,5-dimethylhydantoin, respectively. These 4-halo-3-hydroxy-derivatives were generally convertible with base into the corresponding 1-acyliminoisochromenes and thence into the related isocoumarins. The chlorohydrin of 2-acetyl-1-cyano-1,2-dihydroisoquinoline was transformed by sodium ethoxide into 1-ethoxy-4-formyl-3-methylisoquinoline, in the expected manner. However, the bromohydrin of 2-benzoyl-1-cyano-1,2-dihydro-3-methylisoquinoline, which exists as the tautomeric bromoketone, gave, as the major product, 4-benzoyl-1-ethoxy-3-methylisoquinoline rather than 4-acetyl-1-ethoxy-3-phenylisoquinoline. The mechanism of this new rearrangement is discussed.

THE Reissert derivative (1; R^1 = Ph, R^2 = R^3 = H) of isoquinoline forms a chlorohydrin (2; R^1 = Ph, R^2 = R^3 = H, X = Cl) convertible sequentially with base into the correspondingly substituted compounds (3), (4), and (5) (Scheme 1).[1] We have extended our studies to other Reissert compounds and have discovered, using (1; R^1 = Ph, R^2 = Me, R^3 = H),[2] a new rearrangement which occurs during the formation of the ethoxyisoquinoline system.



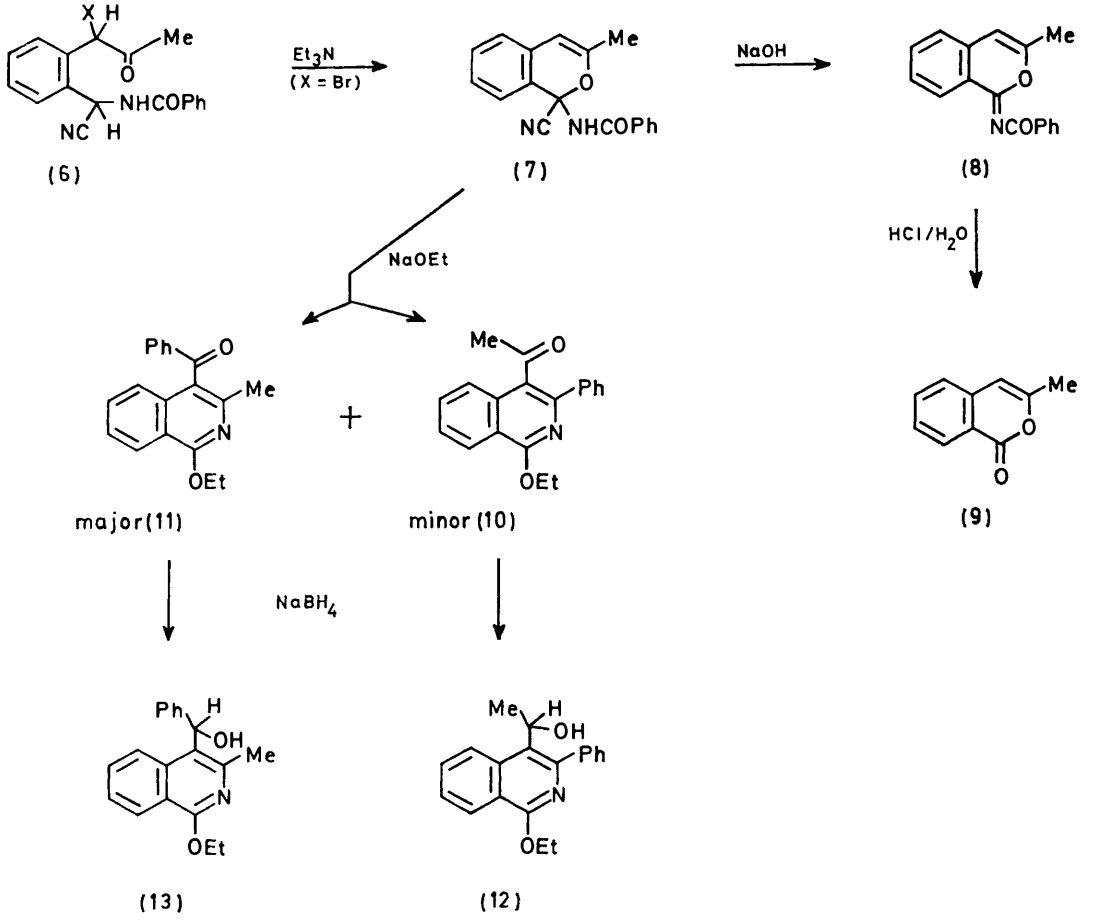
SCHEME 1

Treatment of (1; R^1 = Ph, R^2 = Me, R^3 = H) with hypochlorous acid gave the chloroketone (6; X = Cl) rather than the tautomeric chlorohydrin (2; R^1 = Ph, R^2 = Me, R^3 = H, X = Cl). The product (6; X = Cl) showed i.r. absorption, $\nu_{max.}$(KBr) 1 728 cm^{-1}, for a ketonic carbonyl group and at 1 650 cm^{-1} (amide carbonyl) and n.m.r. signals, for freshly made solutions, at τ[$(CD_3)_2SO$] 0.13 (d, *J* 7 Hz, NH, disappeared on addition of D_2O), 3.31 (d, *J* 7 Hz, CH, collapsed to a singlet on addition of D_2O), 3.70 (s, CH), and 7.85 (s, Me), indicating a ring-opened structure. However, the n.m.r. spectrum changed with time. A new set of signals, τ[$(CD_3)_2SO$] 0.24 (d, *J* 7 Hz, disappeared on addition of D_2O), 3.26 (d, *J* 7 Hz, collapsed to a singlet on addition of D_2O), 3.85 (s), and 7.78 (s), gradually appeared and, after 24 h, attained an intensity approximately equal to that of the original set. This apparent isomerisation did not involve exchange of hydrogen α to either the cyano- or keto-groups since no replacement of CH by CD was observed when (6; X = Cl) was kept in $(CD_3)_2SO$ containing D_2O. The n.m.r. changes may provisionally be attributed to either interconversion of amide rotamers or reversible elimination of hydrogen cyanide with consequent epimerisation of the chiral centre α to the cyano-group. Unfortunately, the preparation of (6; X = Cl) proved to be irreproducible and further investigation was abandoned. Instead (1; R^1 = Ph, R^2 = Me, R^3 = H) was treated in aqueous dioxan with 1,3-dibromo-5,5-dimethylhydantoin [3] to afford, consistently, the bromoketone (6; X = Br), $\nu_{max.}$ 1 719 cm^{-1}. This product formed well-defined crystals, but the n.m.r. spectra of even freshly prepared solutions showed two sets of closely-spaced signals. It appears likely that the bromoketone exists in a single stereochemical form in the crystalline state but forms a mixture of stereoisomers in solution more quickly than does the chloroketone (6; X = Cl).

Treatment of (6; X = Br) with triethylamine in dioxan gave, as expected,[1] the isochromene (2-benzo-

pyran) (7) which was converted by sodium hydroxide into (8). The structure of (8) was confirmed by hydrolysis with dilute hydrochloric acid to yield the known [4] 3-methylisocoumarin (9) (Scheme 2). Treatment of (7) with ethanolic sodium hydroxide, under the usual conditions,[1] gave an oily, ketonic product which was judged initially, from its spectroscopic properties, to be the expected [1] methyl ketone (10) (*cf.* Schemes 1 and 2). However, this product did not crystallise and its n.m.r. spectrum consistently showed a weak signal (τ 7.93, s) attributable to an impurity which was not removed by chromatography. Further, reduction of the impure ketone with sodium borohydride gave, as the major product, a crystalline alcohol which clearly did not have the expected structure (12). The n.m.r. spectrum of this alcohol showed a singlet (τ 7.51), rather than a doublet, for the methyl protons and, after exchange with D_2O, a singlet (τ 3.59) rather than a quartet for the methine (-CHOD) proton. The alternative structure (13) for this alcohol was therefore considered and then established by the following unambiguous syntheses of each of the two isomers (12) and (13).

The isomer (12) was readily obtained by reaction of the aldehyde (5; R^1 = Ph, R^2 = H) with methylmagnesium iodide. The n.m.r. spectrum of (12) showed, *inter alia*, a doublet, τ 8.31 (J 6.5 Hz), for the methyl protons and a corresponding quartet, τ 4.65, for the methine (-C*H*-OH) proton. The synthesis of (13) employed the Reissert compound (1; R^1 = Me, R^2 = R^3 = H) as starting material. Formation of the chlorohydrin (2; R^1 = Me, R^2 = R^3 = H, X = Cl) occurred under the usual conditions as did its conversion into (3; R^1 = Me, R^2 = R^3 = H), 1-acetylimino-3,4-dihydro-3-hydroxy-1*H*-2-benzopyran,* and (5; R^1 = Me, R^2 = H). The structure of the aldehyde (5; R^1 = Me, R^2 =



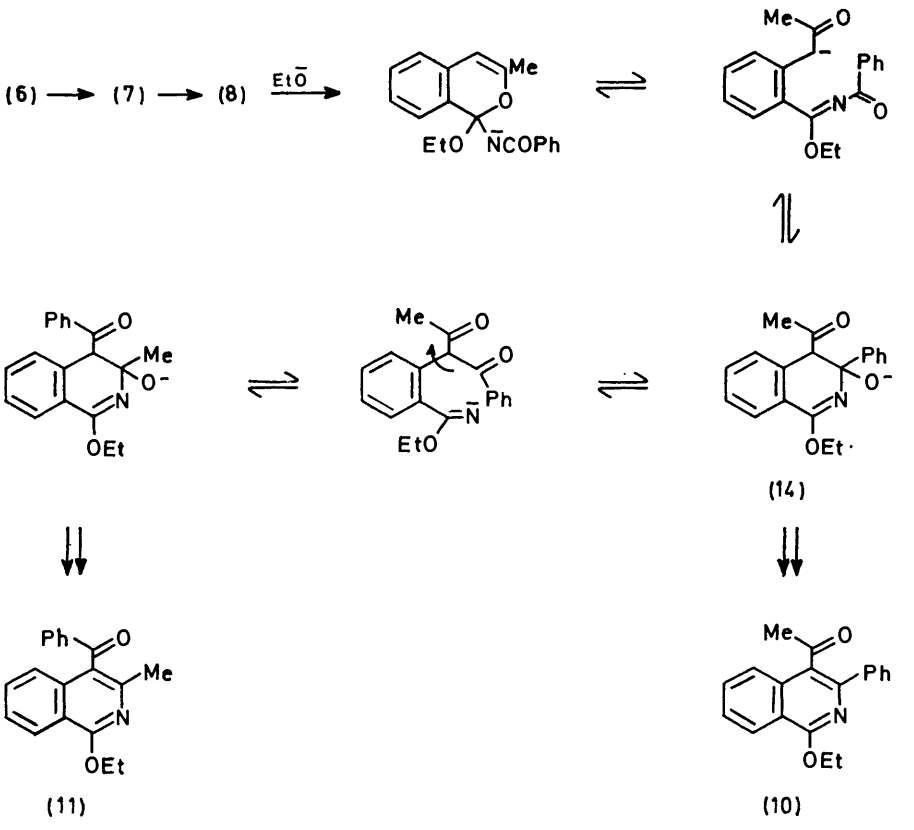
SCHEME 2

H) was confirmed by its decarbonylation with palladium–charcoal to yield 1-ethoxy-3-methylisoquinoline, which was hydrolysed to the known,[5] crystalline 3-methylisocarbostyril. Treatment of (5; R^1 = Me, R^2 = H) with phenylmagnesium bromide gave (13) which was identical in all respects with the major product obtained (Scheme 2) by borohydride reduction of the impure ketone.

It appeared, therefore, that the reaction of (7) with sodium ethoxide had taken place with rearrangement to give the ketone (11) as the major product. Also it

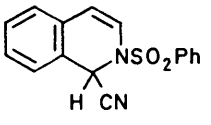
* Treatment of (3; R^1 = Me, R^2 = R^3 = H) with sodium hydroxide did not yield the expected [*cf.* (4)] isochromene. Instead a hydrated derivative was isolated and tentatively formulated as 1-acetylimino-3,4-dihydro-3-hydroxy-1*H*-2-benzopyran; the alternative tautomeric structure, 2-acetyl-3-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline, is not excluded.

seemed likely that the minor product, detected by n.m.r. spectroscopy, was the isomeric ketone (10). This view was supported by the following observations. Reduction of the impure ketone with sodium borohydride and separation of the products by layer chromatography gave (13) and (12) in the ratio *ca.* 5 : 1. Further, the n.m.r. spectrum of the impure ketone corresponded with that expected for a mixture (*ca.* 7 : 1) of the isomers (11) and (10); reference samples of each ketone were prepared by oxidation of (13) and (12) with chromium trioxide–pyridine in dichloromethane. A possible mechanism for the formation of the ketones (10) and (11) is outlined in Scheme 3. The route to (10) parallels that proposed before [1] for the parent halohydrin (2; R^1 = Ph, R^2 = R^3 = H, X = Cl), while the formation of (11) is attributed to ring opening of the intermediate (14) followed by closure in the alternative sense.

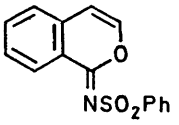


SCHEME 3

The analogous reactions of other Reissert compounds were briefly studied. Particular attention was paid to the formation of halohydrins since these polyfunctional derivatives are potentially valuable for the elaboration of a variety of heterocyclic systems. The derivative (1; R^1 = Ph, R^2 = H, R^3 = Me) of 4-methylisoquinoline formed a bromohydrin (2; R^1 = Ph, R^2 = H, R^3 = Me, X = Br) under the usual conditions. This was converted *via* (4; R^1 = Ph, R^2 = H, R^3 = Me) into 4-methylisocoumarin. Similarly, a chlorohydrin (2; R^1 = EtO, R^2 = R^3 = H, X = Cl) was obtained from the corresponding Reissert compound and converted into the isochromene (4; R^1 = EtO, R^2 = R^3 = H). Finally, treatment of the sulphonyl derivative (15) [6] with hypochlorous acid and chromatography of the crude reaction mixture on alumina gave directly the isochromene (16)



(15)



(16)

EXPERIMENTAL

N.m.r. spectra were measured, unless otherwise stated, for solutions in deuteriochloroform with tetramethylsilane as internal standard. Infrared spectra were run with potassium bromide discs. M.p.s were determined with a Kofler hot-stage apparatus.

Reactions of 2-Benzoyl-1-cyano-1,2-dihydro-3-methylisoquinoline (1; R^1 = Ph, R^2 = Me, R^3 = H).—*With hypochlorous acid.* Aqueous hypochlorous acid was prepared as described earlier.[1] The Reissert compound (1; R^1 = Ph, R^2 = Me, R^3 = H) [2] (2.74 g) in dioxan (20 ml) was treated with aqueous hypochlorous acid (102 ml, 1.1 mol equiv.) dropwise with stirring at room temperature. The solid which separated was collected, washed with water and a small volume of ethanol, and crystallised from methanol to yield *2-benzoylamino-2-[2-(1-chloro-2-oxopropyl)phenyl]-acetonitrile*, m.p. 148—150° (6; X = Cl) (1.21 g) (Found: C, 66.3; H, 4.6; N, 8.6. $C_{18}H_{15}ClN_2O_2$ requires C, 66.2;

H, 4.6; N, 8.6%) (spectra are discussed in the main text). In later preparations the product separated in an oily state and decomposed upon attempted purification. The use of *N*-chlorosuccinimide in aqueous dioxan was similarly unsuccessful.

With 1,3-dibromo-5,5-dimethylhydantoin. The Reissert compound [2] (1.0 g) in 50% aqueous dioxan (20 ml) was treated portionwise with 1,3-dibromo-5,5-dimethylhydantoin [3] (0.34 g, 0.5 mol equiv.) with stirring at room temperature. The precipitate was collected, washed with water, and crystallised from methanol to give *2-benzoylamino-2-[2-(1-bromo-2-oxopropyl)phenyl]acetonitrile* (6; X = Br) (0.84 g), m.p. 153—154° (decomp.) (Found: C, 58.0; H, 4.1; N, 7.6. $C_{18}H_{15}BrN_2O_2$ requires C, 58.2; H, 4.1; N, 7.55%), $\nu_{max.}$ 3 295, 1 719, and 1 655 cm^{-1}; τ[$(CD_3)_2CO$] 1.1 (br s, NH), 3.12 (*ca.* 0.5 H, d, *J* 8 Hz), 3.27 (*ca.* 0.5 H, d, *J* 7 Hz), 3.71 (*ca.* 0.5 H, s), 3.88 (*ca.* 0.5 H, s), 7.61 (*ca.* 1.5 H, s), and 7.74 (*ca.* 1.5 H, s) (upon addition of D_2O the NH signal disappeared and the 2 doublets collapsed to singlets).

Formation of the Isochromenes (7) *and* (8).—The foregoing bromoketone (6; X = Br) (371 mg) in dry dioxan (20 ml) was treated dropwise with triethylamine (1 mol equiv.) at room temperature. The mixture turned purple and a precipitate of triethylammonium bromide appeared. After 3 h, the mixture was filtered and the filtrate evaporated. The residue was chromatographed on silica plates (benzene–ethyl acetate 8 : 2) to give *1-benzoylamino-1-cyano-3-methyl-1H-2-benzopyran* (7) (141 mg), m.p. 133—135° (from ether) (Found: 74.4; H, 4.8; N, 9.6. $C_{18}H_{14}N_2O_2$ requires C, 74.5; H, 4.9; N, 9.7%), $\nu_{max.}$ 3 225 and 1 670 cm^{-1}, *m/e* 290; τ 1.51 (s, NH, exchangeable with D_2O), 2.0—3.0 (m, aryl), 4.15 (q, *J* 1 Hz, 4-H), and 8.05 (d, *J* 1 Hz, Me), and *1-benzoylimino-3-methyl-1H-2-benzopyran* (8) (26 mg), m.p. 119—121° (from ether) (Found: C, 77.6; H, 4.8; N, 5.3. $C_{17}H_{13}NO_2$ requires C, 77.55; H, 5.0; N, 5.3%), $\nu_{max.}$ 1 689, 1 673, and 1 625 cm^{-1}; *m/e* 263; τ 1.5—2.7 (m, aryl), 3.90 (q, *J* 1 Hz, 4-H), and 7.95 (d, *J* 1 Hz, Me).

Treatment of (7) in dioxan with aqueous sodium hydroxide (1 mol equiv.), as before,[1] gave (8) in near quantitative yield. Hydrolysis of (8) with dilute hydrochloric acid afforded 3-methylisocoumarin (9), m.p. 72—74° (lit.,[4] 73—74°), quantitatively together with benzamide.

Reaction of the Isochromene (7) *with Sodium Ethoxide.*—The isochromene (7) (500 mg) in ethanol (100 ml) was treated with sodium hydroxide (200 mg), in a little water, dropwise at room temperature. The mixture was stirred for 3 h and then evaporated. The residue was dissolved in chloroform, dried ($MgSO_4$), and chromatographed on silica plates (benzene–ethyl acetate 8 : 2). The mixture of ketones (10) and (11) was obtained as an oil (Found: *m/e*, 291.125 6. $C_{19}H_{17}NO_2$ requires *M*, 291.125 9), $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1}; τ 1.70 (1 H, m), 2.12 (2 H, m), 2.5 (6 H, m), 5.36 (2 H, q, *J* 7 Hz), 7.60 (3 H, s), and 8.44 (3 H, t, *J* 7 Hz), together with a weak (*ca.* 3/7 H) singlet at τ 7.93. Essentially the same mixture was obtained when the crude product from the reaction of the bromoketone (6; X = Br) with triethylamine (see above) was treated with ethanolic sodium hydroxide.

Reduction of the Ketonic Mixture [(10) + (11)] *with Sodium Borohydride.*—The foregoing mixture (60 mg) in methanol (20 ml) was treated with sodium borohydride (40 mg) at room temperature for one week. The chloroform-soluble products were separated on silica plates (chloroform–ethyl acetate 1 : 1). The alcohols (13) (32 mg) and (12) (6 mg) were identified by comparison with samples prepared as described below.

Preparation of 1-Ethoxy-4-(1-hydroxyethyl)-3-phenylisoquinoline (12) *from* (5; R^1 = Ph, R^2 = H).—The aldehyde (5.9 g) in ether (400 ml) was added to methylmagnesium iodide [prepared from methyl iodide (3.75 g)] in ether (200 ml). The mixture was left overnight at room temperature and worked-up in the usual way. The *isoquinoline* (12) (3.29 g) had m.p. 125—126° (EtOAc) (Found: C, 77.8; H, 6.6; N, 4.75. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.5; N, 4.8%), $\nu_{max.}$ 3 420 cm^{-1}; τ 1.33 (1 H, m), 1.66 (1 H, m), *ca.* 2.5 (7 H, m), 4.65 (1 H, q, *J* 6 Hz), 5.55 (2 H, q, *J* 7 Hz), 7.98 (1 H, br s, exchangeable with D_2O), 8.31 (3 H, d, *J* 6.5 Hz), and 8.57 (3 H, t, *J* 7 Hz).

Oxidation of (12) (60 mg) in dichloromethane (200 ml) by dropwise addition of the reagent [7] prepared from chromium trioxide (51 mg) and pyridine (81 mg) in dichloromethane (15 ml) for 20 min at room temperature gave the ketone (10) which, after chromatography on silica plates, afforded crystals of (10), m.p. 84—85° (EtOAc) (Found: *m/e*, 291.126 8. $C_{19}H_{17}NO_2$ requires *M*, 291.1 259), $\nu_{max.}$ 1 675 cm^{-1}; τ 1.6—2.7 (9 H, m), 5.32 (2 H, q, *J* 7 Hz), 7.91 (3 H, s), and 8.45 (3 H, t, *J* 7 Hz). Reduction of this ketone with sodium borohydride in methanol regenerated the alcohol (12).

2-Acetyl-4-chloro-1-cyano-1,2,3,4-tetrahydro-3-hydroxyisoquinoline (2; R^1 = Me, R^2 = R^3 = H, X = Cl).—The Reissert compound (1; R^1 = Me, R^2 = R^3 = H) (2.3 g), in dioxan (25 ml) was treated with aqueous hypochlorous acid (82 ml, 1.2 mol equiv.) as above to yield the *chlorohydrin* (2; R^1 = Me, R^2 = R^3 = H, X = Cl) (1.52 g), m.p. 182—183° (EtOAc) (Found: C, 57.2; H, 4.25; N, 11.2. $C_{12}H_{11}ClN_2O_2$ requires C, 57.5; H, 4.4; N, 11.2%), $\nu_{max.}$ 3 220 and 1 630 cm^{-1}; τ[$(CD_3)_2SO$] 2.2—2.6 (m, aryl), 3.91 (s, 1-H), 4.10 [t, *J* 3.5 Hz, 3-H (d after D_2O exchange)], 4.60 (d, *J* 3.5 Hz, 4-H), and 7.65 (s, Me).

1-Acetylamino-1-cyano-1H-2-benzopyran (3; R^1 = Me, R^2 = R^3 = H).—The foregoing chlorohydrin (250 mg) in dioxan was treated with 10% aqueous sodium hydroxide (1 mol equiv.) in the usual way.[1] The product mixture was separated on silica plates developed with benzene–ethyl acetate (8 : 2). The *isochromene* (3; R^1 = Me, R^2 = R^3 = H) (83 mg) had m.p. 140—142° (from EtOH) (Found: C, 67.1; H, 4.6; N, 13.1. $C_{12}H_{10}N_2O_3$ requires C, 67.3; H, 4.8; N, 13.1%), τ[$(CD_3)_2SO$] 0.25 (s, NH, exchangeable with D_2O), 2.3—2.7 (m, aryl), 3.19 (d, *J* 6 Hz, 3-H), 3.73 (d, *J* 6 Hz, 4-H), and 8.00 (s, Me).

1-Acetylimino-3,4-dihydro-3-hydroxy-1H-2-benzopyran.—The foregoing isochromene (16) (107 mg) in dioxan (20 ml) was treated with 10% aqueous sodium hydroxide (1 mol equiv.) with stirring at room temperature for 1 h. The chloroform-soluble products were separated on alumina plates (benzene–ethyl acetate 8 : 2) to afford the *isochromene* (see footnote in main text for a comment on the structure) (80 mg), m.p. 151—153° (from EtOAc) (Found: C, 64.6; H, 5.6; N, 6.6. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.8%), $\nu_{max.}$ 3 500 and 1 690 cm^{-1}; τ 1.7—2.8 (m, aryl), 3.75 [m, 3-H (t, *J* 3 Hz, after D_2O exchange)], 6.16 (br s, OH, exchangeable with D_2O), 6.85 (d, *J* 3 Hz, CH_2), and 7.38 (s, Me); *m/e* 205

1-Ethoxy-3-methylisoquinoline-4-carbaldehyde (5; R^1 = Me, R^2 = H).—The chlorohydrin (2; R^1 = Me, R^2 = R^3 = H, X = Cl) (750 mg) in ethanol (100 ml) was treated with 10% aqueous sodium hydroxide (2.7 mol equiv.) dropwise with stirring at room temperature. The deep red

solution was stirred for 3 h then evaporated. The chloroform-soluble products were separated either on silica plates (benzene–ethyl acetate 8 : 2) or on a grade III, neutral alumina column (benzene). The *aldehyde* (5; R^1 = Me, R^2 = H) (350 mg) had m.p. 97—97.5° (from EtOH) (Found: C, 72.6; H, 6.1; N, 6.4. $C_{13}H_{13}NO_2$ requires C, 72.5; H, 6.1; N, 6.5%), $\nu_{max.}$ 1 675 cm^{-1}; τ −0.70 (s, CHO), 0.95 (br d, *J* 8 Hz, 5-H), 1.82 (d with fine splitting, *J* 8 Hz, 8-H), 2.2—2.7 (m, aryl), 5.42 (q, *J* 7 Hz, CH_2), 7.20 (s, Me), and 8.52 (t, *J* 7 Hz, Me); *m/e* 215.

Degradation of the Aldehyde (5; R^1 = Me, R^2 = H).—The aldehyde (50 mg) was heated with 5% palladium–carbon (50 mg) at 200—220° for 2 h. The cooled mixture was shaken with chloroform and the solution was filtered and evaporated. Chromatography on silica plates (benzene–ethyl acetate, 9 : 1) gave 1-ethoxy-3-methylisoquinoline as a viscous oil (16 mg); τ 1.79 (br d, *J* 8 Hz, 8-H), 2.2—2.8 (m, aryl), 3.02 (br s, 4-H), 5.43 (q, *J* 7 Hz, CH_2), 7.49 (s, Me), and 8.52 (t, *J* 7 Hz, Me). This oil was heated under reflux with concentrated hydrochloric acid for 30 min to afford 3-methylisocarbostyril, m.p. 211—212.5° [from light petroleum (b.p. 60—80°)] (lit.,[8] m.p. 214°), identical with material prepared by the method of Robison and Robison.[5]

Preparation of 1-*Ethoxy*-4-(α-*hydroxybenzyl*)-3-*methylisoquinoline* (13) *from* (5; R^1 = Me, R^2 = H).—The aldehyde (450 mg) in ether (50 ml) was added slowly to phenylmagnesium bromide [prepared from bromobenzene (470 mg)] in ether (50 ml) and the mixture was left at room temperature for 24 h. Usual work-up gave the *alcohol* (13) (260 mg), m.p. 123—124° (from EtOAc) (Found: C, 78.1; H, 6.6; N, 4.8. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.5; N, 4.8%) (Found: *m/e*, 293.141 7. $C_{19}H_{19}NO_2$ requires *M*, 293.141 6), $\nu_{max.}$ 3 400 cm^{-1}; τ 1.85 (1 H, m), 2.14 (1 H, m), 2.5—2.9 (m, aryl), 3.59 (br d, *J* 2.5 Hz, CHOH, collapsing to singlet after D_2O exchange), 5.49 (q, *J* 7 Hz, CH_2), 7.09 (d, *J* 2.5 Hz, OH, exchangeable with D_2O), 7.51 (s, Me), and 8.52 (t, *J* 7 Hz, Me).

Treatment of this alcohol (60 mg) in dichloromethane (200 ml) with the reagent[7] prepared from chromium trioxide (102 mg) and pyridine (162 mg) in dichloromethane for 30 min at room temperature gave the ketone (11) (46 mg), m.p. 68—71°, $\nu_{max.}$ 1 665 cm^{-1}; τ 1.70 (1 H, m), 2.12 (2 H, m), *ca.* 2.5 (6 H, m), 5.36 (2 H, q, *J* 7 Hz), 7.60 (3 H, s), and 8.44 (3 H, t, *J* 7 Hz).

2-*Benzoyl*-1-*cyano*-1,2-*dihydro*-4-*methylisoquinoline* (1; R^1 = Ph, R^2 = H, R^3 = Me).—4-Methylisoquinoline[5] (6.2 g) was treated with benzoyl chloride (12 ml) and potassium cyanide (12 g) in dichloromethane–water (two-phase system) following the general procedure.[9] The *Reissert compound* (1; R^1 = Ph, R^2 = H, R^3 = Me) (5.4 g) had m.p. 167—169° (from MeOH) (Found: C, 78.9; H, 5.25; N, 10.3. $C_{18}H_{14}N_2O$ requires C, 78.8; H, 5.1; N, 10.2%).

2-*Benzoyl*-4-*bromo*-1-*cyano*-1,2,3,4-*tetrahydro*-3-*hydroxy*-4-*methylisoquinoline* (2; R^1 = Ph, R^2 = H, R^3 = Me, X = Br).—The Reissert compound (1; R^1 = Ph, R^2 = H, R^3 = Me) (180 mg) was treated (see above) with 1,3-dibromo-5,5-dimethylhydantoin (64 mg) in aqueous dioxan (5 ml) containing a catalytic amount of concentrated hydrochloric acid. The *bromohydrin* (134 mg) had m.p. 133—135° (from EtOAc) (Found: C, 58.15; H, 4.1; N, 7.5. $C_{18}H_{15}BrN_2O_2$ requires C, 58.2; H, 4.1; N, 7.55%), $\nu_{max.}$ 3 310 and 1 670 cm^{-1}; τ[$(CD_3)_2SO$] 2.1—2.6 (m, aryl), 3.1—3.4 (br s, OH, exchangeable with D_2O), 3.86 (s, H-1), 4.38 (br s, 3-H, sharpening after D_2O exchange), and 7.83 (s, Me).

1-*Benzoylimino*-4-*methyl*-1H-2-*benzopyran* (4; R^1 = Ph, R^2 = H, R^3 = Me).—The foregoing bromohydrin (230 mg) in dioxan (15 ml) was treated with 10% aqueous sodium hydroxide (1 mol equiv.) at room temperature for 2 h. The *imine* (4; R^1 = Ph, R^2 = H, R^3 = Me) (120 mg), m.p. 135—136° (from ether) (Found: C, 77.6; H, 5.1; N, 5.3. $C_{17}H_{13}NO_2$ requires C, 77.55; H, 5.0; N, 5.3%), *m/e* 263; τ 1.5—2.8 (m, aryl), 3.15 (q, *J* 1 Hz, 3-H), and 7.95 (d, *J* 1 Hz, Me), was isolated by chromatography on silica plates in the usual way (see above).

Hydrolysis of (4; R^1 = Ph, R^2 = H, R^3 = Me) with dilute hydrochloric acid in dioxan gave 4-methylisocoumarin, m.p. 63—66° (lit.,[10] 65—66°), essentially quantitatively, together with benzamide.

4-*Chloro*-1-*cyano*-2-*ethoxycarbonyl*-1,2,3,4-*tetrahydro*-3-*hydroxyisoquinoline* (2; R^1 = EtO, R^2 = R^3 = H, X = Cl).—1-Cyano-2-ethoxycarbonyl-1,2-dihydroisoquinoline (1.0 g) in dioxan (15 ml) was treated with aqueous hypochlorous acid (45 ml, 1.3 mol equiv.) at room temperature in the usual way. The precipitate was recrystallised from ethyl acetate to give the *chlorohydrin* (670 mg), m.p. 208—210° (Found: C, 55.55; H, 4.8; N, 10.0. $C_{13}H_{13}ClN_2O_3$ requires C, 55.6; H, 4.7; N, 10.0%), $\nu_{max.}$ 3 430 and 1 710 cm^{-1}; τ[$(CD_3)_2SO$)] 2.2—2.6 (m, aryl), 3.90 (s, 1-H), 4.06 (br d, *J* 4 Hz, 3-H), 4.65 (d, *J* 4 Hz, 4-H), 5.70 (q, *J* 8 Hz, CH_2), 6.60 (br s, OH), and 8.68 (t, *J* 8 Hz, Me).

1-*Ethoxycarbonylimino*-1H-2-*benzopyran* (4; R^1 = EtO, R^2 = R^3 = H).—The aforementioned chlorohydrin (1.12 g) in dioxan (30 ml) was treated with 10% aqueous hydroxide (1 mol equiv.) at room temperature for 2 h in the usual way. The *ester* (332 mg) had m.p. 100—102° (from ether) (Found: C, 66.45; H, 5.2; N, 6.8. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.1; N, 6.45%), *m/e* 217, $\nu_{max.}$ 1 710, 1 670, and 1 640 cm^{-1}; τ 1.6—2.8 (m, aryl), 2.92 (d, *J* 6 Hz, 3-H), 3.65 (d, *J* 6 Hz, 4-H), 5.70 (q, *J* 7 Hz, CH_2), and 8.62 (t, *J* 7 Hz, Me).

1-*Benzenesulphonylimino*-1H-2-*benzopyran* (16).—The Reissert compound[6] (15) (1.0 g) was treated with aqueous hypochlorous acid in dioxan in the usual way and the chloroform-soluble products were separated on an alumina column. Elution with benzene gave the *sulphone* (16) (320 mg), m.p. 164—166° (EtOAc) (Found: C, 63.15; H, 4.0; N, 5.0. $C_{15}H_{11}NO_3S$ requires C, 63.2; H, 3.85; N, 4.9%), *m/e* 285, $\nu_{max.}$ 1 649 cm^{-1}.

We thank the S.R.C. (CAPS Studentship to S. E.), Fisons Ltd., Pharmaceutical Division (co-operating body), the P.C.M.U. (accurate mass measurements), and the Carnegie Trust (vacation scholarship to J. W. M. M.) for their support.

[8/1063 *Received*, 7*th June*, 1978]

REFERENCES

[1] G. W. Kirby, S. L. Tan, and B. C. Uff, *J.C.S. Perkin I*, 1979, 270.
[2] I. W. Elliott, *J. Amer. Chem. Soc.*, 1955, **77**, 4408; B. C. Uff and R. S. Budhram, *Heterocycles*, 1977, **6**, 1789.
[3] L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Vol. 1, Wiley, New York, 1967, p. 208.
[4] H. Nogami, *J. Pharm. Soc. Japan*, 1941, **61**, 46.
[5] M. M. Robison and B. L. Robison, *J. Amer. Chem. Soc.*, 1958, **80**, 3443.
[6] J. M. Wefer, A. Catala, and F. D. Popp, *J. Org. Chem.*, 1965, **30**, 3075.
[7] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 1970, **35**, 4000.
[8] J. J. M. Vandewalle, E. de Ruiter, H. Reimlinger, and R. A. Lenaers, *Chem. Ber.*, 1975, **108**, 3898.
[9] F. D. Popp and W. Blount, *Chem. and Ind.*, 1961, 550.
[10] F. Duro and P. Condorelli, *Boll. Sedute Accad. Gioenia Sci. Nat. Catania*, 1960, 606 (*Chem. Abs.* 1963, **58**, 9010f).