Rearrangement Reactions of a Reissert Compound Chlorohydrin

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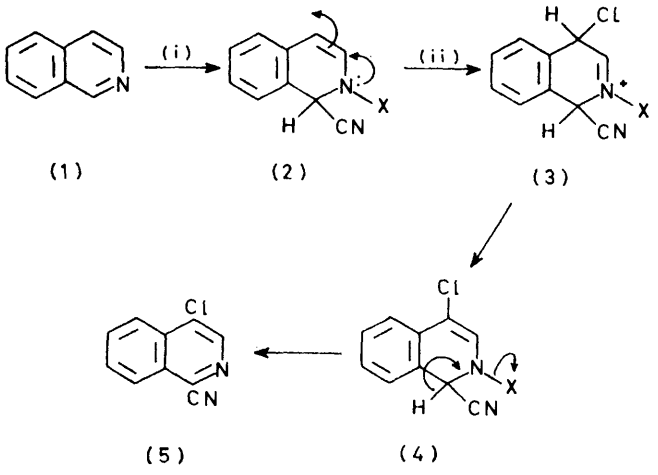
The Reissert compound, 2-benzoyl-1-cyano-1,2-dihydroisoquinoline, reacted with hypochlorous acid to yield a crystalline chlorohydrin. Base-catalysed elimination of hydrogen chloride from this led to an array of rearranged products in a controlled manner. In this way, simple preparative routes to 1-benzoylamino-1-cyanoisochromene, 1-benzoyliminoisochromene (and thence isocoumarin), 1-ethoxy-4-formyl-3-phenylisoquinoline, and 1-ethoxy-3-phenylisoquinoline were devised. The mechanism of the consecutive rearrangements is discussed.

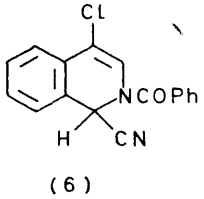
As described in the preceding paper,[1] treatment of isoquinoline (1) with sulphuryl chloride and potassium cyanide gives, under certain conditions, 4-chloro-1-cyanoisoquinoline as the main product. This is considered to arise by electrophilic chlorination at C-4 of an intermediate of type (2; X = SO_2Cl), which then leads to (5) under the basic conditions, as shown (Scheme 1).



SCHEME 1 (i) SO_2Cl_2–KCN; (ii) SO_2Cl_2

RESULTS AND DISCUSSION

To gain further insight into the proposed mechanism we examined [2] the reaction of the Reissert compound (2; X = COPh) with sulphuryl chloride and potassium cyanide under the conditions used previously. Two crystalline materials were isolated from the complex reaction mixture. The minor product (2%) was the expected [(2)→(3)→(4)] chloro-derivative (6) and the

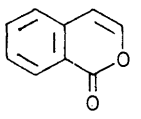


(6)

other (19%) was shown to be the novel chlorohydrin (7) formed, presumably, by hydration of an intermediate of type (3). This compound was readily prepared in good yield by treatment of (2; X = PhCO) with hypochlorous acid in dioxan, or with *N*-chlorosuccinimide in aqueous dioxan, and was subjected to further investigation. The i.r. spectrum of (7) showed bands for hydroxy (3 303 cm^{-1}), cyano (2 248 cm^{-1}), and amide (1 638 cm^{-1}) groups. In the n.m.r. spectrum [in $(CD_3)_2SO$] signals were observed at τ 4.35 (3-H) and 4.65 (4-H) for vicinally coupled (J 3.1 Hz) protons, the former being further split (J 4.3 Hz), by the hydroxy-proton, τ 3.24. The proton at C-1 gave a singlet in the expected region, τ 3.77, of the spectrum. The chlorohydrin (7) appeared from its sharp melting point, 176—178 °C, and n.m.r. spectrum to be a single stereoisomer but the relative configuration of the substituents has not been determined. In principle, addition of hypochlorous acid to the 3,4-double bond of the Reissert compound might have occurred as shown (7), or in the opposite sense with attachment of chlorine at C-3 and hydroxy at C-4. This point was settled, in favour of (7), by deuterium labelling. 4-Bromoisoquinoline was treated with n-butyl-lithium, at −35 °C, and the reaction mixture quenched with deuterium oxide. The resulting 4-deuterioisoquinoline was converted into the 4-deuterio-analogue of (7) as above. The n.m.r. spectrum of this product showed, *inter alia*, an AB quartet, τ 4.40 and 3.25 (J 4.5 Hz) for the protons at C-3 and in the hydroxy-group. The signal at τ 3.25 disappeared when the sample was treated with deuterium oxide and, as expected, the signal at τ 4.40 then collapsed to a singlet; thus the hydroxy-group was attached to C-3 and not C-4.

Treatment of the chlorohydrin (7) with triethylamine (1 equiv.) in dioxan at room temperature produced a yellow colour which faded slowly with concurrent precipitation of triethylamine hydrochloride. The major reaction product (40%) was assigned the isochromene structure (9) on the following grounds. The n.m.r. spectrum [$(CD_3)_2SO$] showed signals for the olefinic protons, τ 3.75 and 3.20 (AB quartet, $J_{3,4}$ 5.9 Hz), and for the NH proton, τ −0.14 (broad singlet), which disappeared upon addition of deuterium oxide. The i.r. spectrum of (9) showed no detectable cyano-absorption but this is to be expected when the cyano-group is attached to carbon carrying oxygen and nitrogen substituents.[3] (The nitrile absorption in Reissert compounds and cyanohydrins is always very weak and sometimes unobservable.) Treatment of (9) with sodium hydroxide in aqueous dioxan caused elimination of hydrogen cyanide with the formation of (10), which was the major (43%) product obtained directly from (7) with

the same reagent. The compound (10) showed n.m.r. signals, τ 3.70 and 3.02 (AB quartet, $J_{3,4}$ 5.8 Hz), for two olefinic protons and a strong, broad i.r. absorption between 1 683 and 1 633 cm^{-1}; no n.m.r. or i.r. bands corresponding to NH or OH groups were observed. Hydrolysis of (10) with dilute hydrochloric acid afforded, virtually quantitatively, isocoumarin (13) and benzamide.



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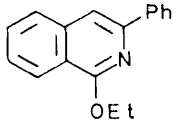
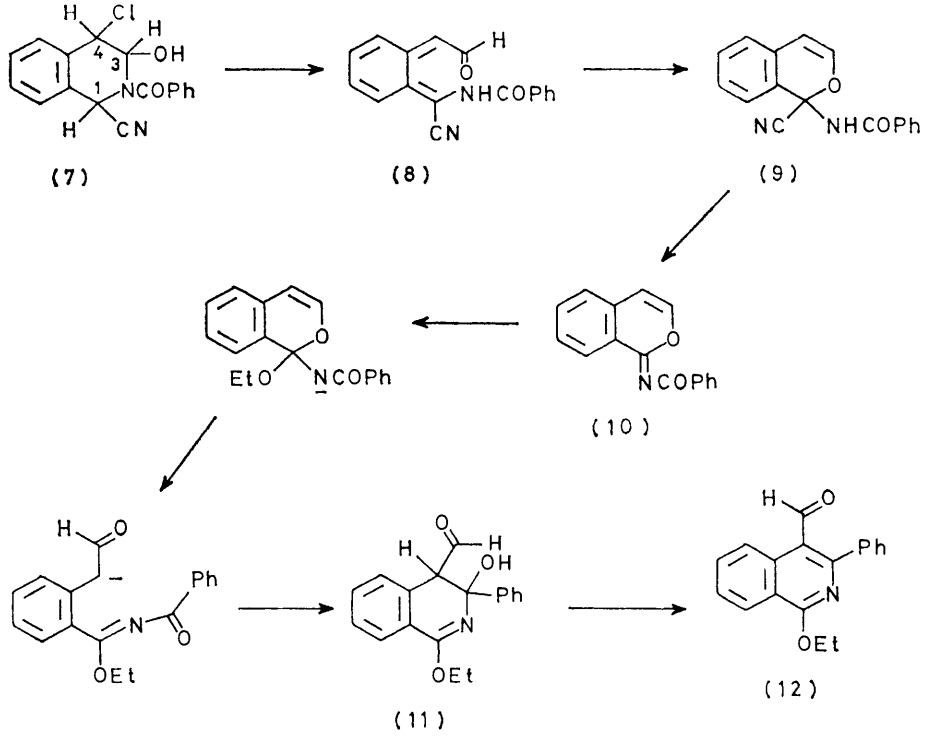


(14)

In contrast, (10) reacted with ethanolic sodium hydroxide at room temperature to yield the isoquinoline derivative (12) as the major product (53%). This was accompanied by the known [4] compound (14), identified by its m.p. and that of the derived 3-phenylisoquinolone.[4,5] A mixture of (12) and (14), together with a small amount of benzamide, was also formed directly from (7) by reaction with ethanolic sodium hydroxide. The presence of an aldehyde group in (12) was revealed spectroscopically [$\nu_{max.}$ 1 671 cm^{-1}; τ −0.14 (s)] and confirmed by reduction with sodium borohydride to yield a primary alcohol [τ 5.10 (s, 2 H, CH_2) and 8.2 (br s, 1 H, exchangeable with D_2O)]. Decarbonylation [6] of (12) with palladium–charcoal (5%) at 220 °C gave (14).

A possible reaction path to account for the formation of the products (9), (10), (11), and (12) from the chlorohydrin (7) is presented in Scheme 2. The product (14) could arise from attack of ethoxide on the formyl group of the intermediate (11) followed by elimination of ethyl formate and hydroxide with concurrent aromatisation. The proposed conversion, (7)→(8), may involve 1,4-conjugated elimination of hydrogen chloride before or after opening of the carbinolamide ring while the subsequent electrocyclic ring closure, (8)→(9), has ample precedent.[7] The remarkable base-induced reactions of (7) thus provide simple preparative routes from isoquinoline to isocoumarin and the highly substituted isoquinoline system (12). The extension of these transformations to other derivatives of the type (7) will be discussed in a later paper.



SCHEME 2

EXPERIMENTAL

General Methods.—N.m.r. spectra were measured, unless otherwise stated, for deuteriochloroform solutions at 60 MHz with tetramethylsilane as internal standard. I.r. spectra were run with potassium bromide discs (for solids) or thin films (for liquids) and u.v. spectra were measured in ethanol. M.p.s were determined with a Kofler hot-stage apparatus.

Reaction of 2-Benzoyl-1-cyano-1,2-dihydroisoquinoline with Sulphuryl Chloride and Potassium Cyanide.—To a stirred mixture of 2-benzoyl-1-cyano-1,2-dihydroisoquinoline (1.3 g) in dichloromethane (20 ml) and potassium cyanide (1 g) in water (10 ml), at 0—5 °C, was added, dropwise, sulphuryl chloride (1 ml); stirring was continued for 4 h. The organic layer was washed successively with water, 2N hydrochloric acid, water, 2N sodium hydroxide, and water,

and then dried (Na_2SO_4). Evaporation gave a mixture of at least four compounds (t.l.c.). Preparative t.l.c. (silica gel) using the solvent system benzene–ethyl acetate (80 : 20) gave 2-benzoyl-4-chloro-1-cyano-1,2-dihydroisoquinoline [1] (28 mg), R_F 0.65, and 2-benzoyl-4-chloro-1-cyano-1,2,3,4-tetrahydro-3-hydroxyisoquinoline (0.29 g) (see below), R_F 0.15.

Preparation of 2-*Benzoyl*-4-*chloro*-1-*cyano*-1,2,3,4-*tetrahydro*-3-*hydroxyisoquinoline* (7).—Mixing aqueous sodium hypochlorite (12% wt./vol. available chlorine) (100 ml) and 2N nitric acid (120 ml) gave hypochlorous acid (0.96% by iodine titration). 2-Benzoyl-1-cyano-1,2-dihydroisoquinoline (6.5 g) in dioxan (50 ml) was treated, dropwise with stirring, with hypochlorous acid (as above) (162 ml). A solid product precipitated and was collected. Extraction of the aqueous solution with chloroform afforded more of the same material. The combined product was crystallised from ethyl acetate to yield 2-*benzoyl*-4-*chloro*-1-*cyano*-1,2,3,4-*tetrahydro*-3-*hydroxyisoquinoline* (7) 4.3 g), m.p. 176—178 °C (Found: C, 65.4; H, 4.4; N, 9.1. $C_{17}H_{13}ClN_2O_2$ requires, C, 65.28; H, 4.18; N, 8.9%); $\nu_{max.}$ 3 303, 2 248, and 1 638 cm^{-1}; *m/e* 312 and 314 (ratio 3 : 1); τ[$(CD_3)_2SO$] 2.1—2.6 (m, aryl-H), 3.24 (d, *J* 4.3 Hz, OH), 3.77 (s, 1-H), 4.35 (dd, *J* 4.3 and 3.1 Hz, 3-H), and 4.67 (d, *J* 3.1 Hz, 4-H).

Alternatively, the Reissert compound (1.3 g) in dioxan (8 ml) was treated with *N*-chlorosuccinimide (0.79 g) in dioxan (8 ml) and water (4 ml). The mixture was heated slowly to 85—90 °C and maintained at this temperature (*ca.* 1.5 h) until the *N*-chlorosuccinimide had been consumed (starch–iodide test). The reaction mixture was diluted with water and extracted with chloroform to yield the product (7) (0.60 g).

2-*Benzoyl*-4-*chloro*-1-*cyano*-4-*deuterio*-1,2,3,4-*tetrahydro*-3-*hydroxyisoquinoline*.—4-Deuterioisoquinoline [τ 0.81 (s, 1-H), 1.54 (s, 3-H), and 1.96—2.76 (aryl-H)], prepared by quenching 4-isoquinolyl-lithium [8] with deuterium oxide, was converted into 2-benzoyl-1-cyano-4-deuterio-1,2-dihydroisoquinoline in the usual way.[9] This deuteriated Reissert compound was converted, as before, using hypochlorous acid, into 2-benzoyl-4-chloro-1-cyano-4-deuterio-1,2,3,4-tetrahydro-3-hydroxyisoquinoline, τ[$(CD_3)_2SO$] 2.2—2.6 (m, aryl-H), 3.25 (d, *J* 4.5 Hz, OH), 3.80 (s, 1-H), and 4.40 (d, *J* 4.5 Hz, 3-H).

Reaction of the Chlorohydrin (7) *with Triethylamine*.—The foregoing chlorohydrin (7) (0.45 g) in dry dioxan (20 ml) was treated with triethylamine (0.21 ml) at room temperature. A yellow colour developed and faded over 2 h with the precipitation of triethylammonium chloride. The mixture was filtered and the filtrate evaporated. The residue was dissolved in chloroform and washed with water. Evaporation gave a mixture separated by preparative t.l.c. [PF_{254} silica plates developed with benzene–ethyl acetate (80 : 20)]. 1-*Benzoylamino*-1-*cyanoisochromene* (9) (R_F 0.42) crystallised from ethanol as plates (108 mg), m.p. 131—133 °C (Found: C, 73.8; H, 4.5; N, 10.0. $C_{17}H_{12}N_2O_2$ requires C, 73.9; H, 4.4; N, 10.1%); $\nu_{max.}$ 3 263 and 1 663 cm^{-1}; $\lambda_{max.}$ 228 (ε 23 300) and 265 (28 500) nm; *m/e* 276; τ [$(CD_3)_2SO$] −0.14 (s, NH), 1.9—2.8 (m, aryl-H), 3.20 (d, *J* 5.9 Hz, 3-H), and 3.75 (d, *J* 5.9 Hz, 4-H). 1-Benzoyliminoisochromene (10) (see below) (R_F 0.55) was also isolated (18 mg), m.p. 113—114 °C.

Reaction of the Chlorohydrin (7) *with Sodium Hydroxide*.—The chlorohydrin (7) (1.0 g) in dioxan (30 ml) was treated with 10% aqueous sodium hydroxide (1 mol equiv.). After 1.5 h at room temperature (the initial yellow colour had faded), the mixture was neutralised with dilute hydrochloric acid. 1-*Benzoyliminoisochromene* (10) was isolated as before. Crystallisation from ether gave flakes (0.34 g), m.p. 113—114 °C (Found: C, 77.0; H, 4.4; N, 5.8. $C_{16}H_{11}NO_2$ requires C, 77.1; H, 4.45; N, 5.6%); $\nu_{max.}$ 1 683—1 633 cm^{-1}; $\lambda_{max.}$ 244 (ε 34 100), 251 (37 850), and 327 (sh) (7 000) nm; *m/e* 249; τ 1.5—2.8 (aryl-H), 3.02 (d, *J* 5.8, 3-H), and 3.70 (d, *J* 5.8, 4-H).

The same product was obtained by treating 1-benzoylamino-1-cyanoisochromene with aqueous sodium hydroxide (1 mol equiv.) in dioxan at room temperature.

Hydrolysis of 1-*Benzoyliminoisochromene*.—1-Benzoyliminoisochromene (9) (62 mg) in dioxan (5 ml) was stirred with 2N hydrochloric acid (2 ml) at room temperature. After 1 h the mixture was neutralised and extracted with chloroform. Preparative t.l.c. (as before) gave isocoumarin (33 mg), m.p. 43—45 °C (lit.,[10] 41—45 °C), identical with an authentic specimen, and benzamide (28 mg), m.p. 128—130 °C.

Reaction of the Chlorohydrin (7) *with Ethanolic Sodium Hydroxide*.—The chlorohydrin (7) (1.24 g) in ethanol (30 ml) was treated with 10% aqueous sodium hydroxide (3 equiv.) at room temperature. The mixture became deep red then faded to orange during 4.5 h. The solvent was evaporated off and the residue partitioned between chloroform and water. The chloroform-soluble fraction was chromatographed (neutral grade III alumina). Elution with benzene then ethyl acetate gave, successively, the following products: 1-ethoxy-3-phenylisoquinoline (14) (0.26 g), m.p. 45—47 °C (ethanol) (lit.,[4] 45—46 °C) (Found: C, 81.8; H, 6.2; N, 5.7. Calc. for $C_{17}H_{15}NO$: C, 81.9; H, 6.1; N, 5.6%); 1-*ethoxy*-4-*formyl*-3-*phenylisoquinoline* (12) (0.34 g), m.p. 110—111 °C (ethanol) (Found: C, 78.1; H, 5.6; N, 5.1. $C_{18}H_{15}NO_2$ requires C, 78.0; H, 5.45; N, 5.05%); $\nu_{max.}$ 2 875, 2 775, and 1 671 cm^{-1}; $\lambda_{max.}$ 247 (ε 34 700) and 329 (ε 10 300) nm; *m/e* 277; τ −0.14 (s, CHO), 0.70 (m, 5-H), 1.65 (m, 8-H), 2.0—2.7 (m, aryl-H), 5.31 (q, CH_2), and 8.51 (t, CH_3); and benzamide (81 mg).

Similarly, treatment of 1-benzoyliminoisochromene (9) in ethanol with 20% aqueous sodium hydroxide (2 equiv.) gave 1-ethoxy-4-formyl-3-phenylisoquinoline as the major (52%) product.

1-Ethoxy-3-phenylisoquinoline was further characterised by hydrolysis in hot, concentrated hydrochloric acid to yield (50%) 3-phenylisoquinolone, m.p. 196—198 °C (ethanol) (lit.,[6] 199—200 °C).

Reduction of 1-*Ethoxy*-4-*formyl*-3-*phenylisoquinoline*.—The isoquinoline (50 mg) in methanol (10 ml) was treated with sodium borohydride (68 mg) at room temperature for 3 h. Evaporation of the solvent and crystallisation of the product from ether–light petroleum (b.p. 40—60 °C) gave 1-*ethoxy*-4-*hydroxymethyl*-3-*phenylisoquinoline* (34 mg), m.p. 130—131 °C (Found: C, 77.6; H, 6.1; N, 5.0. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.1; N, 5.0%); $\nu_{max.}$ 3 374 cm^{-1}; $\lambda_{max.}$ 244 (ε 28 200) and 294 (11 600) nm; *m/e* 279; τ 1.6—2.7 (m, aryl-H), 5.10 (s, CH_2), 5.44 (q, CH_2), 8.2 (br s, OH), and 8.55 (t, CH_3).

Decarbonylation of 1-*Ethoxy*-4-*formyl*-3-*phenylisoquinoline*.—The isoquinoline (50 mg) was heated with 5% palladium–charcoal (50 mg) at 200—220 °C for 1.5 h. The product (29 mg) was identified as 1-ethoxy-3-phenylisoquinoline by spectroscopic comparison with material obtained earlier (see above).

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