33. N-*Substituted Heterocyclic Cations. Part III.*[1] *Reactions of the* 2-*Cyanoisoquinolinium Ion and its Pseudo-base,* 2-*Cyano-*1,2-*dihydro-* 1-*hydroxyisoquinoline.*

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The 2-cyanoisoquinolinium ion has been prepared as the fluoroborate and shown to react with a number of nucleophiles to form stable 1,2-dihydro-isoquinolines. Two of these products, 2-cyano-1,2-dihydro-1-hydroxy- and 2-cyano-1,2-dihydro-1-methoxy-isoquinoline react with bromine in protic solvents to give tetrahydroisoquinolines by addition of (effectively) the bromine cation and a nucleophile, which may be the conjugate base of the solvent or another nucleophile present in the solution. The bromination of the 2-cyanoisoquinolinium ion and of isoquinoline in dilute aqueous acid has been studied; the products are attributed to the formation of di- and tetra-hydroisoquinolines as intermediates.

PREVIOUS work [1] has shown that the 1-cyanoquinolinium ion and its pseudo-base, 1-cyano-1,2-dihydro-2-hydroxyquinoline, are excellent model compounds for the study of cation–pseudo-base equilibria and the general reactions of quinoline pseudo-bases. Although no extensive comparative study of related quinolinium and isoquinolinium pseudo-base systems has been carried out previously, generalisations about the two systems frequently appear. We therefore undertook such a study of the 2-cyanoisoquinolinium ion (Ia) and its pseudo-base (IIa) with particular reference to reactions already studied for the quinolinium system. This Paper is based on bromination, for this system should be a reliable model for intermediates predicted in the bromination [2] and nitration [3] of iso-quinoline in dilute acid.
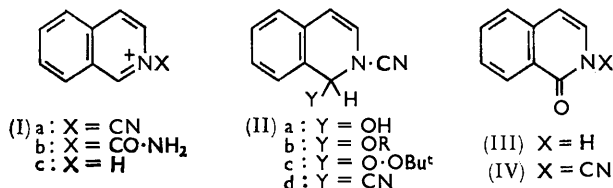
2-Cyanoisoquinolinium Ion.—In contrast to the corresponding quinolinium system, 2-cyanoisoquinolinium fluoroborate is not precipitated when the pseudo-base (IIa) is

[1] Part I (Johnson, *J.*, 1962, 283) and Part II (Johnson and Ridd, *J.*, 1962, 291) were entitled " N-Substituted Quinolinium Ions."
[2] Brown and Harcourt, *Tetrahedron*, 1960, **8**, 23.
[3] Dewar and Maitlis, *J.*, 1957, 944.

recrystallised from fluoroboric acid; instead, 2-carbamoylisoquinolinium (Ib) fluoroborate [4] is obtained. However, 2-cyanoisoquinolinium (Ia) fluoroborate may be obtained fairly pure and in good yield by reaction of the boron trifluoride–ether complex with a solution of the pseudo-base in tetrahydrofuran. Though the salt could not be purified by recrystallisation, the product obtained under various conditions had a consistent infrared spectrum and gave good yields of the pseudo-base on reaction with water. The salt is stable in dry air and has a characteristic ultraviolet spectrum ($\lambda_{max.}$ 381, 306·5, and 297 mμ; log ε 3·70, 3·88, and 3·84) unlike those of other simple 2-substituted isoquinolinium ions [e.g., protonated isoquinolinium ion (Ic), $\lambda_{max.}$ 333, 274, and 266 mμ; log ε 3·51, 3·18, and 3·17], indicating, as for the 1-cyanoquinolinium ion, strong conjugative interaction between the cyano-group and the ring system. It also has a characteristic green fluorescence.

(I) a : X = CN
    b : X = CO·NH$_2$
    c : X = H

(II) a : Y = OH
     b : Y = OR
     c : Y = O·OBu^t
     d : Y = CN

(III) X = H
(IV) X = CN

Reaction of the 2-Cyanoisoquinolinium Ion with Nucleophiles.—This reaction is of less interest than the corresponding reaction in the quinoline system, because nucleophiles can be expected to add only to the 1-position.[2] Thus primary, secondary, and tertiary alkoxide ions in the corresponding alcohol afford stable dihydroisoquinolines of the type (IIb). Similarly, t-butyl hydroperoxide anion in t-butyl hydroperoxide gives the peroxy-ether (IIc). Reaction with water, even in 0·1M-perchloric acid, gives an almost quantitative yield of the pseudo-base (IIa). The reaction of isoquinoline, cyanogen bromide, and hydrogen cyanide to give the compound (IId) has been described previously,[5] but that of the 2-cyanoisoquinolinium ion with an excess of cyanide ions in dimethylacetamide leads to isoquinoline, presumably by attack of cyanide ion (which is highly nucleophilic in this medium [6]) on the 2-cyano-group of compound (IId). Compounds (IIa, b, and c) have comparable ultraviolet spectra ($\lambda_{max.}$ 275 mμ; log ε 4·13), but the ethers (IIb and c) are distinguished from the pseudo-base (IIa) by their stability above the melting point and by their much greater solubility in· ether and hydrocarbons.

2-Cyano-1,2-dihydro-1-hydroxyisoquinoline.—The pseudo-base (IIa) had been prepared previously, but only as an impurity from the reaction between isoquinoline and cyanogen bromide in " anhydrous " solvents. It is, however, readily prepared by the same reaction in aqueous solution. It is somewhat unstable in the air, particularly in the presence of basic impurities. Its structure was deduced from a comparison of its ultraviolet spectrum with those of the ethers (IIb), from infrared bands at 3280 (OH) and 2220 cm.$^{-1}$ (C≡N), and from the formation of 1-isoquinolone (III) in good yield by the action of sodium methoxide on a methanolic solution of the t-butylperoxy-ether (IIc), presumably through the 2-cyanoisoquinolone (IV). Structures (IIa, b, and c) were confirmed by measurement of the proton magnetic resonance spectra at 40 mc./sec.; the pseudo-base, in conditions where the hydroxyl proton was exchanging with the solvent, and the t-butylperoxy ether gave (AB + A) spectra (for protons 4, 3, and 1, respectively) with $J_{AB} = 8 \pm 0.5$ c./sec. whereas the methyl ether (IIb; R = Me) gave rise to an ABX spectrum (for protons 4, 3, and 1, respectively) with $J_{AB} = 8$ c./sec., $J_{AX} \approx 0$, and $J_{BX} \approx 1.5$ c./sec.

The ethers (IIb and c) were also prepared by acid-catalysed reaction of the pseudo-base with the corresponding alcohol or hydroperoxide, presumably owing to prior dissociation of the pseudo-base to the 2-cyanoisoquinolinium ion.

[4] Huckings and Johnson, unpublished work.
[5] Mumm and Herrendörfer, *Ber.*, 1914, **47**, 764.
[6] Parker, *Quart. Rev.*, 1962, **16**, 163.

Bromination of Dihydroisoquinolines.—On addition of one equivalent of bromine to the pseudo-base in aqueous tetrahydrofuran, the bromine colour is immediately discharged. The product is mainly a tetrahydroisoquinoline (V) but, because at least two of the four possible geometric isomers are formed, it was not possible to obtain a pure sample without considerable loss of yield and some decomposition. Bromination of the methyl ether (IIb; R = Me) in methanol gives the tetrahydroisoquinoline (VIa) in good yield. This tetrahydroisoquinoline is more stable and withstood elution from an unwashed alumina column without apparent change; it was obtained crystalline without significant decrease in yield. A similar but less-defined product was obtained on bromination of the methyl ether (IIb; R = Me) in methanol saturated with lithium bromide. This product decomposed extensively during working up and the isolated material liberated hydrogen bromide and cyanogen bromide. By analogy with the other products it probably has the structure (VIb) because bromide ion is non-basic and more nucleophilic

(V)   (VI) a: X = OMe   (VII) X = H or Br   (VIII) X = H or Br
              b: X = Br
              c: X = Cl
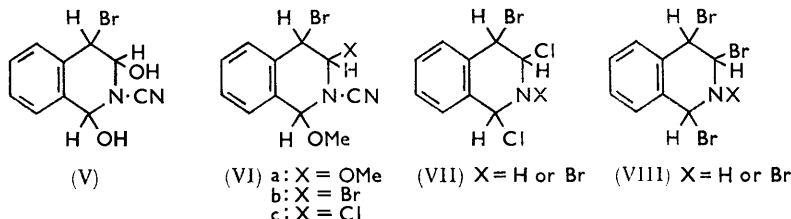
than the solvent in methanolic solution. A fourth product obtained in the presence of a large excess of lithium chloride in methanol probably has structure (VIc); [1] it was not isolated, but was hydrolysed *in situ.* In no case was 4-bromo-2-cyano-1,2-dihydro-1-hydroxyisoquinoline identified.

The four tetrahydroisoquinolines were hydrolysed with hydrochloric acid; the yields of 4-bromoisoquinoline obtained were: (V) 24%; (VIa) 14%; (VIb) 61%; (VIc) 23% (all ±5%). These yields may be rationalised in terms of a double elimination in which hydrogen bromide is lost slightly faster than methanol or water from the 3- and 4-position in one of the stages of the elimination. Thus the loss of hydrogen bromide from the tetrahydroisoquinoline from (VIb) can, but from (V, VIa, and VIc) cannot, result in the formation of 4-bromoisoquinoline. The high yields of 4-bromoisoquinoline and of isoquinoline obtained on acid-catalysed hydrolysis of 4-bromo-2-cyano-1,2-dihydro-1-hydroxyisoquinoline, are consistent with this mechanism.

A solution of the 2-cyanoisoquinolinium ion in 5M-perchloric acid also reacted immediately with one equivalent of bromine; on further hydrolysis, the product contained 4-bromoisoquinoline (8%) together with decomposition products similar to those obtained from the intermediate (V). In view of the resistance of heteroaromatic cations to electrophilic substitution and the rapid equilibration of 2-cyanoisoquinolinium ion and its pseudo-base (*ca.* 0·17% of pseudo-base in 5M-perchloric acid), this bromination probably proceeds through the pseudo-base.* That polybrominated isoquinolines are not produced in this reaction contrasts with the bromination of the 1-cyanoquinolinium ion,[1] but this is readily understood because the intermediate (V) is not a substituted aniline and would not be expected to be brominated at a significant rate.

In order to relate these results to the mechanism of bromination of isoquinoline, the latter reaction was carried out in 2M-hydrochloric acid with one equivalent of bromine. After several weeks the bromine colour had disappeared but the product was mainly isoquinoline, with a small amount of 4-bromoisoquinoline and the mixed product that is obtained also from the tetrahydroisoquinoline (V). The ratio of 4-bromoisoquinoline to

* It is possible that slight decomposition of the 2-cyanoisoquinolinium ion to the 2-carbamoylisoquinolinium ion may take place before or during these reactions, but this ion would also be expected to be brominated through its pseudo-base, leading to products similar to those from the 2-cyanoisoquinolinium ion.

the unknown product (2 ± 1 : 11) is very similar to the ratio of the yields of the same products (1 : 5) obtained from the tetrahydroisoquinoline (V). We infer that a tetra-hydroisoquinoline (VII) is probably an intermediate in the bromination of isoquinoline in these conditions. However, when isoquinoline hydrochloride is heated as a slurry with bromine, the yield of 4-bromoisoquinoline is high; [7] here a tetrahydroisoquinoline (VIII) may be an intermediate.

The ready formation of tetrahydroisoquinolines rather than the direct substitution predicted by Brown and Harcourt is a result of the high reactivity of the 3,4-double bond, similar to that encountered in the corresponding dihydroquinolines [1] and 1-chromens.[8] The predictions were based on direct attack of the electrophile at the 4-position and did not take into account the possible formation of a relatively stable bromonium ion. The latter would be expected to lead to *trans*-addition at the 3,4-double bond, and this is supported by the inability to eliminate all the bromine from the tetrahydroisoquinoline (VIa) on vigorous treatment with methanolic alkali.

EXPERIMENTAL

2-Cyano-1,2-dihydro-1-hydroxyisoquinoline.—2-Cyano-1,2-dihydro-1-hydroxyisoquinoline was prepared from aqueous cyanogen bromide and isoquinoline, as described for 1-cyano-1,2-dihydro-2-hydroxy-quinoline.[1] It has m. p. 112—113° (decomp.) (Found: C, 70·0; H, 5·05; N, 16·2. Calc. for $C_{10}H_8N_2O$: C, 69·7; H, 4·7; N, 16·3%). It was also prepared from 1-cyano-isoquinolinium fluoroborate and water as described previously.[1]

2-Cyanoisoquinolinium Fluoroborate.—2-Cyano-1,2-dihydro-1-hydroxyisoquinoline (12·0 g., 0·07 mole) was dissolved in tetrahydrofuran (100 ml.), and boron trifluoride–ethyl ether complex (30 ml., 0·21 mole) was added with stirring. The pasty mass, which crystallised on stirring, was filtered, and the solid was washed with ether and dried *in vacuo*. The product, 2-cyano-isoquinolinium fluoroborate (15·2 g., 90%) had m. p. 102° (decomp.). No method of purific-ation could be found, and analyses were variable.

4-Bromo-2-cyano-1,2-dihydro-1-hydroxyisoquinoline.—4-Bromoisoquinoline (5 g., 0·0024 mole) was added to a solution of cyanogen bromide (2·6 g., 0·0024 mole) in water. The mixture was stirred for ½ hr. with carbon tetrachloride (5 ml.) and extracted with methylene chloride, which was washed with 0·2M-hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The residue, recrystallised from benzene, had m. p. 147° (decomp.) and was pure *4-bromo-2-cyano-1,2-dihydro-1-hydroxyisoquinoline* (1·5 g., 25%) (Found: C, 47·4; H, 3·0; Br, 32·3; N, 11·2. $C_{10}H_7BrN_2O$ requires C, 47·8; H, 2·8; Br, 31·9; N, 11·2%).

2-Cyano-1,2-dihydro-1-methoxyisoquinoline.—(a) 2-Cyanoisoquinolinium fluoroborate (1·21 g., 0·005 mole) was added with stirring to a mixture of triethylamine (0·51 g., 0·005 mole) and methanol (0·5 ml.). After 2 min. ether (100 ml.) was added and the ethereal phase was separated, washed with 0·05M-sodium hydroxide and water, and dried (Na_2SO_4). The product on evaporation and recrystallisation from light petroleum (b. p. 40—60°) was *2-cyano-1,2-dihydro-1-methoxyisoquinoline*, m. p. 52° (0·67 g., 77%) (Found: C, 71·2; H, 5·7; N, 15·4. $C_{11}H_{10}N_2O$ requires C, 71·0; H, 5·4; N, 15·4%).

(b) 2-Cyano-1,2-dihydro-1-hydroxyisoquinoline (1·72 g., 0·01 mole) was heated with methanol (10 ml.) in the presence of glacial acetic acid (0·1 ml.) for 15 min. The solution was poured into water and extracted with ether. The ethereal phase was washed with 0·05M-sodium hydroxide until the aqueous phase was no longer yellow; it was then washed with water and dried (Na_2SO_4). The product on evaporation was 2-cyano-1,2-dihydro-1-methoxy-isoquinoline, identical with that obtained as above.

Similarly prepared, by both methods, were *2-cyano-1-ethoxy-1,2-dihydro-*, non-crystalline, decomp. below b. p. (Found: C, 72·0; H, 6·5; N, 13·9. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·1; N, 14·0%), *2-cyano-1,2-dihydro-1-isopropoxy-*, m. p. 51—52° (Found: C, 73·0; H, 7·3; N, 13·3. $C_{13}H_{14}N_2O$ requires C, 72·9; H, 6·6; N, 13·1%), *1-t-butoxy-2-cyano-1,2-dihydro-*, m. p. 97° (Found: C, 74·0; H, 7·3; N, 12·0. $C_{14}H_{16}N_2O$ requires C, 73·7; H, 7·1; N, 12·3%), and *2-cyano-1,2-dihydro-1-t-butylperoxyisoquinoline*, m. p. 90° (Found: C, 68·2; H, 7·2; N, 12·1. $C_{14}H_{16}N_2O_2$ requires C, 68·8; H, 6·6; N, 11·5%).

[7] Padbury and Lindwall, *J. Amer. Chem. Soc.*, 1945, **67**, 1268.
[8] Livingstone, *J.*, 1962, 76.

1-*Isoquinolone.*—2-Cyano-1,2-dihydro-1-t-butylperoxyisoquinoline (2·8 g.) was dissolved in M-methanolic sodium methoxide (30 ml.). After 1 min. the solution was poured into water and extracted with chloroform. The product on evaporation of the chloroform and recrystallisation from methanol–water was 1-isoquinolone (1·50 g., 86%), m. p. 208° (lit., 208·5—209°) [benzoate, m. p. 147° (lit.,[9] 147°)].

Bromination of 2-Cyano-1,2-dihydro-1-hydroxyisoquinoline.—To a solution of 2-cyano-1,2-dihydro-1-hydroxyisoquinoline (3·1 g., 0·018 mole) in aqueous tetrahydrofuran (300 ml., 1 : 2 v/v) was added bromine (2·9 g., 0·018 mole). The bromine colour disappeared immediately. The solution was poured into water (1 l.) and extracted with ether. The product after removal of the ether was a non-crystalline solid, largely 4-bromo-2-cyano-1,2,3,4-tetrahydroisoquinoline-1,3-diol (V) (Found: C, 45·4; H, 4·0; Br, 28·9; N, 9·6. Calc. for $C_{10}H_9N_2BrO_2$: C, 44·7; H, 3·4; Br, 29·7; N, 10·3%). This product (2·98 g.) was heated with 2M-hydrochloric acid (50 ml.) on the steam-bath for 2 hr., then diluted with water (100 ml.), and the precipitate was filtered off. The filtrate was extracted with chloroform and the product obtained from the chloroform was combined with the precipitate to give a total of 0·69 g. (60—65% based on hydroxyisoquinolines). The aqueous phase was made alkaline and extracted with ether. Working up the ethereal extract gave 4-bromoisoquinoline (0·56 g., 24%), identical with an authentic sample.

Bromination of 2-Cyano-1,2-dihydro-1-methoxyisoquinoline.—(a) 2-Cyano-1,2-dihydro-1-hydroxyisoquinoline (6·4 g., 0·037 mole) was warmed for 15 min. with methanol (130 ml.) containing a trace of acetic acid. After cooling, bromine (6 g., 0·037 mole) was added. The bromine colour disappeared immediately and the solution was poured into water and extracted with ether. Evaporation of the ether gave a non-crystalline mass, but after a number of treatments, including elution from alumina with benzene and ether, a colourless crystalline material believed to be 4-*bromo-2-cyano-1,2,3,4-tetrahydro-1,3-dimethoxyisoquinoline* (VIa), m. p. 136°, was obtained (4·98 g., 45%) (Found: C, 48·7; H, 4·7; Br, 26·9; N, 9·1. $C_{12}H_{13}N_2BrO_2$ requires C, 48·4; H, 4·4; Br, 26·9; N, 9·4%). Comparison of the infrared spectrum of this product with that of the bulk non-crystalline material suggested that the two were substantially the same material. Hydrolysis of the product with hydrochloric acid as described above for the compound (V) gave 4-bromoisoquinoline in 14% yield and other products in 55% yield (based on hydroxyisoquinolines).

(b) Bromine (1·8 g., 0·011 mole) was added to a solution of 2-cyano-1,2-dihydro-1-methoxy-isoquinoline (2·1 g., 0·11 mole) in methanol (20 ml.) saturated with lithium bromide. The bromine colour disappeared immediately, but the product obtained by working up as described above was unstable. It was not characterised but was hydrolysed directly, as described above, to give 4-bromoisoquinoline in 61% yield.

(c) Bromination as in (b) above, but with lithium chloride in place of lithium bromide, gave an intermediate which was hydrolysed to give 4-bromoisoquinoline in 23% yield.

Bromination of the 2-Cyanoisoquinolinium Ion in Perchloric Acid.—2-Cyanoisoquinolinium fluoroborate (3·6 g., 0·015 mole) was stirred with 5M-perchloric acid (350 ml.) and bromine (2·4 g., 0·015 mole) for 12 hr. The solution was filtered, sodium carbonate solution was added to pH 3, and the solution was extracted with chloroform. The extract was worked up in the usual manner, to yield 4-bromoisoquinoline (0·26 g., 8%). The other products were not investigated in detail.

Bromination of Isoquinoline.—Isoquinoline (1·21 g., 0·009 mole), bromine (1·5 g., 0·0094 mole), and 2N-hydrochloric acid (480 ml.) were heated in sealed tubes for several weeks at 65° until the bromine colour had substantially disappeared. The resulting solution was worked up to give 4-bromoisoquinoline (30 ± 15 mg., 2 ± 1%) and a mixed product (0·15 g., 11% based on hydroxyisoquinolines) similar to that obtained in the decomposition of the tetra-hydroisoquinoline (V).

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[9] Cavallito and Haskell, *J. Amer. Chem. Soc.*, 1944, **66**, 1166.